Doctoral Thesis

Effects of E-cigarettes, Heated Tobacco, and Nicotine Pouches on Cigarette Smoking

Harry Tattan-Birch

A dissertation submitted in partial fulfilment of the requirements for the degree of:

Doctor of Philosophy

Of

University College London

Department of Behavioural Science and Health

Institute of Epidemiology and Health Care

University College London (UCL)

Student Number: 19183898

Date: May 2023

Contents

Abstract

Since the invention of the electronic cigarette (e-cigarette) in 2003, there has been a shift in global nicotine markets. Instead of smoking tobacco cigarettes, people are increasingly turning to alternative nicotine products that avoid combustion, such as e-cigarettes, heated tobacco, and oral nicotine pouches. This thesis aims to understand (i) how and why people's choices of nicotine products have changed and (ii) what effects these changes have had on cigarette smoking prevalence and public health.

The first five chapters examine the changing patterns of nicotine use in Great Britain from 2016 to 2022. E-cigarettes remain the most popular alternative nicotine product, with few (<0.5%) adults using heated tobacco or nicotine pouches. However, smokers' perceptions of the harmfulness of e-cigarettes deteriorated following the 2019 outbreak of lung injury linked to cannabis vaping. There were also changes in the types of e-cigarettes people used. Up to 2020, rechargeable e-cigarettes with refillable tanks were the most widely used device type, but the popularity of disposable e-cigarettes grew rapidly from 2021 onwards, especially among young adults. Despite this, the prevalence of any inhaled nicotine use remained relatively stable, both overall and among young adults.

The penultimate chapter reported results of a randomised trial. It found tentative evidence of the effectiveness of providing e-cigarettes alongside varenicline for smoking cessation. However, results were imprecise as the COVID-19 pandemic and recall of varenicline caused the trial to be stopped early. The final chapter reports a systematic review on heated tobacco, which found that switching from cigarettes to heated tobacco substantially lowers exposure to toxicants and carcinogens, but exposure may be higher compared with stopping all tobacco use. It found no randomised trials on heated tobacco for smoking cessation, but there was population-level evidence that declines in cigarette sales accelerated after heated tobacco was introduced in Japan.

Declarations

I, Harry Tattan-Birch, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis. The following work was carried out at the Department of Behavioural Science and Health at University College London, under the supervision of Prof Jamie Brown, Dr Sarah Jackson, and Mr Martin Dockrell. This thesis has not been submitted, in whole or in part, for any other qualification or at any other university. Funding for this thesis came from Public Health England (now the Office for Health Improvement and Disparities). Correspondence concerning this thesis should be addressed to: **htattanbirch@gmail.com**.

Signed 23rd December 2022

Acknowledgements

I would like to thank my supervisors Jamie Brown, Sarah Jackson, and Martin Dockrell for their invaluable wisdom, guidance, and support. It has been a privilege to work with such fantastic mentors, and I feel extremely lucky to have had the opportunity to learn from them.

I am deeply grateful for the unwavering support that my family and friends have given me throughout the past three years. A special thank you to my partner Bethan, who has been by my side throughout this journey and has provided endless love, encouragement, and understanding.

I would also like to express my sincere gratitude to everyone in the UCL Tobacco and Alcohol Research Group. I am grateful for the opportunity to work alongside such a dedicated and talented team of researchers, who have been role models in producing rigorous research using open science practices. Special thanks go to the co-authors of and collaborators on the seven studies reported in this thesis, including Lion Shahab, Loren Kock, Olga Perski, Martin Jarvis, Robert West, Jamie Hartmann-Boyce, Erikas Simonavicius, and Leonie Brose. This thesis would not have been possible without their expertise and guidance, and I am deeply grateful for their contributions.

Finally, I would like to thank funders Public Health England (now the Office for Health Improvement and Disparities) for my studentship (558585/18073), Cancer Research UK for the Smoking Toolkit Study in England (PRCRPG-Nov21/100002), the UK Prevention Research Partnership for the Smoking Toolkit Study in Scotland and Wales (MR/S037519/1), and GRAND for the E-ASSIST trial.

Impact Statement

Publications

Adapted versions of the chapters in this thesis have been published in peer-reviewed journals:

- Chapter 1 in Scientific Reports (DOI: 10.1038/s41598-021-92617-x).[1]
- Chapter 2 in Tobacco Control (DOI: 10.1136/tobaccocontrol-2020-056354).[2]
- Chapter 3 in in JAMA Network Open (DOI: 10.1001/jamanetworkopen.2020.6981).[3]
- Chapter 4 in Addiction (DOI: 10.1111/add.16044).[4]
- Chapter 5 in Nicotine and Tobacco Research (DOI: 10.1093/ntr/ntac099).[5]
- Chapter 6 in Nicotine and Tobacco Research (DOI: 10.1093/ntr/ntac149).[6]
- Chapter 7 in Cochrane's Database (DOI: 10.1002/14651858.CD013790.pub2).[7]

Scientific conferences

I have presented this research at several leading international conferences, including the Society for Research on Nicotine and Tobacco Annual Meetings, the Society for the Study of Addiction Annual Conferences, Lisbon Addictions, and the 2022 E-Cigarette Summit. I received the New Investigator Award ($1,000) from the Society for Research on Nicotine and Tobacco to present the work from Chapter 4 of this thesis at the 2023 Annual Meeting in San Antonio, Texas.

Policy

I have presented work from this thesis to the directorate at the UK Office for Health Improvement and Disparities and to policymakers attending the E-cigarette Research Forum. Moreover, the work in this thesis has been discussed in UK Parliament.[8] The section on heated tobacco in the most recent update of the McNeill and colleagues report commissioned by Public Health England (now the Office for Health Improvement and Disparities) was based results reported in Chapter 7 of this thesis.[9]

Public and practice

The work in this thesis has been cited in news reports, including those by the BBC, ITV, the Bureau of Investigative Journalism, the New York Times, the Times, and the Guardian. I wrote a simplified version of Chapter 7 as a news article in the Conversation that has been read

67,000 times.[10] I have also discussed the results from Chapters 4, 6 and 7 on two audio podcasts ("Addiction Audio" and Oxford University's "Let's talk e-cigarettes").

I was invited to design and deliver a workshop on recent research into e-cigarettes for practitioners in National Health Service. I was also an invited speaker for the 2022 E-Cigarette Summit at the Royal College of Physicians, which has a diverse audience from the public, medical practice, the sciences, policy, and enterprise.

Work outside of thesis

In addition to work presented in this thesis, I led or co-led several other published research projects. First, I worked on a paper examining changes in children's exposure to secondhand smoke over the past two decades, which was published in the Lancet Regional Health Europe (DOI: 10.1016/j.lanepe.2022.100315).[11] Second, I wrote a book chapter on the psychobiology on nicotine vaping, published by Routledge (ISBM: 9780429296345).[12] Third, I published an editorial in Addiction examining the impact of collider bias on addiction research (DOI: 10.1111/add.15348).[13] Fourth, I led an evaluation of an educational advertising campaign on e-cigarettes conducted by Cancer Research UK (DOI: 10.1093/ntr/ntz236).[14]

I also worked on projects led by others, including reports published in the Lancet Public Health (DOI: 10.1016/S2468-2667(19)30220-8),[15] the Lancet Regional Health Europe (DOI: 10.1016/j.lanepe.2022.100418),[16] Addiction (DOI: 10.1111/add.16029),[17] and Nicotine and Tobacco Research (DOI: 10.1093/ntr/ntac088).[18]

Literature Review

The Tobacco Epidemic

Introduction

One of the defining scientific debates of the 20th century centred on the harms of tobacco smoking on health. This debate spurred on the development of several important epidemiological methods, including some of the first case-control and cohort studies. Moreover, the discipline of causal inference also progressed due to the need to determine whether higher rates of lung cancer among smokers reflected causation (e.g., smoking causes lung cancer) or confounding (e.g., smokers have higher rates of lung cancer as they differ in other ways from non-smokers). Thanks to these methodological developments, we now know that smoking kills approximately 8 million people each year. People have continued smoking despite knowing these risks because cigarettes rapidly deliver nicotine to the brain, which is addictive.[19] Unfortunately cigarette smoking is the most popular and most harmful form of nicotine use.[20–22] Smokers can expect to live 10 fewer years than non-smokers,[23] with the most disadvantaged people in society being the most likely to smoke and to die from smoking-related diseases.[24] In this chapter, I will briefly review research into the harm caused by cigarette smoking, as well as the risks of using nicotine when it is not accompanied by tobacco smoke.

Early studies

The early focus of studies into health harms of smoking was on carcinoma of the lung (i.e., lung cancer), which had risen sharply as a cause of death in Europe and the US during the first half of the 20th century, in line with rises in cigarette smoking that occurred in previous decades (albeit with cancer incidence lagging behind by two to three decades, as would be expected if exposure to smoke incrementally increases risk of cancer each year over decades of use).[25–27] The close correspondence between trends in smoking prevalence and lung cancer incidence could not alone prove a causation. Alternative explanations for the rise were that the increasing incidence was due to more people surviving to later life and better diagnosis and more accurate records of the causes of death.[25,26] Therefore, in addition to these population-level trends, several "case-control" studies were devised to examine whether smoking was more prevalent among those with lung cancer (cases) than those without (controls).

The most influential of these case-control studies was, "A study of the aetiology of carcinoma of the lung" led by Doll and Hill.[28] Their method was simple: for every person identified as having lung cancer (i.e., an incident case) at a participating English hospital, a control was selected of the same sex, age group, and hospital (or as close a hospital as possible). The objective was to compare smoking prevalence in the cases to the controls. The matching on sex, age, and hospital was an attempt to make cases and controls exchangeable, such that they would have similar smoking prevalence were it not for a causal effect of smoking on lung cancer (though not described in those terms at the time). The results found much higher odds of smoking among cases than controls. Moreover, they found a dose-response relationship with number of cigarettes smoked per day, such that heavy smoking was more common among the cases than the controls. Similar studies were conducted (albeit often with poorer methods or less clear reporting) elsewhere, all finding analogous strong associations.[27,29,30] One of the earliest examples of meta-analysis (although not called that at the time) was conducted by Cornfield in 1956, where he combined data from fourteen case-control studies looking at smoking and lung cancer.[31,32] The pooled results from these studies showed that the risk of lung cancer in smokers was seven times what it was in non-smokers. However, the conclusion from these studies that smoking caused this raised risk was not accepted by all in the scientific community. Several high-profile statisticians (including J. Berkson,[33] J. Neyman,[34] and R.A. Fisher[35]) disputed the causal interpretation of these findings as, among other things, they were retrospective.[33,36]

To convince sceptics, there was a need for prospective cohort studies, where individuals would be asked about their smoking habits at baseline and then followed up and asked about their health several years or decades later.[37] The US male veterans' cohort was one of the first to establish a prospective association between smoking and lung cancer.[38] It found that smokers were approximately six times more likely to die from lung cancer during follow-up than non-smokers from the same age group. However, mortality from a myriad of other causes was also raised among smokers — albeit to a lesser extent than with lung cancer.[39] This lack of complete specificity to lung cancer led sceptics to question whether raised risks were due to differences between the kinds of people who chose to smoke versus not (or take part in the study[34]), rather than a causal effect of smoking per se (i.e., "confounding"). For instance, Fisher claimed that genetic factors may cause both smoking and lung cancer, creating a spurious positive association between them.[35]

Cornfield et al.'s 1959 article addressed many of these alternative explanations, triangulating evidence from case-control, cohort, experimental, and population-level data.[26,40,41] They concluded that the evidence was most consistent with a causal effect of smoking on lung cancer. For instance, several experimental studies showed that cancers were induced by placing tobacco-smoke condensates ("tar") on the skin of mice, which supported the hypothesis that inhaling smoke into the lung could induce cancers there.[42] Importantly, Cornfield et al. showed that the size of confounding necessary to fully account for the disparity in lung cancer incidence between smokers and non-smokers — as well as the dose-response pattern found with number of cigarettes smoked per day — would be implausibly large. They concluded that, "this hypothetical agent would have to be at least as strongly associated with lung cancer as cigarette use; no such agent has been found or suggested." Nonetheless, it was not until several other large, prospective cohort studies, including the British Doctors Study;[25,43] influential reports from the UK (e.g., Royal College of Physicians 1962 report[44]) and the US (e.g., Surgeon General's 1964 report[45,46]); and substantial evidence of lower risks of death and disease among those who quit versus continue smoking that these harms were more widely accepted.[23,47–49]

Current consensus

It is now clear that smoking is not only a cause of lung cancer, but also a myriad of other diseases, with the greatest number of deaths due to smoking arising from cancers, cardiovascular diseases, and respiratory diseases.[38,50–52] One influential set of reports came from the British Doctors Study, which examined the overall effect of all these diseases on mortality among British doctors over 50 years.[23] It showed that smokers, on average, live around a decade less than non-smokers, after statistical adjustment for several factors that could cause both smoking and death. Moreover, the authors concluded that mortality among smokers who quit by age 30 is almost identical to those who never smoked (1, 4, and 7 life years lost for those quitting by ages 40, 50 or 60 respectively). This means that quitting smoking, and doing so early, is important for avoiding the health harms of cigarettes. Rates of chronic disease and disability are also much higher among smokers than non-smokers; smoking not only causes death, it also reduces the quality of life.[52]

Global Burden of Disease 2019 estimates that around 8 million deaths are caused by smoking each year.[55] In most high-income countries, efforts to reduce smoking prevalence by promoting abstinence from cigarettes (see next section) have led to some of the largest and most cost-effective improvements in mortality and morbidity in the population.[48,54] Yet

smoking remains one of the leading preventable causes of death in many high-income countries, including the UK, and the tobacco industry continues to expand in several low- and middle-income countries.[53,55] There is a need for novel public health approaches. One such approach is to encourage people to switch from smoking cigarettes to using less harmful sources of nicotine: sources that avoid combustion and do not exposure users to smoke (discussed in the literature review).

Nicotine versus smoke

While nicotine is the primary addictive compound in cigarettes, it is not to blame for the great majority of the excess mortality and morbidity observed among smokers. Instead, several lines of evidence show that chemicals produced when burning tobacco (e.g., smoke/tar and carbon monoxide) are principally responsible for the harm from cigarette smoking (although the route in which nicotine is taken into the body may also affect health risks).[56–58]

Firstly, experimental evidence shows that, while placing tobacco-smoke tar on the skin of animals leads to the development of cancers, placing nicotine alone does not do so.[59] Two groups of compounds produced during tobacco combustion are hypothesised to be especially important carcinogens: tobacco-specific nitrosamines (TSNAs) and polycyclic hydrocarbons (PCH).[60] Animal models have consistently shown that these compounds are carcinogenic or toxic to cells throughout the body.[61] Therefore, compared with cigarette smokers, people who use nicotine products that do not produce high levels of these chemicals are likely at lower risk of the diseases they cause (so long as these alternative products do not expose them to other equally harmful toxicants). Secondly, pharmaceutical nicotine replacement therapy (NRT), such as nicotine patches and gum, and inhalers, have been developed. These appear effective for smoking cessation and, importantly, people who use NRT do not appear to be at substantially increased risk of cancer compared with those who remain abstinent from nicotine entirely.[62] Thirdly, people who use Swedish snus — stamp-sized tobacco pouches that are placed between the lip and gum — appear to not have notably increased risks of cancers relative to non-users, despite these products delivering similar levels of nicotine to cigarettes.[63,64] This suggests that constituents in cigarettes other than nicotine must be responsible for the increased risk of cancers observed among smokers. Population-level comparisons between countries also suggest switching from cigarettes to snus may lower lung cancer risk: Swedish men have anomalously low lung cancer rates relative to other European

countries, likely because snus has replaced cigarettes as the nicotine product of choice in this group.[65]

An area where nicotine may have a harmful effect on the body is in the cardiovascular system, particularly in people who already have cardiovascular disease.[57] Unlike smoking-related deaths from cancers and respiratory disease that are primarily[1] caused by other toxins in tobacco smoke, nicotine itself might play a partial role in the millions of smokers each year who die from heart attack and stroke.[57,67] Nicotine certainly has acute effects on the heart. Nicotine causes sympathetic activation of the autonomic nervous system, which leads to increased heart rate and blood pressure.[57] However, these acute effects of nicotine on the body are not necessarily harmful. Caffeine causes similar rises in heart rate and blood pressure, but is not associated with cardiovascular disease.[68] Epidemiological evidence from snus users shows that long-term use of high levels of nicotine may be associated with heart attack and stroke, but the increase in risk is much less substantial than for cigarettes.[57,69] Studies have not detected a large association between NRT and cardiovascular outcomes, as has been found previously for cigarette smoking.[50,51,70,71] Nonetheless, larger studies would be needed to detect smaller effects of NRT on such rare outcomes.[70]

There are several other ways that nicotine could affect health. First, in the reproductive system, there is some evidence to suggest nicotine lowers both male and female fertility, which is likely caused by dysregulation of endocrine function.[72] Second, evidence in animals shows that nicotine is likely to be at least partially responsible for the increased rates of urinary system disorders (e.g. chronic kidney disease) among cigarette smokers.[73] Third, in the lymphatic system, nicotine use is associated with lower expression of immune-related genes, suggesting nicotine may cause immune suppression.[74] Fourth, some evidence shows improved muscle torque in nicotine-naïve humans who are given nicotine when compared with placebo, but results were inconsistent across tests and nicotine doses..[75] Sixth, nicotine use may affect mental health. In the short-term, people report that nicotine improves mood and helps to alleviate anxiety.[76] However, repeated nicotine use can lead to both physical and psychological dependence, which causes people to experience periods of nicotine withdrawal throughout the day. This could adversely affect their well-being and mental health.[19,77] Finally, nicotine may also affect the digestive, integumentary and skeletal systems; reviews of effect of nicotine on these systems can be found elsewhere[78,79].

[1] However, nicotine may promote tumour growth in people who have developed cancer.[66]

Taken together, this evidence suggests that if smokers switched from cigarettes to other nicotine sources which do not involve combustion, the rates of disease and death in this group could be substantially lowered. In the final section of this literature review, I will examine this "harm reduction" approach, which aims to minimise the negative health effects of continued nicotine use. In the next section, I will explore the most common approach to combating smoking-related disease over the past century, promoting abstinence from all nicotine and tobacco use.

Promoting Abstinence

Introduction

Cigarettes are the most popular nicotine product, partly because they are among the most effective at delivering nicotine rapidly to users. Cigarette smoking is also the most deadly form of nicotine use, with cigarettes causing 90% of deaths arising from tobacco.[19,22,80] It is estimated that up to two thirds of life-long smokers will die from diseases caused by inhaling tobacco smoke.[81,82] Many others, who are exposed to secondhand smoke from family or friends, also develop and die from these diseases.[83,84] Reducing smoking prevalence is one of the most effective ways to improve public health.[52] This is why the English government aim for their country to be 'smoke-free' by 2030, where fewer than 1 in 20 adults smoke.[85] Similar goals have been set in countries across the world.[86] Over the past century, two approaches to achieve these goals have emerged: **promoting abstinence** and **harm reduction**. The former focuses on eradicating nicotine and tobacco use, whereas the latter focuses on reducing the harm caused by continued nicotine and tobacco use. In this section, I will briefly explore the history and science of the abstinence promotion approach. The next section will do the same for harm reduction.

Promoting abstinence from cigarettes and nicotine is an approach that has been advanced by a diverse array of people for at least four centuries — from members of charities and scientists to monarchs and politicians.[87–89] Often, people who smoke are themselves strong proponents of abstinence, wanting to remove their dependence on nicotine entirely rather than continue using it in a less harmful form.[90] These individuals have or had the goal of extinguishing tobacco[2] and nicotine use.[92] Their reasons for opposing tobacco varied, from religious or moral beliefs about the virtue of abstinence,[91] concerns about protecting society from smoking-related disease and death, and desires to stop the tobacco industry from spreading addiction for profit.[87] Despite their differing motives, people and groups pursuing this goal succeeded in reducing smoking prevalence across many countries, including most of the English-speaking world, throughout the latter half of the 20th century.[94] Their successes

[2] Historically, the focus has been on reducing tobacco use, rather than nicotine use per se.[91,92] This is likely because the traditional consumer nicotine products, like snus, chewing tobacco, cigars and cigarettes, were all made from tobacco. Only more recently, with the introduction of e-cigarettes, has there been a consumer nicotine product that does not contain tobacco. Nonetheless, some groups who focused on reducing tobacco use have transferred this goal to nicotine use more broadly.[93]

stem from changes that have occurred across three areas: regulation, quitting support, and social norms/public perceptions.

1. **Regulation** — Governments introduced regulations on the tobacco industry, including taxes, smokefree policies and bans.[21] These controls aim to discourage young people from starting smoking, protect non-smokers from secondhand smoke, and propel smokers to quit.[98]
2. **Quitting support** — Research found several effective treatments to support quitting, and advocacy groups pushed, albeit sometimes unsuccessfully, to make this support available for even the most disadvantaged smokers.[15,94]
3. **Social norms and public perceptions** — Introduction of mass-media campaigns, advertising bans, smokefree policies, warning labels, and plain packaging has helped to sway public perceptions against cigarettes and denormalise smoking.[11,95–97]

Efforts across these three areas were connected; successful changes in one bolstered the other two. For instance, cigarette adverts exposed those quitting smoking to images of the very product they are struggling to resist.[98] Therefore, regulation and bans on cigarette adverts helped support smokers in their attempts to quit. Changes in public opinion were vital for producing political will to introduce regulation and fund stop smoking support services.[95,99] Moreover, much of the impact of regulation on smoking prevalence is mediated by their effect on social norms and public perceptions.[11] Such regulations will be covered in the section on social norms and public perceptions rather than regulation. In this chapter, I will take a brief tour of the history and science into each of these three areas.

Regulation

Most addictive drugs are illegal in most countries.[100] Each year, millions of people are imprisoned for possessing or selling drugs like cannabis, cocaine, amphetamines, or opioids.[101] In some countries, like Singapore, one can be sentenced to death for possessing drugs that cause very little harm to society, like psilocybin.[102] Yet, despite killing millions of people each year, tobacco is legally available across most countries in the world.[21] In addition, throughout most of the 20th century, tobacco companies had almost unrestricted freedom to market and sell cigarettes.[87] Attempting to combat this, tobacco control groups argued that industry should not be given free rein to sell and market products that are addictive and kill

over half of lifelong users.[81] They instead propose that industry should be heavily regulated to account for the toll cigarettes take on public health.[92]

In several high-income countries, these groups succeeded in introducing several restrictive policies across many countries, including taxing tobacco and increasing age of sale.[103] For instance, the UK Government committed to progressively raising tobacco duties each year in 1993, and they increased the age of sale from 16 to 18 years old in 2007.[104] The aim of taxation is twofold. First, to levy the tobacco industry for the damage their products cause society, and second, to reduce smoking prevalence by lowering uptake and motivating smokers to quit.[105] The declining smoking prevalence in countries implementing these policies shows that they can be effective at doing just this.[103,104,106]

There are some criticisms of taxation. Firstly, enforcement of these policies can be difficult, especially in countries without adequate law enforcement to avoid widespread propagation of illicit tobacco. However, tobacco companies may have exaggerated the scale of illicit tobacco trade in low- and middle-income countries as a way to influence policy in their favour.[107] Secondly, people from disadvantaged backgrounds are disproportionately likely to smoke.[94,108] This means that the poorest people in society end up bearing most of the burden from taxation on tobacco. However, these individuals are also more likely to attempt to quit in response to tax rises, meaning that these policies can help to reduce socioeconomic inequalities in smoking-related disease.[109–111] Moreover, revenue generated through taxation can be invested into services that support people in their attempts to quit smoking.

Quitting support

Quitting smoking is difficult as cigarettes are highly addictive. They deliver nicotine rapidly to mouth, throat and lungs, where it is absorbed into the blood.[112] Within seconds, this nicotine passes into the brain, where it binds to nicotinic acetylcholine receptors.[113] This binding causes an influx of positively charged ions into neurons in the ventral tegmental area, which leads to a cascade of dopamine release in the nucleus accumbens — the reward centre of the brain.[114] This rapid release of dopamine is central to many, if not all, drug addictions.[115] It causes behaviours (i.e. smoking) that led to its release to be reinforced, producing strong urges to repeat that behaviour in the future.[115] Smoking, but not other nicotine products, also releases monoamine oxidase inhibitors, which — at least in the short-term -- improve mood and alleviate anxiety.[116,117] Moreover, regular smoking leads to partial tolerance to these effects; abstinence thus causes withdrawal symptoms, including headaches, irritability and, most

importantly, an underlying craving or 'hunger' for cigarettes.[19] It is the combination of this craving alongside powerful momentary urges to smoke that make quitting smoking so difficult,[118] such that nine-in-ten people who attempt to quit without support relapse within a year.[119] Identifying strongly as being a smoker can also impeded quitting.[120] Fortunately, there are several effective methods to help people trying to quit smoking to avoid relapse and thus remain abstinent from tobacco.

For a person to avoid relapse after a quit attempt, whenever the opportunity to smoke arises, their motivation to remain abstinent must outweigh their motivation to smoke.[115] Therefore, effective methods of supporting quitting work by (i) reducing motivation to smoke or (ii) increasing resolve to remain abstinent. Here I will explore three such methods which are thought to be among the most effective: behavioural support, cytisine and varenicline, and NRT.[3]

Behavioural support

Behavioural support is advice or counselling aimed at helping people successfully stop smoking.[121] It can be delivered either one-to-one, to a group, or digitally through a website or mobile application.[122–124] In the UK, behavioural support is provided by specialist advisors at NHS stop smoking services. A recent systematic review showed that behavioural support is effective for smoking cessation, and its effectiveness is proportional to the intensity with which it is delivered.[125]

There are at least 41 behaviour change techniques used by advisors to help smokers remain abstinent.[121] For example, they help to reduce motivation to smoke by providing strategies to handle cravings; increase motivation to remain abstinent by providing encouragement, praise, and accountability (e.g. through carbon monoxide monitoring); and remove opportunities to smoke by advising clients to avoid social situations where others will be smoking. Importantly, the other methods of quitting rely on behavioural support; without guidance from specialists advisors or doctors, medications such as NRT and varenicline are much less effective.[126] Indeed, in most of the research presented below, cytisine/varenicline and NRT was given to smokers alongside behavioural support. Unfortunately, behavioural support is not widely used. Despite being available for free at NHS stop smoking services in many areas of the England, only 3% of smokers who try to quit use it.[127] This is why some

[3] Bupropion is another medication used for smoking cessation. I have excluded it from the discussion here as it is less effective or widely used than varenicline or NRT. It also does not link into any of my studies.

argue regulation, social norms, and possibly commercial nicotine products (e.g. e-cigarettes), are more important drivers of smoking prevalence.[128]

Cytisine and varenicline

Cytisine is a drug that is found naturally in plants. It has been used for smoking cessation in Eastern Europe since the 19th century.[129] Varenicline is very similar to cytisine. In fact, it was developed by the pharmaceutical company Pfizer as an attempt to mimic cytisine.[129,130] Both cytisine and varenicline are nicotine receptor partial agonists, usually given to smokers as tablets.[131] They bind to specific nicotinic acetylcholine receptors, blocking nicotine from attaching to the neuron. Because of this, they diminish the 'reward' people feel when smoking a cigarette, limit withdrawal symptoms, and reduce craving for cigarettes. Thus, cytisine and varenicline prevent relapse by reducing motivation to smoke.

Varenicline has been more thoroughly studied that cytisine.[4] A Cochrane systematic review of 27 trials found varenicline is very effective for smoking cessation; smokers given varenicline were more than twice as likely to remain abstinent for at least 6 months compared with those given placebo pills.[131] It is also more effective than single-form NRT and bupropion. This higher effectiveness was also found in population-level data in England.[132] Non-serious side effects from varenicline, such as vivid nightmares, are common. A concern when varenicline entered the market was that it might increase risk of mental health issues. However, a recent trial with 8,144 participants showed no increase in psychiatric symptoms among those using varenicline.[133,134]

While less studied than varenicline, cytisine does appear to be effective for smoking cessation. A Cochrane review of three RCTs found that cytisine increased abstinence from smoking relative to both placebo and NRT.[131] However, the evidence for this was rated low-quality, so there is some uncertainty about the robustness of this finding. It is currently unclear whether varenicline or cytisine is more effective for smoking cessation, but two large ongoing trials are investigating this.[135,136] If the two drugs are found to be equally effective, scientists have argued cytisine should be preferred as it is less costly.[137] Moreover, as I will discuss in Chapter 6, the only available form of varenicline in the UK, Champix, was recalled in 2021 for

[4] Varenicline was synthesised by Pfizer, who paid to licence it as a medicine and funded research into its effectiveness. Cytisine has not been licenced as a medicine in the UK, US, or EU. This may be because it would be considered unprofitable for a company to pay for licencing when they would be unable to patent cytisine, as it is a naturally occurring compound.

having higher than acceptable levels of N-nitroso-varenicline. This means there is a need for a cytisine or a new supply of varenicline to become available.

Nicotine replacement therapy

Figure L1. Examples of nicotine replacement products that are available over-the-counter in the UK (Location: Boots Pharmacy).[138]

NRT encompasses a vast array of different products (Figure L1). Nicotine patches, gums, inhalers, and lozenges are some of the most popular choices.[139] They can be purchased on prescription or, in some countries (e.g. UK), over-the-counter.[140] These products are designed to give smokers an alternative source of nicotine to cigarettes. NRT is very well studied. A Cochrane review of 136 trials found that NRT increased the proportion of smokers who remained abstinent by 50% relative to placebo.[141] Therefore, NRT is effective for smoking cessation — albeit less-so than varenicline or cytisine.[131]

NRT acts by reducing motivation to smoke. Most NRT regimens are designed to give smokers lots of nicotine at the start of a quit attempt, then gradually wean them off nicotine entirely over several weeks.[19] This reduces withdrawal symptoms compared with quitting without support.[142] The most important symptoms, in terms of predicting relapse, are one's underlying craving for nicotine and experiencing strong momentary urges for the 'nicotine hit' of a cigarette.[143] Nicotine patches are absorbed slowly over the space of several hours, so

they dampen craving for nicotine.[144] Conversely, nicotine spray and, to a lesser extent, gum and lozenges act within seconds or minutes. People can therefore use these fast-acting products to get a rapid hit of nicotine when they experience urges to smoke. This may be why using a combination of both short- and fast-acting NRT is more effective than using either one alone.[142]

As with the other medications, NRT is more effective when given alongside behavioural support.[126,141] Results from population-level surveys show that, when bought over the counter (i.e. without any advice from a doctor or nurse), NRT does not appear to be especially effective.[145] This may be because advisors can guide people to use their products correctly. For instance, many smokers misperceive nicotine as the primary cancer-causing substance in cigarettes.[146] They are therefore hesitant to use 'too much' NRT, which leads many people to use less than required.[147] Advisors, at least in the UK, are trained to dispel this myth — encouraging smokers to use as much nicotine as they need to avoid smoking cigarettes.[142,148]

Summary

Cytisine or varenicline alongside behavioural support is the most effective traditional method of supporting quitting. Combining both slow- and fast-acting NRT with behavioural support is also very effective. By providing these methods, NHS stop smoking services in the United Kingdom helped over 200,000 people quit smoking each year.[149] Yet, at the population level, use of these methods and products is relatively rare. The only product that gained substantial popularity was NRT, bought over the counter.[127] Even this is unlikely to have had much impact on the population-level, as NRT bought over-the-counter is relatively ineffective for smoking cessation.[145] As I will discuss in the next section, to rapidly lower smoking prevalence, there is a need for products that are both effective for smoking cessation and more widely popular.

Social norms and public perceptions

Figure L2. Cigarette adverts from the mid-20th century (Source: Stanford Tobacco Advertisement database).[153]

Adverts such as these (Figure L2) were once seen as benign and commonplace.[87] Now, people view them as 'shocking' and 'outrageous'.[151–153] This displays the shift in public opinion that has occurred from the mid-20th century to today. Prior to 1960, fewer than half of US adults perceived smoking as a cause of lung cancer. By 1990, this had risen to 94%.[95] And public opinion continued to cascade against cigarettes, with a renewed focus on secondhand exposure. Over the next 20 years, the proportion of people who agreed smoking should be banned in restaurants doubled from 30% to 59%.[95] Similar changes occurred in England, leading to a sharp fall in children's exposure to smoke in the home.[83]

Perceptions of cigarettes have soured to such an extent that, by 2008, not only did half of adults in England support an outright ban on tobacco, but over a third of smokers also supported such a ban.[99] Evidence shows that mass media campaigns, advertising bans, smokefree policies, warning labels and plain packaging all may have contributed to the changes that occurred public perceptions and social norms.[83,154]

For example, experimental studies show that warning labels on cigarette packages, especially those which graphic pictures and real people, are effective at altering people's perceptions about the risks of smoking.[155,156] They may also encourage people to quit smoking and remain abstinent, while discouraging young people from starting to smoke.[157] There is a similar body of evidence supporting plain packaging; young people report that cigarettes in brown standardised packaging are less attractive, more risky to health, and less likely to encourage initiation than cigarettes in branded packaging.[158,159] Observational data also shows

that smokers who notice warning labels are more likely to make a quit attempt than those who do not, but confounding cannot be ruled out.[160]

In Chapter 3, I will report a study looking into how public perceptions of the harm of e-cigarettes relative to cigarettes is changing, with discussion of how these changes may affect public health.

Conclusions

Regulation has succeeded in driving down smoking prevalence, and treatment with varenicline or cytisine alongside behavioural support can help many smokers quit. Furthermore, campaigns have succeeded in turning public perceptions against cigarettes; now the overwhelming majority of people in England understand how harmful cigarettes are to health, and half of adults support an outright ban on tobacco. Despite these changes, the harms of cigarettes remain extensive; millions of people continue to die from smoking-related diseases each year, the majority of whom are from the most disadvantaged and vulnerable groups in society.[81,161] More regulation, quitting support, and shifts in social norms and public perceptions will help reduce these harms by further lowering smoking prevalence. However, another approach has emerged to dealing with cigarette smoking, one that aims to reduce these harms without necessarily eradicating nicotine use.

Reducing Harm

Introduction

What is the ultimate goal of drug policy?[5] Many people view the aim as to rid society of drugs, while others want to reduce the harm caused by drugs. Unfortunately, these two goals do not always align.[162] For instance, safe injection sites for opioid use reduce the spread of HIV.[163] This saves lives, but at the expense of sanctioning (albeit safer) drug use. The conflict between these two goals has been a defining feature of the science and politics of addiction since the 1920s.[164] Nicotine is no exception. As discussed in the previous chapter, I refer to these two perspectives as abstinence promotion and harm reduction. Abstinence promotion has been the primary tool used by tobacco control to decrease smoking prevalence, aiming to eradicate long-term[6] tobacco and nicotine use and viewing continued use as a risk to relapse to the most harmful nicotine product: cigarettes.[92] Harm reduction approaches accept that some people will continue using nicotine for long periods after they quit smoking, possibly even indefinitely. It therefore instead aims to minimise the damage caused by continued nicotine use, usually by making less harmful nicotine products available and attractive to smokers.[128] This chapter will explore the history, science, and possible future of harm reduction.

As discussed in the first section of this literature review, smokers have a life expectancy that is a decade shorter than non-smokers, and they experience diseases associated with old age a decade earlier.[48,165] Most smoking-related harm stems from cancers, respiratory and cardiovascular diseases.[22,52] Nicotine is the drug that causes cigarette dependence, but it is not the primary cause of these diseases.[57,113,166] Instead, they result from exposure to the thousands of known carcinogens and toxins produced by burning tobacco.[113] This is why tobacco products that are not burnt[7] and nicotine products that do not contain tobacco are assumed to be less harmful to health than cigarettes.[167]

The development of NRT in the 1960s to 70s was one of the first explicit attempts at nicotine harm reduction.[168] Creators of nicotine gum designed it as a substitute for smoking that, like cigarettes, would induce habitual use.[169] Because of this, it received opposition from

[5] By drug policy, I refer to non-medicinal psychoactive drug policy.
[6] This perspective would allow short-term use of nicotine replacement therapy for smoking cessation — so long as the ultimate goal is for people to eventually stop using nicotine entirely.
[7] Other 'smokeless' tobacco products are fire-cured, fermented and/or pasteurised, which produces carcinogens (tobacco-specific nitrosamines).[69] These products are thus more harmful than Swedish snus, which avoids these procedures.

some tobacco control groups and scientists, who argued that it is backwards to give smokers the very drug they are struggling to quit.[168,170] Decades of research showed that NRT is safe, effective for smoking cessation, and used rarely among long-term ex-smokers and very rarely among never smokers.[141,171,172] Because of this, NRT became accepted by the tobacco control community and has helped many smokers to quit.[58] However, there remain more than a billion people in the world who continue to smoke.[128] There thus remained a need among harm reduction proponents for a less harmful, but popular, product to replace cigarette smoking.[168] Three products have emerged to address this need: oral pouches, e-cigarettes, and heated tobacco products.

1. **Oral pouches**[8] — These stamp-sized pouches are placed between the lip and gums, containing either (i) moist powdered tobacco (called 'snus') or (ii) tobacco-free filler and nicotine (called 'nicotine pouches').
2. **E-cigarettes** — These are electronic devices that produce an aerosol for inhalation by heating a liquid, called an e-liquid, that usually contains nicotine. They do not contain tobacco or produce smoke.[175]
3. **Heated tobacco products** — These are devices that heat tobacco to a temperature that is high enough to produce a nicotine-infused aerosol, but too low to cause self-sustaining combustion.[174]

In the three areas mentioned in the previous section — to introduce regulation, support quitting, and change public perceptions and social norms — scientists and tobacco control groups were largely unified[9].[92] The same cannot be said for the debates into novel nicotine products, which have divided the scientific community.[177] While most agree these products are less harmful than cigarettes, debates remain about how they will impact smoking prevalence. Proponents claim that these three products will accelerate the decline of cigarette smoking and, in the process, save millions of lives.[178] However, critics fear these products might act as a 'gateway' to smoking, undermine quitting, and increase the risk of relapse (as well as having their own risks to health and leading to dependence).[179,180] Others oppose a

[8] This category could be expanded to include other oral nicotine products, such as strips and lozenges. I have focused on nicotine pouches as these are the most widely available oral nicotine product on the UK market.

[9] With some exceptions, including (i) arguments about the value of providing support versus prompting unaided quitting, (ii) concerns that smokers who quit using NRT will remain dependent on nicotine, and (iii) early debates about whether the association between smoking and disease were causal, often spearheaded by scientists who were paid by tobacco companies.[87,175,176]

harm reduction approach entirely, arguing that, even if these products help people quit smoking, policymakers should not support products that perpetuate nicotine addiction.[181]

When considering the harms of these alternative nicotine products to the health of individuals that use them, it is important to distinguish between absolute and relative risks. Absolute risks refer to adverse health effects caused by using these products compared with using nothing. Conversely, relative risks refer to the comparison between the harm of using these products compared with smoking cigarettes. Harm reduction proponents tend to focus on the reduced relative risk, while critics instead point out the raised absolute risks. However, there are also empirical disagreements about the magnitude of the absolute and relative risks, as well as the overall impact of growing use of these products on population-level.

In this chapter, I will briefly review the current scientific literature on these products, with a focus on e-cigarettes as they are the most popular alternative nicotine source globally.[182] In doing so, I will identify key evidence gaps that should be filled to better understand their impact on smoking prevalence and public health.

Oral pouches

Swedish snus is two centuries old.[183] During the cigarette boom of the early-mid 20th century, these oral tobacco pouches[10] fell out of favour among Swedes.[65] But starting in the 1970s, snus made a striking resurgence.[184] Swedish Match[11] rebranded their snus with fresh colourful packaging and invested heavily in adverts targeted at young men.[183] A third of young Swedish men, and a similar proportion in Norway, use snus daily.[65,185] Initially, scientists argued this epidemic of snus use must be halted, especially as it appeared that young people, not established adult smokers, were most attracted to snus.[183] Yet over time, it became clear that the rise in snus use was accompanied by a fall in cigarette sales.[65] Moreover, as discussed previously, epidemiological studies showed that snus use only caused a fraction of the harm of cigarette smoking.[65] Sweden now has far lower prevalence of smoking and lung cancer than any other country in the European Union.[69]

[10] Snus was originally sold loose, not in pouches. However, it was snus pouches that drove increases in its use in the latter half of the 20th century.[69]
[11] Then called 'Tobaksbolaget'.

Popularity of these oral pouches has as yet been low outside of Nordic countries[12]. Snus is rarely used elsewhere in the EU due to a ban[13] on oral tobacco.[69] Even in countries where it has been sold, it has not gained substantial popularity. For instance, in 2015, due to lack of demand, PMI and Swedish Match ended their five-year partnership aimed at expanding snus into the new markets.[186] However, a new set of products have recently launched that might garner greater interest worldwide: tobacco-free nicotine pouches.[187]

Unlike snus, these nicotine pouches do not contain tobacco, so they can be sold legally in the EU. There is currently very little research on their harmfulness or prevalence of use. Therefore, in Chapter 5, I report a study that measures the prevalence and correlates of nicotine pouch use in England. Unless snus or nicotine pouches become more popular outside of Scandinavia, they will be unable to drive enough substitution to substantially affect smoking prevalence.

E-cigarettes

E-cigarettes were created in 2003 by Hon Lik, a smoker who was looking for a less harmful alternative to cigarettes.[188] In the decade following the launch of e-cigarettes onto the UK and US markets (2005 and 2007 respectively), their popularity rose sharply. It is for this reason that e-cigarettes have been at the centre of recent conflicts about nicotine harm reduction.[188,189] Alongside concerns about their harm, these debates have focused on the impact e-cigarettes will have on smoking prevalence. In this section, I will first review research into the harm of e-cigarettes, both in absolute terms and relative to cigarettes. Then, I will examine how growing e-cigarette use ("vaping") may affect smoking prevalence through uptake and quitting.

Harm

The harms from cigarettes primarily arise from the thousands of toxicants and carcinogens in tobacco smoke.[19] E-cigarettes do not contain tobacco or produce smoke.[190] Because of this, when they first entered the market, many scientists assumed that exposure to e-cigarette aerosol was likely to be much less harmful than cigarette smoke.[190] Over a decade of research has confirmed this assumption; reviews from Public Health England, the Royal College of

[12] Similar pouches are also used in the US, but on a much smaller scale than in Sweden or Norway.
[13] Sweden is exempt from this ban.

Physicians, and the NASEM all concluded that e-cigarettes expose users to far fewer toxins than tobacco smoke.[167,190,191] Much of this research was conducted via smoking machines, but studies examining biomarkers of exposure also show that long-term (>6 month) exclusive e-cigarette users who quit smoking have lower levels of biomarkers of exposure to harmful compounds than smokers, with levels comparable to NRT users.[192,193] Thus, the relative risks of using e-cigarettes are likely much lower than cigarettes, but there remain some absolute risks.

Long-term e-cigarette users have similar exposure to nicotine as smokers, so they would have similar risk of nicotine-related harm to the cardiovascular system, if such harm exists.[192,193] Nonetheless, other toxins in cigarette smoke likely cause most of the harm to the cardiovascular system, and these compounds are absent from or present in lower concentrations in e-cigarette aerosol.[57,67] Trial evidence also indicates lower cardiovascular risk from vaping compared with smoking; a recent study found that vascular function improved among people who switched from cigarettes to e-cigarettes, but not among those who continued smoking.[194] Thus, switching from smoking to vaping may improve cardiovascular health. However, more research is needed to verify this.

E-cigarette aerosol contains constituents that can damage the respiratory system, albeit often at much lower concentrations than in cigarette smoke.[191] Thus, it is plausible that long-term vaping by non-smokers would increase respiratory disease risk, and there are specific circumstances where they are likely pose much greater risk.[195,196] When heated to high temperatures, e-cigarettes produce substantial amounts of aldehydes.[197] Exposure to aldehydes is associated with several cancers and respiratory diseases.[191,195] However, vaping at such high temperatures is unpleasant, causing 'dry puffs', which most vapers (around 90%) can identify and avoid.[198,199] Thus, absolute risk of diseases associated with this exposure is likely to be low among most e-cigarette users, and relative risks are likely much lower than from cigarette smoking.[167]

The majority of smoking-related deaths result from cancer, respiratory and cardiovascular disease.[48] Because e-cigarettes exposure users to far lower levels of toxins that cause these diseases, they are likely to cause less harm.[167] This reduced risk needs to be confirmed with epidemiological evidence. Yet, very little reliable research has been done into the association between vaping and these diseases, such as from longitudinal cohort studies.[167] As discussed previously, results from such cohort studies in the 1950s proved the scale to

which smoking devastates health, so it is important to collect similar data for e-cigarettes.[103] However, there are two challenges that make these analyses especially difficult.

The first challenge is that most e-cigarette users have a long history of smoking, and many switch from smoking to vaping when they start experiencing health problems.[191] This interconnectedness between smoking, vaping and health will make it difficult to establish causality or answer questions like: does vaping cause poor health, or do people with poor health vape? Because of these issues, detailed measures of confounders (e.g., smoking history) will be required to avoid residual confounding, and researchers must take care to avoid traps such as collider bias and reverse causality.[13,200,201] An example of where this can go wrong is in cross-sectional studies examining the association between vaping and heart attacks.[202] These studies have sometimes failed to account for the timing of heart attacks. Moreover, even in studies that do take into account the timing of heart attacks, the association should not be interpreted as reflecting a true causal effect of e-cigarettes, given that the data were cross-sectional and thus were prone to confounding and several time-related biases.[203,204]

The second challenge is that smoking-related diseases take decades to develop, but e-cigarettes have only been widely used for just over a decade.[81] Little research has explored the associations between e-cigarette use and health outcomes over a period longer than five years.[191] The full benefits of smoking cessation on health outcomes do not fully appear until many years after quitting.[19] Therefore, it will take similar time — and likely longer due to the issues with establishing causality mentioned above — to determine the extent to which switching from cigarettes to e-cigarettes reduces disease risk. Evidence on cardiovascular events, such as heart attack and stroke, are likely to be available earliest because benefits emerge soon after quitting smoking for these outcomes.[57] Early results from the US PATH cohort study showed relatively similar rates of cardiovascular events among smokers who switched to vaping and those who stopped using nicotine entirely.[205] However, there was a large amount of uncertainty around estimates, and there is a risk of residual or unmeasured confounding, so more long-term data are needed.

Concerns about the safety of e-cigarettes became especially prevalent in 2019, during the US outbreak of vaping-associated lung injury.[206,207] This outbreak was caused by cannabis vaping cartridges that were contaminated with vitamin E, not nicotine e-cigarettes.[208,209] Despite this, news stories covering the outbreak often did not distinguish between nicotine e-cigarettes and cannabis vaping.[210] As I will cover in Chapter 2, this may have caused public perceptions of e-cigarette harm relative to cigarette to worsen. Although this outbreak was

not linked to e-cigarettes, it highlights the importance of regulations that ensure the safety of e-cigarettes. Such regulations have been introduced in the EU and UK, which ban a number of potentially harmful additives from e-cigarette liquid.[211]

An important consideration when assessing the harm of e-cigarettes is how they interact with infectious diseases, most notably COVID-19 — a disease that can cause severe and often deadly respiratory[14] symptoms.[214] Early in the COVID-19 pandemic, several articles were published arguing that nicotine inhalation through vaping or smoking could possibly exacerbate these symptoms.[215,216] Behavioural factors involved in both smoking and vaping, such as regular hand-to-mouth movements, may also increase viral infection and transmission if performed without accompanying protective behaviours such as hand-washing.[217] However, early descriptive epidemiology from the pandemic produced surprising results; limited, mixed-quality evidence suggested lower than expected smoking rates among those testing positive for SARS-CoV-2 infection and those hospitalized with COVID-19.[218,219] This led to the hypothesis that nicotine may protect against a hyperinflammatory response to SARS-CoV-2 infection, thus preventing adverse outcomes such as hospitalization with COVID-19 disease.[220,221] Alternatively, the lower than expected smoking rates may reflect smokers being less likely to become infected due to an unexpected interaction between nicotine and ACE2 receptors, or may simply be an artefact of measurement or sampling issues.[219,222] One possible issue is collider bias, as I discuss elsewhere.[13]

Despite the lack of longitudinal research into health outcomes, decisions must be made under uncertainty about how to regulate e-cigarettes. Current evidence suggests that e-cigarettes are much less harmful than cigarettes.[167,190,191] Thus, switching from smoking to vaping likely improves health and extends life expectancy.[178] In addition to the direct harms of vaping, it is important to consider the effect vaping will have on smoking uptake and quitting.[223]

Uptake

One of the most contentious issues surrounding e-cigarettes, and nicotine harm reduction in general, is youth use. There is a risk that e-cigarettes are attractive to young people, drawing in people who would have otherwise avoided nicotine entirely. A primary fear is that young

[14] COVID-19 also causes harm outside of the respiratory system, including substantially increasing risk of stroke.[212,213]

people, who would not have otherwise tried cigarettes, will become dependent on nicotine through vaping, then later transition to cigarette smoking. This 'gateway' hypothesis predicts that vaping will increase uptake to smoking.[224] Others hold the opposite perspective: the 'reverse gateway' hypothesis.[225] This instead predicts that, as vaping becomes increasingly popular, young people will move away from cigarettes in favour of e-cigarettes — a substitution effect that will decrease uptake to smoking. These competing hypotheses lead to different conclusions about how e-cigarettes should be regulated. If e-cigarettes increase smoking uptake, regulation that makes these products unattractive or unavailable to youth, like bans on non-tobacco flavours, will have a beneficial impact on smoking prevalence (assuming they do not also deter smokers from switching from cigarettes to e-cigarettes). If they decrease it, these regulations could unwittingly protect the cigarette market from its closest competitor.

A meta-analysis of 17 longitudinal studies, across six countries, showed that e-cigarette use among non-smokers is strongly associated with subsequent smoking (odds ratio [OR] = 4.59; 95% compatibility interval [CI] = 3.60 – 5.85).[226] However, this association does not imply e-cigarettes cause smoking. As smoking and vaping are very similar, the factors that cause both behaviours are likely to be almost identical. These common causes (sometimes called 'common liabilities') mean that people who vape have characteristics and live in environments that might also put them at greater risk of smoking. For instance, young people who live in neighbourhoods where smoking and vaping is commonplace would be more likely to initiate each behaviour than those living in areas where nicotine use is rare.[227] Compared with people who do not vape at baseline, those who do would have, on average, higher underlying risk of smoking. Because of these greater underlying risks, people who vape would be more likely to smoke at follow-up even if vaping does not *cause* them to smoke. In fact, strong common causes could even mask a protective effect of vaping on smoking uptake, and results from a study using propensity score matching and behavioural controls provides some evidence for this.[228] The most common method used to deal with these confounding common causes is by adjusting for covariates in regression.

Adjusted results from the above meta-analysis above showed that, after adjustment for measured confounders, the association between vaping and subsequent smoking weakened to OR = 2.92 (95% CI = 2.30 to 3.71).[226] In addition, effect sizes were much lower in studies with better adjustment for confounders. Nonetheless, even after adjustment for measured confounders, the association remained in all included studies. It is still unclear

whether these associations reflect causal effects. There may have been (i) misreporting of smoking among vapers or (ii) residual confounding not captured in the often crude measures used, that led to systematic biases in estimates.[229] Because the common causes of both smoking and vaping are likely to be so similar, it will be extremely difficult to ensure that confounding is fully removed. Even small misspecifications in the set of variables used for adjustment, such as categorising a continuous measure of smoking history, or assuming straight line relationships between continuous confounders, could plausibly introduce a spurious association.[230] While most individual-level results seem to support the gateway hypothesis[15], population-level results paint a different picture.

In the US, there was substantial growth in youth vaping from 2014 to 2019, sparking fears of a new nicotine 'epidemic' targeting young non-smokers (as shown in the quote at the start of this section).[80,225,231] These fears echo those raised in Sweden three decades earlier, when the popularity of snus use soared among youth.[183] Some evidence suggests that, just like with snus, the epidemic rise in youth vaping in the US was accompanied by an accelerating fall in youth smoking, albeit alongside increases in the proportion of youth using any nicotine product.[225] This supports the reverse gateway hypothesis (that e-cigarettes act as a substitute for cigarettes among youth), meaning increases in vaping will be accompanied by decreases in smoking uptake. However, the effect of vaping on uptake of smoking may depend on factors that vary across countries and over time, such as differing regulatory environments, cultures, and patterns of nicotine use. For example, the reverse gateway is more likely in countries where vaping is contained among people who would have otherwise smoked, but less so if vaping reaches a wider cross-section of the youth population.

In conclusion, the literature on the impact of vaping on uptake to smoking has produced conflicting results. Individual-level studies suggest vaping increases risk of subsequent smoking, whereas population-level surveys indicate that greater youth vaping may be associated with falls in youth smoking. There is nonetheless a risk that vaping will increase the proportion of young people using nicotine by attracting people who would never have started smoking.

[15] Not all individual level-analyses support this. In fact, a recent study that matched participants (i) to behavioural controls and (ii) on propensity scores found that young people whose first nicotine product was e-cigarettes were less likely to be ever or established smokers.[228]

Quitting

A Cochrane systematic review of randomised controlled trials into e-cigarettes for smoking cessation found that nicotine e-cigarettes were more effective at promoting smoking cessation than NRT.[232] The delivery of nicotine in e-cigarettes was important: people randomised to receive nicotine e-cigarettes had higher quit success than those given non-nicotine e-cigarettes. Thus, trial evidence indicates nicotine e-cigarettes help people who attempt to quit to achieve long-term success. However, the effectiveness of e-cigarettes for smoking cessation is likely dependent on the type of device used. First-generation cigarette-shaped e-cigarettes are likely to be less effective than second– or third-generation devices, which deliver nicotine more effectively.[233,234] Indeed, this is what trial evidence seems to suggest.[235,236]

Trials have yet to compare the effect of adding e-cigarettes to treatment with varenicline. Varenicline (and possibly cytisine) is the most effective medicine for smoking cessation.[131] Data from the UK NHS stop smoking services shows that of all treatment options, varenicline alongside both behavioural support and e-cigarettes have the highest quit rates.[237] As these results are observational, there is a risk of confounding. So, a randomised controlled trial evaluating the addition of e-cigarettes to treatment with varenicline is needed. If shown to be more effective than varenicline alone, this would introduce a new gold-standard treatment for quitting smoking. In Chapter 6, I present such a trial.

