Electronic Cigarette Research Briefing – March 2018

This research briefing is part of a series of monthly updates aiming to provide an overview of new studies on electronic cigarettes. The briefings are intended for researchers, policy makers, health professionals and others who may not have time to keep up to date with new findings and would like to access a summary that goes beyond the study abstract. The text below provides a critical overview of each of the selected studies then puts the study findings in the context of the wider literature and research gaps.

The studies selected and further reading list do not cover every e-cigarette-related study published each month. Instead, they include high profile studies most relevant to key themes identified by the UK Electronic Cigarette Research Forum; including efficacy and safety, smoking cessation, population level impact and marketing. For an explanation of the search strategy used, please see the end of this briefing.

Past research briefings can be found at www.cruk.org/UKECRF. If you would prefer not to receive this briefing in future, just let us know.

1. The association between smoking and electronic cigarette use in a cohort of young people.

- **Study aims**

  This study looked at the association between e-cigarette use and later smoking, and between smoking and later e-cigarette use in young people in Great Britain. The data came from a survey of 1,152 11-18 year olds in April 2016, with follow up 4-6 months later.

  Respondents were asked if they had ever used an e-cigarette or smoked at baseline. Follow up questions aimed to examine whether those who had never smoked at baseline had tried smoking, and whether ever smokers had increased their smoking. The same measures were used for e-cigarette use. The study then used causal mediation analysis to investigate whether any of the associations found could be due to a causal relationship.

- **Key findings**

  Among never smokers, those who had tried e-cigarettes at baseline were around 12 times more likely to have tried smoking at follow up, compared to those who had never used an e-cigarette (OR = 11.89, 95% CI: 3.56 – 39.72).

Those who had tried e-cigarettes and had increased their use over time were around 8 times more likely to have tried smoking, compared to those who didn't increase their e-cigarette use (OR = 7.89, 95% CI: 3.06 – 20.38).

Among those who had never used an e-cigarette, those who had tried smoking were more than 3 times more likely to have tried e-cigarettes at follow up, compared to those who had never smoked (OR = 3.54, 95% CI: 1.68 – 7.45).

Those who had smoked and increased their smoking were nearly 6 times more likely to have tried e-cigarettes, compared to those who didn't increase their smoking (OR = 5.79, 95% CI: 2.55 – 13.15).

In the causal mediation analysis, ever using an e-cigarette had a direct causal effect on smoking initiation at follow up (OR = 1.34, 95% CI: 1.05 – 1.72), and ever having smoked had a direct causal effect on e-cigarette initiation (OR = 1.08, 95% CI: 1.01 – 1.17).

- **Limitations**

  This study did not assess whether those who had tried smoking or e-cigarettes became regular users, and likely includes those only experimenting with smoking or e-cigarettes. No conclusions can be made from this study about an association between e-cigarette use and regular smoking or vice versa.

  This study couldn't account for all potential confounders that might affect results, such as curiosity, or liking or disliking the effects of smoking and/or e-cigarettes. Therefore, the study cannot conclusively causally link e-cigarette use with later smoking, or smoking with later e-cigarette use.

  The study assumed that the survey questions used were valid and reliable measures of complex potential confounding factors, such as problem behaviour.

  Out of the 132 young people who had ever used an e-cigarette, 84% were also smokers. Therefore, the association between ever e-cigarette use and later smoking was based on a small sample of only 21 people.

  The study used a short follow-up period of 4-6 months, so cannot show any long-term trends or associations.

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

East, K., Hitchman, S.C., Bakolis, I., Williams, S., Cheeseman, H., Arnott, D., McNeill, A. (2018) The association between smoking and electronic cigarette use in a cohort of young people. The Journal of Adolescent Health, doi:10.1016/j.jadohealth.2017.11.301.

2. E-cigarettes associated with depressed smoking cessation: A cross-sectional study of 28 European Union countries.

- **Study aims**

This cross-sectional study from researchers in the USA investigated the relationship between e-cigarette use and smoking cessation among those who had ever smoked, in both the European Union and Great Britain.

