The UK Electronic Cigarette Research Forum

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Electronic Cigarette Research Briefing – May 2022

This research briefing is part of a series of quarterly 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 do not cover every e-cigarette-related study published each quarter. 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.

Let's talk e-cigarettes – University of Oxford podcasts

Jamie Hartmann-Boyce and Nicola Lindson discuss emerging evidence in e-cigarette research. In the April 2022 episode they interview Assistant Professor Alex Liber on his work at the intersection between markets, public policy, and public health.

This podcast is a companion to the Cochrane living systematic review of e-cigarettes for smoking cessation and shares the evidence from the monthly searches.

Subscribe with iTunes or Spotify to listen to regular updates or find all episodes on the University of Oxford Podcasts site.

This podcast series is funded by CRUK.

Cochrane Living Systematic Review of E-cigarettes for Smoking Cessation update

The latest update to the CRUK-funded Cochrane Living Systematic Review of E-cigarettes for Smoking Cessation was published in Sept 2021 and includes 5 new studies. Visit the website (https://www.cebm.ox.ac.uk/research/electronic-cigarettes-for-smoking-cessation-cochrane-living-systematic-review-1) for full information on the review, including briefing documents, and new studies found since the update which will be incorporated in a future version of the review.

Association of quarterly prevalence of e-cigarette use with ever regular smoking among young adults in England: a time–series analysis between 2007 and 2018

- **Study aims**

This study used data from the English Smoking Toolkit Study from January 2007 to December 2018 to investigate any potential population-level gateway effect between e-cigarette use and ever regular tobacco smoking by analysing the extent to which past prevalence of e-cigarette use predicts the future prevalence of regular smoking among young adults (n = 37,105) aged 16-24. Analyses were adjusted for tobacco control policies and monthly mass media expenditure. For non-significant results, Bayes factor analysis was used to assess whether there was stronger evidence for no difference (null hypothesis) or for data not being sufficiently sensitive to detect an effect.

- **Key findings**

  - There was no association between prevalence of e-cigarette use among 16-24-year-olds and ever regular smoking among 16-24-year-olds (p=.341), 16-17-year-olds (p=.102) and 18-24-year-olds (p=.205).

  - Bayes factors indicated that there was a greater likelihood of no association between e-cigarette use prevalence and ever regular smoking prevalence than, on average, an increase of 1 percentage point in e-cigarette prevalence being associated with more than a 0.014 percentage point increase in ever regular smoking among 16–24-year-olds.

  - There was also no association between e-cigarette use among people who had never smoked and ever regular smoking among 18-24-year-olds (p=.321), 16-17-year-olds (p=.262) and 18-24-year-olds (p=.116).

- **Limitations**

  - The study was based on quarterly, cross sectional data, so examines an association between trends rather than a causal link

  - The Smoking Toolkit Study relies on self-reported data, so tobacco use status is not biochemically verified.

  - Data are limited to England and may not be generalisable to other parts of the UK.

  - The study only assessed the short-term (pulse) effects of tobacco control policies, so was not able to consider more prolonged or delayed effects of these legislative changes.

  - Different statistical models were used to analyse the data ('ARIMAX' and 'SVAR'), and results were discrepant between the models. When sensitivity analysis was carried out using 'SVAR' to account for any possible effect of ever regular smoking on prevalence of e-cigarette use, the analysis was not able to rule out a small association with e-cigarette prevalence among 16-17-year-olds.

  - Any possible gateway effect between e-cigarette use and uptake of smoking was explored, but any other potential pathways, for example use of e-cigarettes for smoking cessation could not be captured.

o   For the purposes of this study, regular smoking was defined as daily or non-daily use of cigarettes, which may not be comparable to definitions used internationally.

Beard E, Brown J, Shahab L. Association of quarterly prevalence of e-cigarette use with ever regular smoking among young adults in England: a time-series analysis between 2007 and 2018. Addiction. 2022 Mar 9. doi: 10.1111/add.15838. Epub ahead of print. PMID: 35263816.

Adolescent electronic cigarette use and tobacco smoking in the Millennium Cohort Study

- **Study aims**

This prospective cohort study used data from the nationally representative UK Millennium Cohort to investigate the relationship between e-cigarette and combustible cigarette use. Participants were recruited between September 2000 and January 2002 and e-cigarette and tobacco usage were surveyed in 10,625 participants followed up at ages 14 and 17. Parental and childhood risk factors were obtained in infancy and at age 11 and adjusted for in the analysis. These included parental academic attainment, parental tobacco use, childhood behaviour, delinquency and alcohol use.

