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A Decision-Theoretic Public Health Framework for Heated Tobacco and Nicotine Vaping Products

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Abstract: Markets for nicotine vaping products (NVPs) and heated tobacco products (HTPs) have grown as these products became positioned as harm-reduction alternatives to combusted tobacco products. Herein, we present a public health decision-theoretic framework incorporating different patterns of HTP, NVP, and cigarette use to examine their impacts on population health. Our framework demonstrates that, for individuals who would have otherwise smoked, HTP use may provide public health benefits by enabling cessation or by discouraging smoking initiation and relapse. However, the benefits are reduced if more harmful HTP use replaces less harmful NVP use. HTP use may also negatively impact public health by encouraging smoking by otherwise non-smokers or by encouraging initiation or relapse into smoking. These patterns are directly influenced by industry behavior as well as public policy towards HTPs, NVPs, and cigarettes. While substantial research has been devoted to NVPs, much less is known about HTPs. Better information is needed to more precisely define the health risks of HTPs compared to cigarettes and NVPs, the relative appeal of HTPs to consumers, and the likelihood of later transitioning to smoking or quitting all products. While our analysis provides a framework for gaining that information, it also illustrates the complexities in distinguishing key factors.

Keywords: heated tobacco products; e-cigarettes; ENDS; decision theory; public health; policy

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1. Introduction

The tobacco marketplace has dramatically changed in the last ten years. In the US, while cigarette use has rapidly declined [1], especially among youth [2–4], the use of other nicotine delivery products, such as smokeless tobacco and nicotine vaping products (NVPs) [5–8], has increased. England [9–12] and Canada [12–14] show similar trends in cigarette and NVP use. At the same time, the use of heated tobacco products (HTPs) has rapidly emerged in Japan [15–21] and the Republic of Korea [22–25] and is now also becoming more popular in other countries [26–32]. In many countries, HTPs are readily available along with NVPs [29,31,32]. While sales are currently restricted, young adults [33–35] and smokers [36] have previously shown interest in IQOS (an HTP) in the US, suggesting that HTPs may again find a foothold in the market.

With the growth in new products, the nicotine product landscape now contains an array of products that can increase the number of dependent users, but may also act as a substitute for the deadliest of products, cigarettes. A decision-theoretic framework

was previously developed to evaluate the public health impacts of NVPs [37–39]. With health risks from NVPs less than from smoking [40–44], the framework showed that public health improves when NVPs are used by never smokers who would have instead initiated smoking, by current smokers who would not have otherwise quit smoking, and by former smokers who would have otherwise eventually relapsed. However, public health is worsened when NVP use encourages smoking initiation, discourages smoking cessation, or encourages smoking relapse. That framework [37] has explicitly or implicitly been used in a wide variety of simulation models that have examined the public health implications of smoking relative to NVPs or other potential harm-reducing products [6,38,39,45–53].

With the addition of newly emerging nicotine delivery products, such as HTPs, their potential public health implications become considerably more complex. The impact of these new products depends on their use patterns. Because of its similarities with cigarettes (i.e., heating tobacco) [54–56] and reduced toxicity [57–66], HTPs may be a viable substitute for smoking where NVPs have failed. For example, it has been suggested that "Juul (an NVP) appeals to millennials/hipsters and IQOS appeals to slightly older and more affluent smokers." [67]. However, public health impacts will also depend on the likelihood of transitioning from HTP to cigarette use and HTP health risks relative to both NVPs and cigarettes.

A better understanding of the likely transitions to and from HTP, NVP, and cigarette use is needed to effectively develop tobacco control policies that minimize the harms from nicotine delivery product use. It will be essential to understand how the impact of NVP-, HTP- and cigarette-oriented policies and regulations depends on consumers' use of the targeted product and other products, and any impact of policies on industry behavior. In particular, HTPs have historically been sold only by cigarette companies, while NVPs are also sold by non-cigarette-producing companies [68–70]. Policies may influence industry behavior by cigarette-producing vs. non-cigarette-producing companies.

This paper expands our previous decision-theoretic framework of NVP and cigarette use [37–39] to incorporate HTP use as a second potentially harm-reducing product. In presenting the framework, we discuss recent studies addressing the information needed for modeling the public health impact of heated tobacco products. We also consider the role of industry marketing, focusing on cigarette companies, and the role of policies in developing a comprehensive approach to balance the potential harms of cigarette, HTP, and NVP use. Due to the lack of requisite information on transitions between products and relative risks, we do not attempt to model the public impact of HTPs and NVPs. However, the described framework intends to aid in the extension of previous tobacco products simulation models that only consider one potential harm-reducing product. The Discussion section describes the additional information that can be used to help extend previous simulation models.

2. General Approach

Because cigarette use continues to be the nicotine delivery product most harmful to public health [71,72], our decision-theoretic framework focuses on the potential impact of NVPs and HTPs transitions to and from cigarette use (smoking). Since health outcomes depend primarily on long-term regular use [64], public health impacts are based on regular use, such as use maintained for at least one year [73]. Transitions to regular NVP and HTP use may involve shifts back and forth between experimental HTP and NVP use, but, for simplicity, we focus on transitions to either regular HTP or regular NVP use and not dual-use of HTPs and NVPs. Although NVP and HTP health risks are uncertain, our analysis considers their risk relative to cigarettes. Evidence indicates that NVP use [74–77] and HTP use [57–66] are likely much less harmful than cigarette use. NVP use is often estimated at 5% to 15% of the excess mortality risks of cigarettes [6,40–44,78], although there is considerable controversy on the precise level of the difference [44,79,80]. HTPs are likely more harmful than NVPs, with some estimates ranging from 1.5 to 2 times more harmful than NVPs [43,61,65,81–83], implying HTP risks at about 7.5% to 30% of the excess mortality risks of cigarettes. Due to difficulties in identifying regular patterns of multi-

product use [84], we do not distinguish dual (with either NVPs or HTPs) from exclusive cigarette use and assume the same health risks for dual-use and exclusive smoking. We assume that the health risks of exclusive smoking/dual use are the highest, followed by those of exclusive HTP and then NVP use.

We also extend our previous framework to consider industry behavior. Cigarette markets are an oligopoly in most countries, providing a highly profitable product [68]. In contrast, NVP markets are generally more competitive with many firms. These markets generally include non-cigarette companies with strong business incentives to target cigarette smokers as well as cigarette companies diversifying their products [69,70]. The HTP market typically contains few firms (typically just cigarette firms) [17,27,28,85–92] and is subject to entry barriers (e.g., proprietary technology [69,70]), and thus firms are likely to face minimal competition and receive greater profits from selling HTPs than NVPs.

To reduce the complexity of the analysis and focus on two potential harm reduction products that have already gained acceptance in many countries, we do not consider oral nicotine pouches [93–96] or other emerging products. However, discussed below, many of the same issues would arise when considering these other products.

3. Decision-Theoretic Framework

We separately consider initiation from never users, cessation from current smokers, and relapse from former smokers, as shown in Figures 1–3. The relative impact of final smoking, NVP, and HTP outcomes on public health (e.g., the change in smoking-, NVP- and HTP-attributable deaths) is indicated by shades of green to distinguish potential health gains and shades of red to distinguish potential health losses, with darker shades indicating a greater mortality risk. In each of the analyses, we first consider whether individuals initially engage in regular NVP or HTP use. We then consider potential future transitions (e.g., after one year of NVP/HTP use) from regular NVP or HTP use to exclusive/dual cigarette use, remaining NVP or HTP users, or no use.

3.1. Never Users

As in our previous framework [37–39], the public health impact of NVP and HTP use by those beginning as never smokers depends on the counterfactual scenarios of whether or not these individuals would have otherwise initiated smoking if NVPs and HTPs were not available. The top branch of Figure 1 at node 1.1 is the counterfactual where never users would have otherwise initiated smoking. There are four potential paths of HTP and NVP use. First, in the absence of HTP or NVP use, the individual simply becomes a smoker (node 1.11), but public health is unaffected since the would-be smoker remains a smoker. Second, the use of HTPs by otherwise smokers (node 1.12) may yield public gains if the never smoker was not inclined to try or had tried but discontinued NVP use (e.g., due to dissatisfaction). In this instance, public health gains derive from replacing smoking initiation with HTP use when NVPs would not have been used. If otherwise smokers would have instead used NVPs (node 1.13), public health impacts depend on whether NVPs are in fact used. Third, if otherwise smokers who would have used NVPs instead use HTPs (node 1.131), e.g., due to industry marketing or public policies, HTP use may still yield public health benefits relative to cigarette use. However, due to greater health risk from HTPs than NVPs, less public health benefit is derived than if NVPs were used (node 1.132), the fourth alternative. Thus, public health gains from HTP use are greatest when NVP use would not have otherwise replaced smoking.

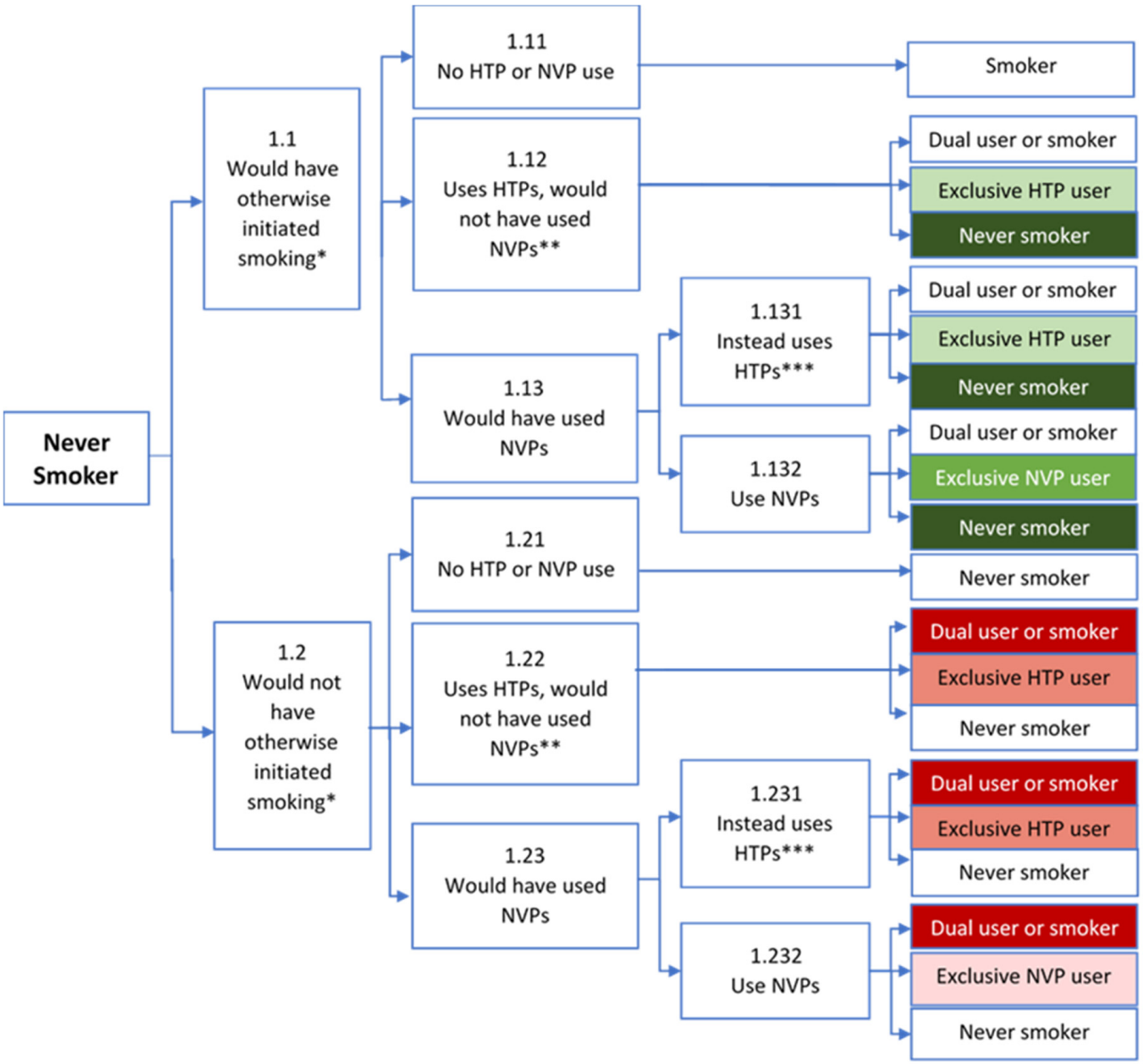

Figure 1. Public Health Impact of NVP and HTP Use Among Former Smokers. Notes: HTP = Heated Tobacco Product, NVP = Nicotine Vaping Product. * Based on the counterfactual of whether smoking initiation would have occurred in the absence of both HTPs and NVPs. ** HTPs are a more desirable alternative to NVPs, e.g., tried NVPs and not found desirable or satisfactory. *** Would have otherwise preferred NVPs, but diverted from use due to industry behavior or government policy. **Green** indicates public health benefit; **Red** indicates public health loss. Darker shades indicate a greater impact.

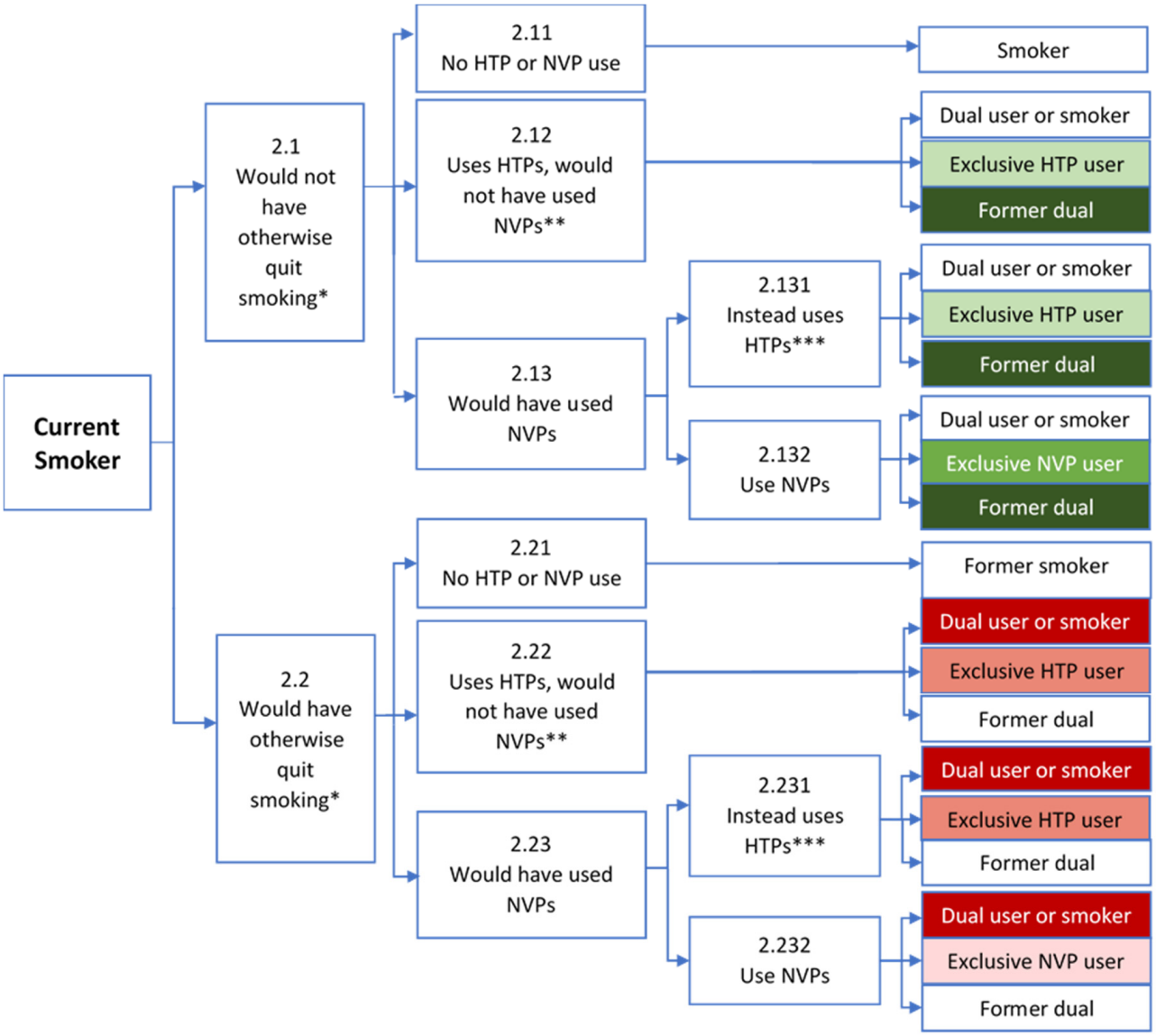

Figure 2. Public Health Impact of NVP and HTP Use Among Current Smokers. Notes: HTP = Heated Tobacco Product, NVP = Nicotine Vaping Product. * Based on the counterfactual of whether smoking cessation would have occurred in the absence of both HTPs and NVPs. ** HTPs are a more desirable alternative to NVPs, e.g., tried NVPs and not found desirable or satisfactory. *** Would have otherwise preferred NVPs, but diverted from use due to industry behavior or government policy. **Green** indicates public health benefit; **Red** indicates public health loss. Darker shades indicate a greater impact.

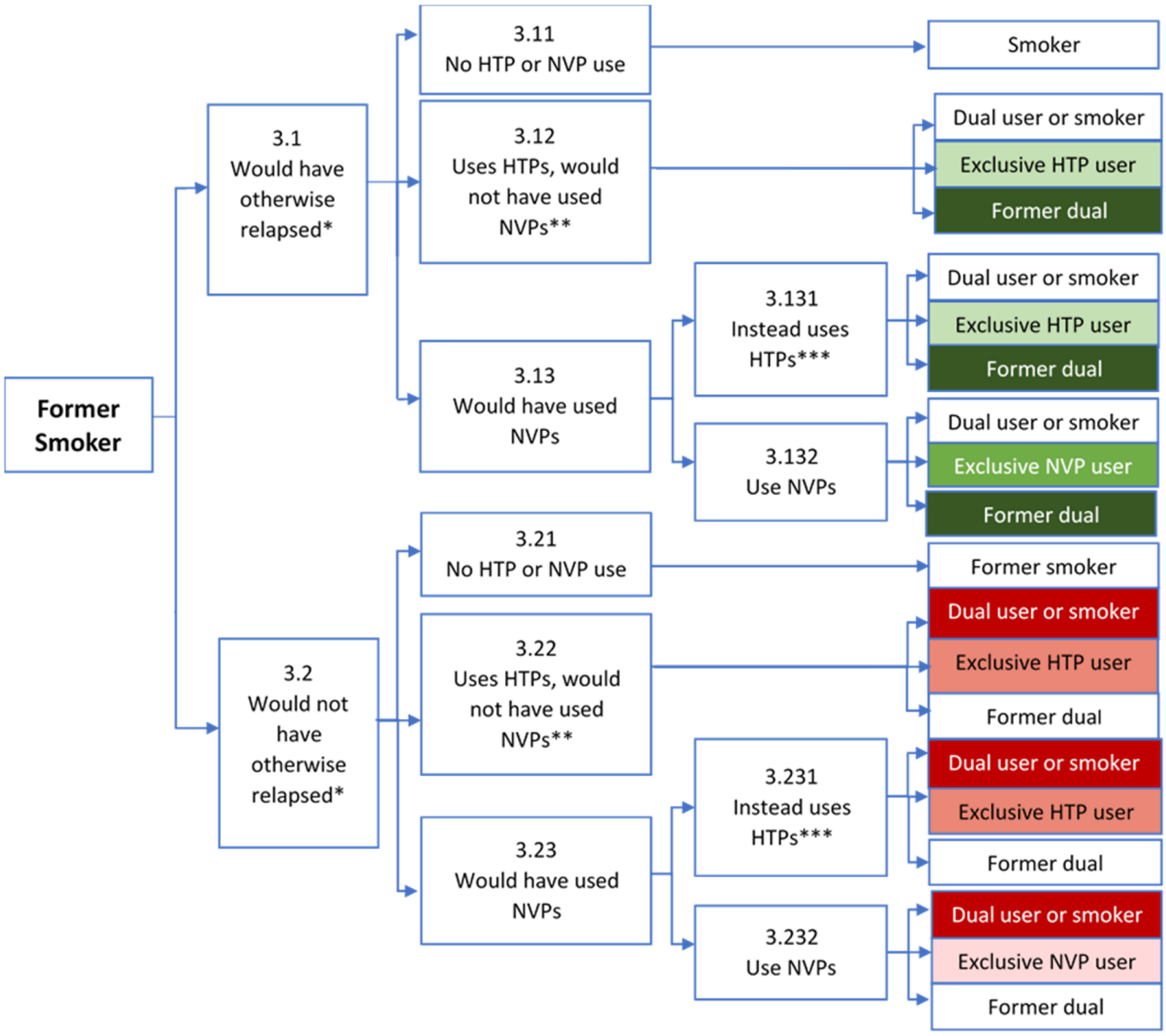

Figure 3. Public Health Impact of NVP and HTP Use Among Former Smokers. Notes: HTP = Heated Tobacco Product, NVP = Nicotine Vaping Product. * Based on the counterfactual of whether smoking relapse would have occurred in the absence of both HTPs and NVPs. ** HTPs are a more desirable alternative to NVPs, e.g., tried NVPs and not found desirable or satisfactory. *** Would have otherwise preferred NVPs, but diverted from use due to industry behavior or government policy. **Green** indicates public health benefit; **Red** indicates public health loss. Darker shades indicate a greater impact.

The second main branch of Figure 1 at node 1.2 denotes the counterfactual where never smokers would not have otherwise initiated smoking. NVP and HTP use yields public health losses, because their use expands the pool of nicotine delivery product users. Lack of HTP or NVP use implies no product use, and, consequently, no smoking or harm (node 1.21). Reflecting the increased health risk of HTP compared to NVP use, HTP use (nodes 1.22 and 1.231) shows greater public health losses than NVP use (node 1.232). The greatest loss occurs when HTPs are used even though NVPs would have been preferred in the absence of industry marketing or public policies (node 1.231). Later transitions to exclusive/dual cigarette use may be more likely for HTPs than NVPs due to their similarity to cigarettes, i.e., HTPs heat tobacco [56] whereas NVPs contain primarily nicotine vapor [96]. While direct evidence on whether HTPs act as a gateway to smoking is limited [96] and youth HTP users are less likely than NVP users to quit cigarettes [25]. Although some

studies indicate NVP use may precede smoking [96], population-level studies find that declines in youth and young adult smoking have rapidly accelerated with greater NVP use [3,4,97–99]. Those initiating HTP use may also be more likely than NVP initiators to continue their use rather than quit all product use, as indicated by higher levels of dependence on HTPs [100,101] compared to NVPs [102–104]. While evidence to date is limited, initial HTP use appears more likely than initial NVP use to lead to exclusive/dual cigarette use and less likely to lead to no use. As such, Figure 1 shows that best final outcomes tend to occur as a result of initial NVP use followed by initial HTP use.

In the above analysis, we considered initial transitions to exclusive regular HTP or NVP use. The public health impact of these choices will ultimately depend on any further transitions in later years to cigarette smoking or quitting NVP or HTP use (as shown in the terminal nodes of Figure 1). Regular use of either product may lead to one of three terminal nodes: (1) exclusive or dual cigarette use, (2) exclusive (continued) NVP or HTP use or (3) non-use of any product. Later transitions to exclusive/dual cigarette use may be more likely for HTPs than NVPs due to their similarity to cigarettes, i.e., HTPs heat tobacco [56] whereas NVPs heat a nicotine-containing liquid [56]. While direct evidence on whether HTPs act as a gateway to smoking is limited, studies find that youth HTP use often precedes smokings [25,97]. Although some studies indicate that NVP use may precede smoking [96], population-level studies find that declines in youth and young adult smoking have rapidly accelerated with greater NVP use since the emergence of NVPs [1,3,4,98,99], suggesting that NVP use is not affecting or may even be enhancing declines in youth cigarette smoking. Those initiating HTP use may also be more likely than NVP initiators to continue their use rather than quit all product use, as indicated by higher levels of dependence on HTPs [100,101] compared to NVPs [102–104]. While evidence to date is limited, initial HTP use appears more likely than initial NVP use to lead to exclusive/dual cigarette use and less likely to lead to no use. As shown in Figure 1, better final outcomes tend to occur with initial NVP use.

Cigarette firms may directly influence future transitions of never smokers. They have incentives to promote HTPs over NVPs due to: (1) higher potential relative profitability of HTPs, (2) a greater likelihood that HTP users will transition to their most profitable product, cigarettes, and (3) a greater likelihood of continuing rather than quitting HTP compared to NVP use. As suggested by the 4-Ps (Product, Promotion, Price, Place) framework [105], cigarette companies may:(1) develop HTPs particularly desirable to youth and young adults, e.g., via specific flavors. (2) target advertising to youth and young adults, (3) charge lower prices to youth and young adults, e.g., through discounting, and (4) target stores and internet locations most frequented by youth and young adults.

3.2. Current Smokers

The public health impact of NVPs and HTPs on current cigarette smokers depends on the counterfactual scenario of whether or not smokers would have quit in the absence of HTPs or NVPs. Node 2.1 in Figure 2 denotes the counterfactual when smokers would not have otherwise quit, i.e., become former smokers. The public health impact is neutral at node 2.1 because the smoker maintains cigarette use without NVPs or HTPs. If current smokers would not have otherwise used NVPs, HTPs yield public health benefits by providing smokers an additional alternative to help them quit cigarette use (node 2.12), e.g., by providing better nicotine delivery [50] or other desired consumer attributes (e.g., taste) compared to NVPs. When smokers would have otherwise used NVPs to quit smoking (node 2.13), HTP use still yields public health gains (node 2.131), but the gains are less than from NVP use (node 2.132) since increased health risk of HTPs offsets some of the gains compared to NVP use.

Node 2.2 in Figure 2 denotes public health losses under the counterfactual where smokers would have otherwise quit smoking in the absence of HTPs and NVPs. The potential public health losses are generally less if NVPs are used (node 2.232). HTPs could yield greater losses (node 2.22), especially if NVPs were preferred to HTPs (node 2.231).

As shown in Figure 2, the ultimate public health impact of HTP and NVP use depends on future transitions to final nodes of dual or exclusive smoker, continued exclusive NVP or HTP use, or no use. Studies indicate that HTP use is associated with reduced intent to quit [106] and successful smoking cessation [65,96,107–110], while NVPs are associated with smoking quit success [110,111]. The nascent literature finds that HTPs are often used with cigarettes [18,19,21,22,30,112,113], suggesting that HTP use may be more likely than NVPs to lead to exclusive smoking or dual-use. HTP users [100,109] also appear less likely than NVP users [102–104] to eventually quit their use. Thus, HTP use may ultimately lead to worse public health outcomes than NVPs due to less likelihood of remaining a former smoker, increased likelihood of continued smoking, and less likelihood of quitting all products (i.e., no cigarette, NVP, or HTP use).

Cigarettes are inexpensive to produce and generate high-profit margins relative to other consumer products [68]. Thus, cigarette companies have a strong incentive to protect their profits from cigarette sales that might be lost from customers switching to HTPs or NVPs. In particular, they may encourage dual use by smokers [17,27,28,84–92], e.g., especially when indoor smoking is restricted [114,115]. When faced with the likely loss of cigarette customers to NVPs, cigarette companies will likely encourage HTP over NVP use. As in our analysis of never smokers, cigarette companies may: (1) modify product characteristics (nicotine content or flavoring), (2) increase promotions to target specific populations (e.g., those of low socioeconomic status [SES] or mental health issues), (3) discount prices, and (4) influence product placement. In particular, cigarette companies may target potential NVP users by advertising HTPs as a better substitute for smoking than NVPs [56], focusing especially on their cigarette customers [28]. Cigarette companies are also well-positioned to target smokers in mass-market retail using shelf-space contracts with retailers [68,69] and online through their websites or discussion groups [70,116].

3.3. Former Smokers

The impact of NVP and HTP use on former smokers will depend on the counterfactual of whether former cigarette smokers would have (Figure 3, node 3.1) or would not have (Figure 3, node 3.2) otherwise relapsed in the absence of HTPs or NVPs. When former smokers would have otherwise relapsed, the greatest public health benefit tends to occur with NVP use (node 3.132), followed by HTP use when NVPs would not have otherwise been used (node 3.12), and finally when HTPs, although less desirable, are used instead of NVPs (node 3.131). When former smokers would not have otherwise relapsed, losses to public health are generally least with NVP use (node 3.232), followed by HTP when preferred (node 3.22) and finally HTP used instead of NVPs (nodes 3.231).

In terms of later transitions to smoking or exclusive NVP or HTP use, and remaining former smokers, some evidence indicates that HTP users [96] may be more likely than NVP users [117] to relapse to smoking. As with current smokers, cigarette companies are well-situated to target former smokers to increase the likelihood of HTP over NVP use and encourage relapse.

3.4. Summary

The potential health gains from HTP use are generally greatest when used by otherwise smokers or continuing smokers to move away from smoking and where NVP use would not have prevented smoking. Similarly, public health losses accrue when HTP use does not prevent smoking, especially if NVPs would not have otherwise been used. The overall public health gains and losses depend on the size of each smoking status group and the likelihood of HTP or NVP users later transitioning to cigarette use or no product use. Each of these transitions will also depend on industry marketing as described above and how consumers and industry respond to public policies towards NVPs, HTPs, and cigarettes as described below.

4. Regulatory Framework

Policy evaluations tend to focus on the impact of a particular policy on the use of the targeted tobacco product and do not consider their impact on other products [118–122]. In developing an overall nicotine product strategy consistent with public health goals, the severity of policies targeting each product should be proportionate to their overall risks [123]. To accomplish that aim, a better understanding of relative product risks is needed [124]. However, as suggested by our framework above, overall risks depend not only on each product's health risk, but also on HTP and NVP availability and consumer preferences, and potential transitions from HTPs and NVPs to cigarette or no nicotine product use. A higher likelihood of transition from HTP use than from NVP use to smoking may justify stricter policies for HTPs than NVPs, e.g., a higher cigarette or HTP tax relative to NVP taxes.

Policies that reduce the appeal of specific products may induce consumers to switch to the use of other products. Stronger NVP-oriented policies relative to HTP-oriented policies may cause those who would have otherwise used NVPs to instead use HTPs. For example, regulations limiting particular NVP flavors (e.g., US Food and Drug Administration [FDA] disapproval of Pre-market Tobacco Product Applications [PMTAs] for menthol or mint NVPs while allowing menthol or mint HTPs) [125] may encourage HTP use when NVPs would have otherwise been preferred. Our analysis also suggests the importance of perceived risks of HTPs relative to cigarettes and NVPs. Government policies, such as through government websites, media campaigns, and health warning requirements, may also directly influence the perception of risks [126–129] both in terms of consumers using HTPs or NVPs instead of cigarettes and in terms of using HTPs instead of NVPs.

While valuations of tobacco control policies generally focus on their immediate effects on consumers, stricter policies towards HTP than NVPs may also be justified to offset the effect of industry marketing to promote HTP over NVP use. Stricter NVP relative to HTP policies may also have indirect effects through their impact on the viability of firms. Regulations that weaken non-cigarette firms and reduce competition may provide cigarette companies greater control of the overall nicotine delivery product market [69,70]. For example, policies restricting NVP flavors without similar restrictions on HTPs may reduce NVP use and ultimately limit the ability of non-cigarette firms to introduce new products or even survive. With reduced competition from non-cigarette firms, cigarette companies may be better positioned to encourage smoking initiation, discourage smoking cessation, and encourage smokers to switch to HTPs rather than NVPs.

Our analysis is in terms of public health impacts, but policymakers may have other goals, such as the elimination of cigarette companies or cigarette use or even more broadly the use of all nicotine delivery products. Such "regulatory stances" [130] classify a regulatory framework by its intent to change the size of a given market in the future compared to the present. For example, based on the evidence of substantially higher health risks from cigarettes than either NVPs or HTPs, a regulatory stance towards cigarettes that is contractionist (reducing the share of that market in the economy) or even prohibitionist (intent to reduce the market's size to zero) may be warranted. Placing the cigarette market at a large enough competitive disadvantage compared to the newer markets could provide much of the market momentum towards these new products achieving policy goals. To the extent that HTPs are used where NVPs had not been effective and do not later lead to cigarette use, an expansionist (increasing the size of the market) or permissive (setting no market size goal) stance towards HTPs may be warranted in the short-run, while moves towards contraction or even prohibition could be considered over the longer run if HTP markets are later found to be unacceptably harmful. Focusing on market size and its connection to public health may help prioritize those policies that most efficaciously improve public health.

5. Discussion

Our decision-theoretic framework shows how HTP use can result in public health gains under certain scenarios, but the impact depends on a complex set of factors, including relative health risks, use patterns, industry behavior, and public policy. If HTPs are used by those who would not have otherwise used NVPs, they may provide public health benefits by enabling additional smokers to quit or discourage smoking initiation. However, public health benefits are generally reduced if HTP use replaces less harmful NVP use, and especially if that use encourages concurrent or exclusive cigarette use by never smokers who would not have otherwise initiated smoking, smokers who would have otherwise quit, or those who would not have otherwise relapsed. The ultimate impact also depends on the likelihood of future transitions to cigarette use or to quitting all nicotine product use.

Our analysis provides a framework for further empirical analysis and modeling. Currently, harm reduction models [6,39,45–53] focus on one potential harm-reducing product. In particular, the two extant HTP simulation models [48,49], both supported by industry, only include HTPs and cigarettes. We have summarized the information from previous studies, but our review suggests the need for further information required to develop models that capture the complexity when more than one harm-reducing product is available.

Separate studies have considered the users of HTP and NVPs among never, current and former smokers, but studies have not generally considered the HTP and NVP use in the context of a setting with multiple harm-reducing products nor the relationship between HTP and NVP users (i.e., overlapping characteristics of users). As illustrated by our counterfactual analysis, the public health impact of harm reduction products will also depend on incorporating risk factors that distinguish would-be smokers among never smokers, would-be quitters among current smokers, and would-be relapsers among former smokers. Studies indicate that these products' use patterns depend on a complex array of attitudes towards risks and the options available to users [97,131–133]. Further, limited attention has been given to later transitions from regular HTP use to cigarette use or no use (i.e., cessation from HTPs and no further cigarette use).

Limited attention has been given in the previous literature to appropriate measures of HTP use, especially in relation to NVP use. We have distinguished initial regular HTP and NVP use from later transitions. The appropriate definitions regarding the duration and intensity of use should depend on empirical analyses and a definition that fits the requirements for gauging public health impacts. Transitions from initial HTP and NVP use to later cigarette use or no product use will similarly require empirical analysis for determining the appropriate time frame.

In our analysis above, we assumed that NVPs pose less health risk than HTPs and that HTP risks are lower than cigarette risks. Over time, as the long-term health consequences of both NVPs and HTPs are better understood, the relative risks may change, and thus the public health implications of HTP vs. NVP transitions may change. While, for simplicity, we did not distinguish dual cigarette and NVP or HTP use from exclusive cigarette use, such analyses should also consider the importance of dual use.

The public health impact of HTP use will depend on how industry behavior impacts the initiation and cessation of NVPs, HTPs and cigarettes. In particular, the profitability of HTPs and cigarettes also plays a role in our analyses of industry behavior, particularly in terms of industry marketing. HTP markets vary widely from country to country. In the US, HTPs were previously sold by Altria, but their IQOS sales were halted due to a patent dispute. Recently, Philip Morris International (PMI) obtained FDA approval to market IQOS 3.0 and may be poised to enter the US market [33–35]. Unlike Altria, PMI does not sell cigarettes in the US, which may lead to a stronger stance towards HTP use. In other countries, cigarette companies will likely have a greater incentive to protect the use of their most profitable products, currently cigarettes, although profit margins on HTPs also appear to be relatively high [134].

Use patterns will also depend on public policies towards HTPs, as well as public policies towards other products. Their direct impact on use patterns, such as through taxes,

enforcement of minimum purchase age, and flavor restrictions, and their indirect impacts, such as through influencing market structure, merit particular consideration. With more stringent policies towards NVPs than HTPs, cigarette companies may face less competition from non-cigarette companies selling NVPs, and thus increased marketing of HTPs and cigarettes. The impact of NVP-oriented and HTP-oriented policies on industry structure and competition between cigarette-producing and non-cigarette NVP firms should be considered in developing a regulatory framework.

Finally, we have not considered modern oral nicotine pouches [93–96] or other emerging nicotine delivery products. Their public health impact, like that of HTPs, would depend on their risks and use patterns relative to cigarette, NVP and HTP use, as well as industry behavior and government policy. A recent paper [135] provides a decision-theoretic framework for oral nicotine products (snus) similar to the framework for evaluating the public health impact of NVP relative to cigarette use [37–39], but still focuses on two products. With the availability of more than two potentially harm-reducing products, public health benefits will tend to increase if such product use replaces additional never smokers who would have initiated smoking, current smokers who would not have quit, or former smokers who would have relapsed. Nevertheless, the complexity increases when evaluating the impact of each additional product relative to that of cigarettes and other potentially harm-reducing products. Consequently, it may be pragmatic to aggregate harm reducing-products in attempting to model the overall public health impact of multiple harm-reducing products. While the complexity of public health analyses increases with each additional product considered, the potential impact of emerging products merits attention, particularly in terms of their substitutability with HTPs and NVPs.

6. Conclusions

To date, substantial research has been devoted to NVPs. Much less is known about HTPs. Information is needed to more precisely define their health risks relative to other products, their appeal to consumers relative to NVPs and cigarettes, and the likelihood of transitioning from HTPs to cigarette use and to quitting all products. While our framework provides a structure for these analyses, it also shows the difficulty in disentangling those relationships. The potential substitution between NVPs and HTPs and their propensity to encourage smoking and quit all product use is particularly complex. Finally, our analysis highlights the importance of incorporating rigorous analyses of industry behavior and the impact of policies on use and industry behavior. Accurate information on each of these factors will be needed to develop comprehensive and effective strategies to promote public health in the increasingly complex nicotine product landscape.

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Article

Patterns of Smoking and Snus Use in Sweden: Implications for Public Health

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Abstract: There has been concern that the availability of alternative less harmful forms of nicotine might inhibit smoking cessation and/or encourage those who would not otherwise have smoked to do so. The plausibility of such effects can be best assessed by looking at population trends in use of smoking in relation to alternatives. This paper looks at the relationships between snus use and smoking in Sweden. Analyses are based on a data set for the period January 2003 to February 2011 from a long-term study covering nationally representative samples of the Swedish population aged 18–79, with a total study population of 60,675 individuals. Questionnaires made it possible to identify detailed tobacco use categories and use trajectories. The results showed that uptake of snus use is much more common in males than females. Those who began daily tobacco use using snus were much less likely to subsequently take up smoking than those who had not, both among males (17.6% vs. 45.9%), and females (8.2% vs. 40.2%). Further, among those who started using snus after starting as smokers, 76.3% of men and 71.6% of women had stopped smoking completely, including 31.5% of the men and 28.6% of the women who had quit all forms of tobacco. Indeed, those who were primary snus users were also more likely to have quit altogether than those who only ever smoked. Snus was also reported as the most common smoking cessation aid among men and yielded higher success rates than nicotine replacement therapy and other alternatives. As conclusions, snus has both contributed to decreasing initiation of smoking and, when used subsequent to smoking, appears to facilitate smoking cessation. All these effects suggest that the availability and use of snus has been a major factor behind Sweden's record-low prevalence of smoking and the lowest level of tobacco-related mortality among men in Europe.

Keywords: public health; snus; smokeless tobacco; smoking cessation; tobacco control; harm reduction

1. Introduction

The ultimate goal for tobacco control is generally stated as "A tobacco-free world." However, there is no reasonable prospect of achieving this in the foreseeable future. As a result, many experts believe that there needs to be a focus on minimizing tobacco-related morbidity and mortality among present tobacco users [1,2]. This is particularly important for disadvantaged people, who evidence shows are less likely to be able to quit smoking successfully and are more likely to take it up [3].

For many years, there has been a debate about the threats and opportunities associated with lower harm forms of nicotine delivery, such as snus (the Swedish kind of low-toxicant smokeless tobacco).

In recent years, the rise of vaporized nicotine products (electronic cigarettes) has sparked a new debate in this field. It is still too early to know exactly how this will turn out, but some insights into likely effects can be gained from the emergence of snus in Sweden since the 1970s. New manufacturing methods for snus were developed by the then government-owned tobacco monopoly to minimize levels of toxicants. The epidemiology is now clear: snus is markedly less harmful than smoking; indeed, there are no clearly established causes of premature death associated with its use [2,4–6], except for a potentially increased risk of fatality after acute myocardial infarction [7,8]. Indeed, neither oral or pancreatic cancer which have been linked to other smokeless tobacco sources are associated with snus [9,10]. Snus does not contain the combustion products in cigarettes and other smoked tobacco products. By contrast, dirtier forms of smokeless tobacco do result in clear adverse health effects [11]. These finding have helped to establish that nicotine itself is a minor cause of the morbidity and mortality related to tobacco use [12]. Therefore, nicotine-delivery products can be used without most of the serious health effects of smoking if the nicotine is not accompanied by high levels of disease-producing toxicants as it is in smoking. This principle is already an established practice in the use of nicotine replacement therapy (NRT)-products as a short-term means of quitting smoking, but the snus story shows that this extends to prolonged use.

There is now a broad consensus that use of non-combustible low-toxicity oral tobacco products like Swedish snus instead of combustible tobacco, will yield beneficial effects for individuals who use snus instead of cigarettes [13,14]. For example, it has been estimated that users of products like Swedish snus have at least 90%–95% less tobacco-related mortality than cigarette smokers and that their reduction of life expectancy is consequently small [5,15]. Indeed, among those who quit smoking for snus, the health benefits are similar to that for people who quit smoking completely.

Notwithstanding, there are concerns that, on the population level, snus use might have negative health effects, such as increasing total prevalence of tobacco use, serving as a gateway to smoking, hampering smoking cessation and leading to dual use of cigarettes and snus [16–18].

At a population level, the net effect of snus use on health is determined not only by the health risks for individual users but also by the way it influences national smoking patterns. The aim of this study is to ascertain the impacts of snus use on both uptake and cessation of smoking as key elements determining the net public health impacts of snus use.

What do we know about the impact of snus on smoking? Sweden and Norway are the two countries with the longest history of snus use, and where most of the research comes from. In Sweden, precursors to the modern snus have a long history but were in decline, only used by old men by the 1970s. However, as a reaction to the scientific evidence about health risks of smoking emerging in the 1960s, Sweden was the first country to institute permanent government funding of public health education on smoking. This triggered an interest, especially among men, in switching to snus that was at that time cheaper than cigarettes. In addition, the Swedish government, while making no health claims, allowed snus to be taxed at a lesser rate than cigarettes. However, in recent years, taxes on snus have been raised, so it is now at least as expensive as cigarettes. Snus use now exceeds smoking among men and has done so since at least 1996 [19]. Among women, daily snus use remained low but in recent years has increased from 1% in 1996 to 4% in 2015. Over the same period, rates of daily smoking have declined from 23% to 11% among women and from 19% to 10% among men. Recently, the growth of daily snus use among men has stalled: rates were 19% both in 1996 and 2015 [20]. This may be due to the increased taxes on snus. The current rate of daily smoking among men is far below any other country in the European Union. EU statistics indicate an overall prevalence (men + women) of 11% for Sweden and, for the rest of EU, from 19% (Finland) to 38% (Greece) with an EU average of 28% [21]. The Swedish pattern of increasing snus use and declining smoking has also occurred in Norway [22].

The above evidence constitutes compelling evidence that snus has not led to more smoking. However, there have been many other tobacco control initiatives in Sweden and progress may have been even more rapid without snus. The question remains: What other evidence is useful in addressing whether snus encourages smoking and/or discourages quitting? The idea that snus might encourage smoking is the so-called gateway effect whereby use of one form of nicotine sensitizes users so they

are more likely to try an alternative form, especially one that is more psychoactive, like smoking. This theory can never be demonstrated at the individual level, because we cannot observe the counterfactual case of those who would have smoked without snus but just happened to use it first from those who would not have smoked except for use of snus. However, at a population level, it is possible to disconfirm various forms of the gateway hypothesis. Indeed, the rise of snus concurrent with a decline in smoking disproves the strong version of gateway that snus is the major factor driving changes in smoking prevalence. The case against any gateway would be strengthened if the rate of decline in smoking was greater in populations where snus use was increasing compared to where it was not (as much) or was declining.

The gateway hypothesis predicts that transitions to smoking will be greater among those who use snus first as compared with those who do not. A finding of lower uptake among snus starters would be fatal to it. However, the prediction of greater uptake is not unique to the gateway hypothesis. A Norwegian study showed that overall primary snus users have social and demographic characteristics that predispose them to smoking [23], thus at least some of any over-occurrence of subsequent smoking among primary snus users could be due to this co-occurrence of risk factors (assuming these findings also apply in Sweden, which seems likely). Thus, both gateway and the co-determinants hypotheses predict greater uptake of smoking among primary snus users than among the rest of the population.

The other concern about snus and other alternative forms of nicotine is that they may be used to sustain smoking by hampering rather than facilitating smoking cessation. Here the focus is on secondary snus use. There would be a clear public health benefit if snus use facilitated smoking cessation, and harm if it inhibited it. On the individual level, it is not possible without randomized trials to conclusively demonstrate that snus facilitates smoking cessation, but at the population level, the randomized trials have to be replaced by population studies. This is particularly the case, if the way snus is used is more to replace smoking, at least temporarily, rather than being used as a form of short-term therapy under external control [24]. To establish effectiveness at a population level, there is a need for evidence both about cessation success in groups using an aid and the extent of usage. Further, it is possible to demonstrate whether snus use hampers quitting at the population level or not. If the rate of smoking cessation among those who have used snus is greater than the proportion quitting who have not, then the simple version of the hampering hypothesis is disproven. Again, finding lower overall quit rates in populations with high snus use would be consistent with hampering, but higher rates would not. Also, similar to uptake, a co-occurrence of determinants of use of snus and smoking could explain lower quit rates, but not higher ones.

This analysis leads to the following main research questions:

1. Is primary uptake of snus associated with increased or decreased uptake of smoking as compared to those who have never been regular snus users?
2. How does smokers' uptake of snus use influence continuation or cessation of tobacco use? In particular, is snus use, particularly secondary use (to smoking), associated with increased or reduced success in smoking cessation?
3. Have the relationships between the two products changed over time?
4. How commonly is snus used as a cessation aid compared to other options, and how does it compare in terms of success rates?

2. Methods

2.1. Data Source

The study is based on a data set for the period January 2003 to February 2011 retrieved from *Your Country and Your Life (YCYL)*, a long-term study of the Swedish people's attitudes, values and behaviors in a large number of societal, political and personal areas such as different living conditions including tobacco use. The study was conducted by the research institute FSI (Study Group for Societal and Information Studies) and was continuously ongoing from 1971.

2.2. Sample

Each year, probability samples of the Swedish population aged 18−79 years were drawn from the Swedish Population Registry ($n \approx 13{,}000$). Representativity of the samples was checked with regard to gender and age. Since 1993, each sample was split into sub-samples ($n \approx 300$) for continuous data collection by weekly distribution of postal questionnaires except during summer and Christmas holidays.

2.3. Survey Procedures

There was a total of four postal reminders where the second contained a new questionnaire and the fourth an abbreviated questionnaire. Every fourth week there was a random telephone follow-up of respondents who had not filled in the questionnaire after the fourth reminder.

The average response rate after non-response analysis was around 65%. The data was weighted to the population estimates by gender, age, education and place of residence.

The retrieved data set contained 62,213 respondents. There were 16 respondents excluded because they lacked registered value of either sex or age. Another 1522 were excluded because they did not have complete answers on tobacco issues. The current study population contains 60,675 respondents. Data analyses were performed using SPSS 13.0 for Windows (Chicago, IL, USA).

2.4. Measures

The data set from the YCYL study contained both demographic and tobacco-related items.

The demographic items included gender, date of birth, education, employment, place of residence, living conditions, national origin, income and financial assets. Register data for age, gender and place of residence were included and used to check the validity of the self-reported data.

The tobacco-related items included five basic questions: Q1. Do you now smoke: Daily, Occasionally, Not at all? Q2. Have you previously smoked: Daily, Occasionally, Never at all? Q3. Same as Q1 but for snus use. Q4. Same as Q2 but for snus use. Q5. Which onset came first: Smoking or snus use? (asked of those answering "Daily" to Q1 and/or Q2 in combination with "Daily" to Q3 and/or Q4). Other items covered time to first cigarette/snus after waking up, quantity of cigarettes/snus per day, age of initiation to daily smoking/snus use, desire to quit smoking, number of smoking cessation attempts, and cessation aid used at most recent attempt.

2.5. Data Processing

Detailed categories of tobacco use at the time of the survey were established based on the answers to the questions regarding smoking frequency.

Individual initiation profiles and tobacco use trajectories were established such that tobacco use can start either with smoking or snus use and that the subsequent progression of tobacco use can include sustained use, initiating the other product and quitting one or both. Based on reported daily use of each and which was used first for daily users of both, the following five categories were established: "Primary daily smoking, no daily snus use," "Primary daily smoking, secondary daily snus use," "Primary daily snus use, no daily smoking," "Primary daily snus use, secondary daily smoking," "No daily tobacco use." NB: Defining initiation with respect to onset of occasional use would result in categories containing a heterogeneous mixture of subgroups that are too disparate to make sense of the data. By cross-tabulation of initiation profile with tobacco use at the time of the survey, it is possible to identify multi-step trajectories that individual tobacco users have followed from initiation to the time of the survey.

Since the prevalence of tobacco use is determined both by cessation and initiation practices, we addressed the question of changes over time in primary initiation. Data regarding decade of birth were used to establish cohort-specific profiles of primary initiation for people born in five consecutive decades. Inter-cohort comparisons will then give an insight into the changes over time in the primary initiation practices.

At various points in the manuscript, we report percentages of smokers as a function of whatever reference group (denominator) we are interested in. In some cases, where the denominator is "ever smokers," the results are reported as quit ratios; i.e., the percentage of ex-smokers as a function of ever smokers.

2.6. Ethical Considerations

Full review by a research ethics committee has not been necessary for this type of data collection according to the rules of the Swedish Law on Research Ethics Review [25].

3. Results

3.1. Primary Initiation of Tobacco Use According to Changes over Time in the Population

In order to analyze patterns of primary initiation at different periods in the past, we have studied separate birth cohorts with respect to the proportions between the three options: Primary initiation of daily smoking, Primary initiation of daily snus use, and No initiation of daily tobacco use. The sequence of cohort-specific data shown in Figure 1 demonstrates how initiation practices in the population have changed over time.