Evidence from population surveys also indicates e-cigarettes are effective for smoking cessation. Firstly, cross-sectional results from the Smoking Toolkit Study in England show that, after adjusting for a number of possible confounders, e-cigarette use is associated with double the odds of successfully quitting smoking.[132] Secondly, longitudinal studies come to similar conclusions, finding that vaping is associated with greater quit success at follow-up.[238] Thirdly, time-series studies show that, at a population level, increases in the prevalence of vaping among smokers are associated with increases in the rate of quit success.[239] Taken together, these results suggest that e-cigarettes can be very effective at helping people to quit smoking.

Summary

In conclusion, e-cigarette aerosols expose users to far lower levels of toxins and carcinogens than cigarette smoke. They are therefore likely to be much less harmful to health. Epidemiological studies are needed to evaluate the extent of this reduced risk. Individual-

level studies show that e-cigarette vaping is associated with higher initiation of smoking among young people, but common liabilities underlying both behaviours mean this association may not be causal. Population-level evidence shows that youth smoking continued to decline as youth vaping increased sharply in the US, but there were rises in overall nicotine use. Randomised controlled trial, cross-sectional, longitudinal, and time-series data show that e-cigarettes are effective at helping people quit smoking.

Heated tobacco products

The history of heated tobacco is awash with failure. In 1988, R.J. Reynolds launched 'Premier', cigarette-like sticks with carbon tips that aimed to heat, but not burn, tobacco.[240] The product was disliked by users and regulators alike; users complained that they were difficult to use and had an unpleasant taste, while regulators doubted the legitimacy of claims about their reduced harm.[241] The poor market performance of Premier, alongside opposition from the FDA and AMA, led them to be pulled after less than a year on the US[16] market.[240] Over the next two decades, many similar prototypes were trialled and tested.[243] They all failed. This changed when Philip Morris International launched[17] 'IQOS' in 2014.[242,243]

IQOS are electronic devices that resemble e-cigarettes, but with one key difference: they heat tobacco leaf/sheet rather than nicotine-infused liquid. IQOS has gained incredible popularity in some countries, which has led competing tobacco companies to launch similar electronic heated tobacco products.[242,243] Heated tobacco use is now widespread in Japan and the Republic of Korea; tobacco sticks for these devices constituted 15.8% and 8.0% respectively of each country's tobacco market in 2018.[244] They have also become popular across many countries in mainland Europe.[245]

The rising popularity of heated tobacco products has been accompanied by growing fears[18] about their safety.[246,247] In addition, as with e-cigarettes, debates have erupted about their effect on uptake of smoking, quitting, and relapse. Two 2018 reviews into heated tobacco products indicated that, like e-cigarettes, these devices expose users to fewer toxicants and carcinogens than tobacco smoke.[167,248] However, these reviews showed a lack of evidence into the effect of heated tobacco products on smoking prevalence. Three years of research have

[16] A similar concept was brought back with the brand "Eclipse" in the 1990s. Moreover, Premier received stronger endorsement in the UK.[240]
[17] IQOS initially launched in Japan and Italy.

accumulated since these reviews were released. Therefore, it is important to provide updated reviews into the safety of these products and how they affect smoking prevalence (see Chapter 7).[174]

In addition, to understand the scale of impact heated tobacco products could have on public health, it is important to track the prevalence of heated tobacco use globally. Currently, there is very little research into the use of heated tobacco products outside of East Asia and North America. Comparisons of use across countries will allow me to investigate the effects of different regulatory environments on product choice. For example, heated tobacco product use might become especially popular in countries where e-cigarettes are banned or heavily restricted, because they would be the only reduced risk aerosolised nicotine product on the market. In Chapter 1, I report trends in the prevalence of heated tobacco use in England, a country that already had a well-established e-cigarette market when heated tobacco products launched in 2016.[127,249]

Research Aims

This thesis aims to understand (i) how and why people's choices of nicotine products have changed and (ii) what effects these changes have had on cigarette smoking prevalence and public health. The focus will primarily be on Great Britain. Each chapter will address a specific research aim:

PART A: Popularity and Prevalence

1. **E-cigarette and Heated Tobacco Use in England** — To measure trends in usage of e-cigarette device types, heated tobacco products and e-liquid nicotine concentrations in England from 2016-2020.

2. **Razor-and-Blades Methods of E-cigarette Pricing** — To investigate how e-cigarette manufacturers' use of razor-and-blades pricing strategies for pod devices may affect the nicotine market and public health.

3. **Deteriorating Perceptions of E-cigarettes** — To examine how smokers' perceptions of the relative harm of e-cigarettes compared with cigarettes changed following the outbreak of vaping-associated lung injury.

4. **Rapid Growth in Disposable Vaping** — To estimate recent trends in the prevalence of disposable e-cigarette vaping in Great Britain, overall and across ages, and to explore these trends in the context of other changes in smoking and vaping prevalence.

5. **Prevalence of Nicotine Pouch Use** — To measure (i) the prevalence of nicotine pouch use among adults in Great Britain and (ii) how use differs by age, sex, social grade, country, and smoking and vaping status.

PART B: Cessation and Harm Reduction

6. **E-cigarettes and Varenicline for Quitting Smoking** — To evaluate the effectiveness of adding e-cigarettes to smoking cessation treatment with varenicline and behavioural support.

7 **Heated Tobacco for Reducing Smoking Prevalence** — To synthesise existing evidence on the effectiveness and safety of heated tobacco products for smoking cessation and the impact of heated tobacco products on smoking prevalence.

In the discussion sections, I will summarise the results from these seven studies, placing them in the context of the wider literature. Then, I will draw several conclusions and provide direction for future research.

Part A: Popularity and Prevalence

Methodology: The Smoking Toolkit Study

Introduction

In this section, I will describe the methodology of the Smoking Toolkit Study (STS), the primary data source used in four of the five studies presented in Part A of this thesis. Details that are specific to individual studies, such as analytic choices and variable coding, will be presented in the methods sections of the relevant chapters (Chapters 1, 3, 4, and 5).

The STS is a monthly repeated cross-sectional survey that has provided detailed information on smoking behaviours and nicotine use in England since November 2006. From October 2020 onwards, the survey was expanded to include data across all three nations in Great Britain (Scotland, Wales and England). Participants give informed consent to take part in the study. All participants are at least the age required (≥16 years) to give informed consent under UK Health Research Authority guidelines.[250] From April 2020 and December 2021 inclusive, data were only collected from participants who were ≥18 years-old. All interview methods are carried out in accordance with relevant regulations and guidelines.

The same sampling process is repeated every month. This means that the samples recruited will be similar from one wave to the next wave. This allows for examination of how characteristics of the population are changing over time. The survey recruits approximately 1700 participants per month (2300 from October 2020 onwards, when the study expanded to cover Scotland and Wales).[253] Ethical approval was provided by the UCL Research Ethics Committee (0498/001).

From November 2006 to February 2020 inclusive, interviews with participants were conducted face-to-face with trained interviewers. From April 2020 onwards, interviews were instead conducted via telephone. This change in methodology was required due to the COVID-19 pandemic. Sampling methods differed for the face-to-face and telephone interviews (described below).

Top-line figures on smoking and vaping from the STS are updated each month and displayed online at: https://smokinginengland.info/, https://smokinginwales.info/, and https://smokinginscotland.info/.

Face-to-face

Data from the face-to-face interviews came from Ipsos MORI's *Capibus* omnibus survey. The *Capibus* uses a combination of random-location and quota sampling. When selecting households for interview, the country is split into output areas, each with ~300 households (the lowest level of locality used for the Census). These output areas are stratified by region and demographic characteristics, before being randomly selected for inclusion on the interview list. Interviews are conducted in these selected areas until quotas based on working status, age, and gender are met. In order to reach quotas, interviewers have flexibility on the types of accommodation they approach. For instance, if there is a lack of young adults being recruited, interviewers may target flats and student accommodation rather than large houses. Potential participants are first approached via a knock on the door or ring of the doorbell. If they agree to participate, computer assisted personal interviewing (CAPI) is performed by skilled interviewers inside the home of participants. Only one person is interviewed per home. Ipsos MORI do not report on non-response rates because these are uninformative when homes within output areas are selected by interviewers in order to reach quotas rather than at random.

Telephone

Data from the telephone interviews came from Ipsos MORI's *CATI* omnibus survey. In the *CATI*, approximately 40% of participants are sampled from landline random digit dialling (RDD), 30% from mobile RDD, and 30% from targeted mobile phone sampling. For landline RDD, each eligible landline telephone number in Great Britain has a probability of being selected for interview proportional to the population density of the given postcode sector. Mobile phone sampling uses a similar method, except the probability of a number being selected is proportional to the market share of the given mobile network provider (rather than based on location). Targeted mobile sampling finds potential participants using Ipsos's data suppliers which collect mobile phone numbers from warrant cards, customer feedback forms and data collaborators. These data sources have additional variables about individuals including age, location, sex, income, and other demographic characteristics, which allows Ipsos to oversample from groups that were underrepresented in the sample recruited from landline RDD and mobile RDD. All individuals selected during targeted mobile sampling opted in to allow their number to be called by third parties.

Weighting

Survey weights are constructed separately for each wave, using raking to adjust data so that the sample matches the demographic profile of the country in terms of sex, age, region, social grade, and working status.[251] This profile is determined each month by combining data from the UK Census, the Office for National Statistics mid-year estimates, and the annual National Readership Survey.

Validation

Comparisons with other national surveys and with cigarette sales data show that the STS provides estimates that are broadly representative with respect to key demographic and smoking-related variables.[252]

To examine whether there were differences in samples recruited face-to-face versus via telephone, a parallel wave of data was collected from both the *Capibus* and *CATI* in March 2022. A comparison of data from this parallel wave showed that the profile of participants recruited from both modalities was generally similar.[254] However, the sample size from the parallel wave of data collection was not large enough to rule out moderate differences between populations represented by samples from face-to-face versus telephone interview and sampling methods. Nonetheless, each individual study reported in this thesis only used data from either face-to-face or from telephone interviews, never both together (thus, trends over time reported here are not affected by the change in modality).

1. E-cigarette and Heated Tobacco Use in England

Abstract

Full Title: Trends in the use of e-cigarette device types and heated tobacco products from 2016 to 2020 in England.

Background: This study examined use trends of e-cigarette devices types, heated tobacco products (HTPs) and e-liquid nicotine concentrations in England from 2016-2020.

Methods: Data were from a representative repeat cross-sectional survey in England. Bayesian logistic regression was used to estimate proportions and 95% credible intervals (CrIs).

Results: Of 75,355 participants recruited from 2016-2020, 5.3% were currently using e-cigarettes or HTPs, with the majority (98.7%) using e-cigarettes. Among e-cigarette users, 53.7% (CrI=52.0%-55.1%) used tank devices, 23.7% (22.4%-25.1%) mods, 17.3% (16.1%-18.4%) pods, and 5.4% (4.7%-6.2%) disposables. Tanks were the most widely used device type throughout 2016-2020. Mods were second until 2020, when pods overtook them. HTP use remains rare among all e-cigarette/HTP users (3.4% in 2016 versus 4.2% in 2020), whereas JUUL use rose from 3.4% in 2018 to 11.8% of e-cigarette/HTP users in 2020. Across years, nicotine concentrations of ≤6mg/ml were most widely (41.0%; 39.4%-42.4%) and ≥20mg/ml least widely used (4.1%; 3.4%-4.9%). Relative to e-cigarette/HTP users who currently smoked, those who were ex-smokers were more likely to use mod and tank e-cigarettes, but less likely to use pods, disposables, JUUL and HTPs.

Conclusions: Despite growing popularity of pods and HTPs worldwide, refillable tank e-cigarettes remained the most widely used device type by adults in England up to 2020.

Status: Published in Scientific Reports (DOI: 10.1038/s41598-021-92617-x).

Introduction

As I introduced in the literature review, the nicotine market is rapidly changing, with frequent launches of new products. Most of this innovation is occurring within two categories: e-cigarettes and heated tobacco products, which together can be referred to as "heated aerosolized nicotine delivery systems" (or "HANDS").[19] Over the past decade, HANDS — principally e-cigarettes — have eclipsed NRT as the most widely used aids for stopping smoking in England.[132] E-cigarettes encompass a variety of different devices, from bulky mod e-cigarettes to small cigarette-shaped "cigalikes". HANDS can vary considerably in their

[19] I define heated aerosolized nicotine delivery systems (HANDS) as handheld devices that heat either nicotine-infused liquid or tobacco sticks, producing an aerosol that can be inhaled.

potential to produce toxicants and carcinogens,[198] delivery of nicotine,[234,255] and effectiveness in helping people stop smoking combustible cigarettes.[232,236,256] It is therefore important to explore how the proportion of people using different device types and nicotine concentrations is changing, within a regulatory environment that may incentivise or discourage use of certain products. In this study, I explore trends in the use of different e-cigarette device types and heated tobacco products in England, from 2016 to 2020.

E-cigarettes

In the literature review we saw that e-cigarette vaping is likely to be much less harmful to health than cigarette smoking, since users are exposed to much lower levels of toxicants and carcinogens.[191] However, public health bodies have differing attitudes towards the overall impact of e-cigarettes on public health; some emphasise their potential use for smoking cessation while others highlight risks to young people who do not smoke cigarettes.[257] The UK has tried to take a balanced policy approach that attempts to maximise the use of e-cigarettes for smoking cessation, while minimising risks from youth use.[258] Evidence from randomised controlled trials[232] and observational studies[132,259] indicates that nicotine e-cigarettes can increase the likelihood that people will succeed in their attempts to stop smoking cigarettes. But their effectiveness for smoking cessation may depend on the specific device used. Here, I categorise[20] e-cigarettes into four device types: disposables, tanks, mods and pods.

Disposable cigarette-shaped devices, also known as cigalikes, were the first type of e-cigarette to enter the market in England. Compared with later devices, these tended to deliver less nicotine and, as a result, may be less effective at helping people quit smoking.[234,256] After the completion of this study in 2020, a new form of disposable e-cigarette entered markets throughout the world. I will discuss this new form of disposable e-cigarette in Chapter 4.

Tank e-cigarettes have a rechargeable battery and a tank that can be replenished with bottled e-liquid. These refillable tank devices tend to have a fixed power output, so the temperature to which e-liquid is heated remains relatively constant. They can deliver a similar amount of nicotine to cigarettes and satisfy cravings to smoke.[260] Two recent randomised

[20] This is just one of a number of different categorisations that could be made, each with their own strengths and limitations. For instance, distinctions are often made between systems with open or closed e-liquid tanks, or between first-, second- and third- generation devices.

controlled trials demonstrated the effectiveness of tank e-cigarettes for smoking cessation. The first found that they almost doubled the rate of successfully quitting smoking after 12 months when compared with nicotine replacement therapy.[236] The second found that, when used in conjunction with nicotine patches, tank e-cigarettes increased abstinence when compared to nicotine patches used alone or with placebo e-cigarettes.[261]

Mod ("modified" or "modular") e-cigarettes are assembled by users from a variety of parts, such as batteries, coils, and mouthpieces. They are also refillable and rechargeable; however, they often have variable power output, which allows vapers to adjust the temperature to which their e-liquid is heated and, thus, the amount of vapour and nicotine they inhale. This can be problematic because hotter e-liquid makes the production of carcinogenic carbonyls, like formaldehyde, more likely.[198] However, as mentioned in the literature review, most users find the aerosol produced at these hotter temperatures to be aversive — creating a so-called "dry puff" — so are unlikely to vape with such high power settings.[199]

Pod devices are the most recent type of e-cigarette to enter the market in England. These are small, low powered, rechargeable e-cigarettes that use disposable cartridges (or "pods") full of e-liquid. Because of their low power output, the nicotine concentration in pod e-liquid usually needs to be much higher than in mod devices to produce the same amount of nicotine per puff.[262] They produce less vapour and lower carbonyl yields than higher powered devices.[263] In this study, I also look specifically into use of one brand of pod e-cigarettes: JUUL. JUUL, a manufacturer of pod e-cigarettes, received intense scrutiny because of the rapid growth in popularity of their devices in the US, especially among young people.[264] Unlike most e-liquids which contain freebase nicotine, JUUL cartridges use a nicotine salts formulation, which has a pH that is more similar to the extravascular fluid in the lung but with similar bioavailability. This allows users to vape much higher concentrations of nicotine without experiencing irritation to the throat, which may explain their popularity.[265] JUUL launched in England in the summer of 2018.[266]

In this study, I explore how the number of people in England using disposable, tank, mod, and pod (including JUUL specifically) devices has changed from 2016 to 2020.

Nicotine concentration

E-cigarette liquid ("e-liquid") usually contains nicotine alongside propylene glycol, glycerol, and flavourings. The amount of nicotine that vapers receive from their e-cigarette per puff depends on the nicotine concentration of their e-liquid, features of the device, such as power output and wick material, and the duration and strength with which they puff. Experimental evidence shows that people self-titrate their nicotine consumption when vaping, such that those who use low nicotine concentration e-liquids tend to puff on their device more often and for longer in order to achieve their desired nicotine intake and, as a result, inhale a greater volume of aerosol.[267] Moreover, people who use variable power devices can raise the temperature of their device, which increases e-liquid consumption and formaldehyde production.[267,268] Therefore, it is important to track how the popularity of various nicotine concentrations is changing in England, within the context of EU TPD regulation that limits nicotine concentration in e-liquid to ≤20mg/ml.

Heated tobacco products

Another form of HANDS with growing popularity globally are heated (or "heat-not-burn") tobacco products,[244] such as IQOS by Philip Morris International. These are handheld devices that heat tobacco to a high enough temperature to produce a nicotine-infused aerosol, and intended to be too low to cause combustion.[248] Unlike e-cigarettes, heated tobacco products contain tobacco sheet/leaf rather than extracted nicotine in the form of a liquid. Because of this, their flavour might closely mimic that of cigarette smoke, which could make them more appealing to smokers trying to quit.[269] However, it is currently uncertain whether heated tobacco products help smokers succeed in their attempts to quit cigarettes.[174] In Chapter 7, I propose a systematic review to evaluate their safety, effectiveness for smoking cessation, and impact on smoking prevalence.

Nonetheless, it is important to know how widely used these products are. The more popular they are, the larger their potential impact on population health. Before their entrance into the UK market in late 2016, heated tobacco products had become very popular in Japan and South Korea.[244] Yet, at least initially, the use of heated tobacco products was rare in England.[167] Here, I explore whether the prevalence of heated tobacco product use in England changed since 2017.

Frequency of use

The effectiveness of e-cigarettes for smoking cessation likely depends on how frequently smokers use their e-cigarette: those who use e-cigarettes daily have higher odds of subsequently quitting smoking when compared with less frequent users.[270] Therefore, I also explore how use of different devices and nicotine concentrations vary between daily and non-daily HANDS users.

Differences by smoking status

Vapers who also smoke (54%) might use different types of e-cigarettes than those who have quit smoking (40%) or never smoked (6%).[249] For instance, devices that are less effective for smoking cessation may be used less often by ex-smokers, because smokers who use them would be unlikely to transition to sole e-cigarette use (unless ex-smokers gradually transition to products that deliver less nicotine after they having stopped smoking cigarettes for some time). In this study, I investigate whether HANDS users who also smoke use different e-cigarette device types, heated tobacco products and nicotine concentrations than those who are former or never smokers.

Research aims

To summarise, I aim to assess annual trends from 2016 to 2020 in England in:

- The proportion of HANDS users who use different types of e-cigarette devices or heated tobacco products.
- The proportion of e-cigarette users who use e-liquids of various nicotine concentrations.

I also aim to compare how use of these products differs between (i) daily and non-daily HANDS users, and (ii) HANDS users who are smokers, ex-smokers and never smokers.

Methods

Design

Data came from the Smoking Toolkit Study in England. Details of the survey design are provided in the previous section.

Study sample

Adults aged ≥16 years who reported that they were currently using e-cigarettes or heated tobacco products. Data were included from July 2016, the month where detailed e-cigarette usage characteristics were first recorded, through February 2020 (latest data available at the point of analysis). Questions about use of JUUL and heated tobacco products were added to the survey in July 2018 and December 2016, respectively.

Measures

Type of e-cigarette or heated tobacco product

Participants were asked a series of questions about whether they currently use e-cigarettes, JUUL or heated tobacco products to cut down the amount they smoke, in situations when they are not allowed to smoke, to help them stop smoking, or for any other reason at all. Their responses were categorised as follows:

- E-cigarette user — "Electronic cigarette"
- Heated tobacco product user — "heat-not-burn cigarette (e.g. IQOS with HEETS, heatsticks)"
- JUUL user — "JUUL"

E-cigarette (non-JUUL) users were asked a follow-up question about the specific device(s) they used: "Which of the following do you mainly use…?" They could respond:

- Disposable — "A disposable e-cigarette or vaping device (non-rechargeable)"
- Tank — "An e-cigarette or vaping device with a tank that you refill with liquids (rechargeable)"
- Mod — "A modular system that you refill with liquids (you use your own combination of separate devices: batteries, atomizers, etc.)"
- Pod — "An e-cigarette or vaping device that uses replaceable pre-filled cartridges (rechargeable)"

Frequency of use

HANDS users were asked: "How many times per day on average do you use your nicotine replacement product or products?" Those who reported using their e-cigarette or heated tobacco product at least once a day were classified as daily users. All others were considered non-daily users.

Nicotine concentration

E-cigarette users (non-JUUL) were asked: "Does the electronic cigarette or vaping device you mainly use contain nicotine?" They could respond "yes", "no", or "don't know". Participants who reported using a non-JUUL e-cigarette with nicotine were asked: "What strength is the e-liquid that you mainly use in your electronic cigarette or vaping device?" They could respond:

- "6mg/ml (~0.6%) or less"
- "7mg/ml (~0.7%) to 11mg/ml (~1.1%)"
- "12mg/ml (~1.2%) to 19mg/ml (~1.9%)"
- "20mg/ml (~2.0%) or more"
- "Don't know"

Smoking status

Participants were asked which of the following best applied to them:

a) "I smoke cigarettes (including hand-rolled) every day"
b) "I smoke cigarettes (including hand-rolled), but not every day"
c) "I do not smoke cigarettes at all, but I do smoke tobacco of some kind (e.g. pipe, cigar or shisha)"
d) "I have stopped smoking completely in the last year"
e) "I stopped smoking completely more than a year ago"
f) "I have never been a smoker (i.e. smoked for a year or more)"

Those who reported currently smoking cigarettes or tobacco of another kind (responses a-c) were considered smokers, and those who reported stopping smoking within the last year or more than a year ago (responses d-e) were considered ex-smokers. All others (response f) were considered never-smokers.

Socio-demographic characteristics

Age, gender, ethnicity (white, non-white), and occupation-based social grade (C2DE includes manual routine, semi-routine, lower supervisory, and long-term unemployed; ABC1 includes managerial, professional and upper supervisory occupations) were recorded.[272]

Analysis

Analytic strategy

I ran the analysis in R and Stan.[272,273] The pre-registered analysis plan is available on the Open Science Framework (https://osf.io/57fvd/). Bayesian inference was used throughout, which allowed me to (i) report the relative plausibility of parameter values given the model and data and (ii) include weakly informative priors, which regularise estimates and thus reduce the risk of overfitting.[274] Priors were selected using prior predictive simulation (details available on https://osf.io/57fvd/).[275] The 95% credible intervals (95%CrIs) represent highest posterior density intervals. I only included data from complete cases across variables included in each model. Survey weights were applied to calculate the overall prevalence of e-cigarette use among adults. All other analyses were unweighted, as they were calculated from a small subsample of the population (current HANDS users).

Device type

I estimated the total proportion of HANDS users who reported using each different device type. To explore how device usage changed from 2016 to 2020, I constructed logistic regression models with year of survey as an explanatory variable. From these models, I reported the proportion of HANDS users who used each device type in each year, alongside 95%CrIs. I then stratified by frequency of use, to compare relative risk (RR) of use of each device type between daily and non-daily users, excluding participants who used combinations of device types or NRT.

Nicotine concentration

I estimated the total proportion of e-cigarette users who reported using each of the different nicotine concentrations listed in the measures section. I again constructed logistic models with year of survey as an explanatory variable. Yearly estimates of the proportion of e-cigarette users who used each nicotine concentration were reported alongside 95%CrIs. I then stratified by frequency of use, to compare daily vs. non-daily use of each nicotine concentration. Finally, I presented the proportion of users of each device type who used each nicotine concentration of e-liquid, excluding participants who used combinations of device types.

Difference by smoking status

To test whether there were differences in device type or nicotine concentration use between smokers, ex-smokers and never smokers, I constructed a set of logistic regression models for each outcome including smoking status as an explanatory variable.

Results

Of the 75,355 adults who responded to the Smoking Toolkit Study between August 2016 and February 2020, 3,986 (unweighted = 5.29%, weighted = 5.53%; 95%CrI = 5.45-5.62%) reported currently using e-cigarettes or heated tobacco products. Of these, 3,786 (95.0%) were complete cases on all variables of interest. Socio-demographic information for users of each device type is shown in Table 1.1.

Table 1.1. Sample characteristics by type of device used (*n* = 3,786). The percentage of HANDS[a] users who used each different device type are shown in brackets.

	Disposable	Pod	Tank	Mod	JUUL[b]	HTP[c]
Age (Years)						
16-24	30 (5.1%)	82 (14.0%)	300 (51.2%)	126 (21.5%)	31 (12.3%)	8 (1.6%)
25-34	33 (4.0%)	94 (11.5%)	414 (50.7%)	225 (27.5%)	13 (3.4%)	14 (1.9%)
35-44	40 (5.6%)	112 (15.8%)	343 (48.2%)	163 (22.9%)	4 (1.4%)	19 (3.1%)
45-54	34 (4.5%)	122 (16.1%)	397 (52.2%)	152 (20.0%)	10 (3.1%)	14 (2.1%)
55-64	30 (4.7%)	123 (19.3%)	309 (48.6%)	129 (20.3%)	9 (3.1%)	10 (1.8%)
65+	34 (7.3%)	102 (22.0%)	203 (43.8%)	76 (16.4%)	20 (9.3%)	12 (2.9%)
Gender						
Men	116 (5.3%)	313 (14.3%)	1087 (49.6%)	510 (23.3%)	56 (5.7%)	37 (1.9%)
Women	85 (4.8%)	323 (18.1%)	880 (49.2%)	362 (20.3%)	34 (4.4%)	41 (2.6%)
Ethnicity						
White	177 (4.9%)	569 (15.7%)	1823 (50.2%)	807 (22.2%)	68 (4.3%)	63 (2.0%)
Other	24 (7.0%)	64 (18.7%)	145 (42.3%)	61 (17.8%)	22 (12.2%)	14 (4.6%)
Social Grade						
ABC1	83 (4.1%)	337 (16.5%)	1008 (49.3%)	445 (21.8%)	66 (7.1%)	37 (2.1%)
C2DE	118 (6.1%)	299 (15.4%)	964 (49.6%)	427 (22.0%)	24 (2.9%)	41 (2.4%)

a. Heated aerosolized nicotine delivery systems (HANDS) include e-cigarettes and heated tobacco products.

b. The denominator used to calculate percentages in this column was the number of HANDS users surveyed from July 2018 — the month in which JUUL use began being recorded — to February 2020 (*n* = 1,760). Note that the columns for disposables, tanks, mods, and pods do not sum to 100% because they are aggregated across all waves, including those where JUUL and HTP were recorded.

c. The denominator used to calculate percentages in this column was the number of HANDS users surveyed from December 2016 — the month in which heated tobacco products (HTPs) use began being recorded — to February 2020 (*n* = 3,520).

Device type

Overall, e-cigarettes were used by 98.7% (95% CrI = 98.4%-99.0%) of HANDS users and heated tobacco products by 2.2% (1.8%-2.7%). Among e-cigarette users, 53.7% (52.0%-55.1%) used tank devices, 23.7% (22.4%-25.1%) used mods, 17.3% (16.1%-18.4%) used pods, and 5.4%

(4.7%-6.2%) used disposables. JUUL e-cigarettes were used by 5.1% (4.1%-6.1%) of HANDS users.

Figure 1.1 shows trends in the prevalence of usage of different device types among from 2016 to 2020. In general, use of different device types remained stable over time, with tank e-cigarettes consistently the most widely used device type. Mod e-cigarettes were the second most commonly used device type until 2020, when pods overtook them. Use of JUUL rose from 3.4% (2.1%-5.3%) of HANDS users in 2018 to 11.8% (7.8%-17.6%) in 2020. Heated tobacco product use remained rare — with 3.4% (1.2%-8.0%) of HANDS users using them in 2016 versus 4.2% (2.2%-7.5%) in 2020. Relative to non-daily e-cigarette users, daily users were more likely to use tank devices, equally likely to use mods, but less likely to use disposables or pods (Table 1.2). HANDS users who currently smoked were less likely than those who never smoked to use JUUL and heated tobacco products, but more likely to use pods. Conversely, they were less likely to use mod and tank e-cigarettes than ex-smokers, but more likely to use pods, disposables, JUUL and heated tobacco products.

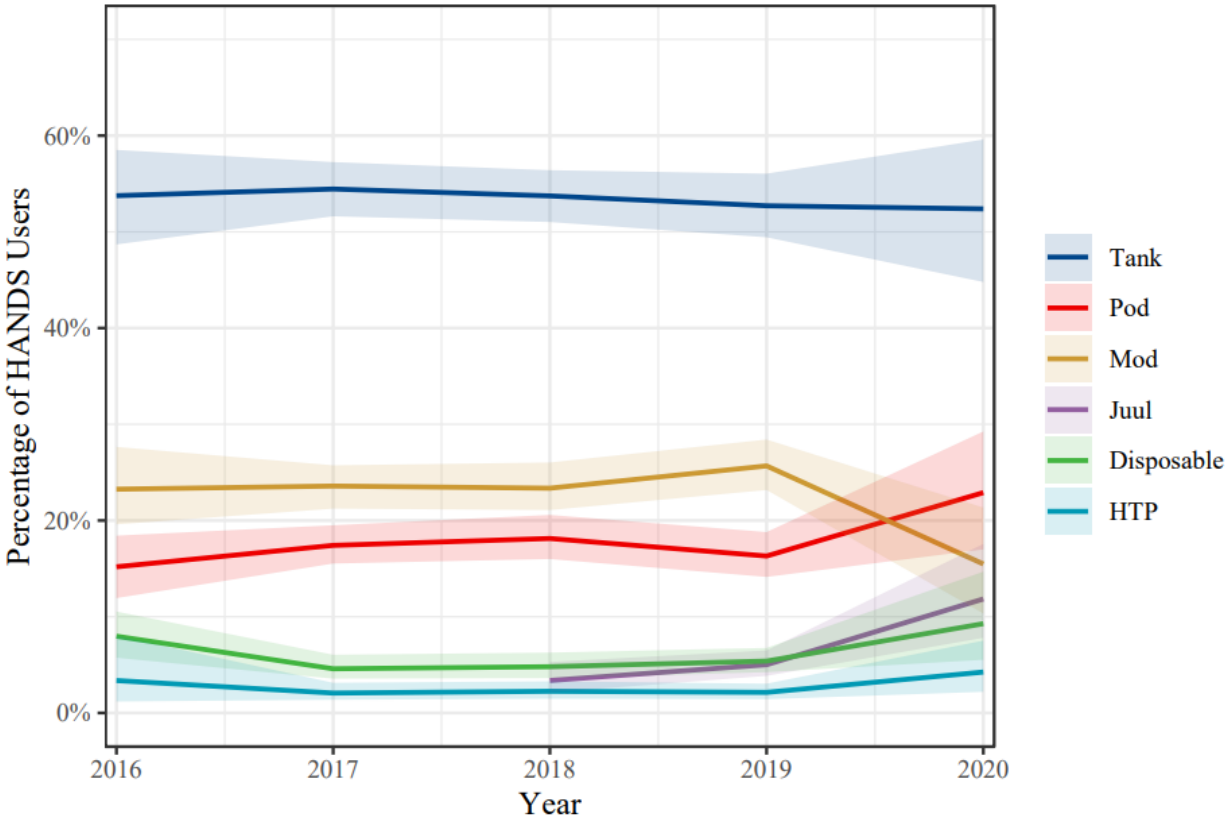


Figure 1.1. Use of different e-cigarette device types and heated tobacco product use among adult heated aerosolized nicotine delivery system (HANDS) users in England from 2016 to 2020. Shaded bands represent 95% CrIs.

Table 1.2. Device type use by frequency of use and smoking status among people who reported using HANDS[a].

		Disposable (95% CrI)	Pod (95% CrI)	Tank (95% CrI)	Mod (95% CrI)	JUUL[b] (95% CrI)	HTP[c] (95% CrI)
Frequency of use[d]							
Non-daily (N = 938)	%	6.0 (4.5-7.6)	21.5 (18.9-24.4)	48.9 (45.8-51.9)	23.3 (20.8-26.1)	-	-
	RR	Ref	Ref	Ref	Ref	-	-
Daily (N = 2337)	%	4.1 (3.4-4.9)	14.3 (12.9-15.7)	57.4 (55.4-59.2)	24.1 (22.5-25.6)	-	-
	RR	0.70 (0.48-0.92)	0.67 (0.57-0.78)	1.18 (1.09-1.25)	1.03 (0.91-1.17)	-	-
Smoking status							
Smoker (N = 2354)	%	6.1 (5.1-7.3)	19.3 (17.7-20.9)	51.0 (48.9-53.0)	22.5 (21.0-24.3)	4.3 (3.2-5.8)	2.6 (2.0-3.3)
	RR	Ref	Ref	Ref	Ref	Ref	Ref
Never smoker (N = 264)	%	6.0 (3.5-10.2)	13.7 (9.8-18.8)	53.1 (47.3-59.0)	28.1 (22.5-34.6)	26.8[e] (20.2-34.6)	4.9 (2.9-8.3)
	RR	1.02 (0.52-1.65)	0.72 (0.50-0.97)	1.04 (0.92-1.16)	1.26 (0.99-1.57)	6.32 (3.89-8.82)	1.96 (0.95-3.05
Ex-smoker (N = 1364)	%	2.6 (1.9-3.7)	14.3 (12.6-16.3)	58.1 (55.1-60.9)	25.0 (22.6-27.4)	1.6 (0.9-2.9)	1.1 (0.6-1.7)
	RR	0.44 (0.28-0.61)	0.75 (0.63-0.86)	1.14 (1.06-1.21)	1.11 (0.98-1.26)	0.39 (0.16-0.67)	0.43 (0.21-0.65)

a. Heated aerosolized nicotine delivery systems (HANDS) include e-cigarettes and heated tobacco products. Percentages are unweighted.

b. Use of JUUL was recorded from July 2018 (*n* = 1,760). Frequency could not be assessed as all JUUL users had used combinations of products.

c. Use of heated tobacco products (HTPs) was recorded from December 2016 (*n* = 3,520). Frequency could not be assessed as all but one HTP user used combinations of products.

d. Participants who used combinations of products or NRT were excluded.

e. The high prevalence of JUUL use among never smoking HANDS users was primarily driven by data from a single month in a specific local authority area. Therefore, it likely represents a localised effect.

Nicotine concentration

The most widely used nicotine concentration was ≤6mg/ml, used by 41.0% (39.4%-42.4%) of e-cigarette users. This was followed by 12-19mg/ml used by 23.4% (21.8%-24.9%), 7-11mg/ml by 13.4% (12.0%-14.6%), no nicotine by 14.2% (13.2%-15.1%), and ≥20mg/ml by 4.1% (3.4%-4.9%). The remaining 3.2% (2.6%-3.8%) did not know. Figure 2 shows trends in use of different concentrations from 2016 to 2020. Use of different nicotine concentrations remained relatively stable, with ≤6mg/ml being the most widely used concentration across all years. Relative to non-daily e-cigarette users, daily users were less likely to use non-nicotine e-liquid and more likely to use nicotine concentrations of ≤6mg/ml and 12-19mg/ml (Table 1.3). Use of non-

nicotine e-liquid was more common among users of disposable e-cigarette than of other device types. Mod and tank users were more likely to use ≤6mg/ml nicotine concentration than disposable e-cigarette users. Relative to never smokers, smokers and ex-smokers were less likely to use non-nicotine e-liquid and nicotine concentrations of ≥20mg/ml.

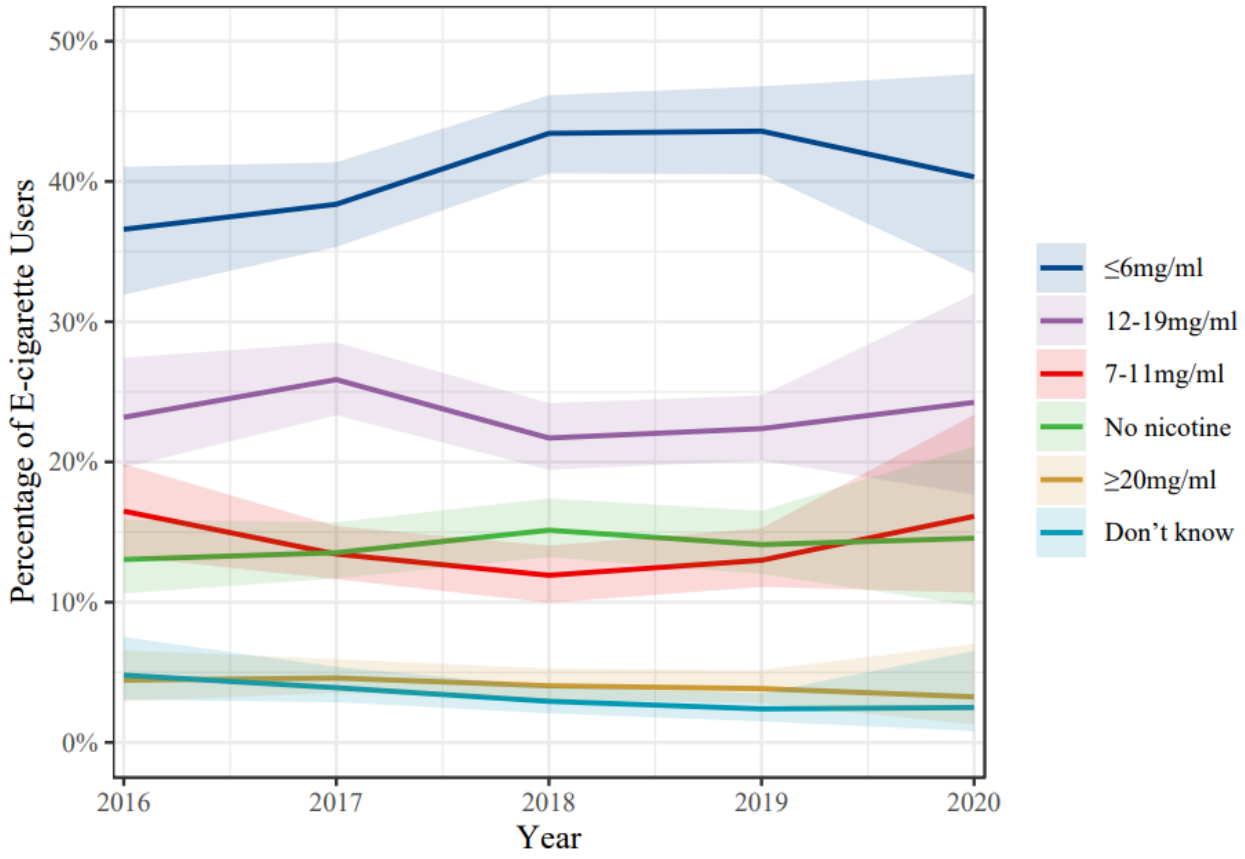


Figure 1.2. Nicotine concentration used in e-cigarettes by adult e-cigarette users in England from 2016 to 2020. Shaded bands represent 95% CrIs.

Table 1.3. Nicotine concentration used by frequency of use, device type and smoking status among e-cigarette users[a].

		No nicotine (95% CrI)	≤6mg/ml (95% CrI)	7-11mg/ml (95% CrI)	12-19mg/ml (95% CrI)	≥20mg/ml (95% CrI)	Don't know (95% CrI)
Frequency of use[b]							
Non-daily (N = 938)	%	18.4 (16.3-20.5)	37.7 (35.0-40.6)	14.9 (13.1-16.9)	17.7 (15.7-19.8)	4.5 (3.5-5.9)	5.4 (4.3-6.7)
	RR	Ref	Ref	Ref	Ref	Ref	Ref
Daily (N = 2337)	%	12.1 (11.0-13.4)	42.5 (40.6-44.2)	12.6 (11.4-14.0)	26.0 (24.4-27.6)	4.0 (3.3-4.8)	2.3 (1.8-3.0)
	RR	0.66 (0.56-0.77)	1.13 (1.04-1.24)	0.85 (0.73-0.99)	1.47 (1.27-1.66)	0.89 (0.59-1.16)	0.44 (0.31-0.59)
Device type							
Disposable (N = 153)	%	21.9 (16.6-28.5)	31.3 (24.8-38.8)	16.4 (11.1-22.9)	20.4 (14.9-27.1)	1.4 (0.4-3.6)	7.4 (4.1-12.4)
	RR	Ref	Ref	Ref	Ref	Ref	Ref
Pod (N = 538)	%	15.2 (12.4-18.5)	30.7 (26.2-35.3)	16.0 (13.2-19.1)	26.3 (22.7-30.3)	5.8 (4.1-7.9)	5.0 (3.4-7.2)
	RR	0.71 (0.49-0.96)	0.99 (0.73-1.24)	1.00 (0.58-1.40)	1.31 (0.90-1.78)	5.00 (1.28-11.69)	0.71 (0.32-1.20)
Tank (N = 1801)	%	13.8 (12.3-15.4)	43.2 (41.1-45.6)	12.8 (11.4-14.4)	23.4 (21.8-25.3)	3.8 (3.0-4.8)	2.7 (2.0-3.5)
	RR	0.64 (0.46-0.86)	1.39 (1.08-1.71)	0.80 (0.54-1.13)	1.17 (0.82-1.55)	3.27 (0.82-7.02)	0.38 (0.18-0.61)
Mod (N = 783)	%	11.1 (8.9-13.5)	50.0 (46.9-53.2)	10.6 (8.2-13.1)	22.8 (19.9-26.1)	4.0 (2.9-5.4)	1.5 (0.8-2.6)
	RR	0.52 (0.36-0.73)	1.61 (1.27-2.02)	0.67 (0.44-0.94)	1.14 (0.77-1.53)	3.45 (0.59-8.08)	0.23 (0.10-0.46)
Smoking status							
Smoker (N = 2266)	%	14.5 (13.1-16.2)	39.9 (38.0-41.9)	15.2 (13.9-16.6)	21.0 (19.4-22.9)	3.8 (3.1-4.7)	4.4 (3.7-5.2)
	RR	Ref	Ref	Ref	Ref	Ref	Ref
Never smoker (N = 250)	%	23.4 (18.1-30.1)	40.3 (33.5-47.4)	9.3 (6.0-13.6)	18.0 (13.3-23.8)	7.0 (4.3-11.2)	2.8 (1.2-5.8)
	RR	1.62 (1.17-2.02)	1.01 (0.83-1.18)	0.62 (0.40-0.90)	0.86 (0.61-1.10)	1.88 (1.04-2.87)	0.68 (0.19-1.23)
Ex-smoker (N = 1319)	%	11.8 (10.2-13.7)	43.2 (40.7-45.8)	10.8 (9.4-12.5)	28.4 (26.4-30.8)	4.2 (3.3-5.3)	1.5 (0.9-2.4)
	RR	0.82 (0.68-0.96)	1.08 (1.01-1.18)	0.72 (0.58-0.83)	1.35 (1.19-1.51)	1.10 (0.81-1.49)	0.36 (0.19-0.54)

a. Percentages are unweighted.

b. Participants who used combinations of products or NRT were excluded.

Discussion

Tank e-cigarettes were consistently the most used device type in England from 2016 to 2020 among adults who used HANDS. Mod e-cigarettes were the second most widely used device type until 2020, where pod e-cigarettes overtook them. JUUL use rose year-on-year from 2018 (when it was first assessed) to the extent that JUUL was used by 1 in 10 people who use HANDS in 2020. Heated tobacco product use remained relatively rare (3.4% of HANDS users in 2016 versus 4.2% in 2020). Compared with people who vaped daily, non-daily vapers were less likely to use tank e-cigarettes and more likely to use disposables. Relative to HANDS users who were current smokers, those who were ex-smokers were more likely to use mod and tank e-cigarettes, but less likely to use pods, disposables, JUUL and heated tobacco products. Additionally, JUUL and heated tobacco product use was more prevalent among HANDS users who were never smokers than ex- or current smokers. Across all years, most e-cigarette users (>80%) used e-liquid that contained nicotine, but lower nicotine concentrations (≤6mg/ml) were most common. Daily vapers were less likely than non-daily vapers to use non-nicotine e-liquid. Relative to HANDS users who were ex- or current smokers, those who had never smoked were more likely to use both non-nicotine and high nicotine (≥20mg/ml) e-liquid.

Comparison of these results with previous studies highlights some differences between England and other countries.[276–278] Tank e-cigarettes remained the most commonly used device type in England up until 2020, while pod e-cigarettes became the most popular in the US — driven by the rise in JUUL use.[264] In the US, JUUL was widely and successfully marketed but advertising was much more limited in England by EU TPD regulations.[264] Pod e-cigarette and JUUL vaping rose only slightly in England from 2019 to 2020. These differences could have arisen from the 20mg/ml cap on nicotine concentration in e-cigarettes in the EU, which may undermine how pod e-cigarettes with nicotine salts allow users to vape high nicotine concentrations without irritation to the throat.[265] However, technological developments may have changed this. JUUL have altered their products for the EU market such that each puff generates a greater volume of aerosol than equivalent products in America. Thus, products in both markets provide similar amounts of nicotine per puff despite using e-liquids with different nicotine concentrations (18mg/ml in EU versus 58 mg/ml in US).[279] This change, enacted in summer 2019, may be one factor that has contributed to the recent increased prevalence of JUUL use in England. Further monitoring is required.

Use of heated tobacco products remained relatively rare in England from 2016 to 2020, unlike in Japan and South Korea where these products have become increasingly popular.[243,244] As I will discuss later, this difference may be a due to England already having a well-established e-cigarette market when heated tobacco products launched in the country.

The data show that disposable e-cigarette vaping remained rare in England up until 2020, which is possibly a result of these old generation cigalike-style disposables having poor nicotine delivery compared with other e-cigarettes.[234] Since 2020, a new type of disposable e-cigarette has entered markets across the world, which has a similar USB drive shape to pod devices.[280] These products use nicotine salts at similar concentrations to pod e-cigarettes like JUUL, and user reports suggest they may provide a stronger 'hit' than other disposable products.[280] This innovation may explain recent data showing an increase in use of disposable products among US youths.[281] In Chapter 4, I will show more recent data showing a similar rise in disposable vaping between 2021 to 2022 in Great Britain — especially among young adults.

As may be expected due to EU TPD regulation, use of high nicotine concentrations (≥20mg/ml) in England was rare. In fact, low (≤6mg/ml) nicotine concentrations were most popular.[282] Although greater use of low nicotine concentrations may appear to benefit public health, the opposite may be the case. People tend to self-titrate their e-cigarette use to reach a desired nicotine level.[267,268] Thus, users of low nicotine concentration e-liquid may use their device more frequently, with longer puffs, and at hotter temperatures than those using high nicotine concentration e-liquids,[283] which could increase their risk of harm.

I found differences in product use according to the frequency with which people vape. Relative to non-daily users, daily e-cigarette users were less likely to use disposable devices and more likely to use tanks. This could indicate that people who try disposable e-cigarettes are unlikely to transition to more frequent use, possibly a result of them being less satisfying than other e-cigarettes.[284] Non-daily e-cigarette users were more likely to use non-nicotine e-cigarettes than daily users. This is unsurprising given that nicotine is the primary dependence-inducing compound in e-cigarettes. So, use of non-nicotine products is unlikely to lead to dependence or more frequent use.

There were also differences by smoking status. Use of pod, disposable, and JUUL e-cigarettes and heated tobacco products was less common among HANDS users who were ex-smokers than current smokers. This might indicate that smokers who use these devices are

less likely to quit smoking cigarettes. However, given the cross-sectional design of this study, it is difficult to infer how effective these products are for smoking cessation from these associations. Prevalence of JUUL and heated tobacco product use was higher among HANDS users who were never smokers than among those who were ex- or current smokers. However, this high prevalence was primarily driven by data from a single month in a specific local authority area, suggesting the difference may arise from a localised effect. Compared with current and ex-smokers, never smokers who used HANDS were more likely to use non-nicotine e-liquid. This is consistent with previous results showing minimal signs of nicotine dependence in e-cigarette users who have never smoked.[80] Never smokers who used HANDS were relatively more likely to use high (≥20mg/ml) nicotine concentrations, but the absolute rate of high nicotine concentration use in this group was low (7.0%). Moreover, the size in this subgroup was small (N = 14).

This study benefitted from using a representative sample of the population in England, having a pre-registered analysis plan, and measuring detailed information on participants' usage of e-cigarettes, heated tobacco products and cigarettes. However, there were several limitations. Firstly, participants who used combinations of HANDS device types and/or NRT (N = 377) were not asked about the nicotine concentration and frequency of use for each product separately, so they had to be excluded from some analyses. Secondly, there were less data for 2016 and 2020 than for other years, which meant that there was greater uncertainty around prevalence estimates. Results for these years may also differ from other years if product use varies across seasons, as estimates were calculated on data from only a few months in the year. In an unplanned sensitivity analysis, I found similar proportions of vapers using each product across all months, suggesting seasonality had little effect on results. Thirdly, there were very few participants surveyed among some subgroups (e.g. HANDS users who had never smoked), which meant there was large uncertainty around prevalence estimates. Fourth, I included Bayesian 95% credible intervals, which possess the properties that researchers often misinterpret frequentist compatibility intervals as having (i.e. there is a 95% probability that the true parameter value lies within the 95% credible interval, given the data and assumptions).[285] Upon reflection, a frequentist approach would have been sufficient in this study given that there was little scientific information that could be used to inform priors. Fifth, the analysis did not account for survey weights, meaning the estimates may not be generalisable to the population in England. An improved analysis of trends over time could

have either standardised or weighted data on key demographics or adjusted for these variables as covariates.

Conclusions

In England, choices of HANDS device types remained relatively stable from 2016 to 2020, with tank e-cigarettes consistently the most widely used device type. Use of JUUL and heated tobacco products remains rare among HANDS users; however, there is some evidence JUUL use was becoming more common by 2020. Daily e-cigarette users were less likely to use disposable products. The vast majority of e-cigarette users used e-liquid that contained nicotine, but lower nicotine concentrations (≤6mg/ml) were most popular. Relative to HANDS users who currently smoked, those who were ex-smokers were more likely to use mod and tank e-cigarettes, but less likely to use pods, disposables, JUUL and heated tobacco products. The e-cigarette and heated tobacco industries are adapting rapidly, with new innovations introduced each year. It is therefore essential to continue tracking which types of nicotine products are commonly used, and how this is changing. Since completing this study, other changes have occurred in the vaping market in Great Britain. Modern disposable vapes became available throughout the country, and advertising for tobacco-free nicotine pouches grew more widespread. These new products will be examined in Chapters 4 and 5. In the next chapter, I describe a pricing strategy that may have helped pod e-cigarettes grow in popularity up until 2020.

2. Razor-and-Blades Methods of E-cigarette Pricing

Abstract

Full Title: "Give 'em the vape, sell 'em the pods": razor-and-blades methods of pod e-cigarette pricing

Summary: The razor-and-blades model is a pricing strategy of selling base products at a loss but making profits on repeated sales of complementary goods. Recently, e-cigarette manufacturers have started using razor-and-blades methods for their devices that use disposable pods of e-liquid; they provide a base e-cigarette device cheaply or for free but make large profits on sales of these device-specific pods. This article discusses potential consequences of this strategy on the e-cigarette market and public health.

Status: Published in Tobacco Control (DOI: 10.1136/tobaccocontrol-2020-056354).

Full article

The razor-and-blades model is a pricing strategy of selling base products, like razor handles, at a loss but making profits on repeated sales of complementary goods, like blades. This is reflected by the proverb, "Give 'em the razor, sell 'em the blades", which is widely misattributed to King C. Gillette.[286] This strategy has been used across a myriad of industries, from games consoles to inkjet printers.[286] More recently, it has been adopted by pod e-cigarette manufacturers.