- **Key findings**

    o   Youth who had never used tobacco at age 14 but had used e-cigarettes (n=9,046) were over five times as likely to have started smoking tobacco by age 17 (OR = 5.25, 95% CI = 3.28–8.38, p<0.001) and nearly three times as likely to smoke frequently (defined as usually seven or more cigarettes per week) (OR = 2.91, 95% CI = 1.56–5.41, p=0.001).

    o   Respondents who had never used e-cigarettes by the age of 14 but had smoked combustible cigarettes (n=9,078) were three times as likely to start using e-cigarettes by age 17 than those who had never smoked (OR = 2.98, 95% CI = 1.74–5.09, p<0.001) and nearly three times as likely to use e-cigarettes frequently (defined as usually using e-cigarettes seven or more times per week) (OR = 2.90, 95% CI = 1.21–6.95, p=0.018).

    o   Through coarsened exact matching ('CEM'), comparing individual participants who had used e-cigarettes by age 14 with participants who had not and had a similar risk, a similar odds ratio of 5.09 was found, compared with 5.25 before matching.

    o   Risk factors observed in those who had used e-cigarettes by age 14 and those who had used tobacco cigarettes by age 14 were different, in that those who had used tobacco cigarettes exhibited 15 statistically significant risk factors compared with 10 for those who had used e-cigarettes.

- **Limitations**

    o   As an observational study rather than an interventional trial, it is able to identify associations but not indicate causality.

    o   Although many potential confounding factors were adjusted for, such as exposure to smoke in infancy, parental education and occupation and whether participants had ever had an alcoholic drink, it is possible that other factors were present which have not been included.

    o   Reliance on self-reported data meant that responses could not be biochemically verified and subject to potential recall and social desirability biases.

o The analysis was not pre-registered, and so the results should be considered exploratory.

o As a longitudinal, long-term study, the MCS is subject to non-random attrition, so the sample may not remain representative of the underlying population, although measures were taken to adjust for this.

Staff J, Kelly BC, Maggs JL, Vuolo M. Adolescent electronic cigarette use and tobacco smoking in the Millennium Cohort Study. Addiction. 2022 Feb;117(2):484-494. doi: 10.1111/add.15645. Epub 2021 Aug 13. PMID: 34286880.

Exposure to Toxicants Associated With Use and Transitions Between Cigarettes, e-Cigarettes, and No Tobacco

- **Study aims**

This longitudinal cohort study used data from waves 1 (2013-14) and 2 (2014-15) of the US Population Assessment of Tobacco and Health ('PATH') study to determine changes in biomarkers of exposure (BOE) in participants (n=11,522) by transitions in tobacco or e-cigarette use status. Biomarkers studied included nicotine metabolites (TNE2 and cotinine), tobacco-specific nitrosamines (NNAL and NNN), heavy metals (cadmium and lead), polycyclic aromatic hydrocarbons (2-NAP, 3-FLU and 1-PYR) and volatile organic compounds (AAMA, CEMA and CYMA). Participants were classified as "exclusive cigarette smokers", "exclusive e-cigarette users" and "dual users" at baseline and follow up.

- **Key findings**

o About 70% of baseline exclusive smokers remained exclusive smokers at follow-up.

o Over half (57.2%) of baseline exclusive e-cigarette users continued exclusive vaping almost a quarter (24.4%) stopped using e-cigarettes and the remainder became exclusive smokers or dual users at follow-up.

o Among dual users at baseline, almost half (49.1%) transitioned to exclusive cigarette use. Only 37.9% maintained dual use. The remainder stopped using both products or became exclusive e-cigarette users at follow-up

o Participants who switched from using both tobacco cigarettes and e-cigarettes at baseline to exclusively vaping showed significant reductions in most BOE, including those related to nicotine. For example, cotinine levels reduced from 2791.8ng/mg creatinine (95% CI 1697.4-4591.9) at wave 1 to 1192.4ng/mg creatinine (487.1-2918.8) at wave 2, p=0.01 and NNAL levels reduced from 143.4 pg/mg creatinine (86.7-237) to 6.3pg/mg creatinine (3.5-11.4), p<.001. There were no significant changes in cadmium (p=.62) and lead (p=.26) levels.

o Participants who transitioned from dual use to exclusive smoking did not show significant changes in levels of TNE2 (p=.6), cotinine (p=.63) or any of the other biomarkers analysed.