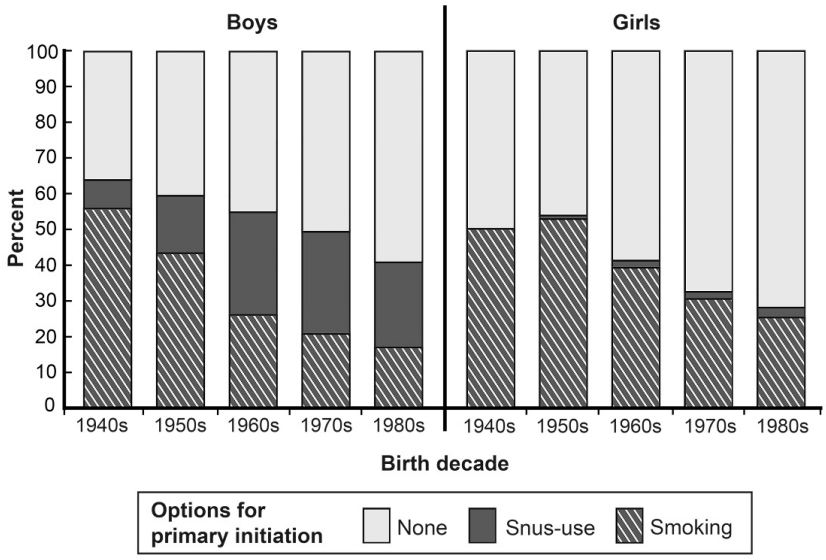

Figure 1. Changes over time concerning primary initiation. The bars represent cohorts from five consecutive birth decades. The segments show the proportions of different options for primary initiation in each cohort.

Among males born in the 1940s, a large proportion initiated daily tobacco use through smoking and a rather small proportion through snus use. Among those from later birth decades, primary initiation of daily snus use steadily increased along with decreased primary initiation of daily smoking and increased proportions never becoming daily tobacco users. In the cohort born in the 1980s, a majority of the boys never became daily tobacco users, and most of the boys who did initiate daily tobacco use started with snus use, with very few starting with smoking.

Among those born in the 1940s, primary initiation of smoking was more common among boys than girls, and primary initiation of snus use in girls was virtually non-existent. Among those born in the 1950s and later, primary initiation of smoking was more common in girls than boys, and the decrease from cohort to cohort was less pronounced in girls than in boys. Girls born in the 1950s were the first ones to show an appreciable level of primary initiation of snus use and this was the cohort in which overall tobacco use peaked. There have been some increases in primary initiation of snus in younger cohorts, but rates are still rather low (Figure 1).

3.2. Initiation of Daily Smoking According to Primary Daily Snus Use

Table 1 presents aggregated data from YCYL 2003−2011 in a way that makes it possible to compare differences in initiation of daily smoking as a function of prior daily snus use.

Table 1. Progression of tobacco use by profile of initiation of tobacco use.

		Profile of Initiation					
Tobacco use at the time of the survey		**Primary daily smoking**		**Primary daily snus use**		**No daily tobacco use**	**Total**
		no daily snus use	**secondary daily snus use**	**no daily smoking**	**secondary daily smoking**		
Men		*n* = 6943	*n* = 3737	*n* = 4144	*n* = 877	*n* = 12,601	*n* = 28,302
Daily smoking (combined with)							
daily snus use	*(a)*	–	9.0% *n* = 337	–	15.9% *n* = 139	–	1.7% *n* = 476
occasional snus use	*(b)*	3.9% *n* = 273	0.9% *n* = 33	–	2.0% *n* = 18	–	1.1% *n* = 324
no snus use	*(c)*	36.3% *n* = 2517	3.2% *n* = 120	–	6.0% *n* = 53	–	9.5% *n* = 2690
Occasional smoking (combined with)							
daily snus use	*(d)*	–	8.4% *n* = 315	10.7% *n* = 443	10.3% *n* = 90	–	3.0% *n* = 848
occasional snus use	*(e)*	0.5% *n* = 31	0.6% *n* = 22	0.7% *n* = 29	0.8% *n* = 7	0.7% *n* = 83	0.6% *n* = 172
no snus use	*(f)*	4.1% *n* = 283	1.6% *n* = 59	2.1% *n* = 85	2.5% *n* = 22	3.7% *n* = 468	3.2% *n* = 917
Quit daily smoking, now occasional smoking (sum of d +e + f)		4.6% *n* = 314	10.6% *n* = 396	N/A	13.6% *n* = 119	N/A	2.9% *n* = 829
No smoking (combined with)							
daily snus use	*(g)*	–	43.8% *n* = 1636	58.4% *n* = 2421	37.3% *n* = 327	–	15.5% *n* = 4384
occasional snus use	*(h)*	1.0% *n* = 71	1.0% *n* = 37	3.5% *n* = 145	0.9% *n* = 8	1.7% *n* = 216	1.7% *n* = 477
no snus use *(tobacco free)*	*(i)*	54.3% *n* = 3768	31.5% *n* = 1178	24.6% *n* = 1021	24.3% *n* = 213	93.9% *n* = 11,834	63.7% *n* = 18,014
Quit daily smoking, now completely smoke free (sum of g + h + i)		55.3% *n* = 3839	76.3% *n* = 2851	N/A	62.5% *n* = 548	N/A	25.6% *n* = 7238
Total (a − i)		100%	100%	100%	100%	100%	100%
Women		*n* = 11,794	*n* = 961	*n* = 484	*n* = 43	*n* = 19,091	*n* = 32,373
Daily smoking (combined with)							
daily snus use	*(j)*	–	7.3% *n* = 70	–	7.0% *n* = 3	–	0.2% *n* = 73
occasional snus use	*(k)*	1.6% *n* = 183	1.8% *n* = 17	–	11.6% *n* = 5	–	0.6% *n* = 205
no snus use	*(l)*	38.2% *n* = 4511	4.4% *n* = 42	–	20.9% *n* = 9	–	14.1% *n* = 4562
Occasional smoking (combined with)							
daily snus use	*(m)*	–	11.2% *n* = 108	11.8% *n*=57	11.6% *n* = 5	–	0.5% *n* = 170
occasional snus use	*(n)*	0.3% *n* = 38	1.4% *n* =1 4	1.4% *n*=7	2.3% *n* = 1	0.3% *n* = 58	0.4% *n* = 118
no snus use	*(o)*	6.3% *n* = 748	2.2% *n* = 22	2.3% *n* = 11	2.3% *n* = 1	4.5% *n* = 863	5.1% *n* = 1645
Quit daily smoking, now occasional smoking (sum of m + n + o)		6.6% *n* = 786	14.8% *n* = 144	N/A	16.2% *n* = 7	N/A	2.9% *n* = 937
No smoking (combined with)							
daily snus use	*(p)*	–	41.3% *n* = 397	55.8% *n* = 270	27.9% *n* = 12	–	2.1% *n* = 679
occasional snus use	*(q)*	0.4% *n*=44	1.7% *n* = 16	4.5% *n* = 22	0.0% *n* = 0	0.6% *n* = 118	0.6% *n* = 200
no snus use *(tobacco free)*	*(r)*	53.2% *n* = 6270	28.6% *n* = 275	24.2% *n* = 117	16.3% *n* = 7	*94.6% n* = 18,052	*76.4% n* = 24,721
Quit daily smoking, now completely smokefree (sum of p + q + r)		53.6% *n* = 6314	71.6% *n* = 688	N/A	44.2% *n* = 19	N/A	21.7% *n* = 7021
Total (j − r)		100%	100%	100%	100%	100%	100%

Note: N/A inserted in cells where percentages for *Tobacco use at the time of the survey* by *Initiation profile* are not applicable. Dash (–) inserted in cells where data can only assume the value 0 (zero).

Overall, 40.8% (95% confidence interval (CI) 40.2–41.4) of the men (11,557 of 28,302) initiated daily smoking. There were 5021 (4144 + 877) primary daily snus users, and 44.5% (12,601) never daily tobacco users. This means there were 23,281 (28,302–5021) non-primary snus users; i.e., primary smokers and never tobacco users. Among the 5021 primary snus users there were 877 men, i.e., 17.6% (95% CI 16.4–18.6), who initiated daily smoking. Among the 23,281 non-primary snus users there were 10,680 (6943 + 3737) men, i.e., 45.9% (95% CI 45.3–46.5), who initiated daily smoking, a markedly higher figure.

Overall, 39.5% (95% CI 39.0–40.0) of the women (12,798 of 32,373) initiated daily smoking. Correspondingly, among the 527 (484 + 43) women with primary daily snus use, there were 43, i.e., 8.2% (95% CI 5.8–10.5), who initiated daily smoking. Among the 31,846 (32,373 − 527) women without primary daily snus use, there were 12,755 (11,794 + 961), i.e., 40.2% (95% CI 39.7–40.7), who initiated daily smoking—over four times the level in primary daily snus users.

Looked at another way, among the total of 11,557 men who ever initiated daily smoking there were just 877, i.e., 7.6% (95% CI 7.1–9.1) who proceeded to smoking from daily snus use (i.e., were primary snus users). The corresponding proportion among women was less than 0.1% (43 of 12,798).

Figure 1 shows that **primary** initiation of daily snus use has been increasing over time. Table 2 shows that the propensity for **secondary** initiation of daily snus use has also been increasing among men. This is occurring in a context of a massive decline in primary uptake of smoking and a small decline in secondary uptake. Members of later-born cohorts have lower age at the time of the survey and have therefore had a shorter time available for quitting smoking as reflected by the downward figures for quit ratios. However, there is an upward trend in the difference in quit ratios between primary smokers with and without uptake of secondary snus use. That is, use of snus in established smokers is associated with increased quitting in the latter cohorts wherein snus use is more prevalent. This observation lends further support to the hypothesis that snus use facilitates cessation, as opposed to hamper it. The first column of the table shows that the move away from primary uptake of smoking occurred in the cohort born in the 1960s; i.e., those who started to use tobacco from the mid-1970s to the end of the 1980s. It is notable that even in the context of this massive shift in initial use patterns, in all cohorts the proportion of primary smoking uptake was always greater among non-primary snus users than among primary ones.

Table 2. Occurrence and effects of secondary snus use in different birth cohorts of men in Sweden.

Born in	Proportion of uptake of daily nicotine use that is primary smoking	Proportion of non-primary snus users becoming smokers	Proportion of primary snus users becoming smokers	Proportion of primary smokers who take up secondary daily snus use	Quit ratios (quitting smoking completely)	
					Primary smokers without daily snus use	Primary smokers with daily snus use
1940s	87.3%	60.4%	19.6%	34%	0.60	0.83
1950s	73.4%	53.8%	22.8%	40%	0.48	0.77
1960s	46.8%	36.6%	18.6%	41%	0.40	0.72
1970s	42.5%	28.7%	13.5%	45%	0.31	0.66
1980s	40.1%	21.8%	14.3%	46%	0.19	0.47

3.3. Quitting Smoking According to Uptake of Daily Snus Use

Table 1 also presents data regarding quitting smoking and tobacco use at the time of the survey. In the total population (all initiation profiles), the proportion of daily smokers among males at the time of the survey (rows a + b + c) was 12.3% (95% CI 11.9–12.7) and the proportion of daily snus users (rows a + d + g) was 20.2% (95% CI 19.7–20.7). Corresponding values for females were 14.9% (95% CI 14.5–15.3) and 2.8% (95% CI 2.6–3.0). These data represent means over the data collection period 2003–2011.

Among the 10,680 male primary daily smokers, 34.9% (95% CI 34.0–35.8) had later taken up secondary daily snus use. Among women, the corresponding proportion was 7.5% (95% CI 7.0–8.0).

Those who had taken up secondary snus use constituted 42.7% (95% CI 41.7–43.7) of all "ever daily snus users" in men and 64.6% (95% CI 62.2–67.0) in women. Table 1 also shows the proportion of ever daily smokers who had quit smoking in each of those different subgroups.

Among men with secondary daily snus use, 86.9% (95% CI 85.8–88.0) had ceased smoking daily (rows d–i) either quitting smoking completely (rows g–i) or reducing to occasional smoking (rows d–f). The corresponding proportion among women was 86.4% (95% CI 84.2–88.6). The proportion who had quit smoking completely was 76.3% (95% CI 74.9–77.7) among men and 71.6% (95% CI 68.7–74.5) among women. The corresponding proportions of secondary snus users who had quit all tobacco use (snus and smoking) were 31.5% (95% CI 30.0–33.0) among men and a similar 28.6% (95% CI 25.7–31.5) among women.

Among men without secondary daily snus use, 59.9% (95% CI 58.7–61.1) had ceased smoking daily. The corresponding proportion among women was 60.2% (95% CI 59.3–61.1). The proportion who had quit smoking completely was 55.3% (95% CI 54.1–56.5) among men and 53.6% (95% CI 52.7–54.5) among women.

Overall, secondary snus use is associated with success in smoking cessation. As shown in Table 2, this is true in all birth cohorts, especially with the larger proportion of secondary snus users.

Levels of cessation of smoking among primary snus users with uptake of smoking were intermediate (76.1% for men and 60.4% for women). Turning now to dual use, among men with secondary daily snus use, 18.9% (95% CI 17.6–20.2) had some kind of current use of both smoking and snus use (rows a + b + d + e). The corresponding proportion among women (rows j + k + m + n) was 21.7% (95% CI 19.1–24.3). More than half of these dual users had reduced from daily to occasional use of one or both products. In the total population, the proportion with daily use of both products was 1.68% (95% CI 1.53–1.83) among men and 0.23% (95% CI 0.18–0.21) among women.

Table 3 presents an overview of smoking cessation among daily smokers with different experience of daily snus use, this time reported in terms of quit ratios rather than percentages. Quit ratios are shown separately for "never" vs. daily snus users.

Table 3. Quit ratios for smoking—by gender and history of daily snus use. (Proportion of "Ever daily smokers" in different subgroups who have quit smoking completely at the time of the survey.)

	Men		Women	
	QR	**95% CI**	**QR**	**95% CI**
Never daily snus users (Men: *n* = 6943, Women: *n* = 11,794)	0.55	(0.54–0.56)	0.54	(0.53–0.55)
Secondary snus users (Men: *n* = 3737, Women: *n* = 961)	0.76	(0.75–0.77)	0.72	(0.69–0.75)
Secondary smokers (Men: *n* = 877, Women: *n* = 43)	0.63	(0.60–0.66)	0.44	(0.29–0.59)
All of any daily snus users (Men: *n* = 4614, Women: *n* = 1004)	0.74	(0.73–0.75)	0.70	(0.67–0.73)
All ever daily smokers (Men: *n* = 11,557, Women: *n* = 12,798)	0.63	(0.62–0.64)	0.55	(0.54–0.56)

Note: QR = Quit ratio, CI = Confidence interval.

3.4. Self-Treatment Smoking Cessation: Different Cessation Aids and Their Effectiveness

Both among men and women, 93% of all ever daily smokers reported that they had made at least one attempt to quit smoking. Most of them indicated that they had not had any professional assistance. However, around 40% of these unassisted quit attempters, both men and women, reported self-treatment by use of some self-administered nicotine-delivery product as a cessation aid. These quit attempters have been grouped in categories according to the choice of aid at the most recent quit attempt. Figure 2 shows both the relative size of these aid-usage categories and the outcome of the quit attempts in each category.

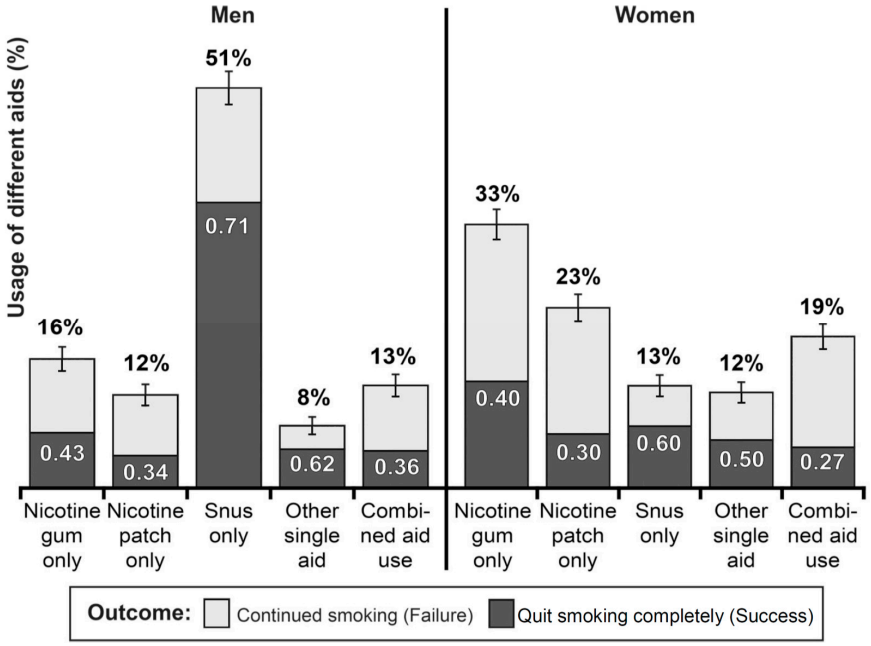

Figure 2. Self-treatment smoking cessation/quit attempts with use of different self-administered cessation aids and outcome of these quit attempts. The height of each bar illustrates the percentage of quit attempts that were made with the aid(s) in question, indicated numerically at the top of each bar by percentages adding up to 100% for each set. The segments of each bar represent outcome with the aid in question—failure (light-grey) or success (dark-grey). The numerical data in the dark-grey segments indicate the proportion of successful quit attempts for each cessation aid.

Among men, snus is the most commonly used self-treatment product, but among women, nicotine gum or patch is more common. The outcome of quit attempts with different aids shows that use of snus as cessation aid yields higher success rates than any of the other alternatives—for both men and women.

The combination of high usage and high successfulness means that, among men, snus has been the most effective product for self-treatment smoking cessation. In Figure 2, the size of each dark-grey segment corresponds to the quantity of successful quit attempts in the category in question. Using the numerical values for usage and success rate in each category, it can be calculated that among men "Snus only" was used in 64% of the successful quit attempts, while nicotine gum was used in 12% and the patch in 7%.

4. Discussion

The findings of this study are overwhelmingly supportive of snus playing both a role in protecting against the uptake of daily smoking and of facilitating smoking cessation, thus becoming an important contributor to improved public health. Both in men and women, quit ratios are significantly higher among smokers with than without experience of daily snus use, and this was most pronounced in secondary snus users. In each subgroup of snus use, there is no significant difference in quit ratio between men and women, while the much lower prevalence of snus use in women produces a gender difference among all ever daily smokers (Table 3).

4.1. Role of Snus in Initiation of Tobacco Use

The data presented in Figure 1 show that during the last 50 years in Sweden there has been a gradual increase of primary initiation of snus use accompanied by decreasing initiation of primary smoking and increasing proportions without initiation of any kind of daily tobacco use. There have been concerns that an increase of snus initiation would lead to increasing total initiation of tobacco use.

However, the data presented in Figure 1 show that this has not happened. Indeed, the proportion of primary daily snus users who have progressed to any daily smoking has also declined marginally over this period (Table 2).

The "gateway" hypothesis is more definitively refuted by the findings reported in Section 3.2 that, both among boys and girls, the proportion of those that ever started daily smoking was significantly lower among primary snus users (17.6% among boys, 8.2% among girls) than among those without previous snus use (45.9% among boys, 40.2% among girls). Furthermore, this effect occurs when analyzing by cohort, demonstrating it is not a factor of the declining tobacco market. These findings are remarkable, and they suggest even stronger preventive effects of snus than we found as the risk factors for primary uptake of snus and smoking likely overlap. These findings based on retrospectively established individual trajectories are also consistent with findings from other studies [26–32]. The EU Scientific Committee on Emerging and Newly Identified Health Risks [14] summarized the evidence by concluding that "*The Swedish data, with its prospective and long-term follow-up do not lend much support to the theory that smokeless tobacco (i.e., Swedish snus) is a gateway to future smoking.*" We would go further and conclude that the above findings and other factors completely discount gateway as a credible hypothesis, at least for snus use in Sweden. If any gateway exists, it is dwarfed by other factors which are net protective. The evidence strongly points towards snus playing a positive preventative role. We can think of no alternative explanation for the patterns observed here and in the bulk of the existing literature.

4.2. Role of Snus Use in Cessation of Smoking

Secondary initiation of daily snus use occurred in around one-third of male primary smokers and represented almost half of all snus initiation. Among women, the secondary snus initiators were fewer than among men, but they constituted a majority of all female snus initiators.

Both male and female secondary snus users had substantially higher rates of quitting smoking than smokers without a history of snus use (Table 1). This was true both for quitting daily smoking by reducing to occasional and for quitting smoking completely. These findings demonstrate that smokers' uptake of snus use favors smoking cessation; at least some of this uptake is motivated by an interest in quitting smoking.

Almost one-third of secondary snus users eventually quit all snus use and became entirely tobacco-free. This finding refutes the common assumption that uptake of snus use would entail lifelong perpetuation of nicotine dependence, based on the belief that snus use is as addictive as smoking. However, the high quit rates from snus are consistent with both clinical and pharmacokinetic studies indicating that snus has a lower dependence potential than cigarettes [33].

Further, the likelihood of eventual cessation of smoking was also greater among primary snus users with secondary smoking than only smokers. This may be in part due to the dual use as well as to snus being reengaged with assisting in quitting smoking.

Our findings refute the concerns that have been raised that dual use would hamper motivation to quit smoking, again consistent with other studies [34,35].

There has been a widespread concern that uptake of secondary snus use among daily smokers would usually result in permanent dual use and increase the risk of tobacco-related morbidity and mortality above the risk of single product use [17]. However, we found that more than eight out of ten secondary snus users had quit daily smoking and that almost one-third of them had become completely free of daily tobacco use. Consequently, there are strong reasons to assume that "dual use" is usually a transient rather than permanent state or an endpoint. It could then be seen as part of a multistep behavioral change where primary daily smokers use secondary uptake of snus as a stepping-stone towards changing/quitting their tobacco use. At least some of those who were actual dual users at the time of the survey should therefore not be regarded as permanent dual users—many may well at that time have been in a transient state on their way to cessation. Unfortunately, we do not have data on duration of use or of ambitions to change to sole use of one product.

To get some sense of how the quit ratios found here compare with other countries, we have sourced data from a Eurobarometer report [21]. Sweden exhibits a higher overall quit ratio than any

other EU country (0.76), followed by the Netherlands and Denmark (both 0.57) then Finland (0.56). The quit ratio for the EU as a whole is 0.44. NB: The Eurobarometer data are not directly comparable with those in our study, since they include both former occasional and former daily smokers in the calculation of quit ratios.

The importance of snus for smoking cessation is reinforced by the findings of outcomes of "self-treatment quit attempts," i.e., made without professional assistance in terms of medical and/or psychological treatment/counselling (this constitutes most such attempts) [31]. Among men, snus was both the most used, while for women it was only a minor method. In both genders, snus was the cessation aid that yielded the highest success rates compared to NRT-products or any other option, and it did so by a substantial margin. We do not know whether this higher success rate is due to higher success on any individual attempt or to making more attempts using snus, but from a public health point of view, this is not critical. The net benefit of using snus as a cessation aid is clear.

The high proportion of quit attempters using snus combined with their high successfulness has resulted in a majority, almost two-thirds, of male aid users who have succeeded in quitting smoking by using snus. This is more than double that of nicotine gum and nicotine patch together. The high effectiveness of snus as smoking cessation aid, appears to be an important contributory factor behind the high quit ratios in Sweden, particularly among men, and it implies a potential for snus to facilitate real large-scale smoking cessation, provided that both the product itself and objective information about its properties is freely available [36]. Again, these findings are consistent with other studies [22,34] and the key conclusions in authoritative reviews [37,38].

4.3. Implications for Other Harm-Reduced Products

Finally, we comment on the plausibility of generalizing results from this study to other harm-reduced products, particularly vaping. We can see no good reasons why a similar scenario to that which we have found for snus use should not develop with vaping, as it also protects against smoking and facilitates cessation. Substitute use of either represents a minor sacrifice in enjoyment for a large reduction in risks to health, a sacrifice many have not been able or willing to make when the alternative is abstinence (a large loss of enjoyment). However, it is important to assess possible impacts of differences between the two products. On the one hand, vaping is behaviorally closer to smoking, and the extraordinary expansion of use, almost entirely among smokers, strongly suggests it is a more easily accepted alternative to smoking than snus in many countries, although perhaps not in Scandinavia or in South Asia and other places where smokeless tobacco use is widespread despite the non-harm-reducing nature of smokeless tobaccos in South Asia. Second, the health effects of snus use are now established [6], while we only have theoretical analysis to estimate the impact of vaping; therefore, less confidence can be used in promoting it as relatively safe. That said, snus use has developed without actively promoting its reduced harmfulness, so this may not make much difference. We do not know whether vaping will prove to be more or less addictive than snus use, so we cannot be sure about relative likelihood of abstinence versus long-term nicotine use. We also do not know what the impact will be of vaping non-nicotine aerosols, an area where there is no direct parallel. It is likely to increase the normalization of vaping, but whether it does this in a way that encourages greater use of nicotine or not is unclear.

On the down side, it is likely over time that there will be some increase in total nicotine use, as there has been for snus. If vaping turns out to be more attractive than snus use, as seems likely, total nicotine use may be somewhat greater. In our opinion, this is a small price to pay if vaping is at least as effective as a means of both preventing and facilitating transitions away from smoking.

5. Limitations

This study has focused on transitions related to daily use, rather than occasional use as has often been done in other studies. We believe this is a strength, as it is prolonged daily use that is the major health risk factor, and because it avoids relying on inferences whose foundations are uncertain because of the heterogeneity that is inherent in the term "occasional use." Further, from a health standpoint,

occasional use is only of real importance when it can be used as a predictor of subsequent daily use. We believe the focus on daily smoking is particularly important for understanding dual use. The term "dual use" has often been used to denote any combination of smoking and snus use, daily or non-daily, and this has sometimes resulted in categories that are too heterogeneous to allow distinct interpretation of the observed data. In the current study, we have therefore focused on one clearly defined and homogeneous category of dual use, namely daily use of both kinds. As our data shows, this is relatively rare, though we do not know how stable it is. However, given that most secondary snus use leads to cessation of smoking, at least some appears to be transitory. It would be instructive to gain a better understanding of trajectories of dual use.

We also acknowledge that the reports on which form of tobacco came first are based on self-report, in many cases decades after starting, and that there is likely some error. However, we can think of no systematic source of error, or any explanation of how error in memory could have influenced the extremely strong associations we have observed.

We also acknowledge that this study was restricted to one country. It does not show that gateway effects or inhibition of quitting cannot happen anywhere. However, if it were to occur, it strongly suggests that it would have social determinants and thus should be preventable through public policy means. That said, we would be surprised if the findings were not directly generalizable.

6. Conclusions

The findings of this study indicate that the widespread use of snus has had a major influence on the development of smoking habits in Sweden. It appears that snus has contributed to decreasing initiation of smoking rather than serving as a gateway to smoking. Smokers who have taken up snus use have quit smoking to a significantly greater extent than smokers without snus use, and a substantial proportion has eventually quit snus use as well and become tobacco-free. These effects have been consistent across five decades and very different frequencies of snus use. Prolonged daily dual use is uncommon and, in general, dual use appears to be a transient state that does not hamper motivation to quit smoking but serves as a stepping-stone to cessation. Both among men and women, quit ratios are significantly higher for those with than for those without a history of snus use. Snus is the most commonly used self-treatment aid for smoking cessation. Quit attempters using snus as a cessation aid have a significantly higher success rate than those using other aids. All these effects yield favorable consequences for public health, suggesting that snus has been a major factor behind Sweden's record-low prevalence of smoking and its position as the country with Europe's lowest level of tobacco-related mortality among men based on analysis of data from a WHO report [39,40].

Acknowledgments: We dedicate this paper to the memory of our colleague, the late Tom Wikmans. Tom was instrumental in undertaking the groundwork for this study, identifying the potential of the YCYL study to address the research questions, extracting the data, performing most of the analyses and participating in the preparation of an initial draft before his untimely death. He is greatly missed.

Author Contributions: Lars Ramström and Tom Wikmans conceived and designed the study; all authors contributed to the data analysis, the interpretation of the results and the preparation of the manuscript.

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Article

What Is Accounting for the Rapid Decline in Cigarette Sales in Japan?

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Abstract: This study describes how trends in the sale of cigarettes in Japan between 2011 and 2019 correspond to the sales of heated tobacco products (HTPs) that were introduced into the Japanese market in late 2015. Data used for this study come from the Tobacco Institute of Japan and Philip Morris International. The findings show that the accelerated decline in cigarette only sales in Japan since 2016 corresponds to the introduction and growth in the sales of HTPs.

Keywords: cigarettes; marketing; policy; nicotine; prevention; epidemiology

1. Introduction

The substitution of non-combustion products has the potential to be a highly effective and non-coercive risk reduction strategy given the well-documented health risks of long-term smoking [1]. Heated tobacco products (HTPs) are devices that use heat processed tobacco rather than burn the tobacco directly in order to generate a nicotine aerosol for inhalation, which appears to have a lower risk profile compared to conventional tobacco cigarettes [2]. Japan has been a testing ground for HTPs [3–6]. IQOS (i.e., stands for "I Quit Ordinary Smoking"), marketed by Philip Morris International (PMI), was first introduced in 2014, followed in 2016 by the launches of Ploom TECH by Japan Tobacco International (JTI) and glo by British American Tobacco (BAT). According to market analyst reports, Japan has the most developed HTP market of all countries worldwide, accounting for 85% of HTP sales in 2018 [7].

This study describes how trends in the sale of cigarettes in Japan correspond to the sales of HTPs using data collected between 2011 and 2019.

2. Methods

The limited data for the study comes from two sources: the Tobacco Institute of Japan (TIOJ) (https://www.tioj.or.jp/data/pdf/190424_02.pdf), and Philip Morris International, and was available for 2011 through 2019. The data from TIOJ is in Japanese, but an English translation copy is available upon request from the authors. Table 1 provides the raw data used in this study. Sales data are available for individual years, with sales measured in billion sticks. Trend analyses were performed in Joinpoint 4.7.0.0 to February 2019. Joinpoint regression models are used to describe continuous changes in trends using the grid-search method to fit the regression function with unknown joinpoints assuming constant variance and uncorrelated errors. More details about this free statistical tool can be found at https://surveillance.cancer.gov/joinpoint/ and in the paper by Kim et al. [8]. In brief, this is a software that fits the simplest joinpoint model to a set of data points. The program tests the statistical significance of no joinpoints (straight line) compared to one or more joinpoints. It displays a graph that includes the points, the fitted regression line, and the significant joinpoints (Supplementary Figure S1).

Table 1. Sales of tobacco products in Japan, 2011–2019 [1].

Calendar Year	Cigarettes		IQOS (I Quit Ordinary Cigarettes)		Other HTP		Total HTPs		Grand Total
	N	%	N	%	N	%	N	%	
2011	195.3	100.0							195.3
2012	196.6	100.0							196.6
2013	192.6	100.0							192.6
2014	186.2	100.0							186.2
2015	182.3	100.0							182.3
2016	173.8	97.1	5.1	2.9			5.1	2.9	179.0
2017	151.2	88.2	18.5	10.8	1.8	1.0	20.3	11.8	171.5
2018	132.7	79.3	25.9	15.5	8.7	5.2	34.6	20.7	167.3
2019	120.9	76.5	26.9	17.0	10.2	6.5	37.1	23.5	158.1

[1] The data sources for the information included in Table 1 come from several sources. Conventional cigarette volume comes from the Tobacco Institute of Japan (TIOJ): converted to show the volume of sales in a calendar year in billion sticks. Annual cigarette volume prior to 2016 was obtained from PMI's earnings reports (https://www.pmi.com/investor-relations/reports-filings), which itself is based on the TIOJ data. IQOS sales data comes from Philip Morris International's (PMI's) quarterly earnings reports and were calculated from the reported market share of heatsticks. The other heated tobacco product (HTP) volume is computed as the total market volume less heatstick volume less cigarette volume. We recognize that other HTPs such as Ploom TECH consumables pack consist of five tobacco capsules and one liquid cartridge. Japan Tobacco asserts that one pack of Ploom TECH consumables is equivalent to one pack of 20 combustible cigarette sticks. We used this conversion in the data presented in the table. The total HTP figures shown in the table are determined by adding heatstick volume with other HTP volume.

3. Results

Table 1 shows that between 2011 and 2019, overall cigarette sales declined by 38%, and total tobacco sales (i.e., combining cigarettes and HTPs) declined by 19%. Figure 1 plots the available data from Table 1 to display cigarettes sales, HTP sales, and combined cigarette and HTP sales. As illustrated, domestic cigarette sales in Japan appear to have declined at an accelerated pace since 2016 following the introduction of HTPs into the Japanese national marketplace. Using joinpoint analyses, overall cigarette and HTP sales had an annual percent change (APC) of −4.77 ($p < 0.0001$), between 2011 and 2019. Between 2016 to 2019, following the national marketing of HTPs (IQOS in 2016 and other HTPs in 2017), the APC was −6.69 ($p = 0.0092$). However, separating out cigarette sales from HTP sales reveals a different pattern. Between 2011 and 2015, the APC for cigarette sales was −3.10 ($p = 0.1066$); between 2016 and 2019, the APC was −16.38 ($p = 0.0004$), a difference of 13.28 ($p = 0.0033$) representing a five-fold increase compared to the pre-HTP period.

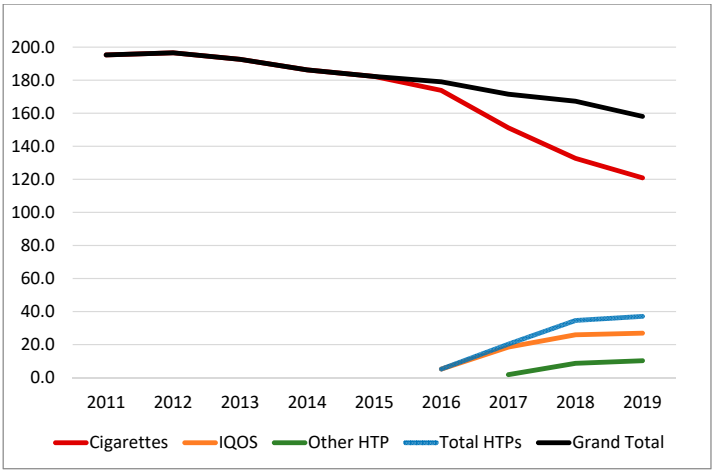

Figure 1. Sales of cigarettes, IQOS, and other HTPs (billion sticks).

4. Discussion

Between 2011 and 2015, cigarette sales in Japan were declining at a slow but steady pace. However, the pace of decline in cigarette sales accelerated beginning in 2016, corresponding to the introduction of HTPs into the marketplace. This finding is consistent with the conclusion of Stoklosa and colleagues [3] who examined data on sales of tobacco products from participating supermarkets and convenience stores in different regions of Japan between 2014 and 2018. The accelerated decline in cigarette sales in Japan after 2016 is rather remarkable since it appears to have happened independent of efforts made by public health groups that have largely opposed the marketing of HTPs [9]. Also, Japan does not have strong smoking control measures in place and prohibits the marketing of electronic nicotine delivery systems (ENDS), which have been associated with declining cigarette sales in the United States and England [10–12].

This study does not address the extent to which individual cigarette smokers are substituting HTPs for conventional cigarettes. A recent study suggests that most HTP users in Japan are also concurrently smoking cigarettes [13]. That said, these data do suggest that in Japan at least, the decline in cigarette sales has been accelerated by the introduction of HTPs. It is hard to know if the findings in Japan can be replicated globally, but reported sales trends in other markets where HTPs have been introduced show a similar inverse association between cigarette and HTP sales [14]. Given the hype associated with HTPs, manufacturers need to do more to share their marketing data with public health officials and investors so that individual-level cigarette substitution and harm reduction from smoking can be accessed. Given the history of the cigarette industry, public health groups have a right to be skeptical of any industry product claims, however assuming all tobacco/nicotine products as equivalently harmful is also counterproductive to public health goals as it only serves to protect the most lethal nicotine product—cigarettes. The evolving marketplace of potentially lower-risk nicotine products of which HTPs are just one category, combined with regulatory authority over tobacco products, represents a new opportunity to dramatically transform the cigarette business in ways that were never imagined when the war on tobacco was raging decades ago. However, this requires embracing risk-proportionate regulatory and taxation policies and providing consumers with accurate public messaging on product relative risks [15]. One can only imagine what might be accomplished if market forces were aligned with public health goals to reduce premature deaths caused by smoking.

5. Conclusions

The accelerated decline in cigarette only sales in Japan since 2016 corresponds to the introduction and growth in the sales of HTPs.

Supplementary Materials: The following are available online at http://www.mdpi.com/1660-4601/17/10/3570/s1, Figure S1: Joinplot analysis of tobacco products (billion sticks).

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Royal College of Physicians

Nicotine without smoke
Tobacco harm reduction

A report by the Tobacco Advisory Group of the Royal College of Physicians

April 2016

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The Royal College of Physicians

The Royal College of Physicians (RCP) plays a leading role in the delivery of high-quality patient care by setting standards of medical practice and promoting clinical excellence. The RCP provides physicians in over 30 medical specialties with education, training and support throughout their careers. As an independent charity representing 32,000 fellows and members worldwide, the RCP advises and works with government, patients, allied healthcare professionals and the public to improve health and healthcare.

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Declaration of contributors' interests

Paul Aveyard is the chief investigator of a trial of nicotine preloading in which NRT is donated by GlaxoSmithKline to the NHS.

Peter Hajek has received research funding from and provided consultancy to Pfizer, Johnson & Johnson, Novartis and GlaxoSmithKline.

Hayden McRobbie has received honoraria for speaking at smoking cessation educational and advisory group meetings, which have been organised by Johnson & Johnson and Pfizer; he has received funding for investigator-led research from Pfizer and was an investigator on a 2008 study of e-cigarettes sponsored by manufacturer Ruyan Group and conducted independently at the University of Auckland.

Marcus Munafò has received research funding from AstraZeneca, Pfizer, Rusan Pharma and Cambridge Cognition, and NRT products for research from GlaxoSmithKline, Pfizer and Rusan Pharma.

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Robert West undertakes research and consultancy for Pfizer, GlaxoSmithKline and Johnson & Johnson.

Amanda Amos, Deborah Arnott, Richard Ashcroft, Linda Bauld, Ilze Bogdanovica, John Britton, Meghan Chenoweth, Jeff Collin, Martin Dockrell, Nick Hopkinson, Tessa Langley, Sarah Lewis, Ann McNeill and Magdalena Opazo Breton have no interests to declare.

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Foreword

The Royal College of Physicians (RCP) exists to improve the care of individual patients, and the health of the population. As tobacco smoking generates more illness and premature death than any other avoidable cause, preventing smoking has been a high priority for the RCP since the health harm of smoking was first recognised over 60 years ago. In the more than 50 years since our first report, *Smoking and health,* in 1962, we have argued consistently for more and better policies and services to prevent people from taking up smoking, and help existing smokers to quit.

Smoking is far less prevalent today than it was in 1962, but remains common, particularly among more disadvantaged individuals in our society. There are still almost nine million smokers in the UK, half of whom will die prematurely unless they quit. The evidence in this report demonstrates sustained progress over recent decades in preventing young people from becoming smokers, but also shows that much more must be done to increase the number of existing smokers who succeed in stopping smoking.

In 2007 the RCP published a report, *Harm reduction in nicotine addiction,* which argued for the application of harm-reduction strategies to tobacco dependence. We suggested that making effective, affordable, socially acceptable, low-hazard nicotine products available to smokers as a market alternative to tobacco could generate significant health gains, by allowing smokers to stop smoking tobacco, without having to stop using the nicotine to which they are addicted. Our report was published just as the prototypes of a new consumer alternative to tobacco, the electronic cigarette (e-cigarette), were first appearing on the UK market.

The rapid growth in use of e-cigarettes by smokers since 2007 demonstrates that many smokers want reduced-harm products, and it is also clear that many smokers have succeeded in quitting simply by substituting electronic for tobacco cigarettes. However, e-cigarettes have also proved to be highly controversial, attracting much criticism as well as support within medicine and public health, and indeed in wider society.

This report therefore aims to provide a fresh update on the use of harm reduction in tobacco smoking, in relation to all non-tobacco nicotine products but particularly e-cigarettes. It concludes that, for all the potential risks involved, harm reduction has huge potential to prevent death and disability from tobacco use, and to hasten our progress to a tobacco-free society. With careful management and proportionate regulation, harm reduction provides an opportunity to improve the lives of millions of people. It is an opportunity that, with care, we should take.

Professor Jane Dacre
President, Royal College of Physicians

Abbreviations

ASA	Advertising Standards Authority
ASH	Action on Smoking and Health
BAT	British American Tobacco
BSI	British Standards Institute
CO	carbon monoxide
COP	FCTC Conference of the Parties
COPD	chronic obstructive pulmonary disease
CTADS	Canadian Tobacco, Alcohol and Drugs Survey
CYP2A6	cytochrome P450 2A6 enzyme
e-cigarette	electronic cigarette
ECITA	Electronic Cigarette Industry Trade Association
EFTA	European Free Trade Association
ENDS	electronic nicotine delivery system
EU	European Union
FCA	Framework Convention Alliance
FCTC	Framework Convention on Tobacco Control
FDA	US Food and Drug Administration
FMO3	flavin-containing monooxygenase 3
GABA	γ-aminobutyric acid
GRPs	gross rating points
HAZ	Health Action Zones
HMRC	HM Revenue and Customs
IGTC	Institute for Global Tobacco Control
ITC	International Tobacco Control policy evaluation project
MAO	monoamine oxidase
MCA	Medicines Control Agency
MHRA	UK Medicines and Healthcare products Regulatory Agency
MMC	mass media campaign
MPOWER	Monitor, Protect, Offer, Warn, Enforce, Raise
nAChR	nicotinic acetylcholine receptor
NICE	National Institute for Health and Care Excellence
NMR	nicotine metabolite ratio
NNN	*N*′-nitrosonornicotine

NNS	nicotine nasal spray
NO	nitric oxide
NRT	nicotine replacement therapy
ONS	Office for National Statistics
PET	positron emission tomography
PHE	Public Health England
PMI	Philip Morris International
RCP	Royal College of Physicians
SALSUS	Schools Adolescent and Lifestyle and Substance Use Survey
SES	socio-economic status
SHARE	Smoking Harm Reduction Education Programme
SHS	second-hand smoke
SPECT	single-photon emission computed tomography
SSS	Stop Smoking Service
STS	Smoking Toolkit Study
TAPA	UK Tobacco Advertising and Promotion Act 2002
TPD	EU Tobacco Products Directive
TSNAs	tobacco-specific nitrosamines
UGT	uridine diphosphate (UDP) glucuronosyltransferase
WHO	World Health Organization

1 Introduction

Harm reduction is a strategy used in medicine and social policy to minimise harm to individuals and/or wider society from hazardous behaviours or practices that cannot be completely avoided or prevented. Examples include providing clean needles and syringes to intravenous drug users to reduce the risk of infection, promoting condom use by sex workers, drink-driving laws, protective clothing in sport, and motor vehicle safety measures and emission controls. Sometimes by appearing to condone or perpetuate hazardous behaviours that could in theory be prevented, harm-reduction approaches can be controversial, particularly in medicine. To their proponents, however, they represent pragmatic solutions to a range of otherwise intractable causes of avoidable death and disability.

Tobacco smoking is addictive and lethal. Half of all lifelong smokers in the UK die as a direct consequence of their smoking,[1] and smokers lose an average of about 3 months of life expectancy for every year smoked after the age of 35; in sustained smokers this amounts to a total loss of around 10 years of life.[1,2] Tobacco smoking harms others, through passive exposure of both adults and children to exhaled and sidestream smoke,[3,4] while smoking in pregnancy impairs fetal growth and development, in some cases to the point of fetal death.[5] Smoking causes fires and litter, reduces economic productivity and social engagement, and exacerbates poverty.[6] Together these effects make smoking responsible for more loss of quality and quantity of life in the UK than any other avoidable cause.[7] As smoking is strongly related to social disadvantage, the burden of ill health caused by smoking falls particularly on the most disadvantaged individuals, making smoking the largest cause of social inequalities in health in the UK.[8]

Smoking is completely preventable, yet, more than half a century after the health harm of smoking first became widely known, almost 1 billion people worldwide still smoke.[9] They do so primarily because they are addicted to the nicotine in tobacco smoke[10] and, as this addiction can be extremely difficult to overcome, many will continue to smoke until they die.[10] Conventional tobacco control policies, embodied in the World Health Organization's (WHO's) Framework Convention on Tobacco Control (FCTC)[11] and MPOWER policy framework

(*M*onitor tobacco use and prevention policies, *P*rotect people from tobacco smoke, *O*ffer help to quit tobacco use, *W*arn about the dangers of tobacco, *E*nforce bans on tobacco advertising, promotion and sponsorship, and *R*aise taxes on tobacco)[12] aim to prevent the uptake of smoking and to help as many existing smokers to quit as possible. These approaches have contributed to a 50% reduction in UK smoking prevalence in the past 35 years,[13] as well as increasing global success in smoking prevention.[9,14] However, although smoking prevalence in the UK is now down to 18%,[15] this figure translates into around 8.7 million current smokers[16,17] sustaining significant harm from smoking. Harm reduction provides an additional strategy to protect this group, and their counterparts in other countries, from the burden of disability and early death that will continue to accumulate until and unless they stop smoking.

In 2007 the RCP published a report promoting the principle of harm reduction in nicotine addiction,[18] arguing that, as most of the harm caused by smoking arises not from nicotine but from other components of tobacco smoke, the health and life expectancy of today's smokers could be radically improved by encouraging as many as possible to switch to a smoke-free source of nicotine. While recognising the primacy of complete cessation of all tobacco and nicotine use as the ultimate goal to prevent harm from smoking, the report argued that promoting widespread substitution of cigarettes and other tobacco combustion products would, for smokers who made the change, achieve much the same thing.[18] Harm reduction, as a complement to conventional tobacco control policies, could therefore offer a means to prevent millions of deaths among tobacco smokers in the UK alone.[18] This argument was accepted and integrated into national tobacco control strategies published by the then Labour and subsequent coalition governments in 2010 and 2011,[19,20] through the extension of the licence for nicotine replacement therapy (NRT) to include harm reduction by the Medicines and Healthcare products Regulatory Agency in 2010,[21] and in guidance issued by the National Institute for Health and Care Excellence in 2013.[22]

At the time of the 2007 report, the product categories available as potential smoking substitutes comprised smokeless tobacco, the least hazardous forms of which were then and still are illegal in the UK,[18] and conventional NRT, which, although effective as a smoking cessation therapy, has proved to have limited appeal to many smokers.[18] E-cigarettes, which appeared in the UK at around the time the 2007 report was published, have transformed this market, becoming the most popular choice of product for smokers hoping to quit or cut down on their smoking[23,24] (see Chapter 5). In the UK and many other countries, however, e-cigarettes have proved highly controversial, attracting both widespread concern and disapproval, and strong support, from individuals and organisations both within and outside medicine. Policies on e-cigarettes vary widely between countries with some, such as the UK, currently allowing their sale as consumer products whereas others, eg Australia, prohibit the product[25] (see Chapter 10).

Harm reduction, and in particular the role of e-cigarettes, has probably split global and, to some extent, national opinion on tobacco control more than any other issue. This report therefore aims to provide an update on harm reduction in the UK, particularly but not exclusively in relation to the role of e-cigarettes.

1.1 The harm of smoking

The harm that smoking causes to individuals and society is extensive and has been reviewed comprehensively in reports published by the RCP over the past 15 years,[3,4,10,26] by the US surgeon general[27–30] and by many other authorities. The main effects of smoking on health and wellbeing, particularly in the context of the UK population, are as follows.

1.1.1 Mortality

The most recent detailed analysis of mortality caused by smoking in the UK uses data from 2010, when tobacco smoking caused an estimated 122,000 deaths in adults, equivalent to more than one in six of all deaths, in the UK.[31] Although due to a wide range of diseases, 70% of these deaths were from three causes: lung cancer, chronic obstructive pulmonary disease (COPD) and vascular disease (Fig 1.1).

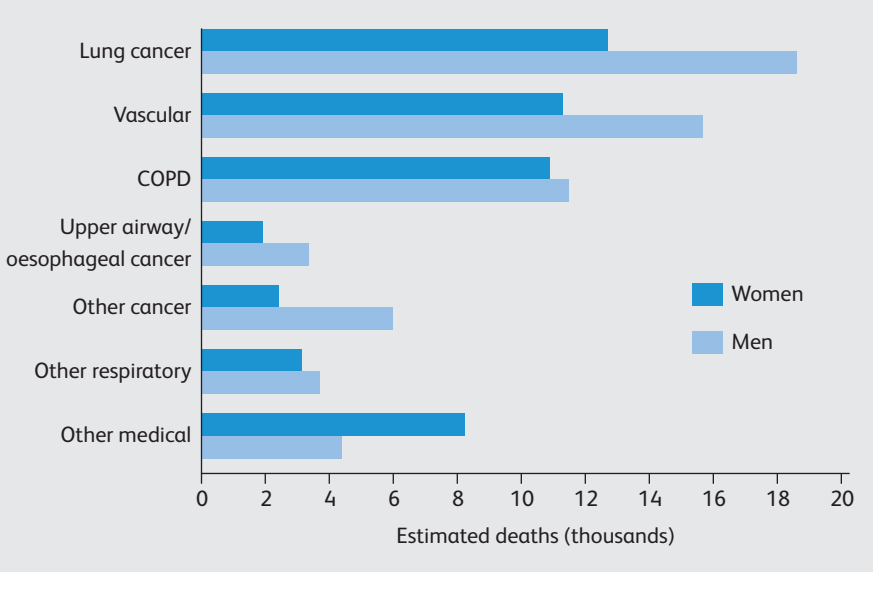

Fig 1.1 Deaths attributable to smoking by disease in men and women, UK, 2009.[31] (Data for figure from Peto *et al.*[31])

Deaths caused by passive smoking are more difficult to estimate with precision, but in 2003 over 10,000 adults in the UK were estimated to have died from lung cancer, cardiovascular disease or COPD caused by passive smoking.[32] The figure today is likely to be lower, as a result of declining smoking prevalence and legislation making UK public places and workplaces smoke free. Among children, around 40 cases of sudden infant death syndrome are caused by smoking in the UK each year,[3] whereas passive exposure of the fetus arising from maternal smoking during pregnancy causes over 5,000 fetal or perinatal deaths each year.[3]

1.1.2 Morbidity

Smoking during pregnancy accounts for around 2,000 premature births and 19,000 cases of low birth weight each year, and increases the risk of fetal anomalies.[3] Among children, passive smoking has been estimated to cause around 165,000 new cases of disease, predominantly middle-ear disease and respiratory infections in 2008,[3] generating over 300,000 primary care consultations and 9,500 hospital admissions in the UK each year.[3] In adults, combined morbidity and mortality from smoking accounted for the loss of around 2 million disability-adjusted life years in the UK in 2010.[7] In 2014 smoking caused over 450,000, or about 4% of all, admissions to hospitals in England.[16] Most of these admissions were for cancer, or respiratory or vascular disease.[16]

1.1.3 NHS and wider societal costs

Smoking costs the NHS more than £2 billion in direct costs, or more than 2% of the total NHS budget, every year.[6,13] Costs of inpatient and primary care caused by passive smoking in children in 2007 exceeded £20 million. The total cost of smoking to society, including healthcare, social care, lost productivity, litter and fires, was conservatively estimated in 2015 to be around £14 billion per year.[13]

1.1.4 Smoking and deprivation

Smoking prevalence is strongly and directly related to all measures of deprivation. Smoking prevalence among those in higher managerial and professional occupations in the UK is now close to 12%,[16] whereas among those in routine and manual occupations the figure is over 28%.[16] Among unemployed people, almost 40% smoke,[33] as do around 40% of people with longstanding mental health problems[26] and more than 70% of people who are homeless or imprisoned.[26]

1.1.5 Normalisation effects

Smoking harms the health of others through behavioural effects, independent of tobacco exposure. It was estimated that, in the UK in 2011, over 200,000 11- to 15-year-olds started smoking[34] and, although smoking rates have since fallen, it is still the case that, every day, hundreds of children become smokers. These new smokers are more likely to come from households that include a smoker[35] or to have been exposed to smoking behaviour in the media[36] or in their wider social environment.[36] These effects tend to perpetuate addiction to smoking among successive generations of families and social groups, and hence also the consequent inequality in quantity and quality of life in disadvantaged groups.