Pod e-cigarettes like JUUL, Vuse, blu, and Logic use disposable cartridges (pods) that are pre-filled with e-liquid. On average, these cartridges cost four times the price of the same amount of bottled e-liquid, making them more expensive in North America than the equivalent number of combustible cigarettes.[287] So how do pod e-cigarette manufacturers overcome this price differential? Across North America and Europe, some have begun using razor-and-blades pricing models; they provide a base e-cigarette device cheaply or for free (Figure 2.1) but make large profits on disposable device-specific pods.[286,288]

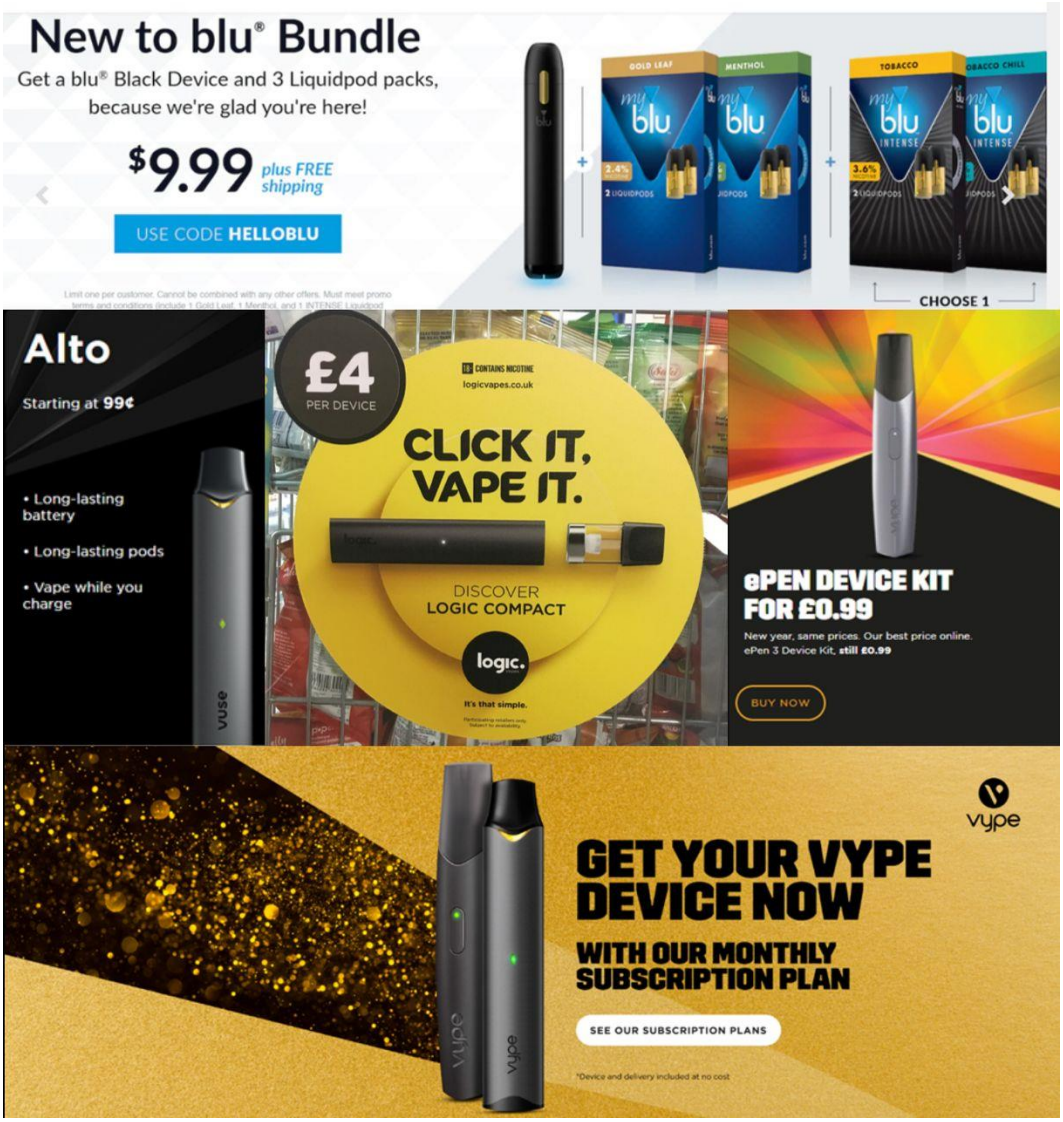


Figure 2.1. Pod e-cigarette advertisements using razor-and-blades methods. (Top) New customer deal on the blu US online store, offering an e-cigarette and six pods for only US$9.99. (Middle-left) Alto pod e-cigarette priced at US$0.99 on the Vuse US online store. (Middle-centre) Point-of-sale advertisement for the Logic Compact, available for £4 (US$5.5) at convenience stores in the UK. (Middle-right) ePen pod e-cigarette priced at £0.99 on Vype's UK website. (Bottom) Promotion for Vype's ePen, which is available for free in Canada when users sign up for a monthly subscription to pods. This promotion was also found on billboard advertisements in the UK.

This strategy may influence both uptake of vaping and the types of devices vapers choose, with potential behavioural, public health, and economic implications. First, it could encourage smokers to try switching to vaping. One of the key barriers that stops smokers from using e-cigarettes is the perceived cost of the devices.[289,290] Greater availability of devices with no or low upfront cost might attract smokers to try e-cigarettes as a way to stop smoking cigarettes — which could have a positive impact on public health.[193] But, once they start

vaping with razor-and-blades priced devices, the increased cost of continued pod use might reduce the number of smokers switching completely compared with other e-cigarettes or nicotine products. Alternatively, the increased cost of pod use might encourage users to switch to refillable e-cigarettes, which can be topped up cheaply with bottled e-liquid.[249]

Second, it might encourage uptake of vaping among young people. The rise in youth vaping in the US between 2017 and 2019 was driven by increased use of pod devices (later by the widespread availability of cheap disposable e-cigarettes, as I will discuss more in Chapter 4 and in the overall discussion of this thesis).[291] Just as cigarette singles and 10 packs were used to attract young people with little disposable income to smoking,[292] the low upfront cost of razor-and-blades priced pod devices may have contributed to rises in youth vaping seen in some countries, such as the US. In the UK, there has been evidence of British American Tobacco distributing Vype (now Vuse) for free without age verification, which resulted in people under 18 receiving free samples.[288] Surprisingly, the activity was not illegal as of December 2022 due to a loophole in the regulatory framework. The loophole requires urgent attention given the UK has thus far succeeded in relatively low youth uptake of e-cigarettes, especially among those who have never smoked.[9,258] The success may be attributable to careful regulation, which included an early ban on advertising that could cross borders and sale of the products to children.[293]

Thirdly, it may draw vapers away from refillable e-cigarettes towards pod devices.[294] As refillable e-cigarettes can be filled with any generic brand of e-liquid, manufacturers cannot make profit by offering these devices for free or selling them at a loss. This could shift the market in favour of e-cigarette brands that are owned by tobacco companies: the most popular pod systems are at least partially owned by tobacco manufacturers, while independent retailers are more likely to sell refillable devices.[295] A shift towards tobacco industry-owned products brings with it the risk that profits made could be used to fund lobbying efforts or expansion into markets in low- and middle-income countries.[55] Moreover, unlike independent e-cigarette manufacturers, tobacco companies are incentivised to encourage — or at least be ambivalent about — dual use of e-cigarettes and combustible cigarettes rather than complete substitution. A counter argument to this would be that, if tobacco companies profit more from selling e-cigarettes than cigarettes, they would be incentivized to get their customers to switch to vaping from smoking.

Finally, it could widen smoking-related economic inequalities. Already, smokers from socio-economically disadvantaged groups spend a much higher proportion of their income

on cigarettes.[296] The low upfront cost of razor-and-blades priced pod e-cigarettes may attract people from these groups, despite the total cost of continued use vastly exceeding that of refillable devices.[297] Since disadvantaged individuals are more likely to continue vaping after they quit smoking cigarettes,[298,299] increased use of pod devices could place an even greater economic burden on disadvantaged individuals.

Pricing strategies are just one driver of consumer demand for different nicotine products. Other factors also likely play a role, including people's perceptions about e-cigarette harm relative to cigarettes, as examined in the next chapter.[3,207,249,300] The introduction of cheap modern disposable e-cigarettes may have also undermined the efficacy of razor-and-blades tactics, as I will discuss later. Nonetheless, there is work to be done exploring the effects of pricing on device choice, youth vaping and e-cigarette use for smoking cessation. If it is apparent that razor-and-blades tactics are boosting the market share of tobacco industry-owned e-cigarettes or encouraging youth vaping, policymakers might consider marketing or pricing restrictions.

3. Deteriorating Perceptions of E-cigarettes

Abstract

Full Title: Association of the US Outbreak of Vaping-Associated Lung Injury with Perceived Harm of e-Cigarettes Compared with Cigarettes.

Background: The 2019 US outbreak of vaping-associated lung injury (EVALI), linked to vitamin E acetate in tetrahydrocannabinol (THC) vaping devices, received extended news coverage worldwide. But media reports often failed to distinguish THC devices from nicotine e-cigarettes. Here, I examined how smokers' perceptions of the relative harm of e-cigarettes compared with cigarettes changed following the outbreak.

Methods: Current smokers (≥16y) were recruited from the Smoking Toolkit Study, a monthly nationally representative survey in England. They were asked whether they think, compared with cigarettes, e-cigarettes are less, equally, or more harmful to health. Following a pre-registered analysis plan, I examined associations between timing of the outbreak (Jan-Jul vs. Aug-Dec 2019) and e-cigarette harm perceptions, before and after adjustment for covariates (sex, age, social grade, ethnicity, and current e-cigarette use).

Results: 3215 current smokers were surveyed in 2019, 1833 before the outbreak (46.3% women, mean [SD] age=43.5 [17.6] years) and 1382 after it (43.7% women, mean [SD] age=43.0 [17.8] years). The proportion of smokers who perceived e-cigarettes as less harmful than combustible cigarettes decreased from before (37.0%) to after (30.9%) the outbreak (Risk Ratio [RR]=0.83, 95%CI = 0.76–0.92, p<0.001). Conversely, there were increases in the proportion who perceived them as equally (39.9% vs. 43.8%, RR=1.10, 1.01–1.19, p=0.01) and more (12.7% vs. 17.2%, RR=1.36, 1.15–1.61, p<0.001) harmful. Differences remained after covariate adjustment.

Conclusions: Following the US outbreak of vaping-associated lung injury, views on e-cigarettes among smokers in England deteriorated: the proportion perceiving e-cigarette use as less harmful than smoking fell, while the proportion perceiving it as more harmful increased by over a third. These results highlight the importance of clear communication from public health bodies about the relative harm of different nicotine products.

Status: Published in JAMA Network Open (DOI: 10.1001/jamanetworkopen.2020.6981)

Background

In the literature review, I reported on the evidence showing how most of the harm caused by cigarette smoking is due to toxins and carcinogens produced by burning tobacco and that e-cigarettes, which do not contain tobacco or produce smoke, expose users fewer of these chemicals than cigarettes. In 2018, the U.S. Food and Drug Administration acknowledged that

tobacco and nicotine products exist on a continuum of risk, with e-cigarettes likely to cause less harm than cigarettes.[167,301] However, many smokers in England and the US believe that e-cigarettes are at least as harmful to health as combustible cigarettes.[167,302] These misperceptions may dissuade smokers who are unable or unwilling to stop using nicotine from switching to e-cigarettes, which could damage public health.

The recent US outbreak of vaping-associated lung injury (EVALI) from 2019 to 2020 received extended news coverage worldwide.[303] Most cases were associated with inhalation of vitamin E acetate, an additive found in some tetrahydrocannabinol vaping devices.[208] However, news reports often failed to distinguish tetrahydrocannabinol devices from standard nicotine-based e-cigarettes, which may have increased confusion about the relative harms of different nicotine products.[210]

This study examined the extent to which perceptions of the harm of e-cigarettes compared with combustible cigarettes changed among smokers after the EVALI outbreak.

Methods

This survey study used data from the Smoking Toolkit Study, a monthly cross-sectional nationally representative survey of adults (aged ≥16 years) in England. Survey methods are described in detail in the methodology section on page 31.

Current smokers were asked, "Compared to regular cigarettes, do you think electronic cigarettes are more, less, or equally harmful to health?" They could also respond, "don't know." Self-reported sex, age, socioeconomic status, race/ethnicity, and current e-cigarette use were also measured. The analysis plan was preregistered (https://osf.io/8wv3f/).

The majority of EVALI hospitalizations were between mid-August and mid-September 2019,[303] and internet searches for vaping and vaping death peaked mid-September.[304] Thus, I compared harm perceptions in 2019 before the EVALI outbreak (January to July 2019) with those after the outbreak (August to December 2019). Log-binomial regression was used to assess the association between timing of the outbreak and the proportion of smokers who believed that e-cigarettes were less harmful than cigarettes before and after adjusting for sociodemographic factors and e-cigarette use. In secondary analyses, I calculated associations between timing of the outbreak and the proportion of people reporting each of the other responses. Analyses were conducted using R version 3.5.3.

Results

A total of 20631 participants were interviewed in 2019, of whom 3240 reported currently smoking. There were 25 (0.8%) smokers who did not provide complete data across all other variables of interest, leaving 3215 complete cases which were used as the analytic sample for this study. Of the 3215 complete cases, 1833 were interviewed before the outbreak (849 [46.3%] women; mean [SD] age, 43.5 [17.6] years) and 1382 were interviewed after (604 [43.7%] women; mean [SD] age, 43.0 [17.8] years). The proportion who perceived e-cigarettes as less harmful than combustible cigarettes decreased from 37.0% (n = 678) before to 30.9% (n = 427) after the outbreak (risk ratio [RR], 0.83; 95% CI, 0.76-0.92; P < .001), and fewer smokers reported not knowing which product was more harmful (112 [8.1%] after vs 191 [10.4%] before; RR, 0.78; 95% CI, 0.63-0.98; P = .03). Conversely, there were increases in the proportion of individuals who perceived e-cigarettes as equally harmful (605 [43.8%] vs 731 [39.9%]; RR, 1.10; 95% CI, 1.01-1.19; P = .01) or more harmful (238 [17.2%] vs 233 [12.7%]; RR, 1.36; 95% CI, 1.15-1.61; P < .001) than cigarettes. Similar differences were found after adjustment for covariates (Table 3.1).

Figure 3.1 shows harm perceptions among smokers from 2016 through 2019. In the final quarter of 2019, the percentage of individuals who perceived e-cigarette use as less harmful than cigarette smoking decreased to the lowest point recorded (239 [29.5%]; 95% CI, 26.5%-32.8%), and the percentage perceiving it as more harmful peaked (155 [19.2%]; 95% CI, 16.6%-22.0%).

Table 3.1. Harm perceptions of e-cigarettes compared with cigarettes among current smokers in England in 2019, before and after the outbreak of vaping-associated lung injury. Adjusted analyses included gender, age, social grade, ethnicity and e-cigarette use as covariates.

	Before outbreak (January – July), *N*=1833	After outbreak (August – December), *N*=1382	RR_{un}, 95%CI	RR_{adj}, 95%CI
Less harmful	37.0%, 34.7%–39.3%	30.9%, 28.5%–33.4%	0.83, 0.76–0.92	0.81, 0.74–0.90
Equally harmful	39.9%, 37.7%–42.2%	43.8%, 41.2%–46.4%	1.10, 1.01–1.19	1.09, 1.01–1.18
More harmful	12.7%, 11.2%–14.3%	17.2%, 15.3%–19.3%	1.36, 1.15–1.61	1.38, 1.17–1.62
Don't know	10.4%, 9.1%–11.8%	8.1%, 6.8%–9.7%	0.78, 0.63–0.98	0.78, 0.62–0.97

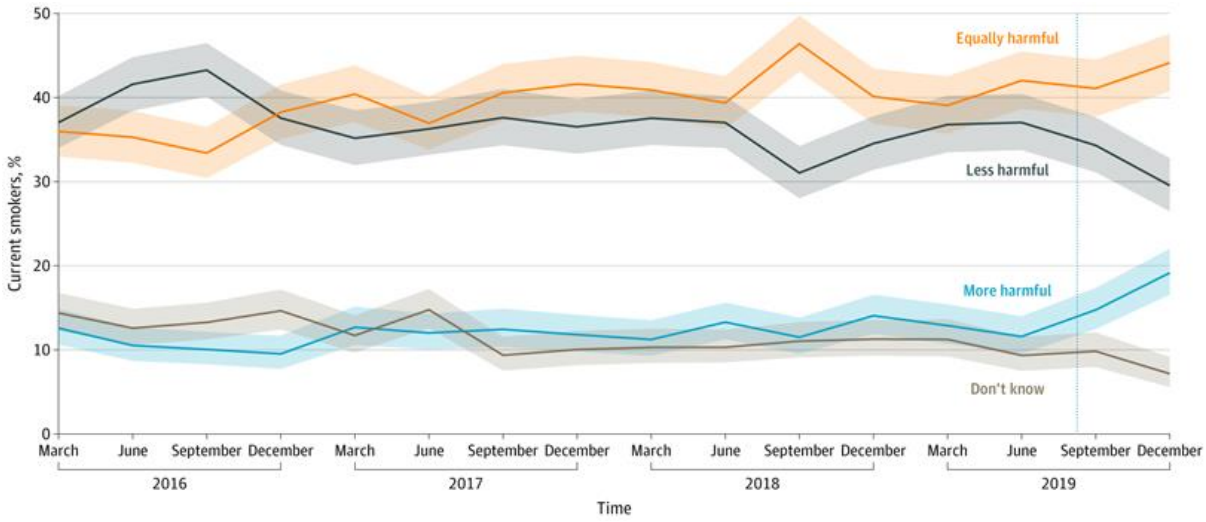


Figure 3.1. Perceived harm of e-cigarettes compared with cigarettes among smokers in England from 2016 to 2019. Solid lines represent means; shaded bands represent 95% CIs; and the dotted vertical line shows the peak of the vaping-associated lung injury outbreak.

Discussion

Smokers' views on e-cigarettes in England deteriorated after the US outbreak of vaping-associated lung injury. The proportion perceiving e-cigarette vaping as less harmful than cigarette smoking decreased, and the proportion perceiving vaping as more harmful increased by over one-third.

It is unclear exactly what effect these worsened harm perceptions will have on population health. There are several possibilities. Firstly, people who had quit smoking cigarettes through vaping might now return to smoking. This could damage their health and increase their risk of smoking-related diseases and death. Secondly, cigarette smokers might be deterred from using e-cigarette devices to help them quit, meaning they would miss out on the improvements in life expectancy associated with quitting discussed in the literature review.[23] Thirdly, young people who have never smoked may be dissuaded from ever trying e-cigarettes, which would benefit these individuals, who would avoid any residual risks to health from using nicotine.

A limitation of this study is that only smokers in England were surveyed. The association between EVALI and harm perceptions may differ across countries. In the North America, where the outbreak occurred and precipitated fierce political debate, there may have been an even greater change. Indeed, a subsequent study I co-authored showed a greater impact of the outbreak on people's perceptions in the US and Canada than in England.[300]

These results highlight the importance of clear communication from public health bodies about the relative harm of different nicotine products. Nonetheless, harm perceptions are only one driver of nicotine use. In the next chapter, I will show that, despite these worsening perceptions, vaping prevalence rose in Great Britain from 2021 to 2022 — driven primarily by the introduction of modern disposable e-cigarettes.

4. Rapid Growth in Disposable Vaping

Abstract

Full Title: Rapid growth in disposable e-cigarette vaping among young adults in Great Britain from 2021 to 2022: a repeat cross-sectional survey

Aims: To estimate recent trends in the prevalence of disposable e-cigarette vaping in Great Britain, overall and across ages, and to measure these trends in the context of changes in smoking and vaping prevalence.

Methods: Data came from the Smoking Toolkit Study, a monthly representative cross-sectional survey in Great Britain. 36,876 adults (≥18 years) completed telephone interviews between January 2021 and April 2022. Current e-cigarette vapers were asked which type of device they mainly use. I estimated age-specific monthly time trends in the prevalence of current disposable e-cigarette use among vapers and inhaled nicotine use (vaping/smoking), smoking, and vaping among adults.

Results: From January 2021 to April 2022, there was an 18-fold increase in the percentage of vapers who used disposables, rising from 1.2% to 22.2% (prevalence ratio [PR]=18.0; 95% compatibility interval [CI]=9.18-49.0). Growth in disposable e-cigarette vaping was most pronounced in younger adults (interaction p-value=.013): for example, the percentage of 18-year-old vapers using disposables rose from 0.4% to 54.8% (PR=129; 95%CI=28.5-4520) while it rose from 2.1% to 10.0% (PR=4.73; 95%CI=2.06-23.6) among 45-year-old vapers. However, the overall percentage of people currently using any inhaled nicotine remained relatively stable over time both among all adults (20.0% vs. 21.2%; PR=1.06; 95%CI=0.92-1.22) and among 18-year-olds (30.2% vs. 29.7%; PR=0.99; 95%CI=0.80-1.22). In 18-year-olds, vaping prevalence grew (11.3% vs. 17.7%; PR=1.57; 95%CI=1.12-2.29) and there was imprecise evidence for a decline in smoking (24.5% vs. 19.5%; PR=0.80; 95%CI=0.63-1.04). In 45-year-olds, there was relatively little change in vaping (PR=1.08; 95%CI=0.88-1.33) or smoking prevalence (PR=1.01; 95%CI=0.88-1.16).

Conclusions: Use of disposable e-cigarettes in Great Britain grew rapidly between 2021 and 2022, especially among younger adults, but the overall prevalence of inhaled nicotine use was stable over time. Most young adult vapers in Great Britain now use disposable products.

Status: Published in Addiction (DOI: 10.1111/add.16044).

Background

As discussed in Chapter 1, early electronic cigarettes ("e-cigarettes") were disposable products that were poor at delivering nicotine. Over time, new e-cigarette types were developed to deliver nicotine contained in e-liquid more effectively through rechargeable devices with refillable tanks or replaceable pods (e.g. Juul).[1] These devices came to dominate the global e-cigarette market and, by 2019, fewer than one-in-ten vapers used disposables in England or the US.[1,249,305]

Since 2020, a new form of disposable e-cigarette has started being sold under brand names like "Puff bar", "Elf bar", or "Geek bar".[306] Unlike earlier disposables, these products deliver nicotine effectively using a similar technology to pod devices, including high-strength (20mg/ml in UK/EU) nicotine salts e-liquid.[307] They retail for around £5 to £7 (US$7 to $9) in the UK — about half the price of a pack of 20 cigarettes. US data show that, in 2021, disposables surpassed pods as the most commonly used type of e-cigarette among adolescents.[305]

Little is known about the popularity of disposables in other countries and older age groups. It is also unclear whether these products attract people who would otherwise smoke cigarettes, vape other types of e-cigarettes, or who would remain abstinent from nicotine entirely. This study aims to estimate recent trends in the prevalence of disposable e-cigarette vaping in Great Britain, overall and across ages, and to explore these trends in the context of other changes in smoking and vaping prevalence.

Methods

Design

The Smoking Toolkit Study (STS) is a monthly cross-sectional survey that recruits a nationally representative sample of adults (≥18 years) in Great Britain. Survey methods are described in detail in the methodology section on page 31.

Participants

Participants (N=36,876) completed telephone interviews between January 2021 and April 2022, inclusive. Of these, 36,876 (99.5%) provided complete information about their smoking status, vaping status, age, and gender. These complete cases were used as the analytic sample.

Measures

All measures used were routinely collected in the STS. Smoking status was ascertained by asking participants which of the following applies to them:

a) "I smoke cigarettes (including hand-rolled) every day"
b) "I smoke cigarettes (including hand-rolled), but not every day"
c) "I do not smoke cigarettes at all, but I do smoke tobacco of some kind (e.g. pipe, cigar or shisha)"
d) "I have stopped smoking completely in the last year"
e) "I stopped smoking completely more than a year ago"
f) "I have never been a smoker (i.e. smoked for a year or more)"

Participants were told that this question referred to cigarettes and other kinds of tobacco, not e-cigarettes or heat-not-burn products. Participants selecting a to c were classified current smokers, d and e former smokers, and f never smokers.

Vaping status was assessed by asking participants whether they were currently using e-cigarettes to cut down on the amount they smoke, in situations when they are not allowed to smoke, to help them stop smoking, or for any other reason. Those who responded positively to any of these questions were considered current vapers.

Current vapers were asked which type of device they mainly use. Those who responded, "a disposable e-cigarette or vaping device (non-rechargeable)", were considered disposable e-cigarette vapers. They could only choose one device type (the one they "mainly" use).

Participants were asked to provide their exact age in years. Those who refused to give their exact age were asked to select their age group from a list. For participants who only responded to the latter question (2% of respondents), exact age was imputed as the mean age within the age group they selected. Participants were also asked for their gender.

Analysis

Weighted logistic regression was used to estimate monthly time trends in the proportion of (i) adults and (ii) current vapers who use disposable e-cigarettes, overall and for specific ages

(using survey weights described earlier). For the overall analysis, models only included predictors for time. For the age-specific analysis, models included time, age and their interaction as predictors — thus allowing for time trends to differ across ages. Both age and time were modelled continuously using restricted cubic splines with three knots (placed at earliest, middle, and latest month for time and 5%, 50%, and 95% quantiles for age among vapers). This allowed the relationship of prevalence with age and time to be flexible and non-linear, while avoiding categorisation.[230] Age was modelled continuously, so I displayed estimates for four specific ages (18-, 25-, 35- and 45-year-olds) to illustrate how trends differed across ages. Note that the model used to derive these estimates included data from participants of all ages, not only those who were exactly 18-, 25-, 35- or 45-years old.

Prevalence ratios (PR) for the change in prevalence across the whole time-series (April 2022 versus January 2021) were presented, alongside 95% compatibility intervals (95%CIs) calculated using bootstrapping.[308–310] I ran analogous analyses to estimate time trends in the proportion of adults who currently (i) vape, (ii) smoke, or (iii) use any form of inhaled nicotine — be that smoked or vaped. Note that prevalence of disposable e-cigarette use was very low in older age groups, which meant we were unable to estimate time trends in these groups. Finally, I reported the percentage of disposable e-cigarette vapers who reported being current, former, or never smokers. Participants with missing data for their smoking or vaping status (<1%) were excluded from analyses that required this information. R version 4.1.0 was used for analyses (code: https://osf.io/km3x6/).

Results

Of the 36,876 eligible adults interviewed who were complete cases on all variables of interest, 51.1% were women, and the average age was 51.5 years (SD=18.6). From January 2021 to April 2022, there was an 18-fold increase in the percentage of vapers that used disposables, rising from 1.2% to 22.2% (prevalence ratio [PR]=18.0; 95%CI=9.18-49.0). Overall, the prevalence of disposable e-cigarette use increased from 0.08% to 1.85% (Table 4.1; PR=22.3; 95%CI=10.8-48.8).

Table 4.1. Age-specific trends in current vaping, smoking and disposable e-cigarette vaping prevalence in Great Britain. Weighted prevalence estimates from logistic regression allowing an interaction between age and month, modelled non-linearly using restricted cubic splines (three knots). Data, analysis code, and estimates for other months available online (https://osf.io/km3x6/).

	Prevalence		Prevalence Ratio (95% CI)
	Jan-21	Apr-22	
Currently using inhaled nicotine (vaped or smoked)			
18-year-olds	30.2%	29.7%	0.99 (0.80-1.22)
25-year-olds	28.7%	30.3%	1.06 (0.94-1.19)
35-year-olds	25.6%	28.6%	1.12 (1.01-1.23)
45-year-olds	21.6%	24.1%	1.11 (0.99-1.24)
All adults	20.0%	21.2%	1.06 (0.92-1.22)
Currently vaping			
18-year-olds	11.3%	17.7%	1.57 (1.12-2.29)
25-year-olds	10.7%	15.2%	1.42 (1.16-1.77)
35-year-olds	9.4%	11.6%	1.23 (1.03-1.47)
45-year-olds	7.6%	8.1%	1.08 (0.88-1.33)
All adults	7.0%	8.2%	1.17 (1.01-1.35)
Currently smoking			
18-year-olds	24.5%	19.5%	0.80 (0.63-1.04)
25-year-olds	22.7%	19.9%	0.88 (0.76-1.02)
35-year-olds	19.7%	19.0%	0.97 (0.85-1.10)
45-year-olds	16.2%	16.3%	1.01 (0.88-1.16)
All adults	15.2%	14.5%	0.95 (0.87-1.05)
Currently vaping disposables			
18-year-olds	0.1%	10.7%	214 (56.7-5590)
25-year-olds	0.1%	4.7%	45.1 (17.1-247)
35-year-olds	0.2%	1.8%	9.84 (3.25-35.9)
45-year-olds	0.2%	0.9%	5.74 (2.57-22.2)
All adults	0.1%	1.9%	22.3 (10.8-48.8)

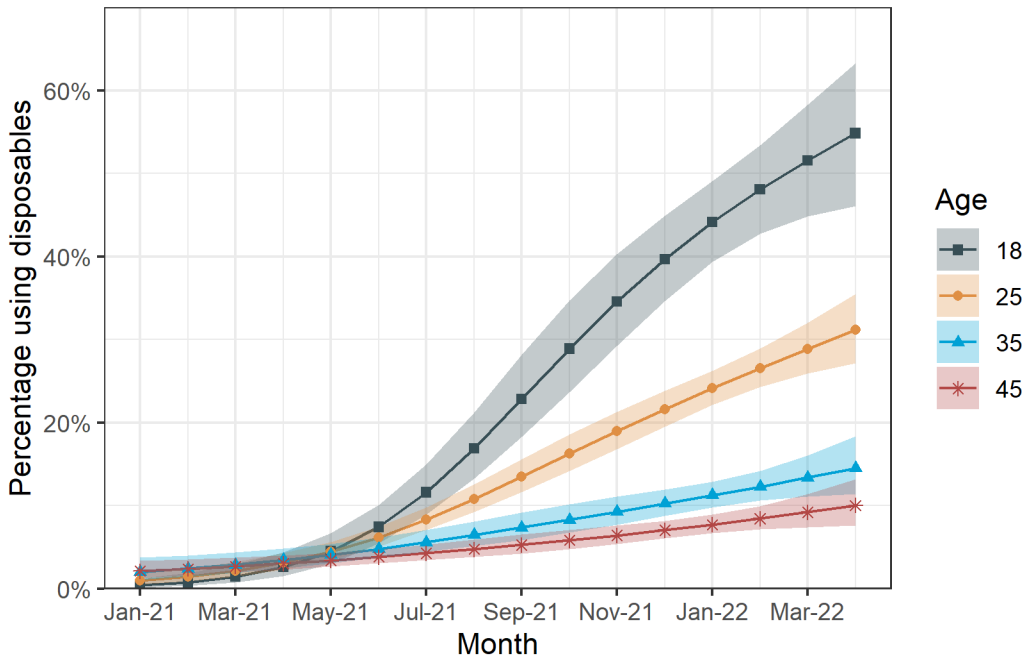


Figure 4.1. Percentage of current vapers using disposable e-cigarettes across ages in Great Britain from 2021 to April 2022. A total of 36,876 eligible adults were surveyed (approximately 2,300 each month). Lines represent point estimates from logistic regression allowing an interaction between age and month, modelled non-linearly using restricted cubic splines (three knots). Shaded areas represent standard errors. Data and analysis code available online (https://osf.io/km3x6/).

Growth in disposable e-cigarette vaping was most pronounced in the youngest participants (Figure 1; interaction p-value=.013). For instance, prevalence of disposable use among 45-year-old vapers rose from 2.1% to 10.0% (PR=4.73; 95%CI=2.06-23.6), whereas among 18-year-old vapers it increased from 0.4% to 54.8% (PR=129; 95%CI=28.5-4520).

Despite this, the overall percentage of adults currently using any inhaled nicotine (smoked or vaped) was relatively stable over the study period (Figure 4.4, Table 4.1; 20.0% vs. 21.2%; PR=1.06; 95%CI=0.92-1.22). Among young adults, where the rise in disposable vaping was most pronounced, inhaled nicotine use remained relatively stable over time, estimated to be 30.2% for 18-year-olds in January 2021 and 29.7% April 2022 (Table 4.1; PR=0.99; 95%CI=0.80-1.22). However, during the period vaping prevalence rose from 11.3% to 17.7% among 18-year-olds (Table 4.1; PR=1.57; 95%CI=1.12-2.29), there was an uncertain decline in smoking prevalence from 24.5% to 19.5% (Table 4.1; PR=0.80; 95%CI=0.63-1.04). Conversely, in ages where vaping prevalence did not substantially increase, there appeared to be little change in smoking. For instance, the prevalence of vaping (Table 4.1; PR=1.08; 95%CI=0.88-

1.33) and smoking (Table 4.1; PR=1.01; 95%CI=0.88-1.16) among 45-year-olds were relatively stable over time. More detailed monthly trends in the prevalence of inhaled nicotine use, vaping, and smoking among adults of different ages are shown in Figures 4.2 to 4.3.

Most disposable e-cigarette vapers were current (71.6%) or former smokers (18.8%), with few reporting never having smoked regularly (9.6%). The proportion of disposable vapers who also smoked was similar across ages, but it may have declined slightly over time (Figures 4.5 and 4.6).

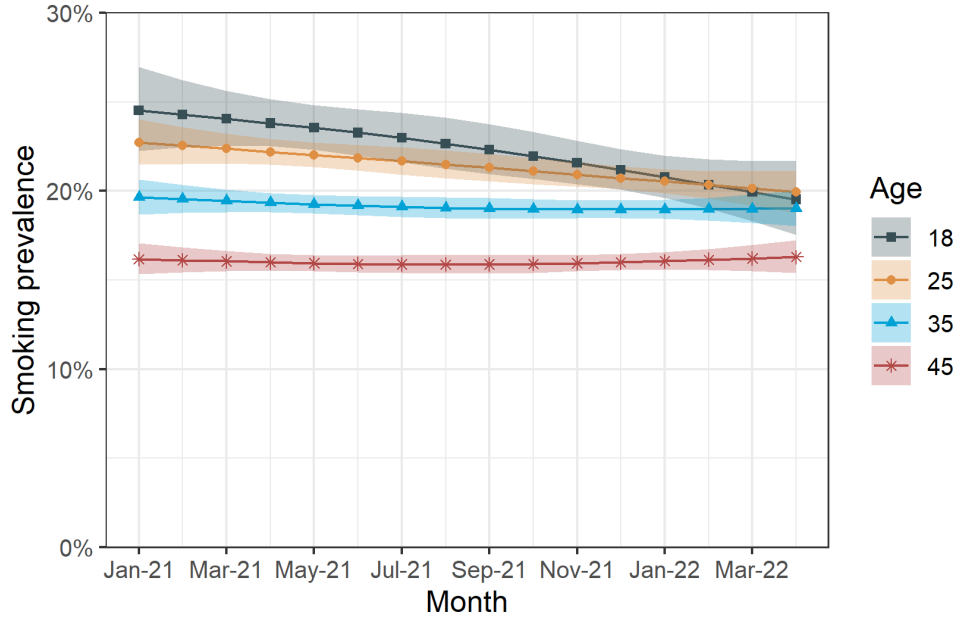


Figure 4.2. Smoking prevalence across ages in Great Britain from 2021 to April 2022. A total of 36,876 eligible adults were surveyed (approximately 2,300 each month). Lines represent point estimates from logistic regression allowing an interaction between age and month, modelled non-linearly using restricted cubic splines. Shaded areas represent standard errors.

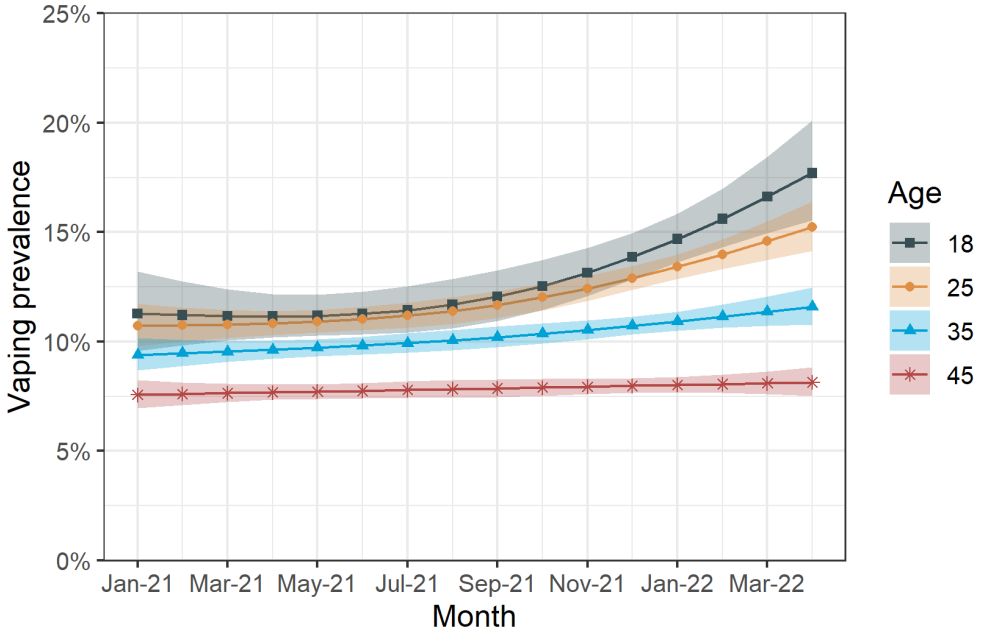


Figure 4.3. Vaping prevalence across ages in Great Britain from 2021 to April 2022. A total of 36,876 eligible adults were surveyed (approximately 2300 each month). Lines represent point estimates from logistic regression allowing an interaction between age and month, modelled non-linearly using restricted cubic splines. Shaded areas represent standard errors.

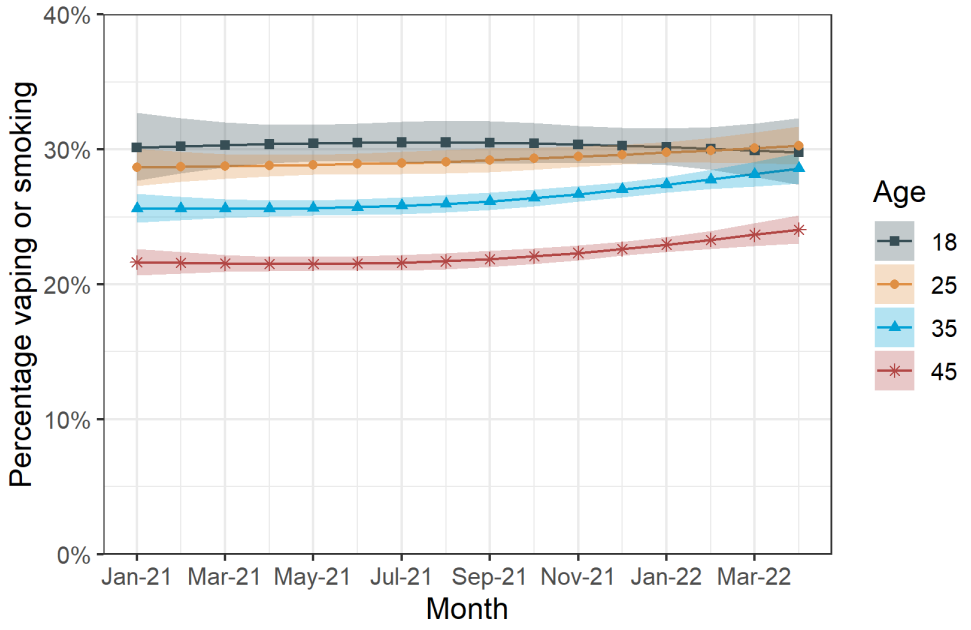


Figure 4.4. Prevalence of inhaled nicotine use (smoking/vaping) across ages in Great Britain from 2021 to April 2022. A total of 36,876 adults were surveyed (approximately 2,300 each month). Lines represent point estimates from logistic regression allowing an interaction between age and month, modelled non-linearly using restricted cubic splines. Shaded areas represent standard errors.

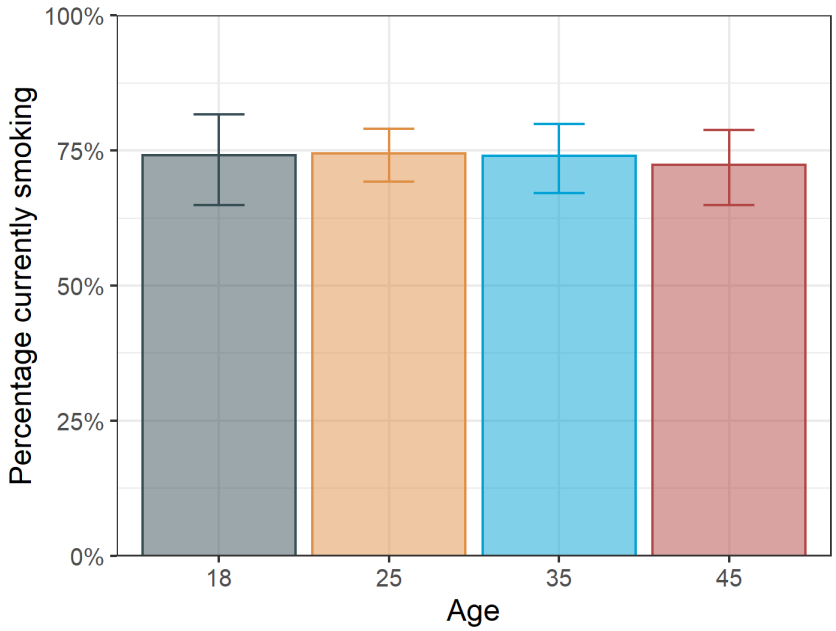


Figure 4.5. Percentage of disposable vapers who currently smoke across ages in Great Britain. Height of bars represent point estimates from logistic regression with age modelled non-linearly using restricted cubic splines. Error bars represent standard errors.

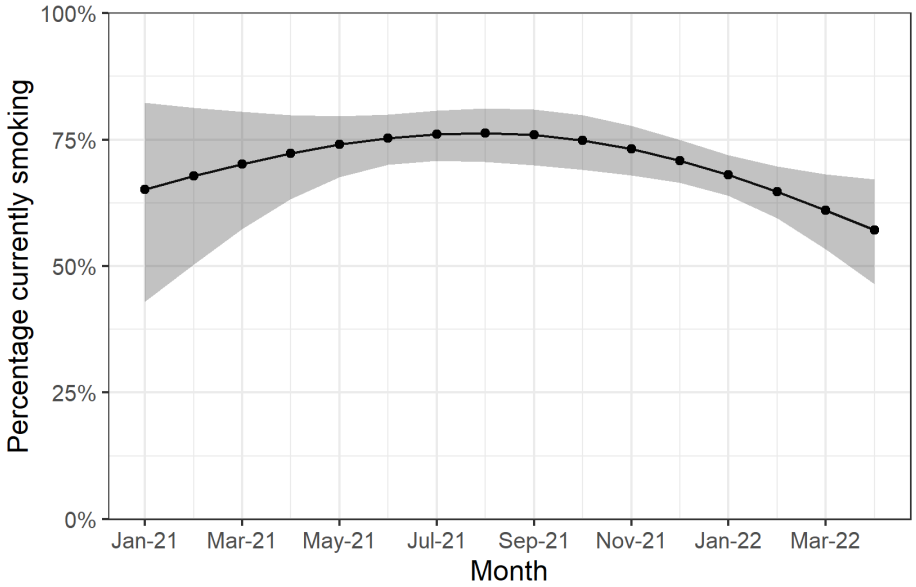


Figure 4.6. Percentage of disposable vapers who currently smoke across months from 2021 to April 2022 in Great Britain. Line represents point estimates from logistic regression with month modelled non-linearly using restricted cubic splines. Shaded bands represent standard errors.

Discussion

Use of disposable e-cigarettes rose sharply between 2021 and 2022 in Great Britain, with the most rapid growth observed among the youngest adults (mirroring trends observed in US adolescents).[305] At the start of 2021, fewer than 1% of 18-year-old vapers used disposables. This increased substantially up to April 2022, such that over half of 18-year-old vapers reported mainly using disposables. Despite this, the overall percentage of young people using any form of inhaled nicotine was stable over time, with an increase in vaping and an uncertain decline in smoking among young adults. This suggests that, in Great Britain up to mid-2022, disposable e-cigarettes have primarily attracted those who would otherwise use rechargeable devices or cigarettes, rather than those who would otherwise not use any nicotine product. Nonetheless, as the sharp increase in disposable vaping presented here shows, patterns of nicotine product use can change rapidly. Early and routine publication of data such as these are needed to guide policy and research.

Study limitations include the wide 95%CIs around prevalence ratios due to few participants reporting disposable e-cigarette use in early months. The measure of disposable e-cigarette vaping also did not distinguish between modern "bar" style disposables from older "cigalikes". Nonetheless, in Chapter 1 I showed that cigalikes were rarely used by vapers between 2016 and 2020, so it is likely that almost all of the sharp increase in disposable e-cigarette vaping was attributable to bar-type devices. Moreover, this question asked about which type of device vapers *mainly* use, so vapers who used disposables as a secondary product were not captured; therefore, the estimated prevalence of disposable vaping actually represents a lower bound for the true prevalence.

There is a need for more research into these modern disposable e-cigarettes. In the overall discussion section of this thesis, I will examine some of the reasons why disposable e-cigarettes may have become the product of choice among young people in Great Britain and the US[305]. I will also propose several areas where further research is needed. Tobacco-free nicotine pouches are another product that has recently entered the global nicotine market. In the next chapter, I present data on the prevalence of nicotine pouch use in Great Britain.

5. Prevalence of Nicotine Pouch Use

Abstract

Full Title: Tobacco-free Nicotine Pouch Use in Great Britain: A Representative Population Survey 2020–2021

Background: Tobacco-free nicotine pouches are products that are placed between the lip and gum, where they deliver nicotine to users. Little is known about nicotine pouch use in Great Britain since they entered the market in 2019.

Methods: Data came from a monthly representative survey of the adult (≥18 years) population in Great Britain (England, Scotland, and Wales) between November 2020 and October 2021 (n = 25 698). We estimated the weighted prevalence of pouch use, overall and stratified by demographics, smoking status, and other nicotine use.

Results: Nicotine pouch use was rare among adults, with a weighted prevalence of just 0.26% (95% compatibility interval [CI] = 0.19–0.35). Prevalence doubled from November 2020 to October 2021 (0.14% to 0.32%; prevalence ratio [PR] = 2.22, 95% CI = 1.33–3.70). Pouch use was over four times more common among men than women (0.42% vs. 0.09%; PR = 4.55, 95% CI = 2.27–9.09) but less common in older age groups ($p < .001$). Pouch use was more prevalent among current smokers (0.87%; PR = 13.60, 95% CI = 5.46–33.89), recent former smokers (0.97%; PR = 15.21, 95% CI = 4.03–57.42), and long-term (>1 year) former smokers (0.24%; PR = 3.71, 95% CI = 1.36–10.15), compared with never smokers (0.06%). Prevalence was also elevated among e-cigarette (1.64% vs. 0.15%; PR = 10.59, 95% CI = 5.74–19.52) and nicotine replacement therapy users (2.02% vs. 0.21%; PR = 9.75, 95% CI = 4.64–20.49).

Conclusions: One in 400 adults in Great Britain use nicotine pouches, but the prevalence increased from 2020 to 2021. Pouch use is largely concentrated among younger and middle-aged men who use other nicotine products and have a history of smoking. Continued monitoring of nicotine pouch use is needed.

Status: Published in Nicotine and Tobacco Research (DOI: 10.1093/ntr/ntac099)

Background

One recent innovation in the global nicotine market is the tobacco-free oral nicotine pouch.[311] In the literature review, I covered how these nicotine pouches are used in the same way as Swedish snus, placed between the lip and gum where they rapidly and effectively deliver nicotine.[312] Unlike snus, they contain nicotine extract rather than processed tobacco leaf. This lack of tobacco leaf means that nicotine pouches are exempt from the EU and United Kingdom ban on oral tobacco (note Sweden are exempt from the ban).[313] Nicotine pouches were first introduced to European markets outside of Scandinavia in 2019.[314] All major tobacco companies now sell them, with popular brands including Zyn, Velo, and Nordic Spirit.[315]

Little is known about how prevalent nicotine pouch use is among adults globally; research to date has come from an online questionnaire in the Netherlands[316] and three non-representative or selective samples in the United Kingdom, North America, and Australia.[317-319] One other study among adolescents using data from International Tobacco Control Policy Evaluation Project (ITC) Youth Tobacco and Vaping Survey, found very low prevalence of nicotine pouch up until 2019 in England, the US and Canada.[320] Knowing how many people use nicotine pouches, and tracking how this is changing over time, is necessary to determine the scale to which these products could affect public health, either positively — by encouraging cigarette smokers to switch to a lower risk product, or negatively — by, for example, attracting people who would otherwise avoid nicotine entirely. I aimed to estimate the prevalence of nicotine pouch use among adults in Great Britain, assessing how use differs by age, gender, social grade, country of residence, smoking status, and use of other nicotine products.

Methods

Design

Data were from the Smoking Toolkit Study, a monthly cross-sectional survey that recruits a representative sample of adults (≥18 years) in Great Britain (England, Scotland, and Wales).[253,321] Survey methods are described in detail in the methodology section on page 31.

Participants

This analysis included participants who completed telephone interviews between November 2020, the first wave to ask about nicotine pouch use, and October 2021, the latest available data at the time of analysis.

Measurements

Nicotine pouch use was ascertained by asking participants whether they currently use "tobacco-free nicotine pouch/pod or 'white pouches' that you place on your gum (eg, Zyn, On!, Nordic Spirit, Dryft/Velo, Lyft, Skruf)". Demographic variables were age, gender, occupational social grade (National Readership Survey classification of AB, C1, C2, D, and E), and country of residence (England, Scotland, and Wales). Smoking status (current, recent [≤1 year] former, long-term [>1 year] former, and never smoker), current e-cigarette use (vaping), and current nicotine replacement therapy (NRT) use were also measured.

Analysis

I calculated the number and percentage of participants who used nicotine pouches. Log-binomial regression was used to estimate the weighted prevalence of nicotine pouch use, both overall and stratified by demographic characteristics, smoking status, and use of other nicotine products. One-way associations between nicotine pouch use and each of these variables were reported as prevalence ratios (PRs) with 95% compatibility ("confidence") intervals (95% CIs).[309] To measure time trends in prevalence, I ran a log-binomial regression with survey month modelled using restricted cubic splines with three knots placed at quantiles, thus allowing for non-linear relationships.[230] The same method was used to model trends in prevalence across ages.

Results

A total of 27 020 adults were interviewed in Great Britain from November 2020 to October 2021, of whom 25 698 (95.1%) were complete cases on all variables of interest. Of the complete cases, 54 (0.21%) reported currently using nicotine pouches. After applying survey weights, the estimated prevalence of nicotine pouch use was 0.26% (95% CI = 0.19–0.35). Figure 5.1

shows that pouch use became more common over time, increasing from 0.14% in November 2020 to 0.32% in October 2021 (PR = 2.22, 95% CI = 1.33–3.70).

Table 5.1 shows the weighted prevalence of pouch use among different demographic groups. Prevalence was similar in England (0.25%), Scotland (0.32%), and Wales (0.25%). There were gender differences, with men being over four times as likely to use nicotine pouches as women (0.42% vs. 0.09%; PR = 4.55, 95% CI = 2.27–9.09). Prevalence of nicotine pouch use was lower in older than middle-aged and young adults, as shown in Figure 5.2 (0.06% for ≥65-year-olds compared with 0.49% for 16- to 24-year-olds and 0.54% for 35- to 44-year-olds; $p < .001$). It is unclear how pouch use differs by occupational social grade, a measure of socioeconomic position, because of the low numbers of pouch users (e.g., 3 users in social grade E) surveyed in each occupational group ($p = .083$).

Pouch use was more common among current smokers (0.87%; PR = 13.60, 95% CI = 5.46–33.89), recent former smokers (0.97%; PR = 15.21, 95% CI = 4.03–57.42), and long-term (>1 year) former smokers (0.24%; PR = 3.71, 95% CI = 1.36–10.15), compared with never smokers (0.06%). Prevalence was also elevated among people who were currently using e-cigarettes (1.64% vs. 0.15%; PR = 10.59, 95% CI = 5.74–19.52) or NRT (2.02% vs. 0.21%; PR = 9.75, 95% CI = 4.64–20.49). Figure 5.3 shows the proportion of nicotine pouch users with each smoking status and with or without current use of other nicotine (through e-cigarettes or NRT).

Table 5.1. Nicotine pouch use across demographics in Great Britain.

	Current nicotine pouch use				
	No, *N* (%)	**Yes,** *N* (%)	**Prevalence,** % (95% CI)	**Prevalence ratio,** (95% CI)	***p*** †
Overall	25,577	66	0.25 (0.19-0.33)		
Social grade					.175
AB	7,060 (27.6%)	15 (23.5%)	0.22 (0.12-0.40)	Ref	
C1	6,782 (26.5%)	11 (16.8%)	0.16 (0.10-0.28)	0.74 (0.33-1.67)	
C2	5,436 (21.3%)	22 (33.2%)	0.40 (0.22-0.71)	1.83 (0.79-4.23)	
D	3,830 (15.0%)	15 (22.3%)	0.38 (0.19-0.79)	1.75 (0.68-4.50)	
E	2,468 (9.7%)	3 (4.2%)	0.11 (0.04-0.34)	0.52 (0.15-1.80)	
Age (years)					<.001
18-24	2,651 (10.4%)	13 (20.0%)	0.49 (0.23-1.08)	Ref	
25-34	4,362 (17.1%)	13 (19.2%)	0.29 (0.15-0.56)	0.59 (0.21-1.63)	
35-44	4,094 (16.0%)	22 (33.7%)	0.54 (0.32-0.91)	1.09 (0.43-2.80)	
45-54	4,399 (17.2%)	8 (12.7%)	0.19 (0.08-0.43)	0.39 (0.12-1.19)	
55-64	4,004 (15.7%)	6 (9.0%)	0.15 (0.06-0.36)	0.30 (0.09-0.98)	
65+	6,028 (23.6%)	3 (5.3%)	0.06 (0.02-0.18)	0.12 (0.03-0.47)	
Gender§					<.001
Men	12,578 (49.2%)	53 (81.2%)	0.42 (0.30-0.60)	Ref	
Women	12,999 (50.8%)	12 (18.8%)	0.09 (0.05-0.17)	0.22 (0.11-0.44)	
Country					.815
England	22,049 (86.2%)	55 (84.1%)	0.25 (0.18-0.36)	Ref	
Scotland	2,276 (8.9%)	7 (11.2%)	0.32 (0.18-0.58)	1.29 (0.65-2.57)	
Wales	1,252 (4.9%)	3 (4.7%)	0.25 (0.10-0.63)	0.99 (0.36-2.69)	
Smoking status					<.001
Never	14,809 (57.9%)	9 (14.4%)	0.06 (0.03-0.14)	Ref	
Long-term (>1yr) former	6,051 (23.7%)	14 (21.9%)	0.24 (0.13-0.43)	3.71 (1.36-10.15)	
Recent (≤1yr) former	557 (2.2%)	5 (8.3%)	0.97 (0.34-2.78)	15.21 (4.03-57.42)	
Current	4,160 (16.3%)	36 (55.4%)	0.87 (0.57-1.32)	13.60 (5.46-33.89)	
E-cigarette use					<.001
No	23,841 (93.2%)	37 (56.1%)	0.15 (0.10-0.23)	Ref	
Yes	1,736 (6.8%)	29 (43.9%)	1.64 (1.04-2.58)	10.59 (5.74-19.52)	
NRT use					<.001
No	24,888 (97.3%)	52 (78.4%)	0.21 (0.15-0.29)	Ref	
Yes	689 (2.7%)	14 (21.6%)	2.02 (1.04-3.90)	9.75 (4.64-20.49)	

† *p*-values ascertained using likelihood ratio tests against an intercept only model.

