Electronic Cigarette Research Briefing – April 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.

Please note that the Tobacco Advisory Group is open for expressions of interest until 22nd May. Please visit here for full details or contact TAG@cancer.org.uk with any further questions.

1. E-cigarettes: comparing the possible risks of increasing smoking initiation with the potential benefits of increasing smoking cessation

- **Study aims**

  This US modelling study aimed to assess the population-level benefits and harms of e-cigarette use in the US from 2020 - 2070.

  It predicted the total number of life-years gained or lost with different assumptions on the impact of e-cigarette use on additional smoking initiation in never-smoking adolescents, and additional smoking cessation in current smokers. In sensitivity analyses, these assumptions were varied to demonstrate the effect of a higher rate of additional smoking initiation and a lower rate of additional smoking cessation.

- **Key findings**

Scenario A assumed that e-cigarette use carries a cost of an additional 2% smoking initiation in never-smoking adolescents, but no benefit of additional smoking cessation in current smokers.

This model predicted no smoking-related life-years lost in 2020, and 258,359 life-years lost by 2070. In sensitivity analyses, there was a maximum of 775,058 life-years lost in 2070.

Scenario B assumed that e-cigarette use carries no cost of additional smoking initiation, but does carry a benefit of an additional 10% smoking cessation.

This model predicted 29,147 life-years saved in 2020, and 3,526,607 life-years saved by 2070. In sensitivity analyses, there was a minimum of 1,352,421 life-years saved in 2070.

Scenario C assumed that e-cigarette use carries both a cost of an additional 2% smoking initiation, and a benefit of an additional 10% smoking cessation.

This model predicted 29,147 net life-years gained in 2020, and 3,273,771 net life-years gained by year 2070. In sensitivity analyses, there was a minimum of 583,398 life-years saved in 2070.

- **Limitations**

Modelling studies are dependent on the validity of the assumptions of the model, and any limitations of the individual data sources used. Much of the current evidence on e-cigarette use and the impact on smoking initiation and cessation is unable to conclude causation or fully control for all possible confounders.

Modelling studies are only partially generalizable to real situations, and cannot account for effects of future policy or social change, so conclusions about the real-world effect of e-cigarettes cannot be confirmed.

This study did not consider former smokers who may have already successfully quit or avoided relapse through e-cigarettes. It also did not consider any benefit of smoking reduction among dual users. This may under-estimate the future benefits of e-cigarettes among ever smokers.

This model assumes no smoking initiation or relapse after age 18, which may under-estimate any undesired effect of e-cigarette use in never-smoking adults or former smokers.

Warner, K.E., Mendez, D. (2018). E-cigarettes: comparing the possible risks of increasing smoking initiation with the potential benefits of increasing smoking cessation. Nicotine & Tobacco Research, doi: 10.1093/ntr/nty062

2. Electronic cigarettes: a systematic review of available studies on health risk assessment

- **Study aims**

This systematic review summarized four articles from between 2000 – 2015 that provided a quantified health risk assessment of e-cigarette use.

Three articles assessed a range of chemicals, namely nicotine, propylene glycol and glycerol, and one study examined heavy metals.

The review authors then calculated the hazard quotient (HQ) and lifetime cancer risk (LCR) using data on e-liquid concentrations and e-cigarette usage patterns from the original studies. A HQ of more than 1 suggests the presence of non-carcinogenic health risks.

- **Key findings**

  This study found inconsistencies between the calculated hazard quotients between studies.

  The HQ for nicotine was available from two studies and ranged from 0.2571 to 475.

  The HQ of glycerol and propylene glycol (PG) was available from three studies. The calculated HQ for glycerol ranged from 0.0145 to 4.95, and the HQ for PG ranged from 0.0042 to 24.1.

  Ethylene glycol was measured in only one study and was found to have a HQ of 5.25. Cadmium, nickel, aluminium and titanium were measured in only one study each and had calculated HQs of 28.5, 1.6, 9.4, 2.4 respectively.

  All other chemicals measured were not found to exceed levels that indicate the presence of non-carcinogenic health risks.

  The only chemicals for which an LCR could be estimated were cadmium, chromium, lead, nickel, and acetaldehyde, and none were found to be at 'unacceptable' levels.