- o Participants who exclusively smoked at baseline and transitioned to exclusive vaping at wave 2 exhibited significant reductions in both TNE2nmol/mg creatinine (25.6 (14.93-43.91) to 10.48nmol/mg creatinine (5.07-21.69), p=.01) and cotinine (1833.2ng/mg creatinine (1003.3-3349.6) to 713.0ng/mg creatinine (346.3-1468.2), p=.01). NNAL levels decreased significantly (168.4pg/mg creatinine (102.3-277.1) to 12.9pg/mg creatinine (6.4-25.7), p=.001), however there was no significant change in NNN levels (p=.48). Neither cadmium nor lead levels showed a statistically significant change (p=.62 and .26 respectively). All biomarkers of PAHs and VOCs reduced significantly.

  - o Among participants who exclusively smoked at baseline and transitioned to dual use at wave 2, only cadmium showed a statistically significant change, although it was relatively small (0.3 ng/mg creatinine (0.26-0.34) to 0.29 ng/mg creatinine (0.24-0.35), p=.02).

- **Limitations**

  - o This paper did not analyse differences in the levels for all biomarkers that were measured as part of this study. It's not clear whether the choice in biomarkers reported was systematic.

  - o Differences between groups for all biomarkers weren't adjusted for current or previous patterns of previous tobacco use or exposure, although they were adjusted for age, sex, race and ethnicity, and education. Therefore, differences might be caused by other factors such as patterns of use, previous tobacco use or other demographic characteristics.

  - o Some sub-group sample sizes were small which may reduce certainty of estimates. In particular, only 1.2% of baseline exclusive smokers and 5.6% of dual users switched to exclusive e-cigarette use

  - o The study was confined to waves 1 and 2 of PATH, as fewer biomarkers were available for analysis in the third wave, so follow-up was limited to a year.

  - o Waves 1-2 of the PATH study were completed between 2013-2015, so the study does not include more recent evolutions of ENDS devices and e-liquids.

Dai H, Benowitz NL, Achutan C, Farazi PA, Degarege A, Khan AS. Exposure to Toxicants Associated With Use and Transitions Between Cigarettes, e-Cigarettes, and No Tobacco. JAMA Netw Open. 2022 Feb 1;5(2):e2147891. doi: 10.1001/jamanetworkopen.2021.47891. PMID: 35142830; PMCID: PMC8832174.

Effectiveness of e-cigarettes as aids for smoking cessation: evidence from the PATH Study cohort, 2017‑2019

Study aims

This longitudinal study used data from the US Population Assessment of Tobacco and Health (PATH) study to compare the effectiveness of e-cigarettes with other methods of smoking cessation. 12+ months' abstinence at wave 5 was assessed in participants who were current or recent former

smokers at Wave 3 (2016) and/or 4 (2017) and reported a recent quit attempt. The effectiveness of e-cigarettes for relapse prevention was also investigated by determining smoking status at wave 5 (2019) in participants who were recent former smokers at wave 4. Propensity score matching was used to determine the adjusted risk difference in cessation success and relapse prevention for e-cigarettes compared with other tools.

- **Key findings**

    o 9.9% (95% CI 6.6%-13.2%) of respondents who had used e-cigarettes in their last quit attempt reported abstinence from cigarettes at wave 5, compared with 15.2% (95% CI 12.3-18.1%) of those who used only nicotine replacement therapy (NRT) or pharmaceutical therapy and 18.6% (95%CI16.0-21.2%) who used no cessation aids.

    o 3.5% (1.5-5.5%) of respondents who reported abstinence from all tobacco products including e-cigarettes in 2019 had used e-cigarettes in their last quit attempt prior to wave 4, compared with 12.5% who used NRT or pharmaceutical therapy (9.6-15.4%) and 13.9% (11.4-16.5%) who used no cessation aids.

    o Among a continuing cohort of participants for whom data were also available from waves 1-3 of the PATH Study, the 12+ month cigarette abstinence rate of those who used an e-cigarette at their last quit attempt before wave 4 was lower than for those who used NRT or pharmaceutical aids (adjusted risk difference −7.3, 95% CI −14.4 to −0.4).

    o There was no statistically significant difference in relapse rate by wave 5 among recent former smokers who had switched to e-cigarettes compared with those who had not.