§ All nicotine pouch users identified as either a man or women.

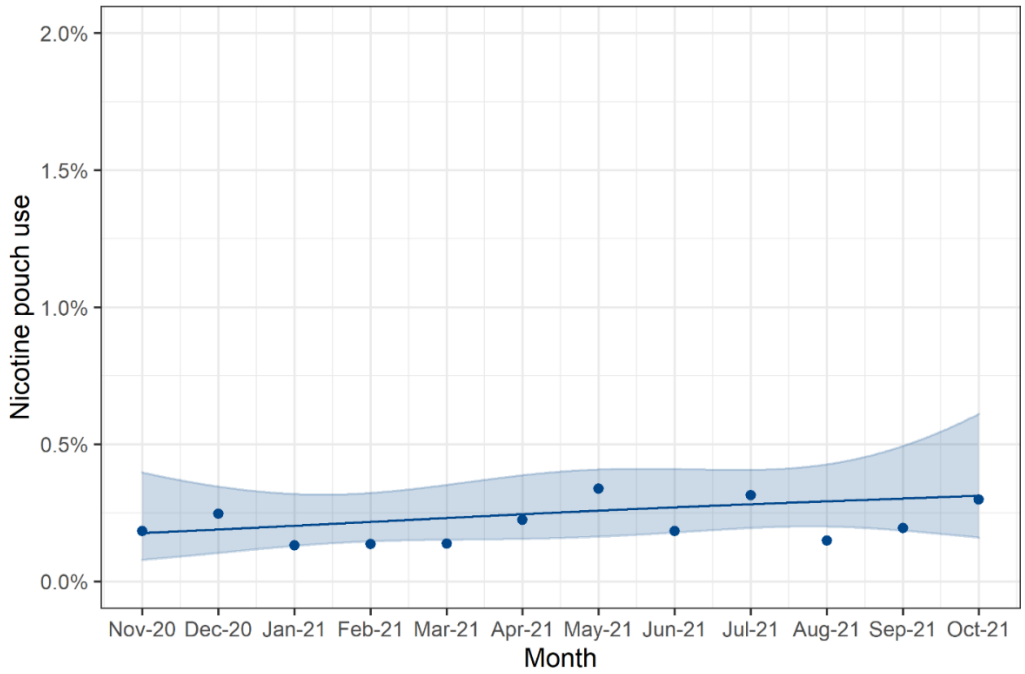


Figure 5.1. Trends in prevalence of nicotine pouch use in Great Britain from November 2020 to October 2021. Shaded bands represent 95% CIs. Points show the unweighted percentage of participants who reported nicotine pouch use in each month. Fitted values come from weighted log-binomial regression, with age modelled using restricted cubic splines with three knots (placed at the first month, middle month, and final month).

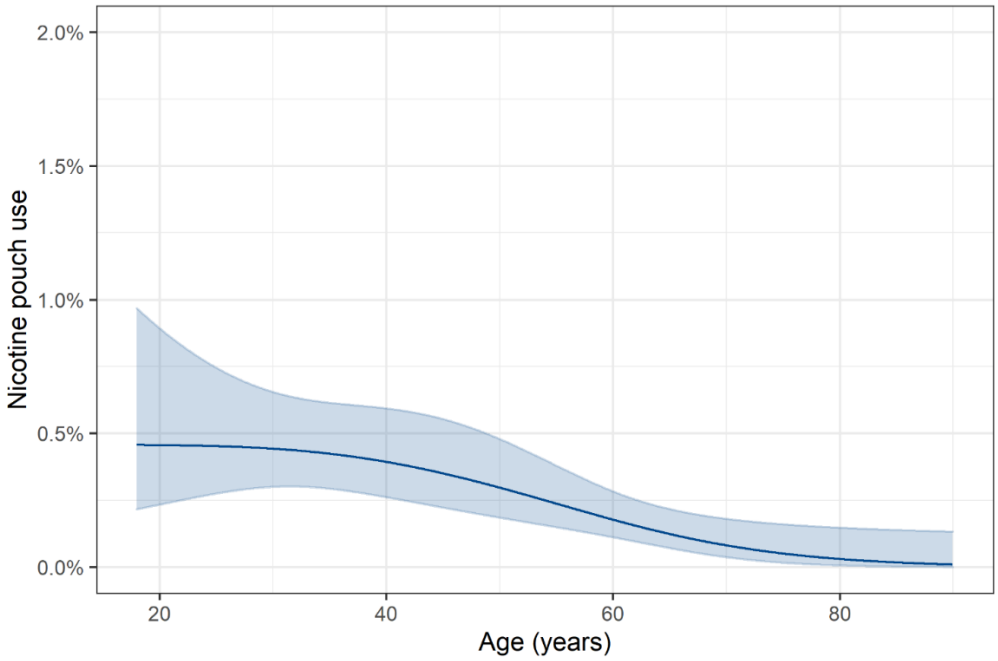


Figure 5.2. Prevalence of nicotine pouch use by age in Great Britain. Shaded bands represent 95% CIs. Fitted values come from weighted log-binomial regression, with age modelled using restricted cubic splines with three knots (placed at the minimum value, median, and maximum value).

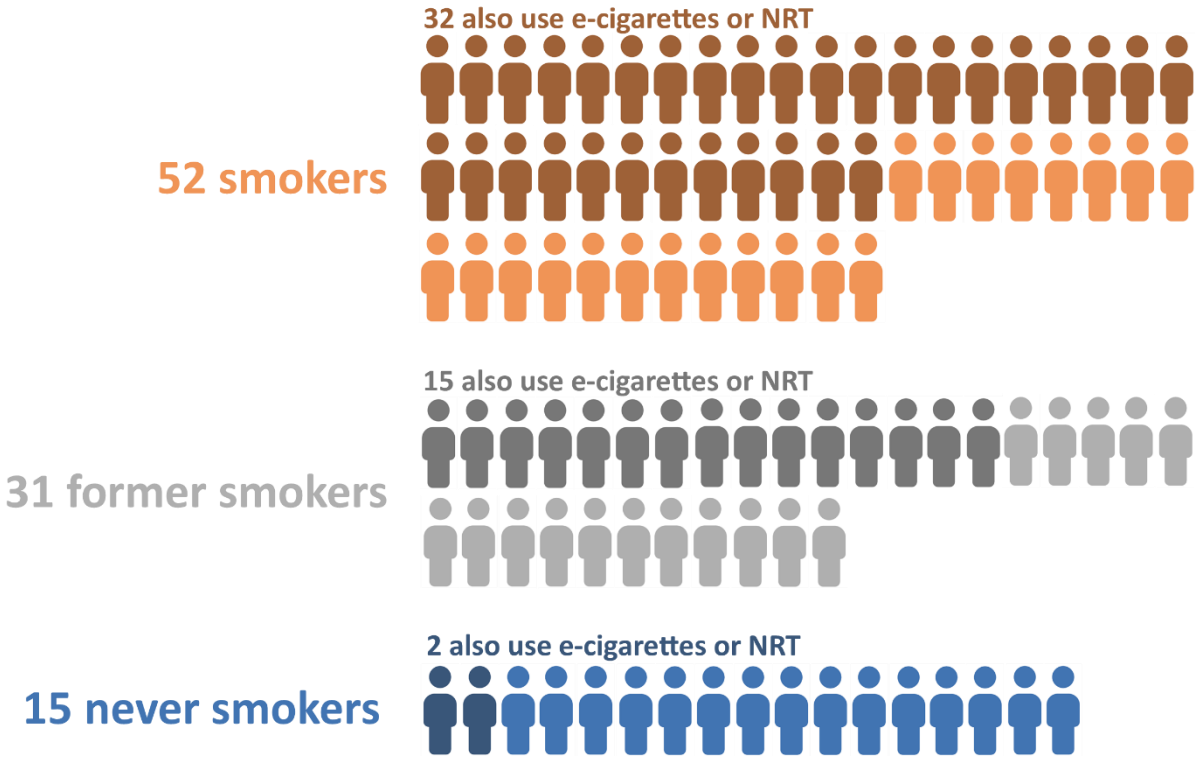


Figure 5.3. Isotype graph showing the expected distribution of smoking status and e-cigarette/NRT use of 100 nicotine pouch users in Great Britain.

Discussion

Nicotine pouch use is rare in Great Britain, with just one in every 400 adults currently using these products. This equates to a total of 130,000 (95% CI = 100,000–180,000) nicotine pouch users across Great Britain: 110,000 (80,000–160,000) in England, 14,000 (8,000–25,000) in Scotland, and 6,000 (2,500–16,000) in Wales. Prevalence is increasing over time, with twice as many people using pouches in October 2021 as in November 2020.

Prevalence is higher among men than women and among young or middle-aged adults than older adults. These results are consistent with data from online surveys in the Netherlands,[316] the United Kingdom,[317] Australia, Canada, and the United States,[319] which also found a relatively low prevalence of nicotine pouch use in women and older adults. They also mirror historic gender differences in the use of snus (tobacco-containing pouches) in Nordic countries.[63]

I found that nicotine pouch use is concentrated among adults who use other nicotine products and have a history of smoking. This means pouches are currently unlikely to be attracting substantial numbers of people who would otherwise avoid nicotine entirely in

Great Britain. Nonetheless, it could take years for nicotine pouches to achieve widespread popularity. It is possible that, following the diffusion of innovations,[322] the *early adopters* of nicotine pouches have different characteristics than the majority of users once the market reaches saturation. For instance, early adopters of e-cigarettes may have come from more advantaged groups than later users.[323,324] Therefore, continued monitoring of the characteristics of people using nicotine pouches is needed.

This study benefits from using a representative survey of the population in Great Britain, collecting detailed data on demographics and nicotine use. The repeat cross-sectional design allows us to track changes over time — which was useful for this study in examining changes from 2020 to 2021 and will also be important for continued monitoring in the future (as examined in the discussion section of this thesis). Limitations include the absence of a measure of former nicotine pouch use, which meant we could only examine the percentage of people who were currently using nicotine pouches when interviewed, not the percentage who had ever tried them. There was also no measure of whether pouches were the first nicotine product a person used, but as pouches were only introduced to Great Britain in 2019, it is unlikely that participants tried pouches before cigarettes, e-cigarettes, or NRT. While it is not clear what caused the prevalence of pouch use to increase over time, the trend is unlikely to be explained by factors associated with COVID-19 because the pandemic was present throughout the entire period studied.

In conclusion, while nicotine pouch use is currently uncommon in Great Britain, it grew between 2020 and 2021. Pouch use is largely concentrated among younger and middle-aged men who also use other nicotine products and have a history of smoking

This ends Part A of my thesis, where I examined the popularity and use prevalence of e-cigarettes, heated tobacco, and nicotine pouches. In Part B, I will examine the extent to which these alternative nicotine products might help people to quit smoking cigarettes and reduce the prevalence of smoking in the population. Specifically, the first study is a randomised trial estimating the effectiveness of adding e-cigarettes to varenicline treatment at English Stop Smoking Services. The second is a systematic review of the safety, effectiveness for cessation, and impact on smoking prevalence of heated tobacco.

Part B: Cessation and Harm Reduction

6. E-cigarettes and Varenicline for Quitting Smoking

Abstract

Full Title: E-cigarettes to Augment Stop Smoking In-person Support and Treatment with Varenicline (E-ASSIST): A Pragmatic Randomized Controlled Trial

Background: This study aimed to examine whether, in adults receiving behavioural support, offering e-cigarettes with varenicline helps more people stop smoking cigarettes than varenicline alone.

Methods: A two-group, parallel-arm, pragmatic randomised controlled trial was conducted in six English stop smoking services from 2019-2020. Adults enrolled onto a 12-week programme of in-person one-to-one behavioural smoking cessation support (N=92) were randomised to receive either (i) a nicotine e-cigarette starter-kit alongside varenicline or (ii) varenicline alone. The primary outcome was biochemically-verified abstinence from cigarette smoking between weeks nine-to-12 post quit-date, with those lost to follow-up considered not abstinent. The trial was stopped early due to COVID-19 restrictions and a varenicline recall (92/1266 participants recruited).

Results: Nine-to-12-week smoking abstinence rates were 47.9% (23/48) in the e-cigarette-varenicline group compared with 31.8% (14/44) in the varenicline-only group, a 51% increase in abstinence among those offered e-cigarettes; however, the compatibility interval (CI) was wide, including the possibility of no difference (risk ratio [RR]=1.51, 95%CI=0.91-2.64). The e-cigarette-varenicline group had 43% lower hazard of relapse from continuous abstinence than the varenicline-only group (hazard ratio [HR]=0.57, 95%CI=0.34-0.96). Attendance for 12 weeks was higher in the e-cigarette-varenicline than varenicline-only group (54.2% versus 36.4%; RR=1.49, 95%CI=0.95-2.47), but similar proportions of participants in both groups used varenicline daily for ≥8 weeks after quitting (22.9% versus 22.7%; RR=1.01, 95%CI=0.47-2.20). Estimates were too imprecise to determine how adverse events differed by group.

Conclusion: Tentative evidence suggests offering e-cigarettes alongside varenicline to people receiving behavioural support may be more effective for smoking cessation than varenicline alone. The evidence is tentative because our sample size was smaller than planned — caused by COVID-19 restrictions and a manufacturing recall. This meant our effect estimates were imprecise, and additional evidence is needed to confirm that providing e-cigarettes and varenicline together helps more people remain abstinent than varenicline alone.

Status: Published in Nicotine and Tobacco Research (DOI: 10.1093/ntr/ntac149).

Background

Rates of cigarette smoking are declining in many high-income countries,[323] in part due to the availability of treatments that help people stop smoking.[325] As I discussed in the literature review, varenicline — a partial nicotinic acetylcholine receptor agonist — is one of the most effective treatments, especially when paired with behavioural support.[133] Nonetheless, even with varenicline, fewer than one-in-five people remain abstinent from smoking for a year or more after quitting,[326] so there remains a need to find more effective ways to help people quit. As discussed in the literature review, e-cigarettes have become a popular method of quitting cigarette smoking in England, used in a third of quit attempts.[327] E-cigarettes can deliver similar amounts of nicotine as cigarettes but, by avoiding tobacco combustion, expose users to much lower levels of toxicants.[192,328,329] Offering e-cigarettes alongside varenicline and behavioural support may help people maintain abstinence from smoking conventional cigarettes.

The rationale for providing e-cigarettes alongside varenicline is two-fold. First, e-cigarettes mimic the sensory and behavioural aspects of smoking that contribute to dependence,[330] something which is not provided by varenicline. Second, the pharmacological effects of varenicline may be enhanced by providing additional nicotine. The main target of varenicline is the α4β2 subtype of nicotinic acetylcholine receptors, an important mediator of nicotine dependence.[331] However, there are other functionally important subtypes (e.g., α6β2) that may not be fully saturated by varenicline, allowing nicotine from other sources to bind to increase receptor activation. Moreover, varenicline does not fully stop the dopaminergic effects of smoking, and additional nicotine may bind to other receptors important to dependence that varenicline does not affect.[332] It may also be that the pharmacokinetics of varenicline and alternate nicotine delivery devices complement one another to provide a more favourable agonistic effect on receptors.[332]

Observational data from English stop smoking services show that people who use nicotine e-cigarettes, varenicline, and behavioural support together are more successful in their attempts to quit smoking than those using any other treatment.[149] Moreover there is trial evidence that combination therapy of nicotine replacement therapy (NRT) and varenicline is safe and well-tolerated and may increase abstinence rates compared with varenicline alone,[332] particularly for more dependent smokers,[333] and compared with NRT alone in alcohol-dependent smokers.[334] However, there are no trial data on combination therapy of e-cigarettes with varenicline. E-cigarettes may offer an additional advantage over NRT not only because they more closely mimic cigarettes, but also because they have been found to be more

effective nicotine delivery devices, increasing abstinence rates compared with NRT.[232,236] One trial in New Zealand had aimed to evaluate the effectiveness and safety of combining varenicline with nicotine e-cigarettes for smoking cessation among those with mental health illnesses, but it was stopped due to difficulties in recruiting participants.[335] As far as we are aware, there are no studies taking place investigating combination therapy of varenicline with e-cigarettes against varenicline alone in routine stop smoking services. If found to be effective in an RCT, this could become a new gold standard treatment for smoking cessation.

This pragmatic trial (referred to as the "E-ASSIST" for the remainder of this thesis) aims to answer the following question: in adults receiving one-to-one behavioural support at English stop smoking services, does offering nicotine e-cigarette starter kits together with varenicline increase cigarette abstinence rates compared with varenicline alone? I also aim to examine how offering e-cigarettes to clients affects attendance at stop smoking services, adherence to varenicline, and e-cigarette use.

Methods

Design

This is a two-group, parallel arm, pragmatic randomized controlled trial. It was conducted between April 2019 and March 2020 in stop smoking services in England, which are free to access for smokers trying to quit. Fifteen services were approached to take part in the study, of which eight (53%) agreed to participate and six (40%) started enrolment. Reasons for not participating included lack of staff capacity, incompatible models of service delivery, and concerns about e-cigarettes (Supplementary Table S6.1).

Services recruited participants and delivered the intervention during one-to-one in-person counselling sessions with trained stop smoking advisors. Participants were randomized (1:1 ratio in blocks of 6 or 8 participants, stratified by service) using a computer-generated random sequence with allocation concealed within opaque envelopes. Due to the nature of the intervention, participants and advisors could not be blinded to treatment assignment.

Ethical approval was granted by both University College London (8323/003) and the NHS Health Research Authority (19/LO/0239). The study was overseen by both a trial steering and a data monitoring committee. The trial protocol and analysis plan were registered prior to participant recruitment (ISRCTN16931827) and were peer-reviewed as a registered report at *Nicotine and Tobacco Research*. Updates were approved by the data

monitoring committee prior to unblinding or analysis of data. These updates added secondary analyses of continuous abstinence and respiratory symptoms, as well as sensitivity analyses for the primary outcome (Supplementary Table S6.2). The original and updated protocols are available online, alongside a summary of changes (https://osf.io/vm4g3/).

Procedures

In their first session, smokers were asked to set a target quit date, usually within one to 4 weeks, and advisors used a checklist to assess eligibility for inclusion in the trial. Cigarette smokers were eligible if they were proficient in English, were not pregnant or breastfeeding, opted to use varenicline, were willing to try e-cigarettes, and had not regularly used e-cigarettes in the past 6 months.

Advisors gave eligible smokers trial information and a consent form (https://osf.io/vm4g3/). After smokers provided written informed consent, advisors recorded baseline characteristics, took an exhaled carbon monoxide (CO) reading, and opened opaque envelopes to reveal whether smokers were randomized to the e-cigarette-varenicline group or the varenicline-only group.

This study was designed to avoid interfering with standard service protocols. Following existing practice, participants in both randomized groups were prescribed varenicline and given behavioural support during regular in-person sessions with their advisor. They were offered weekly or fortnightly support until 12 weeks after their quit date. Behavioural support aimed to minimize participants' motivation to smoke, maximize their motivation to remain abstinent, and guide their use of pharmacotherapy — as described in detail elsewhere.[336] During each session, advisors recorded smoking status, exhaled CO, adherence, adverse events, and respiratory symptoms using existing software (*QuitManager* or *PharmOutcomes*).

The COVID-19 pandemic led all in-person sessions to be stopped after March 2020. Advisors remotely followed up with those (n = 5) who had yet to complete their final 12-week appointment, using CO-monitors that had been posted to participants to verify abstinence.

Varenicline-only group

Participants were prescribed the standard 12-week course of varenicline, starting approximately 2 weeks prior to their target quit date. They were advised to take one 0.5 mg pill daily for the first 3 days, then two 0.5 mg pills daily for days 4 to 7, and finally two 1 mg

pills daily for the remaining 11 weeks. As this was a pragmatic trial, participants were not asked to avoid using e-cigarettes.

E-cigarette-varenicline group

These participants also received a standard 12-week course of varenicline described above. In addition, they were given an e-cigarette starter kit prior to their quit date. The starter kit contained an *Aspire PockeX* e-cigarette (as used in previous trials),[236] e-liquid to last for approximately 4 weeks, and an information booklet about e-cigarettes (available here: https://osf.io/59adw/). Participants could choose a total of eight 10 ml e-liquid bottles (from Aspire or Totally Wicked) in any combination from a selection of three flavours (fruit, menthol, and tobacco) and three nicotine concentrations (6, 12, and 18 mg/ml). Participants were encouraged to buy further bottles from local vape shops. Advisors gave participants brief in-person advice about how to use e-cigarettes and asked them to try the e-cigarette during the session. As this pragmatic trial aimed to test the effect of offering — not using — an e-cigarette, participants were asked but not required to use them.

Measurements

At every session after quitting, participants were asked whether they had smoked cigarettes since their previous session, with exhaled CO-readings of below 10 ppm used to verify cigarette abstinence.[337] They were also asked, since their last session, how frequently they had used varenicline or e-cigarettes and whether they had experienced specific adverse events (sleep disturbance, nausea, and throat/mouth irritation) or respiratory symptoms (phlegm, cough, shortness of breath, and wheezing). Advisors were required to report serious adverse events to the trial team, but none occurred throughout the trial. Further details about questionnaire items are available in Supplementary Table S6.3.

Nine-to-12-week smoking abstinence was the primary outcome, with participants considered abstinent if they (1) reported not smoking cigarettes between weeks 9 and 12 after their quit date and (2) gave a CO-reading below 10 ppm at week 12 or later. Participants with missing data for the primary outcome were assumed not to be abstinent.

Secondary abstinence outcomes included two-to-four-week smoking abstinence (defined as above) and length of continuous abstinence before relapse. The latter outcome was not included in the original protocol but was added to the updated protocol and registered prior to data analysis (https://osf.io/vm4g3/). It was measured as the number of

weeks, from the quit date onwards, that each participant remained continuously abstinent from smoking before relapsing.

Attendance was assessed using two outcomes. Firstly, whether or not a participant continued attending sessions until at least 12 weeks after the quit date. Secondly, the number of sessions, of a possible four, a participant attended in their first 4 weeks after their quit date.

Two outcomes assessed adherence to varenicline. Firstly, whether or not participants reported using varenicline daily for at least 1 week after their quit date and, secondly, whether they used varenicline daily until at least 8-weeks after their quit date. The latter allows up to 4 weeks of varenicline use prior to quitting. E-cigarette outcomes were daily use for at least 1 week after the quit date and daily use at every session attended after their quit date.

Time to first experience of each adverse event and respiratory symptom were recorded for each participant.

Analysis

I conducted data analyses blinded to treatment assignments using R version 4.1.3.[338] Anonymized data and analysis code are openly available (https://osf.io/vdngh/). The primary and other binary outcomes were reported as risk ratios (RR) with 95% compatibility intervals (95% CIs). Analyses of binary smoking abstinence outcomes followed the intention-to-treat principle, where all those with missing follow-up data were treated as having relapsed (0% abstinent).

In sensitivity analyses for the primary outcome, RRs were calculated with a range of different assumed abstinence rates (e.g., 10%, 20%, 30%, and 40%) in those lost to follow-up (who thus had missing data for the primary outcome).

Moreover, for length of continuous abstinence from quit date onwards, the hazard ratio (HR) for relapse was estimated using a Cox proportional-hazards model. A HR of less than one means that participants in the e-cigarette-varenicline group had a lower rate of relapse and thus remained abstinent for longer than those in the varenicline-only group. Participants who were lost to follow-up were assumed to have relapsed in the week after the final stop smoking session they attended where CO-measurements were taken. Participants who were still abstinent at week 12 were considered censored after this time.

Unplanned sensitivity analyses for the primary outcome adjusted for e-cigarette nonadherence (i.e., people in the e-cigarette-varenicline group who did not try e-cigarettes) and contamination (i.e., people in the varenicline-only group who tried e-cigarettes), using a

method described by Cuzick et al..[339] This provides an estimate of the effect of trying e-cigarettes (daily use for at least a week) among co-operators: individuals who would try e-cigarettes if they were assigned to the e-cigarette-varenicline group, but would not try them if assigned to the varenicline-only group.[340]

Cox models were also used to estimate the HR for time to first experiencing each adverse event and respiratory symptom. These were reported alongside the incidence rate for each randomized group (i.e., the number of people who reported an event divided by the person-weeks-at-risk), with the incidence rate ratio (IRR) estimated using a log-rate model. For these analyses, participants were considered censored after the final week they attended a follow-up session, up to a maximum of 12 weeks post quit date.

Sample size and early stopping

As described in the original study protocol (https://osf.io/vxw8r/), previous literature suggested an expected risk ratio of 1.26 for our primary outcome.[149,332] It was determined that a sample of 633 participants per group would provide at least 90% power to detect this effect size in a two-tailed analysis.

Restrictions introduced in response to the COVID-19 pandemic caused services to move sessions online, which meant advisors could not provide e-cigarettes to participants or take in-person CO-readings. This led the trial to be paused in March 2020, before the target number of participants had been recruited (92/1266). I and the trial team started planning amendments to the procedures to allow the trial to continue remotely, including behavioural support being given via telephone or video call and cigarette abstinence being verified remotely using saliva anabasine and anatabine. These plans were halted when, in July 2021, Pfizer recalled Champix (the only form of varenicline available in England) due to levels of N-nitroso-varenicline that were higher than considered acceptable by the European Medicines Agency.[341] In agreement with the funder, Pfizer, the trial was stopped in November 2021.

Process evaluation

Quantitative process evaluation included summaries of attendance at stop smoking services, varenicline adherence, and e-cigarette adherence and/or contamination.

Results

Participants

Of the 92 cigarette smokers randomized at stop smoking services between April 2019 and March 2020, 48 were assigned to the e-cigarette-varenicline group and 44 to the varenicline-only group. Participants had a mean age of 43.9 (SD = 13.1), 51% (n = 47) were women, 79% (n = 73) were white, and 29% (n = 27) had routine or manual occupations (Table 6.1). Table 6.1 shows that participants in both randomized groups had similar baseline characteristics. Of those randomized, 46% (n = 42) attended follow-up sessions for at least 12 weeks after their quit date (Figure 6.1).

Table 6.1. Baseline characteristics*.

	E-cigarette	Control	Combined
N	48	44	92
Age	43.8 ± 12.1	44.0 ± 14.2	43.9 ± 13.1
Gender			
Woman	52% (25)	50% (22)	51% (47)
Man	48% (23)	50% (22)	49% (45)
Ethnicity			
White	79% (38)	80% (35)	79% (73)
Black or Asian	17% (8)	11% (5)	14% (13)
Other or mixed	4% (2)	9% (4)	7% (6)
Occupation			
Managerial or professional	40% (19)	39% (17)	39% (36)
Routine or manual	27% (13)	32% (14)	29% (27)
Other†	33% (16)	30% (13)	32% (29)
Free prescription			
Not reported	71% (34)	66% (29)	68% (63)
Yes	29% (14)	34% (15)	32% (29)
Anxious or depressed			
No	77% (37)	68% (30)	73% (67)
Yes	24% (11)	32% (14)	27% (25)
Cigarettes per day‡			
≤10	15% (3)	30% (7)	23% (10)
11-20	45% (9)	48% (11)	47% (20)
21-30	30% (6)	22% (5)	26% (11)
≥31	10% (2)	0% (0)	5% (2)

* Age presented as mean ± standard deviation. All other characteristics summarised as % (n).

† Includes people who are retired, unemployed or home carers.

‡ Only recorded for 43 participants: 20 in the e-cigarette-varenicline (e-cigarette) group and 23 in the varenicline-only (control) group.

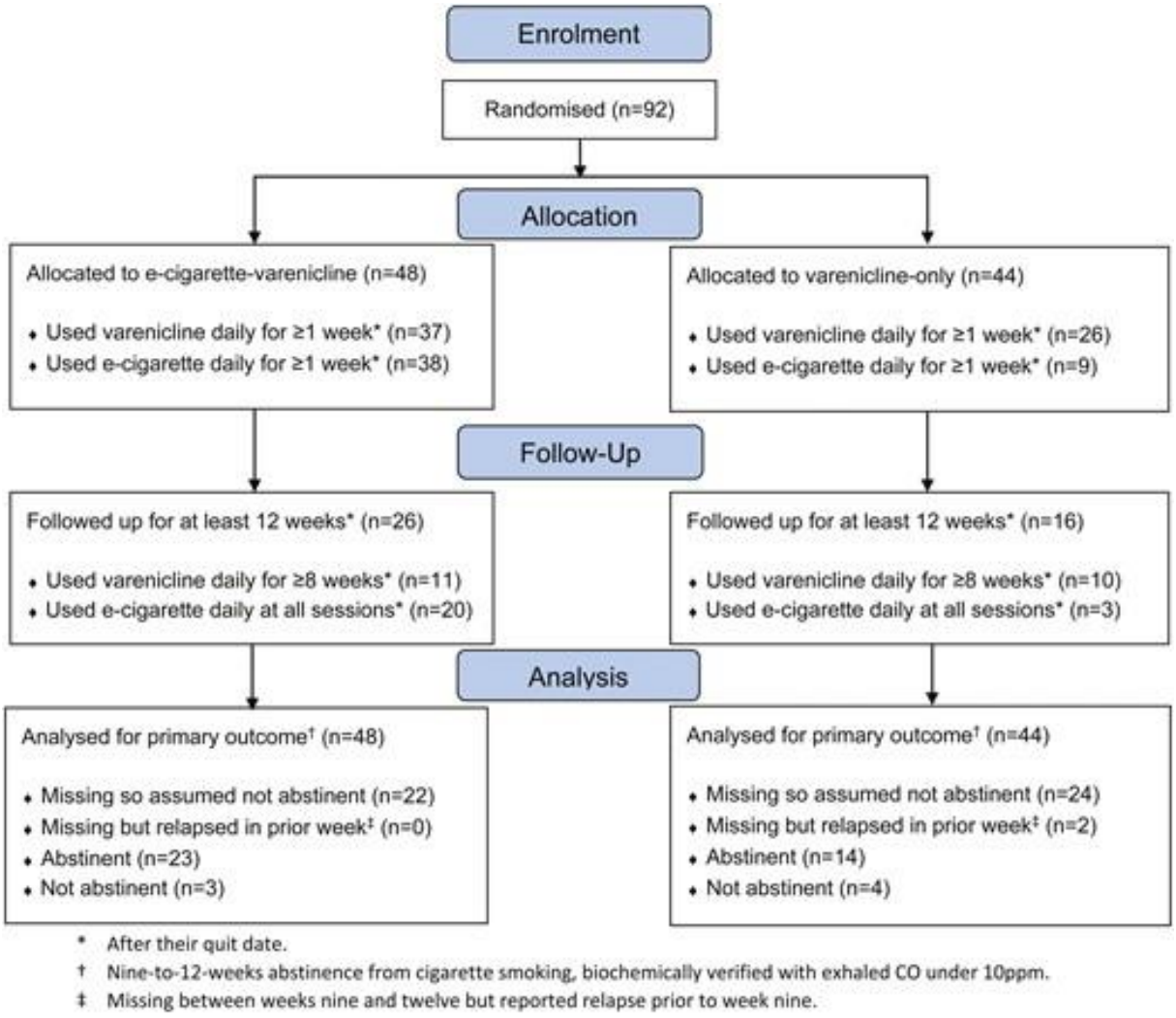


Figure 6.1. CONSORT flow diagram. A software issue meant it was only possible to determine the number of participants who were both eligible for and willing to take part in the trial, not the total number who were approached. Reasons for loss to follow-up were not recorded due to the pragmatic nature of the trial. *After their quit date. †Nine-to-12-weeks abstinence from cigarette smoking, biochemically verified with exhaled CO under 10 ppm. ‡Missing between weeks 9 and 12 but reported relapse prior to week 9.

Smoking Abstinence

Primary—Nine-to-12-week abstinence

Nine-to-12-week abstinence rates were 47.9% (n = 23) in the e-cigarette-varenicline group compared with 31.8% (n = 14) in the varenicline-only group. This equates to a 1.51-fold increase in abstinence rates in those offered e-cigarettes; however, the compatibility interval was wide and included the possibility of no difference (RR 1.51, 95% CI .91–2.64). Bayes factors are shown in Supplementary Table S6.4. Results were similar when including quits that were self-reported but not biochemically verified (52.1% versus 34.1%; RR 1.53, 95% CI .95–2.60).

Supplementary Table S6.5 shows sensitivity analyses that relaxed the assumption that all participants missing for the follow-up had relapsed. These show that the higher the percentage of missing participants who were abstinent, the smaller the estimated effect size (e.g., RR 1.38 if 20% of missing participants were abstinent).

Secondary — Two-to-four-week abstinence

Two-to-four-week abstinence rates were 1.37 times higher in the e-cigarette-varenicline than varenicline-only group, but the compatibility interval was compatible with effects ranging from just under no difference to 2.01 times higher rates in those offered e-cigarettes (68.8% versus 50.0%; RR 1.37, 95% CI .98–2.01).

Secondary — Relapse from Continuous Abstinence

The e-cigarette-varenicline group had a 43% lower (instantaneous) rate of relapse from continuous cigarette abstinence than those in the varenicline-only group (Cox model; HR 0.57, 95% CI .34–0.96). Figure 3.5.2 shows a Kaplan-Meier plot for the length of time each participant remained continuously abstinent from cigarettes before relapsing. Note that these analyses were not included in the original protocol but were added to the updated protocol which was registered prior to data analysis.

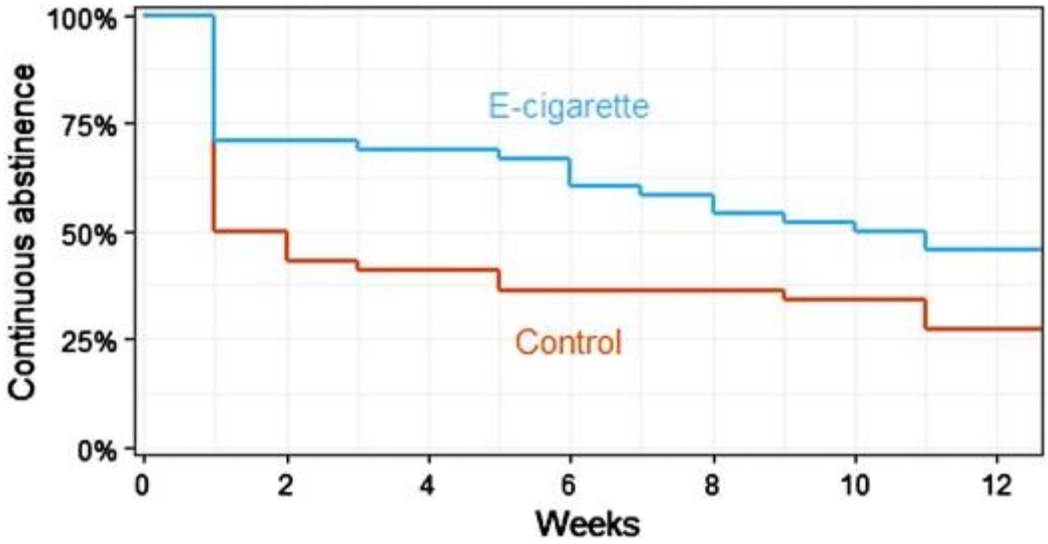


Figure 6.2. Kaplan–Meier plot showing the percentage of participants continuously abstinent (CO < 10 ppm) from cigarette smoking at each week after their quit date. Participants who were lost to follow-up were assumed to have relapsed in the week after the final session they attended.

Safety

Adverse events

Overall, 59.8% (n=55) of participants experienced at least one adverse event between their quit date and final session. Sleep disturbance was reported by 44.6% (n=41) of participants, nausea by 34.8% (n=32), and throat or mouth irritation by 27.2% (n=25). Comparisons of event incidence rates and hazard ratios between the e-cigarette-varenicline and varenicline-only group are shown in Table 6.2. These estimates were too imprecise to determine the size or direction of differences between groups (e.g., any adverse event; HR 0.69, 95%CI 0.40-1.20). Risks of adverse events among those followed-up for at least 12 weeks are shown in Supplementary Table S6.6. No serious adverse events were reported in either group.

Respiratory symptoms

Respiratory symptoms were reported by 47.8% (n=44) of participants at least once between their quit date and the final session they attended. Phlegm was reported by 35.9% (n=33) of participants, cough by 33.7% (n=31), shortness of breath by 21.7% (n=20), and wheezing by 14.1% (n=13). Table 6.2 shows that rates of respiratory symptoms were similar in the e-cigarette-varenicline and varenicline-only group (e.g., any symptom; HR 1.05, 95%CI 0.57-1.92), but compatibility intervals included the possibility of meaningful differences between groups.

Table 6.2. Incidence of adverse event and respiratory symptoms.

	Group*	Events	Weeks †	Rate‡	IRR (95%CI)‡	HR (95%CI)‡
Adverse events						
Any	Control	24	144	1.67	Ref	Ref
	E-cigarette	31	193	1.61	0.96 (0.57-1.66)	0.69 (0.40-1.20)
Sleep	Control	21	163	1.29	Ref	Ref
disturbance	E-cigarette	20	283	0.71	0.55 (0.30-1.02)	0.64 (0.34-1.20)
Nausea	Control	14	209	0.67	Ref	Ref
	E-cigarette	18	261	0.69	1.03 (0.51-2.11)	0.84 (0.41-1.72)
Throat/mouth	Control	7	244	0.29	Ref	Ref
irritation	E-cigarette	18	310	0.58	2.02 (0.88-5.21)	1.11 (0.45-2.74)
Respiratory symptoms						
Any	Control	19	164	1.16	Ref	Ref
	E-cigarette	25	258	0.97	0.84 (0.46-1.54)	1.05 (0.57-1.92)
Phlegm	Control	13	210	0.62	Ref	Ref
	E-cigarette	20	293	0.68	1.10 (0.55-2.27)	0.75 (0.37-1.53)
Cough	Control	14	200	0.70	Ref	Ref
	E-cigarette	17	301	0.56	0.81 (0.40-1.66)	1.49 (0.72-3.08)
Shortness of	Control	8	225	0.36	Ref	Ref
breath	E-cigarette	12	332	0.36	1.02 (0.42-2.59)	1.22 (0.48-3.10)
Wheezing	Control	6	249	0.24	Ref	Ref
	E-cigarette	7	381	0.18	0.76 (0.25-2.37)	0.85 (0.26-2.82)

* There were 44 participants in the varenicline-only (control) group and 48 in the e-cigarette-varenicline (e-cigarette) group.

† Total person-weeks at risk of first event. For each person, this is the number of weeks from the quit date until they either experienced the event/symptom, were lost to follow-up, or completed the study (12 weeks post-quit).

‡ Incidence rate calculated per 10 person-weeks. Incidence rate ratios (IRR) and corresponding 95% compatibility intervals (95%CI) estimated using log-linear rate models. Hazards ratios (HR) and corresponding 95% CIs estimated using Cox proportional-hazards models. Schoenfeld tests found some evidence for non-proportional hazards for throat/mouth irritation (p=.046) and cough (p=.032), but all other outcomes were compatible with proportionality (p>.31).

Process evaluation: Quantitative data

Attendance

Of the 92 participants randomised, 45.7% (n=42) continued attending stop-smoking service sessions for at least 12 weeks after their quit date. Attendance for 12 weeks was 54.2% (n=26) in the e-cigarette-varenicline group compared with 36.4% (n=16) in the varenicline-only group (RR 1.49, 95%CI 0.95-2.47). On average, participants in the e-cigarette-varenicline group attended 3.1 out of a possible four sessions in the first four weeks after quitting, while those in the varenicline-only group attended 2.8 sessions (proportional-odds model; OR 1.69, 95%CI 0.93-2.45).

Varenicline adherence

In the e-cigarette-varenicline group, 77.1% (n=37) of participants used varenicline daily for at least one week after their quit date, compared with 59.1% (n=26) in the varenicline-only group (RR 1.30, 95%CI 0.99-1.79). Daily varenicline use for at least eight weeks after quitting was reported by 22.9% (n=11) of participants in the e-cigarette-varenicline group and 22.7% (n=10) in the varenicline-only group (RR 1.01, 95%CI 0.47-2.20).

E-cigarette adherence and contamination

In the e-cigarette-varenicline group, 79.2% (n=38) used e-cigarettes daily for at least one week after their quit date, and 41.7% (n=20) reported daily use at every session they attended after quitting. There was some contamination: 20.5% (n=9) of participants in the varenicline-only group used e-cigarettes daily for at least one week after their quit date, and 6.8% (n=3) reported daily use at every session they attended after quitting.

In an unplanned analysis of the primary outcome that adjusted for non-adherence (i.e., being assigned to try e-cigarettes but not doing so) and contamination (i.e., being assigned to the control group but trying e-cigarettes), trying e-cigarettes was estimated to increase nine-to-12-week abstinence by 2.66 times (RR 2.66, 96%CI 1.17-6.05).[339]

Discussion

Summary

This study provides tentative evidence that, among people receiving one-to-one behavioural support, offering e-cigarettes alongside varenicline may be more effective for cigarette smoking cessation than varenicline alone. The evidence is tentative because the sample size was smaller than planned — caused by COVID-19 and a manufacturing recall — which meant our effect estimates were imprecise (highly compatible with 9% lower to 164% greater nine-to-12-week abstinence rates in those given e-cigarettes). More data are needed to confirm whether providing e-cigarettes and varenicline together helps more people remain abstinent than varenicline alone.

Interpretation

Nonetheless, this study adds to a wider literature on the effects of offering alternative nicotine products alongside varenicline. The results closely align with a previous meta-analysis finding the 50% higher odds of cigarette abstinence in those given NRT alongside varenicline than varenicline alone (OR 1.50, 95%CI 1.14–1.97).[332] However, another recent study showed that adding nicotine patches to varenicline had little effect on abstinence rates (OR 0.99, 95% CI 0.87–1.12).[342] It is possible that fast-acting nicotine products — including gums, sprays, and e-cigarettes — are better at helping varenicline users remain abstinent, as they can satisfy momentary urges for nicotine.[142] Moreover, the behaviour and sensory experience of using an e-cigarette is similar to that of smoking a cigarette, which could make e-cigarette more effective for smoking cessation than other nicotine products.

Process evaluation

Adherence to e-cigarettes was moderately high, with over three-quarters of those in the e-cigarette group reporting using e-cigarettes daily for at least one week. There was also some contamination; one-fifth of those in the control group used e-cigarettes daily for at least one week after their quit date. This is a similar level of adherence and contamination as found in previous trials of e-cigarettes in NHS stop smoking services.[236]

In interviews reported elsewhere, participants reported that they viewed the e-cigarettes, varenicline, and behavioural support to be acceptable and complementary, but some were concerned about continued nicotine use and the harshness of vaping.[6,343] These concerns may be alleviated by providing information around the relative harms of smoking versus vaping,[344,345] giving advice about titrating inhalation to avoid harshness, or providing products that are less harsh to inhale such as those using lower pH nicotine salts e-liquid.[345,346] Our results align with previous studies showing that people who are worried about the addictiveness of nicotine use too little NRT, which stops them from benefiting from it.[347] These worries may be especially pronounced for e-cigarettes, both because long-term use is more common with e-cigarettes than NRT[236] and because negative perceptions about the harms of e-cigarettes have become increasingly prevalent over time, as shown in Chapter 3.[249,300]

Strengths and limitations

The study benefited from using randomized assignment, which provides internal validity (exchangeability), and a pragmatic design within stop smoking services that guarantees some degree of ecological validity (given that this is the setting where such an intervention would likely be implemented). However, there were several limitations.

First, clients could not be blinded to their assigned group. This is an inherent limitation of many smoking cessation trials. We partially militated against it by using objective biochemical measures (CO readings) to verify abstinence from cigarette smoking, which reduces the risk of outcome assessment being biased by assessors knowing which group participants were assigned to. Second, services only followed up with clients for 12 weeks after quitting, and because this is a pragmatic trial, we did not ask them to extend this period. This meant abstinence was measured for less than the 6 months recommended by Russell Standard guidelines for smoking cessation trials.[348] Third, just under half of the participants continued attending services until their final 12 week follow-up session, with 50% greater loss to follow-up in the e-cigarette-varenicline than varenicline-only group. The primary analysis assumed those with missing follow-up data had relapsed, which is likely a reasonable assumption as people tend to only continue attending services if they remain abstinent. Nonetheless, in sensitivity analyses, I quantitatively assessed how certain violations of this assumption would affect results.[349] I did not model assumed abstinence rates for those lost to follow-up being higher in the control than for the intervention group. This would have been the most conservative assumption but unlikely in the context of our trial where both arms were receiving similarly intensive in-person support. Fourth, a fifth of those in the varenicline-only group used e-cigarettes while a fifth of those in the e-cigarette-varenicline group did not. This contamination and nonadherence would dilute any effect of using (rather than being offered) e-cigarettes on abstinence, but I accounted for this in a sensitivity analysis. Fifth, I compared combination treatment with e-cigarettes and varenicline to varenicline alone among smokers receiving intensive behavioural support. The results do not provide information about the effectiveness of e-cigarettes alone relative to varenicline alone. They also may not be generalizable to settings where smokers receive little to no support. Finally, trial enrolment was stopped early due to the COVID-19 pandemic and recall of varenicline by Pfizer. This meant the study did not have a large enough sample to precisely estimate effects.

Conclusion

In conclusion, this study found preliminary evidence that, among people receiving one-to-one behavioural support, providing e-cigarettes alongside varenicline may be more effective than offering varenicline alone. However, estimates were imprecise due to the lower than planned sample size; for the primary outcome, anything from 9% lower to 164% higher abstinence rates remained highly compatible with the data (at the 95% compatibility level). More data are needed to clarify the effect of adding e-cigarettes to smoking cessation treatment with varenicline. Alongside e-cigarettes, heated tobacco products may also provide promise as a method for cigarette smoking cessation. In the next chapter, I will review the literature into the effectiveness of heated tobacco for smoking cessation, as well as their safety and population-level impact.

7. Heated Tobacco for Reducing Smoking Prevalence

Abstract

Full Title: Heated Tobacco Products for Smoking Cessation and Reducing Smoking Prevalence: A Cochrane Systematic Review.

Background: To regulate heated tobacco products (HTPs) appropriately, policy makers need to understand their impact on health, cigarette smoking cessation, and smoking prevalence.

Methods: This systematic review included randomised controlled trials (RCTs) where people were randomised to switch to exclusive HTPs use or a control condition. Time-series studies were also eligible if they examined the population-level impact of HTPs on cigarette smoking prevalence or sales.

Results: There were no studies reporting on cigarette smoking cessation, so the effectiveness of HTPs for this purpose remains uncertain. Eleven RCTs were identified, all of which were funded by tobacco companies. There was insufficient evidence for differences in risk of adverse/serious adverse events between people randomised to switch to HTPs, smoke cigarettes, or attempt abstinence from all tobacco. There was moderate-certainty evidence that HTP users have lower exposure to toxicants/carcinogens than cigarette smokers and very low- to moderate-certainty evidence of higher exposure than those attempting abstinence from all tobacco. Two time-series studies suggested that the rate of decline in cigarette sales accelerated after the introduction of HTPs to market in Japan, but this may not reflect a causal effect of HTPs.

Conclusions: There is moderate-certainty evidence that HTPs expose users to fewer toxicants/carcinogens than cigarettes, and weaker evidence of higher exposure than using no tobacco, but independent replication is needed. There is a need for evidence on smoking cessation and adverse events. Declines in cigarette sales appeared to accelerate after the introduction of heated tobacco to market in Japan, but it is unclear whether this association is causal or if it translated to declines in smoking prevalence.

Status: Published in Cochrane's Database (DOI: 10.1002/14651858.CD013790.pub2).

Background

Heated tobacco products

In the literature review, I introduced heated (or heat-not-burn) tobacco products (HTPs): devices that are designed to heat tobacco leaf/sheet to a high enough temperature to release nicotine-infused aerosol, without burning it or producing smoke. Many of the toxic and carcinogenic products of cigarette smoking are formed during combustion. HTPs are marketed as less harmful and as alternatives to conventional cigarettes because they are engineered to avoid combustion.[246] The extent to which they help people quit smoking is largely unknown, and their impact on youth uptake to smoking is contentious.[276] Therefore, it is unclear what impact HTPs will have on smoking prevalence across the population.

'Premier' was the first HTP made available for consumers. It resembled a cigarette, but the tobacco was not directly burned, instead it was heated by lighting a *carbon-tip*. Premier was introduced to test markets throughout the US by RJ Reynolds in 1988, but it was not widely used and was discontinued in 1989.[240] In the early 2000s, RJ Reyolds introduced another carbon-tip HTP, 'Eclipse', and they funded research to support marketing claims that it reduced health risks relative to cigarettes. A court case in the US succeeded in challenging these reduced risk claims, but trial evidence did suggest users of Eclipse had lower exposure to toxicants than people smoking cigarettes.[350,351]

The first electronic HTPs were produced by Philip Morris International (PMI). They introduced 'Accord' into the US in 1997 and a similar product, 'Heatbar', in Germany in 2007.[240] While these products have both since been discontinued, they acted as predecessors to 'IQOS'.

The current HTP market is dominated by electronic rather than carbon-tip devices. Current brands include IQOS by PMI, 'glo' by British American Tobacco, and 'Ploom Tech' by Japan Tobacco International. IQOS and glo produce aerosol by directly heating tobacco sticks which resemble small cigarettes. Conversely, Ploom Tech produces aerosol by heating a similar liquid to that found in e-cigarettes. This aerosol is then drawn through a bulb of tobacco to infuse it with flavour. Of these products, IQOS was the first to launch in 2014 in Japan and Italy, and it has since entered markets across Asia, Europe, and the Americas. Most recently, in 2019, the US Food and Drug Administration (FDA) permitted the sale of IQOS and in 2020 authorised their marketing as a modified-exposure tobacco product.[352] At the time of writing, HTPs were most popular in Japan and the Republic of Korea; tobacco sticks for

HTPs constituted 15.8% and 8.0% respectively of each country's tobacco market in 2018.[353] Market research by Euromonitor estimates that HTPs had an increased share of the retail value of all nicotine or tobacco products between 2017 and 2018, which was similar to e-cigarettes globally.[354] However, HTP use remains rare in Canada, the US and much of Europe, as shown for England in Chapter 6.[1,320]

Nicotine is the primary addictive compound in cigarettes. Neuroadaptation to repeated nicotine delivery from smoking causes people who quit to experience withdrawal and cravings.[19,331] Like cigarettes, HTPs contain nicotine. They may aid smoking cessation in a similar way to NRT and e-cigarettes: people can use them to relieve nicotine cravings without smoking cigarettes.[139] HTPs may also provide certain advantages over NRT. One limitation of NRT is that it poorly addresses the behavioural and sensory cues associated with cigarette smoking, such as repeated hand-to-mouth actions and the scratch at the back of the throat when inhaling smoke. Evidence shows that denicotinised cigarettes reduce cravings and withdrawal symptoms among abstinent smokers, despite containing negligible levels of nicotine.[355] This suggests that these cues contribute to cigarette dependence. HTPs may more closely replicate these cues than NRT. Because HTP aerosol is delivered to the throat and lungs, nicotine absorption likely occurs more rapidly than from patches, gum, or lozenges, which are absorbed through the skin or buccal mucosa.[248] The speed with which nicotine is absorbed may be one of the key determinants of dependence,[356] so HTPs may provide a better replacement for cigarette smoking than NRT. E-cigarettes also deliver nicotine rapidly to the throat and possibly lungs[233] and, like HTPs, they mimic the hand-to-mouth actions of cigarette smoking. But only HTPs contain tobacco leaf/sheet, so their flavour may more closely resemble cigarette smoke,[269] which may make them more attractive to smokers.[357] Moreover, in some countries, the sale of nicotine e-cigarettes is banned or heavily restricted.[358] In such environments, HTPs may be the only consumer product available that delivers nicotine rapidly through a potentially less harmful medium than tobacco smoke.

I refer to the complete replacement of cigarettes with HTPs as 'switching'. A substantial proportion of people who use HTPs for smoking cessation may continue using these products for some time after they stop smoking cigarettes, as is the case with e-cigarettes.[236] Encouraging people to switch from smoking cigarettes to using HTPs would only be beneficial if HTPs are less harmful to health or if HTPs eventually help people taper off nicotine entirely. The safety of HTPs to users depends on both the acute harm, measured by adverse and serious

adverse events, and the long-term harm of repeated inhalation of damaging compounds in HTP aerosols.