- **Limitations**

  This study didn't control for the quality or limitations of the individual studies from which it calculated HQs and LCRs. Only a small sample of four studies was available, which varied in the measurements provided. This may reduce comparability of results and may not be necessarily representative of the range of devices and e-liquids currently available or what people are exposed to during use.

  There was no evidence assessing biomarker measures in e-cigarette users. Therefore, conclusions cannot be made about the real-world health effects on users.

  There was no evidence covering other chemicals, including carcinogenic compounds associated with tobacco such as tobacco-specific nitrosamines (TSNA).

  The researchers relied on estimated lifetime e-cigarette usage patterns to calculate its HQs and LCRs. We lack data on average lifetime e-cigarette use, so it's unclear how reliable these estimates may be.

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

Zulkifli, A., Abidin, EZ., Abidin, NZ., Amer Nordin, AS., Praveena, SM., Syed Ismali, SN., Rasdi, I., Karuppiah, K., Rahman, AA. (2018). Electronic cigarettes: a systematic review of available studies on health risk assessment. Reviews on Environmental Health, 33 (1): 43-52.

3. E-cigarette initiation and associated changes in smoking cessation and reduction: the population assessment of tobacco and health study, 2013 – 2015

- **Study aims**

  This US study used nationally representative data to estimate how the uptake of e-cigarettes is associated with cigarette cessation and changes in cigarette smoking intensity in adults.

  The data came from 5124 adults aged 25 and older who were current regular smokers but not e-cigarette users at baseline. Smoking and e-cigarette use data was collected at follow up around one year later.

- **Key findings**

  Current smokers at baseline who had initiated daily e-cigarette use at follow-up were significantly more likely to have quit smoking compared to non-users of e-cigarettes (OR = 7.88, 95% CI: 4.45 – 13.95). This was true for those who began using non-cartridge based e-cigarettes (mostly second and third generation e-cigarettes), but not for those who used cartridge based or refillable e-cigarettes (mainly first generation).

  Current smokers who initiated e-cigarette use 'some days' or experimentally, were not significantly more likely to have quit smoking at follow-up compared to non-users (OR = 0.51, 95% CI: 0.17 – 1.47 and OR = 0.51, 95% CI: 0.26 – 1.00 respectively).

  Those who began using e-cigarettes every day but did not quit smoking were significantly more likely to have reduced their daily cigarette use by at least 50% compared to non-users of e-cigarettes (OR = 5.70, 95% CI: 3.47 – 9.35). This group reduced their average daily cigarette use by 5.60 (95% CI: 3.52 – 7.68) more cigarettes than non-users.

  E-cigarette users on 'some days' and e-cigarette experimenters who had not quit smoking at follow up did not significantly change their cigarette consumption compared to non-users of e-cigarettes (OR = 1.00, 95% CI: 0.58 – 1.74 and OR = 1.08, 95% CI: 0.78 – 1.48 respectively).

- **Limitations**

  This study cannot establish how recently behaviours changed between baseline and follow up, nor conclude whether e-cigarette initiation preceded cigarette cessation or reduction. Therefore, conclusions about causation cannot be made from this study.

  The data had a relatively short follow-up period of around 12 months, which may be unable to show long-term trends or associations.

  Although this study controlled for a good range of confounders such as previous quit attempts, it did not test for all potential confounders that might affect results.

  This data is not able to compare the efficacy of e-cigarettes on smoking cessation with other modes of quitting such as NRT.

  This study defined former smokers at follow-up as those who had not smoked any cigarettes in the 30 days prior. This may not capture longer-term cigarette use or sustained smoking cessation beyond 30 days.

  The study was unable to consider former smokers who may have already used e-cigarettes to successfully quit.

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

Berry, KM., Reynolds, LM., Collins, JM., Siegel, MB., Fetterman, JL., Hamburg, NM., Bhatnagar, A., Benjamin, EJ., Stokes, A. (2018). E-cigarette initiation and associated changes in smoking cessation and reduction: the population assessment of tobacco and health study, 2013 – 2015. Tobacco Control, doi: 10.1136/tobaccocontrol-2017-054108.