1.2 Principles of tobacco harm reduction

Tobacco smoke contains thousands of constituents that determine the flavour and other characteristics of the smoke; but, crucially, they also combine to deliver nicotine to the lung in an aerosol, with physical properties that allow rapid absorption into the pulmonary circulation. Although other components of tobacco smoke may enhance the addictiveness of tobacco smoke, the main driver of tobacco smoking is addiction to nicotine.[10,18] The mechanisms of nicotine addiction are complex, but it is evident that smokers experience an initial sensation of reward from exposure to nicotine; after sustained use and consequent desensitisation to nicotine's effects, smokers seek nicotine primarily to relieve the symptoms of nicotine withdrawal.[10,18] Regular nicotine use also confers rewards in some of the stimuli and behaviours associated with nicotine delivery, such as the sense of smoke in the throat, and the physical acts that are integral to smoking, such as unwrapping, sharing or handling cigarettes.

Nicotine is not, however, in itself, a highly hazardous drug (see Chapters 4 and 5). It increases heart rate and blood pressure, and has a range of local irritant effects, but is not a carcinogen.[37] Of the three main causes of mortality from smoking, lung cancer arises primarily from direct exposure of the lungs to carcinogens in tobacco smoke, COPD from the irritant and proinflammatory effects of smoke, and cardiovascular disease from the effects of smoke on vascular coagulation and blood vessel walls. None is caused primarily by nicotine. For practical purposes, as argued by Mike Russell in the 1970s, 'smokers smoke for nicotine but are killed by tar'.[38] Although the nature and extent of any long-term health hazard from inhaling nicotine remain uncertain, because there is no experience of such use other than from cigarettes, it is inherently unlikely that nicotine inhalation itself contributes significantly to the mortality or morbidity caused by smoking. The main culprit is smoke and, if nicotine could be delivered effectively and acceptably to smokers without smoke, most if not all of the harm of smoking could probably be avoided.

It is also clear that many smokers would prefer not to have to smoke to get nicotine, provided that they can access the drug in doses and formulations that they find satisfying and acceptable. The availability and use of an oral tobacco product known as *snus* in Sweden, documented in more detail in our 2007 report (and revisited in Chapter 7), demonstrates proof of the concept that a substantial proportion of smokers will, given the availability of a socially acceptable and affordable consumer alternative offering a lower hazard to health, switch from smoked tobacco to the alternative product.[18] Particularly among men, the availability of *snus* as a substitute for smoking has helped to reduce the prevalence of smoking in Sweden,[39] which is now by far the lowest in Europe.[40] The magnitude of the contribution made by the availability of *snus* over and above conventional tobacco control measures is difficult to quantify, but a recent study of the effect of withdrawal of *snus* from the market in Finland in 1995, when both Finland and Sweden joined the EU, but only Sweden was allowed to continue its use, estimates that over the following 10 years the availability of *snus* reduced smoking prevalence in Sweden by an additional 3.7 percentage points.[41] Trends in *snus* use in Norway are similar to, and perhaps stronger than, those in Sweden, and there the use of *snus* is strongly associated with quitting smoking.[42]

1.3 Role of harm reduction in tobacco control policy

In 1962, the RCP's *Smoking and health* report promoted a range of smoking prevention measures, including a list of policies that, under the heading 'Possible action by the government', probably represented the first published comprehensive tobacco control strategy.[43] The core components – preventing tobacco advertising, increasing prices, making public places smoke free, providing treatment for smokers, educating the public and restricting young people's access to cigarettes – remain at the centre of modern tobacco control strategy as promoted by the WHO[44] and the FCTC.[11]

These policies are effective and, when countries and states adopt them comprehensively, the prevalence of smoking falls,[45] slowly. Australia, Canada and the UK have implemented increasingly extensive ranges of tobacco control policies over recent decades and, in these countries, over the past 10 years or so, prevalence has fallen respectively by around 0.6, 0.75 and 0.7 percentage points per year.[23,46,47] Adult smoking prevalence is now below 20% in all of these countries, but, even if these rates of decline can be sustained, it will take more than two decades before rates start to approach zero. Meanwhile, substantial numbers of people in these countries continue to smoke: nearly 9 million in the UK, 4.6 million in Canada and 3 million in Australia remain exposed to the harm of smoking. Tobacco control policies may have a greater effect when introduced together for the first time in a high-prevalence setting: in Uruguay,

for example, a comprehensive package of tobacco control measures was introduced in 2005, when adult smoking prevalence was around 34%, and led to a reduction in smoking prevalence of around 1.1 percentage points per year for the next 6 years.[48] However, even if this rate of decline can be sustained, it will take three decades to eradicate smoking, during which most current smokers will continue to be harmed or killed by their addiction. It is therefore important to complement this approach with strategies to reduce or prevent harm in those who will otherwise continue to smoke.

To date, harm-reduction strategies have tended to focus on reducing emissions and absorption of toxins from conventional cigarettes, eg through the use of filters and attempts to limit tar yields, although the latter proved to be more of a marketing device for the tobacco industry than a genuine reduction in harm potential. More radical strategies, such as promoting alternative sources of nicotine as a sustained substitute for smoking, have until recently been pursued only in the context of therapies for individual smokers attempting to quit. The potential for more widespread nicotine product substitution at a population level, with the primary objective of changing the source of nicotine used by smokers rather than ending all nicotine use, has not to date been widely adopted as a public health policy. The evidence from Sweden suggests that the harm reduction could add a further 0.4 percentage points per year to the rate of decline in smoking prevalence,[41] and hence make a substantial contribution to public health.

1.4 Developments since the publication of the 2007 RCP report and the need for this update

When the RCP published its last report on harm reduction in 2007, options for alternative nicotine products for use in a population-level harm-reduction strategy were limited to smokeless tobacco, the supply of which in the UK is subject to severe constraints under the terms of legislation passed in 1992,[49] and medicinal NRT products, which many smokers find unsatisfactory as a long-term substitute for smoking.[18] However, the nicotine harm-reduction landscape has since been transformed by the emergence of e-cigarettes which, as documented later in this report, have demonstrated a popularity among smokers akin to that of *snus* in Sweden. The emergence of e-cigarettes has also provoked substantial controversy among those involved in tobacco control, wider public health policy and practice, and the general population, and a spectrum of regulatory responses in different countries that range from free market access to outright prohibition. This report has been produced to review developments relevant to tobacco harm reduction since the publication of the 2007 RCP report *Harm reduction in nicotine addiction*,[18] to look in particular at the effect that this new product category has had on smoking and nicotine use in the UK, and to make further

recommendations as to how the potential for this approach to prevent death and disability from tobacco use might be realised, within an appropriate and proportionate regulatory framework.

1.5 Summary

- Tobacco smoking is addictive, and causes an extensive range of harm to health and wellbeing in individuals and wider society.
- Tobacco smoking contributes more to social inequalities in health, and to overall death and disability, than any other avoidable cause.
- Smoking is preventable, and smoking prevalence falls progressively when countries implement a comprehensive range of tobacco control policies.
- The rate of decline is slow, however, with millions of smokers in the UK alone continuing to be exposed to the immediate and long-term hazards of smoking.
- Harm reduction aims to reduce or prevent harm in those smokers who do not respond to conventional tobacco control approaches by quitting smoking.
- Harm reduction works by providing smokers with the nicotine to which they are addicted without the tobacco smoke that is responsible for almost all of the harm caused by smoking.
- E-cigarettes are a new product class that has proved popular with smokers and offers a viable harm-reduction option.
- E-cigarettes have proved highly controversial and have provoked widely different regulatory responses in different countries.
- It is therefore important to look carefully at the role that these and other novel nicotine products might play in helping to prevent death and disability caused by smoking, and to consider how regulation should be applied proportionately to maximise this benefit.

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2 Smoking in Britain

2.1 Recent trends and current prevalence of smoking in the UK

Reliable national data on the prevalence of smoking among adults in Britain were collected from 1972 to 2011 in the General Household Survey,[1] and since that date in the Opinions and Lifestyle Survey[1] and the Integrated Household Survey.[2] Data from these sources demonstrate that, over the more than four decades for which survey data are available, smoking prevalence fell from 51% of men and 41% of women in 1972,[1] to 21% of men and 16% of women in 2014[2] (Fig 2.1). Applying age- and gender-specific smoking rates to the 2013 population estimates of the Office for National Statistics (ONS),[3] there are approximately 8.7 million adult smokers in the UK, of whom 4.8 million are men and 3.9 million women.

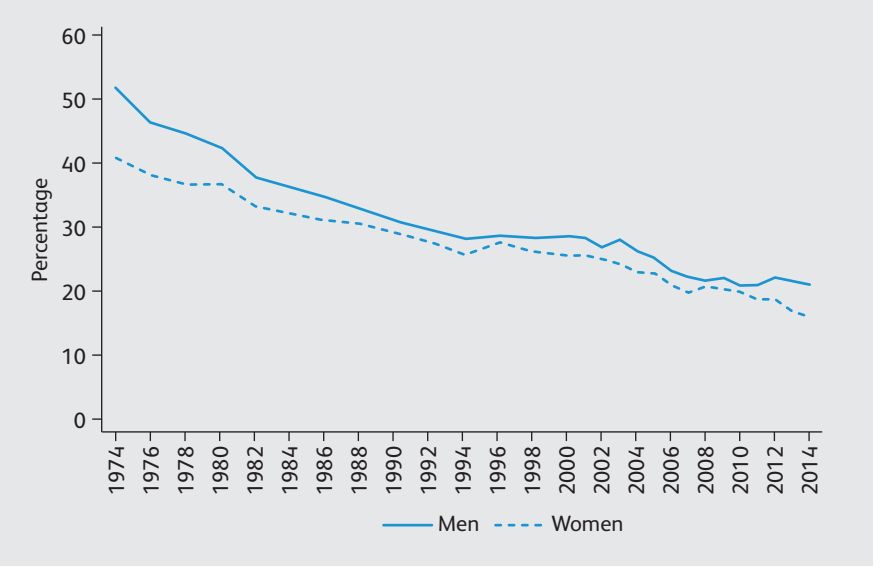

Fig 2.1 Smoking prevalence in men and women in Britain, 1972–2013[1] and 2014.[2] (Adapted with permission from the Office for National Statistics[1,2] under Open Government Licence.)

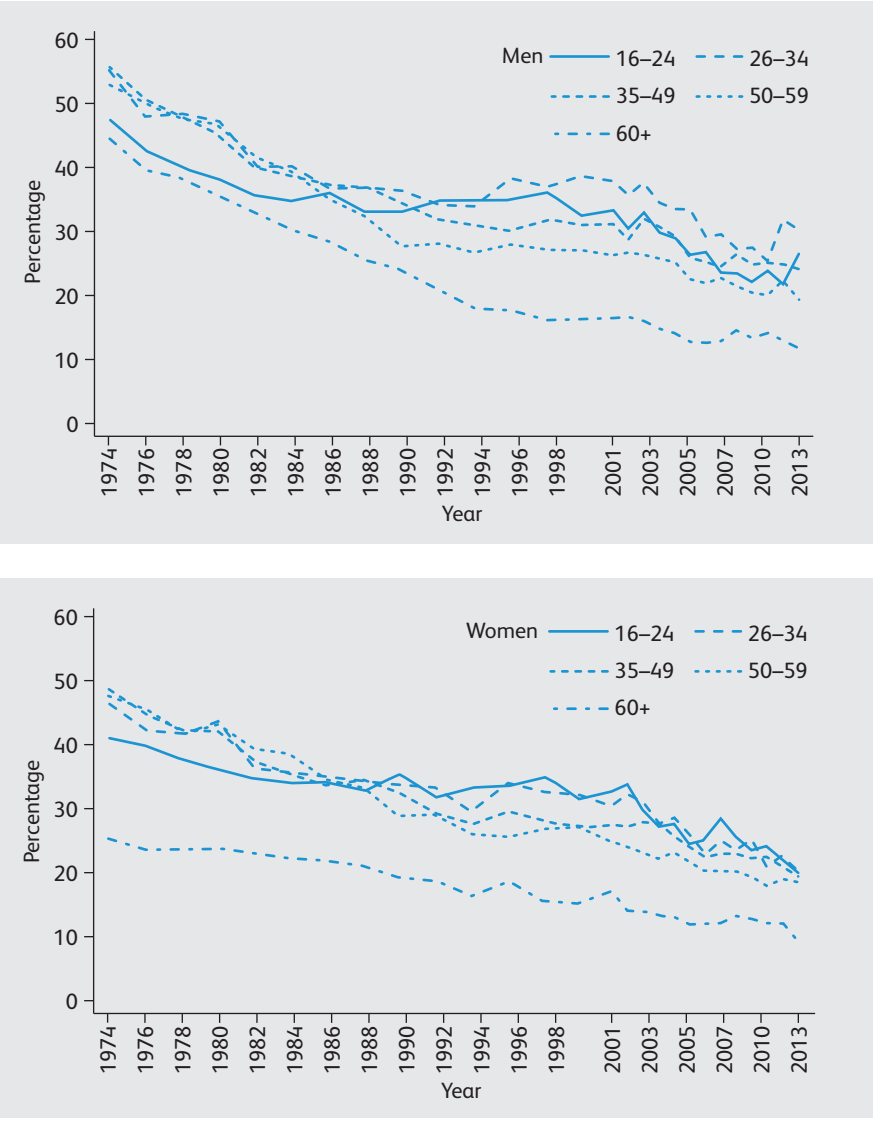

Fig 2.2 Smoking among men and women in Britain, by age 1974–2013.[1] (Adapted with permission from the Office for National Statistics[1] under Open Government Licence.)

Smoking has always been more common among men than women, and is also related to age and socio-economic status. Especially over the past two decades, smoking tends to be most common among young adults, and least so among older people, but is following a predominantly downward trend in all age groups (Fig 2.2).

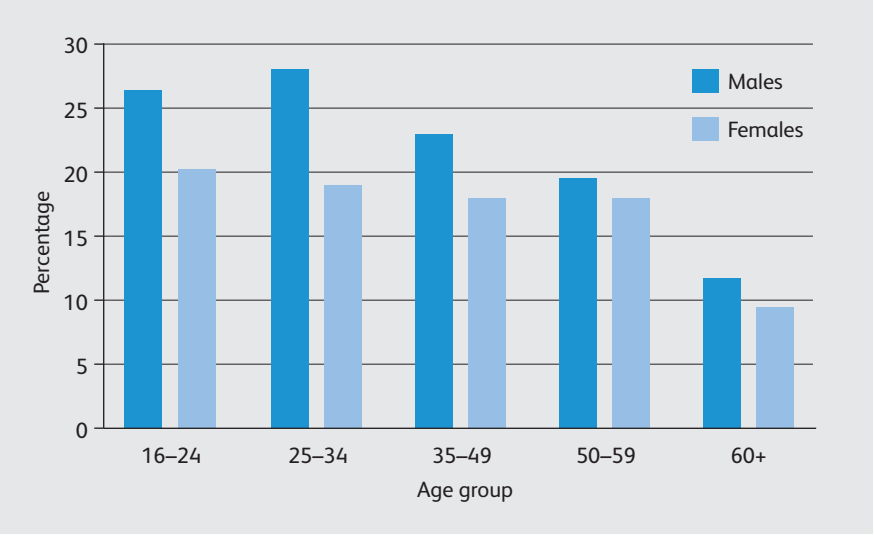

Fig 2.3 Prevalence of smoking by age group and gender in Britain, 2014.[2] (Adapted with permission from the Office for National Statistics[2] under Open Government Licence.)

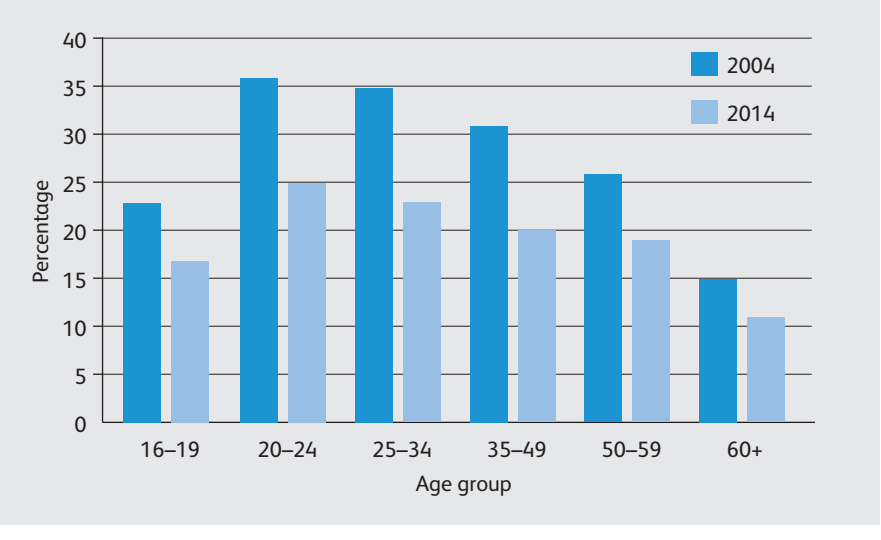

Fig 2.4 Smoking in Britain by age group, 2004[1] and 2014.[2] (Adapted with permission from the Office for National Statistics[1,2] under Open Government Licence.)

Cross-sectional prevalence data by age demonstrate that smoking is currently most common among young adults, and particularly among men aged 25–34 (Fig 2.3). Age-group data also demonstrate marked falls in smoking prevalence

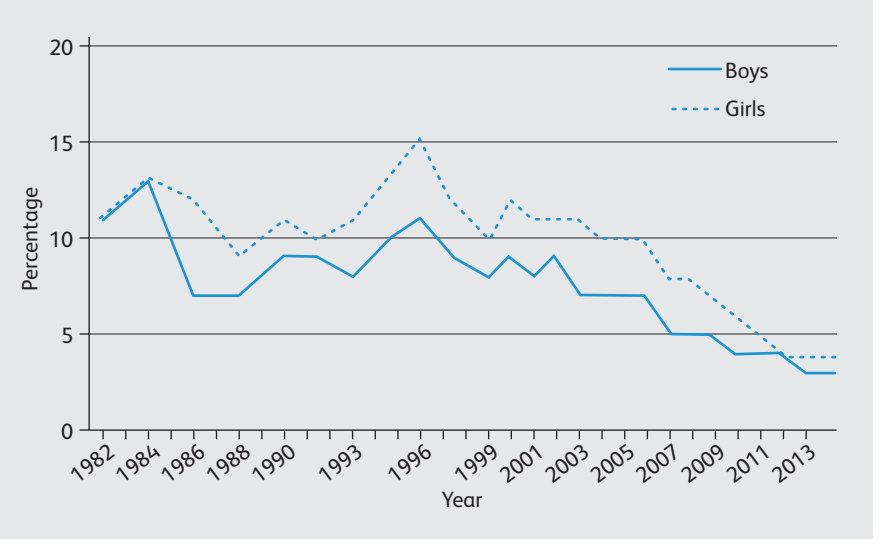

Fig 2.5 Prevalence of regular smoking among children aged 11–15 in England 1982–2014.[4] (Adapted with permission from the Health and Social Care Information Centre[4] under Open Government Licence.)

over the decade from 2004 to 2014 in all age groups, but particularly in younger adults (Fig 2.4).

Smoking among children is also falling, even more markedly than among young adults. Figure 2.5 shows that the proportion of children aged 11–15 in England who report that they currently smoke at least one cigarette a week has fallen by around two-thirds since the 1990s, to figures of 4% and 3%, respectively, in girls and boys.[4] Over the past 10 years the prevalence of smoking in all people aged 11–15 has fallen from 9% to 3%, with smoking among the youngest participants (those aged 11 and 12) falling to almost zero[4] (Fig 2.6). Similarly substantial declines in smoking prevalence among young people have also occurred in Scotland.[5]

2.2 Smoking and disadvantage

Smoking is strongly associated with socio-economic disadvantage, however defined or measured. Figure 2.7 shows prevalence trends over time in Britain according to occupational socio-economic status, and demonstrates a falling prevalence in all groups since 2001, but also prevalence that is twice as high, and falling more slowly, among those in routine and manual occupations relative to the managerial and professional group.

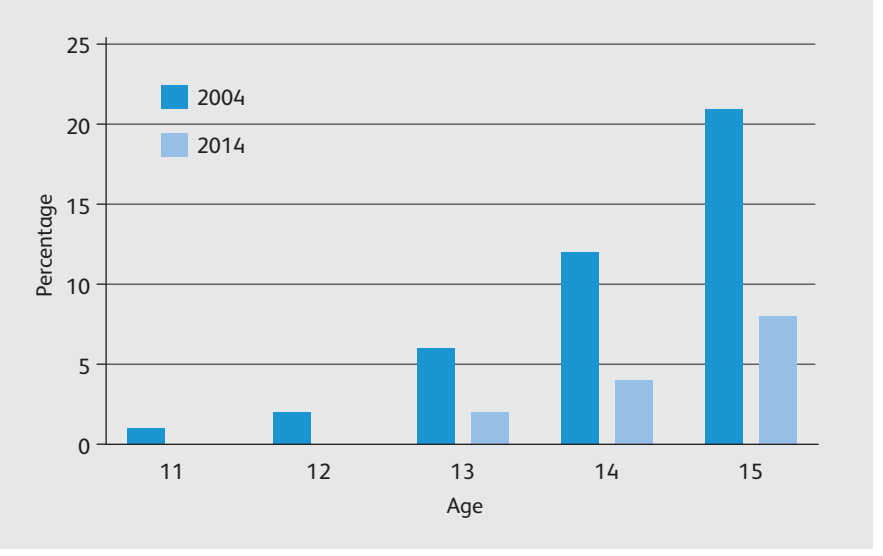

Fig 2.6 Smoking by age: children aged 11–15 in England, 2004 and 2014.[4] (Adapted with permission from the Health and Social Care Information Centre[4] under Open Government Licence.)

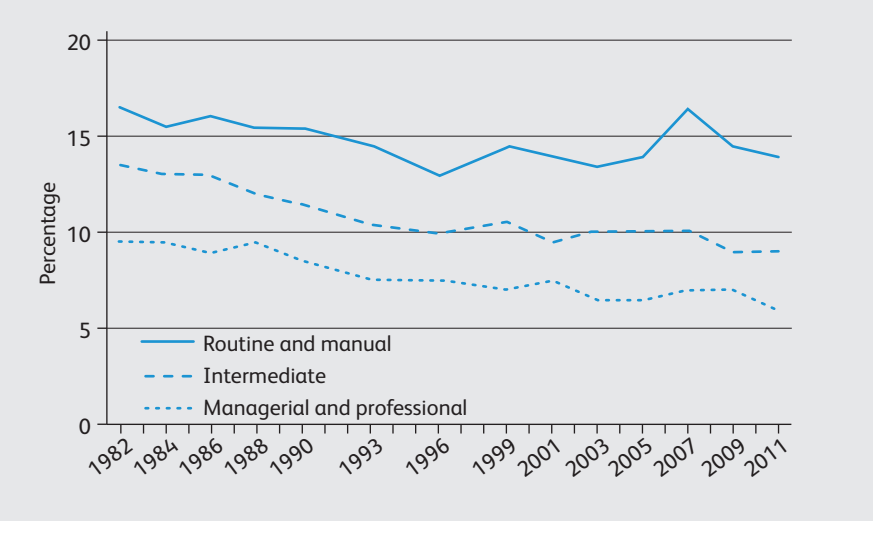

Fig 2.7 Prevalence of smoking by occupational socio-economic status, Britain 2001–13[1] and 2014.[2] (Adapted with permission from the Office for National Statistics[1,2] under Open Government Licence.)

A more detailed breakdown of smoking by occupation, from the Integrated Household Survey, demonstrates a clear and direct relationship between smoking

prevalence and occupational social group, being highest in the least skilled occupations (Fig 2.8).

In 2013, smoking in Britain was almost twice as prevalent among unemployed people (35%) as among those in employment (19%), and in those with incomes below £20,000 per year (23%) than those with incomes greater than £40,000 (11%).[1] Smoking is about twice as prevalent among those with a long-standing mental health condition than in those without (Fig 2.9), and similar among those with schizophrenia or other psychosis in 2010[6] to those in the general population in the 1970s.[1] Among other severely deprived groups, such as those who are homeless, imprisoned, or dependent on other drugs or other substances, most smoke.[6] The strong relationship between smoking and deprivation means that passive exposure to tobacco smoke, particularly in children, tends to be much higher among children living in relatively deprived households.[7]

Socio-economically disadvantaged people not only are more likely to be smokers, but also tend to be more heavily dependent on smoking. Levels of cotinine, a metabolite of nicotine (see Chapter 4) and a marker of nicotine dependence, are consistently higher among relatively disadvantaged smokers across all age groups[8] (Fig 2.10).

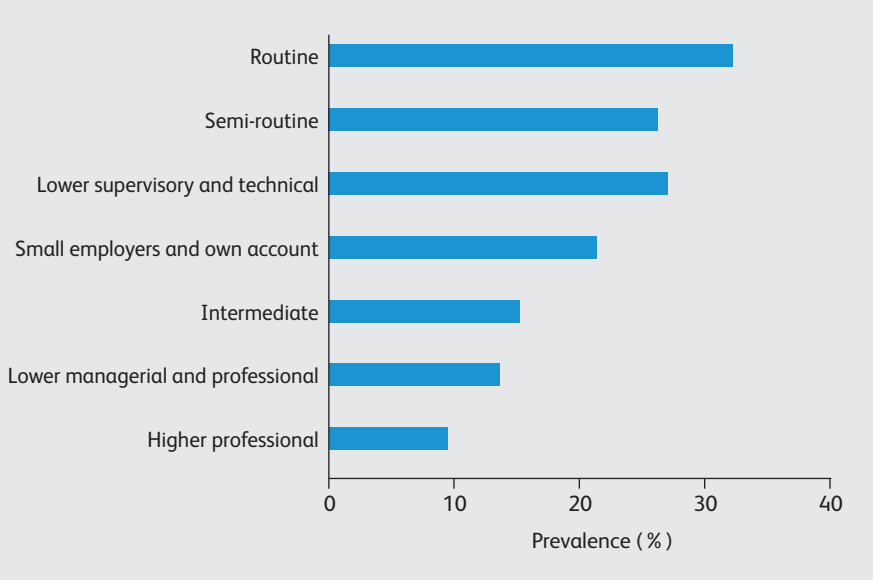

Fig 2.8 Smoking by occupation in Britain 2014.[2] (Adapted with permission from the Office for National Statistics[2] under Open Government Licence.)

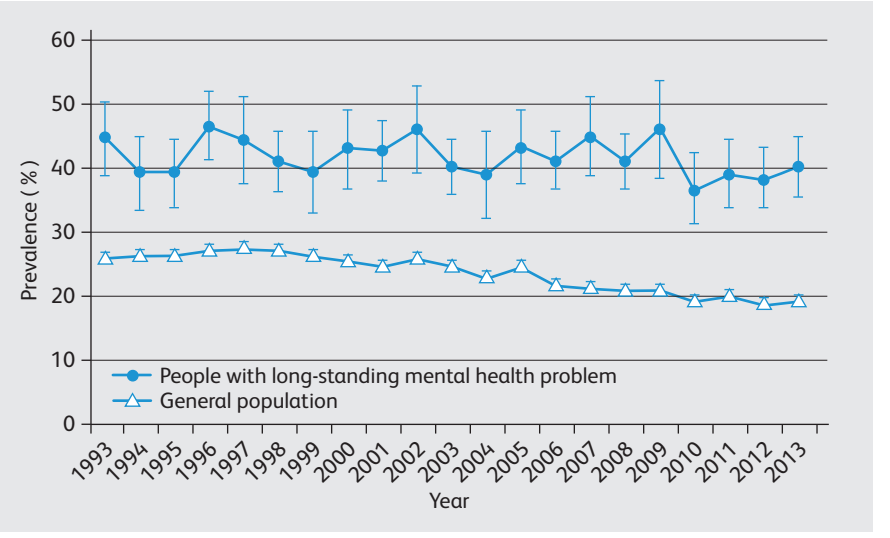

Fig 2.9 Smoking prevalence among people with a long-standing mental health problem, and in the general population, UK 1993–2013. (Updated for this report from the RCP.[6])

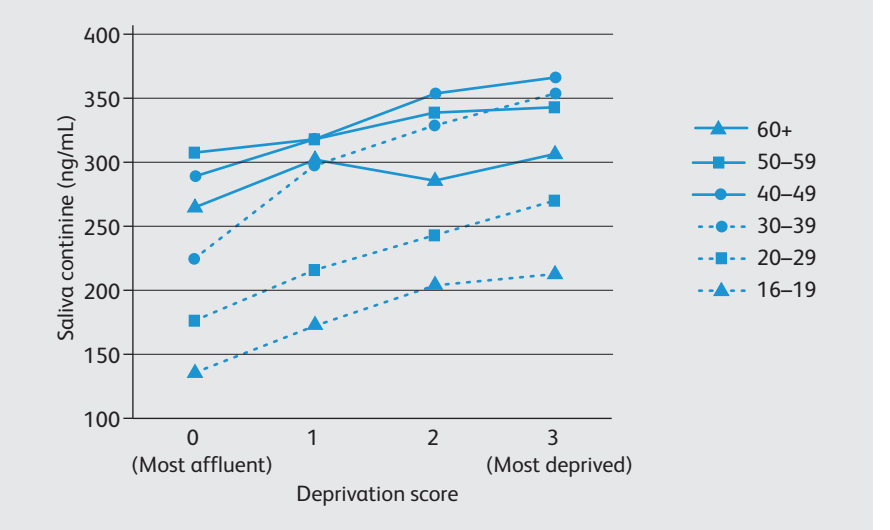

Fig 2.10 Saliva cotinine levels in smokers in relation to age and deprivation (data from 1998 to 2003).[8] (Adapted with permission from Action on Smoking and Health.[8])

2.3 Trends in the uptake and progression of smoking in the UK

2.3.1 Smoking uptake

Most smokers in the UK start smoking during their teenage or early adult years. In Britain in 2011, the most recent year for which data are accessible, 68% of male and 65% of female current smokers, respectively, reported that they started smoking before age 18, and 95% and 93%, respectively, before age 25.[9] Children in lower socio-economic status households tend to start smoking at an earlier age: 43% of smokers in 2011 who grew up in households in which the main wage earner was employed in a manual or routine occupation took up smoking before age 16, compared with 31% of those from professional and managerial households.[9] Uptake after age 25 is rare in men and women, and in all socio-economic groups.[9]

Smoking status in young people tends to be less dichotomous than in adults, because much early use is occasional and experimental, with a relatively low likelihood of leading to sustained smoking. Comparison of smoking behaviour between children and adults is also complicated by the different survey questions used to define smoking in national surveys in these groups. Thus, by the age of 15 in 2014, 35% of children in England had tried smoking at least once, 5% had smoked occasionally but less than once per week and 8% were smoking regularly, which in this survey is defined as smoking at least once a week.[4] From age 16, the question used to define regular smoking changes to 'Do you smoke cigarettes at all nowadays?',[10] and by this definition 17% of those aged 16–19 in 2014 were regular smokers.[2] Among those aged 20–24, smoking prevalence was 25% (see Fig 2.4).

However, these are cross-sectional data, so the prevalence of smoking in those aged 20–24 in 2014 will not necessarily apply to younger cohorts when they reach that age. As Figs 2.6 and 2.7 demonstrate, uptake of smoking among children and young people is falling rapidly, indicating that children born since the early 1990s may be substantially less likely than their predecessors to take up smoking, at least in their teens; and, unless these cohorts take up smoking in their 20s to a much greater degree than has typically been the case in the past, it appears that today's children and young people in the UK are much less likely than their predecessors to become smokers. The marked decline in smoking prevalence among 11- to 15-year-olds began in 2006 (see Fig 2.6) and is likely to be attributable primarily to the major tobacco control interventions of the decade: the phased removal of tobacco advertising in the UK from 2002 and smoke-free legislation, which was in place across the UK by the end of 2007.

2.3.2 Quitting

The proportion of people who have smoked regularly in the past but do not smoke now increases progressively with age. Taking data for 2011,[9] around 2% of

men and 4% of women aged 16–19 describe themselves as ex-smokers, whereas, of those aged 60 and over, the respective proportions are 45% and 30%. Although the latter figures are likely to be biased upwards by the higher mortality in continuing smokers, this bias will be less marked among those aged 50–59. In this age group in 2011, 27% of men and 24% of women were ex-smokers, whereas 20% and 18%, respectively, were still smoking.[9] These data therefore indicate that over half of those who had ever been regular smokers quit before they reached the age of 60, but that over 40% continue to smoke beyond that age.

2.3.3 Uptake and quitting within birth cohorts

Cross-sectional data on current smoking prevalence and past quitting are not representative of trends within cohorts of UK individuals born at different times. Figure 2.11 shows General Household/General Lifestyle Survey data from 1972 to 2011, provided by the UK Data Service, analysed to estimate smoking prevalence within 5-year birth cohorts over the duration for which data are available. Figure 2.11 demonstrates that, in more recent birth cohorts, smoking prevalence tends to be highest at around 25 years of age, but also that the peak within-cohort

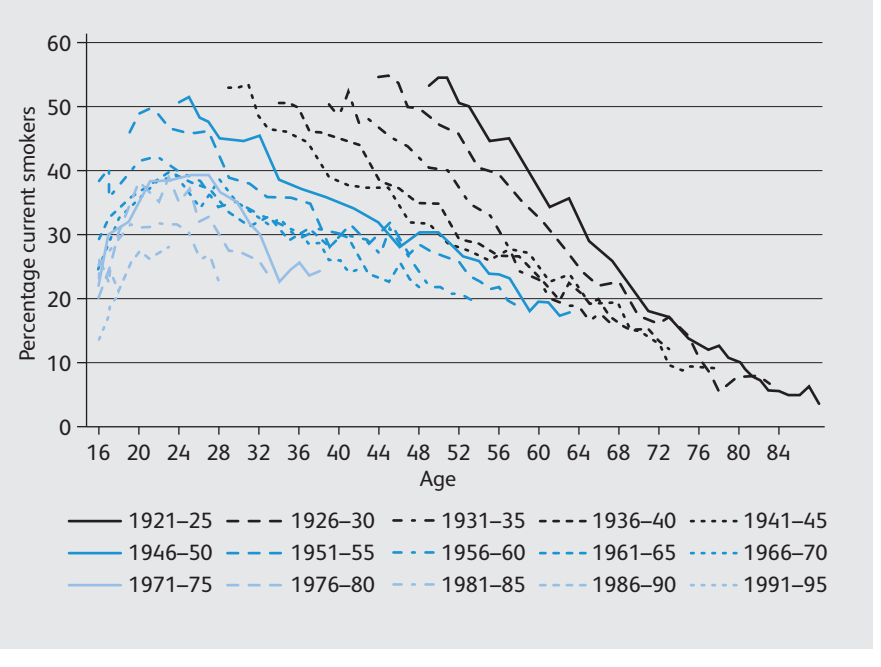

Fig 2.11 Smoking prevalence in Britain from 1972 to 2011, by 5-year birth cohort in people born since 1920.

prevalence has fallen progressively in successive cohorts from almost 50% in those born between 1951 and 1955, to under 30% in those born since 1986. Peak prevalence levels in earlier cohorts are not known, but the steady downward trend in prevalence in all of them indicates that they were probably substantially higher. After age 24 the prevalence of smoking declines in all cohorts, and this decline is likely to be attributable primarily to quitting smoking during mid-adult life, and also to earlier mortality among smokers in older age groups. The rate of this decline in smoking prevalence within recent cohorts is of the order of 1 percentage point per year, which, if sustained, indicates that, by the time today's 20- to 24-year-olds reach the age of 50, their smoking prevalence is likely to have fallen from around 30% (see Fig 2.4) to about 5%.

2.4 Current and expected future mortality and morbidity from smoking

Mortality from smoking tends to lag behind smoking prevalence by several decades, and reached a peak of around 151,000 deaths per year in the UK in the mid-1980s (Fig 2.12).[11] This total has since declined progressively to 103,000 in 2009.[11] Data for England since 2009 suggest that this trend has continued, with an estimated 78,200 people,[12] equivalent to about 93,000 in the UK, killed by smoking in 2014.[12] The decline has to date been due predominantly to a relatively marked fall in cardiovascular mortality (Fig 2.13), although modest

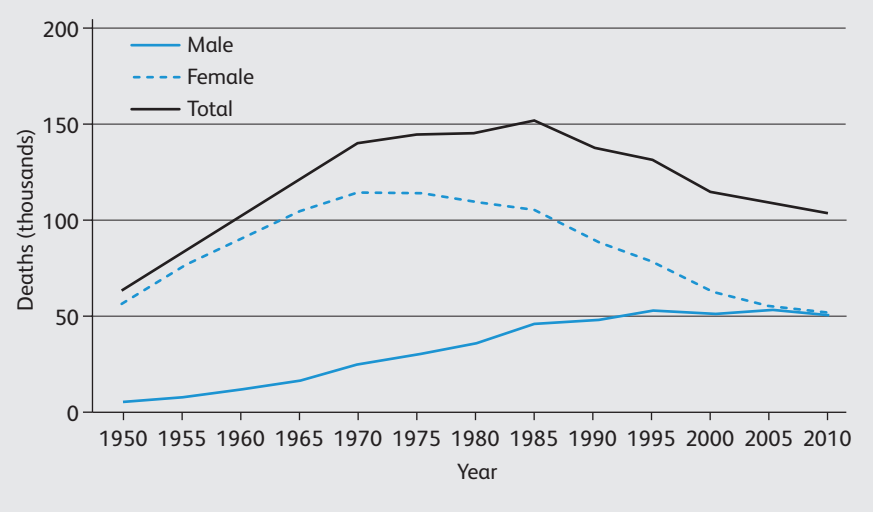

Fig 2.12 Deaths from smoking, total and by gender, UK 1950–2009.[11] (Data for figure from Peto *et al.*[11])

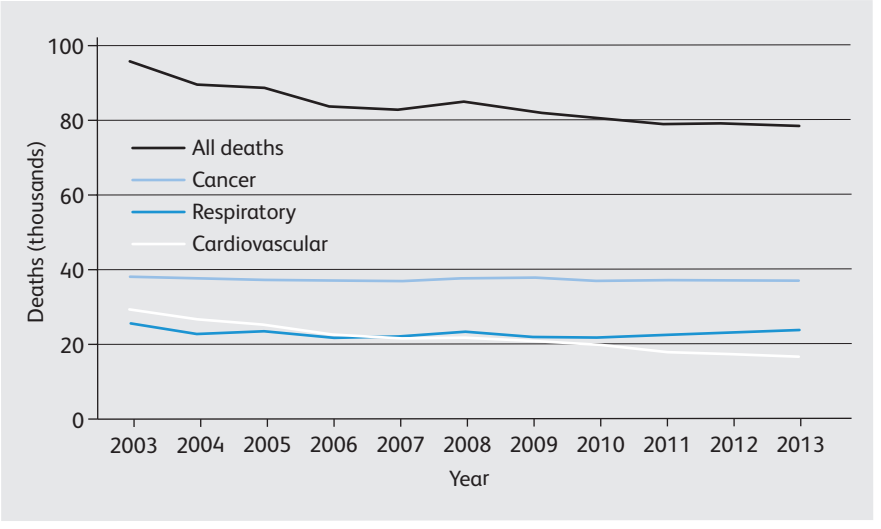

Fig 2.13 Deaths from smoking in England, by cause, 2003–13.[12] (Adapted with permission from the Health and Social Care Information Centre[12] under Open Government Licence.)

declines in all causes of premature mortality among smokers are expected over the coming decades.

Generating estimates of morbidity from smoking is a more complex process and direct data are not available. However, figures on hospital admissions attributable to smoking provide a proxy for morbidity, and demonstrate a sustained rise over the past decade, from 1.38 million in 2003–4 to 1.63 million in 2013–14.[12]

2.5 Summary

- Smoking prevalence has been falling for several decades in the UK, in all age groups, in both men and women.
- Smoking prevalence has fallen particularly markedly since 2007 among children and young people.
- Smoking remains much more prevalent among socio-economically disadvantaged individuals and those with mental health problems.
- Uptake of smoking appears to be falling progressively, whereas quit rates appear to be remaining relatively constant across successive cohorts.
- Smoking remains most prevalent among disadvantaged individuals, and addiction to nicotine tends to be higher in more disadvantaged smokers.

- This means that the approximately 8.7 million smokers in the UK today include a high proportion of the most disadvantaged individuals in society, who as a result of higher levels of addiction are likely to find it particularly difficult to quit smoking.
- Smoking is likely to be rare among today's young people as they approach older age, but continuing efforts to reduce child uptake of smoking are vital.
- However, smoking continues to cause significant mortality and morbidity, in part as a consequence of higher smoking rates in past decades.
- Helping disadvantaged smokers to quit or else reduce the harm caused by smoking is therefore a key priority to prevent current and future death and disability.

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3 Effectiveness of current and future tobacco control policy

3.1 Background

In 1962, when most men and almost half of all women in the UK were regular smokers, the RCP's report, *Smoking and health,* identified tobacco smoking as the primary cause of the twentieth-century global epidemic of lung cancer and proposed a range of policies to reduce smoking prevalence.[1] Progress with implementation of these policies remained slow, however, until the first comprehensive UK tobacco control policy document, *Smoking kills*, was published in 1998.[2] *Smoking kills* recognised the devastating effect of tobacco smoking on UK public health, and committed to reduce smoking in children and young people, help adults to stop smoking, prioritise reducing the prevalence of smoking in manual occupational groups as a means of decreasing health inequalities, and offer particular help to pregnant smokers. Drawing heavily on the policy recommendations of *Smoking and health*, *Smoking kills* defined a package of tobacco control policies including the following:

- a ban on tobacco advertising and sponsorship
- tobacco tax rises
- enforcement of underage sales laws
- reducing point-of-sale tobacco advertising
- introducing smoking cessation services
- facilitating access to smoking cessation medication
- voluntary measures to reduce passive smoke exposure in public places and workplaces.

Shortly after *Smoking kills* was published, powers for key policy areas, including health, were devolved to the newly established Scottish Parliament, Welsh Assembly and Northern Ireland Assembly, although some powers relevant to tobacco, such as fiscal policy (via the Treasury), remained within the remit of the Westminster government. However, *Smoking kills* had set the scene for tobacco policy changes throughout the UK and, in the years that followed, the main policies it recommended were implemented throughout England and the devolved nations. These new measures included comprehensive smoke-free

legislation, which was implemented in Scotland in 2006 and throughout the rest of the UK by the end of 2007. Each of the UK nations has since produced their own tobacco control strategies, with some variation in emphasis and the timing of how policies were introduced. The core strategies are, however, broadly similar and articulated in the most recent tobacco control plan for England, which was published in March 2011.[3] This plan committed to:

- implementing legislation to end tobacco displays in shops
- considering and consulting on plain packaging of tobacco products
- continuing to defend tobacco legislation against legal challenges by the tobacco industry
- continuing to follow a policy of using tax to maintain the high price of tobacco products
- promoting effective local enforcement of tobacco legislation
- encourage more smokers to quit by using the most effective forms of support, through local stop smoking services
- publish a 3-year marketing strategy for tobacco control.

Progress has been made on all these objectives, particularly in ending point-of-sale tobacco displays and passing legislation mandating standardised packaging for tobacco products. The plan also proposed adopting a harm-reduction strategy based on helping tobacco users who cannot or are unwilling to quit smoking to substitute alternative safer sources of nicotine for tobacco,[3] to be supported by guidance from the National Institute for Health and Care Excellence (NICE), which was in development at the time but published in due course in 2013,[4] and undertook to encourage the development of new, affordable and acceptable nicotine products.[3] The UK government elected in 2015 has committed to a new tobacco strategy, although a publication date has not been set.

In addition to national and devolved government actions, tobacco control policy in the UK is significantly influenced by international treaties and initiatives. UK tobacco policy is shaped by the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC), a global health treaty[5] ratified by most of the world's countries, including the UK, that defines a comprehensive range of tobacco control policies and practices that all political parties undertake to implement. At the European level, European Union (EU) single market rules have also been a driver of significant policy initiatives across all EU member states in recent years, including legislation banning tobacco advertising (2003/33/EC)[6] and mandating health warnings on tobacco packs (2001/37/EC, known as the Tobacco Products Directive, or TPD).[7,8] A revision of the TPD (2014/40/EU), which comes into force in 2016, will impose a minimum pack size of 20 cigarettes (and 50 g hand-rolling tobacco), require combined pictorial and text health warnings to cover 65% of the front and back of the pack, and end

cigarette flavouring.[8] The new TPD will also set out product standards and regulations on the sale of e-cigarettes (see Chapter 9). UK tobacco control policy thus continues to be shaped by both national initiatives and international agreements and legislation. The combination of these processes has led to the UK becoming the European leader in tobacco control policy implementation.[9]

3.2 Tobacco control policy effectiveness and implementation in the UK

3.2.1 Increasing the price of tobacco products

Fiscal measures, including tobacco taxation, are a key element of tobacco control. In the UK, tobacco tax increased in the mid- to late 1990s, through an escalator of 3% above inflation from 1993 to 1997 and 5% above inflation from 1997 to 2000. From 2001 to 2008 taxes rose in line with inflation, until, in 2009, a tax escalator was reintroduced, which is currently set at 2% above inflation, a commitment that runs until the end of the current parliament in 2020. Overall, between 1980 and 2012 the affordability of tobacco declined by 28%,[10] although, relative to the 1960s' prices, tobacco was approximately 50% more affordable in 2006 than when *Smoking and health* was published in 1962, and remains more affordable today.[11] The price of the most popular price category cigarettes, a metric that initially reflected the price of the most popular brand or brands on the market, but now typically represents the prices of the more expensive (premium-brand) cigarettes, has increased consistently over the last three decades (Fig 3.1), with the result that the UK now has some of the highest premium-brand prices in Europe. However, the price of cigarettes in the ultra-low price category favoured by younger and more disadvantaged smokers has remained virtually static in recent years, thus undermining the effects of tobacco tax rises.[12,13]

The World Bank suggests that price increases through higher taxation are the single most effective and cost-effective tobacco control measure. Its estimates from the late 1990s suggested that a price increase of 10% typically decreases adult consumption by around 4% in developed countries.[14,15] A 1996 study in the UK produced an estimate consistent with the World Bank figure, with a price increase of 10% reducing consumption by 5% and with evidence that lower socio-economic groups were more responsive than those in higher socio-economic groups to changes in the price of cigarettes.[16] These figures were disputed in a recent paper by HM Revenue and Customs (HMRC), which estimated that the price elasticity of demand for cigarettes increased in the period from 1982 to 2009,[17] suggesting that a 10% increase in price now reduces consumption by 10%. However, this study included duty-paid manufactured cigarettes only, and did not take into account other types of tobacco, such as

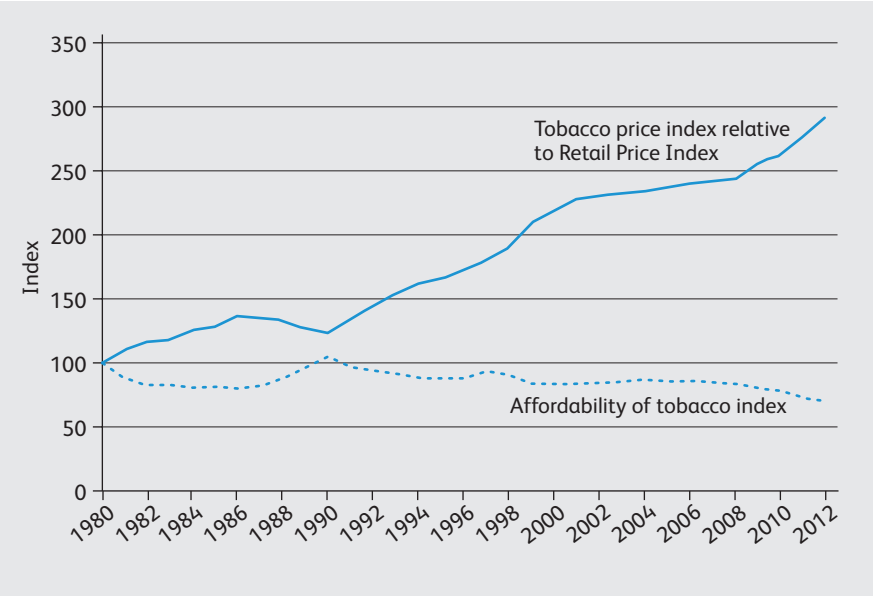

Fig 3.1 Price and affordability of tobacco, 1980–2012.[10] (Adapted from the Health and Social Care Information Centre[10] under Open Government Licence.)

hand-rolling tobacco, to which many smokers downtrade when prices for manufactured cigarettes rise.[18]

Evidence from a wide range of settings consistently demonstrates the effectiveness of price increases as a tobacco control measure. From 1990 to 2005, France tripled inflation-adjusted cigarette prices by raising taxes 5% or more every year in excess of inflation and, during the same period, cigarette consumption halved and smoking prevalence fell by a quarter.[19] Comparable price increases in South Africa achieved similar reductions in consumption.[19] However, the available evidence relates predominantly to the effects of relatively small, incremental price rises over time; the effects of sudden large price rises are less well defined.[20] Data from France indicate that a single large increase in tobacco taxation in 2003, which caused the price of a packet of premium-brand cigarettes to rise in real terms by almost 20%, resulted in a 13.5% decline in sales.[21] This implies that sudden large price increases may be more effective than repeated smaller rises.

There is also consistent international evidence that raising taxes to increase the price of tobacco reduces smoking among young people, who as a group are more responsive than adults to price increases.[22–24] The US surgeon general's report on preventing youth smoking concluded that increases in cigarette prices reduce

initiation, prevalence and intensity of smoking among both children and young adults.[23] Evidence from developed countries indicates that a 10% increase in price reduces youth consumption by between 5 and 12%.[24] There is also evidence from high-income countries that low socio-economic status (SES) groups are more responsive to price increases, indicating that tobacco price increases have a key role to play in reducing inequalities in health caused by tobacco use.[25] Two systematic reviews have recently assessed the equity impact of tobacco control in high-income countries, in terms of differential impact on SES groups, in both young people and adults.[26,27] The reviews found that the clearest and most consistent evidence of a positive equity impact (ie reduced inequalities in smoking) for all types of tobacco control in adults, and to a lesser extent in young people (as there are fewer studies on this), related to price increases.