Biomarkers can be used to measure exposure to these harmful toxicants and carcinogens. Important exposure biomarkers include: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a marker of tobacco-specific N-nitrosamine (TSNA) exposure that is linked to numerous cancers;[359] 1-hydroxypyrene (1-OHP) and 1- and 2-naphthol, indicators of exposure to polycyclic aromatic hydrocarbons that are associated with cancers and kidney and liver damage; 3-hydroxypropylmercapturic acid (3-HPMA), a marker of exposure to acrolein that is linked to respiratory disease;[360] and carboxyhaemoglobin (COHb), a measure of recent carbon monoxide (CO) intake.

Full details about biomarkers of exposure to toxicants and carcinogens that will be included in this review are listed below:

- TSNA exposure (measured using the biomarker urinary NNAL). Several TSNAs are group 1 or 2A carcinogens, implicated in the increased incidence of cancer among smokers;[359] NNAL is the most widely investigated biomarker of TSNA exposure;[361] and NNAL is found in high quantities among cigarette smokers, but very low quantities among NRT and e-cigarette users.[193] It therefore also gives an indication of the safety profile of HTPs when compared with other smoking cessation aids.
- Polycyclic aromatic hydrocarbon exposure (measured using the urinary biomarkers 1-hydroxypyrene and 1- and 2-hydroxynaphthalene). Polycyclic aromatic hydrocarbons are produced though incomplete combustion of organic compounds, as occurs through cigarette smoking. Exposure to these compounds is linked to cancers along with DNA, kidney, and liver damage.[362]
- Exposure to the volatile organic compounds acrolein, heavy metals, and butadiene (measured using the biomarkers 3-HPMA, heavy metals, and MHBMA3 respectively). Acrolein is implicated as the key compound associated with smoking-induced respiratory disease.[360] 3-HPMA is a widely used urinary biomarker of acrolein exposure.[363] Carcinogenic heavy metals, like lead and cadmium, are present in cigarette smoke.[359] Butadiene is a group 1 carcinogen.
- Carbon monoxide exposure (measured using exhaled carbon monoxide or carboxyhaemoglobin in blood). High exposure to carbon monoxide among sole HTP users would indicate that the tobacco in HTPs has undergone pyrolysis or combustion.

Carbon monoxide exposure is linked to the increased risk of cardiovascular disease among smokers.[364]

Manufacturers of HTPs claim that the aerosol they produce contains substantially lower levels of toxicants than cigarette smoke and, as a result, that they have reduced risk potential or are less harmful.[365,366] Two systematic reviews supported claims about lower toxicant levels, but found that most research into HTPs was funded through sources affiliated with the tobacco industry.[248,367] In addition, reduced exposure does not necessarily indicate reduced harm. One also needs to examine changes in markers of health. Moreover, the safety of longer-term use, cannot be addressed with confidence until long-term cohort studies have collected sufficient data on the rates of disease and death in HTP users.

Rationale for this review

Countries vary in the regulatory approaches they take to HTPs. For policymakers to regulate HTPs effectively and proportionately, there is a need for evidence to inform a judgement on their likely public health impact. The overall impact of HTPs on public health will depend on a variety of factors. HTPs would benefit public health are if they increase smoking cessation, decrease smoking prevalence, and are less harmful than cigarette smoking. Conversely, even if these products are shown to be much less harmful than cigarettes, HTPs could damage public health if they hinder smoking cessation or increase smoking prevalence.

The effect of HTP use on smoking prevalence will depend on whether they influence rates of attempted quitting among cigarette smokers, the proportion of these attempts that are successful, cigarette uptake among non-smokers, and relapse among people who had previously quit smoking. Therefore, we are not only interested in studies that report individual-level effects of HTPs on smoking cessation, but also those that estimate their population-level effects on smoking prevalence. This review investigates up-to-date evidence for both, using appropriate study designs.

The growing popularity of HTPs means that people who smoke may be increasingly likely to seek advice from practitioners who need to know whether HTPs are effective for smoking cessation and how their safety compares with cigarettes and other alternative nicotine products. If HTPs are found to be safe and effective for smoking cessation, they would offer a novel treatment for cigarette addiction. Moreover, evidence on associations between HTP use and smoking prevalence will help to guide the regulation of HTPs.

Licensed smoking cessation medications tend to be used for a short time while quitting, whereas people may continue using HTPs for extended periods after they quit. This means that it is especially important to evaluate indicators of the long-term safety of HTP use (such as exposure to toxicants and carcinogens) in addition to adverse events occurring in the short term.

Study aim

To evaluate the effectiveness and safety of HTPs for smoking cessation and the impact of HTPs on smoking prevalence.

Methods

Protocol

The protocol of this review was registered prior to the literature search, screening, data extraction, and analysis (https://doi.org/10.1002/14651858.CD013790).

Inclusion criteria: Study design

The methods of this review are divided into three subsections, representing the different objectives: effectiveness for smoking cessation, safety, and smoking prevalence.

Effectiveness for smoking cessation:

Individual-level and cluster-randomised controlled trials (RCTs) to examine the effectiveness (or efficacy) of HTPs for tobacco smoking cessation.

Safety

Individual-level, randomised cross-over and cluster-RCTs to explore adverse and serious adverse events and biomarkers of toxicant and carcinogen exposure. RCTs in optimised settings for smoking cessation, such as those where participants stayed in a clinic with restricted access to tobacco products, were eligible for inclusion, as were studies in naturalistic or ambulatory settings.

Smoking prevalence

Interrupted and multiple time-series studies were included to examine the population-level effect of HTPs on cigarette smoking prevalence. Smoking cessation interventions do not represent the way most people use HTPs: without support from a researcher or trained specialist. Moreover, even if HTPs encourage smoking cessation among those trying to quit, their impact on smoking prevalence depends on how they affect smoking initiation and the number of people who make a quit attempt and are successful in remaining abstinent. We used time-series studies to assess how changes in HTP prevalence are associated with changes in smoking prevalence (or cigarette sales), with the limitation that associations might not reflect causal effects.

Inclusion criteria: Participants

Effectiveness and safety

We included adults who were defined as current cigarette smokers by the study at the time of enrolment.

Smoking prevalence

We did not restrict by participant characteristics, as we are interested in population-level data. We focused on any individuals who indicated their smoking status or consumption and HTP use or consumption, measured by survey or by record of sales.

Inclusion criteria: Interventions

HTPs, defined as hand-held devices that aim to heat tobacco to a temperature high enough to produce a nicotine-infused aerosol but too low to cause self-sustaining combustion. HTPs differ from e-cigarettes in that they heat compressed tobacco leaf rather than a liquid that is infused with nicotine.

Effectiveness and safety

We are interested in studies that compared HTPs, or the addition of HTPs, to no treatment (i.e., continued tobacco smoking), placebo or any other smoking cessation treatment, including NRT, e-cigarettes, snus, varenicline, bupropion, and behavioural support. HTPs

could be provided in addition to any other smoking cessation treatment, providing there was equivalent provision of the additional treatment for the control group. We only included studies where participants in the HTP arm were instructed to stop smoking combustible cigarettes for at least seven days.

Smoking prevalence

For interrupted time-series studies, the interventions of interest were the introduction of HTPs to market or the time point where HTPs began gaining popularity. For multiple time-series studies, we were interested in the extent to which changes in the prevalence of HTP use were associated with changes in the prevalence of cigarette smoking (or cigarette sales as a proxy), after adjusting for other influences that could affect changes in the prevalence of smoking at the population level.

Inclusion criteria: Primary outcomes

Effectiveness

Tobacco smoking cessation at the longest follow-up point available, using intention-to-treat and biochemically verified abstinence where possible. While HTPs contain tobacco, they are designed to avoid or minimise combustion and smoke. Therefore, HTP use was not classified as tobacco smoking. If review updates find studies reporting smoking cessation, we will only include those which report abstinence at four-week follow-up or longer. We will use the strictest definition of abstinence recorded, that is, prolonged or continuous abstinence over point prevalence, and biochemically verified over self-reported abstinence. Typically, Cochrane Tobacco Addiction Group reviews only include data on smoking cessation at six months or longer. Short-term outcomes will be included in the next update of this review because a paucity of longer-term data is anticipated. In subsequent updates, as and when more data become available, the inclusion criteria may change accordingly.

Safety

Number of people reporting adverse events and serious adverse events. We defined serious adverse events as medical incidents that are potentially life-threatening, require hospitalisation, result in disability or death, or a combination of these. Adverse events were

medical problems — including cough, headache, and dry mouth — that did not fulfil the above criteria to be considered serious.

Smoking prevalence

Change in the prevalence of cigarette smoking, measured as the proportion of people in a given locality that regularly smoke cigarettes or other combustible tobacco products, over a defined time period. We included cigarette sales as a proxy for prevalence, measured as the number of cigarettes sold in a given locality over a given time period. This was used as a proxy because, in a population where mean cigarette consumption among smokers remains stable, declines in cigarette sales imply falls in smoking prevalence. However, it should be considered an indirect measure of prevalence because smokers can reduce their cigarette consumption without quitting.

Inclusion criteria: Secondary outcomes

Safety

All secondary outcomes are measures of safety. We only included studies that reported safety outcomes at one-week follow-up or longer.

Biomarkers of toxicant and carcinogen exposure. We included measures of exposure to tobacco-specific N-nitrosamines, polycyclic aromatic hydrocarbons, volatile organic compounds, and CO, as discussed in detail the background section.

Biomarkers of harm, also known as surrogate endpoints. We included measures of lung function (forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and FEV1/FVC), blood pressure, heart rate, heart rate variability, and blood oxygen saturation.

Study search methods

The following databases were searched on 19 January 2021:

- Cochrane Tobacco Addiction Group's Specialised Register;
- Cochrane Central Register of Controlled Trials;
- MEDLINE;
- Embase;

- PsycINFO;
- Business Source Complete;
- Factiva;
- ClinicalTrials.gov;

World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).

The search was restricted to studies published since 2008, three years before the first internet searches for HTPs began.[368]

The search terms were: heated tobacco OR carbon-heated tobacco OR heat-not-burn OR heat not burn OR tobacco heating system$ OR tobacco heating device$ OR tobacco heating product$ OR tobacco vapor product$ OR tobacco vapour product$. We also searched for the term smoking AND (iqos OR glo OR ploom OR ifuse OR fuse OR pulze OR teeps OR pax OR mok OR lil OR iuoc OR htp OR thp OR ths OR chtp).

As we are only interested in studies that used humans, we excluded those with the terms animal$ OR mice OR rat$ OR in vitro OR in silico OR in vivo in their title.

We searched the reference lists of eligible studies found in the literature search. In order to identify government reports and unpublished studies, I contacted relevant charities and authors of published research or trial protocols. Searches of ClinicalTrials.gov and the ICTRP detailed above were used to identify trial registry records.

Selection of studies

I and one other review author independently pre-screened titles and abstracts of articles identified in the search, using a screening checklist. We resolved disagreements through discussion or referral to a third review author. We conducted screening using Covidence software.

I and one other review author independently screened the full text of articles that passed pre-screening. We consulted a third review author to resolve any disagreements that were not resolved through discussion.

Data extraction

I produced two custom data extraction forms: one for effectiveness and safety, and the other for smoking prevalence. I and one other review author independently extracted data from included studies. When discrepancies could not be resolved through discussion, we referred to a third review author. We contacted authors of included studies if additional information was needed.

Risk of bias

Effectiveness and safety

I and one other review author independently assessed risks of bias for all included RCTs using the Cochrane risk of bias tool version 1. We followed the guidance as set out in the Cochrane Handbook for Systematic Reviews of Interventions to evaluate the following domains: sequence generation; allocation concealment; blinding of outcome assessment; incomplete outcome data; selective reporting; and other sources of bias.[369]

Smoking prevalence

I and one other review author independently assessed risk of bias for included time-series studies using the ROBINS-I tool.[370]

Measures of treatment effect

Effectiveness and safety

We extracted or calculated risk ratios (RRs) and 95% compatibility intervals (CIs) for dichotomous outcomes.

For continuous safety data, we extracted or calculated mean differences on the raw (MD) or log transformed (LMD) scale and the corresponding 95% CIs between the heated tobacco and control groups at follow-up. When studies reported geometric means, we converted these onto the (natural) log scale, and when studies being pooled reported mixtures of geometric and arithmetic means, we converted them all onto the log scale, using Method 1 described in Higgins 2008 where appropriate.

We used the longest follow-up data reported, with treatment effects calculated on an intention-to-treat basis where possible.

Smoking prevalence

For interrupted time-series studies, the treatment effect could have been reflected by the step change and change in trends in smoking prevalence or cigarette sales following the introduction of HTPs to the market (or the time point where they started gaining popularity), after adjusting for confounding variables.

For multiple time-series studies (in future review updates), the treatment effect of interest will be the association between HTP prevalence and smoking prevalence or cigarette sales, after adjusting for confounding variables. Where variables are log-transformed, the resulting coefficient describes the percentage change in cigarette smoking prevalence associated with a 1% change in HTP prevalence.

Unit of analysis issues

Effectiveness and safety

For RCTs with more than two intervention arms, we combined data from all relevant intervention conditions where HTPs were offered. For RCTs with more than two control arms, we combined data from each of these arms, and we chose the most appropriate comparator. If it is not appropriate to pool the intervention arms (in future updates) then we will split the control arm to act as a comparator to each separate intervention arm. If future updates of this review identify cluster-RCTs, we will attempt to extract an estimate of the effect that accounts for the cluster design of the study. Where this is not reported, we will attempt to perform the correct analysis if required data are available.

Dealing with missing data

Effectiveness

If we assess smoking cessation in future updates of this review, we will assume that people with missing data at follow-up have not stopped smoking, as is common in the field. However, we will investigate violations of this assumption in the same way to described in Chapter 7, imputing the abstinence rate among those with missing follow-up data as 10%, 20%, 30% and 40%.

Safety

When assessing adverse and serious adverse events, we calculated the proportion of those available at follow-up who experienced an event (when such data are available) rather than the proportion of people who were randomised, when follow-up information was reported. When assessing biomarkers, we removed participants with missing follow-up data from the analysis.

Smoking prevalence

We did not expect issues with missing data in time-series studies.

Assessment of heterogeneity

To assess whether to conduct meta-analyses, we considered the characteristics of included studies to identify substantial clinical or methodological heterogeneity. If we deemed the studies to be sufficiently homogeneous to be combined meaningfully, we assessed statistical heterogeneity using the I^2 statistic. If the I^2 statistic was greater than 50%, we reported substantial heterogeneity. If I^2 was greater than 75%, we considered the appropriateness of presenting pooled results, and based this decision on consistency in the direction of effect across included studies.

Assessment of reporting bias

I planned to assess reporting bias using funnel plots if we deem it appropriate to pool 10 or more studies in any analysis. The greater the asymmetry in the plots, the higher the risk of reporting bias. However, there were fewer than 10 studies included in any specific analysis, so no funnel plots were generated.

Data synthesis

Effectiveness

The primary outcome of smoking cessation provides dichotomous data. Following the standard methods of the Cochrane Tobacco Addiction Group, we aimed to combine RRs and 95% CIs from individual studies using a Mantel-Haenszel random-effects model, to calculate pooled overall RRs with 95% CIs.

Safety

For dichotomous safety outcomes (i.e., adverse and serious adverse events), we combined RRs and 95% CIs from individual studies using a Mantel-Haenszel random-effects model to calculate pooled overall RRs with 95% CIs.

For continuous safety outcomes measuring biomarkers, we pooled the MDs or LMDs and measures of variance of individual studies using an inverse variance random-effects model.

Smoking prevalence

We aimed to calculate pooled estimates and their standard errors using a random-effects model for each of three coefficients, when reported: step change in smoking prevalence or cigarette sales following the introduction of HTPs; change in these trends after the introduction; and changes associated with changes in prevalence or sale of HTPs.

Subgroup analyses

For biomarker outcomes, we undertook subgroup analyses to investigate differences by whether analyses were per-protocol or intention-to-treat. Per-protocol analyses were defined as those that only included participants who exclusively (or almost exclusively) used the product they were assigned, whereas intention-to-treat analyses include all participants regardless of actual product use. If appropriate for future updates of this review, subgroup analyses will investigate differences by:

- intensity of behavioural support provided;
- characteristics of HTP device (e.g. model used).

Sensitivity analyses

We aimed to carry out sensitivity analyses removing studies:

- judged at high risk of bias for at least one domain;
- with a minimum length of follow-up of less than four weeks (safety outcomes only);
- where participants were given carbon-tip, rather than electronic, HTPs.

If appropriate for future updates of this review, we will also carry out the following sensitivity analyses:

- remove studies that are funded by (or authors have received funding from) the tobacco industry;

- only classify participants as HTP users if they use their product daily (smoking prevalence only);
- only include interrupted time-series studies in localities where HTPs achieved widespread use after they were introduced to market.

Assessment of certainty of evidence

I created summary of findings tables using GRADEpro GDT for all primary outcomes and for two biomarkers of exposure (NNAL and COHb), following the guidelines in Cochrane Handbook of Systematic Reviews of Interventions. NNAL and COHb were chosen because they are well-established indicators of tobacco smoke exposure.[361,364] Five GRADE considerations (risk of bias, inconsistency, imprecision, indirectness, and publication bias) were used to assess the certainty of the body of evidence for each of these outcomes.

Forest plots

In this thesis, we have presented results for the primary outcomes and for two important biomarkers (NNAL and COHb) in forest plots. Results for all other outcomes are presented in summary tables, with full forest plots available online.

Search Results

The database searches identified 1504 non-duplicate records (Figure 7.1). A further four records were identified through screening references in the papers identified through electronic searches. After screening titles and abstracts, the full texts of 121 potentially relevant articles were obtained. After screening and checking the full texts, we included 23 records, representing 13 completed (Details of included studies available online) and three ongoing studies. During full text screening, 98 records were excluded.

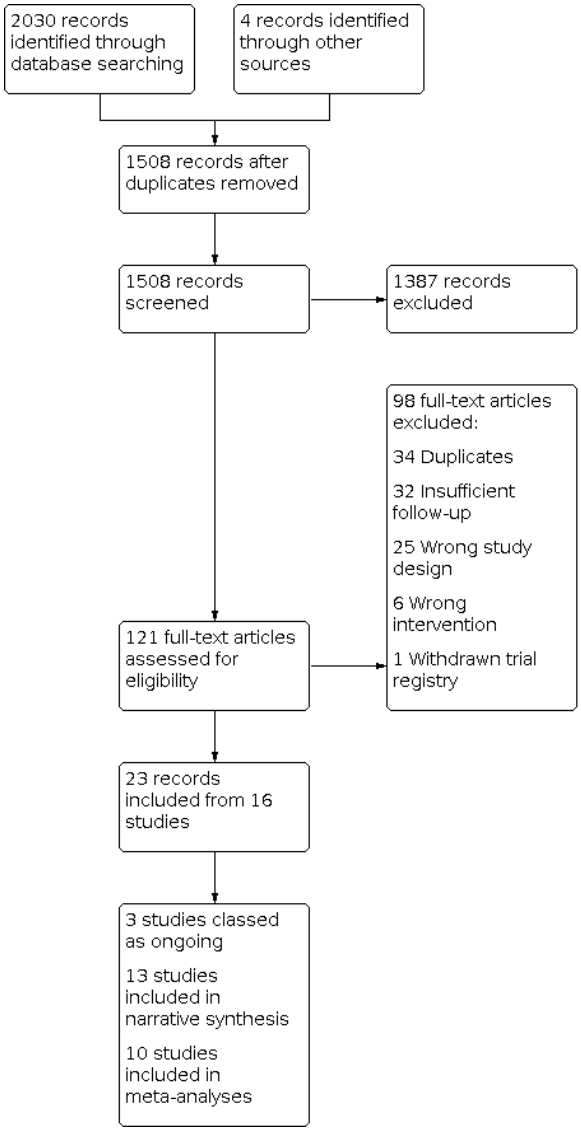


Figure 7.1. Consort Diagram showing results from literature search.

Included studies

Participants

Of the 13 included studies, 11 collected data from participants.[371-383] Details for each study are available in characteristics of included studies tables online. Two studies used sales data and are thus excluded from subsequent discussion of participant characteristics. A total of 2666 participants were recruited across the 11 RCTs. Three studies were conducted in Japan, three in the USA, two in Poland, two in the UK, and one in South Korea. These studies were conducted in adults who smoked cigarettes. Seven studies exclusively recruited participants who were not motivated to quit smoking cigarettes. One study only recruited participants diagnosed with generalised chronic periodontitis. Three studies only recruited people who were Japanese or of "Japanese ethnicity", while one study only recruited those of "Caucasian ethnicity".

Participants stayed in confinement in a clinic for the duration of the trial in three studies. Another three studies started with a confinement period of five days, before moving to an ambulatory setting for the rest of the trial. The remaining five studies used an ambulatory setting with regular clinical visits. Median follow-up length was 13 weeks, and three studies had less than four weeks of follow-up.

Interventions and comparators

All 11 included RCTs gave HTPs to participants. Two studies provided participants with the carbon-tip products 'CHTP 1.2' and 'Eclipse'. All others provided electronic heating devices alongside tobacco sticks, with PMI's IQOS-family products (or their predecessors) provided in eight studies and BAT's glo-family products in one study.

All 11 RCTs compared participants randomised to receive a HTP or to continue smoking cigarettes. Five studies also had tobacco abstinence as an additional comparator and one study had snus use as an additional comparator

There were two interrupted time-series studies using cigarette sales data from Japan. The intervention in these studies was the introduction of heated tobacco to market, with the launch of IQOS in 2015 or 2016 (depending on region).

Outcomes

Of the 13 included studies:

- none reported smoking cessation rates;
- 10 reported data on adverse events (four of which did not provide data in each trial arm). Commonly reported adverse events included cough, headache, gastrointestinal issues (e.g. diarrhoea), dry mouth, hyperglycaemia, and decreased haemoglobin;
- 10 reported data on serious adverse events. Most studies defined serious adverse events as medical incidents that were potentially life-threatening, require hospitalisation, resulted in disability or death, of a combination of these;
- 11 reported data on at least one biomarker of toxicant and carcinogen exposure;
- five reported data on at least one biomarker of harm;
- none reported time-series data on smoking prevalence;
- two reported time-series data on cigarette sales.

Study types and funding

Eleven studies were RCTs and two were observational time-series studies. All 11 RCTs were funded by the tobacco industry. One time-series study was funded through government grants, while the other had no specific funding.

Risk of bias

Overall, eight of the 11 included RCTs were judged at unclear risk of bias and three at high risk of bias, assessed using the ROB v1 criteria.[369] Figure 7.2 shows judgements across the risk of bias domains for each RCT.

Risk of bias for the two included time-series studies was assessed using the ROBINS-I tool (Sterne 2016). One time-series study was at moderate risk of bias, while the other was at serious risk. Detailed risk of bias assessments for these time-series studies can be found online.

Allocation

All included RCTs were at unclear risk of selection bias, as there was no or insufficient information about random sequence generation or allocation concealment, or both.

Blinding

All studies were judged to be at low risk of detection bias, as most reported outcomes were biochemical and hence judged at low risk of differential misreport. We planned to assess performance bias for smoking cessation outcomes, with studies judged at low risk if intervention and control arms received similar levels of behavioural support. As no study reported on smoking cessation outcomes, performance bias was not assessed.

Incomplete outcome data

Seven studies were at low risk of attrition bias, due to high and similar rates of follow-up across treatment and comparator arms (Bosilkovska 2020; Gale 2020; Lüdicke 2018; Lüdicke 2019; Martin 2012; NCT03364751; Ogden 2015). Three studies were at unclear risk as they did not provide sufficient details about attrition (Tricker 2012a; Tricker 2012b; Tricker 2012c). Haziza 2019 was at high risk of attrition bias due to substantial loss to follow-up that was greater in the heated tobacco arm.

Selective reporting

Five studies were at low risk of reporting bias, as all prespecified outcomes were reported (Bosilkovska 2020; Gale 2020; Haziza 2019; Lüdicke 2019; NCT03364751). Five studies were at unclear risk as there was no preregistered study protocol (Martin 2012; Ogden 2015; Tricker 2012a; Tricker 2012b; Tricker 2012c). Lüdicke 2018 was at high risk of reporting bias, as one preregistered outcome of interest was not reported (FEV1/FVC).

Other potential sources of bias

One study was at high risk of other bias as it did not report results across randomised trial arms (NCT03364751). Instead, they only reported results based on actual product use.

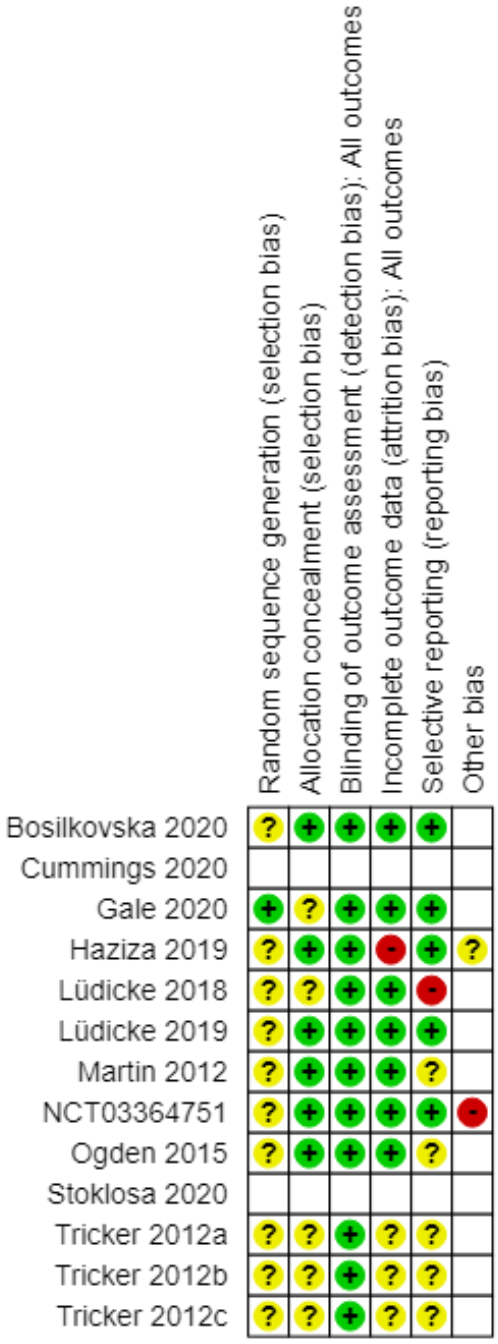


Figure 7.2. Risk of bias of included RCTs, assessed using the ROB v1 tool. Risk of bias for non-RCTs (Stoklosa 2020 and Cummings 2020) was assessing using a separate tool and is reported online.

Results

Effectiveness

Tobacco Smoking Cessation

No studies reported on the effectiveness of heated tobacco for smoking cessation.

Safety compared with smoking

Adverse events

Pooled data from six studies showed insufficient evidence of a difference in the number of participants reporting **adverse events** between those in the heated tobacco use and cigarette smoking groups, but the CI contained the possibility of small but clinically meaningful differences in both directions (RR 1.03, 95% CI 0.92 to 1.15; I^2 = 0%; 1713 participants; Supplementary Figure S7.1; Table 7.1). Two studies were at high risk of bias, while the remaining four were at unclear risk. Removing studies judged at high risk of bias did not substantially change the interpretation of results (RR 0.98, 95% CI 0.87 to 1.11; I^2 = 0%; 1472 participants), neither did removing the two studies that used carbon-tip, rather than electronic, HTPs (RR 1.04, 95% CI 0.82 to 1.30; I^2 = 35%; 1510 participants). All six studies had a follow-up of at least four weeks.

Serious adverse events

Pooled data from four studies showed insufficient evidence of a difference in **serious adverse events** reported in the heated tobacco use compared with cigarette smoking group, with a wide CI that were compatible with no difference as well as the possibility of more events in either group (RR 0.79, 95% CI 0.33 to 1.94; I^2 = 0%; 1472 participants; Supplementary Figure S7.2; Table 7.1). All pooled studies were at unclear risk of bias and had a follow-up of at least four weeks. Removing the two studies that used carbon-tip, rather than electronic, HTPs did not substantially change the interpretation of results (RR 0.93, 95% CI 0.34 to 2.58; I^2 = 0%; 1269 participants). In a further five studies, there were no serious adverse events reported, which meant their data could not be pooled (Haziza 2019; Lüdicke 2018; Tricker 2012a; Tricker 2012b; Tricker 2012c).

Toxicant and carcinogen exposure

Pooled data from 1960 participants across 10 studies showed:

- lower **1-OHP** at follow-up in heated tobacco use compared with cigarette smoking groups (LMD −0.42, 95% CI −0.67 to −0.17). Heterogeneity was high at I^2 = 94%, but the direction of the difference was consistent across all studies except Ogden 2015, where carbon-tip HTPs were provided. It was also consistent across sensitivity analyses removing two studies at high risk of bias, two studies using carbon-tip HTPs, and three studies with less than four weeks of follow-up (Supplementary Table S7.1);
- lower **3-HPMA** at follow-up in heated tobacco use compared with cigarette smoking groups (LMD −0.40, 95% CI −0.62 to −0.17). Heterogeneity was high at I^2 = 95%, but the direction of the difference was consistent across sensitivity analyses and all studies except Ogden 2015 (Supplementary Table S7.1);
- lower **MHBMA** at follow-up in heated tobacco use compared with cigarette smoking groups (LMD −1.15, 95% CI −1.52 to −0.78). Heterogeneity was high at I^2 = 94%, but the direction of the difference was consistent across studies and sensitivity analyses (Supplementary Table S7.1);
- lower **NNAL** at follow-up in heated tobacco use compared with cigarette smoking groups (LMD −0.81, 95% CI −1.07 to −0.55; Supplementary Figure S7.3; Supplementary Table S7.1). Heterogeneity was high at I^2 = 92%, but the direction of the difference was consistent across sensitivity analyses and all studies except Ogden 2015 (Supplementary Table S7.1). Another study also reported NNAL; as data were analysed based on actual product use rather than randomised group, it was not pooled (NCT03364751). It found results that were compatible with those from pooled data (LMD −1.46, 95% CI −1.81 to −1.10; 151 participants).

Pooled data for nine studies showed lower levels of COHb at follow-up in heated tobacco use compared with cigarette smoking groups (LMD −0.74, 95% CI −0.97 to −0.52; 1807 participants; Supplementary Figure S7.4; Supplementary Table S7.1). Heterogeneity was high at I^2 = 96%, but estimates from each study were consistently in favour of the heated tobacco group. Results were similar after removing two studies at high risk of bias, two studies using carbon-tip HTPs, and three studies with less than four weeks of follow-up (Supplementary Table S7.1).

In addition, pooled data from three studies showed lower levels of exhaled CO at follow-up in heated tobacco use compared with cigarette smoking groups (MD −9.13ppm,

95% CI −10.49 to −7.78; 1322 participants). There was low heterogeneity at I^2 = 4% and effects for each study were in the same direction. All three studies were at unclear risk of bias, used electronic HTPs, and had at least four weeks of follow-up.

Ogden 2015 reported data from 63 participants showing insufficient evidence of a difference in 1-naphthol between the heated tobacco use and cigarette smoking groups, with the CI containing the possibility of clinically meaningful effects in either direction (MD 2.60 µg/24 hours, 95% CI −16.11 to 21.31). The study also found that 2-naphthol was lower in the heated tobacco use group compared with the cigarette smoking group; however, the CIs were wide (MD −4.00 µg/24 hours, 95% CI −7.89 to −0.11). This study was at unclear risk of bias, used a carbon-tip HTP, and had a follow-up of greater than four weeks (Supplementary Table S7.1).

No studies reported on exposure to lead or cadmium.

Biomarkers of harm

Pooled data from five studies showed greater lung function, measured using **FEV_1** , at follow-up among participants in the heated tobacco use compared with cigarette smoking groups (LMD 0.02, 95% CI 0 to 0.03; I^2 = 0%; 1290 participants). Results were similar after removing two studies at high risk of bias and one study using carbon-tip HTPs. All five studies had a follow-up of at least four weeks (Supplementary Table S7.1).

Pooled data from 196 participants across two studies found no evidence of a difference in **FVC** between those randomised to heated tobacco use versus cigarette smoking, but the CI contained the possibility of clinically meaningful differences in both directions (MD −0.12 L, 95% CI −0.45 to 0.21; I^2 = 38%). Both studies had at least four weeks of follow-up, were judged at high risk of bias, and provided electronic rather than carbon-tip devices (Supplementary Table S7.1).

Pooled data from 288 participants across three studies showed no evidence of a difference in **systolic blood pressure** (LMD 0.00, 95% CI −0.02 to 0.02; I^2 = 0%) or **diastolic blood pressure** (LMD 0.00, 95% CI −0.03 to 0.03; I^2 = 0%) at follow-up between heated tobacco use and cigarette smoking groups. Results were similar after removing two studies at high risk of bias and one study using carbon-tip HTPs. All three studies had a follow-up of at least four weeks (Supplementary Table S7.1).

No studies reported on **FEV_1/FVC**, **heart rate**, or **blood oxygen saturation**.

Table 7.1. Summary of findings table for the effectiveness of heated tobacco for smoking cessation and safety of heated tobacco relative to cigarette smoking.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with cigarette smoking	**Risk with heated tobacco use**			
Smoking cessation - not measured	-	-	-	-	-
Adverse events assessed with: self-report	235 per 1,000	**242 per 1,000** (216 to 270)	**RR 1.03** (0.92 to 1.15)	1713 (6 RCTs)	⨁⨁◯◯ Low[a,b]
Serious adverse events assessed with: self-report and medical records	13 per 1,000	**10 per 1,000** (4 to 24)	**RR 0.79** (0.33 to 1.94)	2009 (9 RCTs)	⨁◯◯◯ Very low[a,c]
NNAL assessed with: urinary biomarkers		MD **0.81 lower** (0.55 lower to 1.07 lower)	-	1959 (11 RCTs)	⨁⨁⨁◯ Moderate[a,d,e]
COHb assessed with: urinary biomarkers		MD **0.74 lower** (0.52 lower to 0.92 lower)	-	1807 (9 RCTs)	⨁⨁⨁◯ Moderate[a,d,e]

*The risk in the intervention group **(and its 95% compatibility interval) is based on the assumed risk in the comparison group and the** relative effect **of the intervention (and its 95% CI).**

CI: **compatibility interval;** MD: **mean difference;** RR: **risk ratio**

GRADE Working Group grades of evidence
High certainty: **We are very confident that the true effect lies close to that of the estimate of the effect.**
Moderate certainty: **We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.**
Low certainty: **our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.**
Very low certainty: **we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.**

a. Downgraded one level for risk of bias: all studies were at either unclear or high risk of bias.

b. Downgraded one level for imprecision: compatibility intervals contain clinically-meaningful benefit and clinically-meaningful harm.

c. Downgraded two levels for imprecision: compatibility intervals contain large clinically-meaningful benefit and clinically-meaningful harm.

d. Downgraded one level for inconsistency: there was a high level of heterogeneity across studies. However, the direction of effect was consistent across studies.

e. Upgraded one level for large effect

Safety compared with abstinence

Adverse events

Pooled data from two studies showed insufficient evidence of a difference in the number of participants reporting **adverse events** between the heated tobacco use and attempted tobacco abstinence groups, with the CI containing the possibility of clinically meaningful differences in both directions (RR 1.12, 95% CI 0.86 to 1.46; I^2 = 0%; 237 participants; Supplementary Figure S7.5; Table 7.2). Both studies were at high risk of bias, used electronic HTPs, and had a follow-up of at least four weeks.

Serious adverse events

Five studies reported that no **serious adverse events** occurred across either the heated tobacco or tobacco abstinence groups (Haziza 2019; Lüdicke 2018; Tricker 2012a; Tricker 2012b; Tricker 2012c), which meant that data could not be pooled (533 participants; Supplementary Figure S7.6, Table 7.2). Two studies were at high risk of bias, while the remaining three were at unclear risk. All studies used electronic HTPs and two had at least four weeks of follow-up.

Toxicant and carcinogen exposure

All five studies reporting on biomarkers of toxicant and carcinogen exposure for this comparison used electronic rather than carbon-tip HTPs. Pooled data from 382 participants across these studies showed:

- higher **1-OHP** at follow-up in heated tobacco use groups compared with tobacco abstinence groups, but CIs were wide and contained no difference (LMD 0.12, 95% CI −0.03 to 0.28). Heterogeneity was moderate with an I^2 of 54%, which reduced to 12% in a sensitivity analysis where the two studies at high risk of bias were removed. The direction of the effect was unchanged after removing these studies and after removing three studies with less than four weeks of follow-up (Supplementary Table S7.2);
- inconsistent results for **COHb** across subgroups, with I^2 = 77% for subgroup differences. Subgroup results showed higher COHb in heated tobacco use compared with tobacco abstinence groups for intention-to-treat analyses (LMD 0.69, 95% CI 0.07 to 1.31; I^2 = 96%; 3 studies, 212 participants; Supplementary Figure S7.8), but lower COHb, limited by imprecision, for per-protocol analyses (LMD −0.32, 95% CI −1.04 to

0.39; I^2 = 91%; 2 studies, 170 participants; Supplementary Figure S7.8). Because of these subgroup differences and high overall heterogeneity (I^2 = 99%), we did not present pooled results (Table 7.2). Heterogeneity was 96% after removing the two studies at high risk of bias and 91% when removing the three studies with less than four weeks of follow-up. The direction of the difference was reversed when studies with less than four weeks of follow-up were removed (Supplementary Table S7.2);

- higher **3-HPMA** in heated tobacco use compared with tobacco abstinence groups (LMD 0.56, 95% CI 0.33 to 0.80). Heterogeneity was high with an I^2 of 85%, which reduced to 0% when removing three studies with less than four weeks of follow-up. Differences were smaller after removing these studies (LMD 0.35, 95% CI 0.20 to 0.50; 170 participants), but larger after removing two studies at high risk of bias (LMD 0.64, 95% CI 0.32 to 0.96; 212 participants; Supplementary Table S7.2);
- higher **MHBMA** in heated tobacco use compared with tobacco abstinence groups (LMD 0.67, 95% CI −0.12 to 1.45), but CIs contained the potential for no difference. Heterogeneity was high with an I^2 of 96%, which reduced to 0% when removing three studies with less than four weeks of follow-up. Differences were smaller when removing these studies (LMD 0.07, 95% CI −0.16 to 0.30; 170 participants), but larger when removing two studies at high risk of bias (LMD 0.97, 95% CI 0.02 to 1.92; 212 participants; Supplementary Table S7.2);
- higher **NNAL** in heated tobacco use compared with tobacco abstinence groups (LMD 0.50, 95% CI 0.34 to 0.66; I^2 = 0%; Supplementary Figure S7.7; Table 7.2). Results were similar in sensitivity analyses removing two studies at high risk of bias and three studies with less than four weeks of follow-up (Supplementary Table S7.2).

No studies reported on exposure to **1-naphthol**, **2-naphthol**, **exhaled CO**, **lead**, or **cadmium**.

Biomarkers of harm

Both of the studies that reported on biomarkers of harm were at high risk of bias, used electronic rather than carbon-tip HTPs, and had at least four weeks of follow-up. Pooled data from 170 participants across these two studies showed:

- insufficient evidence of a difference in lung function, measured using **FEV_1** at follow-up, among participants in the heated tobacco use compared with tobacco abstinence

groups, with the CI including the possibility of clinically meaningful differences in both directions (LMD −0, 95% CI −0.06 to 0.06; I^2 = 38%);

- higher **systolic blood pressure** at follow-up in the heated tobacco use compared with tobacco abstinence groups, but the CI included no difference (LMD 0.02, 95% CI −0.01 to 0.05; I^2 = 0%);
- insufficient evidence of a difference in **diastolic blood pressure** at follow-up between heated tobacco use and tobacco abstinence groups, with the CIs including the possibility of clinically meaningful differences in both directions (LMD 0, 95% CI −0.04 to 0.04; I^2 = 0%).

Both studies also reported data from 172 participants on **FVC**, with insufficient evidence for a difference between those randomised to use heated tobacco versus tobacco abstinence (MD −0.02 L, 95% CI −0.29 to 0.26; I^2 = 0%). The CIs contained the possibility of clinically meaningful differences in both directions.

No studies reported **FEV_1/FVC**, **heart rate**, or **blood oxygen saturation**.

Table 7.2. Summary of findings table for safety of heated tobacco relative to no tobacco.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with abstinence from tobacco	**Risk with heated tobacco use**			
Smoking cessation - not measured	-	-	-	-	-
Adverse events assessed with: self-report	468 per 1,000	**525 per 1,000** (403 to 684)	**RR 1.12** (0.86 to 1.46)	237 (2 RCTs)	⨁⨁◯◯ Low[a,b]
Serious adverse events assessed with: self-report and medical records	not pooled	not pooled	not pooled	533 (5 RCTs)	⨁◯◯◯ Very low[c,d]
NNAL assessed with: urinary biomarkers		MD **0.5 higher** (0.34 higher to 0.66 higher)	-	382 (5 RCTs)	⨁⨁⨁◯ Moderate[c]
COHb assessed with: urinary biomarkers		MD **0.3 higher** (0.38 lower to 0.97 higher)	-	382 (5 RCTs)	⨁◯◯◯ Very low[c,e,f]

*The risk in the intervention group **(and its 95% compatibility interval) is based on the assumed risk in the comparison group and the** relative effect **of the intervention (and its 95% CI).**

CI: **compatibility interval;** MD: **mean difference;** RR: **risk ratio**

GRADE Working Group grades of evidence
High certainty: **We are very confident that the true effect lies close to that of the estimate of the effect.**
Moderate certainty: **We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.**
Low certainty: **our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.**
Very low certainty: **we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.**

a. Downgraded two levels for risk of bias: all studies were considered at high risk of bias.

b. Downgraded one level for imprecision: compatibility intervals contained clinically-meaningful benefit and clinically-meaningful harm.

c. Downgraded one level for risk of bias: two of the five studies were considered high risk of bias, while three had uncertain risk of bias.

d. Downgraded two levels for imprecision: no serious adverse events occurred so compatibility intervals could not be constructed.

e. Downgraded one level for imprecision: compatibility intervals contained no difference.

f. Downgraded one level for inconsistency: there was high heterogeneity.

Smoking prevalence

Cigarette sales

Cummings 2020 found that the yearly percentage decline in cigarette sales accelerated after the introduction of HTPs in Japan, increasing from a mean decline of −3.10% across 2011–2015 to −16.38% across 2016–2019. This study was considered at serious risk of bias due to the limited number of time points (five) used to calculate the pre-intervention trend. Stoklosa 2020 found similar results using a different method and monthly rather than annual data; it found that per capita cigarette sales were increasing at a rate of 0.10 to 0.14 (depending on statistical approach) per month before the introduction of heated tobacco in Japan. After the introduction, per capita cigarette sales declined at a rate of 0.63 to 0.66 cigarettes per month. This study was at moderate risk of bias, due to possible confounding and lack of a preregistered protocol. However, risk of confounding was partially accounted for using regional controls, with the monthly data enabling a sufficient number of time points used to determine pre- and post-intervention trends across regions.

Discussion

Summary

Our searches found no studies that reported the effectiveness of heated tobacco for smoking cessation, but they did find 11 RCTs assessing the safety of heated tobacco — all of which were funded by tobacco companies. Results on adverse and serious adverse events were inconclusive, with insufficient short-term evidence of differences between smokers randomised to switch to heated tobacco use or to cigarette smoking, attempted tobacco abstinence, or snus use. No studies detected serious harms considered to be related to heated tobacco use. Pooled data showed there was moderate-certainty evidence that exposure to some measured toxicants and carcinogens was lower in smokers randomised to switch to heated tobacco than continue smoking cigarettes, but very low- to moderate-certainty evidence of higher exposures than in those attempting abstinence from all tobacco.

No studies directly assessed how trends in smoking prevalence changed following the introduction of heated tobacco to market, but there were two time-series studies on cigarette sales. Results from both studies showed that the rate of decline in cigarette sales accelerated from before to after the launch of IQOS in Japan. However, declining cigarette sales might not translate to falling smoking prevalence, as smokers can reduce the number of cigarettes they

smoke without quitting entirely. Moreover, because data were observational, it is possible that changes were caused by other factors (e.g., demographic shifts or delayed effects of tobacco control policies).

Completeness of the evidence

Although included studies had conditions in which they asked smokers to switch completely to HTP or attempt abstinence from all tobacco, none reported smoking cessation outcomes. This means that the effectiveness of heated tobacco for smoking cessation remains uncertain. However, we found one ongoing study that will evaluate their effectiveness relative to e-cigarettes.

Safety data came from a wide range of locations across Europe, Asia, and North America. Conversely, both time-series studies used data from a single country (Japan), which limits the generalisability of conclusions. For instance, Japan differs from many countries because it is illegal to sell nicotine e-cigarettes unless they are registered as a pharmaceutical product. This may have left a gap in the market for heated tobacco.

The types of heated tobacco devices produced continue to change over time. While carbon-tip HTPs such as Eclipse were once the only type available, electronic devices such as IQOS and glo now dominate the market. These products could differ in their safety. It is possible that using newer electronic products, such as those that heat tobacco through induction, could lead to different exposures than those reported here. Therefore, it is important to continue tracking the research into new developments in heated tobacco technology.

All studies on safety that were included were funded by tobacco companies. These companies have a financial incentive to produce results that are favourable towards the products they sell. Data from independent sources are, therefore, needed to confirm the results reported in this review. The possibility of publication bias cannot be ruled out.

Safety data came from studies that used optimised settings for switching to exclusive HTP use. Six of the 11 RCTs had an extended period where participants stayed in a clinic, preventing those in the HTP group from easily accessing cigarettes (and vice versa). This means that, while trial data consistently show reduced exposure in people completely substituting HTPs for cigarettes, it remains unclear how exposure changes in people using HTPs in real-world settings where they have greater access to cigarettes.

Serious adverse events were rare as safety data came from studies where participants used heated tobacco for one year at most (median of 13 weeks). Trials with larger samples and longer follow-up periods are likely needed to establish how switching from cigarettes to heated tobacco affects rates of these events.

Biomarker studies assessing exposure to toxicants and carcinogens are only relevant if reducing exposure prevents disease and premature death. Animal studies have shown a dose–response relationship between some exposures, such as nitrosamines, and cancer development, suggesting reduced exposure may indeed reduce disease incidence. Nonetheless, longer-term cohort studies are needed to clarify the impact of switching from cigarettes to heated tobacco. There are several other limitations of biomarker results to consider. First, for biomarkers with an extended half-life in the body, follow-up length in some studies may have been too short to accurately estimate the effect of switching from cigarettes to heated tobacco. Second, all comparisons between heated tobacco and abstinence groups came from RCTs using per-protocol analyses that excluded people who smoked cigarettes. This exclusion may have introduced selection bias without adequately addressing post-randomisation confounding. Finally, we only reported on biomarkers for a sample of the toxicants and carcinogens present in cigarette smoke or heated tobacco aerosol. Previous reviews found similar reductions in exposure to a broader range of potentially harmful chemicals among those switching from cigarettes to heated tobacco.[248,384]

Quality of the evidence

We considered the certainty of evidence for effectiveness and safety of heated tobacco compared with cigarette smoking, tobacco abstinence, and snus use, along with population-level data on smoking prevalence and cigarette sales (Table 7.1; Table 7.2).

Table 7.1 and Table 7.2 show evidence from RCTs. Reasons for downgrading certainty of evidence included: risk of bias, when most studies pooled were judged at unclear or high risk of bias; imprecision, when compatibility intervals were wide and included no difference; inconsistency, when heterogeneity was high and unexplained; and indirectness, when all the studies pooled used carbon-tip HTPs, which differ substantially from the electronic devices currently on the market.

Effectiveness

The effectiveness of HTPs for smoking cessation remains uncertain, as no studies assessed this.

Safety

For all comparisons, effect estimates for adverse events or serious adverse events were of low or very-low certainty, mainly due to imprecision. This means that the direction and size of effects remains uncertain. None of the analyses found serious adverse events that were judged to be caused by HTPs or comparators. For the selected biomarker outcomes NNAL and COHb, evidence was moderate certainty when the comparison was with cigarette smoking; moderate or very-low certainty compared with tobacco abstinence, respectively; and low or very-low certainty compared with snus use. This means we are more confident about the effects of heated tobacco on biomarkers relative to cigarettes than to tobacco abstinence or snus.

Smoking Prevalence

The impact of rising heated tobacco use on smoking prevalence remains uncertain, as no studies directly assessed this. There was very low-certainty evidence for an impact on cigarette sales, meaning our confidence in results is limited. We downgraded certainty one level for risk of bias, as the studies were considered at moderate or serious risk of bias. We also downgraded certainty one level for the indirectness of cigarette sales as a proxy for smoking prevalence. This is because falls in cigarette sales do not necessarily translate to reductions in smoking prevalence; people can reduce the number of cigarettes they smoke rather than stopping smoking entirely.

Potential biases in review

Several steps were taken to ensure the review process was robust. We followed standard methods used by the Cochrane Tobacco Addiction Review Group. The search strategy included a broad range of databases, including the Cochrane Tobacco Addiction Group Specialised Register. We also contacted researchers who have worked on relevant reports by charities or public health bodies to capture studies that we may have otherwise missed. We followed standard Cochrane practice of requiring two review authors to independently screen

studies, extract data, and assess risk of bias. None of the authors of this review were also authors of included studies.

Conclusion

This systematic review found is moderate-certainty evidence that HTPs expose users to fewer toxicants/carcinogens than cigarettes. However, all randomised trials were conducted by researchers that were funded or employed by tobacco companies, so there is a need for independent research into the safety of HTPs. There remains a lack for evidence on smoking cessation and serious adverse events. Two studies reported that declines in cigarette sales accelerated after the introduction of heated tobacco to market, but it is unclear if this acceleration was caused by HTPs or if it extended to smoking prevalence. As I discussed in the literature review of this thesis, longitudinal cohort studies were essential for convincing doctors, policymakers, and the public about the adverse health effects of cigarette smoking. Similar evidence will be required to better understand the harms of HTPs relative to cigarettes, e-cigarettes, and no nicotine.

This ends Part B of my thesis. In the next sections, I will integrate findings from all seven studies presented. I will place the results in context with the wider literature, suggesting some implications for policy, practice and methodology. Finally, I will discuss areas where further research may be fruitful.

Discussion

Summary of Findings

Popularity and prevalence

In the first five studies of my thesis, I examined the popularity and prevalence of different nicotine products in Great Britain. The first study showed that, from 2016 to 2020, rechargeable e-cigarettes with refillable tanks dominated the e-cigarette market — used as the main product by at least two in three vapers in all years. Heated tobacco and JUUL use remained rare. However, there was a slight increase in the percentage of vapers using pod e-cigarettes going into 2020.

The second study discussed how this increased appeal of pod e-cigarettes could have been driven, at least in part, by razor-and-blades pricing methods. This is where a base e-cigarette is sold at a loss, but manufacturers make large profits from repeated sales of device specific pods.

The third study showed how perceptions of e-cigarettes deteriorated among smokers in Great Britain during 2019, following the US outbreak of vaping associated lung injury. Fewer than one third of smokers perceived e-cigarettes to be less harmful than cigarettes.

The fourth study showed that, despite these negative perceptions, vaping prevalence among adults grew between 2021 and 2022. This rise was almost entirely explained by the increasing popularity of modern disposable e-cigarettes, which went from being the main product used by only 1% of vapers in January 2021 to 22% by May 2022. The growth was most pronounced in young vapers, where disposables have become the most widely used type of e-cigarette (used as main product by 55% of 18-year-old vapers). Despite this rise in vaping, the overall prevalence of inhaled nicotine use remained stable, both overall and among young adults.

The fifth study found that the prevalence of tobacco-free nicotine pouch use was low (at 0.26%) in Great Britain, but it may be increasing; twice as many people reported using pouches in October 2021 than in the previous year.

Cessation and harm reduction

In the final two studies of my thesis, I examined the use of e-cigarettes and heated tobacco for smoking cessation. The penultimate study was a randomised trial at English stop smoking services. It showed some uncertain evidence that adding e-cigarettes to cigarette smoking cessation treatment with varenicline and behavioural support might be effective at helping people remain abstinent. However, the results were imprecise, as the COVID-19 pandemic and recall of varenicline meant that the trial was stopped early after only 92 of the planned 1,266 participants had been recruited. More evidence will be needed to establish the effectiveness of e-cigarettes together with varenicline.

The final study was a Cochrane systematic review into heated tobacco products, evaluating their effectiveness for smoking cessation, safety, and population-level impact on cigarette smoking prevalence. There were no randomised trials examining whether giving people heated tobacco helps them to stop smoking conventional cigarettes, so their effectiveness for smoking cessation remains unclear. There was some evidence on safety, with 11 randomised trials, all funded by tobacco companies, looking at levels of toxicants and carcinogens in the urine and blood of smokers asked to switch to heated tobacco versus continue smoking and/or stop all tobacco use. These studies consistently found that switching from cigarettes to heated tobacco lowered exposure to toxicants and carcinogens, but exposure may still be raised relative to people who completely stop using tobacco. However, there was insufficient evidence directly looking at health outcomes such as the rates of cancers, cardiovascular events, respiratory disease, and death — with most studies following up participants for less than six months and reporting that no serious adverse events occurred in either trial arm. Independently funded research on the effectiveness and safety of heated tobacco is needed.

Contextualizing Findings

Introduction

This chapter aims to first place the findings of my thesis into context of the wider literature, covering where other research has found similar or different results — both in Great Britain and globally. Then, it will examine potential implications of the findings for policy, practice, and methodology. Finally, I will reflect on the strengths and limitations of the approach taken in this thesis.