4. Are electronic cigarettes an effective aid to smoking cessation or reduction among vulnerable groups? A systematic review of qualitative and quantitative evidence

- **Study aims**

  This systematic review assessed the effectiveness of e-cigarettes for smoking cessation among vulnerable groups. Vulnerable groups included those receiving treatment for a mental illness, those in treatment or recovery from substance abuse, and homeless individuals.

  The study included five quantitative studies, including four intervention and one cohort study, and four qualitative studies. The researchers also assessed the quality of each study.

- **Key findings**

  In quantitative intervention studies, smoking cessation with an e-cigarette varied from 0% - 14.3%. The one intervention study with a control group found no significant differences between users of a nicotine e-cigarette, non-nicotine e-cigarette, and NRT, whilst another observational study found no difference between those using e-cigarettes or not.

  No severe adverse events were reported. Mild adverse events, such as a cough, were similar between those using a nicotine e-cigarette, non-nicotine e-cigarette, and NRT.

  Barriers to e-cigarette use included side effects (e.g. a sore throat), physical capability to safely access, operate and maintain them (e.g. for those in danger of self-harm), and concerns about addiction.

  Facilitators to e-cigarette use included perception that they were less harmful. Others noted that using e-cigarettes provided an opportunity to take charge of a nicotine addiction, interact with a community, and provided an experience similar to smoking.

- **Limitations**

  This study is vulnerable to the limitations of the individual studies it included, and did not exclude studies based on quality.

  Four of the included quantitative studies were rated as weak quality, with one of moderate quality, and the four qualitative studies were rated as moderate quality.

  Three out of the five quantitative studies were uncontrolled intervention studies and three had small sample sizes of less than 30, meaning that significance testing was sometimes unavailable, and statistical analyses may be unreliable.

  Most of the intervention studies included only free provision of e-cigarettes or information on e-cigarette use, rather than assessing actual use during the study. Therefore, we cannot make causative conclusions about the effect of e-cigarette use on smoking cessation in these groups.

There will likely be some overlap between the 'vulnerable groups' identified in this study. This makes it hard to distinguish the effects of e-cigarettes on smoking cessation between discrete groups. This study also cannot tell us about the effects of e-cigarettes on other vulnerable groups, such as pregnant women.

Only 10% of studies in initial search results were double-screened by a second individual.

Gentry, S., Forouhi, N., Notley, C. (2018). Are electronic cigarettes an effective aid to smoking cessation or reduction among vulnerable groups? A systematic review of quantitative and qualitative evidence. Nicotine & Tobacco Research, doi: 10.1093/ntr/nty054

Overview

This month we include four studies, two from research teams in the USA, one from Malaysia and one from researchers based in the UK.

The first paper is the latest modelling study that examines the future potential impact of e-cigarettes on smoking initiation and cessation in the USA. It focuses on potential life years gained or lost and projects these through to 2070. A base case assuming the complete absence of e-cigarettes is generated from 2010 data using observed smoking initiation rates from 2005-2014 and estimated cessation rates 1990-2014. Several scenarios are modelled. The first scenario assumes that vaping increases the number of adolescents who start smoking by 2% but does not affect the number of current smokers who stop. The second scenario assumes that vaping increases smoking cessation by 10% each year, but does not affect smoking initiation. The last scenario assumes that vaping increases both smoking initiation by 2% and smoking cessation by 10% each year. Sensitivity analyses demonstrate the effect of smoking initiation rising by 6% due to vaping and a more modest increase in cessation (5%). The authors also test the scenario that vaping would reduce the benefits of stopping smoking by 10%. The simulation model tracks the population over time following the numbers of smokers, ex-smokers and never smokers and age and smoking-status specific death rates. Results examine life-years gained or lost for each scenario.

Overall the simulation model found that life years gained from people stopping smoking with vaping would exceed life-years lost due to people starting smoking due to vaping. This was true even for the more pessimistic scenario and after assuming that stopping smoking with vaping yields fewer health benefits than stopping smoking using other methods. The authors argue that their findings suggest that efforts to reduce young people's use of e-cigarettes shouldn't be at the expense of limiting access to adult smokers who could benefit from e-cigarettes for smoking cessation.