- **Limitations**

    o The PATH Study relies on self-reported data, so tobacco use status is not biochemically verified.

    o As this is an observational rather than interventional study, it is unable to control how participants attempt to stop smoking.

    o Although participants were asked if they used e-cigarettes for smoking cessation, their recall may have been inaccurate. Although participants were 'established smokers' at wave 3 of the study in 2016, it is possible that e-cigarette use preceded their cessation attempt.

    o Those who used e-cigarettes and those who did not had different potential confounders, such as sociodemographic factors and cigarette smoking intensity and history. This may have affected estimates.

    o Sample sizes for some of the comparison groups were relatively small (for example, 319 people in the continuing cohort had used e-cigarettes at their last quit attempt), which may have limited statistical power to observe associations.

    o Participants were not asked if they received behavioural support in their cessation attempt, so the effectiveness of e-cigarettes with behavioural support could not be determined.

    o Analyses were not pre-registered so should be considered exploratory.

- o US data, possibly including people using higher-strength e-cigarettes than are legally available in the UK and the EU, limits generalisability to the UK, where the regulatory landscape and official guidance are different.

Chen R, Pierce JP, Leas EC, Benmarhnia T, Strong DR, White MM, Stone M, Trinidad DR, McMenamin SB, Messer K. Effectiveness of e-cigarettes as aids for smoking cessation: evidence from the PATH Study cohort, 2017-2019. Tob Control. 2022 Feb 7:tobaccocontrol-2021-056901. doi: 10.1136/tobaccocontrol-2021-056901. Epub ahead of print. PMID: 35131948.

[Correlates of e-cigarette use before and after comprehensive regulatory changes and e-liquid flavour ban among general population](#)

- **Study aims**

  This repeat cross-sectional study used data from a national Finnish survey of 15-69-year-olds (n= 3229) to compare prevalence of use of e-cigarettes before (2014) and after (2018) a national ban on flavours other than tobacco was implemented in 2016. Patterns and correlates of e-cigarette use in 2018 were also explored. Results were adjusted for gender, age, education, marital status, employment, urbanisation, whether e-cigarettes with nicotine were used, smoking and snus use.

- **Key findings**

  - o Prevalence of current e-cigarette use was around 2% in both 2014 and 2018.

  - o Compared with never use, the prevalence of experimental (adjusted OR 1.28, 95% CI 1.06, 1.54, p <0.05) and former e-cigarette use (aOR 2.75 1.77-4.2, p <0.05) increased from 2014 to 2018.

  - o Of current e-cigarette users in 2018 with available data (n = 316), flavours other than tobacco (such as fruit, sweet and menthol/mint flavours) were the most popular. 43% of respondents reported vaping flavours compared with 41% unflavoured and 24% tobacco-flavoured (participants could report use of more than one flavour, so the total is more than 100%).

  - o Of those who used non-tobacco flavours, fruit flavours were most popular at 43%, followed by other flavours (such as those likened to drinks), sweets flavours at 14% and mint/menthol flavours at 10%.

  - o In the fully adjusted analysis, only experimental (compared with non-experimental) use was significantly associated with use of flavours. Those using e-cigarettes to experiment were more likely to use unflavoured e-cigarettes than another flavour (OR 3.00, 95% CI 1.15-7.82), p<.05).

  - o Gender, age, education, smoking status, snus use, use of e-liquids with or without nicotine, and vaping to stop smoking were not significantly associated with flavour use (unflavoured, tobacco or other flavour) in the fully adjusted analysis.

- o Following the restriction on sale of flavours, respondents to the survey still reported using flavours other than tobacco in 2018.

- **Limitations**

  - o As this was a cross-sectional study with different sets of participants in each year, causality cannot be inferred.

  - o The overall sample size was relatively small so may not be representative of the population.

  - o Sample sizes for some of the comparison groups were particularly small (for example data on flavour use were available for 316 people who currently used e-cigarettes), which may have limited statistical power to observe associations.

  - o The survey relied on self-reported data, and smoking status was not biochemically verified.