Although UK tobacco prices increased throughout the 1990s, the effects of increasing taxation during this period were undermined by, among other things, a rapid increase in the market share for illicit cigarettes, which rose from 3% in 1996–7 to 21% by 2000–1.[28,29] This meant that smokers were switching to cheap, illicit cigarettes rather than quitting in response to price rises. This and a relative absence of other tobacco control measures during this period resulted in little change in UK smoking prevalence, despite year-on-year price rises. From 2000, however, a comprehensive anti-smuggling strategy reduced the supply of illicit cigarettes from 21% in 2000–1 to 9% in 2012–13. This included, from 2006, legislation imposing substantial fines on manufacturers who failed to prevent their products from being smuggled into the UK.[28] Since then, however, tax increases have been undermined by new developments in tobacco industry pricing strategy, with the creation of a range of ultra-low-price cigarettes and the practice of 'overshifting' tax on to more profitable premium brands, leaving ultra-low brand prices relatively unchanged.[12] The consequence of this strategy is that many smokers who might otherwise quit smoking or else reduce their consumption in response to price rises now 'downtrade' to lower-price brands, or indeed switch to hand-rolling tobacco.

3.2.2 Restrictions on smoking in public places, workplaces and cars

The health effects of passive smoke exposure are well documented[30] and, to protect workers and the public from these effects, bans or restrictions on smoking in public places and workplaces are a key component of tobacco control policy. In the UK, smoke-free legislation was introduced first in Scotland in March 2006, in Wales and Northern Ireland in April 2007, and in England in July 2007.

There is now extensive international and UK evidence that smoke-free laws are effective in reducing passive exposure to smoke. Before the 2007 smoke-free legislation, the highest levels of occupational passive exposure to smoke in the

UK occurred in serving staff in bars and pubs.[31] A study of bar workers in England, Scotland and Wales showed that their exposure was reduced on average by between 84% and 93% after introduction of the legislation.[32] Children are particularly vulnerable to the effects of tobacco smoke, and research in Scotland, Wales and Northern Ireland found that passive exposure of children to smoke declined after the introduction of the legislation in these countries.[33] Between 1998 and 2012 in England, passive smoke exposure among children declined by 79%, and the most rapid decline occurred in the period immediately before smoke-free legislation came into force, thus coinciding with national mass media campaigns highlighting the dangers of passive smoke exposure.[34] Smoke-free legislation in the UK has also had positive effects on child and adult health, with substantial reductions in preterm deaths, childhood admissions to hospital with asthma and adult admissions for myocardial infarction.[35–38]

Smoke-free legislation also acts as an incentive to smokers to quit smoking. The Smoking Toolkit Study found that, at the time of the legislation in England, the number of smokers trying to quit smoking increased significantly, with approximately 300,000 additional quit attempts made.[39] Scottish data suggest that quit attempts increased in the 3 months leading up to Scotland's smoke-free legislation,[40] after which there was a temporary fall in prevalence in addition to the secular reducing trend.[40] A further study has suggested that, although smoke-free legislation was not associated with additional reductions in smoking prevalence, existing decreasing trends continued in the 18 months following implementation of the ban.[41]

Two systematic reviews have recently assessed the equity impact of smoke-free policy in high-income countries on young people and adults.[26,27] A youth review found that, of the six studies that had looked at the equity impact of comprehensive smoke-free legislation, two had a neutral effect and four were negative in terms of second-hand smoke (SHS) exposure.[26] Declines in SHS exposure occurred predominantly among children who had low SHS exposure before smoke-free legislation, and who were from more affluent families. Thus, the substantial SES gradients in children's SHS exposure levels remained unchanged. Welsh data showed that, although there was a significant decline among high-SES children perceiving adult smoking as the norm, there was no change among children from low-SES households.[42] Thus, SES disparities in children's perceptions of adult smoking as normative increased, which is of concern because social norms are important influences on smoking uptake. An adult equity systematic review found that comprehensive national smoke-free legislation was much more likely to have a neutral or positive equity impact than voluntary partial policies.[27]

Following the success of smoke-free legislation in the UK, there are continuing efforts to extend smoke-free policies to other settings. Some cities are considering

extending smoke-free laws to outdoor public places including parks or other open spaces. Since October 2015 it has been illegal for drivers in England and Wales to smoke in private cars in the presence of children, and Scotland and Northern Ireland are in the process of introducing similar legislation. Recent UK research suggests that around one-fifth to one-third of 11- to 15-year-olds are exposed to SHS in cars sometimes or often, and that this is concentrated among those from more deprived backgrounds.[43,44] Around three-quarters of adolescents reported disliking being exposed to SHS in cars. Around one-third of 8- to 15-year-olds who reported ever being exposed to SHS in cars felt too embarrassed or frightened to ask someone smoking in a car when they were present to stop. Most children, adults and adult smokers in the UK support a ban on smoking in cars where children are present.[45]

3.2.3 Mass media campaigns

Tobacco control mass media campaigns (MMCs) use television, radio, newspapers and other media channels to reach large numbers of smokers and encourage them to quit smoking, reduce harm to self or others from tobacco use, and prevent young people from taking up smoking. Large-scale MMCs have been a key component of UK tobacco control strategy since the early 2000s, and there is strong evidence that tobacco control MMCs can increase adult smoking cessation and reduce youth uptake.[46–53] Campaigns in England have varied in informational content; approximately half of the adverts between 2004 and 2010 warned of the negative consequences of smoking, whereas half contained information on how to quit smoking.[54] In April 2010, the government ceased spending on national public health MMCs in England. A tobacco control MMC was reintroduced in England in September 2011, but at a much lower rate of funding.[55] Mass media are also used to promote the 'Stoptober' campaign, which has run every year since 2012 and encourages smokers to quit for the month of October. Examples are shown in Fig 3.2.

The magnitude of the independent effect of MMCs on smoking behaviour is difficult to establish when, as is usually the case, they are used together with other tobacco control policies.[51–53] However, several recent studies have assessed the impact of MMCs on a range of measures of quitting behaviour in England (and, to a lesser extent, Wales), including quit-line calls, hits on the national Smokefree website, and measures of cigarette consumption and smoking prevalence.[56–60] Over the period from 2002 to 2009, when adult smoking prevalence in Britain fell from 26% to 21%,[61] an estimated 13.5% of this decline was attributable to the effect of MMCs.[58] A further study showed that positive emotive campaigns – predominantly those promoting the use of NHS Stop Smoking Services – and negative emotive campaigns – generally those containing negative health effects messages – played a statistically indistinguishable role in

Fig 3.2 Examples of imagery from recent UK smoking mass media campaigns (MMCs). (a) Toxic cycle MMC: launched in December 2013, and aimed at reminding smokers of the physical damage caused by tobacco use, while also offering support to help them quit by urging them to go online to get information about stopping smoking, and order a free support pack (Quit Kit), Smokefree app, text and emails, and information on how to contact local NHS Stop Smoking Services.[62] (b) Stoptober: launched in 2012; runs annually. Uses traditional and new media to set people the challenge of staying smoke free for 28 days starting on 1 October. The call to action is reinforced by the positive message that smokers achieving this goal are at least five times more likely to become permanent ex-smokers.[63,64] (Reprinted with permission from Public Health England: https://campaignresources.phe.gov.uk/resources/campaigns/6-stoptober/resources.)

triggering this effect.[60] More recently, the annual English Stoptober campaign, which aims to create a positive quitting trigger around a specific call to action – stopping for 28 days – and which uses a combination of traditional and new

media, was estimated to have generated an additional 350,000 quit attempts and 9,000 permanent quitters in October 2012.[63]

Research from Australia has suggested that the level of exposure to MMCs required to obtain a detectable reduction in smoking prevalence is the equivalent of four exposures per person per month (390 gross rating points, known as GRPs).[47] Between 2004 and the spring of 2010, campaign exposure in England exceeded this threshold in around 40% of months; in other months, exposure was lower, with no campaign at all during 1 in every 5 months.[54] A recent study found that, below 400 GRPs per month, there was little impact of campaigns on quit-line calls in England, and that the effect increased significantly above the 400 GRP threshold,[59] suggesting that efforts should be made to maintain exposure above this level.

The US surgeon general's report on prevention of smoking in youth concluded that MMCs can be one of the most effective strategies in changing social norms and preventing youth smoking.[23] The surgeon general concluded that the characteristics of effective campaigns included evoking strong negative emotions (eg health effects, deceptiveness of the tobacco industry), an appealing format, clear messages, intensity and adequate repetition (at least four advertising exposures per month over a 4-month period). There was strong evidence that MMCs aimed at adults also decreased smoking among young people.

Two recent systematic reviews have looked at the equity impact of MMCs on youth and adults. The youth equity review found only one study that had assessed the equity impact of MMCs on young people by SES.[26] This was an evaluation of the US Truth campaign, which had mixed equity effects depending on the outcome measure used.[65] The adult review found 30 studies that had looked at the equity impact of MMCs.[27] These studies included a diverse range of approaches and messages, including some aimed at increasing quit motivations and/or attempts, and some aimed at increasing calls to quit-lines or uptake of free nicotine replacement therapy (NRT). The equity impact of these campaigns was inconsistent. This is perhaps not surprising given the diversity of messages, media formats and levels of exposure. There was some evidence that certain types of message, such as those with a higher emotional narrative, are more effective with low-SES smokers. A previous review also found that the impact of campaigns can vary by SES depending on the type of message, media format and mechanisms of engagement.[66,67]

3.2.4 Health warnings

Health warnings on tobacco packages are a means of communicating the risks of tobacco use to smokers. Text warnings became a legal requirement in the UK in

Fig 3.3 Examples of UK text and graphic health warnings.[68] (Adapted from Department of Health[68] under Open Government Licence; Crown copyright.)

1971, and since 2008 graphic pictorial warnings covering 40% of the back of the pack, and text warnings covering 30% of the front of the pack, have been required (Fig 3.3). The new EU TPD will see a further increase in the prominence of health warnings, with picture and text warnings covering at least 65% of the front and back of tobacco packaging by May 2016.

Studies from a wide range of countries indicate high levels of awareness of pack health warnings among both smokers and non-smokers.[69,70] Large text warnings have been shown to be linked to increased knowledge about the health risks of smoking[71] and increased motivation to quit.[72–77] In the UK, a study of text-only warnings found that they were noticed by over half of smokers,[78,79] and that those noticing warning labels were more likely to know about the health risks of smoking.[78] Pictorial warnings are likely to be most effective because they are more likely to be noticed, improve memory for the health message, and are associated with stronger beliefs about the risks of smoking and increased motivation to quit.[69]

Determining whether exposure to health warnings is causally related to changes in smoking behaviour has been difficult, owing to the challenges of disentangling their effect from those of other interventions.[69–80] Research has suggested that pictorial health warnings increase the likelihood of a quit attempt.[81] Further studies, in which UK data were analysed together with data from Australia, the USA and Canada, concluded that forgoing cigarettes as a result of noticing warnings and cognitive reactions to warnings is a predictor of quit attempts,[82] and that health warnings can help to prevent relapse.[83] Some studies have investigated the effect of health warnings on smoking prevalence,[81–84] with some suggesting positive effects,[81] although other factors may also have contributed.[69] The US surgeon general's report on prevention of smoking in youth concluded that small text-only health warning labels have limited impact on youth and

young adults, but that larger text or pictorial warnings that elicit strong emotional reactions are significantly more effective at discouraging tobacco use.[23]

Systematic reviews of the equity impact of tobacco control policies found no studies that had assessed the equity impact of health warnings in young people,[26] and five studies of the effect of health warning labels in adults.[27] EU text-only health warnings and the addition of a quit-line number to new pictorial health warnings were found to have had a greater impact on low-SES groups, and the rest were equity neutral.

3.2.5 Comprehensive bans on the advertising and promotion of all tobacco products, logos and brand names

Prohibiting advertising and promotion of tobacco products is a key element of tobacco control. Television advertising for tobacco products was banned in the UK in 1965 under the Television Act 1964, almost 25 years earlier than an EU directive that prohibited television advertising across the EU in 1989 (Television without Frontiers Directive (89/552/EEC)).[85] This directive was replaced by the Audiovisual Media Services Directive (2007/65/EC) adopted in December 2007.[86] Subsequently, the UK Tobacco Advertising and Promotion Act 2002 (TAPA) banned print media and billboard advertising from February 2003, tobacco direct marketing from May 2003 and sponsorship within the UK in July 2003.

Advertising bans have been shown to reduce smoking uptake in children by lessening its social desirability, and also to reduce tobacco consumption in adults. The introduction of comprehensive advertising bans in Norway, Finland and France resulted in significant reductions in tobacco sales in the period following the introduction of the legislation.[87] The US surgeon general's report on prevention of smoking among youth concluded that there is a causal relationship between tobacco advertising and promotion, and the initiation and progression of smoking in young people.[23] It also concluded that comprehensive cigarette advertising bans reduce youth smoking. The World Bank has estimated that comprehensive advertising bans can reduce consumption by around 7%.[88]

A recent systematic review found four studies that had assessed the equity impact of restrictions and bans on advertising and promotion, all of which had a neutral equity effect.[27] A similar review on the equity impact on young people found four US studies indicating that, when there is no enforced control of advertising, promotion or marketing of tobacco, there is the potential for increased inequality in youth smoking.[26]

The main exclusions from TAPA, and hence the key remaining forms of promotion, were displays of tobacco packs at the point of sale in shops, and the

Fig 3.4 Examples of tobacco point-of-sale displays in small retailers in England, before and after prohibition.

pack itself. Legislation ending both of these exclusions has now been passed in the UK. Point-of-sale displays were removed from large retailers such as supermarkets in England, Northern Ireland and Wales from April, October and December 2012, respectively, and April 2013 in Scotland. Point-of-sale displays in smaller shops were prohibited across the UK from April 2015 (Fig 3.4). Studies of the removal of point-of-sale displays in Iceland and Ireland suggest that the policy is supported by the public and that there are signs that prohibition helps to denormalise smoking.[89] A recent systematic review of the impact of point-of-sale promotion on youth smoking found that there was a positive association between exposure and smoking-related outcomes, including smoking and smoking susceptibility.[90] The review also found that point-of-sale bans may contribute to a shift in youth perceptions about peer smoking prevalence, but found no evidence of short-term population-level impacts on smoking.

Fig 3.5 Examples of current and proposed standardised cigarette packs. (Reprinted with permission from Cancer Research UK and Action on Smoking and Health.)

Legislation to introduce standardised tobacco packaging in the UK was approved in March 2015, and from May 2016 imposes a standard plain dark-green/brown design and a large graphic health warning on all tobacco packaging, and limits branding to a name and descriptor in a specified and standard plain font (Fig 3.5). A systematic review published in 2012 found that plain packs were rated as less attractive than branded equivalent packs, or unattractive, by young people.[91] An independent review into standardised packaging published in 2014 concluded that the measure is likely to lead to a modest but important reduction in smoking, including among children.[92] Public support for the measure is also reported to be high: in January 2015, a YouGov survey conducted for Cancer Research UK found that 72% of those polled supported standardised packaging.[93]

In 2012, Australia became the first country to introduce standardised packaging, and early evaluations suggest that the removal of branding from packaging has reduced the ability of the tobacco industry to use the pack to communicate to

young people and adults, and made products less appealing.[94–96] There is also evidence that standardised packaging has increased both thoughts about quitting and quit attempts in adult smokers, and reduced smoking prevalence.[97,98] Concerns that standardised packaging would lead to reductions in the price of cigarettes and increases in illicit tobacco consumption appear not to have been borne out.[99,100]

With point-of-sale and standardised packaging legislation complementing TAPA, there are few remaining means by which smoking can be promoted in the UK. However, tobacco and related imagery remains prevalent in the media, including films, television programmes, magazines and social media. Although paid-for product placement is illegal under the terms of TAPA, smoking imagery remains common in popular films, computer games and on prime-time UK television.[101,102] Evidence suggests that there is a clear association between exposure to such imagery in the media and young people starting smoking.[103] Smoking in the media thus remains a major driver of smoking uptake among children and young people, and needs to be addressed.

3.2.6 Restricting young people's access to tobacco products

Measures to reduce young people's access to tobacco have been recommended as a means of reducing uptake of smoking. Evidence arising mostly from the USA indicates that reducing youth access to tobacco by implementation of the minimum age-of-sale laws reduces smoking prevalence among young people, although this is highly dependent on levels of enforcement and access to alternative non-retail sources of cigarettes.[104,105] European evidence indicates that access to cigarette-vending machines was significantly associated with regular smoking by young people.[106]

Across the UK, the minimum age at which young people are permitted to purchase tobacco was raised from 16 to 18 in 2007, and legislation prohibiting vending machines was implemented between 2011 and 2013.[107] The increase in minimum purchase age in England was associated with a significant reduction in regular smoking among 11- to 15-year-olds[107] and a decline in smoking prevalence among 16- to 17-year-olds.[108] The percentage difference in current smoking pre- and post-legislation was significantly greater among those under 18 than in older age groups. However, the effect of the legislation is undermined by substitution of other means of access, particularly proxy purchasing by adults.[109,110] Scotland banned such sales in 2010 and England from 2015, although the Scottish legislation appears not to have been successful in reducing proxy sales.[111]

A recent systematic review of the equity impact of tobacco control policies found only five studies that have assessed the equity impact of such measures on

youth.[26] Two were equity positive (greater impact on low-SES youth), two neutral (no difference by SES) and one negative (greater impact on high-SES youth). Thus, no overall conclusion can be drawn about their equity impact. However, stronger (ie comprehensive and enforced) US state-level, age-of-sale laws were associated with lower smoking initiation and a reduction in low-SES adolescent girls moving on to regular smoking. In England, raising the age of sale from 16 to 18 was associated with a significant reduction in regular smoking among those aged 11–15 years, with no difference by SES (measured by eligibility for free school meals).[112] However, although the percentage of high-SES pupils who found it difficult to buy cigarettes from a shop increased, this was not the case for low-SES pupils.

3.2.7 Treatments to help dependent smokers stop, including increasing access to medications

Evidence-based smoking cessation treatments typically comprise behavioural interventions, delivered as brief advice from healthcare professionals, telephone quit-lines, more intensive one-to-one or group counselling, and pharmacotherapies, including NRT, bupropion and varenicline.[113] The UK was one of the first countries to make these services easily available to all smokers as a tobacco control policy. In England and Wales, NHS Stop Smoking Services (NHS SSSs), free at the point of use, were launched in areas of high deprivation defined as Health Action Zones (HAZs) in 1998–9, and extended to the rest of England and Wales in 2000–1. The number of people using NHS SSSs grew year on year, rising to over 800,000 in 2011–12, although they have fallen each year since then to a total of 450,582 in 2014–15.[114]

These services, which use evidence-based guidelines[115] and strongly recommend the use of pharmacotherapy, have been shown to be effective over a number of years. A national evaluation conducted in the early years after their establishment found that 53% of attendees confirmed abstinence at 4 weeks, with 15% still abstinent at 1 year.[116] This study has recently been updated, and 1-year abstinence rates are now lower, at 8%;[117] however, some of this change may be attributable to the growth of less intensive and hence less effective forms of support, such as one-to-one interventions in pharmacies rather than individual or group behavioural support delivered by smoking cessation specialists.[117] In the UK, cessation support is also available to smokers through stop smoking helplines and websites where smokers can speak to or converse online with a trained expert adviser. In a recent trial using the NHS Stop Smoking helpline, approximately 20% of smokers who agreed to set a quit date were abstinent at 6 months.[118] The number of calls to the NHS quit-line is small, however, averaging 20,000 per month between 2005 and 2010.[60]

Pharmacological therapies such as NRT, bupropion and varenicline are highly effective when delivered with behavioural support (see Chapter 5), and initiatives to increase access to these treatments by smokers should improve the success of quit attempts. Making cessation therapies available on reimbursable prescriptions and NRT products available on general sale, which occurred in the UK between 1999 and 2002, resulted in a rapid increase in the proportion of quit attempts supported by medication from 28% to 61%.[119] However, a great deal more could be done to extend delivery of stop smoking interventions, particularly by making intervention a component of all NHS care delivery, including secondary care.[120]

Smoking cessation services tend to be more effective in adults than in young smokers. The US surgeon general's report on prevention of smoking in youth concluded that several cessation programmes for youth are efficacious in the short term but that, in contrast to adults, there is little evidence of the efficacy of pharmacotherapies in youth cessation.[23] Data from the NHS SSSs indicate that relatively few under-18-year-olds access these services, and that those who do have lower quit rates than other age groups.[121] A recent systematic review found only two studies that had assessed the equity impact on youth of cessation services.[26] Participants in both studies were mobile phone owners in their late teens / early 20s, who were motivated to quit and received text messaging support. Only one study demonstrated a long-term effect on quitting and this was significant only in low-SES intervention participants.

The contribution of NHS SSSs to the reduction in smoking prevalence over recent years has been estimated at between 0.1 and 0.3% above the background quit rate per year.[122,123] Although the impact on prevalence of policies and initiatives to improve access to treatment is modest, these interventions have been successful in reaching smokers in the most disadvantaged areas,[123] who tend to be more addicted and have the most difficulty stopping.[124] A recent systematic review of cessation studies concluded that untargeted smoking cessation interventions across Europe are, on balance, likely to have increased inequalities in smoking. However, the same review found that the comprehensive UK stop smoking services, which are targeted at low-SES smokers, have reduced inequalities in the harm caused by smoking, because higher reach among low-SES smokers compensates for lower quit rates.[27]

3.3 Cumulative impact of conventional tobacco control policies and future challenges

Although evidence of the impact of individual interventions on smoking prevalence is limited by the difficulty of separating out the independent effects on smoking prevalence of individual components from a wider package of measures, the multi-component approach adopted in the UK appears to be

effective, for both adults and young people. The effectiveness of comprehensive packages of tobacco control policies has been further demonstrated in a recent study of the association between MPOWER policies – a list of measures developed by the WHO that are intended to assist in the implementation of interventions required by the FCTC (*M*onitor tobacco use and prevention policies, *P*rotect people from tobacco smoke, *O*ffer help to quit tobacco use, *W*arn about the dangers of tobacco, *E*nforce bans on tobacco advertising, promotion and sponsorship, and *R*aise taxes on tobacco) – and changes in prevalence, by scoring countries according to their implementation of MPOWER measures. The study showed that countries with higher MPOWER composite scores experienced greater decreases in current tobacco smoking between the years 2006 and 2009, and therefore underlines the need to implement the widest possible range of policies.[125] The study also assessed the effect of changes in each MPOWER measure on changes in current tobacco smoking, and confirmed existing evidence that price increases are the most effective tobacco control measure.

Figure 3.6 demonstrates the declines that have occurred in smoking prevalence among adults and young people in Britain since *Smoking kills* was published in 1998, in relation to the timeline of policies introduced. The reduction of adult

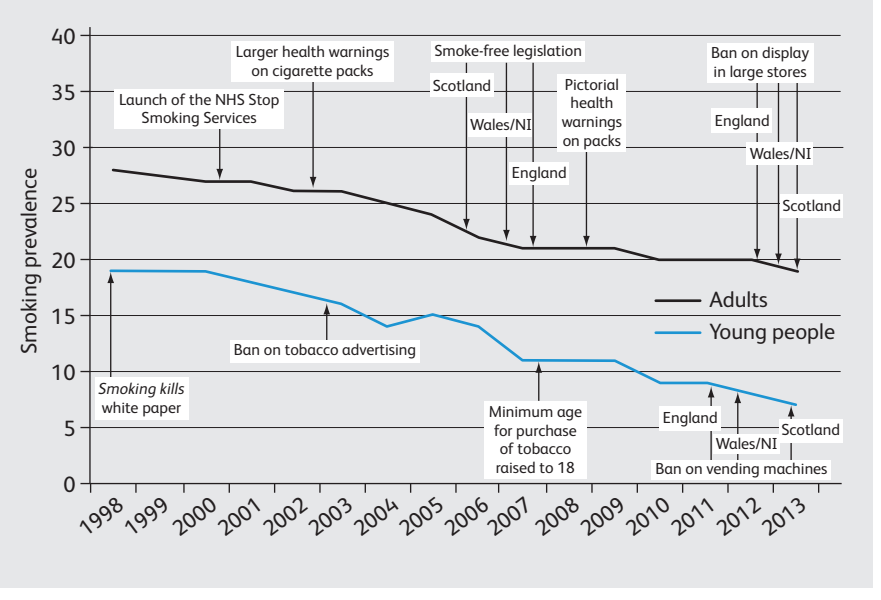

Fig 3.6 Smoking prevalence in adults in Great Britain and young people (current and occasional smokers) in England,[61,126] and key dates for implementation of tobacco control policy. (Adapted from ONS[61] and HSCIC[126] under Open Government Licence.)

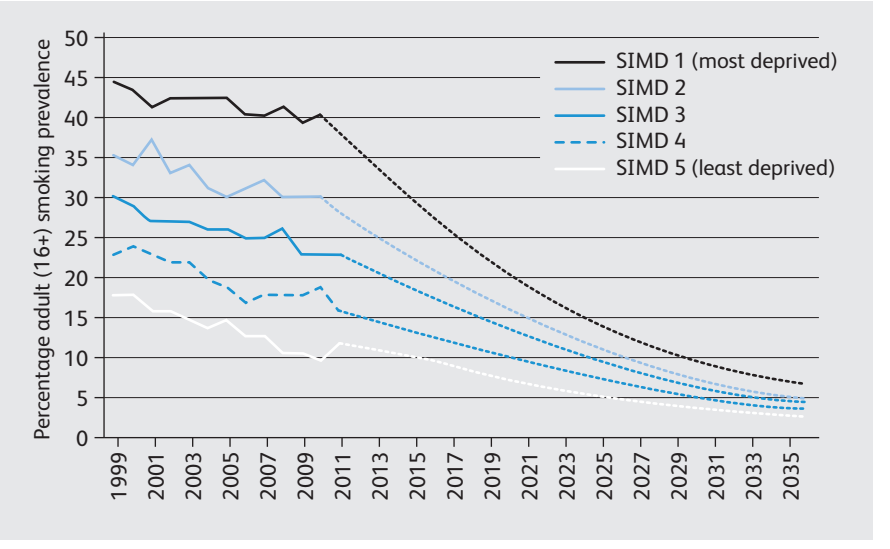

Fig 3.7 Adult smoking prevalence in Scotland by Index of Multiple Deprivation: 1999 to 2011 (actual), 2012–2036 (target projections).[127] (Adapted from ASH Scotland[127] under Open Government Licence.)

smoking by around one-third, and by almost twice that proportion among young people, represents a substantial success for tobacco control policy. However, these figures also demonstrate that, despite this progress, smoking remains a significant public health problem in the UK, with around one in five adults still smoking regularly.[61,128] These smokers, who are increasingly predominantly from the more deprived SES groups in UK society,[61] have by definition proved resistant to policies applied to date, and also by definition are in desperate need of measures to help them stop smoking.

The Scottish Government has recently set a target for Scotland to become 'tobacco free', defined as a smoking prevalence below 5%, by 2034. Figure 3.7 demonstrates how challenging it will be to meet this objective given current trends in smoking prevalence, particularly among low-SES groups, and it will be equally challenging in the rest of the UK. If such an ambition is to be realised, new tobacco control approaches that can bring about substantial declines in smoking among the most deprived individuals in society are urgently needed.

3.4 Developing a more effective tobacco control policy approach

There are many ways in which existing UK tobacco control policies could be improved and complemented to achieve faster declines in smoking

prevalence.[129,130] In addition to policy measures already in place, greater investment in innovative MMCs, reversing declines in the uptake of SSSs and wider integration of smoking cessation interventions into NHS service delivery, extending smoke-free polices to a wider range of public places, preventing smoking promotion through media imagery and other loopholes in advertising and promotion legislation, and tighter measures to prevent youth access would all make contributions to this end.

However, the most effective policy measure is price. Repeated substantial increases in tobacco price, and removal of the price differentials for premium cigarettes, budget cigarettes and hand-rolling tobacco, would have a substantial impact, particularly among low-SES groups. The effect of taxes can be further enhanced if some of the revenue generated is used to support comprehensive tobacco control strategies. However, the negative effect of price rises on the incomes of those who continue to smoke, as well as the need to do more in general to provide smokers with alternative means to stop smoking, demands additional alternative approaches. Making non-tobacco nicotine products available to smokers, as envisaged in the Tobacco Control Plan for England[3] and advocated in this report, could not only reduce the prevalence of smoking but also offset the negative effect of increased tax on continuing smokers by providing a more affordable and acceptable alternative product.

3.5 Summary

- Increasing the price of cigarettes reduces smoking prevalence, particularly among young and relatively disadvantaged smokers.
- Price increases may be more effective if introduced in single large rather than multiple small increments.
- The effect of price increases is undermined by the availability of illicit tobacco, and the option for smokers to downtrade to ultra-low-price cigarettes and hand-rolling tobacco.
- Smoke-free legislation has reduced passive exposure of children and adults to smoke, and may also have generated some further reduction in smoking prevalence.
- MMCs reduce smoking in all age groups and are an important factor in enhancing the effectiveness of other interventions, but are effective only if sufficiently well funded.
- Graphic health warnings on packs discourage smoking uptake, and encourage and sustain quit attempts.
- Removal of tobacco advertising is particularly effective in reducing smoking uptake, and both point-of-sale display prohibition and standardised packaging of tobacco products further reduce exposure to tobacco branding.

- Smoking imagery in the media, both branded and unbranded, remains a strong promotional driver of smoking, particularly among young people.
- Raising the minimum age of sale, and prohibiting vending machine sales, reduces smoking among young people.
- Providing cessation support to smokers helps them to quit smoking and, if widely available, increases the rate at which smoking prevalence declines.
- Smokers from low-SES groups are particularly likely to respond to price increases and graphic health warnings.
- Existing tobacco control policy could be enhanced by: further reducing the affordability of tobacco, particularly of budget cigarettes and hand-rolling tobacco; investing in MMCs; preventing smoking imagery in the media, including social media; and extending smoke-free policies to outdoor areas.
- NHS SSSs need to be expanded, and appropriately funded to be integrated and actively promoted in clinical care pathways.
- However, even with all such measures in place, millions of people in the UK will continue to smoke for the foreseeable future. Alternative approaches, particularly for young and disadvantaged smokers, are urgently needed.
- Promoting the use of alternative, acceptable and more affordable nicotine products as a harm-reduction strategy has the potential to complement existing tobacco control policy, and in particular to offset the potentially regressive nature of tobacco tax rises.

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4 Nicotine pharmacology and pathophysiology

4.1 Nicotine chemistry and absorption

Nicotine is a naturally occurring alkaloid present in the leaves of the tobacco plant, and is the major psychoactive compound and mediator of addiction to tobacco use.[1] Nicotine absorption across cell membranes is highly pH dependent, because only non-ionised nicotine can cross biological membranes and be absorbed into the bloodstream.[2] Nicotine is a weak base with a pK_a of approximately 8,[2] so, in the relatively acidic medium of cigarette smoke with a pH typically ranging from 6.0 to 7.8, more than half of the nicotine in tobacco smoke is protonated[3] and cannot be absorbed. Manipulating the pH of tobacco smoke to make it more alkaline thus increases nicotine absorption.[4]

The average nicotine content of commercially available manufactured cigarettes is around 10 mg, but, as a result of loss in sidestream smoke, retention in the cigarette stub and delivery of nicotine in ionised form, only about 1 mg is absorbed from each cigarette smoked.[5] When tobacco smoke is inhaled, nicotine passes through the alveolar membranes of the lung into the pulmonary venous circulation. It is then carried into the heart, and then directly into the arterial system, reaching the brain within 10–20 s. The rate of increase in arterial nicotine concentration achieved by inhaling nicotine is thus faster even than that achieved by intravenous administration, with peak arterial concentrations occurring at around 20 and 30 s, respectively.[6] After smoking a single cigarette, arterial nicotine concentrations differ according to the type of cigarette and the way in which it is smoked. Thus, one study reported arterial levels of only about 20 ng/mL,[6] but some smokers can achieve arterial nicotine concentrations of about 60 ng/mL with just a few puffs[7] and arterial concentrations of 100 ng/mL have been reported after smoking a single cigarette.[8] The arterial blood nicotine levels achieved by inhaling nicotine are much higher than in the venous circulation[8] (Fig 4.1). As the rate at which an addictive drug reaches the brain influences its addictive potential,[9] the fast absorption and delivery of nicotine after inhaling tobacco smoke underpin the rapid behavioural reinforcement of smoking.[10]

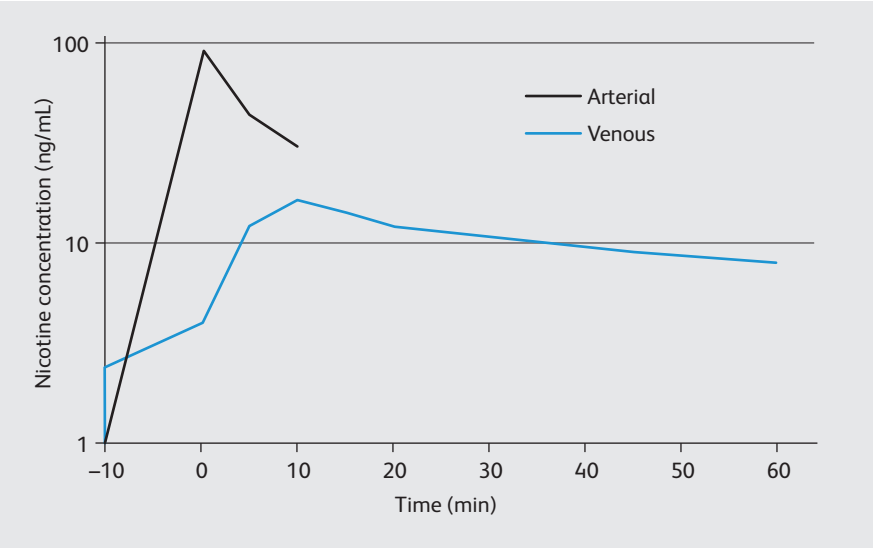

Fig 4.1 Arterial and venous plasma nicotine levels after smoking a cigarette. (Adapted and reprinted from Le Houezec[8] with the permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union.)

In contrast, when nicotine is swallowed, it is absorbed from the gastrointestinal tract into blood that flows into the portal veins and hence to the liver, where it undergoes substantial first-pass metabolism. Oral nicotine therefore generates very low and similar systemic venous and arterial blood levels. Conventional nicotine replacement therapy (NRT) products avoid this first-pass metabolism by delivering nicotine via the skin, mouth or nose, blood from which drains directly into the systemic venous system. NRT thus generates higher arterial nicotine levels than those achieved by gastrointestinal absorption, but levels in arterial blood are similar to those in venous blood and much lower than those achieved by inhalation. There are also marked differences in venous plasma concentrations of nicotine achieved, depending on the form and dose of NRT used[11] (Fig 4.2). The variation in time to reach maximal nicotine plasma concentration is due, in part, to differences in administration duration as well as absorption time that occur with each route of delivery.[11]

The relatively slow delivery of nicotine to the brain achieved by NRT is much less reinforcing, and hence much less likely to generate dependence, than cigarette smoking.[12] However, forms of NRT that deliver nicotine relatively quickly, such as the nasal spray, are thought to be more likely to generate dependence than others. Overall, however, the addictive potential of cigarettes is much higher than that of NRT or other non-inhaled nicotine products.[13] Clinically, very few users of NRT become dependent on it.

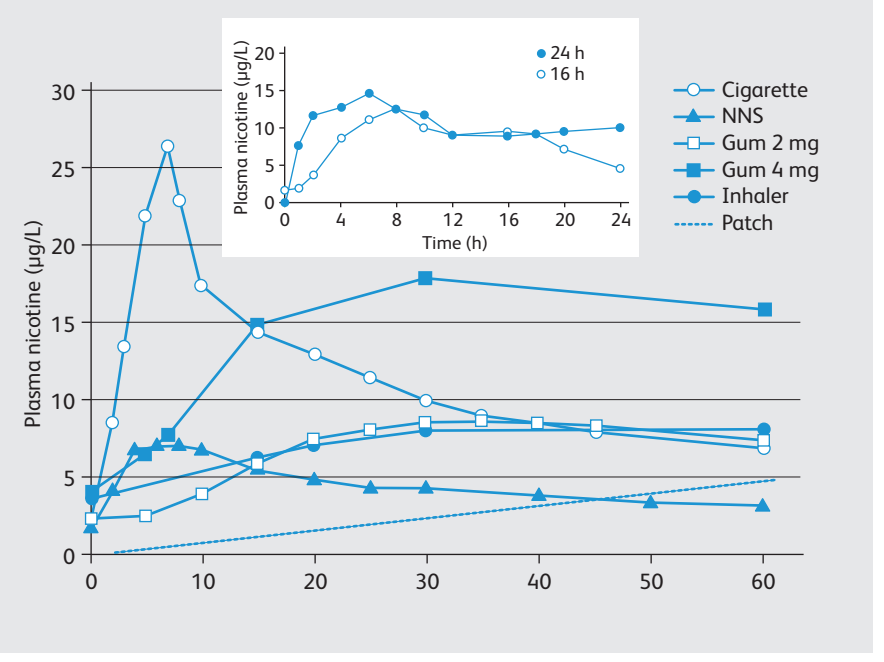

Fig 4.2 Venous plasma nicotine concentrations achieved over 1 h by a single cigarette and by single doses of various forms of nicotine replacement therapy (NRT – nicotine nasal spray (NNS), 2 and 4 mg gum, and nicotine patch). Inset: nicotine levels after a 16- and 24-h course of nicotine patch treatment over a 24-h period. (Reproduced from: Schneider NG, Olmstead RE, Franzon MA, Lunell E. The nicotine inhaler: clinical pharmacokinetics and comparison with other nicotine treatments. *Clinical Pharmacokinetics* 2001;40:661–84.[8] With permission from Springer.)

4.2 Nicotine metabolism

Around 70–80% of absorbed nicotine is metabolised to cotinine,[14] and around 90% of this metabolism is via the hepatic cytochrome P450 (CYP) 2A6 enzyme.[15] The majority of cotinine is then further metabolised to 3′-hydroxycotinine in a reaction mediated exclusively by CYP2A6.[16] Both nicotine and its metabolites are excreted in urine. As most nicotine clearance occurs via metabolic (ie non-renal) means, variability in nicotine metabolism is likely to cause substantial variation in the rate of nicotine clearance between individuals.[17,18] The ratio 3′-hydroxycotinine:cotinine is known as the nicotine metabolite ratio (NMR), which serves as a phenotypic indicator of CYP2A6 enzymatic activity. As CYP2A6 represents the major route of nicotine clearance, the NMR is also strongly correlated with the rate of nicotine clearance.[18]

Variation in the *CYP2A6* gene, which has an impact on the functionality of the CYP2A6 enzyme, is common and associated with alterations in the rate of nicotine clearance, together with a variety of smoking behaviours.[19] Slower nicotine metabolism, as inferred from *CYP2A6* genotypes or as measured directly by the NMR, is associated with lower cigarette consumption,[20,21] lower nicotine dependence,[22] lower smoking-related reward[22] and lower risk of being a current smoker.[20] Slower nicotine metabolism is also associated with an increased likelihood of unaided cessation (ie cessation without behavioural or pharmacological support)[23,24] and cessation in clinical trials, in which slow metabolisers are typically more likely to achieve abstinence on both placebo[25,26] and NRT.[27,28] A separate study that used an alternative *CYP2A6* phenotype measure also found associations between slow nicotine metabolism and higher abstinence rates.[29] The prevalence of slower nicotine metabolism differs according to ethnicity, predominantly owing to interethnic variability in patterns of *CYP2A6* allele expression. The frequency of *CYP2A6* alleles conferring reduced or loss of CYP2A6 activity is generally higher in African and East Asian populations than in European populations, as reflected by a higher prevalence of reduced nicotine metabolism in populations of African and East Asian descent (approximately 40–50%) versus European descent (approximately 10–25%).[30–32]

In addition to CYP2A6-mediated nicotine inactivation, nicotine can be inactivated through *N*-glucuronidation and *N*′-oxidation, through metabolism by uridine diphosphate (UDP) glucuronosyltransferase (UGT) 2B10 and flavin-containing monooxygenase (FMO) 3, respectively. The resulting minor nicotine metabolites, nicotine *N*-glucuronide and nicotine *N*′-oxide, account for up to 5% and 7% of a nicotine dose that can be recovered from urine, respectively.[2] In individuals with no functional CYP2A6 activity, FMO3- and UGT-mediated nicotine metabolism may be more important for nicotine clearance;[33] however, reduced FMO3 function did not substantially affect nicotine metabolism in individuals with reduced CYP2A6 activity.[32] UGT2B10 can also metabolise cotinine to cotinine *N*-glucuronide, comprising 12–17% of a nicotine dose recovered from urine.[14] A second UGT enzyme, UGT2B17, metabolises 3′-hydroxycotinine to 3′-hydroxycotinine *O*-glucuronide, and accounts for about 9% of a nicotine dose recovered from urine.[2]

Several of these minor enzymes involved in the nicotine and cotinine metabolic pathway (FMO3, UGT2B10 and UGT2B17) are highly polymorphic, with some genetic variants leading to altered activity of these enzymes. Variation in *FMO3* is associated with minor alterations in nicotine metabolism, but appears to be of insufficient magnitude to alter cigarette consumption or total tobacco dose in light smokers of African-American ancestry.[32] In heavy smokers of European ancestry, variation in *FMO3* has little effect on consumption, unless restricted to those with faster CYP2A6 activity (a difference of about three cigarettes a day).[34] The influence of *UGT* genetic variation, tested to date on variation in nicotine

metabolism, is also relatively modest and does not appear to alter smoking behaviours substantially.[35,36] Although *UGT2B17* genetic variation is associated with altered 3′-hydroxycotinine metabolism,[36] variation in genes for UGTs that alters cotinine and 3′-hydroxycotinine metabolism is unlikely to affect smoking behaviours because cotinine and 3′-hydroxycotinine are essentially inactive metabolites of nicotine.

4.3 Systemic and central nervous system effects

4.3.1 Nicotinic acetylcholine receptors

Nicotine exerts its pharmacological effects through binding to nicotinic acetylcholine receptors (nAChRs). These receptors are universally expressed in cells throughout the body,[37] including the central and peripheral nervous systems, where they play a key role in mediating nicotine dependence and addiction. The nAChRs are ligand-gated ion channels composed of five transmembrane subunit proteins arranged around a central pore. Neuronal nAChRs consist of α (α_2–α_{10}) and β (β_2–β_4) subunits,[38] each of which is encoded by a single gene (denoted with a '*CHRN*' prefix), and may be homomeric or heteromeric in terms of subunit composition. Different combinations of subunits result in receptors differing in pharmacological and physiological profiles.[39,40] Individual subtypes differ, eg in their affinity for nicotine, and sensitivity to upregulation and desensitisation after nicotine exposure.[40]

Each nAChR subtype has a distinct distribution profile within the brain, which can be determined through assessment of subunit mRNA using techniques such as *in situ* hybridisation, and through imaging techniques such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), using subtype-selective radioligands.[40] The differential expression of specific subunits, with distinct biological functions in brain regions mediating specific behaviours, allows nicotine to exert a broad range of effects.[41] The $\alpha_4\beta_2$ receptor is the most commonly expressed subtype in the human brain, and historically has been implicated through animal models as critical to the experience of nicotine's reinforcing effects (eg Picciotto *et al*[42]). In recent years, however, the importance of the less studied α_3- and α_5-receptor subunits in mediating nicotine dependence has been recognised. The α_5-receptor subunit appears to play a key role in determining aversive responses to high doses of nicotine.[43]

4.3.2 Systemic and central nervous system effects

Nicotine, at relatively low doses, is a stimulant. It increases heart rate, and has been reported to have beneficial effects on cognition and performance,

improving attention, memory and fine motor skills.[44] Tolerance to nicotine can develop rapidly (within a few days of use), and cessation of use then results in the experience of withdrawal symptoms, both somatic and affective, such as anxiety, restlessness, inability to concentrate, irritability and change in appetite.[45] Chronic exposure to nicotine results in a number of neuroadaptions,[46] including desensitisation of nAChRs and upregulation in their expression,[47] both of which are linked to nicotine tolerance and withdrawal.

4.3.3 Mechanisms of effect

Nicotine exerts its complex effects (including arousal, mood modulation and pleasure) via several neurotransmitter pathways. Once bound to neuronal nAChRs, nicotine facilitates the release of dopamine, serotonin and a host of other neurotransmitters including γ-aminobutyric acid (GABA), glutamate, noradrenaline, acetylcholine and endorphins.[47] The mesolimbic dopamine pathway has, perhaps, been the most widely studied in relation to nicotine dependence.[46] Dopamine release in the nucleus accumbens, resulting from nicotinic stimulation of dopaminergic neurons in the ventral tegmental area, is crucial to the processing of rewarding and reinforcing the effects of nicotine. Indeed, dopamine release in the nucleus accumbens appears to be critical in the experience of the rewarding effects of many drugs of abuse. Continued pairing of the rewarding/reinforcing effects of nicotine with specific sensory and environmental stimuli (which could include, for example, the smell of tobacco smoke or the sight of a pack of cigarettes – smoking-related behaviours) results in these stimuli also acquiring reinforcing properties. These cues (conditioned reinforcers) have been linked to the maintenance of smoking, smoking-related cravings and relapse.[47]

4.4 Toxicity and potential hazards

4.4.1 Toxicity of nicotine

Although nicotine is a toxic compound, overdosing on nicotine products used as directed is almost impossible, given the individual ability to titrate dose and the short half-life of nicotine (see Development of addiction below – Section 4.5). However, ingestion of high doses (purposeful or accidental) can be fatal. Historically, the lethal dose of nicotine for a human adult has consistently been stated to be about 60 mg,[48] corresponding to an oral median lethal dose (LD_{50}) of approximately 0.8 mg/kg. However, this figure has recently been disputed in the light of reports of non-fatal suicide attempts or accidents involving nicotine ingestion, leading to an estimate that the lower dose limit for fatal outcomes is likely to be 500–1,000 mg ingested nicotine, equivalent to an oral LD_{50} of 6.5–13 mg/kg.[48]

4.4.2 Potential hazards of short- and long-term nicotine use

At commonly used dose levels, short-term nicotine use does not result in clinically significant harm. The safety of NRT products, which have typically been used for days or weeks in the context of an attempt to quit smoking, is well established[49] (see Chapter 5 for further detail), with no evidence of any increase in the risk of heart attack, stroke or death.[50,51]

Evidence about long-term nicotine or NRT use is relatively scarce, and concerns have been raised that long-term NRT use may increase cancer risk, in part owing to endogenous formation of carcinogens such as *N*′-nitrosonornicotine (NNN).[52] However, studies carried out in experimental animals largely indicate that nicotine alone is not carcinogenic.[53] *In vitro* and *in vivo* studies in animals do, however, suggest that nicotine can have tumour-promoting effects through activation of intracellular signalling pathways. Such effects include cell proliferation, enhanced angiogenesis and decreased apoptosis.[37,49] However, it is important to note that many studies in this area have used nicotine at higher doses than those achieved in heavy smokers.[54] *In vitro* research suggests that nicotine can have a negative impact on the function of some cells within the cardiovascular system,[55] and adverse effects on glucose metabolism.[56] However, robust evidence on the safety of long-term nicotine use in humans from the 5-year Lung Health Study, in which participants were actively encouraged to use NRT for several months and many continued to consume NRT for a much longer period, demonstrates no association between sustained NRT use and the occurrence of cancer (lung, gastrointestinal or any cancer) or cardiovascular disease.[57,58] In addition, a recent clinical trial comparing 8, 24 and 52 weeks of NRT treatment found that treatment duration was not associated with any adverse effects, further supporting the safety of long-term NRT use.[59]

Although there is little evidence on the safety of using nicotine for periods longer than 5 years, and no data on the safety of long-term use of nicotine by inhalation other than when delivered by tobacco smoke, it is widely accepted that any long-term hazards of nicotine are likely to be of minimal consequence in relation to those associated with continued tobacco use. Notably, and in recognition of this fact, the UK Medicines and Healthcare products Regulatory Agency (MHRA) recently approved an extension to the indication of NRT to include 'harm reduction',[60] defined as 'for use as a substitute or partial substitute for smoking tobacco, both for those making an attempt to quit and those not currently intending to make a quit attempt, *without any restriction on its duration of use*'.[61] Guidelines on harm-reduction approaches to smoking from the National Institute for Health and Care Excellence (NICE) further state that 'it is safer to use licensed nicotine-containing products than to smoke' and 'there is reason to believe that lifetime use of licensed nicotine-containing products will be considerably less harmful than smoking'.[62]

Research from animal studies suggests that fetal exposure to nicotine may lead to adverse postnatal health consequences[63] and that cognitive function and development are adversely affected by nicotine exposure during both the fetal and the adolescent periods.[64] The relevance of these findings to human brain development remains uncertain, however. There is evidence that smoking in adolescence is associated with cognitive and attentional impairments in later life, and possibly an increased risk of mental health problems,[65] but it is difficult to exclude the effects of confounders of this association in the observational studies available.[66]

4.5 Development of addiction

Nicotine is the primary addictive component in cigarettes and other tobacco products. It establishes and maintains addiction, thereby sustaining use, through a range of complex actions on brain neurochemistry, which have been reviewed in detail elsewhere.[67,68] However, the addictiveness of any nicotine-containing product depends on several factors beyond merely the presence of nicotine. These factors primarily include the rate at which nicotine is absorbed and delivered to the brain, and the dose of nicotine delivered. Other factors, such as the speed at which the drug is metabolised and how soon withdrawal symptoms occur, play a role. This is particularly relevant to nicotine, given its short half-life (about 2 h), but this is a feature of the drug more than the product delivering the drug. A nicotine-containing product will therefore be more or less addictive depending on the dose and rate at which the nicotine is delivered. Essentially, a product that delivers a high dose rapidly will have a greater liability for addiction than one that delivers a low dose slowly. In this section, we describe the importance of these factors.

4.5.1 Dose effects on addiction potential

Dose is an important factor in the development of nicotine dependence. Animal models clearly demonstrate an inverted-U relationship between nicotine dose and self-administration, although there is interindividual variability in the shape of this curve, some of which is under a genetic influence.[43] Therefore, increasing the dose is associated with increased self-administration up to a point, after which higher doses become increasingly aversive and ultimately toxic. One advantage of the short half-life of nicotine is, however, that it enables consumers to self-titrate their achieved dose. The dose (ie plasma concentration) of nicotine achieved via use of different nicotine-containing products varies considerably (see Fig 4.1 – the total dose achieved is reflected by the area under the curve for each product). Figure 4.1 also illustrates the considerable variability in speed of delivery across these products which, as discussed above, also contributes to addiction liability.