The paper's findings are similar to another recent modelling study from the USA in terms of concluding that vaping will have substantial net benefits for population health even after accounting for any link between youth vaping and subsequent smoking. However, they differ from a further recent paper (also from the USA) which concluded that vaping would result in substantial levels of youth smoking initiation in the future and only modest gains in adult cessation. All three papers employ different methods and are not directly comparable. The differences in findings also relate to the data sources used to populate the models. In the future further data should be available to allow us to assess whether some of the trends predicted in these papers occur in practice.

This month's second paper is a systematic review of studies that aimed to quantify health risks from e-cigarette usage by using a health risk assessment (HRA) approach. HRA is an established

methodology used to assess carcinogenic and non-carcinogenic risks from human exposure to chemicals or other factors that might affect human health.

Only four articles were identified that used an HRA approach. The authors aimed to compare the data in the studies using a Hazard Quotient (HQ) value and Lifetime Cancer Risk (LCR). To do this they had to calculate an average daily dose and lifetime average dose of the constituents in question and used information on a 'typical' pattern of e-cigarette usage from a further study not included in the review.

The four included studies looked at: HRA of an NJOY e-cigarette; a chemical risk assessment of a nicotine-free shisha pen; a risk assessment of metals in e-cigarettes; and a study examining the concentration of a range of elements in e-liquid. Taken together these studies included six constituents that were present at levels (in at least one or more studies) that could contribute to non-carcinogenic health risks to users including: nicotine, propylene glycol, glycerol, cadmium, ethylene glycol, nickel, aluminium and titanium. Lifetime Cancer Risk could be calculated for some constituents but none were found at harmful exposure levels. However, as the authors point out the hazard quotients calculated from different individual studies varied widely, and the individual studies assessed different types of devices and e-liquids. Another major challenge was assessing the relationship between the levels or presence of chemicals and how these would translate to exposure in human users. The authors made the assumption that usage patterns reported from a very early survey of a selective sample of vapers might be representative of how e-cigarettes are routinely used, which is not ideal. They point to the clear need for more health risk assessment studies of e-cigarettes that use standard steps or measures, and better data on typical patterns of use to inform future HRA research.

Our third paper is the latest from the nationally-representative longitudinal PATH study in the USA. The focus of the research was the transition between e-cigarette initiation and smoking cessation or reduction. Participants in wave 1 (2013-2014) were followed up a year later in wave 2 (2014-2015). In this analysis, the focus was on smokers aged 25 and above who were not using e-cigarettes at wave 1. Short term (one month) quit rates and smoking reduction of at least 50% were the main outcomes.

Participants who started vaping between waves and reported that they were vaping at least daily at wave 2 were over seven times more likely to have stopped smoking compared to participants who were not vaping. Those who started vaping and used an e-cigarette daily, but didn't stop smoking, were almost six times more likely to have reduced their cigarette consumption compared with non-users of e-cigarettes. Occasional vaping (less than daily) was not associated with smoking cessation or reduction. Differences were also found in terms of the type of product used in a supplementary analysis. Daily users of second and third generation e-cigarettes were more likely to have stopped smoking at wave 2 compared to non-users of e-cigarettes, but those who used cartridge (commonly 1st generation) products were not.

This paper supports findings from smaller studies that suggest that frequency of use of e-cigarette products makes a difference to smoking cessation outcomes, and also research that suggests that later generation e-cigarettes are more effective for smoking cessation. These findings may have implications for practical advice to smokers about vaping, and about transitioning from dual use (which studies suggest has few, if any, health benefits). As the authors of the article make clear, questions about frequency of use and also product type should be included in any studies aiming to assess smoking reduction or cessation with e-cigarettes.

Finally we include a systematic literature review conducted by researchers at the Universities of East Anglia and Cambridge that aimed to identify data on the effectiveness of e-cigarettes for smoking cessation or reduction among vulnerable groups. This included people with mental illness, substance misuse, homeless people or those in the criminal justice system.

Only nine studies were identified that met the inclusion criteria. Five were quantitative studies and four were qualitative. Six included participants with a mental health condition, two homelessness and one with adults with substance use problems. No studies with participants in a criminal justice setting were found. All but one of the quantitative studies was rated as weak following quality appraisal (the exception being a secondary analysis of the ASCEND trial in New Zealand with people with mental illness, which was rated moderate quality). All the qualitative studies were graded as moderate quality.