Comparison with literature

Comparison of results from Chapter 1, 2.4 and 2.5 with the literature outside of Great Britain shows countries vary in the types of nicotine products they use. Despite JUUL, heated tobacco and nicotine pouch use increasing elsewhere, my results show that these products are rarely used in Great Britain. While the US and Canada saw a sharp rise in JUUL use from 2017 to 2019, there was only a small increase in Great Britain.[1,385,386] Similarly, use of heated tobacco products such as IQOS has become increasingly prevalent in Japan, South Korea and — more recently — parts of Europe (e.g., Italy, Latvia, and the Czech Republic), but it remains rare in England.[243,245] Finally, tobacco and nicotine pouches are yet to gain widespread popularity outside of Nordic countries, but in those countries, they are the most widely used type of nicotine product among men.[64,65,387]

These differences in the adoption of novel nicotine products may be explained by the social, cultural and economic environment of the country when the products entered the market. For instance, heated tobacco may have become especially popular in Japan due to their de facto ban on e-cigarettes, which made heated tobacco products the only legally-available non-combustible inhaled nicotine product.[7] No such ban existed in the UK, and e-cigarettes were already widely used by the time heated tobacco entered the British market, which may, at least partly, explain why there was less demand for heated tobacco. Another example is that Nordic countries have a long cultural history of oral tobacco use.[63] Such a history does not exist in the UK, where tobacco has mostly been smoked and oral tobacco is banned.[313] This may explain why nicotine pouches, which are tobacco-free alternatives to oral tobacco, remain rarely used in Great Britain.[5]

In Chapter 3, I presented data showing how smokers' perceptions of e-cigarettes have deteriorated in England from before to after the outbreak of vaping-associated lung injury in North America. These findings have since been replicated using data from the International Tobacco Control (ITC) survey of youth in the US, Canada, and England.[300] This study also found that the effects of the outbreak were most pronounced in North America, where the outbreak occurred.[300] Recent data from Great Britain show that, as of 2022, harm perceptions have not recovered to the level they were prior to the outbreak.[393,394] Further studies have examined the media coverage of the outbreak.[207,210] They found that news articles often failed to highlight that contaminated cannabis vapes were largely responsible for the outbreak, not nicotine e-cigarettes.[210] Many articles mentioned JUUL and the rise youth nicotine vaping. It is therefore likely that misleading news coverage of the outbreak contributed towards the worsening harm perceptions of e-cigarettes compared with cigarettes.

Chapter 2 introduced razor-and-blades pricing models as a potential driver of the increasing popularity of pod e-cigarettes. More recently, modern disposable vapes (e.g., Elf Bar) may have undermined the utility of razor-and-blades methods for pod e-cigarette manufacturers. This is because the primary draw of razor-and-blades priced e-cigarettes is the low upfront cost of starting to use the products. However, disposable vapes can now be bought for under £5.[397] This low cost, combined with the convenience of using a device that does not need to be charged, may be major reasons why disposable e-cigarette vaping has grown so rapidly in Great Britain — as reported in Chapter 4.

Research from the National Youth Tobacco Survey in the US showed that the rise in disposable vaping we found among young adults (e.g., 18–24 year olds) in Great Britain was also observed elsewhere.[305] Similarly, a study from ASH found that disposable e-cigarettes have also become popular among adolescents (11–17 year olds) in Britain,[400] and data from the ITC youth survey found increases in disposable vaping among 16-19 year olds in Canada, the US, and England.[401] There are several reasons why disposable e-cigarettes may be especially attractive to young people. First, having a low upfront cost is especially important to children and younger adults, who often have little disposable income and are more motivated by avoiding present costs than waiting for future gain.[402] This is why cigarette singles and 10 packs were especially popular with younger smokers (providing rationale for minimum pack size regulations).[403] Second, these devices are convenient as they do not require charging, changing coils, or selecting and filling with an appropriate e-liquid. One can use it within seconds of purchase. This means that people who use nicotine intermittently,

especially those who use nicotine after drinking alcohol or while at social gatherings, may find it convenient to buy a disposable e-cigarette for a day or a weekend when they may have previously bought a pack of cigarettes.[404] Third, products like Elf Bar are widely marketed on social media platforms, primarily TikTok and Instagram.[405] This includes paid sponsorships of celebrities or influencers on the platform, who can be paid to discuss certain nicotine products.[406] Advertisers can also gift nicotine products to influences in the hope they will be featured in the videos or photos, a form of product placement.[407] Adolescents and young adults are the heaviest users of social media, so may be most affected by sponsors and advertisements on these platforms.[407,408]

Results from the E-ASSIST randomised trial presented in Chapter 6 showed some uncertain evidence that providing e-cigarettes alongside varenicline and behavioural support may be effective for smoking cessation. Despite the imprecision in effect estimates due to the smaller than expected sample size, this trial adds to a wider literature on the effects of offering nicotine products alongside varenicline. The results closely align with a previous meta-analysis that found 50% higher odds of cigarette abstinence in those given NRT alongside varenicline than varenicline alone (OR 1.50, 95%CI 1.14–1.97).[332] However, another recent study showed that adding nicotine patches to varenicline had little effect on abstinence rates (OR 0.99, 95% CI 0.87–1.12).[342] It is possible that fast-acting nicotine products — including gums, sprays, and e-cigarettes — are better at helping varenicline users remain abstinent, as they can satisfy momentary urges for nicotine.[142] Moreover, the behaviour and sensory experience of using an e-cigarette is similar to that of smoking a cigarette, which could make e-cigarettes more effective for smoking cessation than other nicotine products. I will discuss this more in the sub-section examining implications for practice.

Results from the review on heated tobacco, presented in Chapter 7, were aligned with other reviews on the topic. For instance, our results were similar to Simonavicius 2018,[248] a systematic review that concluded heated tobacco products expose people to toxicants and carcinogens, albeit at much lower levels than conventional cigarettes. It noted that there were few studies conducted independent from the tobacco industry. Similar results were also found in the 2018 Public Health England report into heated tobacco products.[167] My review differed from these two reports in three ways. It included: (i) only safety data from randomised controlled trials with at least one week of follow-up, while the earlier reviews were more inclusive of weaker designs, (ii) several studies that were published from 2018 to 2021, and (iii) two time-series studies looking at the population-level impact of rising heated

tobacco use on cigarette sales. The chapter on heated tobacco in the most recent update of the McNeill and colleagues' reports commissioned by Public Health England (now the "Office for Health Improvement and Disparities") was based on my systematic review. A systematic review from Jankowski 2019 included studies with various designs, including data in animals and cells and studies into the toxicology and chemical composition of heated tobacco aerosol.[367] These more liberal inclusion criteria meant that their literature search identified a greater number of studies (97 versus 16).[367] Their results were nonetheless similar: "in vitro and in vivo assessments of HTP aerosols revealed reduced toxicity, but these were mainly based on studies sponsored by the tobacco industry". They also concluded that heated tobacco likely exposes people to more toxicants than not using any tobacco product. A review by Znyk in 2021 found, as I did, that no studies had looked at the effectiveness of heated tobacco for smoking cessation.[384] Their results on toxin exposure from heated tobacco also aligned with mine and earlier reviews. Finally, prior to the US FDA allowing marketing of IQOS as a "reduced exposure" tobacco product in the US, it reviewed evidence into the safety of these products compared with conventional cigarettes.[352] This review concluded that "switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals". It emphasised that, "the evidence is not sufficient to demonstrate substantiation of either of the claims about reduced risk of tobacco-related disease or harm". These comments align with my conclusions about the completeness of the evidence on heated tobacco.

Policy implications

The results I have presented in this thesis have several implications for policy. For example Chapter 3 reported that smokers' perceptions of the harm of e-cigarettes relative to cigarettes are worsening over time in England, with even more pronounced changes occurred in the US and Canada.[300] The misleading media coverage of the 2019 outbreak of cannabis vaping associated lung injury may have contributed to this worsening of perceptions.[210] These results highlight the importance of clear communication from public health bodies and the media of the relative harm of different health behaviours, an issue that has become especially important during the COVID-19 pandemic.[400] It is possible that these misperceptions deterred cigarette smokers from switching to e-cigarettes, or led those who had switched to return to smoking.[401] Yet, despite this deterioration, Chapter 4 reported that vaping prevalence increased among

young adults from 2021 to 2022 in Great Britain (from 11% to 18% in 18-year-olds). More research is required to understand how changing comparative harm perceptions affect vaping prevalence in the long-term.

The rise in disposable vaping, especially among young people, should interest policymakers. If these products attract young people who would otherwise avoid nicotine entirely — increasing uptake to nicotine and possibly smoking — then they could have a net negative impact on public health.[402] As of April 2022, it did not appear that the growing popularity of disposables had increased the prevalence of inhaled nicotine use among young adults in England. However, other research from ASH and the ITC Youth Tobacco and Vaping Survey does show some, albeit uncertain, evidence that the total number of youth (11-17 year-olds for ASH and 16-19 for ITC) using nicotine increased from 2018 to 2022, and that this increase may have been driven by disposable vaping.[388,403] Similarly, data from New Zealand, Canada, and the US show that growth in vaping can lead to a rise in nicotine use among youth.[305,320,404] Therefore, it may be important for policymakers to take steps to avoid uptake of both smoking and vaping among youth. These steps could include: better enforcement of age-of-sale laws so that children cannot easily obtain e-cigarettes; introducing or better enforcing restrictions on social media marketing of e-cigarettes aimed towards young people;[405] and restrictions on flavour descriptions and packaging to avoid products that disproportionally attract children. Another concern with disposables is their impact on the environment. If the environmental impact of these products is considered too large, policymakers may consider raising taxes or bringing in an outright ban on disposable products. Demand for e-cigarettes among young people is also more responsive to increasing prices,[406] so taxation may deter youth disposable vaping while also acting as payment for the negative externalities introduced by the environmental impact of disposable products.[407] However, this may be at the expense of potentially discouraging lower income smokers, who are also more responsive to price increases, from switching from cigarettes to e-cigarettes.[48,110]

Practice implications

The worsening perceptions about the harmfulness of e-cigarettes relative to cigarettes, discussed above and in Chapter 3, also affected the E-ASSIST trial. Some services or advisors declined to participate in the trial due to their perceptions about the harmfulness of e-cigarettes. Qualitative interviews also showed that some smokers who took part in the trial

were hesitant to use the e-cigarette because of worries about becoming more dependent on e-cigarettes than they were to cigarettes. It may therefore be important to disseminate evidence on e-cigarettes to practitioners in stop smoking services as well as to doctors and nurses, who might also hold misperceptions about the relative harmfulness and addictiveness of different nicotine products.[409]

In my review of evidence on heated tobacco products (Chapter 7), the systematic literature search found that there have been no trials into the effectiveness of these products for smoking cessation. This contrasts with nicotine e-cigarettes, where the Cochrane systematic review of 40 studies concluded that they were more effective for smoking cessation than nicotine replacement therapy and non-nicotine e-cigarettes.[7] One might assume that, given the similarity of heated tobacco products to e-cigarettes, heated tobacco is also likely to be effective for cessation. However, there are several reasons why it is preferable to recommend e-cigarettes over heated tobacco. First, there is direct evidence from RCTs showing that e-cigarettes help people quit smoking, whereas evidence for heated tobacco is only indirect.[6,7,236] It is possible that differences between the products may lead one to be a better cessation aid than the other. For instance, the experience of using heated tobacco is more similar to smoking cigarettes than vaping is. This similarity could be a barrier to people completely switching, as people using heated tobacco may be less likely to adopt a non-smoker identity than those using e-cigarettes.[336] A recent interview study showed that IQOS users often label their heated tobacco use as "smoking" and HEET sticks as "cigarettes", highlighting a failure to fully separate the two behaviours.[412,413] Second, heated tobacco contains processed tobacco leaf rather than an e-liquid containing extracted nicotine. There may be additional risk to users from heating tobacco leaf, and there is some evidence that heated tobacco products sometimes fail to avoid combustion.[410] This may explain why Chapter 7 reported that levels of certain toxicants and carcinogens appeared higher in cigarette smokers who switched to heated tobacco compared with those who switched to no tobacco use. Third, all the major heated tobacco brands are owned by manufacturers who primarily sell cigarettes. Some stop smoking services may wish to avoid buying or recommending products from which traditional cigarette manufacturers can profit. However, the counter argument would be that buying these products might help incentivise cigarette manufacturers to drive their customers away from cigarettes and towards lower risk products (which may yield larger profit margins).

Methodological implications

Results from the E-ASSIST trial showed that modelling abstinence using a Cox model and reporting a hazard ratio can be more efficient than using a logistic or log-binomial regression (reporting a odds or risk ratio). This is because the Cox model uses more information, taking into account the length of time someone remained abstinent, rather than a binary measure of whether or not they were abstinent at an arbitrary time-point.[411] This means that trials where abstinence is measured and verified frequently (e.g., at weekly or fortnightly sessions) would benefit from using Cox models, which would allow them to detect effects with greater power and estimate effects with greater precision, or to reduce the required number of participants. More research is needed into the potential limitations of this approach, possibly by comparing how it performs when reanalysing data from previously published trials and with simulated data.

The COVID-19 pandemic has accelerated the move from face-to-face sessions to remote meetings in stop smoking services. This means that trials in these services need to find ways to (i) deliver interventions and (ii) verify nicotine or tobacco abstinence remotely, as both these activities have historically been done by advisors during face-to-face meetings with smokers. Remote carbon monoxide monitors can be used to verify abstinence from tobacco smoke, such as devices that can be connected to a mobile phone through a wire into the headphone jack or wirelessly using Bluetooth. However, we found that these devices were not compatible with all mobile phones, and some participants found them difficult to use. Another option is to ask participants to provide saliva samples, which can be mailed to participants alongside a return slip. These can be analysed for cotinine to verify abstinence from nicotine, and anabasine or anatabine to verify abstinence from tobacco smoking — a distinction that is important with e-cigarettes, where participants may still have a large nicotine intake even after they stop smoking cigarettes.[412–414] Nonetheless, the sensitivity and specificity of anabasine and anatabine is relatively low, so there may be scope to develop better methods of remote verification.

Throughout the thesis, I used restricted cubic splines to model continuous predictors in regression. This allows for flexible and non-linear relationships between predictors and outcomes. This approach is superior to traditional approaches of dichotomising or categorising predictors, which reduces power and precision.[230,415] It is also more robust than assuming linearity by default, as I found that relationships between predictors and outcomes

in this thesis rarely followed or closely approximated a straight line (even when they did, restricted cubic splines were able to model linearity correctly).[230,416] Researchers examining tobacco and nicotine products would benefit from using more robust approaches to modelling continuous predictors, such as restricted cubic splines.

Strengths and weaknesses

The overall approach I have taken in this thesis has several strengths and weaknesses. First, this thesis includes data from a variety of different outcomes and study designs, including analyses of time trends, biomarker data, cross-sectional surveys, and randomised trials. As highlighted in the literature review, triangulation of several lines of evidence is needed to address complex problems like vaping and smoking.[402,417–419] Randomised trials are useful for looking at short-term effects of switching from cigarettes to e-cigarettes or heated tobacco on toxicant exposure, but observational cohort studies or population-level trend analyses are needed to generalise findings and see effects on long-term health outcomes. Data from randomised trials alone is insufficient as it does not accurately reflect the way most people use nicotine outside trial settings, while data from observation studies is limited in what can be said with confidence about causality.

Second, most of the studies, with the exception of the systematic review and E-ASSIST trial, used data from a representative population survey. This means that the results can be generalised more directly from sample to population than if I had used convenience samples of undergraduate students or members of an unrepresentative online research panel.[420] The E-ASSIST randomised trial was also conducted within NHS stop smoking services, the natural setting in which the intervention would be introduced. This means that it is more valid to generalise these results to practice than if I had conducted the trial in a more artificial setting.

Third, I adapted the thesis to address issues that had urgent implications for practice and policy. For instance, the chapters examining effects of disposable e-cigarettes and the US outbreak of lung injury linked cannabis vaping directly addressed research questions that were important to policymakers at the time. This adaptability is important in the nicotine market which, as we showed in Chapter 4, can change rapidly. The Smoking Toolkit Study was an especially useful resource for this, as data are collected monthly and are available for analysis within a month of being collected. This allowed me to react quickly to important events and changes to the nicotine market.

There were several notable weaknesses. First, the disruption of the E-ASSIST trial caused by the COVID-19 pandemic and manufacturer recall of varenicline meant we were unable to recruit the planned number of participants. Therefore, our effect estimates were imprecise, so conclusions about the effectiveness of adding e-cigarettes to varenicline were tentative.

Second, while I mentioned the adaptability of the research to current events as a strength, this is also a limitation when bringing these studies together into a thesis, as it has arguably produced a less cohesive thesis overall than if I had continued with the studies as planned in my upgrade. Nonetheless, it would have meant that each chapter would likely have had less of an impact on policy or research.

Third, several of the studies could have benefited from stating an explicit directional hypothesis. For instance, for the E-ASSIST trial, I could have stated that we predict that adding e-cigarettes to varenicline and behavioural support will increase the proportion of participants who remain abstinent from cigarette smoking weeks 9-12 post quit date. However, to avoid hypothesising after results are known ("HARKing"), I have not added hypotheses that were not registered a priori.[421]

Fourth, the Smoking Toolkit study moved from face-to-face to telephone interviewing following the COVID-19 pandemic and associated social distancing measures. The change in mode could affect results in at least two ways. The population being recruited from in one mode could systematically differ from the other. Moreover, even if both modes recruit from the same population, the responses individuals give may differ when being interviewed via telephone rather than face-to-face. To examine differences, data were collected from both modes simultaneously in one wave (March 2022). Comparisons across the different modes were unable to detect differences on most measures, but small sample sizes mean that there was insufficient evidence to rule out moderately-sized differences.[421,422] Having said that, each of the analyses reported here either used data solely from face-to-face or solely from telephone interviews. Thus, estimates of trends over time are not confounded by the change in mode.

Finally, other than the E-ASSIST trial, the thesis does not contain longitudinal data from cohort studies, where individuals are followed up at several time points. This kind of data will be important to estimate effect of heated tobacco, e-cigarettes, cigarettes, and no nicotine use on health outcomes. In the next section, I will look at important areas for future research, some of which can address these limitations.

Future Research

In order to understand the impact of novel nicotine products on smoking prevalence and cessation, and on public health more broadly, there are several areas of future research to be explored.

First, because the E-ASSIST trial (Chapter 6) was terminated early, it remains uncertain the extent to which e-cigarettes together with varenicline — or another partial nicotinic receptor agonist like cytisine — is more effective for smoking cessation than varenicline alone. Therefore, there is still a need for another trial on this question. Given that varenicline is currently not available on European markets, it might be better to study the effects of adding e-cigarettes to other drugs that act in the same way on the brain (i.e., partial agonists of nicotinic acetylcholine receptors). Cytisine is a good target given that there is now a wealth of research showing that it has a similar or superior effectiveness than varenicline, with fewer side effects and a lower cost.[129,136,137] Cytisine is yet to be supplied in the UK but, if it is, this would be a useful replacement for varenicline, and it would be important to test the effectiveness of adding e-cigarettes alongside Cytisine in practice at NHS stop smoking services.

Second, as found in the systematic review (Chapter 7), there is currently no randomised trial evidence looking at the effectiveness of heated tobacco for smoking cessation. For these to be recommended by practitioners over e-cigarettes or licenced medicines, there would need to be a trial comparing the relative abstinence rates in people randomised to get heated tobacco versus one of these other treatments (likely alongside behavioural support). Moreover, time series data are needed to examine whether growing popularity of heated tobacco products has caused a reduction in smoking prevalence, with existing data only showing a reduction in cigarette sales (which could be caused by smokers consuming fewer cigarettes rather than quitting entirely). Such analyses would only be possible in countries (e.g., Japan) where heated tobacco has become popular enough to have had a detectable effect on smoking prevalence.[243]

Third, longitudinal cohort studies for both heated tobacco and e-cigarettes will be needed to estimate the effects of using these products on health. As we saw in the literature review, the consequences of cigarette smoking on health were only widely accepted after long-term cohort studies showed the disparity between smokers and non-smokers (after

stratifying, matching on or adjusting for confounding variables).[26,32] The same is likely true for e-cigarettes and heated tobacco products. There are currently very few longitudinal studies on the health effects of vaping, and most of those that have been conducted do not adequately account for confounding by smoking history.[205] This will be especially difficult given that the vast majority of vapers have a history of smoking, and it is hard to fully adjust for this (e.g., see Pleasants et al. for issues with using cigarette pack-years for adjustment).[249,388,422] Looking only at those who report never having smoked cigarettes may not adequately remove confounding, because people who vape are also much more likely to have engaged in a myriad of other risky health behaviours including using illicit drugs, being violent, having sex without a condom, getting seriously injured, drinking excessive quantities of sugary soda, and delinquency.[229,423] Properly accounting for these will be a challenge. In addition, many studies fail to define "time zero" or account for time-varying confounding, meaning that they become prone to a number of other time-related biases.[424–426] Case-control studies are also likely to be useful, but only if care is taken to account for confounding by a person's history of smoking and time-related biases, which can be even more difficult retrospectively.[427,428]

Fourth, the causes and consequences of the rise in disposable vaping remain uncertain. Therefore, there is scope to research several important areas. Qualitative interviews with users would help us understand motivations for using disposable products, such as whether people view cost, convenience, a smooth nicotine hit, advertising, availability, social network effects, or other factors as important drivers of their use. It is important to determine the counterfactual scenario for people using these products. What would they be doing if disposables were not available? For people who would otherwise be smoking cigarettes, disposables will have a positive effect on their health. For those who would otherwise be vaping rechargeable devices, disposables may have minimal health impact unless they have different likelihoods for affecting their future smoking behaviour (but the environmental effects are concerning, as discussed in previously). For those who would otherwise be using no nicotine, disposables are likely causing them harm. A time series study looking at the change in trends in the prevalence of smoking, vaping and any nicotine use would provide insight into the relative proportions of these three types of users in the population. A stagnation or reversal of the downward trend in the prevalence of any nicotine use following the introduction of disposables would suggest that these products have attracted people who would otherwise have avoided nicotine entirely. One could also use older age groups, where

disposable vaping has remained relatively rare, as a natural control (i.e., to test whether change in trend is greater in younger than older ages). A potential problem with this approach is that a large amount of data would be required to detect even moderate-sized differences between age groups (as one would need to estimate a three-way interaction).[429] Therefore, it is likely most studies would only be able to detect large effects, and be unable to rule out moderate or small effects. A final question is whether disposables differ from other types of e-cigarettes in their effectiveness for helping people stop smoking conventional cigarettes. This could be examined in a trial where smokers are randomised to receive either disposable or rechargeable devices, then measuring the proportion who are abstinent from smoking at several future follow-up points (allowing one to measure time to relapse or censoring, which can be used in a Cox model, as discussed in the previous chapter).

Fifth, it is important to understand how dependent people become on different types of nicotine products. A concern is that people who switch from exclusively smoking cigarettes to dual using e-cigarettes and cigarettes might become more dependent on nicotine.[430–432] We observed this concern in interviews for the E-ASSIST trial (Chapter 6), where participants were worried about that using an e-cigarette might amplify their addiction to nicotine. Most of the studies that have currently looked at this have been cross-sectional.[430–432] Stronger evidence would come from within-person studies, where one can compare how nicotine intake and dependence changes when people switch from cigarettes to different types of e-cigarettes. A good data source for this would be the Population Assessment of Tobacco and Health (PATH), which has collected data from thousands of users in the US across five waves, including urine samples that can be analysed for cotinine concentration (a precise indicator of recent nicotine intake).[356,433,434] Two studies have examined changes in nicotine intake in people to switching from cigarettes to e-cigarettes, but none have looked at self-reported markers of dependence.[413,435]

Concluding Remarks

Over the past five years, we have witnessed a shift in nicotine market in Great Britain. It is no longer dominated by the cigarette, as it was throughout most of the 20th century. Despite growing public concern about the harmfulness of e-cigarettes, vaping prevalence has risen while smoking rates have continued to decline. Between 2021 and 2022, modern disposable e-cigarettes rapidly became the most popular device type among young vapers, replacing refillable tank e-cigarettes as their product of choice. Heated tobacco and nicotine pouches, on the other hand, did not gain widespread popularity. These rapid changes highlight the importance of continually tracking smoking and nicotine use in the population. In Great Britain, this is accomplished through the Smoking Toolkit Study, which provides ongoing data on these behaviours each month.

The full consequences of these changes in nicotine use are unclear. E-cigarettes have shown to be more effective at helping people stop smoking than nicotine replacement therapy, and the data presented in Chapter 6 provide some tentative evidence that they may be useful when given alongside varenicline. Moreover, while it does not appear that the disposable-driven rise in vaping among young adults has led to an increase in overall nicotine use as of yet, it is unclear whether this will hold in the future. If trends continue, the products may well attract people who would otherwise avoid nicotine entirely. One must balance this risk against potential benefits for people who would otherwise be smoking cigarettes were it not for e-cigarettes helping them to quit. Policy should therefore aim to limit the uptake of vaping and smoking among youth while maximising the utility of e-cigarettes for smoking cessation.

Bibliography

1. Tattan-Birch H, Brown J, Shahab L, Jackson SE. Trends in use of e-cigarette device types and heated tobacco products from 2016 to 2020 in England. *Sci Rep*. 2021;11(1):13203. doi:10.1038/s41598-021-92617-x

2. Tattan-Birch H, Brown J, Jackson SE. 'Give 'em the vape, sell 'em the pods': Razor-and-blades methods of pod e-cigarette pricing. *Tobacco Control*. 2021;0:1-2. doi:10.1136/tobaccocontrol-2020-056354

3. Tattan-Birch H, Brown J, Shahab L, Jackson SE. Association of the US Outbreak of Vaping-Associated Lung Injury With Perceived Harm of e-Cigarettes Compared With Cigarettes. *JAMA Network Open*. 2020;3(6):e206981. doi:10.1001/jamanetworkopen.2020.6981

4. Tattan-Birch H, Jackson SE, Kock L, Dockrell M, Brown J. Rapid growth in disposable e-cigarette vaping among young adults in Great Britain from 2021 to 2022: a repeat cross-sectional survey. *Addiction*. Published online 6 September 2022. doi:10.1111/add.16044

5. Tattan-Birch H, Jackson SE, Dockrell M, Brown J. Tobacco-free nicotine pouch use in Great Britain: a representative population survey 2020-2021. *Nicotine Tob Res*. Published online 13 April 2022. doi:10.1093/ntr/ntac099

6. Tattan-Birch H, Kock L, Brown J, et al. E-cigarettes to Augment Stop Smoking In-person Support and Treatment with varenicline (E-ASSIST): a pragmatic randomised controlled trial. *Nicotine Tob Res*. Published online 23 June 2022. doi:10.1093/ntr/ntac149

7. Tattan-Birch H, Hartmann-Boyce J, Kock L, et al. Heated tobacco products for smoking cessation and reducing smoking prevalence. *Cochrane Database Syst Rev*. 2022;1:CD013790. doi:10.1002/14651858.CD013790.pub2

8. Churchill J, Jones D. Written questions and answers (UIN 36587). UK Parliament. Published 20 July 2021. Accessed December 22, 2022. https://questions-statements.parliament.uk/written-questions/detail/2021-07-20/36587

9. Ann McNeill, Erikas Simonavičius, Leonie Brose, Eve Taylor, Katherine East, Elizabeth Zuikova, Robert Calder, Debbie Robson. *Nicotine Vaping in England: 2022 Evidence Update Summary*. Office for Health Improvement and Disparities; 2022. Accessed December 16, 2022. https://www.gov.uk/government/publications/nicotine-vaping-in-england-2022-evidence-update/nicotine-vaping-in-england-2022-evidence-update-summary

10. Tattan-Birch H, Brown J, Hartmann-Boyce J. Heated tobacco: a new review looks at the risks and benefits. *The Conversation*. Published online 6 January 2022. Accessed December 22, 2022. http://theconversation.com/heated-tobacco-a-new-review-looks-at-the-risks-and-benefits-173110

11. Tattan-Birch H, Jarvis MJ. Children's exposure to second-hand smoke 10 years on from smoke-free legislation in England: Cotinine data from the Health Survey for England 1998-2018. *Lancet Reg Health Eur*. 2022;15:100315. doi:10.1016/j.lanepe.2022.100315

12. Tattan-Birch H, Shahab L. The Psychobiology of Nicotine Vaping: Impact on addiction, cognition, mood, anxiety and appetite. *Psychobiological Issues in Substance Use and Misuse*. Published online 2020:265-288.

13. Tattan-Birch H, Marsden J, West R, Gage SH. Assessing and addressing collider bias in addiction research: the curious case of smoking and COVID-19. *Addiction*. Published online 2020. doi:10.1111/add.15348

14. Tattan-Birch H, Jackson SE, Ide C, Bauld L, Shahab L. Evaluation of the Impact of a Regional Educational Advertising Campaign on Harm Perceptions of E-Cigarettes, Prevalence of E-Cigarette Use, and Quit Attempts Among Smokers. *Nicotine Tob Res*. 2020;22(7):1148-1154. doi:10.1093/ntr/ntz236

15. Kock L, Brown J, Hiscock R, Tattan-Birch H, Smith C, Shahab L. Individual-level behavioural smoking cessation interventions tailored for disadvantaged socioeconomic position: a systematic review and meta-regression. *The Lancet Public health*. 2019;4(12). doi:10.1016/S2468-2667(19)30220-8

16. Garnett C, Oldham M, Shahab L, Tattan-Birch H, Cox S. Characterising smoking and smoking cessation attempts by risk of alcohol dependence: A representative, cross-sectional study of adults in England between 2014-2021. *Lancet Reg Health Eur*. 2022;18:100418. doi:10.1016/j.lanepe.2022.100418

17. Cox S, Tattan-Birch H, Jackson SE, Dawkins L, Brown J, Shahab L. Cutting down, quitting and motivation to stop smoking by self-reported COVID-19 status: Representative cross-sectional surveys in England. *Addiction*. Published online 15 August 2022. doi:10.1111/add.16029

18. East K, Reid JL, Burkhalter R. Exposure to Negative News Stories About Vaping, and Harm Perceptions of Vaping, Among Youth in England, Canada, and the United States Before and After the …. *Nicotine and*. Published online 2022. https://academic.oup.com/ntr/article-abstract/24/9/1386/6562888

19. West R. Tobacco smoking: Health impact, prevalence, correlates and interventions. *Psychol Health*. 2017;32(8):1018-1036. doi:10.1080/08870446.2017.1325890

20. World Health Organisation. Tobacco. Published 2019. https://www.who.int/news-room/fact-sheets/detail/tobacco

21. World Health Organization. *WHO Report on Global Tobacco Epidemic, 2019*.; 2019.

22. Drope J, Schluger NW. *The Tobacco Atlas: Deaths*. 6th ed.; 2018.

23. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ*. 2004;328(7455):1519. doi:10.1136/bmj.38142.554479.AE

24. Action on Smoking and Health. Economic and Health Inequalities Dashboard. Action on Smoking and Health. Published February 2022. Accessed October 14, 2022. https://ash.org.uk/resources/view/economic-and-health-inequalities-dashboard

25. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst*. 1981;66(6):1191-1308. doi:10.1093/jnci/66.6.1192

26. Cornfield J, Haenszel W, Hammond EC, Lilienfeld AM, Shimkin MB, Wynder EL. Smoking and lung cancer: recent evidence and a discussion of some questions. *J Natl Cancer Inst*. 1959;22(1):173-203. doi:10.1093/jnci/22.1.173

27. Schairer E, Schöniger E. Lung cancer and tobacco consumption. *Int J Epidemiol*. 2001;30(1):24-27; discussion 30-1. doi:10.1093/ije/30.1.24

28. Doll R, Hill AB. A study of the aetiology of carcinoma of the lung. *Br Med J*. 1952;2(4797):1271-1286. doi:10.1136/bmj.2.4797.1271

29. Stocks P, Campbell JM. Lung cancer death rates among non-smokers and pipe and cigarette smokers; an evaluation in relation to air pollution by benzpyrene and other substances. *Br Med J*. 1955;2(4945):923-929. doi:10.1136/bmj.2.4945.923

30. Segi M, Fukushima I, Fujisaku S, et al. An epidemiological study on cancer in Japan. *Gann*. 1957;48:1-63. doi:10.20772/cancersci1907.48.suppl_1

31. Cornfield J. A statistical problem arising from retrospective studies. In: *Contributions to Biology and Problems of Health*. University of California Press; 1956:135-148. doi:10.1525/9780520350717-010

32. Smith GD. Smoking and lung cancer: causality, Cornfield and an early observational meta-analysis. *Int J Epidemiol*. 2009;38(5):1169-1171. doi:10.1093/ije/dyp317

33. Berkson J. The statistical study of association between smoking and lung cancer. *Proc Staff Meet Mayo Clin*. 1955;30(15):319-348. https://www.ncbi.nlm.nih.gov/pubmed/13245839

34. Neyman J. Statistics—servant of all science. *Science*. 1955;122(3166):401-406. doi:10.1126/science.122.3166.401

35. Fisher RA. Dangers of Cigarette-smoking. *Br Med J*. 1957;2(5039):297. Accessed October 14, 2022. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1961712/

36. Hammond EC, Horn D. The relationship between human smoking habits and death rates: a follow-up study of 187,766 men. *J Am Med Assoc*. 1954;155(15):1316-1328. doi:10.1001/jama.1954.03690330020006

37. Cuyler Hammond E, Horn D. SMOKING AND DEATH RATES—REPORT ON FORTY-FOUR MONTHS OF FOLLOW-UP OF 187,783 MEN. *JAMA*. 1958;166(11):1294-1308. doi:10.1001/jama.1958.02990110030007

38. Dorn HF. Tobacco consumption and mortality from cancer and other diseases. *Acta Unio Int Contra Cancrum*. 1960;16:1653-1665. doi:10.2307/4590516

39. Doll R, Hill AB. Lung cancer and other causes of death in relation to smoking; a second report on the mortality of British doctors. *Br Med J*. 1956;2(5001):1071-1081. doi:10.1136/bmj.2.5001.1071

40. Vandenbroucke JP. Commentary: 'Smoking and lung cancer'--the embryogenesis of modern epidemiology. *Int J Epidemiol*. 2009;38(5):1193-1196. doi:10.1093/ije/dyp292

41. Cox DR. Commentary: Smoking and lung cancer: reflections on a pioneering paper. *Int J Epidemiol*. 2009;38(5):1192-1193. doi:10.1093/ije/dyp290

42. Orris L, Van Duuren BL, Kosak AI, Nelson N, Schmitt FL. The carcinogenicity for mouse skin and the aromatic hydrocarbon content of cigarette-smoke condensates. *J Natl Cancer Inst*. 1958;21(3):557-561. doi:10.1093/jnci/21.3.557

43. Doll R, Hill AB. Mortality in relation to smoking: Ten years' observations of British doctors. *Br Med J*. 1964;1(5396):1460-7 CONCL. doi:10.1136/bmj.1.5396.1460

44. The Royal College of Physicians. *Smoking and Health*. Pitman Medical Publishing; 1962.

45. Warner KE. 50 years since the first Surgeon General's report on smoking and health: a happy anniversary? *Am J Public Health*. 2014;104(1):5-8. doi:10.2105/AJPH.2013.301722

46. United States. Surgeon General's Advisory Committee on Smoking and Health. *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*. U.S. Department of Health, Education, and Welfare, Public Health Service; 1964. https://play.google.com/store/books/details?id=6bRpAAAAMAAJ

47. Gallup, Inc. Long-Term Gallup Poll Trends: A Portrait of American Public Opinion Through the Century. Accessed October 13, 2022. https://news.gallup.com/poll/3400/longterm-gallup-poll-trends-portrait-american-public-opinion.aspx

48. Jha P, Peto R. Global Effects of Smoking, of Quitting, and of Taxing Tobacco. *N Engl J Med*. 2014;370(1):60-68. doi:10.1056/nejmra1308383

49. Peto R. Smoking And Death: The Past 40 Years And The Next 40. *BMJ: British Medical Journal*. 1994;309(6959):937-939. http://www.jstor.org/stable/29725053

50. Wolf PA, D'Agostino RB, Kannel WB, Bonita R, Belanger AJ. Cigarette smoking as a risk factor for stroke. The Framingham Study. *JAMA*. 1988;259(7):1025-1029. doi:10.1001/jama.1988.03720070025028

51. Freund KM, Belanger AJ, D'Agostino RB, Kannel WB. The health risks of smoking. The Framingham Study: 34 years of follow-up. *Ann Epidemiol*. 1993;3(4):417-424. doi:10.1016/1047-2797(93)90070-k

52. Reitsma MB, Fullman N, Ng M, et al. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990-2015: A systematic analysis from the global burden of disease study 2015. *Lancet*. 2017;389(10082):1885-1906. doi:10.1016/S0140-6736(17)30819-X

53. Reitsma MB, Kendrick PJ, Ababneh E, et al. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. *Lancet*. 2021;397(10292):2337-2360. doi:10.1016/S0140-6736(21)01169-7

54. Contreary KA, Chattopadhyay SK, Hopkins DP, et al. Economic Impact of Tobacco Price Increases Through Taxation: A Community Guide Systematic Review. *Am J Prev Med*. 2015;49(5):800-808. doi:10.1016/j.amepre.2015.04.026

55. Gilmore AB, Fooks G, Drope J, Bialous SA, Jackson RR. Exposing and addressing tobacco industry conduct in low-income and middle-income countries. *The Lancet*. 2015;385(9972):1029-1043. doi:10.1016/S0140-6736(15)60312-9

56. Russell MA. Cigarette smoking: natural history of a dependence disorder. *Br J Med Psychol*. 1971;44(1):1-16. doi:10.1111/j.2044-8341.1971.tb02141.x

57. Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. *Trends in Cardiovascular Medicine*. 2016;26(6):515-523. doi:10.1016/j.tcm.2016.03.001

58. Hajek P. The development and testing of new nicotine replacement treatments: from 'nicotine replacement' to 'smoking replacement'. *Addiction*. 2015;110(S2):19-22. doi:10.1111/add.12905

59. Haussmann HJ, Fariss MW. Comprehensive review of epidemiological and animal studies on the potential carcinogenic effects of nicotine per se. *Crit Rev Toxicol*. 2016;46(8):701-734. doi:10.1080/10408444.2016.1182116

60. Sanner T, Grimsrud TK. Nicotine: Carcinogenicity and effects on response to cancer treatment - A review. *Front Oncol*. 2015;5:196. doi:10.3389/fonc.2015.00196

61. Hoffmann D, Rivenson A, Chung FL, Hecht SS. Nicotine-derived N-nitrosamines (TSNA) and their relevance in tobacco carcinogenesis. *Crit Rev Toxicol*. 1991;21(4):305-311. doi:10.3109/10408449109017917

62. Murray RP, Connett JE, Zapawa LM. Does nicotine replacement therapy cause cancer? Evidence from the Lung Health Study. *Nicotine Tob Res*. 2009;11(9):1076-1082. doi:10.1093/ntr/ntp104

63. Foulds J, Ramstrom L, Burke M, Fagerström K. Effect of smokeless tobacco (snus) on smoking and public health in Sweden. *Tob Control*. 2003;12(4):349-359. doi:10.1136/tc.12.4.349

64. Ramström L, Borland R, Wikmans T. Patterns of Smoking and Snus Use in Sweden: Implications for Public Health. *Int J Environ Res Public Health*. 2016;13(11). doi:10.3390/ijerph13111110

65. Clarke E, Thompson K, Weaver S, Thompson J, O'Connell G. Snus: A compelling harm reduction alternative to cigarettes. *Harm Reduction Journal*. 2019;16(1):62. doi:10.1186/s12954-019-0335-1

66. Tyagi A, Sharma S, Wu K, et al. Nicotine promotes breast cancer metastasis by stimulating N2 neutrophils and generating pre-metastatic niche in lung. *Nat Commun*. 2021;12(1):1-18. doi:10.1038/s41467-020-20733-9

67. Benowitz NL. The role of nicotine in smoking-related cardiovascular disease. *Prev Med* . 1997;26(4):412-417. doi:10.1006/pmed.1997.0175

68. Zulli A, Smith RM, Kubatka P, et al. Caffeine and cardiovascular diseases: critical review of current research. *European Journal of Nutrition*. 2016;55(4):1331-1343. doi:10.1007/s00394-016-1179-z

69. Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). *Health Effects of Smokeless Tobacco Products*. The European Commission; 2008. http://ec.europa.eu/health/ph_risk/risk_en.htm

70. Greenland S, Satterfield MH, Lanes SF. A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. *Drug Saf*. 1998;18(4):297-308. doi:10.2165/00002018-199818040-00005

71. Kimmel SE, Berlin JA, Miles C, Jaskowiak J, Carson JL, Strom BL. Risk of acute first myocardial infarction and use of nicotine patches in a general population. *J Am Coll Cardiol*. 2001;37(5):1297-1302. doi:10.1016/s0735-1097(01)01124-x

72. Weathersbee P. Nicotine and Its Influence on the Female Reproductive System. *J Reprod Med*. 1980;25(5):243-250. https://pubmed.ncbi.nlm.nih.gov/6256547/

73. Jain G, Jaimes EA. Nicotine signaling and progression of chronic kidney disease in smokers. *Biochemical Pharmacology*. 2013;86(8):1215-1223. doi:10.1016/j.bcp.2013.07.014

74. Martin EM, Clapp PW, Rebuli ME, et al. E-cigarette use results in suppression of immune and inflammatory-response genes in nasal epithelial cells similar to cigarette smoke. *American Journal of Physiology - Lung Cellular and Molecular Physiology*. 2016;311(1):L135-L144. doi:10.1152/ajplung.00170.2016

75. Mündel T, Machal M, Cochrane DJ, Barnes MJ. A Randomised, Placebo-Controlled, Crossover Study Investigating the Effects of Nicotine Gum on Strength, Power and Anaerobic Performance in Nicotine-Naïve, Active Males. *Sports Medicine - Open*. 2017;3(1). doi:10.1186/s40798-016-0074-8

76. Fluharty M, Taylor AE, Grabski M, Munafò MR. The Association of Cigarette Smoking With Depression and Anxiety: A Systematic Review. *Nicotine Tob Res*. 2017;19(1):3-13. doi:10.1093/ntr/ntw140

77. Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P. Change in mental health after smoking cessation: systematic review and meta-analysis. *BMJ*. 2014;348:g1151. doi:10.1136/bmj.g1151

78. Daffner SD, Waugh S, Norman TL, Mukherjee N, France JC. Nicotine Increases Osteoblast Activity of Induced Bone Marrow Stromal Cells in a Dose-Dependent Manner: An in vitro Cell Culture Experiment. *Global Spine Journal*. 2012;2(3):153-158. doi:10.1055/s-0032-1326946

79. Ortiz A, Grando SA. Smoking and the skin. *Int J Dermatol*. 2012;51(3):250-262. doi:10.1111/j.1365-4632.2011.05205.x

80. Jarvis M, Jackson S, West R, Brown J. Epidemic of youth nicotine addiction? What does the National Youth Tobacco Survey 2017-2019 reveal about high school e-cigarette use in the USA? *Qeios*. Published online 2 September 2020. doi:10.32388/745076.5

81. Britton J. Death, disease, and tobacco. *Lancet*. 2017;389(10082):1861-1862. doi:10.1016/S0140-6736(17)30867-X

82. Banks E, Joshy G, Weber MF, et al. Tobacco smoking and all-cause mortality in a large Australian cohort study: findings from a mature epidemic with current low smoking prevalence. *BMC Med*. 2015;13:38. doi:10.1186/s12916-015-0281-z

83. Jarvis MJ, Feyerabend C. Recent trends in children's exposure to second-hand smoke in England: Cotinine evidence from the Health Survey for England. *Addiction*. 2015;110(9):1484-1492. doi:10.1111/add.12962

84. Hirayama T. Nonsmoking wives of heavy smokers have a higher risk of lung cancer: A study from Japan. *Br Med J* . 1981;282(6259):183-185. doi:10.1136/bmj.282.6259.183

85. Song F, Elwell-Sutton T, Naughton F, Gentry S. Future smoking prevalence by socioeconomic status in England: A computational modelling study. *Tob Control*. 2020;0:1-6. doi:10.1136/tobaccocontrol-2019-055490

86. Ikeda T, Cobiac L, Wilson N, Carter K, Blakely T. What will it take to get to under 5% smoking prevalence by 2025? Modelling in a country with a smokefree goal. *Tob Control*. 2015;24(2):139-145. doi:10.1136/tobaccocontrol-2013-051196

87. Brandt A. *The Cigarette Century: The Rise, Fall, and Deadly Persistence of the Product That Defined America*. Basic Books; 2009. https://www.waterstones.com/book/the-cigarette-century/allan-brandt/9780465070480

88. Starks TA. A Revolutionary Attack on Tobacco: Bolshevik Antismoking Campaigns in the 1920s. *Am J Public Health*. 2017;107(11):1711-1717. doi:10.2105/AJPH.2017.304048

89. King James I of England. *A Covnter-Blaste to Tobacco*. Robert Barker; 1604. Accessed October 17, 2022. https://www.nypl.org/events/exhibitions/galleries/beginnings/item/3556

90. Loud EE, Duong HT, Henderson KC, et al. Addicted to smoking or addicted to nicotine? A focus group study on perceptions of nicotine and addiction among US adult current smokers, former smokers, non-smokers and dual users of cigarettes and e-cigarettes. *Addiction*. 2022;117(2):472-481. doi:10.1111/add.15634

91. Stanhope BJ, Burdette WJ, Cochran WG, et al. *Report of the Advisory Committee to the Surgeon General of the Public Health Service*.; 1964.

92. World Health Organisation. *WHO Framework Convention On Tobacco Control*. World Health Organisation; 2003.

93. Truth Initiative. What We Do. Published 2021. https://truthinitiative.org/what-we-do

94. Action on Smoking and Health. *Health Inequalities and Smoking*. Action on Smoking and Health; 2019. http://ash.org.uk/category/information-and-resources/briefings/1

95. Pacheco J. Trends--Public Opinion on Smoking and Anti-Smoking Policies. *Public Opin Q*. 2011;75(3):576-592. doi:10.1093/poq/nfr031

96. Harris F, MacKintosh AM, Anderson S, et al. Effects of the 2003 advertising/promotion ban in the United Kingdom on awareness of tobacco marketing: Findings from the International Tobacco Control (ITC) Four Country Survey. *Tob Control*. 2006;15(SUPPL. 3):26-33. doi:10.1136/tc.2005.013110

97. Hammond D, Fong GT, Zanna MP, Thrasher JF, Borland R. Tobacco denormalization and industry beliefs among smokers from four countries. *Am J Prev Med*. 2006;31(3):225-232. doi:10.1016/j.amepre.2006.04.004

98. Shiffman S, Dunbar M, Kirchner T, et al. Smoker reactivity to cues: effects on craving and on smoking behavior. *J Abnorm Psychol*. 2013;122(1):264-280. doi:10.1037/a0028339

99. Shahab L, West R. Public support in England for a total ban on the sale of tobacco products. *Tob Control*. 2010;19(2):143-147. doi:10.1136/tc.2009.033415

100. Csete J, Kamarulzaman A, Kazatchkine M, et al. Public health and international drug policy. *Lancet*. 2016;387(10026):1427-1480. doi:10.1016/S0140-6736(16)00619-X

101. Kaeble D. *Probation and Parole in the United States*. Bureau of Justice Statistics; 2018. https://www.bjs.gov/index.cfm?ty=pbdetail&iid=6188

102. Nutt DJ, King LA, Phillips LD. Drug harms in the UK: A multicriteria decision analysis. *Lancet*. 2010;376(9752):1558-1565. doi:10.1016/S0140-6736(10)61462-6

103. Holford TR, Meza R, Warner KE, et al. Tobacco control and the reduction in smoking-related premature deaths in the United States, 1964-2012. *JAMA - Journal of the American Medical Association*. 2014;311(2):164-171. doi:10.1001/jama.2013.285112

104. Beard E, Brown J, Jackson S, et al. Long-term evaluation of the rise in legal age-of-sale of cigarettes from 16 to 18 in England: A trend analysis. *BMC Med*. 2020;18(1):85. doi:10.1186/s12916-020-01541-w

105. Zimring FE, Nelson W. Cigarette taxes as cigarette policy. *Tob Control*. 1995;4(Suppl 1):S25-S35. doi:10.1136/tc.4.suppl1.s25

106. West R, Coyle K, Owen L, Coyle D, Pokhrel S. Estimates of effectiveness and reach for 'return on investment' modelling of smoking cessation interventions using data from England. *Addiction*. 2018;113:19-31. doi:10.1111/add.14006

107. Maldonado N, Llorente B, Escobar D, Iglesias RM. Smoke signals: monitoring illicit cigarettes and smoking behaviour in Colombia to support tobacco taxes. *Tob Control*. 2020;29(Suppl 4):s243-s248. doi:10.1136/tobaccocontrol-2018-054820

108. Reid JL, Hammond D, Driezen P. Socio-economic status and smoking in Canada, 1999-2006: has there been any progress on disparities in tobacco use? *Can J Public Health*. 2010;101(1):73-78. doi:10.1007/BF03405567

109. Fuchs A, Meneses FJ. Are Tobacco Taxes Really Regressive? Evidence from Chile. Published online 1 March 2017. Accessed October 21, 2022. https://papers.ssrn.com/abstract=2931799

110. Jha P, Gelband H, Irving H, Mishra S. Tobacco-related cancers and taxation of tobacco in low- and middle-income countries. In: Vaccarella S, Lortet-Tieulent J, Saracci R, Conway

DI, Straif K, Wild CP, eds. *Reducing Social Inequalities in Cancer: Evidence and Priorities for Research*. International Agency for Research on Cancer; 2021. https://www.ncbi.nlm.nih.gov/pubmed/33534502

111. Global Tobacco Economics Consortium. The health, poverty, and financial consequences of a cigarette price increase among 500 million male smokers in 13 middle income countries: compartmental model study. *BMJ*. 2018;361:k1162. doi:10.1136/bmj.k1162

112. Benowitz NL. Pharmacology of Nicotine: Addiction and Therapeutics. *Annu Rev Pharmacol Toxicol*. 1996;36(1):597-613. doi:10.1146/annurev.pa.36.040196.003121

113. Benowitz NL. Pharmacology of Nicotine: Addiction, Smoking-Induced Disease, and Therapeutics. *Annu Rev Pharmacol Toxicol*. 2009;49(1):57-71. doi:10.1146/annurev.pharmtox.48.113006.094742

114. Feduccia AA, Chatterjee S, Bartlett SE. Neuronal nicotinic acetylcholine receptors: Neuroplastic changes underlying alcohol and nicotine addictions. *Frontiers in Molecular Neuroscience*. 2012;5:83. doi:10.3389/fnmol.2012.00083

115. West R, Brown J. A theory of addiction. In: *Theory of Addiction*. ; 2013. doi:10.1002/9781118484890.ch9

116. Quitkin F, Rifkin A, Klein DF. Monoamine Oxidase Inhibitors: A Review of Antidepressant Effectiveness. *Arch Gen Psychiatry*. 1979;36(7):749-760. doi:10.1001/archpsyc.1979.01780070027003

117. Picciotto MR, Brunzell DH, Caldarone BJ. Effect of nicotine and nicotinic receptors on anxiety and depression. *NeuroReport*. 2002;13(9):1097-1106. doi:10.1097/00001756-200207020-00006

118. Fidler JA, West R. Enjoyment of smoking and urges to smoke as predictors of attempts and success of attempts to stop smoking: A longitudinal study. *Drug Alcohol Depend*. 2011;115(1-2):30-34. doi:10.1016/J.DRUGALCDEP.2010.10.009

119. Jackson SE, McGowan JA, Ubhi HK, et al. Modelling continuous abstinence rates over time from clinical trials of pharmacological interventions for smoking cessation. *Addiction*. 2019;114(5):787-797. doi:10.1111/add.14549

120. Tombor I, Shahab L, Brown J, West R. Positive smoker identity as a barrier to quitting smoking: findings from a national survey of smokers in England. *Drug Alcohol Depend*. 2013;133(2):740-745. doi:10.1016/j.drugalcdep.2013.09.001

121. Michie S, Hyder N, Walia A, West R. Development of a taxonomy of behaviour change techniques used in individual behavioural support for smoking cessation. *Addict Behav*. 2011;36(4):315-319. doi:10.1016/j.addbeh.2010.11.016

122. Perski O, Crane D, Beard E, Brown J. Does the addition of a supportive chatbot promote user engagement with a smoking cessation app? An experimental study. *Digit Health*. 2019;5:2055207619880676. doi:10.1177/2055207619880676

123. Bricker JB, Mull KE, Santiago-Torres M, Miao Z, Perski O, Di C. Smoking cessation smartphone app use over time: Predicting 12-month cessation outcomes in a 2-arm randomized trial. *J Med Internet Res*. 2022;24(8):e39208. doi:10.2196/39208

124. Brown J, Michie S, Geraghty AWA, et al. A pilot study of StopAdvisor: a theory-based interactive internet-based smoking cessation intervention aimed across the social spectrum. *Addict Behav*. 2012;37(12):1365-1370. doi:10.1016/j.addbeh.2012.05.016

125. Berndt N, De Vries ·. H., Lechner ·. L., et al. High intensity smoking cessation interventions: Cardiac patients of low socioeconomic status and low intention to quit profit most. *Netherlands Health Journal*. 2016;25:24-32. doi:10.1007/s12471-016-0906-7

126. Hartmann-Boyce J, Hong B, Livingstone-Banks J, Wheat H, Fanshawe TR. Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. *Cochrane Database Syst Rev*. Published online 5 June 2019. doi:10.1002/14651858.CD009670.pub4

127. West R, Kock L, Kale D, Brown J. *Monthly Trends on Smoking in England from the Smoking Toolkit Study*. UCL Tobacco and Alcohol Research Group; 2021.