4.5.2 Rate of nicotine clearance

Nicotine is metabolised principally in the liver, with a half-life for elimination of approximately 2 h (although, as discussed above, this varies considerably between individuals). As a result of this short half-life, plasma nicotine concentrations drop rapidly after nicotine administration, leading to withdrawal symptoms, prompting further nicotine administration in regular users, eg in a typical heavy, dependent smoker, nicotine levels increase rapidly after smoking a cigarette (by about 5–30 ng/mL), then drop before increasing again after smoking the next cigarette. Over the course of a day, plasma nicotine concentrations rise gradually to a steady state of between about 10 and 50 ng/mL.[8] The combination of a short half-life and regular administration via frequent smoking (eg hourly) results in a distinctive pattern of nicotine concentrations, as represented in Fig 4.3. Critically, overnight abstinence leads to the almost-complete elimination of nicotine from the body, leading to marked withdrawal on waking, and the need to consume nicotine in order to reverse these symptoms.

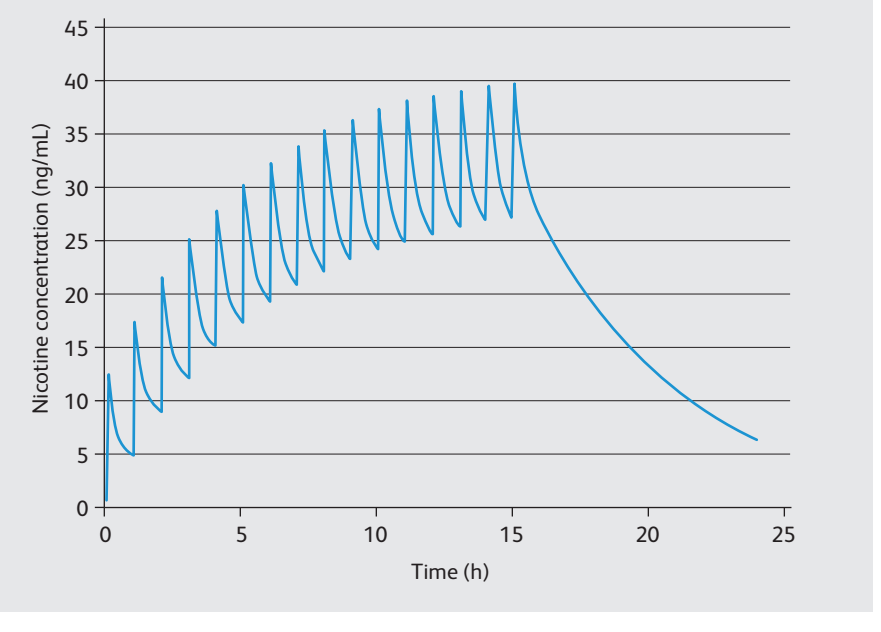

Fig 4.3 Simulated plasma nicotine concentrations obtained after smoking a cigarette every hour for 16 h. (Adapted and reprinted from Le Houezec[8] with the permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union.)

4.6 Smoke constituents influencing the addictive potential of cigarette smoke

The addictive potency of cigarettes (and indeed other tobacco products) is influenced by not only their nicotine content but also other aspects of product design, including substances added to the cigarette to enhance nicotine delivery and absorption. Monoamine oxidase (MAO) inhibitors in tobacco smoke increase the levels of amines in the brain, such as dopamine and serotonin, and may subsequently potentiate the reinforcing effects of nicotine.[69] Indeed, animal studies have demonstrated that MAO inhibitors facilitate nicotine self-administration and enhance its motivational properties.[70,71] These findings may also contribute to the strong reinforcing properties of nicotine from cigarettes.

Sugars and polysaccharides are commonly added to tobacco products[72] to increase the formation of aldehydes, including formaldehyde and acetaldehyde, in tobacco smoke. Acetaldehyde itself has addictive potential,[73] as demonstrated through self-administration experiments in animals,[74] but it also enhances the addictive potential of nicotine. The interaction between these compounds also generates a rewarding effect that exceeds the additive effects of either component in rodent studies.

Menthol and other flavourings (including cloves and liquorice) increase the palatability of cigarette smoke and, in the case of menthol and cloves, facilitate deeper inhalation and therefore a higher nicotine dose (owing to their cooling/local anaesthetic effects). These are widely added at levels below those used in what are conventionally considered to be 'flavoured' cigarettes. Flavours may also become conditioned reinforcers in themselves, as a consequence of their repeated pairing with nicotine.[75] In addition, menthol inhibits metabolism of nicotine to cotinine, purportedly through inhibition of CYP2A6 enzyme activity,[76] thus increasing the effect of nicotine. Cocoa and chocolate, which contain theobromine, are also common additives in tobacco. Theobromine is a bronchodilator, and thus has been proposed to enhance nicotine absorption in the lungs. However, the theobromine content of cigarettes was deemed too low to exert bronchodilatation in a recent review.[77] Levulinic acid is an additive with a sweet caramel taste, but it also alters the pH and so reduces the 'harshness' of inhaled smoke.[78] This, similarly to menthol, facilitates a higher nicotine dose.

Alkaline additives such as ammonia compounds are among the most common additives used in cigarette manufacture.[79] These substances are added to cigarettes (and other tobacco products) to manipulate the pH. As discussed above, increasing the pH increases the proportion of non-ionised, or freebase, nicotine, which is more physiologically active than the ionised form, crossing biological membranes more readily. Tobacco industry scientists have extensively investigated the potential of pH manipulation to optimise nicotine delivery (see

Hurt and Robinson[79]). Curing methods used in the production of tobacco can also influence the pH of tobacco smoke. In particular, air-cured tobacco, as used in cigars, generates nicotine at a relatively high pH, facilitating absorption from oral and upper airway mucosa. Cigarette tobacco is largely flue cured, resulting in nicotine at a lower pH and lower upper airway absorption, hence requiring inhalation into the much larger surface area of the lung alveoli to achieve significant absorption.

4.7 Impact of cigarette design characteristics on nicotine delivery

A number of physical characteristics of cigarettes have been engineered to influence nicotine delivery, including cigarette dimensions, filtration, ventilation, paper porosity and tobacco shred size.[79] Ventilation, for example, serves to manipulate nicotine, tar and carbon monoxide levels through dilution of tobacco smoke, and is achieved through the introduction of holes in both the filter and the paper wrap.[77] Ventilation technology was used in the production of 'light' or 'low-tar' cigarettes, which were promoted by the tobacco industry as healthier alternatives to full-strength cigarettes. However, these descriptions have been shown to be misleading and for this reason have been banned in the UK. Although smoking machine assessments give readings indicating that these cigarettes yield lower doses of nicotine, studies in humans have shown that smokers compensate by altering their smoking topography (ie the way in which people smoke their cigarettes). Thus, smokers use deeper inhalation, increased number of puffs per cigarette, etc when smoking these cigarettes, in order to achieve the same dose of nicotine attained when smoking stronger brands.[80] This results in equivalent levels of exposure to the harmful constituents of tobacco smoke.[81]

Smoking topography also affects nicotine delivery. Smokers can make changes to their blood nicotine levels by altering depth and frequency of inhalation and volume of smoke inhaled. A 20-a-day smoker can halve the number of cigarettes that they smoke, but sustain the same plasma nicotine levels by taking larger and deeper puffs. It is this compensatory behaviour that leads to a lack of association between machine-determined nicotine levels in cigarettes and the nicotine dose and quantity of toxic smoke inhaled by a smoker (see below). This may be why reductions in the amount individuals smoke, although making it easier for them to go on to quit, have a relatively limited impact on health outcomes compared with quitting altogether. There are also sex differences in smoking topography (women typically take smaller puffs than men) and ethnicity (African-American individuals typically smoke more of their cigarette than people of European descent).[2] Mood may also affect the way in which people smoke, with positive effect being associated with a greater increase in blood nicotine levels.[82]

4.8 Lessons from cigarette design for harm-reduction product development

Nicotine is the primary addictive component sustaining tobacco use, but is not the cause of the vast majority of harm associated with tobacco use. Therefore, a product that delivers nicotine in the absence of other constituents of tobacco will be associated with dramatically less harm. The safety of NRT demonstrates this and, although long-term use is relatively uncommon, there is sufficient evidence to conclude that any harm from long-term nicotine use will still be negligible compared with the harm of tobacco use. However, nicotine-containing products such as NRT, although very low in harm, are also substantially less satisfying to smokers than, for example, cigarettes, as evidenced by their modest efficacy as smoking cessation products. As discussed above, this is due to the favourable nicotine delivery characteristics and unique range of behavioural reinforcers associated with cigarette smoking. The ideal harm-reduction device should therefore deliver nicotine in a manner as similar as possible to cigarettes, while at the same time maximising palatability and nicotine delivery to approximate the experience of cigarette smoking more closely.

4.8.1 Targeting the determinants of addictiveness

The principal determinants of the addictiveness of a nicotine-containing product are the dose that it delivers, and the speed with which the dose is delivered. Given that most cigarette smokers are dependent (at least to some degree) on nicotine, targeting these determinants is a critical requirement of any harm-reduction product. The use of additives in tobacco products and the design of the cigarette are both engineered to enhance nicotine delivery from the cigarette, by modifying both the palatability of the cigarette smoke (and therefore the ease with which it can be inhaled, facilitating rapid delivery and self-titration) and the bioavailability of the nicotine contained within it. Other factors, such as the taste and smell of cigarette smoke, and the behavioural action of smoking, can themselves become conditioned reinforcers over time and, although secondary to the effects of nicotine, are important drivers of continued smoking .

4.8.2 E-cigarettes and harm reduction

E-cigarettes meet many of the criteria for an ideal tobacco harm-reduction product. Although nicotine delivery from e-cigarettes depends on a number of factors, including level of user experience and device characteristics,[83] they can in principle deliver a high dose of nicotine, in the absence of the vast majority of the harmful constituents of tobacco smoke (or at least at negligible levels), in a way that enables accurate self-titration (see Chapter 5). They also provide some of the

cues associated with cigarette smoking, such as taste and throat rasp, as well as behavioural actions such as hand-to-mouth movement. At present therefore, although little is known of the kinetics of nicotine uptake from e-cigarettes into arterial blood, e-cigarettes offer a substitute to smoking that is more likely, on theoretical grounds, to prove satisfying and acceptable to smokers than NRT.

4.9 Summary

- Nicotine is the primary addictive component of tobacco smoke.
- When inhaled into the lungs, nicotine from tobacco smoke is absorbed and delivered to the brain much more quickly, and in higher doses, than can be achieved by other routes of absorption.
- This rapid delivery of repeated high doses of nicotine to the brain is thought to underpin the addictive nature of cigarettes.
- Nicotine is metabolised quickly, causing blood levels to fall rapidly after dosing. People who metabolise nicotine more slowly, and therefore maintain more constant blood levels, tend to be less heavily addicted.
- Nicotine is a stimulant that improves concentration and fine motor skills. However, once tolerance is acquired, unpleasant withdrawal symptoms occur when nicotine blood levels fall.
- Sustained use of nicotine is reinforced by some of the co-stimuli of smoking, such as the taste and sensation of tobacco in the throat, and the smells and behaviours associated with smoking.
- The tobacco industry has manipulated other constituents and additives in tobacco to enhance the addictiveness of nicotine in smoke.
- NRT products may not be effective in some smokers because they replicate few of the delivery, sensory or behavioural characteristics of cigarettes.
- E-cigarettes have the capacity to replace more of the characteristics of tobacco cigarettes than conventional NRT, and therefore have potential as effective smoking substitutes.

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5 Non-tobacco nicotine products

5.1 Introduction

For many years, the range of non-tobacco nicotine products available in the UK has been dominated by nicotine replacement therapy (NRT) products, developed and licensed as medicines to aid smoking cessation. The range of NRT products available has grown to include transdermal patches, chewing gum, lozenges, nasal spray, oral pouch, oral spray, oral strips and the 'inhalator', a device that provides a nicotine vapour for oral absorption. In recent years the licences for these products have been extended in several countries, including the UK, to include use to assist smoking reduction and temporary abstinence.

There is strong evidence from randomised controlled clinical trials that NRT can be an effective smoking cessation therapy. A Cochrane review carried out in late 2012 identified 150 such trials, and concluded that all commercially available forms of NRT increase the likelihood of successful cessation among smokers making a quit attempt.[1] NRT products also have a very good safety record.[2] The products differ in the speed of nicotine delivery and the degree of behavioural replacement for smoking that they provide, but are fairly similar in the amount of nicotine that their strongest formulation delivers. Some require specific techniques for correct use (eg chewing gum and nasal spray), whereas others (eg the transdermal patch) are very simple to use. None, however, reproduces the rapid delivery of high doses of nicotine achieved by inhaling tobacco smoke, and few smokers find them enjoyable or satisfying.

NRT products have traditionally been produced and marketed by the pharmaceutical industry, but in recent years tobacco companies have also begun to acquire or develop products manufactured to standards similar to those of NRT products. Examples of these 'clean', non-tobacco nicotine products include Zonnic nicotine gum, marketed by Niconovum, part of Reynolds American Inc, and Verve nicotine-containing discs marketed by NuMark, part of Philip Morris. In the past 5 years, however, the non-tobacco nicotine market has been transformed by the emergence of e-cigarettes, which are now the most widely used form of non-tobacco nicotine. Unlike NRT, they have been marketed as

consumer products rather than therapeutic goods, and also, unlike most forms of NRT, they retain several important features of smoking other than nicotine delivery, including similar hand-to-mouth movements, behavioural rituals, an inhaled sensory stimulus and a range of flavours. These characteristics make e-cigarettes attractive to a wide range of smokers, including many who do not or would not use NRT; hence, they provide a potentially viable, lower-hazard market competitor to tobacco cigarettes. As consumer products, they are subject to varying degrees of regulation in different countries, and are evolving quickly as the technology improves. Most e-cigarettes are marketed by independent companies importing products from China, but some production is now based in the UK. Several leading brands have now been bought by tobacco companies (see Chapter 8).

The non-tobacco nicotine market in the UK and many other countries is thus in a state of rapid change, with use of e-cigarettes already eclipsing that of pharmaceutical NRT (see Chapter 7), and an increasingly wide range of new products that deliver nicotine at or close to medicinal standards, some of them marketed by the tobacco industry, becoming available. Indeed the status quo of the nicotine market, whereby medicines have to date been made exclusively by pharmaceutical companies, has recently been challenged by the award of medicines licences to two new products: a nicotine-metered dose inhaler (Voke*)*, and an e-cigarette (E-Voke), both of which are being brought to market by Nicoventures, a subsidiary of British American Tobacco.

This chapter provides a summary of currently available non-tobacco nicotine products, their pharmacokinetic profile, safety, addiction potential and trends in their use. Where blood or plasma nicotine levels are given, they relate to those in venous blood (see Chapter 4) unless stated otherwise.

5.2 NRT products

5.2.1 Transdermal nicotine

5.2.1.1 Doses and pharmacokinetics

Commercially available transdermal nicotine patches provide nicotine at a controlled rate for absorption through the skin into the systemic venous circulation. Products vary in dose from around 7 to 25 mg per patch, and deliver nicotine for either 16 or 24 h. High-dose examples include patches that deliver 25 mg over 16 h, or 21 mg over 24 h; lower doses, which are intended for weaning some weeks after smoking cessation, deliver (for example) 15 or 10 mg over 16 h, or 14 or 7 mg over 24 h. The rationale behind the 24-h patch is that it delivers nicotine during sleep and thus provides some protection against urges to smoke immediately after waking. The occasional drawback of 24-h delivery,

which is avoided by 16-h formulations, is that nicotine can cause vivid dreams or otherwise disturbed sleep.

The rate of absorption of nicotine from transdermal patches is slow, although there are some differences in pharmacokinetic profile between available products. In general, after application of the patch there is a delay of up to 2 h before plasma nicotine levels start to rise. High-dose products can generate maximum venous plasma concentrations of 16–18 ng/mL at around 6–12 h.[3,4] Plasma nicotine levels at 24 h are about 11 ng/mL with the 24-h patch, and 3 ng/mL with the 16-h patch.[3] During use a small reservoir of nicotine accumulates in the skin under the patch, which means that nicotine continues to be absorbed into the blood for an hour or so after the patch has been removed.

5.2.1.2 Safety profile

The nicotine patch has a good safety profile, even when more than one high-dose patch is applied simultaneously.[5] In addition to the generic nicotine effects outlined briefly in Chapter 4, which apply to all the products described in this section, the most common side effects of the nicotine patch are insomnia, abnormal dreams, and skin irritation at the application site. There were early case reports of cardiovascular adverse effects, but more robust reviews suggest that these were not caused by NRT.[6]

5.2.1.3 Addiction potential

The addiction potential of nicotine products is generally related to the speed of nicotine delivery, with faster delivery systems more likely to be used long term.[7,8] As transdermal patches deliver nicotine very slowly, long-term dependence is not expected to be a problem, and empirical evidence confirms that this is indeed the case.[7,9]

5.2.2 Oral and nasal nicotine

5.2.2.1 Doses and pharmacokinetics

Oral and nasal NRT products deliver nicotine more rapidly than nicotine patches, typically achieving peak plasma nicotine concentrations within 30–60 min. However, this kinetic profile is due in part to the sustained-release formulations used in many oral products, and faster absorption is possible. Formulations that spray nicotine solutions directly on to the mouth or nasal linings are among the most quickly absorbed NRT products, achieving peak levels within about 10 min of dosing. Nicotine absorption is influenced by the pH of the oral lining, being faster in relatively alkaline conditions. As with all oral or nasal products, nicotine that is swallowed undergoes extensive first-pass

metabolism (see Chapter 4) and makes no appreciable contribution to levels of nicotine in the blood.

Nicotine gum

Nicotine gum is available in two strengths, 2 mg and 4 mg, with the higher dose recommended for more dependent smokers. The nicotine contained within the gum is released on chewing and absorbed through the tissues lining the mouth. After chewing a single 2-mg piece of gum, peak plasma concentrations of 3–5 ng/mL are observed within 30–60 min,[10,11] and chewing a 2-mg piece of gum every hour results in plasma nicotine concentrations of between 12 and 16 ng/mL. The maximum concentration (C_{max}) for a single dose of 4-mg gum is around 10 ng/mL, and regular dosing can generate plasma nicotine concentrations of between 27 and 32 ng/mL.[11]

Nicotine oral disc

A recently developed nicotine oral disc has similar characteristics to the gum. It is a non-dissolving polymer disc containing 1.5 mg tobacco-derived nicotine, which is released when it is chewed. Chewing for 15 min results in an increase in plasma nicotine concentration of around 2 ng/mL.[12]

Nicotine oral pouch

The nicotine in this product is in a powder, contained in a small pouch designed to be held in the mouth. A single 4-mg pouch, if held against the inner lining of the cheek for 30 min, produces a peak plasma concentration of approximately 10 ng/mL.[13]

Nicotine lozenges and sublingual tablets

Products in this NRT category differ in how quickly they dissolve in the mouth, and in their dose and pharmacokinetic profile. A single 1-mg lozenge creates a peak plasma concentration of around 2 ng/mL,[10] a 2-mg lozenge between 4 and 5 ng/mL and a 4-mg lozenge about 10 ng/mL, all within about 60 min. A study of a 2.5-mg nicotine lozenge showed that single use resulted in a maximum plasma concentration of 10.8 ng/mL in 30 min.[14] Regular use of lozenges (eg one every 1–1.5 h) results in plasma nicotine concentrations of between 10 and 15 ng/mL for the 1- and 2-mg lozenges[10,11] and 20 and 26 ng/mL for the 4-mg lozenge.[11] The pharmacokinetic profile of the 2-mg sublingual tablet is similar to that of the 2-mg lozenge.[15]

Nicotine oral film

This product contains 2.5 mg nicotine in a thin film, designed to be applied to the roof of the mouth, where it dissolves in less than 5 min. Use of a single strip

produces a peak plasma nicotine concentration, similar to the 2-mg lozenge and gum, of between 4 and 5 ng/mL.

Nicotine inhalator

The nicotine inhalator consists of a plastic tube holding a replaceable cartridge containing either 10 or 15 mg nicotine. When the user inhales through the device, nicotine vapour is generated, which deposits on and is absorbed through the lining of the mouth. Although used by inhalation, this product does not achieve appreciable pulmonary delivery or absorption, and the pharmacokinetic profile is similar to that of other oral NRT products. After 20 min intensive use, around 2 mg nicotine is released from the device, resulting in peak plasma concentrations of up to 8 ng/mL and, if this use is repeated hourly for 10 h, levels of around 20–25 ng/mL are achieved.[16] Most users do not, however, use the device with this level of intensity, so lower plasma levels, similar to those achieved by 2-mg gum, are more typical. Nicotine release from this device decreases with ambient temperature[17] so, in cold conditions (<15°C), users should be advised to keep the inhalator warm.

Nicotine nasal and mouth sprays

The nasal spray delivers nicotine solution to the nasal mucosa and, after a single 1-mg dose (two sprays containing 0.5 mg nicotine), a peak plasma nicotine concentration of about 5–6 ng/mL is observed within 10–15 min.[18] Taking an hourly dose results in a steady-state plasma concentration of about 10 ng/mL. Although one of the fastest-acting NRT products, the nasal spray is also one of the most aversive to use initially.

The nicotine mouth spray also delivers nicotine quickly. Each spray delivers 1 mg nicotine and results in a peak plasma concentration of around 3–4 ng/mL within 10 min.[19] A 2-mg dose gives a plasma concentration of around 5–6 ng/mL. Another mouth spray formulation has shown higher maximum plasma concentration (10 ng/mL) with a 2-mg dose, but with a slightly longer time (15 min) to reach this.[14]

5.2.2.2 Safety profile

Similar to the nicotine patch, oral and nasal nicotine products have a good safety profile. The most commonly reported adverse effects are related to mouth and throat irritation, and hiccups. The nasal spray is a local irritant to the nasal lining.[20]

5.2.2.3 Addiction potential

Some 5% of smokers who use oral nicotine products to stop smoking will continue to use them for a year or longer.[9] With the nicotine nasal spray, this figure is closer to 10%,[9] which probably reflects the faster nicotine delivery of this product. Long-term users are usually people who were highly dependent on nicotine from their cigarettes and who would be relatively unlikely to maintain long-term abstinence from smoking without such help.[21] There are no documented cases of non-smokers becoming dependent on NRT.

5.2.3 Dual use of NRT and smoked tobacco products

NRT appears to be safe and well tolerated when used together with smoking.[22,23] Randomised placebo-controlled trials of dual use indicate that the occurrence of expected symptoms of nicotine overdose, such as nausea and palpitations, is uncommon.[24,25] A meta-analysis of NRT use before quitting found no increase in adverse events in patch users compared with those on placebo.[26] No reported concerns over the use of NRT while smoking have arisen from post-marketing surveillance. Smokers who also use NRT (known as 'dual users') are approximately twice as likely in the following months to make a quit attempt, and to quit smoking, than those who do not.[27,28]

5.3 E-cigarettes

E-cigarettes provide nicotine for inhalation in a vapour generated by heating a solution containing water, nicotine, propylene glycol, vegetable glycerine and typically also some flavouring. E-cigarettes were developed and first marketed in China in around 2003, and appeared on the market in the UK about 4 years later. The quality of early devices was variable, as was the consistency of the nicotine solutions (e-liquid) that they contained[29] and their ability to deliver nicotine, which, in some cases at least, was poor.[30] Newer studies have demonstrated some improvements in quality, at least in relation to declared nicotine content.[31,32]

The many brands and models of e-cigarettes available can be grouped into three broad categories of different appearance (Fig 5.1). The original or first-generation e-cigarettes were designed to be of similar size and appearance to a conventional cigarette, and hence are sometimes known as 'cigalikes'. These devices typically comprise two components: a battery and a 'cartomiser', a section of the device that contains nicotine solution and a vaporiser. Although some cartomisers are refillable, most are disposable, ie designed for single use and replacement when empty. Second-generation e-cigarettes are larger,

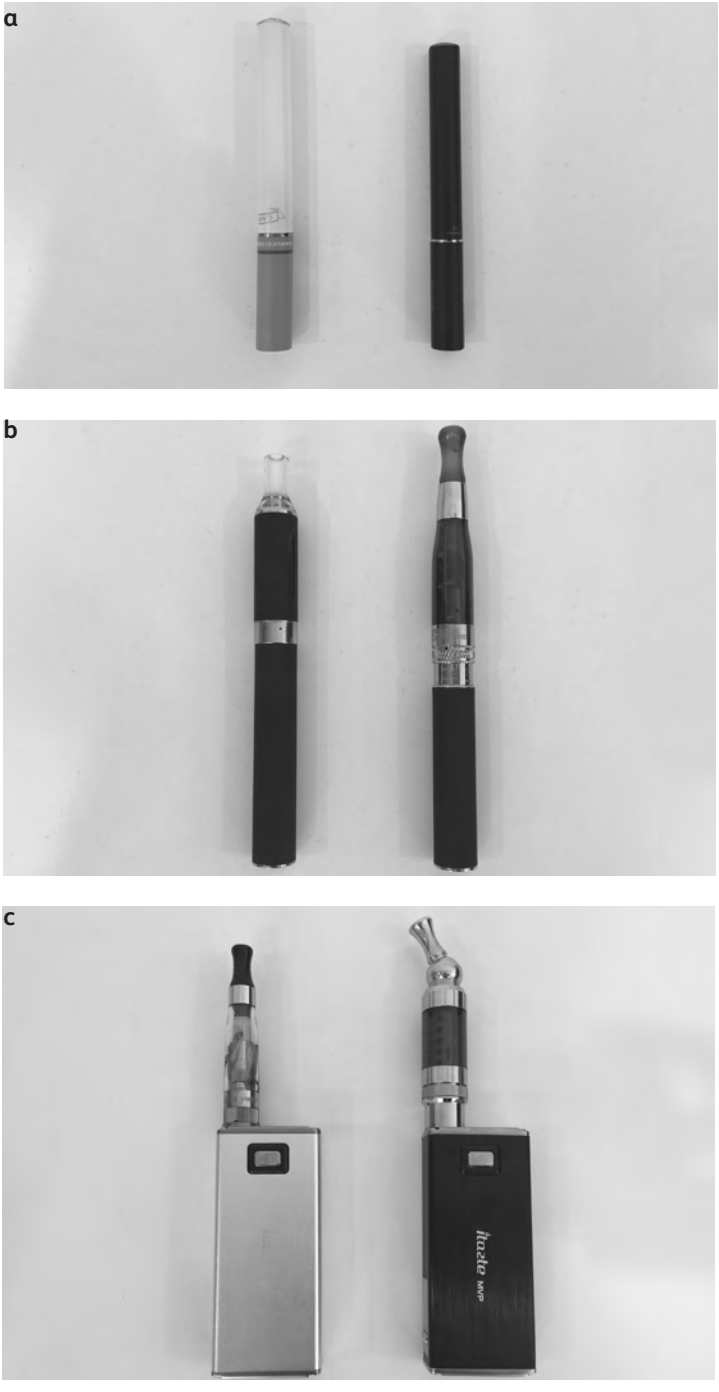

Fig 5.1 The three generations of e-cigarettes: (a) first generation; (b) second generation; and (c) third generation. (Images provided by Anna Phillips.)

typically the size of a large fountain pen, and incorporate a more powerful battery linked to a permanent vaporiser, and a tank system that users can refill with nicotine solution. Third-generation devices are typically larger still, with a still more powerful battery, usually with two heating elements (coils), and allow users to vary power and sometimes also the draw resistance of the device. Third-generation devices are also designed to allow modifications and substitution of individual components according to preference. Second- and third-generation devices generally deliver nicotine more effectively than first-generation devices (see below). The nicotine, propylene glycol, glycerine and flavouring contents of e-liquids also vary substantially, particularly in relation to nicotine content (with some being nicotine free), and in the ratio propylene glycol:glycerine.

5.3.1 Pharmacokinetics

Nicotine delivery from e-cigarettes is influenced by the concentration of nicotine and other constituents of the e-liquid, and the puffing ('vaping') technique used, and has generally increased with successive generations of the technology.[33] The earliest first-generation devices delivered little or no nicotine, eg two early products containing a 16 mg/mL nicotine solution; when tested in smokers who had not previously used e-cigarettes, it was found that the devices delivered either very little nicotine, achieving a maximum blood level of 1.3 ng/mL at 20 min,[34] or none at all.[35] However, with improved technology and more experienced users, nicotine delivery is improved, eg whereas one study found that, among naive users, 5 min free use of an e-cigarette containing 24 mg/mL nicotine produced a peak plasma concentration of 4.6 ng/mL within 5 min, after 4 weeks' practice the same users were achieving levels of 5.7 ng/mL.[36] A study of a more advanced first-generation e-cigarette containing 18 mg/mL nicotine, and using a longer puffing (vaping) regimen (10 puffs 30 s apart on six occasions every 30 min), resulted in a maximum plasma nicotine concentration of 7.4 ng/mL at 2.5 h after the first puffing bout.[37] In experienced users, using the same 10 puffs in a 5-min regimen, plasma nicotine levels can rise by around 8–16 ng/mL within 5 min of the first puff.[38,39]

Use of higher nicotine concentrations in the e-liquid increases nicotine delivery, as does the inclusion of propylene glycol. In a study that examined nicotine delivery from a first-generation e-cigarette containing either 16 or 24 mg/mL nicotine, in either 75% glycerine or a 50% glycerine:20% propylene glycol e-liquid, peak plasma nicotine concentrations after 30 min of controlled puffing were highest (18 ng/mL) with the 24 mg/mL nicotine in the mixed glycerine:propylene glycol formulation, and lowest (10 ng/mL) with the 16 mg/mL nicotine in 75% glycerine solution[40] (Fig 5.2). The propylene glycol:glycerine mix formulation delivered more nicotine at either dose than the

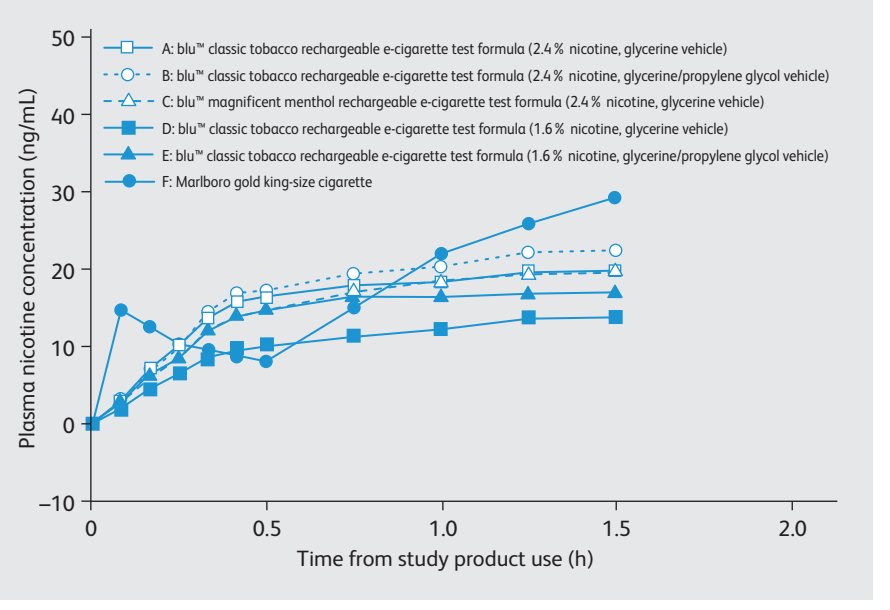

Fig 5.2 Venous blood nicotine levels from low and high nicotine concentrations, glycerine or propylene glycol:glycerine mix solutions, and from a conventional cigarette.[40] (Reproduced from: Sherwin Yan X, D'Ruiz C. Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes. *Regulatory Toxicology and Pharmacology* 2015;71:24–34.[40] With permission from Elsevier.)

75% glycerine solution. This higher delivery is thought to result from the lower boiling point of propylene glycol (187.6°C) than of glycerine (290°C).

Nicotine delivery is generally better from second- and third-generation devices, eg in a direct comparison with first-generation devices using a prescribed 5-min puffing regimen, second-generation e-cigarettes produced significantly higher rises in plasma nicotine concentration (by 4 ng/mL vs 2 ng/mL) at 5 min[41] (Fig 5.3), and with repeated use these devices can sustain venous blood levels comparable with those expected in smokers.[42] In a study examining the nicotine delivered by a third-generation device, experienced vapers were able to achieve a greater rise in blood nicotine levels than naive users under the same prescribed 5-min puffing regimen (5.8 ng/mL vs 2.7 ng/mL at 5 min),[43] although the speed of nicotine delivery remains much slower than from cigarettes.

Levels of the nicotine metabolite cotinine, which reflect nicotine intake over the past 3–4 days,[44] are similar in experienced e-cigarette users to those observed in smokers,[45–47] indicating that e-cigarettes are capable of delivering

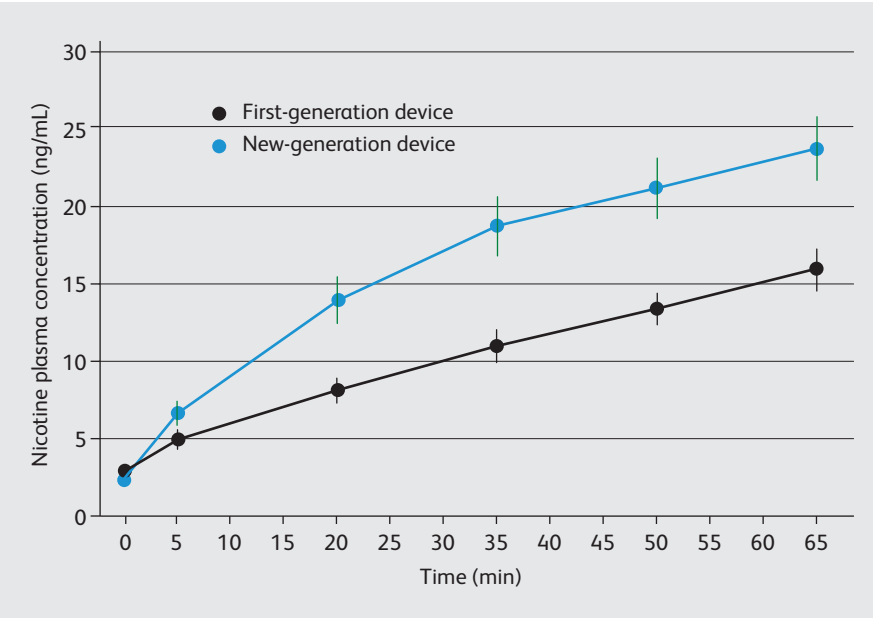

Fig 5.3 Nicotine absorption from first- and new-generation e- cigarettes.[41] (Reproduced from: Farsalinos KE, Spryrou A, Tsimopoulou K *et al*. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Scientific Reports* 2014;4:4133.[41])

total doses of nicotine similar to those from cigarettes. However, because, at the time of writing, available data relate only to venous blood levels, the extent to which e-cigarettes deliver nicotine for absorption into the pulmonary circulation, and hence reproduce the high arterial levels achieved by cigarettes, remains uncertain.

5.3.2 Safety profile

E-cigarettes are generally well tolerated. Similar to oral NRT products, reported short-term adverse effects relate predominantly to mouth and throat irritation, and tend to be self-limiting.[29,48,49] As with all new products, however, long-term or rare adverse effects will remain uncertain until e-cigarettes have been in widespread use for several decades. Discussion of the potential long-term adverse effects of e-cigarette use is therefore limited to consideration of the likely effects of sustained inhalation of the known constituents of e-cigarette vapour.

Analysis of vapour generated by e-cigarettes has identified a number of potentially harmful constituents delivered alongside the nicotine and other

e-liquid components. These include volatile organic compounds, carbonyls, aldehydes, tobacco-specific nitrosamines (TSNAs) and metal particles, but all at much lower levels than in cigarette smoke.[50–64] Levels of formaldehyde and other aldehydes can be relatively high when vaporisation occurs at high temperatures,[65,66] although in practice this overheating generates an aversive taste known as a 'dry puff', which vapers avoid.[66,67] Recent reviews of the health effects of toxins inhaled during normal use of e-cigarettes have expressed concerns over potential adverse effects based on the presence of these contaminants,[68–70] but not their levels, which are generally the more important determinant of toxicity. In normal conditions of use, toxin levels in inhaled e-cigarette vapour are probably well below prescribed threshold limit values for occupational exposure,[71] in which case significant long-term harm is unlikely. Some harm from sustained exposure to low levels of toxins over many years may yet emerge, but the magnitude of these risks relative to those of sustained tobacco smoking is likely to be small. However, consideration of the potential harm of long-term e-cigarette use should serve as a guide to evidence-based product development, regulation and monitoring.

5.3.3 Areas of potential concern over hazards arising from vapour exposure

Areas of potential concern over the long-term effects of e-cigarette use include the effects of vapour constituents depositing in the mouth, upper airway and lungs, and systemic effects of vapour components absorbed as a result of swallowing or inhalation. The vapour constituents to be considered consist of those that should be present in e-liquids, and hence also the vapour, including: nicotine, propylene glycol, glycerine and flavours; those arising from impurities and contaminants in the e-liquid, which vary between batches and suppliers;[72] and toxins, particles and other components created by the vaporisation process. The long-term adverse effects of nicotine are likely to be minimal[73] (see also Chapters 4 and 7), although it is acknowledged that the effects of sustained inhalation of nicotine, in isolation from tobacco smoke and as opposed to absorption by another route, have not been studied. There are, however, no grounds to suspect that inhaled nicotine will have an appreciably different risk profile from nicotine delivered via other routes of absorption. The following discussion therefore relates to the effects of other constituents of e-cigarette vapour.

Inhaled vapours deposit first, and often substantially, in the mouth and upper airway. Much of this deposition is then swallowed, absorbed from the gastrointestinal tract and excreted, mostly in urine, either unchanged or after metabolism. This process of deposition, absorption and excretion of TSNAs and other carcinogens in tobacco smoke probably accounts for the increased risks of

cancer of the oropharynx, stomach, bladder and other organs involved in the absorption and excretion process in smokers. The presence of carcinogens in e-cigarette vapour therefore increases the risk of similar outcomes but, in view of the very low levels of exposure generated by e-cigarette vapour, the magnitude of any increase in risk, in either relative or absolute terms, is likely to be low.

After passing through the mouth and upper airway into the lungs, larger particles and droplets in inhaled vapours deposit substantially throughout the intrapulmonary airways, to be either absorbed and excreted as above, or expectorated.[74] Vapour components <5 μm in diameter reach the alveoli, where they either deposit and are then absorbed or cleared through phagocytosis or other processes, or are exhaled.[74] In tobacco smoking, the deposition of carcinogens carried in tobacco smoke results in an increased risk of lung cancer, whereas oxidants and other toxins and irritants in smoke cause direct and inflammation-induced damage to lung tissues, which leads to chronic bronchitis and emphysema (chronic obstructive pulmonary disease (COPD))[64] and to pulmonary fibrosis.[75,76] Smoke components absorbed from the lung, including particles and carbon monoxide, contribute to the increased risk of cardiovascular disease in smokers[64] and, together with local effects, to an increased risk of infection.[77] Although e-cigarette vapour contains a far less extensive range of toxins, and those present are typically at much lower levels, than in tobacco smoke, it is appropriate to consider potential hazards of e-cigarettes in relation to this spectrum of harm.

5.3.3.1 Generic effects of vapour

Data on the effects of e-cigarette vapour on the airways are limited to studies of short-term exposure. Use of an e-cigarette in healthy individuals for 5 min has been shown to reduce exhaled nitric oxide (NO) and increase airway resistance,[78] consistent with an irritant effect on the airways resulting in mucosal oedema, smooth muscle contraction or increased production of lung secretions in response to the vapour. Another study reported a reduction in exhaled NO after inhaling vapour from an e-cigarette, with or without nicotine, of an order of magnitude similar to that provoked by conventional cigarette smoke.[79] However, short-term e-cigarette use has been found to have no effect on spirometric markers of lung function,[80] and another study found no difference in reported adverse events over 12 weeks' use of an e-cigarette with or without nicotine, or conventional NRT.[81] It is therefore far from clear whether these short-term airway effects will translate into long-term airway damage. Furthermore, as smoking cessation is associated with a reduction in respiratory symptoms in people with respiratory disease,[82,83] many smokers who switch to an e-cigarette are likely to experience improvements in respiratory symptoms. This is illustrated in a study that followed a small cohort of patients with asthma, in whom improvements in symptoms and respiratory function were observed after

switching from smoking to vaping.[84] These observations therefore provide reassurance about short-term use of e-cigarettes in relation to adverse respiratory effects. One survey from Hong Kong has reported a higher prevalence of respiratory symptoms among Chinese adolescents who were ex- or never-smokers, and reported any use of an e-cigarette in the preceding month.[85] However, e-cigarettes were used by only 1.1% of the total sample and 0.1% of never-smokers and, as use of e-cigarettes was not quantified, there is no evidence that those reporting symptoms were using the product regularly.

E-cigarette vapour has been reported to influence resistance to infection, and to delay recovery from influenza infection, in an animal model,[86] although the validity of these findings and relevance to the effects in humans are far from clear. At the time of writing we are not aware of any published evidence on cardiovascular effects of e-cigarette use other than those attributable to nicotine.[40] It is known, however, that the vapour does not deliver appreciable amounts of carbon monoxide,[87,88] which represents a significant advantage relative to tobacco smoke. A study of carcinogen excretion in participants' urine after use of e-cigarettes or tobacco cigarettes found significantly lower levels of TSNAs, benzene and polyaromatic hydrocarbons with e-cigarettes,[89] demonstrating systemic absorption of these carcinogens and hence some degree of potential cancer risk, although clearly much less than that associated with smoking.

5.3.3.2 Propylene glycol and glycerine

Propylene glycol is an active ingredient of the solutions used to generate the synthetic smoke widely used in the performing arts and nightclubs, and in this context is generally considered to be safe.[90] In animal studies, a month of exposure to propylene glycol vapour produced no apparent tissue toxicity of the lung, liver or kidney in beagles or rats,[91] although 90 days' nasal inhalation in rats was associated with an increase in the number of goblet cells and mucin production in the nasal mucosa at levels of exposure >1.0 mg/L.[92] An early study examined long-term exposure to propylene glycol vapour over 12–18 months in rats and monkeys, and identified no lung or other adverse effects.[93] However, acute exposure to propylene glycol has been shown to induce airway irritation and cough in humans, together with minor airflow obstruction.[61] One study also found an association between levels of propylene glycol exposure in the home, and asthma and rhinitis in children.[94]

Evidence on the adverse effects of inhaled glycerine is limited to a single case report of lipoid pneumonia with onset of symptoms associated with commencing e-cigarette use. The pneumonia was attributed to glycerine-based oils in the e-liquid,[95] although commentators pointed out that glycerine is an alcohol and not a lipid.[96] There have been no further reported cases of this

outcome. Studies of repeated inhalation in rats found no evidence of damage to the lungs.[97,98]

5.3.3.3 Flavours

Although the flavours used in the e-cigarette liquid are generally those considered safe when ingested orally, some are irritant to the airways and the safety of most flavours after heating and inhalation is unknown.[99] Diacetyl is an example of a flavour used in popcorn, and some other foods, that is safe for oral consumption but which, when heated and inhaled in large doses over long periods of time, can cause irreversible bronchiolitis.[100] Vapour produced from e-liquids containing flavours has been demonstrated to be more cytotoxic than unflavoured vapour[101] and, although both are far less so than tobacco smoke, this exposure may increase airway inflammation.[102] *In vitro* experimental studies have also reported increased susceptibility of airway cells to viral infection after direct contact with e-liquid[103] and evidence of cytotoxicity from cinnamon flavours, although the relevance of direct effects of contact with e-liquid, as opposed to vapour, is unclear.[50] Although no study so far shows any clear hazards of flavours in e-cigarette vapour, those derived from flavours seem the most likely to pose appreciable health risks from long-term use.

5.3.3.4 Components generated by vaporisation

Heating propylene glycol or glycerine can cause decomposition to low-molecular-mass carbonyl compounds including formaldehyde and acetaldehyde, which can be carcinogenic in large doses.[104] A study investigating the effect of varying the heating element voltage in e-cigarettes found that, at low voltage, levels of these compounds were up to 800-fold lower than in tobacco smoke, but that, at higher voltage (4.8 V), the levels were similar.[56] In a study involving a third-generation – or variable-voltage – e-cigarette, negligible levels of formaldehyde were generated at lower (normal) power settings, but, when used at maximum power with 3- or 4-s puffs, levels 5–15 times higher than those found in cigarette smoke were observed.[65] However, in a study simulating this 'dry puff' use, generating high levels of formaldehyde (up to 355 μg), acetaldehyde (up to 206 μg) and acrolein (up to 210 μg), experienced vapers were easily able to detect dry puffs and none could tolerate them.[66] Under normal conditions of use, the levels were negligible.[66]

Two studies have examined urinary levels of aldehydes in vapers. One was a cross-sectional study that demonstrated considerably lower levels of urinary acrolein and crotonaldehyde in vapers than in smokers.[89] The other was a cohort study that examined the change in urinary acrolein level when smokers switched to vaping. Significant decreases in acrolein concentrations were observed in smokers who switched completely to e-cigarettes as well as in those who were

both smoking and vaping, showing that 'dual use' of tobacco cigarettes and e-cigarettes leads to a reduction in smoke intake.[88]

In addition to the vaporised liquid, e-cigarette devices include metals, ceramics and rubber, all of which may become aerosolised in the process of vapour generation,[62,105,106] eg copper particles of respirable size (0.450–2.02 μm) have been demonstrated in e-cigarette vapour at a level six times that seen in conventional cigarette smoke;[57] levels of nickel and silver that are also higher than those in tobacco smoke have been noted.[60] Whether these exposures comprise a significant health hazard remains uncertain. Potential toxicity of metal and other fine particles include carcinogenicity, cardiovascular disease and diseases such as COPD and interstitial lung disease, which are characterised by sensitisation, chronic inflammation or tissue remodelling.[107] Inhalation of small particles, over both the short and the long term, also increases the risk of cardiovascular events.[108] However, this is probably not a major concern because levels of exposure are well below recognised safety thresholds,[109] and could be reduced still further by improving manufacturing processes and standards.

5.3.3.5 Hypersensitivity reactions

Hypersensitivity pneumonitis has been described in response to a range of inhaled organic materials. Allergy to nickel, which can be present in very small amounts in e-cigarette vapour, is a relatively common problem in clinical practice,[110] although there has been no reported case of this problem in e-cigarette users. A case of eosinophilic pneumonia has been reported in a smoker who tried an e-cigarette,[111] but again this has not been replicated and hence is of uncertain relevance.

5.3.3.6 Relevance to potential long-term harms

The above observations indicate that e-cigarettes deliver a much smaller range of toxins at much lower concentrations than cigarettes, and therefore indicate that harm from e-cigarette use is likely to be far less than that from smoking. They also demonstrate a possibility that some harm from long-term e-cigarette use cannot be dismissed. From first principles, we would expect repeated and sustained inhalation of the generally low concentrations of particulates, oxidants, carcinogens and other constituents to pose some risks to health, particularly in relation to COPD and lung cancer. However, the absolute magnitude of any risk attributable to e-cigarette use is likely to be very small in absolute terms, and hence substantially smaller than that arising from tobacco smoking. A recent evidence review concluded that e-cigarette vapour can contain some of the toxins present in tobacco smoke, but at much lower levels, and that the long-term health effects of e-cigarette use, although unknown, are likely to be much less, if

at all, harmful to users or bystanders than cigarette smoke.[29] An analysis based on expert opinion quantified the likely harm to health and society of e-cigarettes at about 5% of the burden caused by tobacco smoking,[112] and a recent report by Public Health England supported this conclusion.[113]

With appropriate product standards to minimise toxin and contaminant exposure in e-cigarette vapour, it should be possible to reduce risks of physical health still further. It is also possible, although unlikely, that other, unexpected harm from inhaling e-cigarette vapour over the longer term might yet emerge. Although it is not possible to quantify the long-term health risks associated with e-cigarettes precisely, the available data suggest that they are unlikely to exceed 5% of those associated with smoked tobacco products, and may well be substantially lower than this figure.

5.3.3.7 Effects of passive exposure to e-cigarette vapour

Users of e-cigarettes exhale the vapour, which may therefore be inhaled by others, leading to passive exposure to nicotine.[114] There is, so far, no direct evidence that such passive exposure is likely to cause significant harm, although one study has reported levels of polycyclic aromatic hydrocarbons that were outside defined safe-exposure limits.[106] It is clear that passive exposure will vary according to fluid, device and the manner in which it is used.[52] Nicotine from exhaled vapour can be deposited on surfaces,[115] but at such low levels that there is no plausible mechanism by which such deposits could enter the body at doses that would cause physical harm.

5.3.4 Addiction potential

Speed of nicotine delivery seems to be important for smokers' satisfaction and addiction potential. As outlined in Chapter 4, as a consequence of pulmonary absorption, cigarettes deliver nicotine to the brain very quickly. Although there are no available data on arterial nicotine levels after e-cigarette use, its venous delivery kinetics appear similar to those of products delivering to the mouth or upper airway, suggesting that pulmonary absorption from currently available e-cigarettes is low. In addition to this, the addictiveness of cigarettes is probably also related to other chemicals in tobacco smoke that enhance nicotine's effects. These observations tally with other evidence, eg e-cigarette users report that they feel less dependent on them than on tobacco cigarettes,[116] and empirical evidence from adolescent use suggests that, although adolescents experiment with e-cigarettes, few – if any – never-smokers who do so become regular e-cigarette users.[117,118] The addiction potential of currently available e-cigarettes is therefore likely to be low. NRT and e-cigarettes may satisfy smokers who are already using nicotine, but they have little appeal for never-smokers. This may

change in the future, however, if e-cigarette and other nicotine inhalation technology improves sufficiently to achieve significant pulmonary absorption.

5.3.5 Dual use of e-cigarettes and tobacco cigarettes

Observational population-level evidence indicates that dual users of both tobacco and e-cigarettes are more likely to make an attempt to stop smoking than smokers who do not also use e-cigarettes, but it is not yet clear whether they are more likely to succeed[119,120] (see Chapter 6). Some researchers have found a lower subsequent cessation rate among smokers who tried e-cigarettes but continued to smoke than among smokers who did not try e-cigarettes, but this could be explained by self-selection and exclusion of smokers who switched completely to e-cigarettes. One study found that daily users of the more advanced models had a higher cessation rate.[120] Experience with NRT suggests that e-cigarette use is likely to increase the proportion of smokers making a quit attempt, but appropriate evidence on this effect is not yet available. A recent study has shown that dual users maintain their intake of nicotine, but reduce their intake of smoke and related toxins significantly.[88] Obtaining nicotine from an alternative source leads to a reduction in smoking.[22]

5.3.6 Use to inhale other drugs

Refillable e-cigarettes can be used to inhale other materials including cannabis oil or narcotics. Although such use is outside the scope of this report, use of e-cigarettes to deliver cannabis is likely, as is the case for nicotine, to be substantially less hazardous than conventional inhalation of cannabis smoke either alone or mixed with tobacco.

5.4 Products in development

At the time of writing there is a range of non-tobacco nicotine products in development, most of which are variations on the formulations outlined above, but some of which represent genuinely novel approaches, with the potential to deliver nicotine by inhalation with significant pulmonary absorption. As this is the route of absorption that generates the fastest increases in arterial blood levels, this range of products may prove to be the most effective, and also possibly the most addictive, smoking substitutes.