The data came from the 2014 Eurobarometer survey of 28 EU countries. This included 12,608 current and former smokers from the EU, and 411 current and former smokers from Great Britain. Those who had only experimented with e-cigarettes were excluded.

- **Key findings**

  Among ever smokers in the EU, those who had used e-cigarettes were significantly less likely to be former smokers (OR = 0.43, 95% CI: 0.32 – 0.58), compared to those who had never used an e-cigarette.

  This was true for daily users of e-cigarettes (OR = 0.52, 95% CI: 0.36 – 0.73), occasional users (OR = 0.33, 95% CI: 0.23 – 0.47), and experimenters (OR = 0.32, 95% CI: 0.25 - 0.41).

  In Great Britain, ever smokers who had used e-cigarettes were also significantly less likely to be former smokers (OR = 0.42, 95% CI: 0.20 – 0.87).

  This was found to be significant for occasional users (OR = 0.19, 95% CI: 0.04 – 0.84) and experimenters (OR = 0.32, 95% CI: 0.11 – 0.93).

  However, ever smokers who used e-cigarettes daily in Great Britain were not significantly less likely to be former smokers (OR = 0.55, 95% CI: 0.25 – 1.21).

- **Limitations**

  This study does not include information on when former smokers stopped smoking, so is likely to include people who quit before e-cigarettes were available. Therefore, the results may not be an accurate picture of recent trends.

  This study did not test for all potential confounders that might affect results, such as intention to quit or nicotine dependency. Therefore, it cannot causally associate e-cigarette use with current or former smoking.

  Several of the analyses in this study include some relatively small sample sizes. For example, the analysis of current or former smokers who were occasional e-cigarette users in Great Britain only included 17 people.

  The stratified results of this study include some with relatively small sample sizes, such as the analysis on occasional e-cigarette users in Great Britain which only included 17 ever smokers.

  Those who had only experimented with e-cigarettes were excluded from the overall results as it was assumed that they did not use e-cigarettes enough to impact smoking behaviour.

  This is a self-reported, cross-sectional survey, which may be subject to recall bias.

Kulik, M.C., Lisha, N.E., Glantz, S. A. (2018). E-cigarettes associated with depression smoking cessation: a cross-sectional study of 28 European Union countries. American Journal of Preventative Medicine, doi: 10.1016/j.amepre.2017.12.017.

3. Quantifying population-level health benefits and harms of e-cigarette use in the United States

- **Study aims**

  This US modelling study aimed to assess the population-level benefits and harms of e-cigarette use. The model used a range of data sources, including census data, national tobacco and e-cigarette surveys, and published randomised controlled trials and cohort studies.

  It aimed to predict the total life-years gained or lost from the additional current smokers in 2014 estimated to quit through the use of e-cigarettes, and the additional never smokers estimated to initiate smoking through the use of e-cigarettes, in order to quantify net population harms or benefits.

- **Key findings**

  The model estimated that an additional 2,070 (95% CI: -42,900 – 46,200) current smokers who use e-cigarettes in 2014 would quit smoking for 7 or more years compared to those who do not currently use e-cigarettes.

  It was estimated that in total, these additional long-term quitters would lose 3000 years of life (95% CI: -351,000 – 325,000).

  The model also estimated that an additional 168,000 (95% CI: 114,000 – 229,000) never-smoking young adults and adolescents who had ever used e-cigarettes would initiate regular smoking compared to those who had never used e-cigarettes.

  It was estimated that in total, these additional smokers would lose 1,510,000 years of life (95% CI: 1,030,000 – 2,060,000).

  Overall, the model estimated that e-cigarette use in 2014 would lead to 1,510,000 years of life lost (95% CI: 920,000 – 2,160,000).