128. Abrams DB, Glasser AM, Pearson JL, Villanti AC, Collins LK, Niaura RS. Harm Minimization and Tobacco Control: Reframing Societal Views of Nicotine Use to Rapidly Save Lives. *Annual Review of Public Health*. 2018;39:193-213. doi:10.1146/annurev-publhealth-040617-013849

129. Prochaska JJ, Das S, Benowitz NL. Cytisine, the world's oldest smoking cessation aid: Growing evidence for its use as an affordable treatment globally. *BMJ (Online)*. 2013;347(7923). doi:10.1136/bmj.f5198

130. Jordan CJ, Xi ZX. Discovery and development of varenicline for smoking cessation. *Expert Opin Drug Discov*. 2018;13(7):671-683. doi:10.1080/17460441.2018.1458090

131. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*. Published online 9 May 2016. doi:10.1002/14651858.CD006103.pub7

132. Jackson SE, Kotz D, West R, Brown J. Moderators of real-world effectiveness of smoking cessation aids: a population study. *Addiction*. 2019;114(9). doi:10.1111/add.14656

133. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): A double-blind, randomised, placebo-controlled clinical trial. *Lancet*. 2016;387(10037):2507-2520. doi:10.1016/S0140-6736(16)30272-0

134. Beard E, Jackson SE, Anthenelli RM, et al. Estimation of risk of neuropsychiatric adverse events from varenicline, bupropion and nicotine patch versus placebo: secondary analysis of results from the EAGLES trial using Bayes factors. *Addiction*. 2021;116(10):2816-2824. doi:10.1111/add.15440

135. Thomas D, Farrell M, McRobbie H, et al. The effectiveness, safety and cost-effectiveness of cytisine versus varenicline for smoking cessation in an Australian population: a study protocol for a randomized controlled non-inferiority trial. *Addiction*. 2019;114(5):923-933. doi:10.1111/add.14541

136. Walker N, Smith B, Barnes J, et al. Cytisine versus varenicline for smoking cessation for Māori (the indigenous people of New Zealand) and their extended family: protocol for a randomized non-inferiority trial. *Addiction*. 2019;114(2):344-352. doi:10.1111/add.14449

137. West R, Zatonski W, Cedzynska M, et al. Placebo-Controlled Trial of Cytisine for Smoking Cessation. *N Engl J Med*. 2011;365(13):1193-1200. doi:10.1056/NEJMoa1102035

138. Boots. Choosing nicotine replacement therapy. Published 2021. Accessed March 10, 2021. https://www.boots.com/wellness-advice/stop-smoking-advice/choosing-nicotine-replacement-therapy-advice

139. Wadgave U, Nagesh L. Nicotine replacement therapy: An overview. *International Journal of Health Science*. 2016;10(3):425-435. doi:10.12816/0048737

140. West R, DiMarino ME, Gitchell J, McNeill A. Impact of UK policy initiatives on use of medicines to aid smoking cessation. *Tob Control*. 2005;14(3):166-171. doi:10.1136/tc.2004.008649

141. Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database Syst Rev*. Published online 31 May 2018. doi:10.1002/14651858.CD000146.pub5

142. Lindson N, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews*. 2019;2019(4). doi:10.1002/14651858.CD013308

143. West R. The multiple facets of cigarette addiction and what they mean for encouraging and helping smokers to stop. In: *COPD: Journal of Chronic Obstructive Pulmonary Disease*. Vol 6. Taylor & Francis; 2009:277-283. doi:10.1080/15412550903049181

144. Molyneux A. Nicotine replacement therapy. *British Medical Journal*. 2004;328(7437):454-456. doi:10.1136/bmj.328.7437.454

145. Kotz D, Brown J, West R. 'Real-world' effectiveness of smoking cessation treatments: A population study. *Addiction*. 2014;109(3):491-499. doi:10.1111/add.12429

146. Wilson S, Partos T, McNeill A, Brose LS. Harm perceptions of e-cigarettes and other nicotine products in a UK sample. *Addiction*. 2019;114(5):879-888. doi:10.1111/add.14502

147. Shiffman S, Ferguson SG, Rohay J, Gitchell JG. Perceived safety and efficacy of nicotine replacement therapies among US smokers and ex-smokers: relationship with use and compliance. *Addiction*. 2008;103(8):1371-1378. doi:10.1111/j.1360-0443.2008.02268.x

148. Ncsct. NCSCT e-learning: Smoking Cessation Support Training for Practitioners. https://elearning.ncsct.co.uk/

149. NHS Digital. Statistics on NHS Stop Smoking Services in England - April 2017 to March 2018. Published 2018. https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-nhs-stop-smoking-services-in-england/april-2017-to-march-2018#resources

150. Stanford Research into the Impact of Tobacco Advertising. Accessed March 9, 2021. http://tobacco.stanford.edu/tobacco_main/main.php

151. Smoking adverts and the 'outrageous' cigarette promotions of the past - BBC News. https://www.bbc.co.uk/news/newsbeat-30935575

152. Outrageous vintage cigarette ads - CBS News. Accessed March 9, 2021. https://www.cbsnews.com/pictures/outrageous-vintage-cigarette-ads/

153. Heinmann J. *20th Century Alcohol & Tobacco Ads. 100 Years of Stimulating Ads*. Vol TASCHEN Books. TASCHEN Books; 2018. https://www.taschen.com/pages/en/catalogue/popculture/all/49389/facts.20th_century_alcohol_tobacco_ads_100_years_of_stimulating_ads.htm

154. Emery S, Kim Y, Choi YK, Szczypka G, Wakefield M, Chaloupka FJ. The effects of smoking-related television advertising on smoking and intentions to quit among adults in the United States: 1999-2007. *Am J Public Health*. 2012;102(4):751-757. doi:10.2105/AJPH.2011.300443

155. Hammond D, Reid JL, Driezen P, Boudreau C. Pictorial health warnings on cigarette packs in the United States: an experimental evaluation of the proposed FDA warnings. *Nicotine Tob Res*. 2013;15(1):93-102. doi:10.1093/ntr/nts094

156. Huang LL, Thrasher JF, Reid JL, Hammond D. Predictive and External Validity of a Pre-Market Study to Determine the Most Effective Pictorial Health Warning Label Content for Cigarette Packages. *Nicotine Tob Res*. 2016;18(5):1376-1381. doi:10.1093/ntr/ntv184

157. Hammond D. Health warning messages on tobacco products: a review. *Tob Control*. 2011;20(5):327-337. doi:10.1136/tc.2010.037630

158. Hammond D, White C, Anderson W, Arnott D, Dockrell M. The perceptions of UK youth of branded and standardized, 'plain' cigarette packaging. *Eur J Public Health*. 2014;24(4):537-543. doi:10.1093/eurpub/ckt142

159. Moodie C, Hoek J, Hammond D, et al. Plain tobacco packaging: progress, challenges, learning and opportunities. *Tob Control*. 2022;31(2):263-271. doi:10.1136/tobaccocontrol-2021-056559

160. Moodie C, Best C, Hitchman SC, et al. Impact of standardised packaging in the UK on warning salience, appeal, harm perceptions and cessation-related behaviours: a longitudinal online survey. *Tob Control*. Published online 15 July 2021. doi:10.1136/tobaccocontrol-2021-056634

161. Hiscock R, Bauld L, Amos A, Fidler JA, Munafò M. Socioeconomic status and smoking: a review. *Ann N Y Acad Sci*. 2012;1248(1):107-123. doi:10.1111/j.1749-6632.2011.06202.x

162. Wodak A, McLeod L. The role of harm reduction in controlling HIV among injecting drug users. *AIDS*. 2008;22 Suppl 2(Suppl 2):S81. doi:10.1097/01.aids.0000327439.20914.33

163. Watters JK, Estilo MJ, Clark GL, Lorvick J. Syringe and Needle Exchange as HIV/AIDS Prevention for Injection Drug Users. *JAMA*. 1994;271(2):115-120. doi:10.1001/jama.1994.03510260047027

164. Inciardi J, Harrison L. *Harm Reduction: National and International Perspectives*. 1st ed. SAGE Publications; 1999.

165. United States Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress A Report of the Surgeon General. *Annu Rep Surg Gen U S*

Navy Chief Bur Med Surg Secr Navy Relat Stat Dis Inj U S Navy. Published online 2014. https://www.ncbi.nlm.nih.gov/pubmed/24455788

166. Donny EC, Houtsmuller E, Stitzer ML. Smoking in the absence of nicotine: Behavioral, subjective and physiological effects over 11 days. *Addiction*. 2007;102(2):324-334. doi:10.1111/j.1360-0443.2006.01670.x

167. McNeill A, Brose LS, Calder R, Bauld L, Robson D. *Evidence Review of E-Cigarettes and Heated Tobacco Products 2018*. Public Health England; 2018.

168. Elam MJ. Nicorette reborn? E-cigarettes in light of the history of nicotine replacement technology. *International Journal of Drug Policy*. 2015;26(6):536-542. doi:10.1016/j.drugpo.2015.02.002

169. Fernö O, Lichtneckert SJA, Lundgren CEG. A substitute for tobacco smoking. *Psychopharmacologia*. 1973;31(3):201-204. doi:10.1007/BF00422510

170. Tibbling L. Abuse and intoxication potential of nicotine chewing gum. *British Medical Journal*. 1976;2(6039):812. doi:10.1136/bmj.2.6039.812

171. Shahab L, Dobbie F, Hiscock R, McNeill A, Bauld L. Prevalence and Impact of Long-term Use of Nicotine Replacement Therapy in UK Stop-Smoking Services: Findings From the ELONS Study. *Nicotine & Tobacco Research*. 2016;20(1):ntw258. doi:10.1093/ntr/ntw258

172. Etter JF. Addiction to the nicotine gum in never smokers. *BMC Public Health*. 2007;7(1):159. doi:10.1186/1471-2458-7-159

173. Munafo M. Are e-Cigarettes Tobacco Products? Published 2018. Accessed July 9, 2020. https://academic.oup.com/ntr/article/21/3/267/5041976

174. Tattan-Birch H, Jackson S, Shahab L, et al. Heated tobacco products for smoking cessation and reducing smoking prevalence. *Cochrane Database Syst Rev*. 2020;(11). doi:10.1002/14651858.CD013790

175. Chapman S, MacKenzie R. The Global Research Neglect of Unassisted Smoking Cessation: Causes and Consequences. *PLoS Med*. 2010;7(2):e1000216. doi:10.1371/journal.pmed.1000216

176. Warner KE, Slade J, Sweanor DT. The emerging market for long-term nicotine maintenance. *JAMA*. 1997;278(13):1087-1092. doi:10.1001/jama.1997.03550130061038

177. Warner KE. How to Think—Not Feel—about Tobacco Harm Reduction. *Nicotine Tob Res*. 2019;21(10):1299-1309. doi:10.1093/ntr/nty084

178. Levy DT, Borland R, Lindblom EN, et al. Potential deaths averted in USA by replacing cigarettes with e-cigarettes. *Tob Control*. 2018;27(1):18-25. doi:10.1136/tobaccocontrol-2017-053759

179. Glantz SA. The Evidence of Electronic Cigarette Risks Is Catching Up With Public Perception. *JAMA network open*. 2019;2(3):e191032. doi:10.1001/jamanetworkopen.2019.1032

180. Gartner CE, Hall WD, Chapman S, Freeman B. Should the Health Community Promote Smokeless Tobacco (Snus) as a Harm Reduction Measure? *PLoS Med*. 2007;4(7):e185. doi:10.1371/journal.pmed.0040185

181. Zeller M. The Future of Nicotine Regulation: Key Questions and Challenges. *Nicotine Tob Res*. 2019;21(3):331-332. doi:10.1093/ntr/nty200

182. Jerzyński T, Stimson GV, Shapiro H, Król G. Estimation of the global number of e-cigarette users in 2020. *Harm Reduct J*. 2021;18(1):109. doi:10.1186/s12954-021-00556-7

183. Nordgren P, Ramstrom L. Moist snuff in Sweden—tradition and evolution. *Br J Addict*. 1990;85(9):1107-1112. doi:10.1111/j.1360-0443.1990.tb03435.x

184. Henningfield JE, Fagerstrom KO. Swedish Match Company, Swedish snus and public health: A harm reduction experiment in progress? *Tob Control*. 2001;10(3):253-257. doi:10.1136/tc.10.3.253

185. Lund I, Lund KER. How has the availability of snus influenced cigarette smoking in Norway? *Int J Environ Res Public Health*. 2014;11(11):11705-11717. doi:10.3390/ijerph111111705

186. Swedish Match. Swedish Match and Philip Morris International to dissolve smokeless joint venture. *Swedish Match Press Releases and News*. https://www.swedishmatch.com/Media/Pressreleases-and-news/Press-releases/2015/Swedish-Match-and-Philip-Morris-International-to-dissolve-smokeless-joint-venture/. Published June 16, 2015.

187. Robichaud MO, Seidenberg AB, Byron MJ. Tobacco companies introduce 'tobacco-free' nicotine pouches. *Tobacco Control*. 2020;29(e1):E145-E146. doi:10.1136/tobaccocontrol-2019-055321

188. Zatoński M, Brandt A. Divide and conquer? E-cigarettes as a disruptive technology in the history of tobacco control. In: *The Regulation of E-Cigarettes*. Edward Elgar Publishing; 2019:24-49. doi:10.4337/9781788970464.00010

189. Malone RE. Conflicts and controversies in contemporary tobacco control. *Tobacco Control*. 2017;26(e1):e1-e2. doi:10.1136/tobaccocontrol-2017-053727

190. RCP policy: public health and health inequality. *Nicotine without Smoke: Tobacco Harm Reduction*. Royal College of Physicians; 2016. https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction

191. Stratton K, Kwan L, Eaton D. *Public Health Consequences of E-Cigarettes*. (Eaton DL, Kwan LY, Stratton K, eds.). National Academies of Sciences (US); 2018. doi:10.17226/24952

192. Goniewicz ML, Smith DM, Edwards KC, et al. Comparison of Nicotine and Toxicant Exposure in Users of Electronic Cigarettes and Combustible Cigarettes. *JAMA network open*. 2018;1(8):e185937. doi:10.1001/jamanetworkopen.2018.5937

193. Shahab L, Goniewicz ML, Blount BC, et al. Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users. *Ann Intern Med*. 2017;166(6):390. doi:10.7326/M16-1107

194. George J, Hussain M, Vadiveloo T, et al. Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes. *J Am Coll Cardiol*. Published online 2019. doi:10.1016/j.jacc.2019.09.067

195. DeJarnett N, Conklin DJ, Riggs DW, et al. Acrolein exposure is associated with increased cardiovascular disease risk. *J Am Heart Assoc*. 2014;3(4). doi:10.1161/JAHA.114.000934

196. Sleiman M, Logue JM, Montesinos VN, et al. Emissions from Electronic Cigarettes: Key Parameters Affecting the Release of Harmful Chemicals. *Environ Sci Technol*. 2016;50(17):9644-9651. doi:10.1021/acs.est.6b01741

197. Jensen RP, Luo W, Pankow JF, Strongin RM, Peyton DH. Hidden Formaldehyde in E-Cigarette Aerosols. *N Engl J Med*. 2015;372(4):392-394. doi:10.1056/NEJMc1413069

198. Farsalinos KE, Gillman G. Carbonyl Emissions in E-cigarette Aerosol: A Systematic Review and Methodological Considerations. *Front Physiol*. 2018;8:1119. doi:10.3389/fphys.2017.01119

199. Farsalinos KE, Voudris V, Spyrou A, Poulas K. E-cigarettes emit very high formaldehyde levels only in conditions that are aversive to users: A replication study under verified realistic use conditions. *Food Chem Toxicol*. 2017;109:90-94. doi:10.1016/j.fct.2017.08.044

200. Greenland S. Quantifying biases in causal models: Classical confounding vs collider-stratification bias. *Epidemiology*. 2003;14(3):300-306. doi:10.1097/00001648-200305000-00009

201. Gage SH, Munafò MR, Davey Smith G. Causal Inference in Developmental Origins of Health and Disease (DOHaD) Research. *Annu Rev Psychol*. 2016;67(1):567-585. doi:10.1146/annurev-psych-122414-033352

202. Retraction Watch. Journal retracts hotly contested paper on vaping and heart attacks. Published 2020. https://retractionwatch.com/2020/02/18/journal-retracts-hotly-contested-paper-on-vaping-and-heart-attacks/#more-118947

203. Hernan MA, Robins JM. *Causal Inference*. CRC Press; 2021.

204. Rodu B, Plurphanswat N. A re-analysis of e-cigarette use and heart attacks in PATH wave 1 data. *Addiction*. 2020;115(11):2176-2179. doi:10.1111/add.15067

205. Berlowitz JB, Xie W, Harlow AF, et al. E-cigarette use and risk of cardiovascular disease: A longitudinal analysis of the PATH study (2013-2019). *Circulation*. 2022;145(20):1557-1559. doi:10.1161/CIRCULATIONAHA.121.057369

206. Office on Smoking and Health. Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products. Published 2020. Accessed September 10, 2020. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html

207. Dave D, Dench D, Kenkel D, Mathios A, Wang H. News that takes your breath away: risk perceptions during an outbreak of vaping-related lung injuries. *J Risk Uncertain*. 2020;60(3):307. doi:10.1007/s11166-020-09329-2

208. Nyakutsikwa B, Britton J, Bogdanovica I, Langley T. Vitamin E acetate is not present in licit e-cigarette products available on the UK market. *Addiction*. Published online 16 January 2020:add.14920. doi:10.1111/add.14920

209. Hall W, Gartner C, Bonevski B. Lessons from the public health responses to the US outbreak of vaping-related lung injury. *Addiction*. Published online 30 May 2020:add.15108. doi:10.1111/add.15108

210. Algiers O, Wang Y, Laestadius L. Content Analysis of U.S. Newspaper Coverage of Causes and Solutions to Vaping-Associated Lung Injury. *Subst Use Misuse*. 2021;56(4):522-528. doi:10.1080/10826084.2021.1883663

211. European Parliament and the Council of the European Union. Directive 2014/40/EU of the European Parliament and the Council. *Official Journal of the European Union*. Published online 2014.

212. Merkler AE, Parikh NS, Mir S, et al. Risk of Ischemic Stroke in Patients with Coronavirus Disease 2019 (COVID-19) vs Patients with Influenza. *JAMA Neurol*. 2020;77(11):1366-1372. doi:10.1001/jamaneurol.2020.2730

213. Fifi JT, Mocco J. COVID-19 related stroke in young individuals. *The Lancet Neurology*. 2020;19(9):713-715. doi:10.1016/S1474-4422(20)30272-6

214. Windsor-Shellard B, Kaur J. *Coronavirus (COVID-19) Related Deaths by Occupation, England and Wales - Office for National Statistics*. Office for National Statistics; 2020. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/bulletins/coronaviruscovid19relateddeathsbyoccupationenglandandwales/deathsregistereduptoandincluding20april2020#women-and-coronavirus-related-deaths-by-occupation

215. Cai G. Bulk and single-cell transcriptomics identify tobacco-use disparity in lung gene expression of ACE2, the receptor of 2019-nCov. Published online 2 March 2020. doi:10.20944/preprints202002.0051.v3

216. Brake SJ, Barnsley K, Lu W, McAlinden KD, Eapen MS, Sohal SS. Smoking Upregulates Angiotensin-Converting Enzyme-2 Receptor: A Potential Adhesion Site for Novel Coronavirus SARS-CoV-2 (Covid-19). *J Clin Med Res*. 2020;9(3):841. doi:10.3390/jcm9030841

217. Simons D, Perski O, Brown J. Covid-19: The role of smoking cessation during respiratory virus epidemics. *BMJ News*. https://blogs.bmj.com/bmj/2020/03/20/covid-19-the-role-of-smoking-cessation-during-respiratory-virus-epidemics/.

218. Farsalinos K, Barbouni A, Niaura R. Smoking, vaping and hospitalization for COVID-19. *Qeios*. Published online 4 April 2020. doi:10.32388/z69o8a.13

219. Simons D, Shahab L, Brown J, Perski O. The association of smoking status with SARS-CoV-2 infection, hospitalisation and mortality from COVID-19: A living rapid evidence review with Bayesian meta-analyses (version 7). *Addiction*. Published online 2 October 2020:add.15276. doi:10.1111/add.15276

220. Kloc M, Ghobrial RM, Kubiak JZ. How nicotine can inhibit cytokine storm in the lungs and prevent or lessen the severity of COVID-19 infection? *Immunology Letters*. 2020;224:28-29. doi:10.1016/j.imlet.2020.06.002

221. Farsalinos K, Niaura R, Le Houezec J, et al. Editorial: Nicotine and SARS-CoV-2: COVID-19 may be a disease of the nicotinic cholinergic system. *Toxicology Reports*. Published online 30 April 2020. doi:10.1016/j.toxrep.2020.04.012

222. Tattan-Birch H, Marsden J, West R. Assessing and addressing collider bias in addiction research: the curious case of smoking and COVID-19. *Addiction (Abingdon*. https://www.ncbi.nlm.nih.gov/pmc/articles/pmc7753816/

223. Levy DT, Sánchez-Romero LM, Li Y, et al. England SimSmoke: the impact of nicotine vaping on smoking prevalence and smoking-attributable deaths in England. *Addiction*. Published online 8 October 2020:add.15269. doi:10.1111/add.15269

224. Khouja JN, Suddell SF, Peters SE, Taylor AE, Munafò MR. Is e-cigarette use in non-smoking young adults associated with later smoking? A systematic review and meta-analysis (pre-print). *medRxiv*. Published online 2 January 2020:19007005. doi:10.1101/19007005

225. Levy DT, Warner KE, Michael Cummings K, et al. Examining the relationship of vaping to smoking initiation among US youth and young adults: A reality check. *Tob Control*. 2019;28(6):629-635. doi:10.1136/tobaccocontrol-2018-054446

226. Khouja JN, Suddell SF, Peters SE, Taylor AE, Munafò MR. Is e-cigarette use in non-smoking young adults associated with later smoking? A systematic review and meta-analysis. *Tob Control*. 2021;30(1):8-15. doi:10.1136/tobaccocontrol-2019-055433

227. Giovenco DP, Spillane TE, Merizier JM. Neighborhood Differences in Alternative Tobacco Product Availability and Advertising in New York City: Implications for Health Disparities. *Nicotine Tob Res*. 2019;21(7):896-902. doi:10.1093/ntr/nty244

228. Shahab L, Beard E, Brown J. Association of initial e-cigarette and other tobacco product use with subsequent cigarette smoking in adolescents: a cross-sectional, matched control study. *Tob Control*. 2020;30(2):tobaccocontrol-2019-055283. doi:10.1136/tobaccocontrol-2019-055283

229. Chan GCK, Stjepanović D, Lim C, et al. Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation. *Addiction*. Published online 5 October 2020:add.15246. doi:10.1111/add.15246

230. Howe CJ, Cole SR, Westreich DJ, Greenland S, Napravnik S, Eron JJ. Splines for trend analysis and continuous confounder control. *Epidemiology*. 2011;22(6):874-875. doi:10.1097/EDE.0b013e31823029dd

231. U.S. Food & Drug Administration. Results from 2018 National Youth Tobacco Survey show dramatic increase in e-cigarette use among youth over past year. Published 15 November 2018. Accessed March 9, 2021. https://www.fda.gov/news-events/press-announcements/results-2018-national-youth-tobacco-survey-show-dramatic-increase-e-cigarette-use-among-youth-over

232. Hartmann-Boyce J, McRobbie H, Lindson N, et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev*. Published online 2022. doi:10.1002/14651858.CD010216.pub4

233. Hajek P, Pittaccio K, Pesola F, Myers Smith K, Phillips-Waller A, Przulj D. Nicotine delivery and users' reactions to Juul compared with cigarettes and other e-cigarette products. *Addiction*. Published online 29 January 2020:add.14936. doi:10.1111/add.14936

234. Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: Comparison between first and new-generation devices. *Sci Rep*. 2014;3(1):1-7. doi:10.1038/srep04133

235. Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: A randomised controlled trial. *Lancet*. 2013;382(9905):1629-1637. doi:10.1016/S0140-6736(13)61842-5

236. Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of E-cigarettes versus nicotine-replacement therapy. *N Engl J Med*. 2019;380(7):629-637. doi:10.1056/NEJMoa1808779

237. Corbin L HP, Spearing E LD. Adding E-Cigarettes to Specialist Stop-Smoking Treatment: City of London Pilot Project. *J Addict Res Ther*. 2015;06(03):1-4. doi:10.4172/2155-6105.1000244

238. Kalkhoran S, Chang Y, Rigotti NA. E-cigarettes and Smoking Cessation in Smokers With Chronic Conditions. *Am J Prev Med*. 2019;57(6):786-791. doi:10.1016/j.amepre.2019.08.017

239. Beard E, West R, Michie S, Brown J. Association of prevalence of electronic cigarette use with smoking cessation and cigarette consumption in England: a time–series analysis between 2006 and 2017. *Addiction*. 2020;115(5):961-974. doi:10.1111/add.14851

240. Elias J, Ling PM. Invisible smoke: Third-party endorsement and the resurrection of heat-not-burn tobacco products. *Tob Control*. 2018;27(Suppl 1):s96-s101. doi:10.1136/tobaccocontrol-2018-054433

241. Fairchild A, Colgrove J. The Life, Death, and Rebirth of the Safer Cigarette in the United States. Published online 2004.

242. Tabuchi T, Gallus S, Shinozaki T, Nakaya T, Kunugita N, Colwell B. Heat-not-burn tobacco product use in Japan: Its prevalence, predictors and perceived symptoms from exposure to secondhand heat-not-burn tobacco aerosol. *Tob Control*. 2017;27. doi:10.1136/tobaccocontrol-2017-053947

243. Hori A, Tabuchi T, Kunugita N. Rapid increase in heated tobacco product (HTP) use from 2015 to 2019: from the Japan 'Society and New Tobacco' Internet Survey (JASTIS). *Tob Control*. Published online 5 June 2020:tobaccocontrol-2020-055652. doi:10.1136/tobaccocontrol-2020-055652

244. World Health Organisation. *Heated Tobacco Products (HTPs) Market Monitoring Information*. World Health Organization; 2018. https://www.who.int/tobacco/publications/prod_regulation/htps-marketing-monitoring/en/

245. Laverty AA, Vardavas CI, Filippidis FT. Prevalence and reasons for use of Heated Tobacco Products (HTP) in Europe: an analysis of Eurobarometer data in 28 countries. *Lancet Reg Health Eur*. 2021;8:100159. doi:10.1016/j.lanepe.2021.100159

246. Mathers A, Schwartz R, O'Connor S, Fung M, Diemert L. Marketing IQOS in a dark market. *Tob Control*. 2019;28(2):237-238. doi:10.1136/tobaccocontrol-2017-054216

247. Bialous SA, Glantz SA. Heated tobacco products: Another tobacco industry global strategy to slow progress in tobacco control. *Tob Control*. 2018;27(Suppl 1):s111-s117. doi:10.1136/tobaccocontrol-2018-054340

248. Simonavicius E, McNeill A, Shahab L, Brose LS. Heat-not-burn tobacco products: A systematic literature review. *Tob Control*. 2018;28(5). doi:10.1136/tobaccocontrol-2018-054419

249. Action on Smoking and Health. *Use of E-Cigarettes (Vaporisers) among Adults in Great Britain*. ASH; 2021. https://ash.org.uk/information-and-resources/ash-fact-sheets/

250. UK Health Research Authority. Policies, standards and regulations: research involving children. Published 19 March 2018. https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/research-involving-children/

251. Lumley TS. *Complex Surveys*. John Wiley & Sons; 2017.

252. Jackson SE, Beard E, Kujawski B, et al. Comparison of Trends in Self-reported Cigarette Consumption and Sales in England, 2011 to 2018. *JAMA network open*. 2019;2(8):e1910161. doi:10.1001/jamanetworkopen.2019.10161

253. Fidler JA, Shahab L, West O, et al. 'The smoking toolkit study': a national study of smoking and smoking cessation in England. *BMC Public Health*. 2011;11(1):479. doi:10.1186/1471-2458-11-479

254. Kock L, Tattan-Birch H, Jackson S, Shahab L, Brown J. Socio-demographic, smoking and drinking characteristics in GB: A comparison of independent telephone and face-to-face Smoking and Alcohol Toolkit surveys conducted in March 2022. *Qeios*. Published online 16 August 2022. doi:10.32388/clxk4d

255. Hajek P, Pittaccio K, Pesola F, Myers Smith K, Phillips-Waller A, Przulj D. Nicotine delivery and users' reactions to Juul compared with cigarettes and other e-cigarette products. *Addiction*. Published online 29 January 2020:add.14936. doi:10.1111/add.14936

256. Hitchman SC, Brose LS, Brown J, Robson D, McNeill A. Associations Between E-Cigarette Type, Frequency of Use, and Quitting Smoking: Findings From a Longitudinal Online Panel Survey in Great Britain. *Nicotine Tob Res*. 2015;17(10):1187-1194. doi:10.1093/NTR/NTV078

257. Gravely S, Driezen P, Ouimet J, et al. Prevalence of awareness, ever-use and current use of nicotine vaping products (NVPs) among adult current smokers and ex-smokers in 14 countries with differing regulations on sales and marketing of NVPs: cross-sectional findings from the ITC Project. *Addiction*. 2019;114(6):1060-1073. doi:10.1111/add.14558

258. McNeill A, Brose LS, Calder R, Bauld L, Robson D. *Vaping in England: 2020 Evidence Update Summary*. Public Health England; 2020.

https://www.gov.uk/government/publications/vaping-in-england-evidence-update-march-2020/vaping-in-england-2020-evidence-update-summary#vaping-among-adults

259. Beard E, West R, Michie S, Brown J. Association of prevalence of electronic cigarette use with smoking cessation and cigarette consumption in England: a time–series analysis between 2007 and 2017. *Addiction*. Published online 4 December 2019:add.14851. doi:10.1111/add.14851

260. Wagener TL, Floyd EL, Stepanov I, et al. Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. *Tob Control*. 2017;26(e1):e23-e28. doi:10.1136/tobaccocontrol-2016-053041

261. Walker N, Verbiest M, Kurdziel T, et al. Effectiveness and safety of nicotine patches combined with e-cigarettes (with and without nicotine) for smoking cessation: Study protocol for a randomised controlled trial. *BMJ Open*. 2019;9(2). doi:10.1136/bmjopen-2018-023659

262. Jackler RK, Ramamurthi D. Nicotine arms race: JUUL and the high-nicotine product market. *Tob Control*. 2019;28:623-628. doi:10.1136/tobaccocontrol-2018-054796

263. Talih S, Salman R, El-Hage R, et al. Characteristics and toxicant emissions of JUUL electronic cigarettes. *Tob Control*. 2019;28(6):678-680. doi:10.1136/tobaccocontrol-2018-054616

264. Huang J, Duan Z, Kwok J, et al. Vaping versus JUULing: How the extraordinary growth and marketing of JUUL transformed the US retail e-cigarette market. *Tob Control*. 2019;28(2):146-151. doi:10.1136/tobaccocontrol-2018-054382

265. Caldwell B, Sumner W, Crane J. A systematic review of nicotine by inhalation: is there a role for the inhaled route? *Nicotine Tob Res*. 2012;14(10):1127-1139. doi:10.1093/ntr/nts009

266. Reuters. Fast-growing e-cigarette maker Juul to launch in UK. Published 2018. Accessed March 9, 2020. https://www.reuters.com/article/us-juul-britain/fast-growing-e-cigarette-maker-juul-to-launch-in-uk-idUSKBN1K62WC

267. Dawkins L, Cox S, Goniewicz M, et al. 'Real-world' compensatory behaviour with low nicotine concentration e-liquid: subjective effects and nicotine, acrolein and formaldehyde exposure. *Addiction*. 2018;113(10):1874-1882. doi:10.1111/add.14271

268. Kośmider L, Kimber CF, Kurek J, Corcoran O, Dawkins LE. Compensatory Puffing With Lower Nicotine Concentration E-liquids Increases Carbonyl Exposure in E-cigarette Aerosols. *Nicotine Tob Res*. 2018;20(8):998-1003. doi:10.1093/ntr/ntx162

269. Poynton S, Sutton J, Goodall S, et al. A novel hybrid tobacco product that delivers a tobacco flavour note with vapour aerosol (Part 1): Product operation and preliminary aerosol chemistry assessment. *Food Chem Toxicol*. 2017;106:522-532. doi:10.1016/j.fct.2017.05.022

270. Kalkhoran S, Chang Y, Rigotti NA. Electronic Cigarette Use and Cigarette Abstinence Over 2 Years Among U.S. Smokers in the Population Assessment of Tobacco and Health Study. *Nicotine Tob Res*. 2020;22(5):728-733. doi:10.1093/ntr/ntz114

271. Social Grade in National Readership Survey. Accessed November 7, 2019. http://www.nrs.co.uk/nrs-print/lifestyle-and-classification-data/social-grade/

272. Hoffman MD, Gelman A. *The No-U-Turn Sampler: Adaptively Setting Path Lengths in Hamiltonian Monte Carlo*. Vol 15.; 2014:1593-1623. http://mcmc-jags.sourceforge.net

273. R Development Core Team. R: A Language and Environment for Statistical Computing. *the R Foundation for Statistical computing*. Published online 2011. doi:10.1007/978-3-540-74686-7

274. Lemoine NP. Moving beyond noninformative priors: why and how to choose weakly informative priors in Bayesian analyses. *Oikos*. 2019;128(7):912-928. doi:10.1111/oik.05985

275. McElreath R. *Statistical Rethinking : A Bayesian Course with Examples in R and Stan*.; 2019:469.

276. Czoli CD, White CM, Reid JL, Oconnor RJ, Hammond D. Awareness and interest in IQOS heated tobacco products among youth in Canada, England and the USA. *Tob Control*. Published online 1 January 2019. doi:10.1136/tobaccocontrol-2018-054654

277. Patel M, Cuccia A, Willett J, et al. JUUL use and reasons for initiation among adult tobacco users. *Tob Control*. 2019;28(6). doi:10.1136/tobaccocontrol-2019-054952

278. Kyriakos CN, Filippidis FT, Hitchman S, et al. Characteristics and correlates of electronic cigarette product attributes and undesirable events during e-cigarette use in six countries of the EUREST-PLUS ITC Europe Surveys. *Tobacco Induced Diseases*. Published online 2018. doi:10.18332/tid/93545

279. Mallock N, Trieu HL, Macziol M, et al. Trendy e-cigarettes enter Europe: chemical characterization of JUUL pods and its aerosols. *Arch Toxicol*. 2020;94(6):1985-1994. doi:10.1007/s00204-020-02716-3

280. Delnevo C, Giovenco DP, Hrywna M. Rapid proliferation of illegal pod-mod disposable e-cigarettes. *Tobacco Control*. 2020;0:1-2. doi:10.1136/tobaccocontrol-2019-055485

281. Hahn S. *National Survey Shows Encouraging Decline in Overall Youth E-Cigarette Use, Concerning Uptick in Use of Disposable Products*. U.S. Food and Drug Administration; 2020. https://www.fda.gov/news-events/press-announcements/national-survey-shows-encouraging-decline-overall-youth-e-cigarette-use-concerning-uptick-use?utm_source=Eloqua&utm_medium=email&utm_term=Stratcomms&utm_content=statement&utm_campaign=CTP%20News%3A%20September%209%20Announcements%20-%209920

282. Romberg AR, Miller Lo EJ, Cuccia AF, et al. Patterns of nicotine concentrations in electronic cigarettes sold in the United States, 2013-2018. *Drug Alcohol Depend*. 2019;203:1-7. doi:10.1016/j.drugalcdep.2019.05.029

283. Smets J, Baeyens F, Chaumont M, Adriaens K, Van Gucht D. When Less is More: Vaping Low-Nicotine vs. High-Nicotine E-Liquid is Compensated by Increased Wattage and Higher Liquid Consumption. *Int J Environ Res Public Health*. 2019;16(5):723. doi:10.3390/ijerph16050723

284. Chen C, Zhuang YL, Zhu SH. E-Cigarette Design Preference and Smoking Cessation: A U.S. Population Study. *Am J Prev Med*. 2016;51(3):356-363. doi:10.1016/j.amepre.2016.02.002

285. Hoekstra R, Morey RD, Rouder JN, Wagenmakers EJ. Robust misinterpretation of confidence intervals. *Psychon Bull Rev*. 2014;21(5):1157-1164. doi:10.3758/s13423-013-0572-3

286. Picker RC. The Razors-and-Blades Myth(s). *Univ Chic Law Rev*. 2011;77(1):225-256.

287. Cheng KW, Shang C, Lee HM, et al. Costs of vaping: evidence from ITC Four Country Smoking and Vaping Survey. *Tob Control*. Published online 21 February 2020:tobaccocontrol-2019-055344. doi:10.1136/tobaccocontrol-2019-055344

288. Doward J. Legal loophole allows children to get free vape samples. *The Guardian*. https://www.theguardian.com/society/2020/oct/25/legal-loophole-allows-children-to-get-free-vape-samples. Published October 25, 2020.

289. Berg CJ. Preferred flavors and reasons for e-cigarette use and discontinued use among never, current, and former smokers. *Int J Public Health*. 2016;61(2):225-236. doi:10.1007/s00038-015-0764-x

290. Jackson SE, Shahab L, Kock L, West R, Brown J. Expenditure on smoking and alternative nicotine delivery products: a population survey in England. *Addiction*. 2019;114(11):2026-2036. doi:10.1111/add.14709

291. Barrington-Trimis JL, Leventhal AM. Adolescents' Use of "Pod Mod" E-Cigarettes — Urgent Concerns. *N Engl J Med*. 2018;379(12):1099-1102. doi:10.1056/NEJMp1805758

292. Persoskie A, Donaldson EA, Ryant C. How tobacco companies have used package quantity for consumer targeting. *Tob Control*. 2019;28(4):365-373. doi:10.1136/tobaccocontrol-2017-053993

293. Moore G, Brown R, Page N, et al. Young people's use of e-cigarettes in Wales, England and Scotland before and after introduction of EU Tobacco Products Directive regulations: a mixed-method natural experimental evaluation. *International Journal of Drug Policy*. 2020;85:102795. doi:10.1016/j.drugpo.2020.102795

294. Huang J, Tauras J, Chaloupka FJ. The impact of price and tobacco control policies on the demand for electronic nicotine delivery systems. *Tob Control*. 2014;23(suppl 3):iii41-iii47. doi:10.1136/tobaccocontrol-2013-051515

295. Hsu G, Sun JY, Zhu SH. Evolution of Electronic Cigarette Brands From 2013-2014 to 2016-2017: Analysis of Brand Websites. *J Med Internet Res*. 2018;20(3):e80. doi:10.2196/jmir.8550

296. Siahpush M, Farazi PA, Maloney SI, Dinkel D, Nguyen MN, Singh GK. Socioeconomic status and cigarette expenditure among US households: Results from 2010 to 2015 Consumer Expenditure Survey. *BMJ Open*. 2018;8(6):e020571. doi:10.1136/bmjopen-2017-020571

297. de Wit H, Flory JD, Acheson A, McCloskey M, Manuck SB. IQ and nonplanning impulsivity are independently associated with delay discounting in middle-aged adults. *Pers Individ Dif*. 2007;42(1):111-121. doi:10.1016/j.paid.2006.06.026

298. Green MJ, Gray L, Sweeting H, Benzeval M. Socioeconomic patterning of vaping by smoking status among UK adults and youth. *BMC Public Health*. 2020;20(1):183. doi:10.1186/s12889-020-8270-3

299. Kock L, Brown J, Shahab L. Association of Socioeconomic Position With e-Cigarette Use Among Individuals Who Quit Smoking in England, 2014 to 2019. *JAMA network open*. 2020;3(6):e204207. doi:10.1001/jamanetworkopen.2020.4207

300. East K, Reid JL, Burkhalter R, et al. Exposure to negative news stories about vaping, and harm perceptions of vaping, among youth in England, Canada, and the US before and after the outbreak of E-cigarette or Vaping-Associated Lung Injury (EVALI). *Nicotine Tob Res*. Published online 3 April 2022. doi:10.1093/ntr/ntac088

301. U.S. Food and Drug Administration. *FDA Announces Comprehensive Regulatory Plan to Shift Trajectory of Tobacco-Related Disease, Death*. U.S. Food and Drug Administration; 2018. https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regulatory-plan-shift-trajectory-tobacco-related-disease-death

302. Nyman AL, Huang J, Weaver SR, Eriksen MP. Perceived Comparative Harm of Cigarettes and Electronic Nicotine Delivery Systems. *JAMA Network Open*. 2019;2(11):e1915680. doi:10.1001/jamanetworkopen.2019.15680

303. The Centers for Disease Control and Prevention. *Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products*. The Centers for Disease Control and Prevention; 2019. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#latest-outbreak-information

304. Google. Interest in 'Vaping' and 'Vaping Deaths' from 2018 to 2019. Google Trends. Published 2019. https://trends.google.com/trends/explore/TIMESERIES/1574436000?hl=en-GB&tz=0&geo=GB&q=vaping,vaping+deaths&sni=3

305. Park-Lee E, Ren C, Sawdey MD, et al. Notes from the Field: E-Cigarette Use Among Middle and High School Students - National Youth Tobacco Survey, United States, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(39):1387-1389. doi:10.15585/mmwr.mm7039a4

306. Wang TW, Gentzke AS, Neff LJ, et al. Disposable E-cigarette use among U.s. youth - an emerging public health challenge. *N Engl J Med*. 2021;384(16):1573-1576. doi:10.1056/NEJMc2033943

307. Talih S, Salman R, Soule E, et al. Electrical features, liquid composition and toxicant emissions from 'pod-mod'-like disposable electronic cigarettes. *Tob Control*. Published online 12 May 2021. doi:10.1136/tobaccocontrol-2020-056362

308. Efron B, Tibshirani RJ. *An Introduction to the Bootstrap*. Chapman & Hall; 1993. https://play.google.com/store/books/details?id=gLlpIUxRntoC

309. Rafi Z, Greenland S. Semantic and cognitive tools to aid statistical science: replace confidence and significance by compatibility and surprise. *BMC Med Res Methodol*. 2020;20(1):244. doi:10.1186/s12874-020-01105-9

310. Cole SR, Edwards JK, Greenland S. Surprise! *Am J Epidemiol*. 2021;190(2):191-193. https://academic.oup.com/aje/article-abstract/190/2/191/5869593

311. Stanfill S, Tran H, Tyx R, et al. Characterization of Total and Unprotonated (Free) Nicotine Content of Nicotine Pouch Products. *Nicotine Tob Res*. 2021;23(9):1590-1596. doi:10.1093/ntr/ntab030

312. Lunell E, Fagerström K, Hughes J, Pendrill R. Pharmacokinetic Comparison of a Novel Non-tobacco-Based Nicotine Pouch (ZYN) With Conventional, Tobacco-Based Swedish Snus and American Moist Snuff. *Nicotine Tob Res*. 2020;22(10):1757-1763. doi:10.1093/ntr/ntaa068

313. Patwardhan S, Fagerström K. The New Nicotine Pouch Category- A Tobacco Harm Reduction Tool? *Nicotine Tob Res*. Published online 4 October 2021. doi:10.1093/ntr/ntab198

314. Swedish Match. *Swedish Match Annual Report 2020.*; 2020. https://www.swedishmatch.com/globalassets/reports/annual-reports/2020_swedishmatchannualreport_interactive_en.pdf

315. Patwardhan S, Fagerström K. Nicotine pouches- a research and regulatory policy agenda to maximise public health benefits and minimise harms. *Qeios*. Published online 20 April 2021. doi:10.32388/l4tiaf.4

316. Havermans A, Pennings JLA, Hegger I, et al. Awareness, use and perceptions of cigarillos, heated tobacco products and nicotine pouches: A survey among Dutch adolescents and adults. *Drug Alcohol Depend*. 2021;229(Pt B):109136. doi:10.1016/j.drugalcdep.2021.109136

317. Brose LS, McDermott MS, McNeill A. Heated Tobacco Products and Nicotine Pouches: A Survey of People with Experience of Smoking and/or Vaping in the UK. *Int J Environ Res Public Health*. 2021;18(16). doi:10.3390/ijerph18168852

318. Plurphanswat N, Hughes JR, Fagerström K, Rodu B. Initial Information on a Novel Nicotine Product. *Am J Addict*. 2020;29(4):279-286. doi:10.1111/ajad.13020

319. Li L, Borland R, Cummings KM, et al. Patterns of non-cigarette tobacco and nicotine use among current cigarette smokers and recent quitters: Findings from the 2020 ITC Four Country Smoking and Vaping Survey. *Nicotine Tob Res*. Published online 2021. https://academic.oup.com/ntr/advance-article-abstract/doi/10.1093/ntr/ntab040/6162489

320. East KA, Reid JL, Rynard VL, Hammond D. Trends and patterns of tobacco and nicotine product use among youth in Canada, England, and the United States from 2017 to 2019. *J Adolesc Health*. 2021;69(3):447-456. doi:10.1016/j.jadohealth.2021.02.011

321. Kock L, Shahab L, Moore G, et al. Protocol for expansion of an existing national monthly survey of smoking behaviour and alcohol use in England to Scotland and Wales: The Smoking and Alcohol Toolkit Study. *Wellcome Open Research*. 2021;6(67):67. https://wellcomeopenresearch.org/articles/6-67/v1?src=rss

322. Rogers EM. Diffusion of preventive innovations. *Addict Behav*. 2002;27(6):989-993. doi:10.1016/s0306-4603(02)00300-3

323. Hartwell G, Thomas S, Egan M, Gilmore A, Petticrew M. E-cigarettes and equity: A systematic review of differences in awareness and use between sociodemographic groups. *Tob Control*. 2017;26(e2). doi:10.1136/tobaccocontrol-2016-053222

324. Kock L, Shahab L, West R, Brown J. E-cigarette use in England 2014-17 as a function of socio-economic profile. *Addiction*. 2019;114(2):294-303. doi:10.1111/add.14446

325. Raupach T, West R, Brown J. The most 'successful' method for failing to quit smoking is unassisted cessation. *Nicotine Tob Res*. 2013;15(3):748-749. doi:10.1093/ntr/nts164

326. Ferguson J, Bauld L, Chesterman J, Judge K. The English smoking treatment services: one-year outcomes. *Addiction*. 2005;100 Suppl 2:59-69. doi:10.1111/j.1360-0443.2005.01028.x

327. Kock L, West R, Beard E, Kale D, Brown J. Trends in electronic cigarette use in England. Smoking in England. Published 2022. Accessed March 8, 2022. https://smokinginengland.info/graphs/e-cigarettes-latest-trends

328. Hecht SS, Carmella SG, Kotandeniya D, et al. Evaluation of toxicant and carcinogen metabolites in the urine of e-cigarette users versus cigarette smokers. *Nicotine Tob Res*. 2015;17(6):704-709. doi:10.1093/ntr/ntu218

329. Shahab L, Goniewicz ML, Blount BC, et al. Nicotine, carcinogen, and toxin exposure in long-term E-cigarette and nicotine replacement therapy users. *Ann Intern Med*. 2017;166(6):390. doi:10.7326/m16-1107

330. Rose JE, Salley A, Behm FM, Bates JE, Westman EC. Reinforcing effects of nicotine and non-nicotine components of cigarette smoke. *Psychopharmacology (Berl)*. 2010;210(1):1-12. doi:10.1007/s00213-010-1810-2

331. Benowitz NL. Nicotine addiction. *N Engl J Med*. 2010;362(24):2295-2303. doi:10.1056/NEJMra0809890

332. Chang PH, Chiang CH, Ho WC, Wu PZ, Tsai JS, Guo FR. Combination therapy of varenicline with nicotine replacement therapy is better than varenicline alone: a systematic review and meta-analysis of randomized controlled trials. *BMC Public Health*. 2015;15:689. doi:10.1186/s12889-015-2055-0

333. Ramon JM, Morchon S, Baena A, Masuet-Aumatell C. Combining varenicline and nicotine patches: a randomized controlled trial study in smoking cessation. *BMC Med*. 2014;12(1):172. doi:10.1186/s12916-014-0172-8

334. King A, Vena A, de Wit H, Grant JE, Cao D. Effect of Combination Treatment With Varenicline and Nicotine Patch on Smoking Cessation Among Smokers Who Drink Heavily: A Randomized Clinical Trial. *JAMA Netw Open*. 2022;5(3):e220951. doi:10.1001/jamanetworkopen.2022.0951

335. Bullen C, Verbiest M, Galea-Singer S, et al. The effectiveness and safety of combining varenicline with nicotine e-cigarettes for smoking cessation in people with mental illnesses and addictions: study protocol for a randomised-controlled trial. *BMC Public Health*. 2018;18(1):596. doi:10.1186/s12889-018-5351-7

336. West R, Walia A, Hyder N, Shahab L, Michie S. Behavior change techniques used by the English Stop Smoking Services and their associations with short-term quit outcomes. *Nicotine Tob Res*. 2010;12(7):742-747. doi:10.1093/ntr/ntq074

337. Brose LS, Tombor I, Shahab L, West R. The effect of reducing the threshold for carbon monoxide validation of smoking abstinence--evidence from the English Stop Smoking Services. *Addict Behav*. 2013;38(10):2529-2531. doi:10.1016/j.addbeh.2013.04.006

338. R Core Team. R: A language and environment for statistical computing. Published online 2023. doi:10.2307/1390807

339. Cuzick J, Edwards R, Segnan N. Adjusting for non-compliance and contamination in randomized clinical trials. *Stat Med*. 1997;16(9):1017-1029. doi:10.1002/(sici)1097-0258(19970515)16:9<1017::aid-sim508>3.0.co;2-v

340. Greenland S. An introduction to instrumental variables for epidemiologists. *Int J Epidemiol*. 2000;29(4):722-729. doi:10.1093/ije/29.4.722

341. Medicines and Healthcare Products Regulatory Agency. Class 2 Medicines Recall: Pfizer Ltd, Champix (all strengths) film-coated tablets, EL (21)A/25. UK Government. Published 14 October 2021. Accessed March 8, 2022. https://www.gov.uk/drug-device-alerts/class-2-medicines-recall-pfizer-ltd-champix-all-strengths-film-coated-tablets-el-21-a-slash-25

342. Baker TB, Piper ME, Smith SS, Bolt DM, Stein JH, Fiore MC. Effects of Combined Varenicline With Nicotine Patch and of Extended Treatment Duration on Smoking Cessation: A Randomized Clinical Trial. *JAMA*. 2021;326(15):1485-1493. doi:10.1001/jama.2021.15333

343. Kock L. *The Impact of E-Cigarettes and Individual-Level Interventions on Socio-Economic Inequalities in Smoking Cessation*. PhD. University College London; 2020. doi:https://discovery.ucl.ac.uk/id/eprint/10108576/

344. Svenson M, Green J, Maynard OM. Tackling Smoker Misperceptions About E-cigarettes Using Expert Videos. *Nicotine Tob Res*. 2021;23(11):1848-1854. doi:10.1093/ntr/ntab104

345. Benowitz NL, St Helen G, Liakoni E. Clinical Pharmacology of Electronic Nicotine Delivery Systems (ENDS): Implications for Benefits and Risks in the Promotion of the Combusted Tobacco Endgame. *J Clin Pharmacol*. 2021;61 Suppl 2:S18-S36. doi:10.1002/jcph.1915

346. Benowitz NL. The central role of pH in the clinical pharmacology of nicotine: Implications for abuse liability, cigarette harm reduction and FDA regulation. *Clin Pharmacol Ther*. 2022;111(5):1004-1006. doi:10.1002/cpt.2555

347. Mersha AG, Gould GS, Bovill M, Eftekhari P. Barriers and Facilitators of Adherence to Nicotine Replacement Therapy: A Systematic Review and Analysis Using the Capability, Opportunity, Motivation, and Behaviour (COM-B) Model. *Int J Environ Res Public Health*. 2020;17(23). doi:10.3390/ijerph17238895

348. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction*. 2005;100(3):299-303. doi:10.1111/j.1360-0443.2004.00995.x

349. Lash TL, Fox MP, MacLehose RF, Maldonado G, McCandless LC, Greenland S. Good practices for quantitative bias analysis. *Int J Epidemiol*. 2014;43(6):1969-1985. doi:10.1093/ije/dyu149

350. Anderson SJ, Ling PM. 'And they told two friends...and so on': RJ Reynolds' viral marketing of Eclipse and its potential to mislead the public. *Tob Control*. 2008;17(4):222-229. doi:10.1136/tc.2007.024273

351. Rennard SI, Umino T, Millatmal T, et al. Evaluation of subclinical respiratory tract inflammation in heavy smokers who switch to a cigarette-like nicotine delivery device that primarily heats tobacco. *Nicotine Tob Res*. 2002;4(4):467-476. doi:10.1080/1462220021000018407

352. US Food and Drug Administration. US Food and Drug Administration.FDA authorizes marketing of IQOS tobacco heating system with 'reduced exposure' information. FDA Press Announcements. Published 2020. Accessed August 1, 2021. www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-iqos-tobacco-heating-system-reduced-exposure-information

353. World Health Organisation. Heated Tobacco Products (HTPs) Market Monitoring Information. WHO.

354. Euromonitor International. *Smokeless Tobacco, e-Vapour Products and Heated Tobacco in World*. Euromonitor Passport; 2020.