A metered-dose inhaler using propellants to deliver small droplets of nicotine to the respiratory tract has been developed.[121] Ten puffs of a 50-µg nicotine/puff inhaler, inhaled via a spacer, resulted in peak plasma nicotine concentrations of

12.5 ng/mL within 6 min of finishing the 10 puffs. A 100-µg dose was also tested and resulted in slightly lower peak nicotine concentrations (9.4 ng/mL), most probably owing to the greater adverse effect of coughing at the higher dose. Voke is an inhaler device that is similar in shape and size to a conventional cigarette; it is charged and recharged with an aerosol containing nicotine, propylene glycol and a propellant from a small pressurised canister (similar to those used in asthma inhalers), housed in a pack about the size of a pack of 20 cigarettes. Inhalation of the entire contents of the device provides 0.45 mg of nicotine to the user, with nicotine measurable in arterial blood (mean 2.06 ng/mL) within 2 min of the first inhalation, suggesting at least some pulmonary absorption. A C_{max} of 3.7 ng/mL in arterial blood was reached in 7 min. A C_{max} in venous blood of approximately 3 ng/mL was reached within 15–20 min. Hourly use results in steady-state plasma nicotine levels of between 8 and 10 ng/mL.[122] The product has now been awarded a medicines licence, and hence is likely to be brought to market, although at the time of writing no date has been set.

Nicotine pyruvate is formed from the combination of nicotine and pyruvic acid. Its salts are small (similar in size to the particulate matter in cigarette smoke) and so can be carried deeper into the respiratory tract in the process of inhalation, and are less harsh than pure nicotine to inhale. An inhaler has been developed that contains pyruvic acid and nicotine, which are combined when the user draws air through the device. In participants taking 10 controlled inhalations over 5 min, plasma nicotine levels rose to 5 ng/mL within 5 min when using a dose of 20 µg nicotine pyruvate per puff, and to 8.3 ng/mL with a 30-µg dose.[123] This technology was purchased by Philip Morris International Inc in 2011,[124] but has not yet been brought to market.

The Aradigm AERx system, which was developed for inhalation of insulin, has also been tested for nicotine delivery.[125] There are limited published data about nicotine delivery, but those that are available on the company website[126] suggest that nicotine delivery is rapid. The product has not, however, yet been commercialised.

5.5 Summary

- The market in non-tobacco nicotine products in the UK has been dominated for several decades by NRT.
- NRT is licensed as a medicine to help smokers quit smoking, and there is strong clinical trial evidence of effectiveness in this role.
- NRT is also licensed for use to help smokers cut down on smoking, and for temporary abstinence.
- NRT products have an excellent safety profile and present negligible risks to users.
- However, NRT products do not reproduce the rapid, high-dose delivery of

tobacco smoke, and reproduce few if any of the behavioural components of tobacco smoking.

- The dominance of NRT has been challenged in recent years by a growing range of consumer nicotine products, some of which are made to high standards of purity but not necessarily licensed as medicines, and by e-cigarettes, which are now more widely used than NRT.
- Unlicensed nicotine products made to high standards of purity are also likely to have very little risk for users.
- Currently available e-cigarettes are manufactured to variable standards, and many are therefore likely to be more hazardous than NRT.
- Nicotine delivery from e-cigarettes is variable and, with some first-generation devices, very low.
- However, e-cigarette design is evolving quickly, with newer models delivering higher doses of nicotine than their predecessors, and hence being more satisfying for smokers.
- Some of the carcinogens, oxidants and other toxins present in tobacco smoke have also been detected in e-cigarette vapour, raising the possibility that long-term use of e-cigarettes may increase the risks of lung cancer, COPD, cardiovascular and other smoking-related diseases.
- However, the magnitude of such risks is likely to be substantially lower than those of smoking, and extremely low in absolute terms.
- These potential health risks arise primarily from contaminants and components generated by the vaporisation process, which should be amenable to reduction through technological and purity improvements.
- New nicotine products in development are likely to extend the range of choices available to smokers further, increasing purity and safety, and, in those achieving greater pulmonary absorption, addictiveness.
- Although it is not possible to precisely quantify the long-term health risks associated with e-cigarettes, the available data suggest that they are unlikely to exceed 5% of those associated with smoked tobacco products, and may well be substantially lower than this figure.

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6 Quitting smoking

6.1 Introduction

Quitting smoking is the most effective means by which smokers can avoid the premature death and disability caused by smoking. This chapter describes current patterns of smoking cessation in the UK, to provide context in which to consider the position and role of harm-reduction policies. As in Chapter 5, data are again drawn from the Smoking Toolkit Study (STS: www.smokinginengland.info),[1] the only national survey within the UK that provides detailed data on smoking cessation behaviour in a representative general population sample. Although limited to smokers in England, STS data are likely to be broadly representative of trends across the UK. This chapter uses STS and other data to explore recent trends in quitting behaviour, and the association between e-cigarette use and smoking prevalence, and to consider approaches to increasing the number of quit attempts made. It also describes patterns of use of e-cigarettes among young people

6.2 Quit attempts and quit success

STS data indicate that the proportion of smokers making at least one quit attempt each year has fallen over the past 8 years, from 43% in 2007 to 32% in the first 9 months of 2015 (Fig 6.1). This overall trend was reversed in 2012 and 2013, when 34% and 39% made quit attempts, but has since fallen again.

These attempts were slightly more likely to occur in women and younger adults and, in 2014 and 2015, among those in non-manual occupations (Fig 6.2).

The proportion of these attempts that are successful in the short term, which can be identified as survey responses from individuals reporting that they have made a quit attempt in the past year and are now not smoking, is around 16%, a slight increase since 2011 (Fig 6.3). There were no marked differences in the proportion of successful attempts in relation to age or gender, but success was more likely among those in higher occupational groups (Fig 6.4).

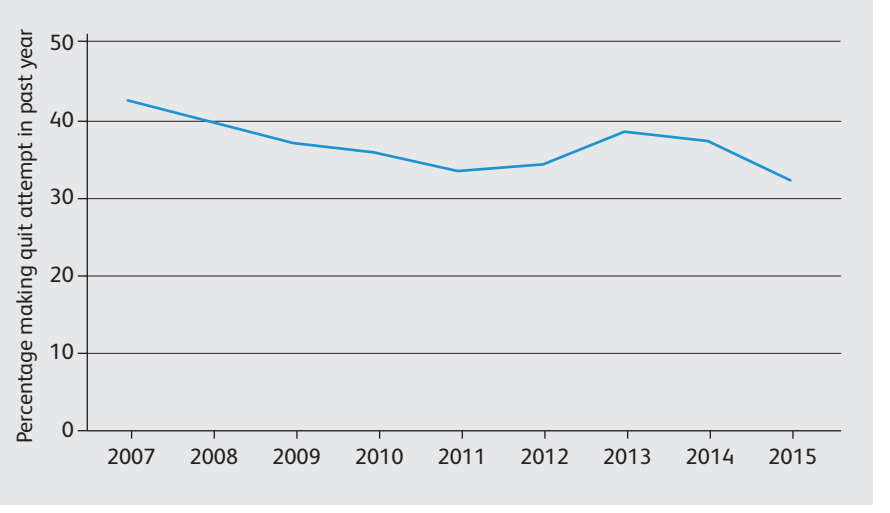

Fig 6.1 Proportion of people who have smoked in the past year who made at least one serious quit attempt in that year[1] (data from 42,386 people who smoked in the past 12 months; 2015 figures based on January to September data). (Adapted from the Smoking Toolkit Study[1] with permission.)

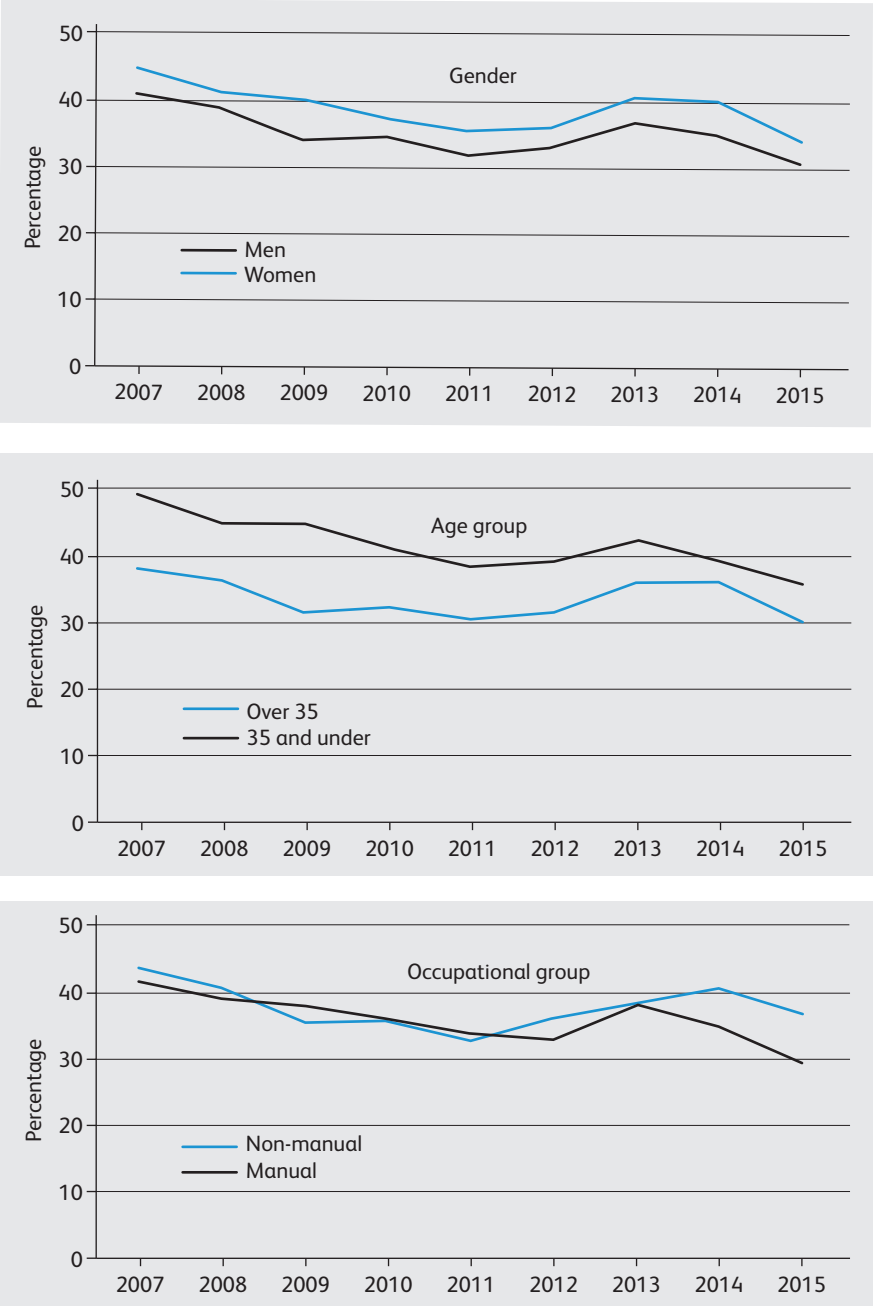

Fig 6.2 Proportions of people who have smoked in the past year making at least one serious quit attempt in that year, by gender, age and occupational group (data details as per Fig 6.1).[1] (Adapted from the Smoking Toolkit Study[1] with permission.)

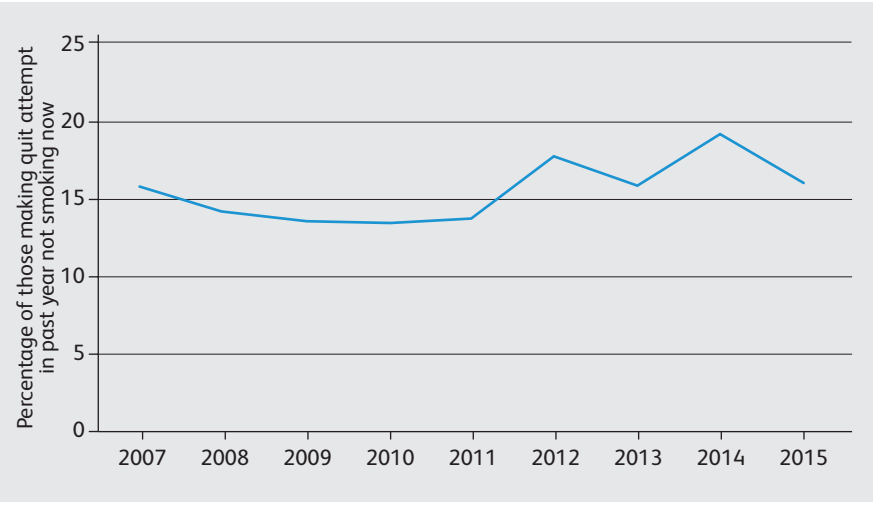

Fig 6.3 Proportion of people who have tried to stop in the past year and are currently not smoking[1] (data from 15,720 people who tried to stop smoking in the past 12 months; 2015 figures based on January to September data). (Adapted from the Smoking Toolkit Study[1] with permission.)

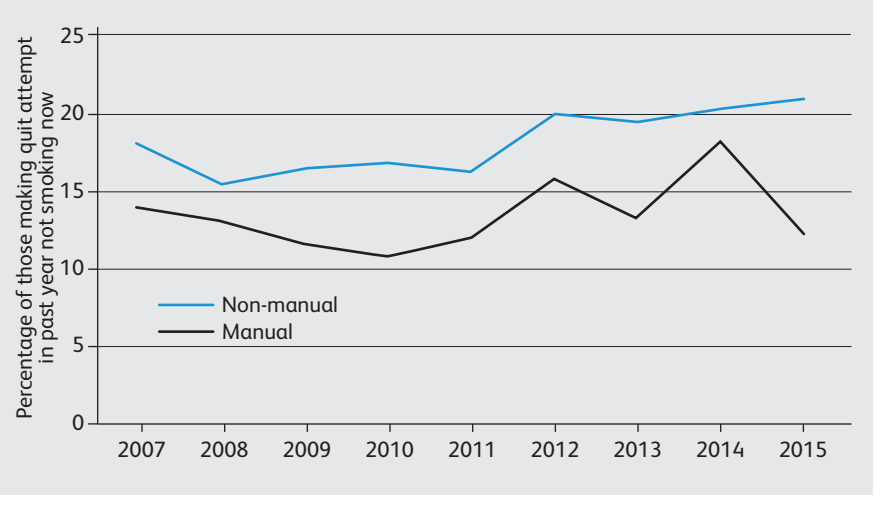

Fig 6.4 Proportion of people who have tried to stop in the past year and are currently not smoking by occupational social group (data details as per Fig 6.3).[1] (Adapted from the Smoking Toolkit Study[1] with permission.)

6.3 Methods used to quit

The methods chosen by smokers in England to help them to quit, reported in the STS study between 2007 and 2015, are represented in Fig 6.5. Until 2013, the most commonly used aid to cessation was nicotine replacement therapy (NRT) bought over the counter, but NRT has been displaced as the most popular choice by a rapid increase in the use of e-cigarettes in England since 2012 (see also Chapter 5). The proportion of smokers who use no aid to cessation has fallen progressively over recent years, but remains above 40%.

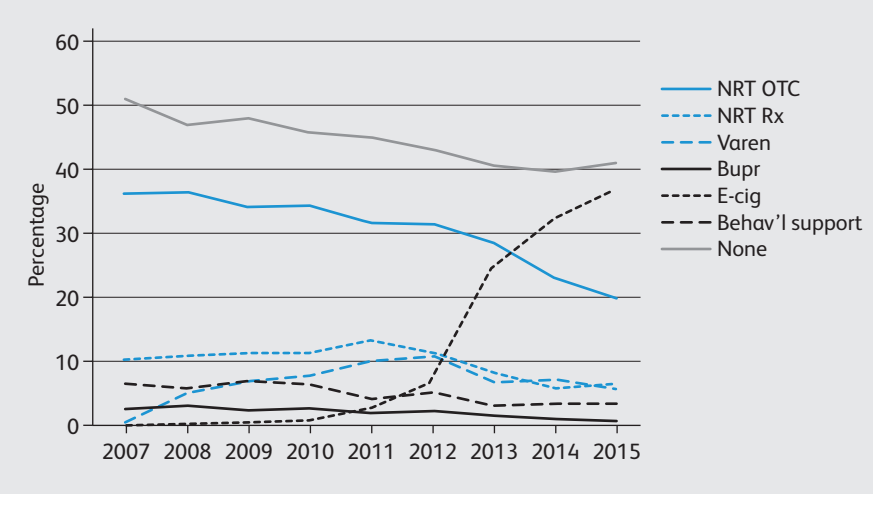

Fig 6.5 Percentage of smokers using different aids to cessation in at least one quit attempt in the past year[1] (data from 15,720 people who tried to stop smoking in the past year; 2015 figures based on January to September data; respondents may use more than one method per quit attempt). NRT OTC = nicotine replacement therapy bought from a shop; NRT Rx = nicotine replacement therapy obtained on prescription; Varen = varenicline (Champix) prescribed therapy; Bupr = bupropion (Zyban) prescribed therapy; E-cig = e-cigarette; Behav'l support = one-to-one sessions with an adviser or group support; None = none of the aforementioned. Use of other methods such as telephone quit-lines is very low. (Adapted from the Smoking Toolkit Study[1] with permission.)

Evidence from randomised trials[2] and English population data[3–6] indicate that there are three main categories of quit attempt in terms of aids used; these are grouped below in relation to their relative likelihood of success.

6.3.1 Lowest likelihood of success

The approaches to quitting associated with the lowest likelihood of success are those that are unaided, including use of over-the-counter NRT and use of NRT without professional support. STS data suggest that there is little or no difference in the likelihood of quitting using either of these methods.[5,6] This observation contrasts with randomised trial evidence that NRT can increase the likelihood of cessation,[7] and suggests that trial procedures, and perhaps in particular an element of professional instruction and follow-up, may be crucial to NRT effectiveness. This, in turn, indicates that providing even minimal behavioural support to purchasers of NRT could improve the likelihood of successful quitting. As one in five smokers who tried to quit smoking in 2015 did so using NRT purchased from a shop or pharmacy, the low effectiveness of this approach represents a considerable lost opportunity to promote cessation.

6.3.2 Intermediate likelihood of success

Quit attempts among STS participants are around 50% more likely to succeed if they involve NRT, varenicline or bupropion obtained on prescription (and hence involving at least some contact with a health professional), or an e-cigarette bought from a shop.[3–6] These methods are typically used by more heavily addicted smokers who would otherwise be expected to have a lower chance of success than those using the methods of lowest effectiveness.[8] The fact that NRT obtained on prescription yields higher success rates than over-the-counter NRT suggests that, again, with this product, some form of clinical supervision or involvement is required for NRT to have an effect. This may be because without supervision smokers use NRT incorrectly, eg by using too little, or use the therapy for too short a time. However, this in turn raises the question of why use of e-cigarettes, which in the limited clinical trials available to date appear to be of similar efficacy to NRT,[9] appears to be effective even without this supervision. There are, however, a number of possible explanations, as follows.

6.3.2.1 Nicotine delivery kinetics

Although early-generation e-cigarettes delivered relatively little nicotine, experienced e-cigarette users, particularly when using a later-generation product, can achieve venous blood levels similar to those obtained from smoking[10] (see Chapter 5). Although this is also possible with NRT, it generally requires very frequent dosing with a short-acting product used in combination with a nicotine transdermal patch,[11] and few consumers of NRT are likely to be aware of the need to follow this kind of dosing regimen. It is therefore possible that users

adopting e-cigarettes without direction on optimal use are more likely to achieve satisfactory nicotine substitution than those choosing NRT.

6.3.2.2 Duration of use

There is a tendency for e-cigarettes to be used for longer than NRT. Although some smokers who use NRT to stop smoking continue to use NRT for months or even years after quitting, they are in a minority; most discontinue the product within a few weeks. In contrast, many users of e-cigarettes continue using the product both before and after quitting smoking, and for a longer period after quitting than most NRT users.[12–15]

6.3.2.3 Sensory replacement

Unlike NRT, e-cigarettes replicate many of the sensory characteristics of smoking. As outlined in Chapter 4, nicotine addiction is sustained not only by the rewarding characteristics of nicotine itself, but also by reward given to the stimuli and behaviours associated with nicotine delivery.[16] As sensory replacement can reduce tobacco withdrawal symptoms,[17] the sensation of vapour in the back of the throat, the plume of exhaled vapour, the hand-to-mouth action, and various other sensory and behavioural similarities with cigarettes may help to make e-cigarettes a closer sensory substitute for tobacco smoking than NRT products.

6.3.2.4 Cultural acceptability

Particularly among smokers, e-cigarettes are a socially and culturally accepted direct substitute for smoking. E-cigarette users can still share smoking breaks with and be accepted by other smokers, thus sustaining a social identity as a smoker, but can also tap into the enthusiasm, knowledge sharing and social support for e-cigarette use generated via online user groups and vaping websites. Also, unlike NRT, e-cigarettes are not medicalised, and use does not imply rejection of smoking or a commitment to quitting.

6.3.2.5 Confounding

People who choose to purchase e-cigarettes may differ from those who choose NRT in relation to factors that also influence the likelihood of successful quitting. Although STS analysis suggests that differences in characteristics known to predict smoking cessation outcome, including nicotine dependence, age, social grade and recent history of quit attempts, do not account for the difference in quit rates between those using e-cigarettes and those using NRT,[3–6] it is still possible that unmeasured confounding variables could account for the apparent advantage of e-cigarettes.

Clarifying whether and why over-the-counter e-cigarettes appear to be more effective than NRT purchased in the same way clearly requires further research, comparing e-cigarettes and other cessation pharmacotherapy in head-to-head pragmatic trials, and exploring the importance of sensory replacement and other characteristics of the products involved.

6.3.3 Highest likelihood of success

STS data indicate that the greatest improvement in quit rates comes from use of NRT, varenicline or bupropion together with multi-session, face-to-face specialist behavioural support from a qualified stop smoking adviser. This method tends to be used by the most heavily addicted smokers, who would therefore be expected to have the lowest success rates of the three categories[8] but, after adjustment for characteristics associated with likelihood of cessation,[5,6,18] this approach appears to increase success rates by between two- and threefold.[6] As NHS Stop Smoking Services (SSSs) have only recently started to support quit attempts using e-cigarettes, the available data on success rates are limited, but early experience estimates quit rates to be at least as high as among those using other medication. In the year to March 2015 in England, only 2,221 SSS users made a quit attempt using an unlicensed nicotine product (ie an e-cigarette), from a total of 445,979 setting a quit date.[19] The average quit rate in all smokers using SSSs was around 51%, and among e-cigarette users it was 66%;[19] although factors other than the product itself are likely to be involved in this difference, the finding is certainly consistent with high efficacy as a cessation therapy.

6.3.4 Trends in uptake of different quitting methods over time

Figure 6.6 shows the proportions of quit attempts using these three groups of quitting methods among smokers in England from 2009 to 2015. It demonstrates that use of specialist services is rare among smokers and that, although most of those making a quit attempt still use the least effective methods to do so, the proportion using methods of intermediate effectiveness is increasing, largely as a consequence of increased use of e-cigarettes.

Through use of estimates of relative effectiveness based on Cochrane reviews of trials of medication and behavioural support,[20–23] supplemented by the data from smokers in England described above, the growth in use of intermediate effectiveness methods between 2012 and 2015 from 18% to 40% is likely to have generated many thousands of additional successful quit attempts by 2015; the figure for 2014 is likely to be around 19,000.[24] However, these trends also demonstrate that much more needs to be done to increase the number of smokers attempting to quit, and to increase the proportions

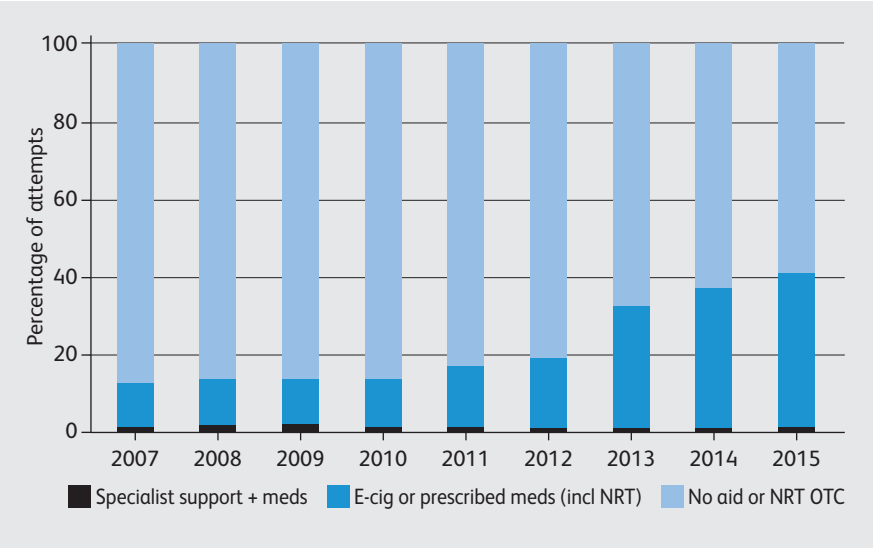

Fig 6.6 Percentages of those attempting to quit smoking in the past year by method used in most recent quit attempt[1] (data from 15,723 people who tried to stop smoking in the past year; 2015 figures based on January to September data). Specialist support = specialist SSS involving behavioural support plus medication/NRT. Meds = NRT or medication on prescription (Rx) or e-cigarette bought over the counter. No aid or NRT OTC = no aid or NRT bought from a shop. (Adapted from the Smoking Toolkit Study[1] with permission.)

using the more effective approaches. The data available from NHS SSSs indicate that there is no reason to believe that the integration of e-cigarettes into treatment support would reduce quit rates.

6.4 What motivates smokers to try to quit and what are the obstacles?

Smokers make a quit attempt when the desire to quit and confidence in success reach an action threshold. Environmental factors can trigger a quit attempt by either momentarily raising motivation above this threshold or reducing the level of the threshold.[25] In this context, the environment includes social norms about the desirability of smoking, as well as triggers such as health campaigns or advice on smoking from health professionals.

Survey data suggest that, in Britain, motivation to quit is driven primarily by health concerns and the financial cost of smoking, whereas factors such as

concern about the effect of smoking on one's family, not liking being addicted to smoking and feeling stigmatised are present but less frequently cited.[26,27] The most important environmental trigger identified from smokers' reports is health professional advice.[26] Mass media campaigns can also play an important role,[28] although this does not appear to be explicitly recognised by smokers.[26] The introduction of a comprehensive ban on smoking in indoor public areas appears to have had a short-term, but not a sustained long-term, effect on quitting.[29]

The main personal barriers to making an attempt to quit smoking appear to be enjoyment of smoking, having a positive smoker identity and low confidence in success.[27,30] Motivation may also be reduced by smoking among other people who are important to the smoker, such as a partner or friends, colleagues and wider family, although evidence for this influence is less strong.[27]

6.5 Why do more smokers not try to quit and how could the numbers be increased?

The figures outlined in this chapter thus far relate to the approximately one in three smokers who make a quit attempt each year. Although is it essential to ensure that as many of those as possible succeed in quitting, it is at least as important to increase quit attempts among the remaining majority of smokers who do not make a quit attempt in any given year. Measures are therefore required to increase the proportion of smokers making any attempt to quit smoking, as well as to increase the likelihood of success among those who try.

Chapter 3 outlined the population measures that can influence both quitting and uptake of smoking, and identified price rises and media campaigns as among the most effective. As studies of smokers also identify that the main drivers of motivation to quit are concerns about the health consequences of smoking and the cost of smoking,[26,27] the evidence is consistent in indicating that the most effective approaches to increase quit attempt numbers in the UK are likely to comprise price rises and media campaigns using health messages. However, advice from a health professional is also identified by smokers as a key trigger for quit attempts,[26] and it would appear that a great deal more could be done to increase the delivery of such advice. Figure 6.7 shows the proportion of smokers in England who report having received advice to stop smoking from their GP in the past year during 2010–15, and reveals that fewer than 40% of smokers recall having received advice to quit; of these, only two-thirds recall having received an offer of help with quitting. Equivalent data from people accessing NHS secondary care services are not available, but anecdotal evidence suggests that delivery of smoking cessation advice and support is also low. As over 1 million

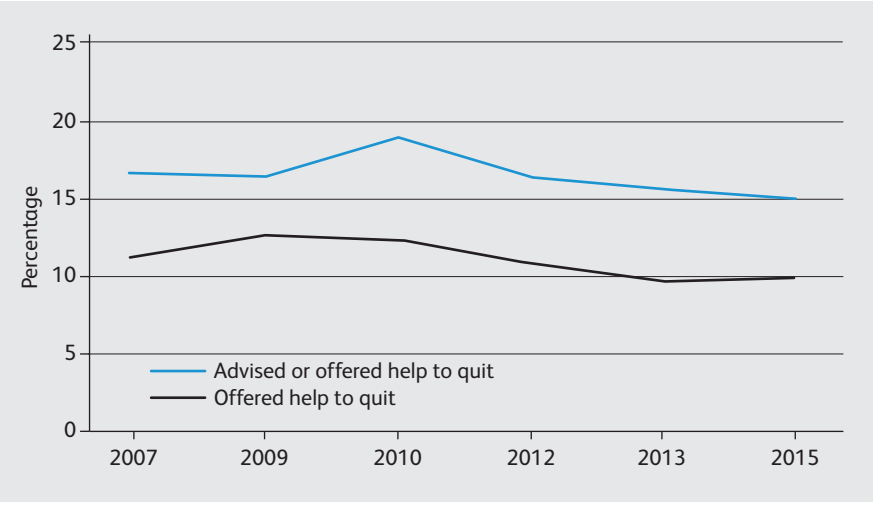

Fig 6.7 Proportion of people who smoked in the past year who reported receiving any advice on stopping or offer of help with stopping from their GP[1] (data from 27,000 smokers; 2015 figures based on January to September data). (Adapted from the Smoking Toolkit Study[1] with permission.)

smokers are admitted to hospitals in the UK each year,[31] this also represents a substantial missed opportunity to initiate and support quit attempts.

These findings indicate that guidance from the National Institute for Health and Care Excellence (NICE), which recommends that health professionals should offer help to quit at every opportunity,[32,33] and support of harm-reduction initiatives among those unwilling to quit,[34] is not being implemented sufficiently widely. Clinical trial evidence also suggests that, although simple advice from a physician to quit is effective, offers of support are more effective, generating quit attempts in around 40% of those receiving the offer.[35] Therefore, there is substantial scope for healthcare professionals to increase the rate of quit attempts by integrating advice and support to quit smoking in all healthcare consultations.

Since 2004, GPs in the UK have received financial incentives to record smoking status and provide advice on smoking, which, although unspecified, is generally interpreted as advice to quit.[36] This scheme applied initially only to smokers with smoking-related conditions and people with serious mental health disorders, but in 2012 was extended to cover everyone who smokes. Moreover, in 2012, the contracted requirement was changed from an offer of advice to an offer of pharmacotherapy and referral for smoking cessation support. Early evidence on the scheme demonstrated that it led to marked increases in the recording of both

smoking status and delivery of advice, but no increase in the prescription of pharmacotherapy[36] over the background trend.[37] A later evaluation of the 2012 change showed a similar result for all smokers, with increased recording by GPs of smoking status, delivery of advice to quit and referral to smoking cessation services, but no actual increase in prescription of pharmacotherapy.[38] A similar scheme that rewarded hospitals for ensuring that opportunistic advice on smoking was given to patients was introduced in 2012, and there is also no evidence that this initiative has had any effect.[39] Reform of these schemes would therefore appear appropriate.

6.6 How could changes in the availability of nicotine products influence quitting behaviour?

Evidence from time-series analyses indicates that increasing the availability of NRT, and introducing new smoking cessation medications to the market, increases the use of these products by smokers trying to stop smoking, but does not increase the proportion of smokers attempting to quit.[40]

Evidence from placebo-controlled trials indicates that use of an NRT product while continuing to smoke can increase the likelihood of a quit attempt (see Chapter 5), and that this effect is due to the nicotine in the products rather than being a placebo response.[41] Population-level data confirm that smokers who use an NRT product while smoking are more likely to try to stop, and eventually to succeed in quitting.[42–45] Although the mechanism for this effect does not appear to involve increased confidence in quitting,[43] it is possible that nicotine from the NRT product interferes with the maintenance of the association between smoking and nicotine reward, and hence reduces the motivation to smoke. It is also possible that encouraging smokers to experiment with nicotine products, including e-cigarettes, would generate more quit attempts and hence increase smoking cessation. The limited available evidence on this indicates that quit attempts are indeed more common among daily e-cigarette users who continue to smoke, but that successful quitting using the early-generation 'cigalike' devices is less common.[46,47] Research into methods of increasing quit rates among people experimenting with alternative nicotine sources, perhaps by finding ways to deliver quitting advice and behavioural support, is therefore needed.

6.7 Summary

- Approximately one in three smokers in the UK currently attempts to quit each year, but only about one in six of those who try to quit remains abstinent for more than a few weeks or months.

- Most smokers who try to quit do so without accessing professional help, preferring either to use no help or support, or else to use NRT or e-cigarettes bought over the counter.
- Those who use over-the-counter NRT appear to be no more likely to quit than those getting no help.
- Smokers who use over-the-counter e-cigarettes or prescribed medications are more likely to succeed.
- The greatest increase in the chances of stopping successfully occurs with prescribed medications used together with specialist behavioural support.
- The effectiveness of e-cigarettes used with behavioural support is uncertain, but early data demonstrate a relatively high quit rate.
- Smokers are motivated to make a quit attempt in particular by cost and health concerns.
- Price rises, media campaigns and brief advice from health professionals are therefore likely to increase the numbers of smokers trying to quit.
- Health professional advice and support to quit smoking should be offered as a routine component of healthcare consultations.
- Smokers who use nicotine products as a means of cutting down on smoking are more likely to make quit attempts. Promoting wider use of consumer nicotine products, such as e-cigarettes, could therefore substantially increase the number of smokers who quit.
- New research is needed to improve the effectiveness of over-the-counter NRT, and to find ways of providing behavioural support to smokers who choose e-cigarettes.

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7 Trends in use of non-tobacco nicotine in Britain

7.1 Sources of data

Although detailed data on the prevalence of smoking in Britain have been collected for some decades (see Chapter 2), sources of survey data on the use of nicotine replacement therapy (NRT) or unlicensed nicotine products are relatively limited. The most detailed source is the Smoking Toolkit Study (STS: www.smokinginengland.info), a monthly, household, face-to-face survey of representative samples of the population of England aged 16 and over, in operation since 2007.[1] Data on all smoking and non-tobacco nicotine-containing products, including e-cigarettes, have been collected since 2007 for smokers, since 2011 for recent ex-smokers (<1 year), and since 2013 for never-smokers and long-term (>1 year) ex-smokers. Other large national surveys have added questions on e-cigarettes much more recently, eg in 2014 in the Opinions and Lifestyle Survey[2] and Scottish Health Survey.[3] Data on use of e-cigarettes by children have also begun to be collected only relatively recently in national surveys in England, Scotland and Wales.[4–6] Action on Smoking and Health (ASH) UK has commissioned annual surveys of e-cigarette use among adults since 2010 and children since 2013, and these extend beyond simple measures of prevalence to include reasons for use, and a range of other factors.[7,8] The STS is the only source of data on NRT use. This chapter draws on all these sources to review trends in use of NRT and e-cigarettes in Britain over recent years. Most of the data presented are drawn from samples of smokers and recent ex-smokers participating in the STS.

7.2 Trends in the use of non-tobacco nicotine products among adults

Before the widespread uptake of e-cigarette use began in around 2011, NRT was being used by between 15% and 20% of smokers in England (Fig 7.1). However, use of non-tobacco nicotine products has risen sharply since 2011, primarily as a result of a marked increase in e-cigarette use, which has more than offset a more sustained decline in use of licensed NRT. In 2015 about 28% of smokers were

using at least one non-tobacco nicotine product, and more than 20% an e-cigarette (Fig 7.1).

Among recent (<1 year) ex-smokers, use of non-tobacco nicotine products also rose between 2012 and 2015, despite a fall in the use of NRT (Fig 7.2). In 2015 more than half of all recent ex-smokers were using a non-tobacco nicotine product, with more than 40% of these being e-cigarette users.

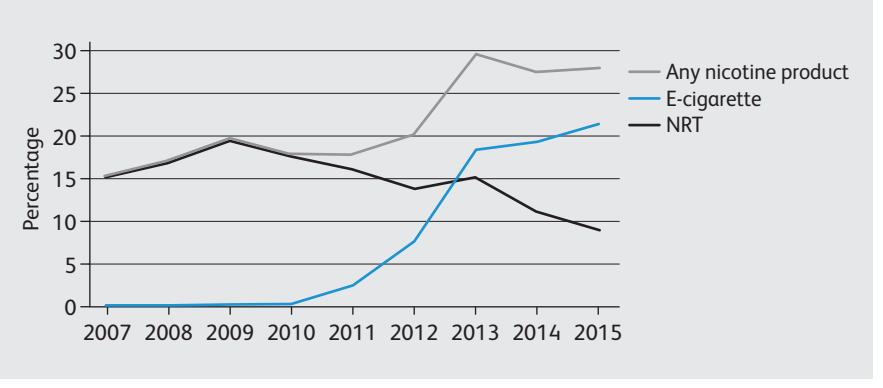

Fig 7.1 Prevalence of use of NRT, e-cigarettes or any non-tobacco nicotine products among current cigarette smokers in England 2007–15[1] (data from 36,896 cigarette smokers; 2015 figures based on January to September data). (Adapted from the Smoking Toolkit Study[9] with permission.)

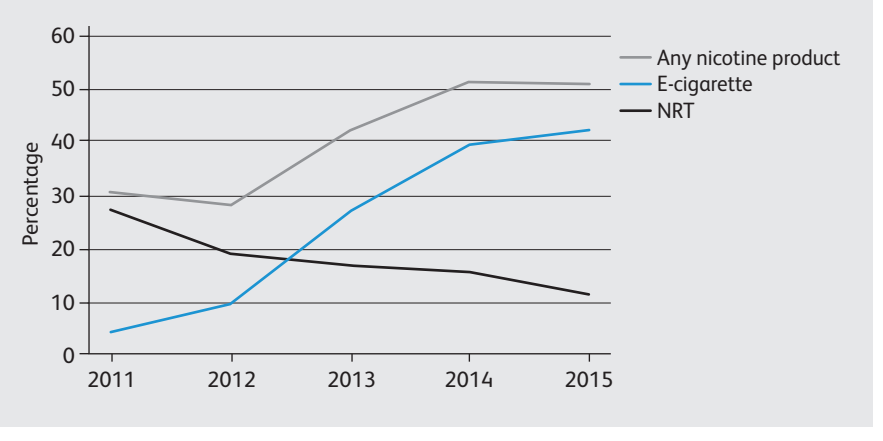

Fig 7.2 Prevalence of use of NRT, e-cigarettes or any non-tobacco nicotine products among recent ex-smokers in England 2011–14[1] (data from 2,318 people who stopped smoking in the past year; 2015 figures based on January to September data). (Adapted from the Smoking Toolkit Study[9] with permission.)

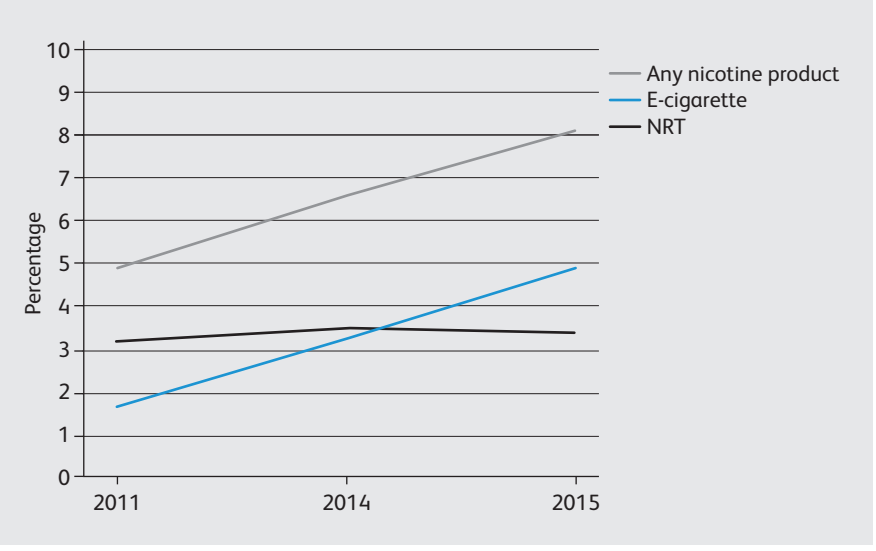

Fig 7.3 Prevalence of use of NRT, e-cigarettes or any non-tobacco nicotine products among long-term ex-cigarette smokers in England 2013–15[1] (data from 6,487 long-term ex-smokers; 2015 figures based on January to September data). (Adapted from the Smoking Toolkit Study[9] with permission.)

Data for longer-term (>1 year) ex-smokers, which are available since 2013, show a slightly different pattern, with generally lower levels of prevalence of use and stable NRT prevalence, whereas e-cigarette use has increased (Fig 7.3).

The explanation for these trends is not certain, but is likely to be mainly due to continued e-cigarette use among people who have used them to quit smoking, because the proportion of smokers in England who have stopped smoking but then take up an e-cigarette within a year of stopping is only about 10%.[1] The ASH survey in 2015 found that the principal reasons given by ex-smokers who are currently vaping are 'to help me stop smoking entirely' (61%) and 'to help me keep off tobacco' (53%). The principal reasons given by current vapers who still smoke are 'to help me reduce the amount of tobacco I smoke, but not stop completely' (43%) and 'to help me stop smoking entirely' (41%).[7] Whether some of these individuals would otherwise have relapsed back to cigarette smoking, had e-cigarettes not been available, is not clear. Exploration of the explanations for these trends is an important area for future research.

Among never-smokers, non-tobacco nicotine use is extremely uncommon. In 2015, 0.1% of never-smokers were using NRT and 0.3% an e-cigarette, and these figures have remained virtually unchanged since 2013 (Fig 7.4).

Among current smokers and recent ex-smokers, e-cigarettes tend to be used by a slightly higher proportion of younger than older smokers (Fig 7.5), but this use does not differ by socio-economic status (Fig 7.6) or gender.

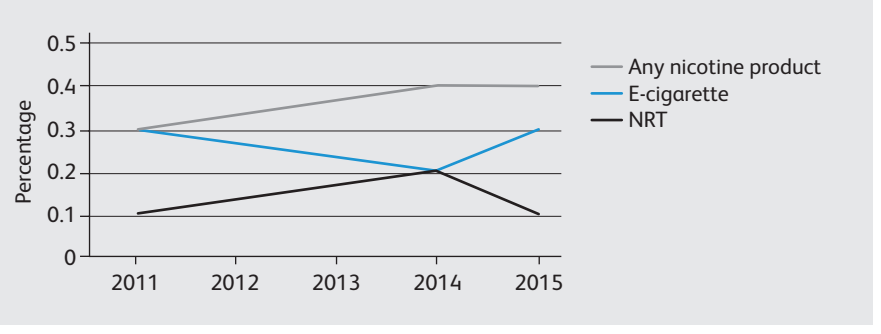

Fig 7.4 Prevalence of use of NRT, e-cigarettes or any non-tobacco nicotine products among never-smokers in England, 2013–15[1] (data from 24,041 never-smokers; 2015 figures based on January to September data). (Adapted from the Smoking Toolkit Study[9] with permission.)

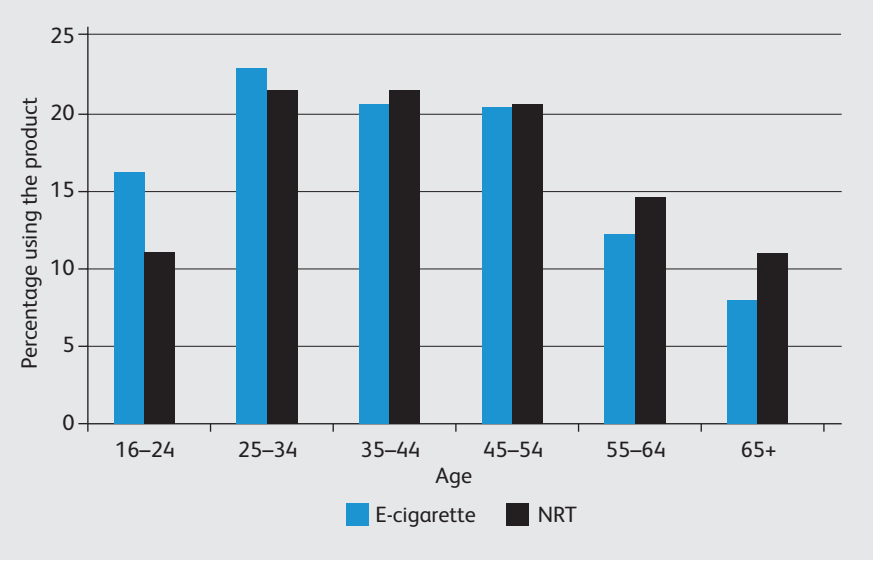

Fig 7.5 Age distribution of e-cigarette or NRT users in 2013–15[1] (data from 11,186 smokers and <1 year ex-smokers; 2015 figures based on January to September data). (Adapted from the Smoking Toolkit Study[9] with permission.)

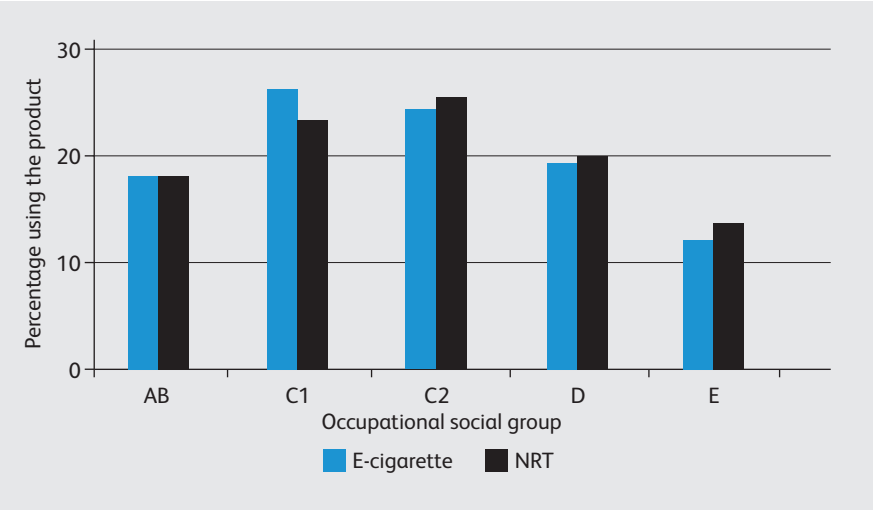

Fig 7.6 Social grade distribution of e-cigarette and NRT users in 2013–15[1] (from 11,186 smokers and <1 year ex-smokers; 2015 figures based on January to September data). AB, professional managerial; C1, clerical; C2, skilled manual; D, semi-skilled manual; E, unskilled manual/unemployed. (Adapted from the Smoking Toolkit Study[9] with permission.)

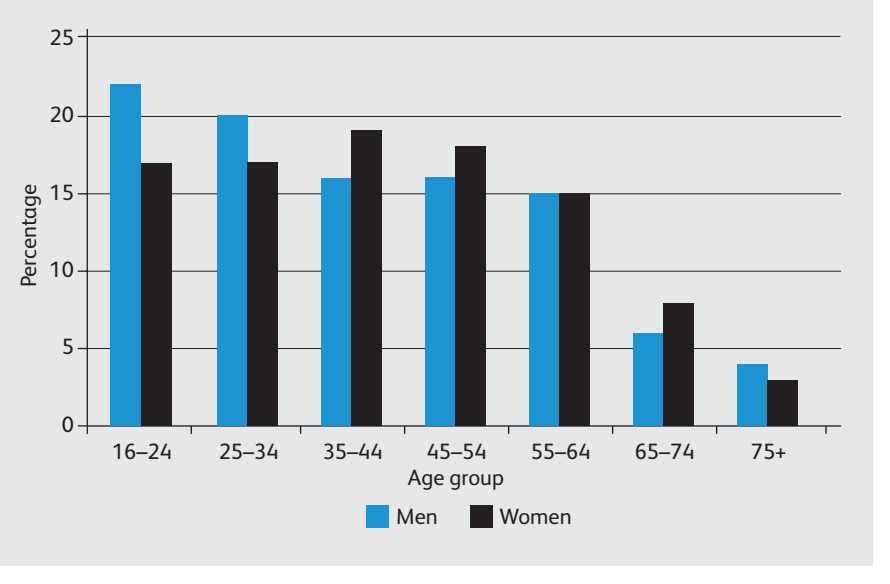

Fig 7.7 Proportion of adults in Scotland in 2014 who had ever used an e-cigarette, by age and sex.[3] (Adapted from the Scottish Government[3] with permission under Open Government Licence.)

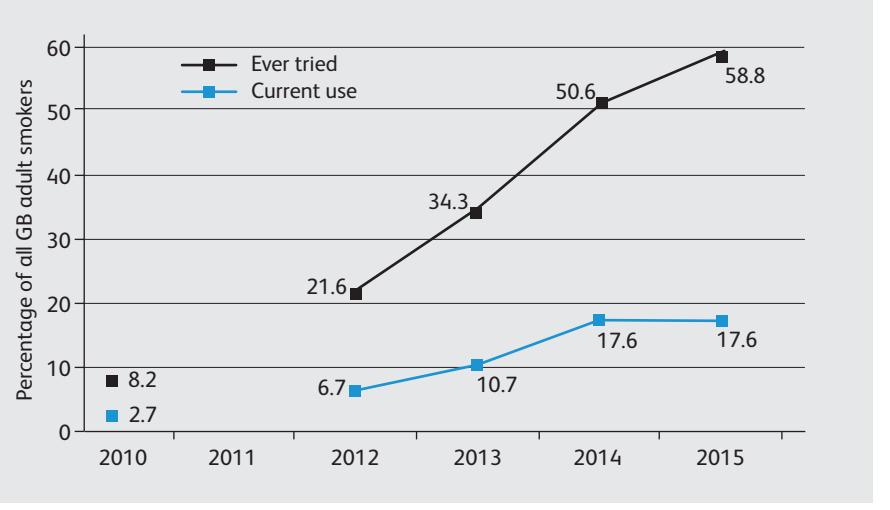

Fig 7.8 Prevalence of ever use and current use of e-cigarettes among adult smokers in Britain, 2010–15.[7] (Adapted from ASH[7] with permission under Open Government Licence.)

The Opinions and Lifestyle Survey estimated that, in the first quarter of 2014, e-cigarettes were being used by 11.8% of smokers, 4.8% of ex-smokers and 0.14% of never-smokers.[2] Data from Scotland indicate that, in 2014, around 15% of men and women reported ever having used an e-cigarette, and about 5% reported current use.[3] This current use was entirely restricted to current smokers (of whom 15% were current e-cigarette users) and ex-smokers (7%). Of never-smokers, 1% reported ever using an e-cigarette, and none were current users. 'Ever use' was much more prevalent among younger people (Fig 7.7).