- **Limitations**

  Modelling studies are dependent on the validity of the assumptions of the model, and can only provide estimates. This model assumes that the use of e-cigarettes will lead to an increase in the number of smokers.

  The model is vulnerable to any limitations of the individual studies and data sources used. Much of the current evidence on e-cigarette use is unable to conclude causation or fully control for all possible confounders.

  Modelling studies are only partially generalisable to real situations and processes. Conclusions about the real-world effect of e-cigarettes cannot be confirmed from this study. Neither can it account for future changes in policy or e-cigarette use which may affect health outcomes.

  This study did not consider former smokers, including those who may have successfully quit or avoided relapse through using e-cigarettes. This may under-estimate the benefits of e-cigarette use among ever smokers.

The results of this model contain large confidence intervals, so the data may not be accurate or precise.

This study doesn't include other measures of benefits or harm from e-cigarette use, such as morbidity or quality-adjusted life years.

Soneji, S.S., Sung, H.Y., Primack, B.A., Pierce, J.P., Sargent, J.D. (2018). Quantifying population-level health benefits and harms of e-cigarette use in the United States. PLoS One, doi: 10.1371/journal.pone.0193328

4. Metal concentrations in e-cigarette liquid and aerosol samples: the contribution of metallic coils

- **Study aims**

This US study evaluated the contribution of the heating coil in e-cigarettes to metal concentrations in e-liquid by testing samples before and after contact with the heating coil (in the refilling dispenser compared to the generated aerosol and remaining e-liquid in the tank).

The study analysed 11 different types of metal in different types of tank-style e-cigarettes taken from a sample of 56 daily e-cigarette users in Maryland, US.

The study estimated whether these metal concentrations could exceed safety regulations such as the Agency for Toxic Substances Disease Registry's daily chronic minimum risk level (MRL).

- **Key findings**

Compared to e-liquid from the refilling dispenser, the concentrations of all 11 metals analysed were significantly higher in both aerosol and tank samples, except for the iron aerosol sample.

57% of nickel aerosol samples, 46-68% of chromium samples, and 14% of manganese samples were estimated to exceed the MRL. 48% of lead aerosol samples were estimated to exceed the US EPA National Ambient Air Quality Standard and 75% of manganese samples exceeded the US EPA daily cancer reference concentration.

Correlations of concentrations of the same metal between the dispenser and aerosol samples were significant for tin, manganese, antimony, and iron. Correlations of concentrations of the same metal between the dispenser and tank were significant for aluminium, manganese, and antimony, and almost all correlations between the aerosol and tank were significant.

Most metal concentrations did not differ by frequency of coil change, except for aluminium, chromium, and manganese which were higher when coils were changed more than twice a month compared to less than twice a month.

No metal concentrations significantly differed by type of coil, except for copper concentrations in the tank samples which were higher with Kanthal coils.

Most metal concentrations did not differ by voltage, except for aluminium, iron, manganese, and nickel in tank samples which were higher in the intermediate voltage tertile (4 – 4.4V) compared to higher and lower voltages.

- **Limitations**

  This study used measures of metal concentrations carried out in a laboratory condition. This cannot make conclusions about people's exposure to metals during e-cigarette use. Neither can it make any conclusions about the health effects of any potential metal exposure on e-cigarette users.

  The study does not compare the concentrations of metals found to those in cigarette smoke or to a suitable background control (e.g. air).

  The researchers carried out a large number of tests for significance, but didn't adjust for this. It's therefore possible that some of the significant differences that were detected in the study arose by chance.

  This study did not test differences in metal concentration by specific devices or e-liquids, age of device, or frequency of use.

  Only a small sample of e-cigarettes were included that are not necessarily representative of the range of devices and e-liquids available. In particular, the study only focused on tank-style devices.

Olmedo, P., Goessler, W., Tanda, S., Grau-Perez, M., Jarmul, S., Aherrera, A., Chen, R., Hilpert, M., Cohen, J.E., Navas-Acien, A., Rule, A.M. (2018). Metal concentrations in e-cigarette liquid and aerosol samples: the contribution of metallic coils. Environmental Health Perspectives, 126 (2): 027010.