  - o Changes in e-cigarette flavour use between 2014 and 2018 were not examined, meaning the impact of the flavour ban on accessibility of flavours is unclear

Ruokolainen O, Ollila H, Karjalainen K. Correlates of e-cigarette use before and after comprehensive regulatory changes and e-liquid flavour ban among general population. Drug Alcohol Rev. 2022 Feb 1. doi: 10.1111/dar.13435. Epub ahead of print. PMID: 35106874.

Overview and commentary

This quarter, we cover four studies evaluating population-level impacts of e-cigarette availability and use, and one study examining biomarkers of exposure based on different transitions between vaping and smoking.

Smoking behaviours and 'gateway' hypothesis

Our first two studies explore the impact of vaping on smoking behaviours in young people, with a particular focus on testing the 'gateway' hypothesis – in other words, the hypothesis that e-cigarettes may act as a 'gateway' into smoking in young people *who would not otherwise have started smoking*. Both use nationally-representative observational datasets. In Beard et al, authors use cross-sectional data from the English Smoking Toolkit Study, and find no evidence of associations between trends in vaping and smoking in young people at the population level. Staff et al, on the other hand, use data from the UK Millennium Cohort Study, and take a different approach – instead of assessing population level trends, this study tracked young people over time. Youth who had not used tobacco but had used e-cigarettes at 14 were over five times more likely have started smoking by age 17. The authors attempted to control for risk factors for smoking, but this had little impact on the results. It is worth noting that both of these studies found data broadly consistent with other studies using the same methods – at the individual level, data tends to show that young people who use e-cigarettes are more likely to go on to smoke. At the population level, though, this does not appear to translate into more young people smoking. Such a discrepancy between data sources highlights the importance of triangulation of data in this area, and of careful examination of population level trends before statements regarding causality can be made.

Biomarkers

Our next two studies use data from the US PATH study (US Population Assessment of Tobacco and Health). The first, from Dai et al, looked at biomarkers of exposure based on transitions between exclusive cigarette smoking, exclusive vaping, and dual use.

Participants who switched from dual use to exclusive vaping showed statistically significant reductions in most biomarkers, but not in cadmium and lead. Similarly, those who exclusively smoked at baseline and transitioned to exclusive vaping showed statistically significant reductions in most biomarkers, but not in cadmium, lead, or NNN (a tobacco specific nitrosamine). There were no statistically significant changes in those transitioning from dual use to exclusive smoking, or vice versa. These data are broadly consistent with scientific consensus and the wider literature base, in suggesting that switching to exclusive e-cigarette use appears to reduce exposure to toxicants, and that the best way to improve health is to quit combustible tobacco use entirely rather than to dual use. However, some randomized controlled trials show improvements in biomarkers of exposure even in those switching from combustible tobacco to dual use, which are not borne out in this dataset. There are many possible explanations for this, including uncontrolled confounding.

Smoking cessation

The second PATH study, conducted by Chen et al, looked at associations between e-cigarette use and smoking cessation. They found no association between e-cigarettes and successful smoking cessation, and some indication that people who used e-cigarettes to quit smoking were less likely to succeed than those using pharmacotherapy, other quit aids, or with no support. It's worth noting that this data is inconsistent with that from a growing body of randomized controlled trials and there were a number of limitations of the study, which are listed in the summary above

Changes to flavour regulation

Finally, the last study we cover aimed to evaluate the impact of regulatory changes in Finland, including a 2016 ban on all e-liquid flavours other than tobacco. This study, by Ruokolainen et al, was cross-sectional in nature with a relatively small, non-representative sample, and hence has some important limitations – however, due to a relative dearth of other published research on the effects of flavours, we judged it worth covering. The authors found no change in prevalence of current e-cigarette use before (2014) and after (2018) the flavour ban, but increases in prevalence of experimental and former e-cigarette use, compared to never use. They also found that, despite the restriction on sale of non-tobacco flavours, 43% of current e-cigarette users in 2018 reported using a flavour other than tobacco (fruit, sweet, menthol/mint). Clearly, much more research is needed evaluating the role of flavours in smoking and vaping trajectories, the implementation and impact of flavour restrictions and the impact on the use of illicit products. We hope to cover such research in future issues of the bulletin.

Search strategy

The Pubmed database is searched in the middle of every third month, for the previous three months 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 OR vaping)).

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 are not included. Please note studies funded by the tobacco industry are also excluded.