Annual surveys by ASH demonstrate data consistent with STS findings, with almost 60% of smokers in Britain ever having tried an e-cigarette, and just under 18% reporting current use in 2015.[7] Similar to the STS findings, current use had remained unchanged between 2014 and 2015 after rapid growth since 2010 (Fig 7.8).

As in the Scottish data, however, this use of e-cigarettes has occurred almost entirely among current and ex-smokers; in 2015, the prevalence of current use of e-cigarettes among never-smokers was 0.2%.[7] The most frequently reported reasons for using e-cigarettes were to quit smoking, to help maintain abstinence having already quit and, among dual users, to cut down on smoking.[7] The ASH survey in 2015 also explored the type of e-cigarettes that respondents were using, and demonstrated that most had started use with first-generation disposable or 'cigalike' devices, but then migrated to second- and third-generation refillable or tank designs (Fig 7.9).[7]

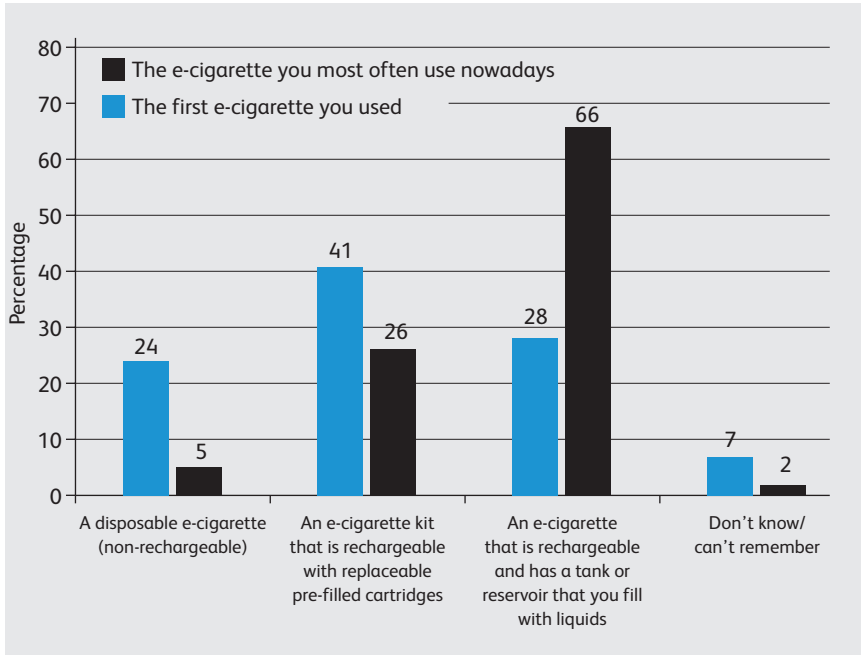

Fig 7.9 Types of e-cigarette tried in the past and now.[7] (Adapted from ASH[7] with permission under Open Government Licence.)

Over 80% of e-cigarette users surveyed by ASH in 2015 were using flavoured e-liquids. Tobacco was the most popular flavour (35% of users), but fruit (25%) and menthol (19%) were also popular.[7]

7.3 Trends in the use of non-tobacco nicotine products among children

Data on the use of non-tobacco nicotine among children are limited to e-cigarette use. Annual surveys by ASH of young people in the UK since 2013 demonstrate that awareness of e-cigarettes has grown substantially, such that, in 2015, only 7% of young people reported no knowledge of these products, and the proportion of young people who had tried e-cigarettes increased over these three surveys from 5% to 13% (Fig 7.10).[8]

However, of the 13% of young people who reported in 2015 ever having tried an e-cigarette, most (80%) had done so only once or twice.[8] Only 2.4% of all participants in the survey had used e-cigarettes once or more a month, and 0.5% once or more a week. The Scottish SALSUS (Schools Adolescent and Lifestyle and Substance Use Survey) study[5] reported similar findings among 13- and 15-

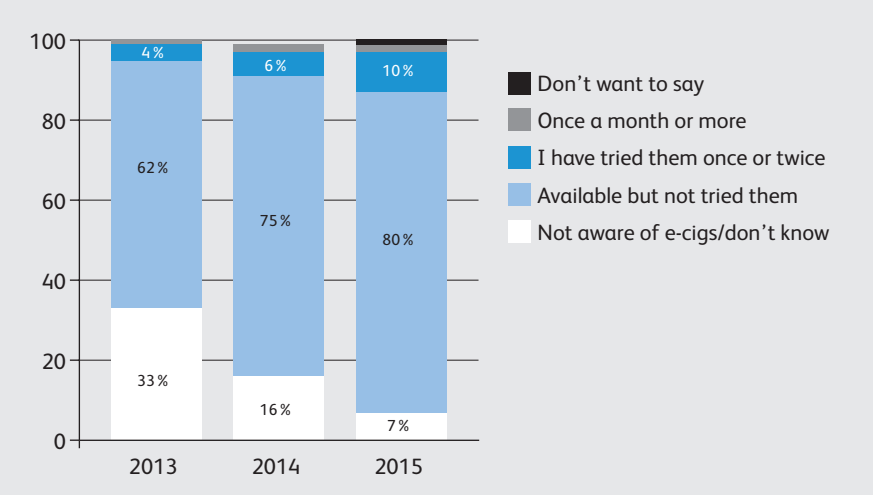

Fig 7.10 Prevalence of awareness and frequency of use of e-cigarettes among young people aged 11–18, UK, 2013–15.[8] (Adapted from ASH[8] with permission under Open Government Licence.)

year-olds in 2013, with 7% and 17%, respectively, reporting ever having tried to use or used an e-cigarette, and only 1% in each age group using the product more than 'once or a few times'. In 2014, the Welsh Health Behaviour in School-aged Children survey of 11- to 16-year-olds in Wales reported that 12.3% of participants had ever used an e-cigarette, and 1.5% were using e-cigarettes at least once a month.[6] The 2014 Smoking, Drinking and Drug Use survey of children aged 11–15 in England found that 22% of participating children had ever used an e-cigarette, but only 1% reported regular use.[4] Regular use of e-cigarettes among young people in the UK thus appears to be very rare. As in adults, it appears that it occurs predominantly among those who are using, or have used, tobacco cigarettes. In 2013 in the Scottish study, all of those who reported having used e-cigarettes more than a few times had been, or were still, smokers (Fig 7.11).[5]

The 2014 Welsh survey reports very similar findings, with young people aged 11–15 who had ever used an e-cigarette being over 20 times more likely than never-users to have ever smoked; those using e-cigarettes more than once a month were more than 100 times more likely to be smoking cigarettes at least once a week.[6] The 2015 ASH survey also reports a strong association between use of e-cigarettes and tobacco cigarettes (Fig 7.12), with almost all e-cigarette users either being current smokers, or having tried or been regular smokers in the past.[8] Regular e-cigarette use in the 2014 English Smoking, Drinking and Drug Use survey was exclusive to children who had at least tried smoking.[4]

Of those using e-cigarettes in the ASH survey, most used a tank or other refillable device, and most used e-liquids with fruit (42%), tobacco (23%) or menthol (13%) flavours.[8]

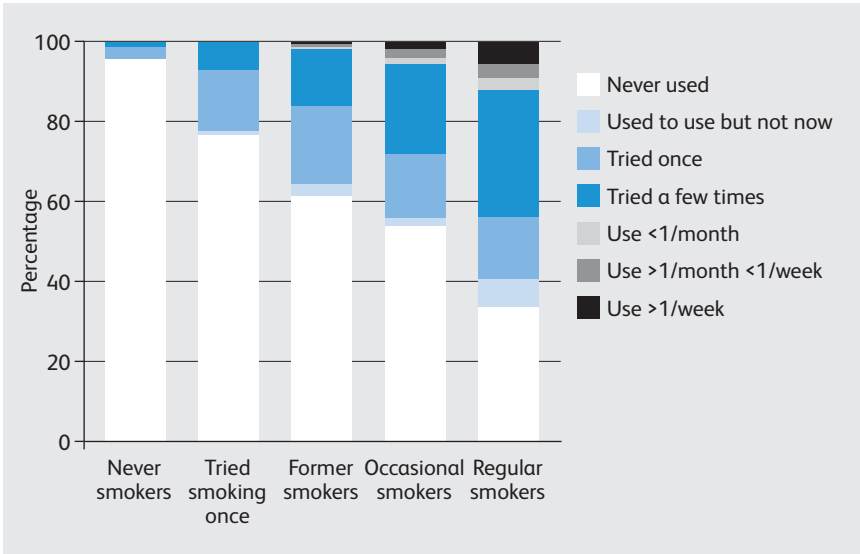

Fig 7.11 Use of e-cigarettes, by smoking status, among 13- and 15-year-olds in Scotland in 2013.[5] (Adapted from NHS National Services Scotland[5] with permission under Open Government Licence.)

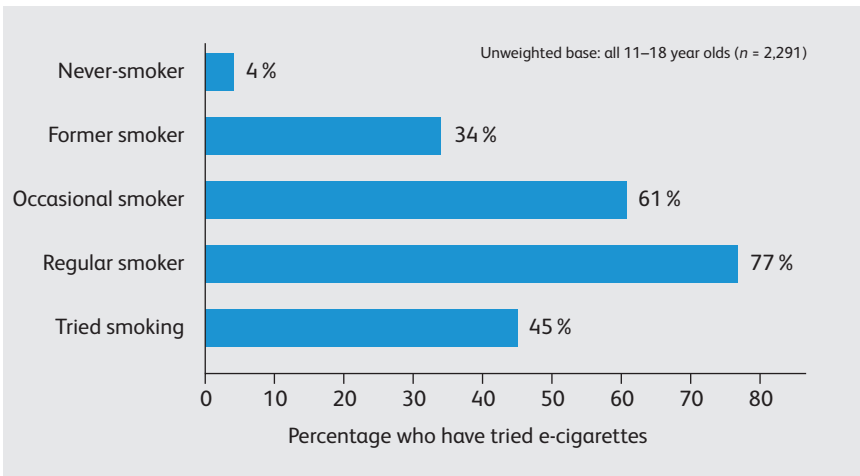

Fig 7.12 Young people aged 11–18 who have ever tried an e-cigarette, by smoking status, UK, 2015.[8] (Adapted from ASH[8] with permission under Open Government Licence.)

7.4 Summary

- Use of e-cigarettes among adults in the UK was rare before 2010, but has since increased to the point that up to one in five smokers now uses an e-cigarette, more than twice as many as use NRT.
- The proportion of smokers using NRT has fallen by about half over this period, but the proportion using any non-tobacco nicotine product has increased to just under 30%.
- These trends are similar but more marked among recent ex-smokers, 40% of whom use an e-cigarette.
- Use of e-cigarettes among adults who have never been regular smokers is very rare.
- There is a slightly greater likelihood that younger adult smokers will use e-cigarettes than NRT; in Scotland, younger men are more likely to use them.
- Adult regular e-cigarette users tend to use tank or other refillable devices, rather than first-generation 'cigalikes', and tobacco-, fruit- or menthol-flavoured nicotine.
- The proportion of young people in Britain aged <18 who have ever used an e-cigarette is increasing, but remains low.
- Most use among young people appears to be single or very occasional experimentation. Use more than once a month is relatively rare and more than once a week extremely rare.
- Regular use is almost exclusively limited to young people who are already either regular or occasional smokers, or have experimented with smoking in the past.
- Young regular users of e-cigarettes also favour later-generation devices, and fruit, tobacco or menthol flavours.
- In adults and young people in the UK, therefore, use of e-cigarettes is limited almost entirely to those who are already using, or have used, tobacco.

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8 Harm reduction and population health

8.1 The need for harm reduction

Prevention of smoking is vital to public health, and much progress has been made in reducing the prevalence of smoking in the UK over recent decades (see Chapter 2). However, the data presented in Chapter 2 also demonstrate that this success has been achieved primarily by reducing uptake of smoking among younger people, more than improvements in the rate at which established smokers quit smoking. It is, however, these established smokers in middle and older age who will generate most of the population burden of morbidity and premature mortality caused by smoking over the next two decades.[1,2] As established smokers today are more likely to be socio-economically disadvantaged or to have mental health problems (see Chapter 2), this burden of disease will fall disproportionately on these groups who, as a result of higher levels of addiction to nicotine, also find it particularly difficult to quit smoking.

Increasingly powerful incentives for existing smokers to try to quit smoking, and strong support to help them succeed, are therefore urgently required. Further application and extension of the conventional policy options summarised in Chapter 3 might be expected, at best, to sustain the decline in smoking prevalence of close to 0.7 percentage point per year achieved over the past decade in the UK (see Fig 2.1, Chapter 2), the consequence of which will be that most of the current smokers in the UK, and particularly the most heavily addicted smokers, will continue to smoke for several decades. The public health imperative in relation to smoking is, however, to reduce prevalence as much and as quickly as possible, for example, to achieve the widely agreed objective of a 'tobacco-free' society (comprising smoking rates of 5% or less in all socio-economic groups) by 2035,[3] and this requires the addition of new strategies. Harm reduction offers the potential to add significantly to the current rate of decline in smoking prevalence among all population groups. The availability of alternatives to tobacco, as a source of nicotine for the most heavily addicted smokers, also allows the application of much higher levels of taxation on tobacco without necessarily exacerbating poverty in those smokers who find themselves unable to quit in response to increases in tobacco prices. In Sweden,

the availability of *snus* has been estimated to have added around 0.4 percentage point per year to the rate of decline in smoking prevalence.[4] E-cigarettes, and other non-tobacco nicotine products, surely have the potential to achieve at least the same in the UK.

Harm-reduction approaches, by promoting substitution of tobacco with less hazardous sources of nicotine, thus represent a potentially powerful complement to existing prevention policy, particularly among the relatively highly addicted and typically disadvantaged smokers who are likely to find it most difficult to quit.[5,6] However, pursuing a harm-reduction strategy also carries risks of unwanted effects in society. This chapter explores some of the harms caused by tobacco smoking in different periods of life, and the probable balance of risks and benefits of harm-reduction approaches based on substitution with NRT or other non-tobacco nicotine products, particularly e-cigarettes.

8.2 Potential hazards of harm reduction

Although harm-reduction approaches have the potential to reduce the hazard of nicotine use among the current smoking population, they also bring potential hazards to wider public health. For example, a product that is half as damaging to health as tobacco smoking has the potential to halve the harm caused by smoking in society, if used exclusively and completely as a substitute for tobacco by current smokers, and young people who would otherwise have become smokers. That benefit would be reduced or even reversed, however, if the new product came to be sufficiently widely used among non-smokers that the benefits to smokers were eclipsed by harm sustained by non-smokers. The benefit of harm reduction to smokers would also be offset at population level if use of harm-reduction products increased the risk of smoking uptake (known as gateway progression, see below), undermined existing tobacco control measures by making the act of smoking socially acceptable again (renormalisation) or discouraged quitting by being used as a partial substitute for tobacco smoking ('dual use'), without progression to complete substitution among smokers who would otherwise have quit. These processes are discussed in more detail below.

8.2.1 Renormalisation

In relation to tobacco smoking, renormalisation refers to processes that undermine or reverse a progressively increasing perception in society that smoking is not a normal or desirable behaviour.[5] For much of the 20th century smoking was part of the fabric of British life, and children grew up perceiving

smoking to be something that many, if not most, adults did. In recent years, however, the acceptability of smoking has changed, particularly as a consequence of prohibition of tobacco advertising, smoking in enclosed public places and point-of-sale displays, and other measures. Although smoking remains relatively common, and hence relatively normal, in some communities or social groups, this is no longer the case in general. Examples of renormalisation might include: the use of e-cigarettes in areas where smoking is prohibited, thus creating an impression that smoking is acceptable; advertising or other imagery that evokes tobacco smoking through e-cigarette use; behavioural modelling from use of e-cigarettes by parents, siblings, peers, friends, celebrities or others; or other processes that in some way make smoking more appealing.[6,7]

8.2.2 Gateway progression

Gateway progression is a process by which, in relation to tobacco smoking, use of non-tobacco nicotine is proposed to cause uptake of smoking that would not otherwise have occurred. Gateway theory has its origins as a descriptive model for progression from use of soft drugs to use of hard drugs, and a recent review of evidence from animal models concluded that nicotine exposure may indeed increase susceptibility to other drug use, independent of other determinants of common liability.[8] In nicotine use, however, the gateway theory has also been applied as a predictive model proposing that use of non-tobacco nicotine is likely to cause progression to use of nicotine through tobacco smoking,[9] and therefore that use of e-cigarettes by non-smokers, and particularly by children, could cause smoking uptake independent of other determinants of smoking initiation. Similar concerns have in the past been expressed in relation to nicotine replacement therapy (NRT) and smokeless tobacco.[9]

8.2.3 Dual use

Dual use refers to the concomitant use of non-tobacco nicotine by smokers who continue to smoke tobacco. As outlined in Chapter 5, reasons for dual use include relief of nicotine withdrawal symptoms at times when smoking is not allowed, or a desire to cut down on smoking without necessarily a commitment to quit. However, concerns have been expressed that dual use may inadvertently sustain smoking by making it easier to abstain when smoking is prohibited and the smoker might otherwise have quit, and that smokers who could otherwise have quit elect for dual use instead, in the mistaken belief that this generates significant health gains. There are particular concerns that the tobacco industry will promote dual use of e-cigarettes as a means of sustaining, rather than cutting down or quitting, tobacco smoking in their customers[10] (see Chapter 9).

8.3 Harm to health and wellbeing of self and others from smoking at different stages of life

Smoking directly damages the health of all who smoke (see Chapter 1), increasing the risk of a wide range of fatal and non-fatal illnesses[11] and causing over 120,000 deaths in the UK in 2010.[12] However, the adverse effects of smoking extend well beyond this direct harm to the individual smoker, and are not limited to the later period of life when the increased mortality in smokers becomes more acute. Through the life course of any individual from the point of conception, maternal smoking (and hence fetal exposure *in utero*) impairs fetal growth and development, and increases rates of fetal and neonatal death, low birth weight, preterm birth and developmental anomalies.[13] Passive maternal smoking during pregnancy increases the risk of stillbirth and developmental anomalies[14,15] and reduces birth weight.[16] In childhood, passive exposure to tobacco smoke causes sudden infant death, respiratory infections, middle-ear disease and exacerbation of asthma.[13] Passive exposure to others' smoke during adulthood causes transient symptoms such as eye and throat irritation at all ages, and in later life contributes to higher mortality from lung cancer, cardiovascular disease and chronic obstructive pulmonary disease (COPD).[17]

Harm from smoking is not limited to that arising from inhaling tobacco smoke. Probably through behavioural modelling and opportunities for experimentation, children whose parents or other household members smoke are more likely to take up smoking themselves,[18] thus perpetuating smoking and its consequent harm in successive generations. Smoking rates in the wider communities and environments that children grow up in also influence smoking uptake, because children whose peers smoke, and those exposed to smoking imagery in the media, are more likely to become regular smokers.[19] Smoking is a significant drain on family budgets, exacerbating poverty,[20] and a drain on wider society, which suffers the opportunity cost of funding over £3.3 billion in direct healthcare and social care costs in the UK, and over £10 billion in lost productivity and other societal costs.[21] Thus, although smoking has little direct effect on the personal health of individual smokers during early adult life,[22,23] the risks to others, especially children, are substantial.

As outlined above, all or almost all of these harms could be prevented or else much reduced by substitution of smoked tobacco with a less hazardous source of nicotine. The potential benefits and risks to individual and societal health of doing so are now considered in relation to the two main options currently available in the UK: conventional NRT products and unlicensed non-tobacco nicotine products, including e-cigarettes.

8.4 Harm reduction with conventional NRT products

8.4.1 Health harms

As use of nicotine alone in the doses used by smokers represents little if any hazard to the user,[24] complete substitution of smoking with conventional NRT products is, for practical purposes, the equivalent of complete cessation in almost all areas of harm to the user. NRT products do not emit vapour and so are not a source of passive exposure for adults or children. Packaging and dose restrictions render accidental poisoning in children highly unlikely. Questions remain about the safety of nicotine in pregnancy[25] and potential effects on fetal development and mortality,[11] although one recent study has reported a lower occurrence of developmental abnormality among children whose mothers used NRT in pregnancy than in those whose mothers did not.[26]

8.4.2 Renormalisation of and gateway to smoking

Only the Nicorette inhalator bears any resemblance to a cigarette, so users of most NRT products provide no behavioural modelling that could encourage primary uptake of, or sustain, tobacco smoking by others. Use of NRT among never-smokers is rare at all ages and, despite early concerns to the contrary, there is no reported evidence that use of the inhalator or any other NRT product in young people has ever acted as a gateway to smoking.

8.4.3 Dual use and gateway from smoking

NRT was developed as a smoking cessation therapy for use after an abrupt and complete cessation of tobacco smoking. The efficacy of NRT used in this way is well established.[27] More recently, however, NRT has been licensed in the UK for use together with continued smoking, to relieve withdrawal symptoms during temporary abstinence from smoking, or to cut down on smoking,[28] ie for dual use. Before the advent of e-cigarettes, up to 15% of current smokers in England used NRT in this way, although the proportion is now closer to 5% (Fig 8.1).[29] Although cutting down on smoking achieves relatively little in terms of health benefits, use of NRT together with tobacco smoking does appear to reduce compensatory smoking to a modest extent[30] and, among smokers with no intention to quit, to increase, by as much as twofold, the likelihood of a subsequent quit attempt.[31] It also protects those around the smoker from the harmful effects of passive smoking. For this and other reasons, dual use of NRT and tobacco smoking is licensed by the Medicines and Healthcare products Regulatory Agency (MHRA)[32] and recommended by the National Institute for Health and Care Excellence

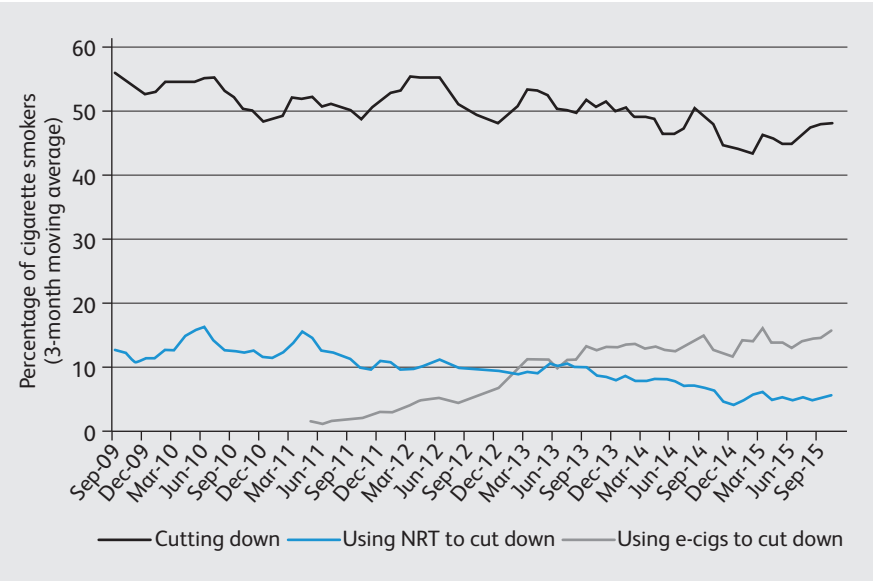

Fig 8.1 Self-reported use of NRT or e-cigarettes to aid cutting down on smoking, England, 2009–15.[29] (Adapted from the Smoking Toolkit Study[29] with permission.)

(NICE) as a tobacco harm-reduction strategy.[3,24] As use of NRT in this way increases the likelihood of quitting, in these circumstances NRT acts as a gateway from smoking.

8.4.4 Population health effects of substitution of smoking by NRT

With the possible exception of use during pregnancy, complete substitution of smoking by NRT achieves much the same in health terms as quitting both smoking and all nicotine completely. Widespread uptake of NRT by non-smokers would therefore result in little harm to public health, but is in any case rare. Gateway progression from NRT to smoking among those who have never smoked does not, for practical purposes, occur. Dual use results in a modest reduction in tobacco smoking of little or no significance to health, but promotes quitting. Promotion of NRT as a reduced harm substitute for smoking is therefore unequivocally good for health. Economic analysis of the use of NRT in a harm-reduction strategy, including a range of scenarios in which opting to cut down rather than quit detracted to different degrees for those who would otherwise have quit, found that all options were cost-effective in relation to preventing major disease costs to the NHS,[33] and hence were acting in favour of population health.

8.5 Substitution with e-cigarettes

8.5.1 Health harm

As e-cigarettes have been in widespread use in the UK and most other countries for less than a decade, the health effects of long-term use are as yet unknown. As outlined in Chapter 5, there is very little evidence that short-term use of e-cigarettes causes any appreciable harm to users or to others, but information on long-term health effects of repeated and sustained inhalation of e-cigarette vapour is of necessity limited to inference, based on knowledge of the vapour's constituents. The oxidant, particulate, carcinogen and other toxin contents summarised in Chapter 5 would be expected, from first principles, to increase the risk of lung cancer, COPD, cardiovascular disease and other diseases caused by smoking, but at much lower levels of risk. For the less common health sequelae of smoking,[11] levels of increased risk are likely to be negligible. The risks attributable to long-term inhalation of nicotine in isolation from tobacco smoke, and of the propylene glycol, glycerine and other components unique to e-cigarettes, are also uncertain but likely to be low. The health harm to long-term users of e-cigarettes is therefore likely to be marginally greater than for those who use conventional NRT.

Harm to others from vapour exposure is negligible (see Chapter 5). The effects of maternal use on the fetus are unknown but, on the grounds of the very low levels of toxins in vapour, are probably close to those of NRT. Accidental poisoning in children from ingestion of e-cigarette solutions, which has been reported and typically results in nausea and vomiting,[34] are preventable through the use of childproof fasteners.

8.5.2 Renormalisation and gateway to smoking

First-generation e-cigarettes were designed to resemble tobacco cigarettes in approximate shape and size, and hence their use provides a behavioural model similar to smoking, which could appeal to young people or smokers trying to quit smoking, appear to undermine smoke-free policy, and be used by the tobacco industry to cross-promote smoking imagery and hence tobacco products through e-cigarette advertising (see Chapter 9). However, even first-generation products are visually distinct from cigarettes, and exhaled vapour easily distinguishable from tobacco smoke in terms of appearance, smell and irritancy, making confusion unlikely between e-cigarettes and tobacco cigarettes in areas covered by smoke-free legislation.[35] Later-generation e-cigarettes have less or no physical resemblance to tobacco cigarettes. Use of e-cigarettes to generate smoking imagery in advertisements is prevented under UK advertising codes of practice.[36,37]

Data from Wales indicate that children whose parents or peers use e-cigarettes are more likely to experiment with e-cigarettes themselves,[38] and to intend to smoke in the future, than children without this exposure.[38] However, as parental e-cigarette use occurs almost exclusively among current or former smokers, children in these households would be expected to have higher smoking intentions,[19] and it is unclear whether this risk is either increased or decreased by the availability of e-cigarettes as opposed to tobacco cigarettes.

The prevalence data on the use of e-cigarettes by both adults and children presented in Chapter 7 demonstrate that e-cigarette use in Britain is, to date, almost entirely restricted to current, past or experimental smokers. As with NRT, there is no evidence thus far that e-cigarette use has resulted, to any appreciable extent, in the initiation of smoking in either adults or children; the extremely low prevalence of use of e-cigarettes among never-smoking adults[39] and children[40–42] indicates that, even if such gateway progression does occur, it is likely to be inconsequential in population terms. Although it remains important to monitor the use of e-cigarettes in young people, to ensure the quick identification of evidence of any increase in uptake of smoking arising from e-cigarette use, it appears that, to date, concerns over gateway progression into smoking are unfounded. The association between e-cigarette and tobacco cigarette use is therefore more likely to arise from common liability to use of these products, and to use of e-cigarettes as a gateway from, rather than to, smoking.

8.5.3 Dual use and gateway from smoking

Office for National Statistics data indicate that, in the first quarter of 2014, 11.8% of smokers, 4.8% of ex-smokers and 0.14% of never-smokers in Britain used e-cigarettes; smoking prevalence data from the same source indicate that these proportions represented approximately 2.2%, 2.6% and 0.08% of the total adult population, respectively.[43] On these figures, therefore, about 45% of e-cigarette users in Britain are using them together with smoking, which is about twice as many as do so with NRT.[44] As dual use of NRT is recommended as a means of increasing the likelihood that smokers will attempt to quit smoking,[3] and early-generation e-cigarettes appear to be approximately as effective as NRT as a cessation aid,[45] it follows that the same is likely to apply to e-cigarettes. Observational data from England confirm that smokers who use e-cigarettes at least daily are indeed twice as likely to make a quit attempt, or else to reduce their smoking, than those who do not, although in this study the likelihood of success among those attempting to quit was not increased by e-cigarette use.[46] Independent clinical trials[45] and observational data from the Smoking Toolkit Study[47] indicate that e-cigarette use is associated with an increased chance of quitting successfully, but further longitudinal and trial data would be helpful to define any such effect more precisely.

These findings suggest, however, that, among smokers, e-cigarette use is likely to lead to quit attempts that would not otherwise have happened, and in a proportion of these to successful cessation. In this circumstance, e-cigarettes act as a gateway from smoking. However, it is not yet known whether, or by how much, e-cigarettes are being dually used by smokers who would otherwise have quit completely, and hence act as a barrier or delay to cessation. It is also not known whether or by how much a preference to try to quit using e-cigarettes is displacing uptake of the more effective conventional NHS Stop Smoking Services (SSSs)[48] or other services combining pharmacotherapy with behavioural support, and hence reducing overall quit numbers, or whether this effect is counteracted by the much broader reach and uptake of e-cigarettes relative to NHS SSSs.

It seems likely that the chance of successful quitting with e-cigarettes would be increased if smokers who chose to use them, whether for cutting down or quitting, could also receive additional behavioural support,[49] and perhaps, given the evidence that the combination of two nicotine products is more effective than one alone, were encouraged to combine e-cigarette use with a nicotine transdermal patch.[50] Research and development of methods are clearly needed to engage and support smokers who start to use e-cigarettes, for whatever reason, to increase the likelihood of successfully quitting .

8.5.4 Population health effects of substitution of smoking with e-cigarettes

Thus far, the availability of e-cigarettes appears to have been positive for UK public health. Uptake has been rapid among adults and limited almost entirely to smokers, and has contributed to a continued downward trend in UK smoking prevalence. Use by children who would not otherwise smoke appears to be minimal. In many ways, therefore, their availability and adoption as a consumer alternative to smoking share many parallels with the use of *snus* as a consumer harm-reduction product in Sweden.[51] Although long-term safety remains a concern, it appears likely that the combined influences of impending regulatory controls (see Chapter 10) and technological advances will lead to significant improvements in the probable long-term hazard profile of these products in the near future. These developments mean that unlicensed e-cigarettes are likely, in the near future, to approximate to NRT in terms of long-term hazard. The arrival on the market of licensed products, whether e-cigarettes or other novel designs, will make that prospect even more of a reality. In that case, e-cigarettes are likely to share the efficacy of NRT as a harm-reduction option under most circumstances.[33]

However, the creation of models of these beneficial effects for products available today, and also those of potentially adverse influences such as widespread uptake

by non-smokers, gateway effects into smoking and sustaining dual use rather than quitting among established smokers, is difficult and inevitably dependent on assumptions about the probable magnitude of these influences. At the time of writing, we are aware of only two published attempts to do so. A proof-of-concept study applying Markov modelling to a cohort of adults aged 18–24 in the USA developed two models of smoking and e-cigarette use, the more conservative of which predicted that the prevalence of adult cigarette smoking within the cohort would increase from 15% at baseline to 21% after 10 years.[52] These figures do not therefore appear applicable to the UK, where a 6 percentage point increase in smoking prevalence after the age of 25 has not happened in over 40 years (see Fig 2.11). A Monte Carlo analysis approach, modelling various scenarios of relative uptake by smokers and non-smokers, and at levels of harm relative to smoking ranging from 1% to 50%, predicted population benefits as long as use of e-cigarettes is concentrated among those who already smoke, or would otherwise have become smokers.[53] As the true magnitude of e-cigarette harm is likely to lie at the low end of that modelled range, and experience to date indicates that use of e-cigarettes is almost entirely confined to smokers, these predictions support the notion that e-cigarettes, within the context of a regulatory environment designed to discourage use among youth and never-smokers, are likely to benefit public health.

8.6 Summary

- Uptake of smoking is falling in the UK, but most current smokers are likely to continue smoking for many years.
- Most of the morbidity and mortality caused by smoking in the short- and near-term future will occur in people who are smoking now.
- More effective measures to help existing smokers to quit smoking, as soon as possible, are therefore urgently needed.
- Harm reduction has the potential to complement conventional tobacco control policy by offering an alternative means for smokers to stop smoking tobacco.
- Substituting medicinal nicotine (NRT) for tobacco almost completely prevents any further damage to self or others from nicotine use.
- Although the long-term hazards of e-cigarette use are not yet clearly defined, e-cigarettes are probably close to NRT in the harm that their use confers on the user and others.
- The long-term hazard associated with e-cigarette use is likely to fall, as a result of regulatory and technological developments.
- There is no evidence that either NRT or e-cigarette use has resulted in renormalisation of smoking.
- None of these products has to date attracted significant use among adult never-smokers, or demonstrated evidence of significant gateway progression into smoking among young people.

- NICE guidance recommends dual use of NRT for harm reduction, largely because dual users are more likely eventually to quit smoking.
- Evidence on the natural history of smoking among dual users of e-cigarettes is less well established, but a similar effect is likely.
- Promotion of the use of non-tobacco nicotine, including e-cigarettes, as widely as possible as a substitute for smoking, in the context of a regulatory framework designed to discourage use among youth and never-smokers, is therefore likely to generate significant health gains in the UK.

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9 E-cigarettes, harm reduction and the tobacco industry

9.1 Introduction

In 2013, the investment bank Goldman Sachs identified e-cigarettes as one of eight emergent themes in the global economy capable of 'creative destruction', representing a new technology that could offer consumers a significantly superior proposition and potentially 'forcing established companies and business models to either adapt or die'.[1] In the same year, *The Economist* newspaper similarly asked whether the rise of e-cigarettes represented the tobacco industry's 'Kodak moment' – 'its version of the point at which the world's leading maker of camera film realised that consumers had gone digital, and it was too late to chase them'.[2] The continuing profitability of the tobacco industry, which arises overwhelmingly from sales of tobacco cigarettes,[3–6] suggests that such reports of the industry's demise are at best premature. However, these claims do highlight the substantial degree of uncertainty about the commercial implications of e-cigarettes for the future of the tobacco industry and therefore for the strategic development of tobacco control.

The disruptive effect of e-cigarettes is not confined to the tobacco industry. The chairman of the pharmaceutical giant GlaxoSmithKline, for example, has acknowledged that, in response to the declining performance of their nicotine replacement therapies (NRTs), the company considered manufacturing e-cigarettes before concluding that such a step would be 'just too controversial'.[7] Leading tobacco companies have, perhaps predictably, made a different decision, implementing a rapid programme of investment in and acquisition of vapour devices. The public health implications of such developments remain uncertain and contested, and reflect broader debates about the role of harm reduction in general. At one end of the spectrum, harm-reduction advocates and researchers see advantages in engaging an industry skilled in marketing nicotine in the promotion of products that could offer a potential exit strategy from selling cigarettes: identifying, for example, the 'need to create a situation in which there are incentives for tobacco companies to gradually become nicotine companies … [such] that their long-term profits are going to be in other products than cigarettes'.[8] At the other end of the spectrum are those who see no such prospect,

claiming, for example, that 'only the most naive or captured advocates for vaping could fail to acknowledge that the tobacco industry wants people who vape to smoke and vape, not vape instead of smoking'.[9] This chapter explores the motives for and potential consequences of the tobacco industry's engagement in harm reduction and, in particular, the emerging e-cigarette market.

9.2 The tobacco industry and e-cigarettes

E-cigarettes have emerged as a significant component of the market in nicotine products with astonishing rapidity, both in the UK and globally. The market research company Nielsen identified e-cigarettes as the fastest-growing product in British supermarkets during 2014, with sales across large grocers increasing by almost 50%.[10] A report on the UK market in nicotine vapour devices by the industry analysts Euromonitor suggested even greater growth, with a category that was worth only £25 million as recently as 2011 having reached overall sales of £459 million in 2014. This growth also reflected changing consumer preferences, with first-generation ('cigalike') devices (see Chapter 5) being displaced in the UK by the rapid expansion of tank systems and of e-liquids, which experienced value growth of 110% and 145% respectively in 2014.[11] This shift is also strongly evident in other leading western European markets, although 'cigalikes' retain majority shares in both Russia and the USA.[12] The UK e-cigarette market is now estimated to be the world's second largest, being exceeded only by the USA,[13] whereas global sales of an estimated $US6.5 billion now dramatically outstrip the declining international market for NRT (US$2.4 billion), and are equivalent in value to cigarette sales in the world's 20th-largest cigarette market.[12]

Having perhaps been taken by surprise by the rise of e-cigarettes, the transnational tobacco companies have all now committed to major initiatives in this emergent industry. A key moment was the April 2012 acquisition of the e-cigarette brand blu™ by the US-based cigarette manufacturer Lorillard for $US135 million,[14] marking the tobacco industry's first major foray into the e-cigarette market. In December 2012, British American Tobacco (BAT) became the first leading tobacco company to buy a British e-cigarette manufacturer through its purchase of CN Creative, the maker of Intellicig.[15] This complemented BAT's earlier formation of what was billed as a stand-alone start-up company, Nicoventures, to 'focus exclusively on the development and commercialisation of innovative regulatory approved nicotine products'.[16] All of the leading international cigarette manufacturers have now made substantial acquisitions or launched strategic initiatives in nicotine products, principally in e-cigarettes. Altria and Philip Morris International (PMI) manage vapour brands including Mark Ten, Nicolites and the heat-not-burn product iQOS; BAT brands include Vype, Intellicig and an inhaled nicotine device called Voke; Japan

Tobacco International have purchased E-Lites and launched Ploom; RJ Reynolds have developed Vuse and Revo, whereas Imperial Tobacco launched Puritane through its Fontem Ventures subsidiary and, in July 2014, obtained the blu™ brand that was sold as part of Reynolds' takeover of Lorillard.[11–12,17]

These investments have, to date, been weighted heavily towards first-generation 'cigalikes', which mimic tobacco cigarettes more closely, but tend to deliver lower doses of nicotine than, later-generation devices (see Chapter 5), and it has been suggested that this is a deliberate strategy to avoid promoting products likely to be effective in aiding cessation.[18] Recent developments suggest diversification, with tobacco companies looking beyond 'cigalikes': the Vivid Vapours e-liquid brand has become increasingly prominent in the UK after its acquisition by PMI, and the blu™ product range is expanding via its e-liquid portfolio.[19] Investments in heat-not-burn technology (positioned as reducing risks associated with combustion by electronically heating tobacco rather than burning it[6]), as well as in non-tobacco nicotine products (see Chapter 5), further increase the diversity of tobacco company initiatives in reduced risk products, and PMI's launch of its iQOS Heatsticks, under its flagship Marlboro brand in test markets in Japan and Italy, suggests that this development is of major strategic importance to PMI.[20] It does appear that tobacco industry efforts to build a market for reduced-risk products are now centred on vapour devices, as epitomised in July 2015 by PMI announcing the dissolution of its *snus* joint venture with Swedish Match while extending its international strategic collaboration with Altria in vaping products.[21]

The engagement of the tobacco industry in the reduced-risk product sector is thus changing rapidly, and in relation to e-cigarette products is likely to continue to do so, given, among other things, the expected changes in regulatory context, new patterns of ownership and investment, the currently fragmented market, absence to date of dominant brands, and continuing technological innovation and shifting consumer preferences. Such uncertainties notwithstanding, however, rapid growth in the e-cigarette market is predicted to continue over the next few years, with Euromonitor suggesting that the global market for vaping products could reach US$50 billion by 2030. This is clearly a substantial and enticing prospect from a commercial perspective, although it needs to be interpreted alongside an expectation that it will remain a fraction of the market in tobacco products, with cigarettes remaining the dominant product category.[22]

9.3 E-cigarette marketing

The first television advertisement for an e-cigarette, promoting the then independently owned E-Lites brand, was broadcast in the UK in January 2013.[11] This was followed a year later by advertisements for Vype, an e-cigarette

marketed by BAT and representing the first overt paid-for television advertisement by a tobacco company in over two decades,[23] and then, later in 2014, by advertisements showing the act of vaping for the VIP e-cigarette brand.[24] Such developments occurred amid considerable ambiguity about how and whether existing regulatory frameworks applied to reduced-risk nicotine products. This led to a public consultation by the Committees of Advertising Practice,[25] followed by the issuance of specific guidance[25,26] intended to govern the period until the implementation of more stringent regulation of advertising, sponsorship and promotion under the 2014 revision of the EU Tobacco Products Directive 2014/40/EU.

The development of television advertising campaigns forms one strand of an extensive array of marketing, sponsorship and promotional efforts that have contributed to the rapid growth of the e-cigarette market. Sports sponsorship deals, for example, have included Nicolites partnering with Birmingham City Football Club, whereas E-Lites secured distribution deals and designated vaping areas in Celtic and Rangers football stadiums in Glasgow, and invoked the strong association between tobacco and motorsport in announcing its sponsorship of the British Superbike Championship.[27–29] E-Lites secured the first product placement for e-cigarettes in a music video by the artist Lily Allen. Packaging innovations have included 'smart packs' produced by blu™ e-cigarettes that vibrate and flash a blue light when within 50 feet of other users, and which can transmit to Facebook and Twitter profiles, whereas Vapestick has created a retro-style computer game named *Electronic cigarette wars*. PMI also offered retailers free retail display shutter cases heavily branded with its Vivid e-liquid and Nicolites e-cigarettes, in preparation for the second stage of UK point-of-sale display legislation, which prohibited point-of-sale display of any tobacco product from April 2015.[30]

Such high-profile activity is indicative of the recent rise of e-cigarette promotions across multiple fields, driven by rapidly escalating expenditure. During 2013, around £8.4 million was spent in the UK promoting five leading brands (E-Lites, Vype, SkyCig, NJOY King and Gamucci) across press, television, radio, the internet and outdoor media, figures that were to be dwarfed in 2014[31] with BAT's television advertising for Vype as part of a £3.6 million marketing campaign and Skycig announcing investment in a £20 million marketing campaign.[27] A similar surge in marketing spending has occurred in the USA, where a study of advertising spending across television, print, radio and the internet found that expenditure in the second quarter of 2013 amounted to $US28 million, some eight times more than that for the equivalent period in 2012.[32]

This escalation of marketing expenditure reflects the increased resources available following the wave of investments in e-cigarettes by the tobacco industry, with the latter's engagement in marketing raising distinct concerns.

Looking at the future development of the market in vapour devices from a commercial perspective, this represents both opportunity and risk, because leading tobacco companies 'have the capital to turn e-liquid brands into household names but also the reputational impairment to attract draconian regulation to the category'.[19] In this context, discussions about how to regulate the marketing of e-cigarettes are inevitably coloured by the tobacco industry's long-standing global reliance on advertising and marketing to promote and maintain cigarette consumption, particularly by targeting young people.[33,34] Health campaigners have raised concerns about the extent to which some e-cigarette advertising has sought to replicate imagery and themes that have long been central to marketing cigarettes. Magazine adverts for e-cigarettes in the USA have, for example, been seen as depicting equivalents to the rugged masculinity of the Marlboro Man or the glamorous independence of the Virginia Slims woman, sponsorship of sports and music events, and the development of sweet flavours are seen as enhancing appeal among youth, and blu™ e-cigarettes' use of a cartoon 'Mr Cool' evoked the notorious Joe Camel cartoons.[35,36] In the UK, rules on advertising limit such opportunities and the Advertising Standards Authority recently upheld complaints about an advert for VIP e-cigarettes that showed a woman vaping 'in a sultry and glamorous way', creating a strong association with traditional smoking and thereby 'indirectly promoting the use of tobacco products'.[37] Complaints about a UK advert for Vape Nation were upheld as encouraging use of e-cigarettes among ex-smokers.[37]

Maintenance of extensive marketing freedom and potentially controversial promotional strategies for e-cigarettes has been defended as likely to appeal to smokers,[38] and it has been argued that excessive regulation is likely to protect the market monopoly of tobacco cigarettes by inhibiting competition from e-cigarettes.[39] Analyses from a social marketing perspective, however, have emphasised risks associated with e-cigarette marketing in general, and the role of tobacco companies within such activities in particular.[15,28] In presenting the promotion of e-cigarettes as a reinvention of tobacco marketing, de Andrade *et al*[28] highlight the active promotion of dual use, in which marketing activities are identified to have been 'promoting long term use as a permanent alternative to tobacco, and a temporary one in public places where smoking is banned'. An analysis of the marketing strategy of tobacco company-owned e-cigarettes for Cancer Research UK was organised around a distinction between marketing targeted at potential consumers and those activities oriented towards 'stakeholders', such as policymakers and public health agencies[28] (Table 9.1).

Although debate about the potential for such campaigns to renormalise or inadvertently promote smoking continues, attention is increasingly focused on the tobacco industry's use of e-cigarettes and the wider harm-reduction agenda to rebuild its links with policymakers, and public health and other key stakeholders. [28]

Table 9.1 Tobacco-owned e-cigarettes – the marketing strategy[15]

Marketing challenge Who	Marketing strategy Consumers	Stakeholders
Objective	Long-term sales of tobacco through 'next-generation' product (especially in developed countries), profit maximisation	Responsibility, legitimacy, credibility, access to policymakers/regulatory processes, public–private partnership, scientific proof
What	Reduced-harm product, safer alternative to cigarettes, used for pleasure, lifestyle products	Harm reduction
How	**Product**: safe nicotine, used anywhere, flavoured lifestyle products	**Product**: harm reduction
	Price: financial – affordable; psychological – safer and glamorous	**Price**: financial – priceless, saving lives; psychological – it would be negligent to ignore this offering
	Promotion: where tobacco products cannot be advertised, lifestyle and celebrity	**Promotion**: health bodies/experts, charities, politicians, regulators
	Place: everywhere tobacco is available, company websites, point-of-sale displays	**Place**: regulated space
	Positioning: safer smoking alternative, necessity, capitalise on consumer's preference	**Positioning**: differentiation from NRT products, reframe perceptions of nicotine use, alternative for those who cannot or will not quit

9.4 Undermining tobacco control

The recognition of a fundamental conflict between public health objectives and tobacco industry interests has become a central tenet of tobacco control, epitomised by Article 5.3 of the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC), which requires countries to protect the setting and implementation of tobacco control policies from the industry's commercial and other vested interests.[40] The emergence of a distinctive model of

health governance, centred on minimising engagement with the industry,[41] has led to tobacco companies experiencing increasing political marginalisation and difficulty obtaining access to policy elites.[42,43] In this context, investments in harm reduction and e-cigarettes offer potential opportunities to claim legitimacy in re-engaging with policymakers, and even to rehabilitate what has become a pariah industry. If realised, these opportunities may therefore undermine tobacco control.