Overview

This month we include one study conducted by researchers in the UK and three from the USA. One of the American studies involved secondary analysis of survey data from Europe.

The first study was funded by CRUK and aimed to look at the associations between e-cigarette use and smoking initiation, and smoking and e-cigarette initiation. It involved causal mediation analysis, which is an approach that tries to disentangle the effects of a treatment, intervention or behaviour into a direct or indirect effect. Data were drawn from a longitudinal survey of young people aged 11-18 in Great Britain. Participants were surveyed in April 2016 (n=2,916) and half of them were successfully followed up between August and October of the same year. One in five of the follow up sample were excluded from the analysis because they indicated they'd never heard of e-cigarettes or didn't respond to key questions, resulting in a final sample of 1,152. At baseline, 229 young people (20%) had ever smoked and of these 111 had also ever vaped. There was also a very small group of never smokers (n=21, 2.3% of the whole study sample) who had tried an e-cigarette at least once at baseline.

At follow up, young people who had tried an e-cigarette at baseline were significantly more likely to have tried smoking. In addition, young people who had tried smoking at baseline were significantly more likely to have tried an e-cigarette at follow up. In other words, an association was found in

both directions - between e-cig use and subsequent smoking and between smoking and e-cig use. These patterns remained even after adjusting in the analysis for a range of factors that might serve as markers of 'common liability' (i.e. that some young people have characteristics, experiences of influences that make them more prone to risk taking behaviour). These factors were explored in the study including problem behaviour, school performance, alcohol use and family and social influences.

Following publication, the study was described by some commentators and in the media as providing further evidence of a 'gateway' effect between vaping and smoking. However, the study authors found that the relative contribution of the causal association between e-cigarette use and smoking initiation, and vice-versa, were very similar in their analysis. In other words, their study suggested that it is around equally likely that trying an e-cigarette 'causes' trying smoking as trying smoking 'causes' trying an e-cigarette. CRUK issued a press release regarding the interpretation of the study in the media.

This month's second study aimed to look at the relationship between e-cigarette use and smoking cessation in the 2014 Eurobarometer survey and was conducted by researchers in the USA. The dataset included only current and former smokers and involved a supplementary analysis of results for respondents in Great Britain. The dataset involved one cross-sectional survey from a single year so statistical tests using logistic regression were applied to try and look at associations after taking into account missing data, country, and a sensitivity analysis excluding smokers who only used cigars, cigarillos or a pipe.

The study found that any regular users of e-cigarette products containing nicotine were less likely to be former smokers compared to smokers who had never regularly vaped. Most forms of use (daily, occasional and experimentation) were associated with lower odds of being a former smoker. The results for Great Britain are similar to the European Union as a whole. The research team also found that daily cigarette consumption was slightly higher among current smokers who reported using or having used an e-cigarette than those who had not vaped. The authors concluded that e-cigarettes inhibit smoking cessation in Europe.

Previous research conducted using the same 2014 survey found that daily use of e-cigarettes was associated with high self-reported rates of smoking cessation and reduction in Europe. This study is at odds with that finding, and also with research from England that associates e-cigarette use with an increase in the number of people stopping smoking, and with recent reports from the USA and the UK that find regular use of e-cigarettes by smokers assists with smoking cessation.

These differences may be explained by the fact that the data in this study were from 2014 but the study did not take into account when former smokers quit, meaning that former smokers could have stopped many years before including in the period when e-cigarettes were not available. It also did not assess whether current or former smokers had intended to quit when using e-cigarettes which previous research has suggested is an important determinant of attempts to stop smoking.