Due to the quality of the studies and also small sample sizes, the review couldn't identify whether e-cigarettes are effective for smoking cessation with vulnerable populations, although the secondary analysis of the ASCEND trial found that vaping was as effective as NRT in people with mental illness. Significant smoking reduction was observed in four small studies and overall no significant adverse events and few side effects were identified. The qualitative studies identified a number of barriers and facilitators to e-cigarette use and smoking cessation with e-cigarettes. These ranged from positive perceptions about harm (viewing e-cigarettes as less harmful than smoking was a facilitator to use) to issues with access, operation and maintenance (refilling, recharging etc) which could be a barrier. Other barriers and facilitators were identified that would be useful to explore in further research.

Overall, this review identifies some significant gaps in the literature. This includes the absence of any studies in prisons or other criminal justice settings, which is currently relevant as prisons in some jurisdictions move to become smokefree and where e-cigarettes may be made available (as is now the case in some prisons in England and Wales). However, even for the other vulnerable groups included, the literature is sparse. Given the high smoking rates in these populations and the inequalities in health that smoking contributes to, this review points to the need for further research on e-cigarettes with vulnerable groups.

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

- Changes in resting state functional brain connectivity and withdrawal symptoms are associated with acute electronic cigarette use
- Factors associated with successful vs. unsuccessful smoking cessation: data from a nationally representative study
- Beliefs about FDA tobacco regulation, modifiability of cancer risk, and tobacco product comparative harm perceptions: findings from the HINTS-FDA 2015
- Acceptance and patterns of personal vaporizer use in Australia and the United Kingdom: results from the International Tobacco Control survey
- The effects of electronic cigarette vapour on the lung: direct comparison to tobacco smoke
- Immunological and toxicological risk assessment of e-cigarettes
- Changes in smoking cessation assistance in the European Union between 2012 and 2017: pharmacotherapy verses counselling verses e-cigarettes
- Tobacco and nicotine delivery product use in a US national sample of women of reproductive age

- Extreme testing of undiluted e-cigarette aerosol in vitro using an Ames air-agar-interface technique
- Cognitive risk factors of electronic and combustible cigarette use in adolescents
- Exposure to electronic cigarette advertising among middle and high school students – United States, 2014 – 2016
- Electronic cigarette use and progression from experimentation to established smoking
- Adolescent exposure to toxic volatile organic chemicals from e-cigarettes
- Ethnic and sex differences in e-cigarette use and relation to alcohol use in California adolescents: the California Health Interview Study
- Adolescents' perceptions of flavoured tobacco products, including e-cigarettes: a qualitative study to inform FDA tobacco education efforts through videogames
- Vape factor fast find-adult (VF3-A): a prototype survey method for recording brand-specific vaping factors in adult populations
- Influence of flavors on the propagation of e-cigarette-related information: social media study
- Lack of substantial post-cessation weight increase in electronic cigarette users
- The association between potential exposure to magazine ads with voluntary health warnings and the perceived harmfulness of electronic nicotine delivery systems (ENDS)
- Affect, risk perception, and the use of cigarettes and e-cigarettes: a population study of US adults
- Assessing electronic cigarette emissions: linking physico-chemical properties to product brand, e-liquid flavouring additives, operational voltage and user puffing patterns
- The association of point-of-sale e-cigarette advertising with socio-demographic characteristics of neighbourhoods
- The association between e-cigarette use characteristics and combustible cigarette consumption and dependence symptoms: results from a national longitudinal study
- E-cigarette-specific symptoms of nicotine dependence among Texas adolescents
- A fMRI study on the impact of advertising for flavoured e-cigarettes on susceptible young adults
- Flavored e-cigarette use and cigarette smoking reduction and cessation – a large national study among young adult smokers
- The effect of electronic cigarette and tobacco smoke exposure on COPD bronchial epithelial cell inflammatory responses
- Patterns, perception and behaviour of electronic nicotine delivery systems use and multiple product use among young adults
- Evaluation of e-liquid toxicity using an open-source high-throughput screening assay
- Association between receptivity to tobacco advertising and progression to tobacco use in youth and young adults in the PATH study
- Association of e-cigarette use with smoking cessation among smokers who plan to quit after a hospitalization: a prospective study
- Use of e-cigarettes among smoker who plan to quit after a hospitalization

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 Clare Hyde 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.