355. Rose JE. Nicotine and nonnicotine factors in cigarette addiction. In: *Psychopharmacology*. Vol 184. Springer; 2006:274-285. doi:10.1007/s00213-005-0250-x

356. Benowitz NL, Hukkanen J, Jacob P 3rd. Nicotine chemistry, metabolism, kinetics and biomarkers. *Handb Exp Pharmacol*. 2009;(192):29-60. doi:10.1007/978-3-540-69248-5_2

357. Tompkins CNE, Burnley A, McNeill A, Hitchman SC. Factors that influence smokers' and ex-smokers' use of IQOS: A qualitative study of IQOS users and ex-users in the UK. *Tob Control*. Published online 21 January 2019. doi:10.1136/tobaccocontrol-2019-055306

358. Dyer O. India bans e-cigarettes by executive order. *BMJ*. 2019;366:l5649. doi:10.1136/bmj.l5649

359. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Personal habits and indoor combustions. A review of human carcinogens. *IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer*. 2012;100(Pt E):1-538. https://www.ncbi.nlm.nih.gov/pubmed/23193840

360. Yeager P, Kushman M, Chemerynski S, et al. Proposed Mode of Action for Acrolein Respiratory Toxicity Associated with Inhaled Tobacco Smoke. *Toxicol Sci*. 2016;151(2):347-364. doi:10.1093/toxsci/kfw051

361. Chang CM, Edwards SH, Arab A, Del Valle-Pinero AY, Yang L, Hatsukami DK. Biomarkers of Tobacco Exposure: Summary of an FDA-Sponsored Public Workshop. *Cancer Epidemiol Biomarkers Prev*. 2017;26(3). doi:10.1158/1055-9965.EPI-16-0675

362. Kim KH, Jahan SA, Kabir E, Brown RJC. A review of airborne polycyclic aromatic hydrocarbons (PAHs) and their human health effects. *Environment International*. 2013;60:71-80. doi:10.1016/j.envint.2013.07.019

363. Schettgen T, Musiol A, Kraus T. Simultaneous determination of mercapturic acids derived from ethylene oxide (HEMA), propylene oxide (2-HPMA), acrolein (3-HPMA), acrylamide (AAMA) and *N,N* -dimethylformamide (AMCC) in human urine using liquid chromatography/tandem mass spectrometry. *Rapid Commun Mass Spectrom*. 2008;22(17):2629-2638. doi:10.1002/rcm.3659

364. Hedblad B, Ögren M, Engström G, Wollmer P, Janzon L. Heterogeneity of cardiovascular risk among smokers is related to degree of carbon monoxide exposure. *Atherosclerosis*. 2005;179(1):177-183. doi:10.1016/j.atherosclerosis.2004.10.005

365. British American Tobacco. *Transforming Tobacco Perfomance Summary 2018*.; 2019.

366. Phillip Morris International R&D. The Difference between Switching to IQOS and Continuing to Smoke Cigarettes. PMI Science. Published 2018. https://www.pmiscience.com/discover/news/the-difference-between-switching-to-iqos-and-continuing-to-smoke-cigarettes

367. Jankowski M, Brożek GM, Lawson J, Skoczyński S, Majek P, Zejda JE. New ideas, old problems? Heated tobacco products - a systematic review. *Int J Occup Med Environ Health*. 2019;32(5):595-634. doi:10.13075/ijomeh.1896.01433

368. Google Trends. Worldwide internet searches for 'heat-not-burn' from 2004-2020. Published 12 March 2020. https://trends.google.com/trends/explore?date=all&q=heat-not-burn

369. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343(7829). doi:10.1136/bmj.d5928

370. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355. doi:10.1136/bmj.i4919

371. Bosilkovska M, Tran CT, de La Bourdonnaye G, Taranu B, Benzimra M, Haziza C. Exposure to harmful and potentially harmful constituents decreased in smokers switching to Carbon-Heated Tobacco Product. *Toxicol Lett*. 2020;330:30-40. doi:10.1016/j.toxlet.2020.04.013

372. Cummings KM, Nahhas GJ, Sweanor DT. What is accounting for the rapid decline in cigarette sales in Japan? *Int J Environ Res Public Health*. 2020;17(10):3570. doi:10.3390/ijerph17103570

373. Gale N, McEwan M, Camacho OM, Hardie G, Murphy J, Proctor CJ. Changes in biomarkers of exposure on switching from a conventional cigarette to the glo tobacco heating product: A randomized, controlled ambulatory study. *Nicotine Tob Res*. 2021;23(3):584-591. doi:10.1093/ntr/ntaa135

374. Haziza C, de La Bourdonnaye G, Donelli A, et al. Favorable changes in biomarkers of potential harm to reduce the adverse health effects of smoking in smokers switching to the menthol Tobacco Heating System 2.2 for 3 months (Part 2). *Nicotine Tob Res*. 2020;22(4):549-559. doi:10.1093/ntr/ntz084

375. Lüdicke F, Picavet P, Baker G, et al. Effects of switching to the menthol tobacco heating system 2.2, smoking abstinence, or continued cigarette smoking on clinically relevant risk markers: A randomized, controlled, open-label, multicenter study in sequential confinement and ambulatory settings (part 2). *Nicotine Tob Res*. 2018;20(2):173-182. doi:10.1093/ntr/ntx028

376. Ansari SM, Lama N, Blanc N, et al. Evaluation of biological and functional changes in healthy smokers switching to the Tobacco Heating System 2.2 versus continued tobacco smoking: Protocol for a randomized, controlled, multicenter study. *JMIR Res Protoc*. 2018;7(8):e11294. doi:10.2196/11294

377. Martin Leroy C, Jarus-Dziedzic K, Ancerewicz J, Lindner D, Kulesza A, Magnette J. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 7: A one-month, randomized, ambulatory, controlled clinical study in Poland. *Regul Toxicol Pharmacol*. 2012;64(2 Suppl):S74-84. doi:10.1016/j.yrtph.2012.08.006

378. Ogden MW, Marano KM, Jones BA, Morgan WT, Stiles MF. Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 2. Biomarkers of exposure. *Biomarkers*. 2015;20(6-7):391-403. doi:10.3109/1354750X.2015.1094134

379. Ogden MW, Marano KM, Jones BA, Morgan WT, Stiles MF. Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 3. Biomarkers of biological effect. *Biomarkers*. 2015;20(6-7):404-410. doi:10.3109/1354750X.2015.1094135

380. Stoklosa M, Cahn Z, Liber A, Nargis N, Drope J. Effect of IQOS introduction on cigarette sales: evidence of decline and replacement. *Tob Control*. 2020;29(4):381-387. doi:10.1136/tobaccocontrol-2019-054998

381. Tricker AR, Jang IJ, Martin Leroy C, Lindner D, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 4: Eight-day randomized clinical trial in Korea. *Regul Toxicol Pharmacol*. 2012;64(2 Suppl):S45-53. doi:10.1016/j.yrtph.2012.08.013

382. Tricker AR, Kanada S, Takada K, et al. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 5: 8-Day randomized clinical trial in Japan. *Regul Toxicol Pharmacol*. 2012;64(2 Suppl):S54-63. doi:10.1016/j.yrtph.2012.08.003

383. Tricker AR, Stewart AJ, Leroy CM, Lindner D, Schorp MK, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 3: Eight-day randomized clinical trial in the UK. *Regul Toxicol Pharmacol*. 2012;64(2 Suppl):S35-44. doi:10.1016/j.yrtph.2012.08.010

384. Znyk M, Jurewicz J, Kaleta D. Exposure to heated tobacco products and adverse health effects, a systematic review. *Int J Environ Res Public Health*. 2021;18(12):6651. doi:10.3390/ijerph18126651

385. Vallone DM, Cuccia AF, Briggs J, Xiao H, Schillo BA, Hair EC. Electronic Cigarette and JUUL Use Among Adolescents and Young Adults. *JAMA Pediatr*. 2020;174(3):277-286. doi:10.1001/jamapediatrics.2019.5436

386. Hammond D, Reid JL, Rynard VL, et al. Prevalence of vaping and smoking among adolescents in Canada, England, and the United States: Repeat national cross sectional surveys. *BMJ*. 2019;365:I2219. doi:10.1136/bmj.l2219

387. Smoking and snus use. Norwegian Institute of Public Health. Accessed December 12, 2022. https://www.fhi.no/en/op/hin/lifestyle/royking-og-snusbruk-i-noreg/

388. Action on Smoking and Health. *Use of E-Cigarettes among Young People in Great Britain 2022*. Action on Smoking and Health; 2022. https://ash.org.uk/uploads/Use-of-e-cigarettes-among-young-people-in-Great-Britain-2022.pdf

389. Hammond D, Reid JL, Burkhalter R, et al. E-Cigarette Flavors, Devices, and Brands Used by Youths Before and After Partial Flavor Restrictions in the United States: Canada, England, and the United States, 2017–2020. *Am J Public Health*. 2022;112(7):1014-1024. doi:10.2105/AJPH.2022.306780

390. Löckenhoff CE, O'Donoghue T, Dunning D. Age differences in temporal discounting: the role of dispositional affect and anticipated emotions. *Psychol Aging*. 2011;26(2):274-284. doi:10.1037/a0023280

391. Blackwell AKM, Lee I, Scollo M, Wakefield M, Munafò MR, Marteau TM. Should cigarette pack sizes be capped? *Addiction*. 2020;115(5):802-809. doi:10.1111/add.14770

392. Mays D, Johnson AC, Jeong M, et al. Tobacco minimum packaging policy to reduce cigarillo use among young people: results of an experimental study. *Tob Control*. Published online 15 July 2022. doi:10.1136/tc-2022-057304

393. Levinson AH, Campo S, Gascoigne J, Jolly O, Zakharyan A, Tran ZV. Smoking, but not smokers: identity among college students who smoke cigarettes. *Nicotine Tob Res*. 2007;9(8):845-852. doi:10.1080/14622200701484987

394. Russell AM, Colditz JB, Barry AE, et al. Analyzing Twitter Chatter About Tobacco Use Within Intoxication-related Contexts of Alcohol Use: 'Can Someone Tell Me Why Nicotine is So Fire When You're Drunk?' *Nicotine Tob Res*. 2022;24(8):1193-1200. doi:10.1093/ntr/ntab195

395. Das S, Ungoed-Thomas J. Chinese vaping giant flouting UK advertising rules on selling to children. *The Guardian*. https://www.theguardian.com/society/2022/jul/17/chinese-vaping-giant-flouting-uk-advertising-rules-on-selling-to-children. Published July 17, 2022. Accessed December 12, 2022.

396. Sun T, Lim CCW, Chung J, et al. Vaping on TikTok: a systematic thematic analysis. *Tob Control*. Published online 26 July 2021. doi:10.1136/tobaccocontrol-2021-056619

397. Gerhards C. Product placement on YouTube: An explorative study on YouTube creators' experiences with advertisers. *Convergence*. 2019;25(3):516-533. doi:10.1177/1354856517736977

398. Auxier B, Anderson M. *Social Media Use in 2021*. Pew Research; 2021. Accessed December 13, 2022. https://www.pewresearch.org/internet/2021/04/07/social-media-use-in-2021/

399. Internet activities performed by age Great Britain 2020. Statista. Accessed December 13, 2022. https://www.statista.com/statistics/321050/internet-activities-in-great-britain-by-age/

400. Gong N, Jin X, Liao J, et al. Authorized, clear and timely communication of risk to guide public perception and action: lessons of COVID-19 from China. *BMC Public Health*. 2021;21(1):1545. doi:10.1186/s12889-021-11103-1

401. Rooke C, Cunningham-Burley S, Amos A. Smokers' and ex-smokers' understanding of electronic cigarettes: a qualitative study. *Tob Control*. 2016;25(e1):e60-6. doi:10.1136/tobaccocontrol-2014-052151

402. Shahab L, Brown J, Boelen L, Beard E, West R, Munafò MR. Unpacking the gateway hypothesis of E-cigarette use: The need for triangulation of individual- and population-level data. *Nicotine Tob Res*. 2022;24(8):1315-1318. doi:10.1093/ntr/ntac035

403. Hammond D, Reid J, Burkhalter R, Rynard V. *ITC Youth Tobacco and Vaping Survey: Technical Report Wave 6*. University of Waterloo; 2023. https://davidhammond.ca/wp-content/uploads/2023/04/P01P3_W6_Technical-Report_Prelim_20230421.pdf

404. ASH Year 10 Snapshot Survey. ASH NZ. Accessed December 12, 2022. https://www.ash.org.nz/ash_year_10

405. Committee of Advertising Practice. The Tobacco and Related Products Regulations 2016: 22. Electronic Cigarettes. Accessed December 12, 2022. https://www.asa.org.uk/type/non_broadcast/code_section/22.html

406. Corrigan JR, Hackenberry BN, Lambert VC, Rousu MC, Thrasher JF, Hammond D. Estimating the price elasticity of demand for JUUL E-cigarettes among teens. *Drug Alcohol Depend*. 2021;218:108406. doi:10.1016/j.drugalcdep.2020.108406

407. Ockenfels A, Werner P, Edenhofer O. Pricing externalities and moral behaviour. *Nature Sustainability*. 2020;3(10):872-877. doi:10.1038/s41893-020-0554-1

408. Ferrey A, Fletcher B, Coker T, et al. *E-Cigarettes and Primary Care: A Cross-Sectional Survey of Nurses and GPs across the UK*. Cancer Research UK; 2019. https://dev.cruk.org/sites/default/files/executive_summary.pdf

409. East KA, Miller CR, Hitchman SC, McNeill A, Tompkins CNE. 'It's not what you'd term normal smoking': a qualitative exploration of language used to describe heated tobacco product use and associated user identity. *Addiction*. Published online 23 September 2022. doi:10.1111/add.16051

410. Mallock N, Pieper E, Hutzler C, Henkler-Stephani F, Luch A. Heated tobacco products: A review of current knowledge and initial assessments. *Front Public Health*. 2019;7:287. doi:10.3389/fpubh.2019.00287

411. Green MS, Symons MJ. A comparison of the logistic risk function and the proportional hazards model in prospective epidemiologic studies. *J Chronic Dis*. 1983;36(10):715-723. doi:10.1016/0021-9681(83)90165-0

412. Sosnoff CS, Caron K, Akins JR, et al. Serum Concentrations of Cotinine and Trans-3'-Hydroxycotinine in US Adults: Results From Wave 1 (2013-2014) of the Population Assessment of Tobacco and Health Study. *Nicotine Tob Res*. 2022;24(5):736-744. doi:10.1093/ntr/ntab240

413. 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;5(2):e2147891. doi:10.1001/jamanetworkopen.2021.47891

414. Dai HD, Leventhal AM, Khan AS. Trends in Urinary Biomarkers of Exposure to Nicotine and Carcinogens Among Adult e-Cigarette Vapers vs Cigarette Smokers in the US, 2013-2019. *JAMA*. 2022;328(18):1864-1866. doi:10.1001/jama.2022.14847

415. Harrell FE Jr. General aspects of fitting regression models. In: *Regression Modeling Strategies*. Springer series in statistics. Springer International Publishing; 2015:13-44. doi:10.1007/978-3-319-19425-7_2

416. Perperoglou A, Sauerbrei W, Abrahamowicz M, Schmid M. A review of spline function procedures in R. *BMC Medical Research Methodology*. 2019;19(1):46. doi:10.1186/s12874-019-0666-3

417. Lawlor DA, Tilling K, Smith GD. Triangulation in aetiological epidemiology. *Int J Epidemiol*. 2016;45(6):1866-1886. doi:10.1093/ije/dyw314

418. Gage SH, Sallis HM, Lassi G, et al. Does smoking cause lower educational attainment and general cognitive ability? Triangulation of causal evidence using multiple study designs. *Psychol Med*. 2022;52(8):1578-1586. doi:10.1017/S0033291720003402

419. Haack S. *Law in Context: Evidence Matters: Science, Proof, and Truth in the Law*. Cambridge University Press; 2014. doi:10.1017/cbo9781139626866

420. Degtiar I, Rose S. A Review of Generalizability and Transportability. *arXiv [statME]*. Published online 23 February 2021. http://arxiv.org/abs/2102.11904

421. Kerr NL. HARKing: hypothesizing after the results are known. *Pers Soc Psychol Rev*. 1998;2(3):196-217. doi:10.1207/s15327957pspr0203_4

422. Pleasants RA, Rivera MP, Tilley SL, Bhatt SP. Both Duration and Pack-Years of Tobacco Smoking Should Be Used for Clinical Practice and Research. *Ann Am Thorac Soc*. 2020;17(7):804-806. doi:10.1513/AnnalsATS.202002-133VP

423. Demissie Z, Everett Jones S, Clayton HB, King BA. Adolescent Risk Behaviors and Use of Electronic Vapor Products and Cigarettes. *Pediatrics*. 2017;139(2). doi:10.1542/peds.2016-2921

424. García-Albéniz X, Hsu J, Hernán MA. The value of explicitly emulating a target trial when using real world evidence: an application to colorectal cancer screening. *Eur J Epidemiol*. 2017;32(6):495-500. doi:10.1007/s10654-017-0287-2

425. Hernán MA, Wang W, Leaf DE. Target trial emulation: A framework for causal inference from observational data. *JAMA*. Published online 12 December 2022. doi:10.1001/jama.2022.21383

426. Harlow AF, Stokes AC, Brooks DR, Benjamin EJ, Barrington-Trimis JL, Ross CS. E-Cigarette Use and Combustible Cigarette Smoking Initiation among Youth: Accounting for Time-Varying Exposure and Time-Dependent Confounding. *Epidemiology*. Published online 29 March 2022. doi:10.1097/EDE.0000000000001491

427. Geneletti S, Richardson S, Best N. Adjusting for selection bias in retrospective, case-control studies. *Biostatistics*. 2009;10(1):17-31. doi:10.1093/biostatistics/kxn010

428. Greenland S. Multiple-bias modelling for analysis of observational data (with discussion). *J R Stat Soc Ser A Stat Soc*. 2005;168(2):267-306. doi:10.1111/j.1467-985x.2004.00349.x

429. Gelman A, Hill J, Vehtari A. *Regression and Other Stories*. Cambridge University Press; 2020. doi:10.1017/9781139161879

430. Strong DR, Pearson J, Ehlke S, et al. Indicators of dependence for different types of tobacco product users: Descriptive findings from Wave 1 (2013–2014) of the Population Assessment of Tobacco and Health (PATH) study. *Drug Alcohol Depend*. 2017;178:257-266. doi:10.1016/j.drugalcdep.2017.05.010

431. Jackson SE, Brown J, Jarvis MJ. Dependence on nicotine in US high school students in the context of changing patterns of tobacco product use. *Addiction*. Published online 22 January 2021:add.15403. doi:10.1111/add.15403

432. Shiffman S, Sembower MA. Dependence on e-cigarettes and cigarettes in a cross-sectional study of US adults. *Addiction*. 2020;115(10):1924-1931. doi:10.1111/add.15060

433. Jarvis MJ, Russell MA, Benowitz NL, Feyerabend C. Elimination of cotinine from body fluids: implications for noninvasive measurement of tobacco smoke exposure. *Am J Public Health*. 1988;78(6):696-698. doi:10.2105/ajph.78.6.696

434. Jarvis MJ, Fidler J, Mindell J, Feyerabend C, West R. Assessing smoking status in children, adolescents and adults: cotinine cut-points revisited. *Addiction*. 2008;103(9):1553-1561. doi:10.1111/j.1360-0443.2008.02297.x

435. Anic GM, Rostron BL, Hammad HT, et al. Changes in Biomarkers of Tobacco Exposure among Cigarette Smokers Transitioning to ENDS Use: The Population Assessment of Tobacco and Health Study, 2013-2015. *Int J Environ Res Public Health*. 2022;19(3). doi:10.3390/ijerph19031462

436. Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions*. 6th ed. Wiley; 2019. doi:10.1002/9781119536604

Appendix

Supplementary Material for Chapter 6

Tables

Table S6.1. Reasons for stop smoking services not participating in the trial.

Service*	Reason for not participating
1	No response after initial contact
2	Delivery of services through pharmacies incompatible with trial procedures
3	Service closed down before the trial started
4	Lack of staff capacity
5	Delivery of services through general practices incompatible with trial procedures
6	No response after initial contact
7	Perceived lack of evidence on e-cigarette harms and use for smoking cessation

* Names of services are excluded for data protection purposes

Table S6.2. Summary of planned and unplanned analyses.*

Planned and registered before data collection	Planned/updated and registered before data analysis	Unplanned
Analyses of smoking-related outcomes following intention-to-treat principle where those lost to follow-up are treated as smokers	Sensitivity analyses for the primary outcome where risk ratios were calculated with a range of different assumed abstinence rates in those lost to follow-up	Sensitivity analysis for the primary outcome adjusting for e-cigarette non-adherence and contamination
Bayes factors for the primary outcome	Hazard ratio (HR) for relapse from continuous abstinence estimated using a Cox model	
Treatment adherence (varenicline adherence and e-cigarette use) across groups	HR and incidence rate ratio for adverse events and respiratory symptoms in the e-cigarette versus control group	
Interviews with ten participants in e-cigarette arm on acceptability and barriers and enablers to participation	Attendance at stop smoking services across groups	

* Reasons for updates to the protocol are discussed in detail online (https://osf.io/vm4g3/).

Table S6.3. Questions added to data collection system at services.

Construct assessed	Question added
Trial eligibility	Eligible participant agreed to participate in UCL trial (*Y/N*)
Trial arm allocation	If Y selected above, enter treatment allocation (*E-cigarette/Control*)
Varenicline adherence	How often have used Varenicline since last session?
	N/A
	Daily
	Weekly
	Less Than Weekly
	Did not use
E-cigarette usage	If the e-cigarette checkbox is checked a further two fields will appear:
	Date device given
	Date field with calendar helper (will retain date from previous session if already populated)
	How often have used e-cigarette since last session?
	Not Applicable
	Daily
	Weekly
	Less Than Weekly
	Did not use
Adverse reactions	Since the last visit/contact, has the participant experienced any of the following adverse reactions:
	Nausea (Y/N)
	Sleep disturbance (Y/N)
	Throat or mouth irritation (Y/N)
Respiratory symptoms	Since the last visit/contact, has the participant experienced any of the following respiratory symptoms:
	Shortness of breath (Y/N)
	Wheezing (Y/N)
	Cough (Y/N)
	Phlegm (Y/N)
Mental health	Please select one of the below that describes the participant's health TODAY:
	Not anxious or depressed
	Slightly anxious or depressed
	Moderately anxious or depressed
	Severely anxious or depressed
	Extremely anxious or depressed

Table S6.4. Bayes factors calculated for the primary outcome, nine-to-12 weeks cigarette abstinence.

Observed RR* (95% CI)	RR under H0	RR under H1‡	Bayes factor†
1.51 (0.91-2.64)	1.00	0.50	0.17
1.51 (0.91-2.64)	1.00	0.66	0.27
1.51 (0.91-2.64)	1.00	0.80	0.44
1.51 (0.91-2.64)	1.00	1.25	1.91
1.51 (0.91-2.64)	1.00	1.50	2.04
1.51 (0.91-2.64)	1.00	2.00	1.69

* Risk ratios (RR) and corresponding 95% compatibility intervals (95% CI) estimated from log-linear risk models.

‡ H1, the alternative hypothesis for log(RR), was modelled as a half normal distribution with a mode at zero and a standard deviation equal to log of the RR listed in this column.

† Bayes factor from online calculator (http://www.bayesfactor.info). Bayes factors above 1 indicate greater support for alternative hypothesis (H1) than the null hypothesis (H0), while those below 1 indicate greater support for H0 than H1.

Table S6.5. Nine-to-12-week cigarette CO-verified abstinence rates when relaxing the assumption that participants with missing follow-up data at week 12 had relapsed (i.e., 0% abstinence rate).

Imputed abstinence rate in missing*	Group	Missing / N	Abstinence rate (n)†	RR†
0%	Control	28 / 44	31.8% (14.0)	Ref
	E-cigarette	22 / 48	47.9% (23.0)	1.51
10%	Control	28 / 44	36.8% (16.2)	Ref
	E-cigarette	22 / 48	50.8% (24.4)	1.38
20%	Control	28 / 44	41.8% (18.4)	Ref
	E-cigarette	22 / 48	53.8% (25.8)	1.29
30%	Control	28 / 44	46.8% (20.6)	Ref
	E-cigarette	22 / 48	56.7% (27.2)	1.21
40%	Control	28 / 44	51.8% (22.8)	Ref
	E-cigarette	22 / 48	59.6% (28.6)	1.15

* Imputed abstinence rate among participants who were missing at the 12 weeks post-quit follow-up appointment.

† Estimated percentage and number (n) of people abstinent from cigarette smoking between weeks nine and 12 post-quit, after imputing the abstinence rate in those missing at follow-up. Risk ratio (RR) calculated from these estimates.

Table S6.6. Adverse event risk among those attending the week 12 follow-up session.

Adverse event	Group	Events*	N	Risk	RR (95%CI)†
Any	Control	12	16	75.0%	Ref
	E-cigarette	21	26	80.8%	1.08 (0.77-1.51)
Sleep disturbance	Control	11	16	68.8%	Ref
	E-cigarette	14	26	53.8%	0.78 (0.48-1.27)
Nausea	Control	6	16	37.5%	Ref
	E-cigarette	14	26	53.8%	1.44 (0.69-2.97)
Throat/mouth irritation	Control	6	16	37.5%	Ref
	E-cigarette	13	26	50.0%	1.33 (0.64-2.80)

* Number of participants experiencing at least one event between their quit date and their final follow-up session.

† Risk ratios (RR) and corresponding 95% compatibility intervals (95% CI) estimated from log-linear risk models.

Table S6.7. Summary of findings on acceptability of the intervention.

TFA domain	Theme	Effect on acceptability*
Affective attitude	Positive affect for advisor	+
Burden	Difficulties with service care pathway	-
	Side-effects from varenicline	-
Ethicality	E-cigarette replaces one addiction with another	-
	Opinions about services providing e-cigarettes	+/-
Intervention coherence	Complementary nature of intervention package	+
Perceived effectiveness	Varenicline reduces urges to smoke	+

* + = enhances acceptability; - = reduces acceptability; +/- = differing effects on acceptability.

See supporting data at https://osf.io/2pgz4/.

Table S6.8. Summary of findings on barriers and enablers to using e-cigarettes for smoking cessation.

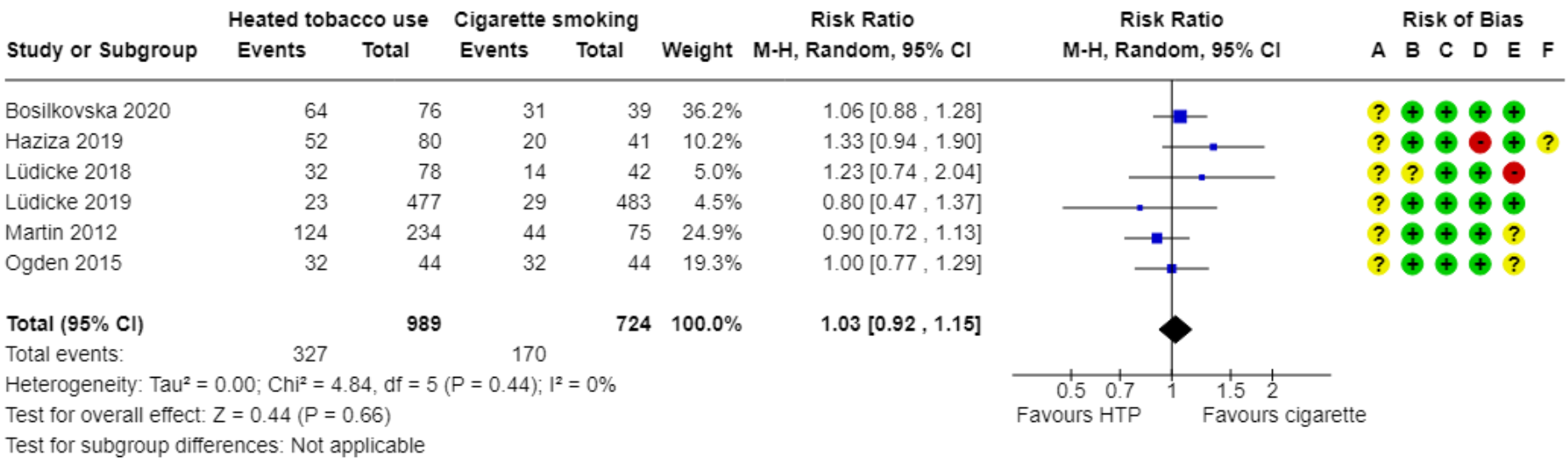
COM-B domain	Theme	Barrier or Enabler *
Automatic motivation	Replacing the habit of smoking	E
Reflective motivation	E-cigarette as a back-up in the quit attempt	E
	E-cigarette is a short-term tool to quit smoking	E/M
Physical capability	Harshness of puffing	B
Physical opportunity	Cost saving	E
	Opportunities to vape	E
Social opportunity	Family support to quit smoking	E

* B = barrier; E = enabler; M = mixed. See supporting data at https://osf.io/2pgz4/.

Supplementary Material for Chapter 7

Figures

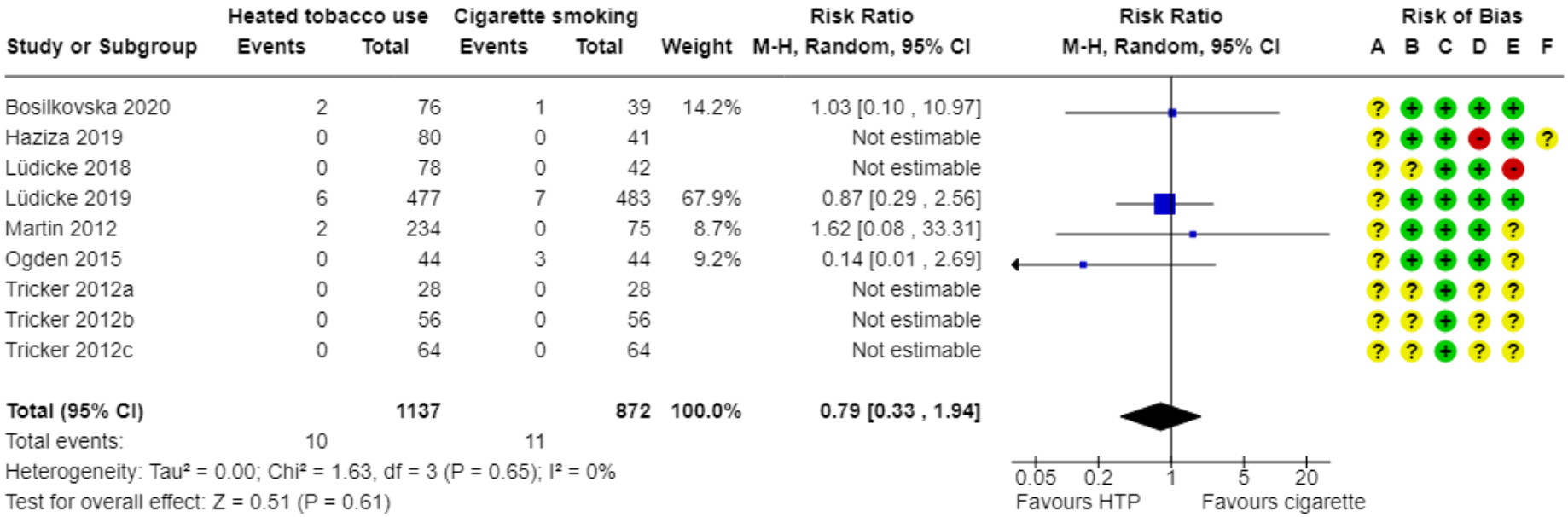
Supplementary Figure S7.1. Heated tobacco compared with cigarettes – Adverse events.



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

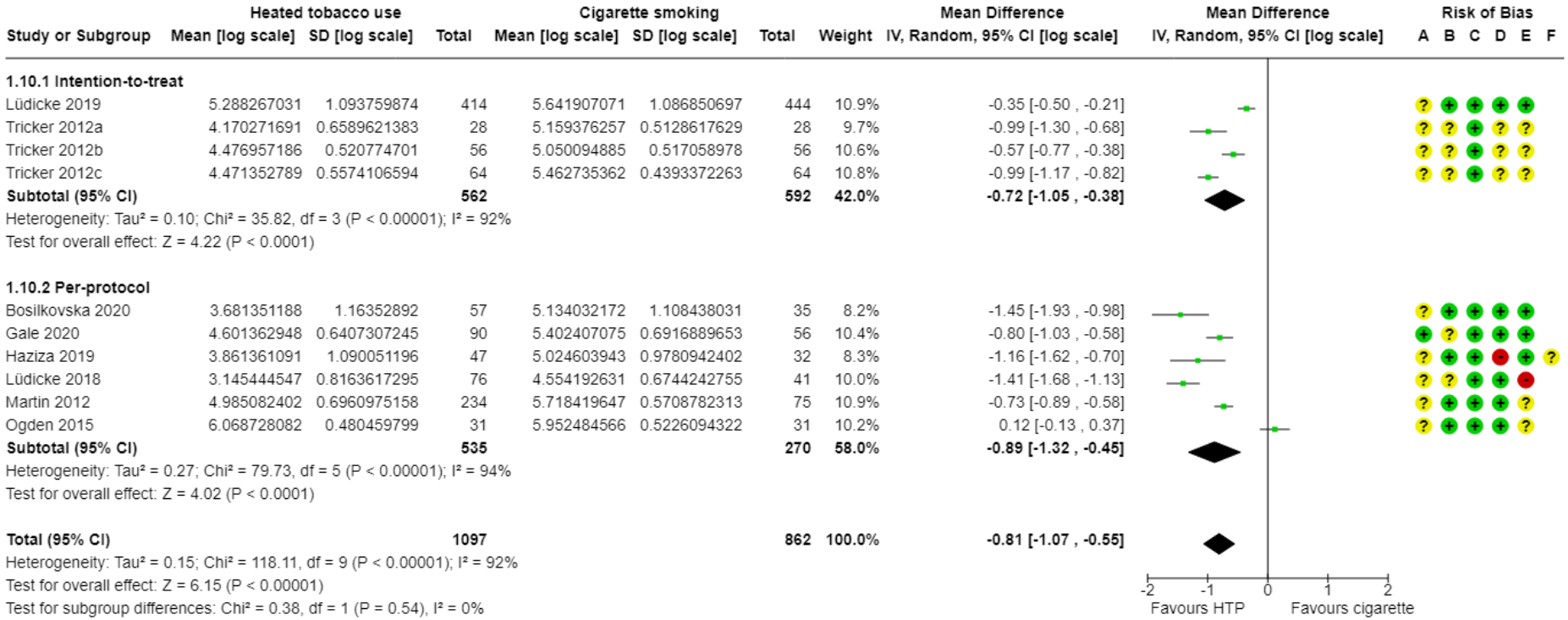
Supplementary Figure S7.2. Heated tobacco compared with cigarettes — Serious adverse events.



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

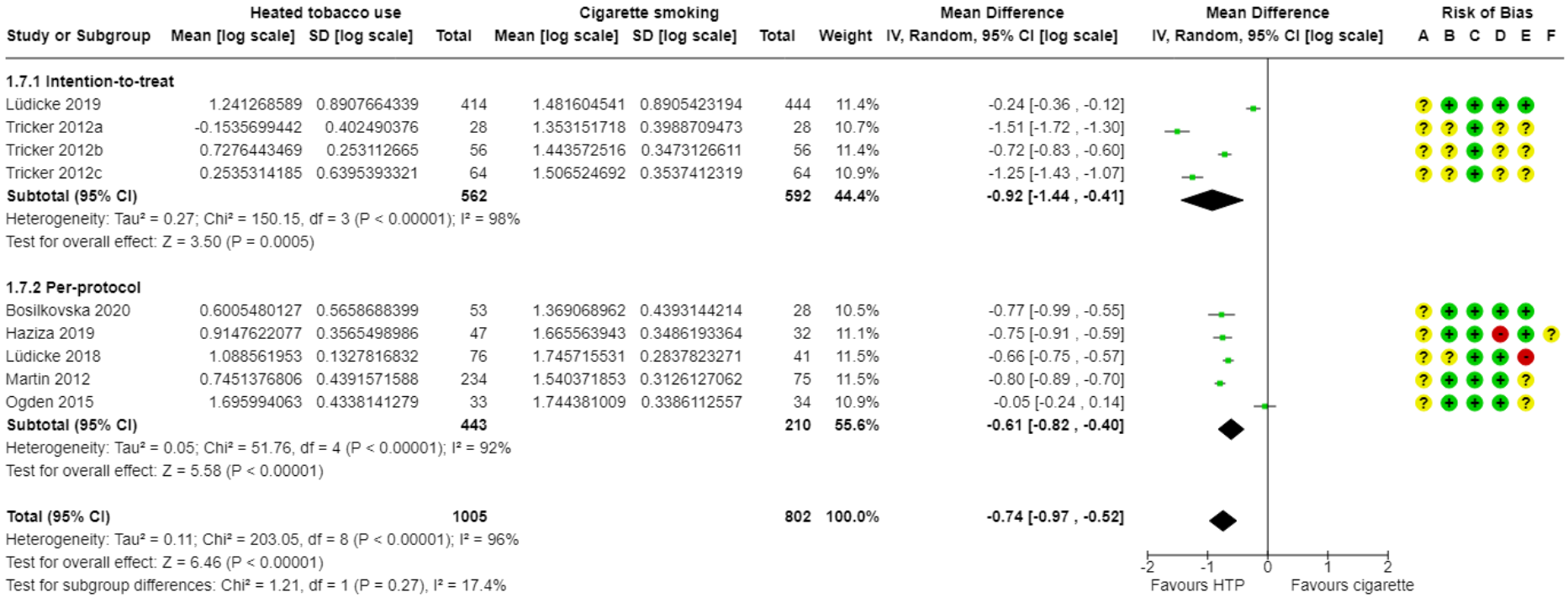
Supplementary Figure S7.3. Heated tobacco compared with cigarettes — NNAL.



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

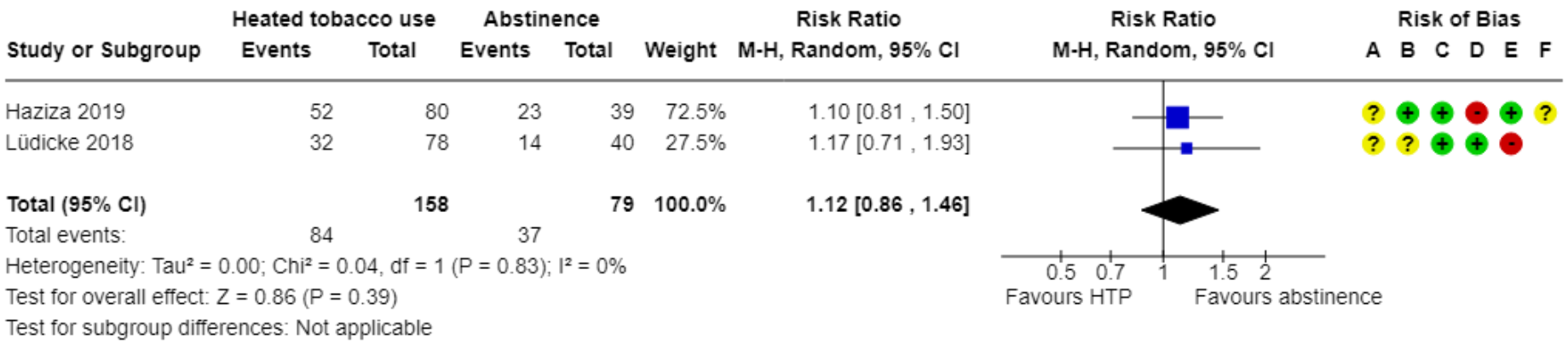
Supplementary Table S7.4. Heated tobacco compared with cigarettes — COHb.



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

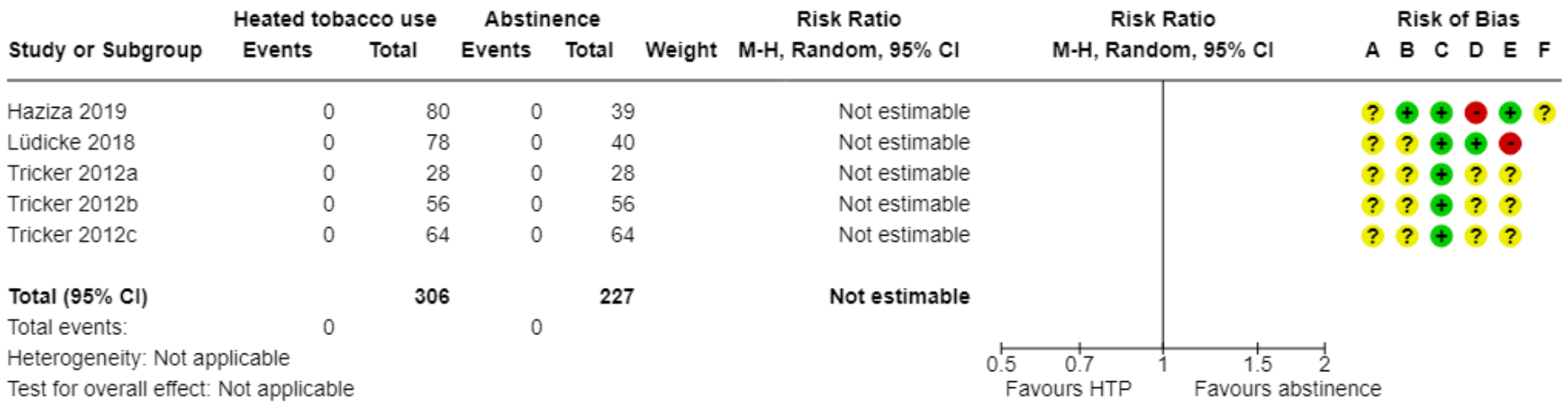
Supplementary Figure S7.5. Heated tobacco compared with no tobacco — Adverse events.



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

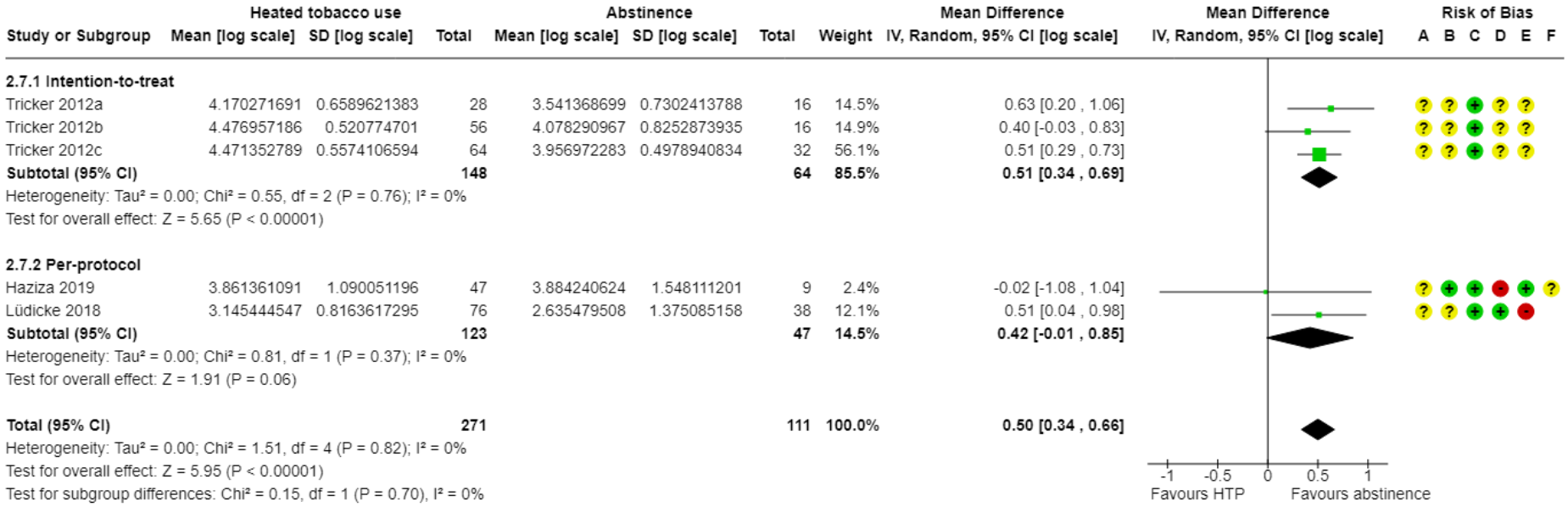
Supplementary Figure S7.6. Heated tobacco compared with no tobacco — Serious adverse events.



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

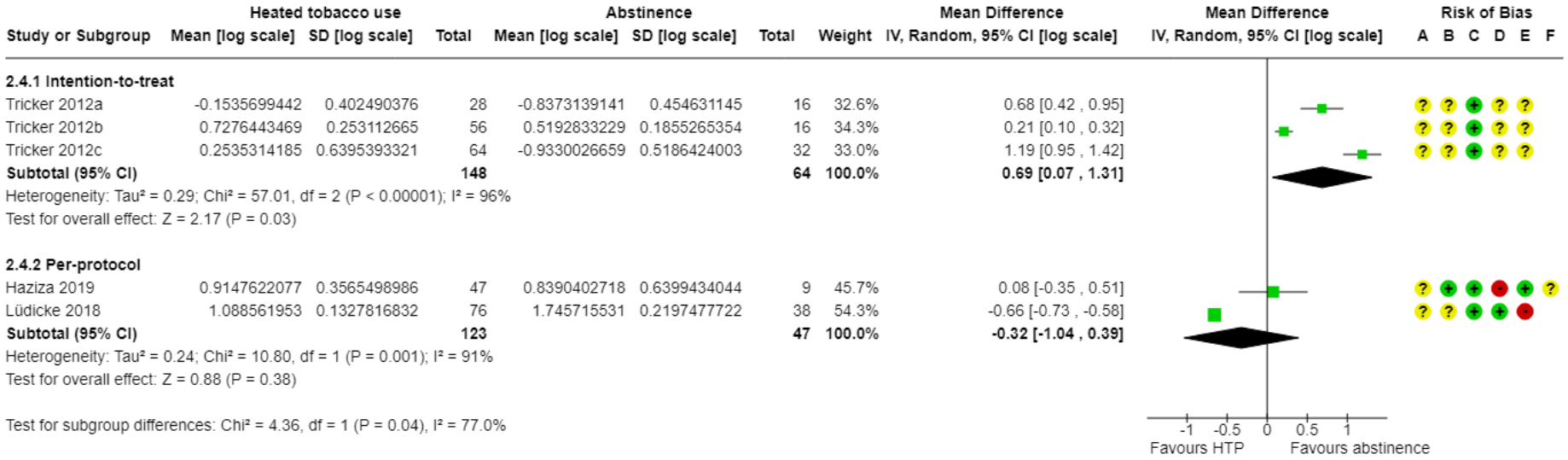
Supplementary Figure S7.7. Heated tobacco compared with no tobacco — NNAL.



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Supplementary Figure S7.8. Heated tobacco compared with no tobacco — COHb.



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Tables

Supplementary Figure S7.1. Heated tobacco compared with cigarette smoking — main analyses and sensitivity analyses for biomarker outcomes. Mean difference (MD) provides the pooled estimate across studies, calculated using a random-effects inverse-variance weighted approach.[436]

Outcomes	All data			No high risk of bias			Only electronic			≥ 4 weeks' follow-up		
	N (studies)	MD (95%CI)	I^2	N (studies)	MD (95%CI)	I^2	N (studies)	MD (95%CI)	I^2	N (studies)	MD (95%CI)	I^2
Biomarkers of exposure												
1-OHP[a]	1960 (10)	−0.42 (−0.67 to −0.17)	94%	1764 (8)	−0.40 (−0.70 to −0.10)	95%	1805 (8)	−0.54 (−0.75 to −0.34)	90%	1664 (7)	−0.28 (−0.57 to 0.00)	93%
1-Naphthol	63 (1)	2.60µg/24 hours (−16.11 to 21.31)	-	63 (1)	2.60µg/24 hours (−16.11 to 21.31)	-	None	-	-	63 (1)	2.60µg/24 hours (−16.11 to 21.31)	-
2-Naphthol	63 (1)	−4.00µg/24 (−7.89 to −0.11)	-	63 (1)	−4.00µg/24 (−7.89 to −0.11)	-	None	-	-	63 (1)	−4.00µg/24 (−7.89 to −0.11)	-
Exhaled CO	1322 (3)	−9.13ppm, (−10.49 to −7.78)	4%	1322 (3)	−9.13ppm, (−10.49 to −7.78)	4%	1322 (3)	−9.13ppm, (−10.49 to −7.78)	4%	1322 (3)	−9.13ppm (−10.49 to −7.78)	4%
COHb	1807 (9)	−0.74 (−0.97 to −0.52)	96%	1611 (7)	−0.76 (−1.07 to −0.44)	97%	1659 (7)	−0.84 (−1.07 to −0.60)	96%	1511 (6)	−0.24 (−0.36 to −0.12)	95%
3-HPMA	1960 (10)	−0.40 (−0.62 to −0.17)	95%	1764 (8)	−0.34 (−0.59 to −0.09)	95%	1805 (8)	−0.43 (−0.63 to −0.22)	93%	1664 (7)	−0.48 (−0.80 to −0.16)	96%
Lead	None	-	-	None	-	-	None	-	-	None	-	-
Cadmium	None	-	-	None	-	-	None	-	-	None	-	-
MHBMA	1960 (10)	−1.15 (−1.52 to −0.78)	94%	1764 (8)	−1.05 (−1.46 to −0.65)	94%	1805 (8)	−1.17 (−1.57 to −0.77)	94%	1664 (7)	−1.26 (−1.77 to −0.75)	96%

NNAL	1959 (10)	−0.81 (−1.07 to −0.55)	92%	1963 (8)	−0.70 (−0.96 to −0.44)	92%	1805 (8)	−0.85 (−1.08 to −0.62)	89%	1663 (7)	−0.80 (−1.16 to −0.44)	94%
Biomarkers of harm												
FEV_1	1290 (5)	0.02 (0.00 to 0.03)	0%	1095 (3)	0.02 (0.01 to 0.03)	0%	1201 (4)	0.02 (0.00 to 0.03)	0%	1290 (5)	0.02 (0.00 to 0.03)	0%
FVC	196 (2)	−0.12 (−0.45 to 0.21)	38%	None	-	-	196 (2)	−0.12 (−0.45 to 0.21)	38%	196 (2)	−0.12 (−0.45 to 0.21)	38%
FEV_1/FVC	None	-	-	None	-	-	None	-	-	None	-	-
Systolic blood pressure	288 (3)	0.00 (−0.02 to 0.02)	0%	92 (1)	0.01 (−0.02 to 0.05)	-	196 (2)	−0.01 (−0.04 to 0.02)	0%	288 (3)	0.00 (−0.02 to 0.02)	0%
Diastolic blood pressure	288 (3)	−0.00 (−0.03 to 0.03)	0%	92 (1)	0.02 (−0.03 to 0.07)	-	196 (2)	−0.02 (−0.06 to 0.02)	0%	288 (3)	−0.00 (−0.03 to 0.03)	0%
Heart rate	None	-	-	None	-	-	None	-	-	None	-	-
Blood oxygen saturation	None	-	-	None	-	-	None	-	-	None	-	-

Supplementary Figure S7.2. Heated tobacco compared with no tobacco — main analyses and sensitivity analyses for biomarker outcomes. Mean difference (MD) provides the pooled estimate across studies, calculated using a random-effects inverse-variance weighted approach.[436]

Outcomes	All data			No high risk of bias			≥ 4 weeks' follow-up		
	N (studies)	MD (95%CI)	I^2	N (studies)	MD (95%CI)	I^2	N (studies)	MD (95%CI)	I^2
Biomarkers of exposure									
1-OHP	382 (5)	0.12 (−0.03 to 0.28)	54%	212 (3)	0.11 (−0.03 to 0.25)	12%	170 (2)	0.22 (−0.32 to 0.75)	84%
1-Naphthol	None	-	-	None	-	-	None	-	-
2-Naphthol	None	-	-	None	-	-	None	-	-
Exhaled CO	None	-	-	None	-	-	None	-	-
COHb	382 (5)	0.30 (−0.40 to 1.00)	99%	212 (3)	0.69 (0.07 to 1.31)	97%	170 (2)	−0.32 (−1.04 to 0.39)	91%
3-HPMA	382 (5)	0.56 (0.33 to 0.80)	85%	212 (3)	0.64 (0.32 to 0.96)	89%	170 (2)	0.35 (0.20 to 0.50)	0%
Lead	None	-	-	None	-	-	None	-	-
Cadmium	None	-	-	None	-	-	None	-	-
MHBMA	382 (5)	0.67 (−0.12 to 1.45)	96%	212 (3)	0.97 (0.02 to 1.92)	96%	170 (2)	0.07 (−0.16 to 0.30)	0%
NNAL	382 (5)	0.50 (0.34 to 0.66)	0%	212 (3)	0.42 (−0.01 to 0.85)	0%	170 (2)	0.51 (0.34 to 0.69)	0%
Biomarkers of harm									
FEV_1	170 (2)	−0.00 (−0.06 to 0.06)	38%	None	-	-	170 (2)	−0.00 (−0.06 to 0.06)	38%
FVC	172 (2)	−0.02 (−0.29 to 0.26)	0%	None	-	-	172 (2)	−0.02 (−0.29 to 0.26)	0%
FEV_1/FVC	None	-	-	None	-	-	None	-	-
Systolic blood pressure	170 (2)	0.02 (−0.01 to 0.05)	0%	None	-	-	170 (2)	0.02 (−0.01 to 0.05)	0%

Diastolic blood pressure	170 (2)	0.00 (−0.04 to 0.04)	0%	None	-	-	170 (2)	0.00 (−0.04 to 0.04)	0%
Heart rate	None	-	-	None	-	-	None	-	-
Blood oxygen saturation	None	-	-	None	-	-	None	-	-