Our third study this month involved simulation modelling to try and assess years of life gained or lost from the impact of e-cigarettes on smoking cessation and any transition to long term smoking among never smokers who ever use e-cigarettes. To do this the researchers, who are based in the USA, drew on a number of data sources. These included the US census, national population surveys of adults and youth from 2014 and reviews and studies that focus on smoking cessation outcomes with e-cigarettes, youth transition from trying e-cigarettes to trying smoking, as well as studies

looking at the odds of becoming a smoker, long term abstinence from smoking and years of life gained or lost from smoking uptake or smoking cessation.

In contrast to a previous modelling study we included in the October 2017 UKECRF bulletin, the current research concluded that e-cigarette use in the USA represents more population harm than benefit. Findings were that relatively few adult smokers in the USA would quit smoking in 2015 by using an e-cigarette and remain ex-smokers for more than 7 years (2,070 additional ex-smokers). In contrast, a significant number of teenage and young adult never smokers who had tried e-cigarettes in 2014 would become daily smokers (168,000) at ages 35-39.

Possible explanations for the difference between these findings and previous modelling in the USA may lie in the content of the underlying data sources used to populate the model in this new study. For smoking cessation outcomes from e-cigarette use, the main source used was a meta-analysis which has received considerable criticism in relation to both its methods and conclusions - summarised recently here. For smoking initiation following e-cigarette use, the main source is a systematic review which brought together a number of longitudinal studies from the USA that did not measure either regular vaping or regular smoking - both important elements to consider when trying to model longer term health impacts. Reliance on these sources may explain why the model findings were that for every one adult smoker aged 25-69 in the USA who quits smoking with e-cigarettes, eighty younger people aged 12-29 will become regular smokers after trying vaping in 2014. If these predictions are accurate, the outcome would be a very large increase in the number of smokers. It will be important to monitor whether this increase happens in practice, but certainly hasn't yet been observed in recent trends in youth and adult cigarette smoking prevalence which continue to decline in both the UK and the USA.

Finally, we include a further study conducted in the USA by an international team of researchers. The research was conducted in a lab and involved testing tank style e-cigarettes and refiling dispensers provided by 56 experienced vapers in Maryland. The participants were asked questions about their e-cigarette brand, voltage used, type of coil and frequency of coil change. Three samples were then taken from each user's products in order to examine metal concentrations in e-cigarette liquid before and after use, and in the aerosol (vapour) produced during use. The researchers aimed to assess whether metals are transferred from the metal coil to the aerosol or e-liquid.

The study looked at eleven types of metals in e-liquid in the refilling dispenser, in the tank of the device and in the aerosol produced. Concentrations of these metals were significantly higher once the e-liquid from the dispenser had been heated and was in the tank, or was released as vapour. Some metals were present at levels of concentration which exceeded safety regulations or standards for daily exposure in some of the samples including nickel, manganese, chromium and lead.

Traces of arsenic and lead were identified even in the unheated e-liquid in the dispenser in some cases. The authors point to the need for more research on this and to identify whether this relates to particular brands or manufacturers. In terms of metals present in the tank and in the aerosol compared to the refilling dispenser, the authors suggest that the source is likely to be the coil which is usually composed of metal alloys, although it may be possible that other parts of the device contribute. Some of the metals found were particularly concerning including lead and at least two, chromium and nickel, are classified as inhalation carcinogens by the International Agency for Research on Cancer. The study wasn't able to fully assess if voltage (which would result in higher temperatures) increase metal concentrations as their measurements of voltage were reliant on what users reported in the baseline survey. It is likely that the age of the tank e-cigarettes in the study may have contributed to metal exposure (via degradation of the coil, for example) but the research

didn't assess this. The discussion section of the paper attempts to make some comparisons with metals in tobacco smoke (from previous research) but the study itself didn't compare e-cigarette vapour with tobacco smoke. The research also didn't look at exposure to these metals in vapers themselves or bystanders, and the researchers acknowledge that biomarker studies would be helpful to assess this.

It is worth noting that the study was conducted with devices available in the USA, whereas in the UK and elsewhere in Europe a system is now in place which requires manufacturers to notify the relevant competent authority (i.e. the MHRA in the UK) about e-liquid and aerosol content and emissions. This follows the implementation of the EU Tobacco Directive and the Tobacco and Related Products Regulations which transposed the TPD into UK law. Metals including cadmium, chromium, iron, lead, mercury and nickel are not permitted as ingredients in e-liquids. The notification scheme also requires manufacturers to provide information on metal emissions following testing. In addition to the notification system, The MHRA also operates a 'yellow card' scheme for the reporting of adverse reactions in users or bystanders. Trading Standards are tasked with responding to complaints about products. Further information on the UK regulations can be found here.

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

- E-cigarette vapour enhances pneumococcal adherence to airway epithelial cells.
- Using the ecological Model to Understand Influences on College Student Vaping.
- Reasons for Electronic Cigarette Use Among Middle and High School Students - National Youth Tobacco Survey, United States, 2016.
- E-cigarette Advertising Exposure, Explicit and Implicit Harm Perceptions, and E-Cigarette use Susceptibility Among Non-Smoking Young Adults.
- A Descriptive Longitudinal Study of Changes in Vape Shop Characteristics and Store Policies in Anticipation of the 2016 FDA Regulations of Tobacco Products, Including E-Cigarettes.
- Qualitative Analysis of E-Liquid Emissions as a Function of Flavor Additives Using Two Aerosol Capture Methods.
- E-cigarette advertising exposure in e-cigarette naïve adolescents and subsequent e-cigarette use: A longitudinal cohort study.
- E-cigarette and Smokeless Tobacco Use and Switching Among Smokers: Findings From the National Adult Tobacco Survey.
- Effect of e-cigarette advertisement exposure on intention to use e-cigarettes in adolescents.
- E-cigarette use in New Zealand-a systematic review and narrative synthesis.
- Acceptability of electronic cigarettes as an option to replace tobacco smoking for alcoholics admitted to hospital for detoxification.
- Predictors of youth e-cigarette use susceptibility in a U.S. nationally representative sample.
- What do medical students know about e-cigarettes? A cross-sectional survey from one U.S. medical school.
- Does Electronic Cigarette Use Predict Abstinence from Conventional Cigarettes among Smokers in Hong Kong?
- Immunological and toxicological risk assessment of e-cigarettes.
- State-Level Differences in E-cigarette and Cigarette Use Among Adults in the United States Between 2012 and 2014: Findings From the National Adult Tobacco Survey.
- [The use of E-Cigarettes in the German Population: Results of the Epidemiological Survey of Substance Abuse 2015].

- Mechanisms of toxicity and biomarkers of flavoring and flavor enhancing chemicals in emerging tobacco and non-tobacco products.
- Vaping versus smoking: A quest for efficacy and safety of E-cigarette.
- Patterns of concurrent cigarette, alcohol, and e-cigarette use: Off-setting or additive behaviors?
- Chronic E-cigarette Exposure Alters the Human Bronchial Epithelial Proteome.
- Vaping Topography and Reasons of Use among Adults in Klang Valley, Malaysia
- Air monitoring at large public electronic cigarette events.
- Educational gradients in the use of electronic cigarettes and heat-not-burn tobacco products in Japan.
- A systematic review of consumer preference for e-cigarette attributes: Flavour, nicotine strength, and type.
- Semen parameter alteration, histological changes and role of oxidative stress in adult rat epididymis on exposure to electronic cigarette refill liquid.

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 Clare Hyde and Carl Alexander from Cancer Research UK with assistance from Professor Linda Bauld at the University of Stirling and the UK Centre for Tobacco and Alcohol Studies, primarily for the benefit of attendees of the CRUK & PHE UK E-Cigarette Research Forum. If you wish to circulate to external parties, do not make any alterations to the contents and provide a full acknowledgement. Kindly note Cancer Research UK cannot be responsible for the contents once externally circulated.