Tobacco companies have long sought to redress the challenge of a toxic reputation by seeking to establish partnerships or common ground with public health researchers and advocates. A key element of PMI's 'Project Sunrise' in the mid-1990s, for example, was to 'enhance our credibility' by linking with 'moderate' tobacco control organisations on issues such as youth access legislation.[44] Tobacco companies' interest in the concept of harm reduction increased markedly following a 2001 Institute of Medicine report,[45] driven by recognition of a dual opportunity to both '(re-)establish dialogue with and access to policymakers, scientists and public health groups and to secure reputational benefits via an emerging corporate social responsibility agenda'.[46] The emergence of pure nicotine alternatives to traditional forms of tobacco consumption has thus created increased opportunities for both interaction with policymakers and the depiction of common ground with public health. In the context of a public consultation on the future of the NHS, for example, Imperial Tobacco met with the then minister for public health,[47] and subsequently made a submission in which the company invoked its interests in harm reduction to argue against exclusion from policymaking and to position itself as a potential partner for the government.[48] Several tobacco industry submissions to a Department of Health consultation on the future of tobacco control similarly used interests in harm reduction as a basis for suggesting that it could positively contribute to the challenge of reducing health inequalities.[49]

Exploiting such opportunities was a key part of the remit of Nicoventures following its establishment by BAT. In 2012, Nicoventures initiated a medical education plan named the Smoking Harm Reduction Education Programme (SHARE), holding a series of meetings with healthcare professionals, including a round table at the Royal Society of Medicine, and publishing proceedings in *GP* and *Pharmacy Magazine*. In June 2013, Nicoventures approached public health officials across various regions in the UK to discuss harm reduction and regulation, with a sales representative describing the company as complying with the regulatory standards required of a pharmaceutical company.[50] BAT also appointed Dr Richard Tubb to their board of directors in January 2013, describing this former physician to the president of the USA and ex-director of the White House Medical Unit as 'a prominent and well respected expert in the field of tobacco harm reduction' whose appointment 'further demonstrates our commitment to putting science at the heart of our business'.[51] The company

devoted its 2013 sustainability focus report to the issue of harm reduction, depicting BAT as a potential partner in a public health revolution; this included an endorsement of the group's strategy by Dr Delon Human, a global health consultant and former head of the International Food and Beverage Alliance, as having the expertise and public commitment to harm reduction to suggest that 'BAT could become part of the solution to addressing the epidemic of tobacco-related disease'.[50,52] The report claims that '(m)ore collaboration between the tobacco industry, academia and tobacco research centres is … key to establishing an evidence-based regulatory framework to assess new products'.[52]

Alongside such examples of formal endorsements, tobacco companies have also opportunistically cherry-picked statements from leading public health organisations and researchers so as to imply common ground and a shared perspective. The harm-reduction section of the PMI website[53] cites a 2014 report from Public Health England (PHE) as recognising a need for 'appropriate regulation, careful monitoring, and risk management' for harm-reduction products;[54] the citation is presented under a headline claim that the 'public and private sectors are starting to embrace the public health opportunity new products provide',[53] but does so without noting that the PHE report highlights the involvement of the tobacco industry among 'potential hazards, unintended consequences, (and) harms to public health'.[54]

A key element of the strategic value of harm-reduction discourse to tobacco companies is its ability to polarise opinions held by those involved in tobacco control policy, fracturing the remarkable degree of political consensus that has characterised the tobacco control movement and been central to its success.[55] PMI's 'Project Sunrise' centred on the recognition of unity as a key strength of tobacco control, and promoting division was seen as critical to combating the movement's success. The company's strategy sought to exploit latent tensions between groups that it labelled 'moderates' and 'prohibitionists',[44] and this finds strong contemporary echoes in the depiction of competing wings of tobacco control comprising 'pragmatists' who favour harm-reduction approaches being opposed by 'idealists'[56] or 'zealots'.[57]

In this context, the very public dispute in 2014 between competing perspectives on harm reduction via 'duelling letters' from public health researchers and practitioners to the director-general of WHO, Dr Margaret Chan, appears very welcome from a tobacco industry perspective.[58] The initial open letter of 24 May 2014 with 53 prominent signatories was prompted by a concern that harm reduction was being 'overlooked or even purposefully marginalised'[59] in preparing for the forthcoming sixth Conference of Parties of the WHO FCTC. The letter began to receive significant media coverage on 29 May 2014,[60,61] and on the same day BAT issued a press release calling 'for tobacco harm reduction to be adopted as a progressive public health policy'.[62] A quotation from a

subsequent letter remains prominent on the harm-reduction pages of BAT's website,[63] emphasising 'the importance of dispassionate presentation and interpretation of evidence' and the challenge to find 'an appropriate framework' of regulation balancing opportunities and risks.[64] These twin themes are also repeatedly invoked in the company's subsequent 2014 harm-reduction report. Its introduction by chief executive Nicandro Durante suggests that 'the challenge is that these are new products which many governments are still unsure how to regulate' and cites 'the growing weight of evidence and arguments in support of harm reduction'.[65] The report highlights a call from a paper by three of the letter's signatories for regulatory decisions to be 'proportional, based on evidence, and incorporate a rational appraisal of likely risks and benefits',[66] presenting a variation on BAT's long-standing claim to 'support sensible regulation'.[67]

Although neither the reputational management nor policy engagement opportunities afforded by harm reduction have yet been exploited with success that can be considered transformational, a number of strategically valuable 'wins' for the tobacco industry can be identified. Notable here is the success of BAT's Nicoventures in securing marketing authority from the UK Medicines and Healthcare products Regulatory Agency (MHRA) for its nicotine inhaler Voke, a success has been described as 'an important waypoint on the industry's journey to self-rehabilitation'.[56] Vype, also owned by BAT's Nicoventures, is marketed as a 'pharmaceutical-grade product' and sold via Lloyds Pharmacy, whereas Puritane e-cigarettes, owned by the Imperial Tobacco subsidiary Fontem, are exclusively available in Boots. Such distribution deals are inconsistent with advice from the Royal Pharmaceutical Society,[27] and both bring reputational benefits of association with prominent high-street chemists and create strategic opportunities. Puritane's deal with Boots is seen as leaving it well placed to benefit from any reclassification of e-cigarettes to 'directly rival smoking cessation aids'.[11]

9.5 E-cigarettes and the future of the tobacco industry

Tobacco companies' investments in e-cigarettes, as with earlier incarnations of the harm-reduction debate, have been characterised by considerable uncertainty, false starts and fluctuations, and there is nothing to suggest that the recent developments outlined above constitute a fixed and settled strategic direction, whether for specific companies or for the industry as a whole. There is, however, now a sufficient basis to draw some preliminary conclusions informed by marketing campaigns, investor presentations and stated strategic priorities. Such conclusions need to be informed by the historical experience of how and why tobacco companies viewed earlier reduced-risk products, with which striking similarities are becoming evident. One potential parallel has recently been drawn

in light of the history of NRT,[68] via tension between two competing conceptions of NRT as a therapeutic device to aid cessation and as a cigarette alternative capable of delivering nicotine in the 'right way'. This analysis highlights the dangers of the potential of e-cigarettes being 'easily compromised in the hands of tobacco companies, reflected by their tendency for imagining nicotine replacements … as creatively complementing rather than creatively destroying the market for combustible tobacco products'.[68]

More broadly, the tobacco industry's recent involvement with e-cigarettes carries echoes of its earlier rise to dominance of the Swedish *snus* market via acquisitions and joint ventures between 2001 and 2009,[69] eg an analysis of BAT corporate documents from this period yielded no substantive evidence of the company encouraging smokers to switch permanently to smokeless tobacco, but indicated instead that these were essentially defensive investments that protected the status quo and the dominance of the cigarette by shifting '*snus* from a threat (a product that may have competed with cigarettes) to a major opportunity' that presented common interests with public health and an alternative future amid long-term decline in cigarette sales.[70]

One significant difference that emerges from comparison with the *snus* experience is the prominence afforded e-cigarettes and reduced-risk products in contemporary investor presentations. This contrasts with a near absence of *snus* from earlier BAT and PMI presentations, which suggest that *snus* was not central to business strategy.[70] The reformulation of BAT's vision statement to become 'the world's best at satisfying consumer moments in tobacco and beyond'[71] indicates newfound strategic centrality for nicotine projects, mirrored in PMI's designation of reduced-risk products as 'our greatest growth opportunity'.[72] Although the reputational and stakeholder engagement advantages of e-cigarettes for tobacco companies are clearly considerable, this does seem also to represent a consumer market in which growth prospects are being taken seriously.

The extent to which this constitutes a transformation of the strategic landscape for tobacco companies should not, however, be overstated. To return to the image of creative destruction, the emphasis seems to be very much on e-cigarettes creatively complementing conventional products within an expanded portfolio, not on displacing the industry's ongoing reliance on the conventional cigarette. Hence BAT has been unequivocal that their 'ambition remains to lead the global tobacco industry',[71] retaining confidence in the growth of the global tobacco business and developing their portfolio of 'beyond tobacco products' within a single integrated view of the consumer. New products are therefore positioned alongside traditional cigarettes, combustible innovations and non-combustible offers in creating multiple satisfying 'consumer moments'.[73] Similarly, PMI chairman Louis Camilleri's speech to the company's 2015 annual meeting emphasised that 'we expect our combustible products to be the core of our

profitability growth for many years to come', notwithstanding the significance attached to investing in and developing reduced-risk products.[74] The decision to launch the company's heat-not-burn iQOS system under the Marlboro brand is also consistent with ongoing concerns that tobacco companies are using e-cigarette marketing to promote dual use,[28] thereby complementing and sustaining rather than challenging the future dominance of the cigarette.

Any suggestion that tobacco companies are using investments in e-cigarettes as a vehicle to secure their long-term exit from the cigarette market therefore looks like misplaced optimism. Their engagement in harm reduction is likely to be better understood in terms of exploring an emerging opportunity that can buttress their core business, and promise the maintenance of both their licence to operate and the prospect of rehabilitation. Appraising the implications of this perspective for the broader role of harm reduction within the future of tobacco control remains contentious, but it does serve to highlight the ongoing importance of protecting health policy from tobacco industry interference and of maximising compliance with guidelines for the effective implementation of WHO FCTC Article 5.3.[75] Although the most optimistic interpretations[8,76] of increased tobacco industry interests in reduced-risk products might suggest the prospect of some degree of shared interest with public health, the economic and political contexts within which such products are being promoted suggests that any such appraisal is dangerously naive and holds the potential significantly to undermine tobacco control policy and practice internationally. Interests in e-cigarettes and other reduced-risk products create important strategic opportunities for the tobacco industry, and therefore compound the complexities confronting public health in dealing with the harm-reduction agenda. The appropriate response is therefore to strengthen and broaden protections against conflicts of interest, protecting 'tobacco control activities from all commercial and other vested interests related to [e-cigarettes], including interests of the tobacco industry'.[77]

9.6 Summary

- The e-cigarette market has demonstrated massive growth in value and, until relatively recently, has been driven by independent e-cigarette companies.
- This success represents a potential challenge to the traditional business model of the tobacco industry, but also creates important commercial and political opportunities.
- After some delay the tobacco industry is now engaging in the e-cigarette market, and the possible reasons for doing so include:
  - promotion of low-efficacy products that are likely to fail and hence minimise the threat to tobacco sales
  - use of intellectual property rights to bring legal challenges against competitors

- ensuring a share in the emerging e-cigarette market to harness a new, disruptive technology
- using these products to sustain tobacco smoking by promoting them as a complement rather than an alternative to tobacco
- using the products also to promote smoking through advertising and promotion to adults and children
- attracting customers who currently use competitors' tobacco products
- creating justification to re-engage with policymakers, hence undermining the WHO FCTC (Article 5.3)
- exploiting harm reduction to build credibility in corporate social responsibility initiatives
- using harm reduction as a pretext to engage with and disrupt the activities of scientists and advocates in tobacco control.

> The engagement of the tobacco industry in the e-cigarette market thus represents a significant potential threat to UK national and global tobacco control.

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10 Regulating nicotine products in the UK

10.1 What does nicotine product regulation need to achieve?

Products are regulated to ensure that they are safe and fit for purpose; the general product regulations that apply to all consumer products sold in the UK, and their equivalents in other countries, are intended to achieve this for general consumer goods. In the case of products for which safety is particularly important, these general product regulations are often supplemented or superseded by higher levels of specific safety regulation, with medicines, for example, being required to meet especially high standards of manufacturing, safety, product information and efficacy. The overall purpose of all of this regulation is, however, to ensure that consumers can access products that serve their purpose within reasonable bounds of safety, quality and efficacy.

The rationale for regulating nicotine products is the same as for any other, but is complicated by the fact that the market leader in nicotine products in the 20th and 21st centuries, the cigarette, is so intrinsically hazardous that it is beyond the scope of conventional general product regulations, and as an addictive product is too entrenched in society to be amenable to prohibition. It is therefore important that the approach to regulating non-tobacco nicotine products recognises the need not only to meet the general requirements of safety and fitness for purpose, but also to encourage the development and uptake of competitive alternatives to the fatally toxic product currently chosen by most habitual nicotine users. Therefore, although regulation of all products should be proportionate to their potential hazard, proportionality in nicotine regulation must also incorporate the consideration that regulation that discourages or delays the development and use of non-tobacco nicotine is likely, in effect, to sustain tobacco smoking and hence perpetuate harm to smokers and wider society.

This report has argued that nicotine use, of itself, presents relatively little risk to users or wider society, and that most of the harm that arises from nicotine use is attributable to the vehicle of delivery, with tobacco smoke being by far the most hazardous. It therefore follows that, although the ideal course of action for any smoker is to quit smoking and all nicotine use, quitting smoking by long-term

substitution with a less hazardous nicotine source is the next best option. Nicotine regulation should therefore be designed to make non-tobacco nicotine a more attractive, available and affordable option for smokers than cigarettes, to prevent, as far as possible, uptake of nicotine use by never-smokers, particularly children, and to make smoked tobacco products as unappealing as possible.

When the RCP last reported on nicotine regulation in 2007,[1] the range of available nicotine products fell into three classes: smoked tobacco, smokeless tobacco and nicotine replacement therapy (NRT). We argued then that the prevailing regulatory structure intrinsically favoured smoked tobacco over both NRT, which was regulated as a medicine, and smokeless tobacco, of which the lowest-hazard product, Swedish *snus,* is prohibited in the UK. The emergence of e-cigarettes has added a whole new product class to this range, and this spectrum of choice is likely to be increased still further by new technologies in development (see Chapter 5). The nicotine regulatory framework has also undergone substantial change since 2007.

This chapter describes recent developments and impending changes in UK nicotine regulation, identifies key areas of concern, and discusses alternative approaches that might increase the public health benefit accrued from the emergence of e-cigarettes and other non-tobacco nicotine. The discussion is based in the UK setting and pertains to the three broad types of nicotine product available on the UK market: tobacco, unlicensed nicotine products (predominantly e-cigarettes) and nicotine products that are licensed as medicines.

10.2 Current regulation of tobacco, and licensed and unlicensed nicotine products

10.2.1 Tobacco products

Since 1998, a comprehensive tobacco control strategy has been introduced in the UK, the component measures of which are discussed in more detail in Chapter 3. Regulatory approaches have included: reducing affordability by increasing taxation and reducing the size of the cheap and illicit market; imposing packaging and labelling requirements (including the implementation of standardised packaging legislation from May 2016); prohibiting all advertising, promotion and sponsorship; restrictions on where, how and to whom tobacco products can be sold; and smoke-free policies determining where tobacco can be used. After unsuccessful attempts to regulate the cigarette itself by restricting tar levels, regulation of product contents and emissions has not been extensively pursued, other than to prevent fires by reducing ignition propensity. The overall package of tobacco control policies in place in the UK is one of the most

advanced in the world, with the UK currently highest in the European tobacco control league table.[2] The new EU Tobacco Products Directive (TPD)[3] will, from May 2016, impose a range of new restrictions on tobacco products, which include a minimum pack size of 20 cigarettes (and 50 g hand-rolling tobacco), restrictions on the shape of packs, combined pictorial and text health warnings that cover 65% of the front and back of the pack, and prohibition of flavourings including, after a delay, menthol.

10.2.2 Unlicensed nicotine products

E-cigarettes (most of which contain nicotine) and other unlicensed nicotine products are currently regulated in the UK by the EU General Product Safety Directive. This has recently been supplemented by legislation in England imposing a minimum purchase age of 18 years, which is currently in the process of being introduced elsewhere in the UK.[4] General product regulations do not require products to be tested before being put on the market, but do allow retrospective action to remove products found to be faulty or harmful. In July 2015, the British Standards Institute (BSI) published a fast-track voluntary standard for e-cigarettes (PAS 54115), which was sponsored by the Electronic Cigarette Industry Trade Association (ECITA (EU) Ltd) and facilitated by the BSI.[5,6] This standard gives guidance on the manufacture, import, labelling, marketing and sale of vaping products, including e-cigarettes, e-shishas and e-liquid mixing kits. However, at the time of writing it is not clear how widely this standard is being adopted by manufacturers and importers.

E-cigarette marketing in the UK has to comply with compulsory advertising codes administered by the Advertising Standards Authority (ASA). Although those codes contain general rules that apply to all advertising, concerns about the promotion of e-cigarettes led the ASA to introduce sector-specific rules in November 2014.[7] These require the following of e-cigarette advertising: to be socially responsible; not to promote any design, imagery or logo that might be associated with a tobacco brand or show the use of a tobacco product in a positive light; to make clear that the advertised product is an e-cigarette and not a tobacco product; not to undermine quit smoking messages; and not to contain health or medicinal claims unless the product holds a medicines licence. There is a commitment to review progress with these rules after 12 months.

Although not subject to the smoke-free legislation that prohibits tobacco smoking in enclosed public places and workplaces, some businesses and organisations prohibit e-cigarette use in places where this legislation already prohibits smoking. Given the lack of evidence on the harmfulness of e-cigarette vapour to others (see Chapter 5), it would be inappropriate for national legislation to prohibit their use in public places and workplaces. At the time of

going to press, an attempt by the Welsh government to legislate to ban the use of e-cigarettes in some enclosed places and workplaces had failed and was considered unlikely to be reintroduced in the next parliament after the elections in May.[8]

There are some circumstances, such as prisons and mental health settings, where tobacco smoking is particularly prevalent. The option to use e-cigarettes where tobacco smoking is banned could help to introduce and sustain fully smoke-free policies, eg the South London and Maudsley NHS Foundation Trust implemented a policy that allows some types of e-cigarette to be used, as part of a care treatment pathway, in private spaces or grounds where smoking is prohibited.[9] Prisons in England and Wales have made single-use e-cigarettes available for sale to prisoners as a smoking substitute, in preparation for implementing fully smoke-free policies across the prison estate which started in late 2015.[10]

10.2.3 Licensed nicotine products

Nicotine products licensed as medicines, generally known as nicotine replacement therapy (NRT), have been available in the UK since 1980. They were initially licensed by the Medicines Control Agency (MCA) for use to relieve nicotine withdrawal symptoms during attempts to quit smoking, and were subject to an extensive range of cautions and contraindications that arose from the use of comparison of adverse effects with those of placebo, rather than continued smoking.

The MCA was replaced in 2003 by the UK Medicines and Healthcare products Regulatory Agency (MHRA), which was established with a wider remit, including a new objective to make 'an effective contribution to public health'. In 2005 the MHRA made some substantial changes to their regulation of NRT products in response to a review and recommendations by the Committee on Safety of Medicines, an advisory committee to the MHRA.[11] These included the adoption of smoking rather than placebo as the comparator for NRT, which allowed some contraindications (eg stable cardiovascular disease) that inhibited use of NRT by smokers to be removed, extending the licence for NRT to include pregnant smokers, and smokers aged 12 and over, and allowing some NRT products to be used for cutting down in order to quit, as well as for abrupt quitting. There has also been a progressive relaxation of restrictions on the availability of NRT over recent years, starting in 2001 when prescriptions of NRT products became reimbursable through the NHS, and subsequently through extensions to retail availability by allowing NRT products to be sold by general retailers as well as pharmacies. Direct advertising of NRT to the public is permitted subject to regulations[12] requiring the following from promotions: they are not misleading and do not imply that products are 'safe'; they are compliant with the details listed in the summary of product characteristics; they are presented objectively to encourage rational use of

the product; and they are not directed exclusively or principally at people aged under 16. Provision of free samples of NRT for promotional purposes remains prohibited. Since 2007, NRT sold over the counter has been subject to VAT at a reduced rate of 5% to help make products more affordable.[13]

In 2010, the MHRA expanded the indication for NRT to allow long-term use as a harm-reduction alternative to smoking for those who were unwilling or unable to quit.[14] The question of whether e-cigarettes should be regulated as medicines was considered by the MHRA at this time, which proposed that nicotine be deemed a medicine by function, thereby requiring that e-cigarettes should either be licensed as medicines or removed from the market. However, as immediate classification as medicines would have caused all e-cigarettes on the market at the time to be withdrawn, and hence potentially cause the many smokers who had already switched from using tobacco cigarettes to e-cigarettes to go back to tobacco smoking, the MHRA consulted on options[15] that included implementing medicines regulation immediately, or after a delay allowing e-cigarette manufacturers and importers to comply, or else imposing no additional regulation. The proposed licensing option was described by the MHRA as 'light touch' and presented as a simplified, and hence quicker and less costly, route to medicines licensing. In particular, the proposed 'light touch' approach assumed that any product that delivered nicotine to a degree comparable with existing licensed nicotine products was clinically effective, thus removing the requirement for manufacturers or importers of e-cigarettes or other nicotine-containing products to carry out clinical trials to demonstrate efficacy.

The consultation received over 1,000 responses, most of which came from e-cigarette users opposed to any regulation, or else supporting regulation introduced in a way that allowed e-cigarettes to remain available to them. Responses from public health organisations, including the RCP, were generally supportive of 'light touch' regulation, but most recommended a delay to allow time for manufacturers to comply. Support for immediate regulation, with removal of unlicensed products from the market within 21 days, came from organisations including pharmaceutical companies, pharmacist and trading standards groups, and Imperial Tobacco.[15] The MHRA responded by allowing e-cigarettes to remain on the market pending further consideration, and in 2013 announced that it would require all nicotine products to be licensed as medicines from the date of implementation of a revision of the TPD (see Section 10.3 below). The TPD version under consideration at that time required medicines regulation for all but very-low-dose products. The MHRA later rebadged the medicines licensing process for nicotine products as 'right touch' regulation.

In 2014, a revised version of the TPD, which superseded the MHRA proposal by providing an alternative route to market for e-cigarettes without a medicines licence, was negotiated and agreed.[3,16] Medicines regulation remained an option

for manufacturers and importers of e-cigarettes, and the MHRA continues to encourage companies to apply voluntarily for licences.[17] However, licensing is no longer mandatory and, at the time of going to press in early 2016, only one e-cigarette, owned by British American Tobacco (BAT), had been awarded a medicines licence by the MHRA and was not yet commercially available.[18] It is not known whether medicines licence applications have been made for other e-cigarette products. A medicines licence has, however, been awarded to a nicotine inhaler (not an e-cigarette) called Voke, developed by Kind Consumer and licensed to BAT, but at the time of going to press this product had not been marketed.[19]

10.3 The 2014 EU TPD

The 2014 revision of the EU TPD,[3] which comes into effect from May 2016, imposes significant new regulations on nicotine products, including e-cigarettes and refill containers that do not have a medicines licence. Although limited areas of flexibility in implementation for member states remain, the main provisions of the TPD in relation to e-cigarettes are as follows:

1 Manufacturers and importers of e-cigarettes must provide a detailed notification to the government-appointed 'competent authority' of a range of details relating to each product, and make this information publicly available. Non-compliant products can be manufactured until 20 November 2016 and sold until 20 May 2017. Products already on the market by 20 May 2016 must be notified by 20 November 2016. New products or substantial modifications introduced into the market between 20 May and 19 November 2016 must be notified at least 1 day in advance of going on sale. From 20 November 2016 all new products or substantial modifications must be notified 6 months in advance of going on sale.

2 Required details include: quantification and toxicological data for all ingredients and emissions, including when heated, and their potential health and addictive effects; nicotine delivery and uptake; a description of the product components and production process; and a declaration of responsibility for the quality and safety of the product when used under normal or reasonable foreseeable conditions.

3 There will be a limit on total nicotine content in e-cigarettes, which will be allowed to contain a maximum of 2 mL nicotine solution at a maximum nicotine concentration of 20 mg/mL. Refill containers will be subject to a maximum volume of 10 mL. Nicotine and all other ingredients used in manufacture must be of high purity and not pose a risk before or after heating, and substances other than those declared should be present only in trace quantities, which are unavoidable during manufacture. Products must be child and tamper proof, and protected against breakage and leakage.

4 Nicotine doses are required to be delivered at consistent levels under normal conditions of use.

5 Products should include a leaflet, which, among other things, contains instructions, warnings, and information on contraindications, possible adverse effects, addictiveness and toxicity. Outside packaging must list ingredients, nicotine content and delivery per dose, carry a batch number, and a health warning stating 'This product contains nicotine which is a highly addictive substance'. Outside packaging must not include any promotional element or feature to suggest that the product is less harmful or has other health or lifestyle benefits.

6 Cross-border advertising, sponsorship and promotion in the press and broadcast and internet media are prohibited, as are cross-border sales unless subject to a registration scheme. Domestic advertising through billboards, at point of sale, on public transport or other local media is permitted unless prohibited by domestic legislation, as is under consideration in Scotland. Provision of information about products online is still legal.

7 Manufacturers and importers must deliver an annual submission on their products to governments, which should include comprehensive data on sales volumes, consumer preferences, mode of sale and market developments. These submissions should be made publicly available unless classified as trade secrets.

8 Manufacturers, importers and distributors of products are required to establish and maintain a system for collecting information about all the suspected adverse effects on human health. Corrective action is required if there are reasons to believe that products are not safe or of good quality, or not conforming to the directive.

9 Regulation of flavours, and age of sale, remains the responsibility of member states.

At the time of going to press, the UK government's intention to transpose the TPD into UK law was still the subject of a legal challenge by an e-cigarette company, Totally Wicked. However, in December 2015 the advocate general dismissed this and other challenges to the TPD[20] and, although a final court ruling is not due until 4 May, it now seems likely that the TPD will be implemented as originally proposed on 20 May 2016. The UK competent authority for e-cigarettes under the EU TPD will be the MHRA.[21] From 20 May 2016, therefore, all e-cigarettes sold in the UK will be regulated by the MHRA either under the provisions of the TPD or as medicines, or both.

10.4 Advantages and disadvantages of medicines and TPD regulation of non-tobacco nicotine

The impending need for e-cigarettes and other non-tobacco nicotine products, either currently on the market or in development, to comply with one of the above regulatory options has significant implications for suppliers of these devices, and for wider public health. Both approaches have significant advantages and disadvantages, which suppliers will have to balance in their decision on which route or routes to pursue. These are as follows.

10.4.1 Medicines licensing

Key advantages to manufacturers who pursue medicines licensing include:

- higher consumer confidence in product quality and safety
- relief from TPD limits on nicotine solution concentration and volume
- freedom to advertise on TV, radio and in printed media, in line with MHRA rules[12]
- freedom to make justified health claims in relation to quitting and harm reduction
- no obligation to carry health warnings informing consumers that nicotine is addictive
- eligibility for use in, and for subsidised prescription through, the NHS
- potentially subject to 5% rather than 20% VAT in the UK.

The main disadvantage of medicines licensing is the cost in time and money of the application process itself, and of the much higher manufacturing standards required of medicines. It is understood that the MHRA estimates first application costs at between £252,000 and £390,000, and annual recurring costs at between £65,000 and £249,000 for each product.[22] In practice, however, it is likely that application costs incurred by companies inexperienced in negotiating this regulatory system may be significantly higher, whereas the additional cost of manufacturing to the medicines standard is estimated at several million pounds.[22] These financial and related opportunity costs inevitably represent a significant barrier to innovation and market entry for new licensed nicotine products, and favour larger, better resourced entities such as pharmaceutical and transnational tobacco companies. Licensing and presentation of products as medicines may also undermine the perception of e-cigarettes as a consumer rather than a medical product, and hence inhibit experimentation and use.

That only one licence has been awarded to an e-cigarette product in the 5 years since the MHRA announced its 'light touch' licensing option, despite the rapid growth and hence evident value of the e-cigarette market and verbal reports from

the MHRA that 'several' e-cigarette companies had enquired about licensing, indicates that mandatory medicines regulation, had it been imposed as originally intended by the MHRA, would indeed have resulted in a period of several years in which no e-cigarettes were available for sale in the UK. Mandatory medicines licensing, as originally proposed, would therefore have been counterproductive to public health. Given the high product quality and safety standards that medicines licensing guarantees, as well as the option of providing products on prescription to those on low incomes, it is clearly desirable that the range of e-cigarette products available to consumers and health professionals includes some that are licensed as medicines. As recommended elsewhere,[22] a review of the MHRA licensing process for e-cigarettes, to minimise the extent to which licensing procedures and demands unnecessarily obstruct the progress of new medicinal products to market, is clearly needed.

10.4.2 TPD regulation

At the time of writing, the exact detail of how the proposed TPD regulation will operate has not been published. It appears likely, however, that regulation under the TPD will offer e-cigarettes and other non-tobacco nicotine products a route to market that is less onerous, and hence quicker and less expensive, than medicines regulation.

The principal benefits of TPD regulation to consumers are that they will ensure that products that claim to deliver nicotine actually do so, and therefore that consumers are likely to find them effective, and provide reassurance that toxins and other by-products in vapour are at known and pragmatically low levels, thus protecting consumers from easily avoidable harm. Although it is inevitable that these reporting and performance requirements will impose costs on manufacturers and importers, these TPD measures appear to be congruent with the basic regulatory objective of ensuring that products are fit for purpose, and reasonably safe.

Other measures imposed by the TPD on e-cigarettes are less overtly constructive, however. The cap on nicotine concentrations may limit the effectiveness of e-cigarettes as a smoking substitute, particularly for heavier smokers. The derogation to member states of limits on the use of flavours, which may be a significant source of oxidant activity in e-cigarette vapour[23] (see Chapter 5), may result in marked differences in relative potential harm of e-cigarettes available in different member states. Restrictions may also result in non-compliance. The restrictions on e-cigarette marketing, in effect limiting these to the point of sale, billboards, bus stops and other advertising that does not cross borders, limits opportunities for inappropriate promotion of e-cigarettes to non-smokers, including children, but also inevitably inhibits promotion to smokers. However,

as most smokers are aware of e-cigarettes, and word of mouth and social media appear to have been the main drivers of use to date, it remains to be seen whether these advertising restrictions will reduce uptake by smokers. The Scottish Parliament is currently considering going further than the TPD to prohibit all advertising of e-cigarettes in Scotland other than at the point of sale.[24]

The requirement for nicotine products covered by the TPD to carry a health warning emphasising the risks of nicotine, when licensed nicotine products do not, appears illogical, as does the restriction on statements comparing the relative risks of e-cigarettes and tobacco cigarettes. The health warning required under the TPD provisions may also reinforce misperceptions about nicotine (see Section 10.7 below).

A further concern about TPD regulation is that, although a facility to recall products from the market is written into the legislation, there are no powers to relax regulations if usage and innovation are unnecessarily or inappropriately constrained by them. Despite requiring a review 3.5 years after implementation and at 2-yearly intervals thereafter, the previous EU TPD was not revised for 13 years, which is of great concern because much quicker mechanisms of feedback and revision will be required to maximise the benefits as well as minimise the risks of e-cigarettes. For these reasons, it is clearly important that TPD implementation be closely monitored to assess the extent of unintended, as well as intended, effects on the availability and use of non-tobacco nicotine products and, in particular, the consequences of these effects on tobacco smoking rates; it should also ensure that prompt action be taken if TPD regulation proves to work against, rather than for, the benefit of public health. We therefore recommend annual review in the UK.

10.5 The future of nicotine regulation

The UK is currently ahead of most countries in having an agreed set of principles on what nicotine regulation should be designed to achieve, which, as stated in our last report, is that 'The current nicotine regulatory framework needs to be changed so that it encourages as many smokers as possible to quit smoking and all nicotine use completely, and encourages those who cannot quit to switch to a safer source of nicotine, while minimising use by people who would not otherwise have used nicotine products'. The UK government has reinforced the need for harm reduction alongside abrupt cessation and preventive approaches to tobacco control by introducing 'new routes to quitting',[25,26] which involve encouraging smokers to reduce their cigarette consumption as a precursor to complete quitting, manage their nicotine addiction by using a safer alternative product when unable to smoke, and dramatically reduce harm to themselves and

others by using a safer alternative to smoking whenever possible at other times. The UK government also encouraged innovation in the design and marketing of nicotine delivery medicines.[25,27] The MHRA, by relaxing its regulation of nicotine-containing products, is following the same path. In 2013, the National Institute for Health and Care Excellence (NICE) produced public health guidance on harm-reduction approaches to smoking,[28] recommending the integration of harm reduction into NHS and other care pathways. Public Health England[29] has also recently endorsed the principles of the approach set out in the RCP's 2007 report,[1] as has civil society, through the more than 120 health-related organisations that endorsed the recent *Smoking still kills* policy document published by Action on Smoking and Health in 2015.[30]

However, there is still some disagreement about the appropriate level of regulation to meet these principles. Some argue that medicines regulation is the best guarantee of safety, although experience to date suggests that it is too restrictive; some argue that the TPD regulatory framework about to be introduced is too stringent and will undermine the growing market for less harmful alternative nicotine products and restrict innovation; some believe that proposed TPD regulation does not sufficiently address the potential short- and long-term hazards of e-cigarette use which, although likely to be far less than those of smoking (see Chapter 5), could be minimised by medicinal quality and safety standards.

In 2007, the RCP argued for the creation of a regulatory authority specifically designed to cover all nicotine products, and to rationalise regulatory controls by making them proportionate to product hazards.[1] However, experience elsewhere of giving powers to regulatory bodies to cover all nicotine products, eg in the USA and Canada, has not been encouraging (see Chapter 11), although in any case the current aversion to new regulation in the UK does not make a new regulatory body a feasible option at present.[31] Some countries have regulated e-cigarettes in the same way as tobacco products, which we believe to be entirely inappropriate because e-cigarettes do not contain tobacco, and have a very different profile of risk. The political reality is therefore that, for the coming years, unless the legal challenge to the TPD is successful (see below), non-tobacco nicotine products in the UK will be regulated either by the TPD or as a medicine, whereas tobacco products will continue to be limited by the TPD and other national restrictions on use and presentation. It remains to be seen whether this approach will benefit public health by encouraging widespread substitution of smoked tobacco by non-tobacco nicotine in current and future smokers, or will in effect sustain smoked tobacco as the most widely used nicotine product. Much will depend on the approach taken by the MHRA in its role as the competent authority for TPD implementation. It is, however, crucial that the UK takes care to implement the revised TPD in such a way as to minimise, as far as is consistent with the regulations, the burden to manufacturers and importers in

meeting the TPD requirements. It is also important to look again at the medicinal licensing route to market, to try to make compliance more attractive to producers.

10.6 If e-cigarettes are removed from the TPD, what are the alternatives?

Following the December advocate general's legal opinion, it seems likely that regulation under the TPD will go ahead. However, starting from the counterfactual[32] allows options for a more appropriate regulatory structure to be set out within a European context. If the legal challenge to e-cigarette regulation under the revised TPD succeeds, then the previous status will prevail, unless and until the EU develops a new regulatory framework. This could be in the form of a new revision to the TPD, but past experience indicates that this would be likely to take years to materialise. An alternative is the earlier MHRA proposal to regulate all nicotine products as medicines, which to date has proved to operate against public health interest and has, in any case, been subject to successful legal challenges in other EU member states.[32] Another option is to develop harmonised EU-wide standards under the General Products Safety Directive process, which could be less costly for manufacturers and importers to comply with than if each member state developed its own.[33] Such standards could build on those being developed under the European CEN/TC 437 process,[34] which is one of the three European standardisation organisations officially recognised by the EU and the European Free Trade Association (EFTA) as responsible for developing and defining voluntary standards at the European level.

A balance is needed to make products attractive, palatable, satisfying and effective substitutes for tobacco smoking, but also as safe as is reasonably possible, and avoiding use by adolescents and never-smokers. A pragmatic approach would retain the reporting requirements on nicotine delivery and toxins in e-cigarette vapour proposed under the TPD (see Section 10.3 above), adhere to industry and product standards, incorporate obvious safety measures such as childproof and tamper-proof seals and design, and simple advice on how to charge e-cigarettes safely. Advertising should be permitted as per current codes of practice administered by the ASA (with regular reviews to ensure that they remain fit for purpose), with the facility to promote claims of reduced risk in relation to tobacco smoking. Limits on nicotine dose and the requirement for health warnings are probably not appropriate. Any voluntary approach would have to build on the current BSI PAS 54115 standard for product regulation and the compulsory advertising codes, which are currently under review. Alternatives to the above approaches have been suggested, such as regulation as food or cosmetics, but neither regulatory structure seems appropriate to a product that is

inhaled. Whatever approach is taken, it will remain essential to monitor sales and uptake of non-tobacco nicotine products, so that early action can be taken to deal with any trends or patterns of use likely to be detrimental to public health interest.

10.7 Providing consistency in messages to smokers

Recent evidence indicates that smokers are confused about the relative risks of tobacco and e-cigarettes,[35] with many coming to believe that the health hazards of e-cigarettes and tobacco cigarettes are similar. Health professionals are also uncertain about the role of unlicensed nicotine products in healthcare provision, with many feeling reluctant to recommend or endorse a product or product class that is relatively unregulated and has unknown long-term health effects. The introduction of a regulatory structure for unlicensed products, as, for example, proposed under the TPD, may help to overcome these reservations, but there is a need for clear guidance on the role of unlicensed nicotine products in clinical services. The National Centre for Smoking Cessation and Training has produced new guidance on integrating e-cigarette use into the provision of smoking cessation services*, but to date NICE, which has issued extensive guidance on smoking cessation and harm reduction to organisations responsible for public health and tackling tobacco use, health professionals and the general public,[28,36–39] has not addressed this issue. Some stop smoking services are providing advice and behavioural support to smokers interested in using e-cigarettes with encouraging results (see Chapter 6), but health professionals have a wider role to play in providing support and reassurance to e-cigarette users in routine contacts. NICE guidance should, therefore, be updated to include pragmatic recommendations on the role of e-cigarettes in tobacco harm reduction.

10.8 Taxation and price

Price is a key driver of consumer behaviour and, if the potential for e-cigarettes and other non-tobacco nicotine products to act as a widespread substitute for smoked tobacco is to be fully realised, it is crucial that they are priced as advantageously as possible in relation to tobacco. It is for this reason that the VAT applied to NRT products in the UK was reduced from 20% to 5% in 2007. Adding to the tax burden of e-cigarettes by including them in the remit of the EU Tobacco Tax Directive, and hence requiring them to be taxed as tobacco products in addition to the current taxation through VAT,[40] would therefore be counterproductive. A rational approach to nicotine taxation would be to apply

*www.ncsct.co.uk/usr/pub/Electronic_cigarettes._A_briefing_for_stop_smoking_services.pdf

tax in proportion to their hazard, in which case the tax on e-cigarettes and other non-tobacco nicotine products should be held stable or even reduced. The availability of these products as a viable alternative for people addicted to nicotine does, however, provide justification for further tax increases on tobacco.

10.9 Summary

- The ideal regulatory framework for nicotine products is one that minimises harm to society arising from nicotine use.
- At present, nicotine is in widespread use in UK society and the most popular source of nicotine, the cigarette, is by far the most hazardous of those available.
- Nicotine regulatory approaches should therefore be designed to encourage as many smokers as possible to either quit all nicotine use, or switch completely from smoking to an alternative source of nicotine.
- Products are regulated to ensure that they are safe and fit for purpose. Regulation of e-cigarettes and other similar products should therefore aim to minimise potential exposure to harmful vapour constituents, ensure that those that deliver nicotine do so in doses that smokers find satisfying, and encourage substitution for smoked tobacco.
- Regulatory restrictions should therefore be designed to safeguard against unnecessary hazard but should also be proportionate, so as not unnecessarily to inhibit the development, availability and use of viable alternatives to smoking.
- Attempts by the MHRA over the past 5 years to adapt medicines licensing to the rapidly developing e-cigarette market has resulted in the award of only two medicines licences for alternative nicotine products, and no licensed e-cigarette has come to market.
- Regulations for e-cigarettes proposed in the new revision of the EU TPD include quality controls that are more permissive and, in our view, more proportionate than medicines regulation, but include some measures that may inappropriately constrain the e-cigarette market and hence inhibit e-cigarette use.
- At the time of going to press, the TPD regulations for e-cigarettes are still the subject of a legal challenge, but are expected to come into effect from 20 May 2016.
- In the event that the legal challenge succeeds, then a replacement regulatory approach should retain the requirements on reporting of nicotine delivery and toxins in e-cigarette vapour proposed under the TPD, and adhere to industry and product standards.
- To encourage smokers to switch from tobacco to less hazardous sources of nicotine, it is vital that non-tobacco nicotine products be excluded from tobacco taxes.

- It is essential that NICE and other health organisations give clear guidance on the role of e-cigarettes, licensed or unlicensed, in smoking cessation and tobacco harm reduction.
- Effective regular surveillance, which we recommend should be annual, will will be required to monitor intended and unintended impacts of regulation, and a rapid feedback mechanism to allow changes to be made to ensure that the potential benefits of e-cigarettes are maximised, while minimising the risks.

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11 Harm reduction and e-cigarettes: an international perspective

11.1 Harm reduction and tobacco control policy implementation in the UK

Since the publication of the white paper *Smoking kills* in 1998,[1] the UK has introduced an extensive and comprehensive range of tobacco control measures (see Chapter 3) and, having been at the forefront of the global smoking epidemic of the 20th century, is now a world leader in smoking prevention.[2] As a result, UK smoking prevalence has declined substantially and at a rate similar to that observed in other countries that have also implemented comprehensive tobacco control programmes such as Australia, Canada, the USA (in California) and Uruguay.[3,4] As discussed in Chapter 10, in addition to this comprehensive package of conventional tobacco control policies, England has also adopted a complementary harm-reduction policy strand that is embedded in national policy through government health and tobacco control strategies,[5–8] guidance by the National Institute for Health and Care Excellence (NICE)[9] and medicines regulation.[10–12] To our knowledge the UK is the only country in the world to have developed, and to be in the process of implementing, a proactive tobacco harm-reduction approach to smoking prevention. This chapter describes the regulation of e-cigarettes and their use in other countries.

11.2 Approaches to regulation of e-cigarettes in other countries

There is a wide variation in approaches taken in different countries to the regulation of e-cigarettes and other unlicensed, non-tobacco nicotine products. The Institute for Global Tobacco Control (IGTC)[13] summarises policy approaches in a total of 123 countries, including 90 from a World Health Organization (WHO) report on e-cigarette policies.[14] Regulations are evolving rapidly, so the discussion here and in the following sections is based on data reported on the IGTC website* unless otherwise stated, and was accurate at the time of going to press. A discussion of whether published regulations have actually been enforced is beyond the scope of this chapter.

*http://globaltobaccocontrol.org

Also at the time of going to press, the use of e-cigarettes had been completely prohibited in three countries (Cambodia, Jordan and the United Arab Emirates), prohibited in enclosed public places in 15 countries and restricted in a further eight, prohibited on public transportation in 19 countries and restricted (or limited to non-nicotine-containing products) on certain public transportation vehicles in three. Restrictions on purchase or sale comprise: a minimum age for e-cigarette purchase which is usually the same as that for traditional cigarettes, and ranges from 18 to 21 years in 16 countries; prohibition (26 countries) or restrictions (21 countries) on the sale of all types of e-cigarette, including restriction or prohibition of sale or requirement for marketing authorisation for products that have nicotine. Of the 47 countries banning or restricting sale, 33 also prohibited or restricted advertising, promotion or sponsorship of e-cigarettes in their policies. Twelve other countries had explicit promotion bans/restrictions. Two countries (Togo and the Republic of Korea) impose taxes on e-cigarettes in addition to general sales taxes. Similar to the UK, some countries, including the USA, allow e-cigarettes to be sold under general consumer product regulations.

The experience of regulating e-cigarettes along with other nicotine products in a single regulatory structure, as proposed by the RCP in 2007,[15] has since proved less encouraging than hoped. The US Food and Drug Administration (FDA), already responsible for regulating medicinal nicotine, was given responsibility for regulating tobacco products in 2009 and, after a legal decision, announced in 2011 that e-cigarettes would be brought within the remit of tobacco product regulation.[16] At the time of writing the FDA still has more stringent regulations on the sale of medicinal nicotine than the UK, and has not yet put a regulatory process for e-cigarettes in place. Similar to the US experience with FDA regulation, Health Canada's jurisdiction over all tobacco and nicotine products, which regulates nicotine under the Food and Drug Act, requires a marketing authorisation for e-cigarettes containing nicotine, and none has yet been awarded. The effect of this is therefore an actual prohibition of sale. In practice, however, this is not being observed, because a recent Canadian House of Commons' report concluded that e-cigarettes with nicotine were still available in Canada.[17] The report put forward recommendations to develop a new legislative framework for e-cigarettes that would probably allow their sale with nicotine, but with strict controls on marketing in line with those for tobacco.[17] In the absence of a clear regulatory approach by Health Canada at the federal level, a number of provinces have already moved to impose strict regulations on e-cigarettes, including prohibition of use in public places, and of advertising and display.*

*See https://ca.news.yahoo.com/quebec-cracks-down-e-cigarettes-111950643.html, www.huffingtonpost.ca/2015/05/12/provincesmove-to-fill-vo_n_7269088.html and www.theglobeandmail.com/life/health-and-fitness/health/provinces-cities-move-to-regulate-e-cigarettes-in-absence-of-federal-rules/article24490523

Thus, the experience of a single regulatory authority in both the USA and Canada is that, in both cases, the authority has been unable to use its powers effectively to regulate nicotine products in relation to their hazard. Indeed, in both cases, single-body regulation of all nicotine products has probably hindered, rather than enabled, access to reduced-hazard nicotine products.

11.3 Awareness and use of e-cigarettes in different countries

Although there is a rapidly growing body of research on the prevalence of e-cigarette use in adults and adolescents internationally, methodological differences in the definition and measurement of ever, past or current use, particularly in adolescent research, make direct comparisons between studies difficult. This section therefore describes trends internationally drawing predominantly on between-country surveys; Section 11.4 analyses the relationship between regulatory frameworks and use where the evidence enables such comparisons to be made.

11.3.1 Awareness and use of e-cigarettes in adults

Significant variability in the prevalence of use of e-cigarettes has been observed between countries over time, but international surveys demonstrate rapid global increases in e-cigarette use across high-, middle- and low-income countries. The earliest between-country study[18] assessed e-cigarette awareness and use among nationally representative samples of smokers and recent ex-smokers based on 2010–11 data from the International Tobacco Control policy evaluation project (ITC) in the UK, the USA, Australia and Canada. In the UK and the USA, e-cigarettes are regulated as consumer products; in Canada, e-cigarettes containing nicotine require authorisation, but none has been authorised; in Australia there is a ban on the sale and importation of e-cigarettes with nicotine, although there is a mechanism for legal import as an unapproved medicine with a doctor's prescription. Awareness and current use were higher in the two countries where there were fewer restrictions (the USA and the UK).

The Canadian Tobacco, Alcohol and Drugs Survey (CTADS) also found, in 2013, much lower levels of e-cigarette use among adults in Canada than in the UK.[19] Another ITC study compared trends in awareness, trial and use of e-cigarettes among nationally representative samples of smokers and ex-smokers in the UK and Australia.[20] Use (defined as less than monthly or more often) of e-cigarettes was 18.8% in the UK and 6.6% in Australia in 2013; however, use increased at the same rate in both countries between 2010 and 2013.[20] It therefore appears that prohibition may have delayed the uptake of e-cigarettes in Australia, but has not prevented a subsequent rapid increase in use.

A further ITC study[21] presented data from 10 countries (the USA, the UK, Australia, Canada, the Netherlands, South Korea, Malaysia, Brazil, Mexico and China) surveyed at different time points between 2009 and 2013. Again, there was considerable variation in e-cigarette awareness and use among them: awareness varied from 88% in the Netherlands (where e-cigarettes are regulated as a consumer product with some restrictions[13]) to 31% in China (where sale and purchase are legal at the national level, although may be restricted in some regions[22]); self-reported trials varied from 20% in Australia to 2% in China; and current use from 14% in Malaysia (where sale, distribution or importation of unlicensed nicotine-containing e-cigarettes is prohibited; nicotine-containing e-cigarettes can be sold only by licensed pharmacies or registered medical practitioners[13]) to 0.05% in China. These differences are likely to be due in part to differences in survey dates, but also to differences in regulations, market forces and enforcement. However, Malaysia had the highest prevalence of e-cigarette use despite tight restrictions on their sale.

The Global Adult Tobacco Survey[23] has also published data on e-cigarette use among smokers and non-smokers from four middle- and low-income countries: Indonesia (in 2011), Malaysia (2011), Qatar (2013) and Greece (2013). At the time of the surveys, all these countries prohibited the sale of e-cigarettes apart from Malaysia, where only nicotine-containing e-cigarettes were restricted.[13] E-cigarette awareness was highest in Greece (88.5%), followed by Qatar (49%), Malaysia (21%) and Indonesia (10.9%). Current use (daily and non-daily) of e-cigarettes among smokers was again highest in Malaysia (in this survey prevalence of use was 10.4%), followed by Qatar (7.6%), Indonesia (4.2%) and Greece (3.4%). Use of e-cigarettes among non-smokers was highest in Greece (1.3%), followed by 0.4% in each of the other three countries. Again, these data demonstrate little evidence that more restrictive national policies on e-cigarettes result in lower levels of use.

The most recent Eurobarometer 429 survey,[24] carried out in November and December 2014, enabled an assessment of use of both tobacco cigarettes and e-cigarettes (defined as e-cigarettes or other similar electronic device) among people aged 15 years and over in the 28 European Union (EU) member states. France, Cyprus and Estonia (where e-cigarettes are regulated as either consumer or medicinal products according to nicotine content)[13,25] had the highest proportions of respondents stating that they had ever tried e-cigarettes (17% or higher); France and the UK had the highest prevalence of current e-cigarette use (both 4%) and the UK had the highest proportion of current smokers who also used e-cigarettes (11%). Fewer than 1% of never-smokers currently used e-cigarettes in every country surveyed. The most common reason given for using e-cigarettes was to stop or reduce smoking. Across the EU, 14% of smokers or ex-smokers who had tried e-cigarettes reported that they had helped them to stop smoking completely, 13% that they had helped them to stop for a while before

relapsing, 45% that they had not reduced their tobacco smoking and 21% that they helped them to reduce, but not stop, tobacco use. Ireland (24%) and the UK (21%) had the highest proportions of respondents who reported successfully stopping smoking with the help of e-cigarettes. The proportion of smokers using e-cigarettes in their quit attempts was highest in countries regulating them as consumer products: the UK and Ireland (19%), France (18%) and Cyprus (16%). The Eurobarometer noted that there were continuing declines in smoking across the EU at a time when e-cigarette use was increasing, as has been observed in UK surveys (see Chapters 2 and 7) and in the USA.[26]

11.3.2 Awareness and use of e-cigarettes by adolescents

We have been unable to find any survey using a consistent methodology to compare awareness and use of e-cigarettes among adolescents in different countries. Data on people aged 15 and over are included in the 2014 Eurobarometer study referred to above,[24] which reported the prevalence of current use of e-cigarettes among people who had never smoked at 0%, suggesting that there were few such users among young or older people.

Survey data on the prevalence of e-cigarette use in young people at the country level are more extensive, but methodological differences, including the use of different definitions or terms to describe the different stages of e-cigarette use (ever, trial, current use), and differences in age ranges studied, limit the comparability of these findings. A recent review concluded that the common pattern emerging in countries where data were available was of very high awareness and increasing trial of e-cigarettes among young people, but very low levels (3% or less) of regular use.[27] However, there were two countries where current use was substantially higher: Poland (where e-cigarettes are classified as consumer products, but with cartridges subject to regulations on chemical mixtures) at around 30%[28] and Hawaii (where e-cigarettes are classified as consumer products), where 29% of the sample of young people had tried e-cigarettes and 18% had used them in the past month.[29]

Serial surveys of young people in the USA have documented a rising prevalence of ever use of e-cigarettes[30–32] and demonstrated that, as in the UK (see Chapter 7), those who use e-cigarettes are more likely also to smoke tobacco.[31] A cohort study from California[33] found that secondary school pupils who had not smoked, but reported having ever tried an e-cigarette, were more likely at 6- or 12-month follow-up to have ever tried a tobacco cigarette. A cohort study of a national US sample of 694 never-smokers who were classified as non-susceptible to tobacco smoking at baseline in 2013–14, and restudied in 2015,[34] found that the 16 participants who reported ever

having used an e-cigarette at baseline were significantly more likely, after controlling for other covariates, to have become susceptible to cigarette smoking or have smoked at least one puff of a cigarette at follow-up. However, claims that these findings indicate that e-cigarette use may cause uptake of tobacco smoking have been challenged on the grounds of common liability (see Chapter 8), lack of measures of more regular use of either e-cigarettes or tobacco cigarettes, and that, during the time that these studies have been carried out, the prevalence of tobacco smoking among young people in the USA fell to a 22-year low.[35–37] There is evidence from the USA that adolescent smokers using e-cigarettes are also more likely to use products such as tobacco hookahs or shisha and blunts (marijuana and tobacco).[38]

11.4 Patterns of use across countries with different regulatory regimens

Although standardised between-country data on e-cigarette use over time are generally lacking, it is clear from the evidence presented above that, whereas countries with more liberal policies (which typically involve regulating e-cigarettes as consumer products) have higher levels of adult e-cigarette use, prohibition and tight restrictions have not prevented increasing uptake of e-cigarette use among adults in other countries. For adolescents the data are less clear but, as an example, the 2013 CTADS of Canadians aged 15 years and older found that 9% had ever tried an e-cigarette, with trials being higher among young people aged 15–19 years at 20%.[19] This latter percentage is not dissimilar from the percentage who had tried e-cigarettes in the UK in 2015 (12.7% of 11- to 18-year-olds). Again, therefore, it appears that prohibition of sale has had little effect on experimentation with e-cigarettes in Canada, at least not in the younger age groups in these studies. A recent US study assessed the impact of state bans on sales of e-cigarettes on smoking rates among 12- to 17-year-olds across the USA,[39] and found that reducing access through age-of-sale laws increased smoking among 12- to 17-year-olds, suggesting that restrictive regulations on e-cigarettes may be counterproductive.

In the EU, as set out in Chapter 10, the introduction of the Tobacco Products Directive[40] will lead to a common regulatory platform from May 2016, although individual member states will be able to go further in prohibiting all advertising (as is under consideration in Scotland), restricting or prohibiting their use in public places (recently under consideration in Wales), legislating for an age of sale (set at 18 in England), restricting or prohibiting flavours, and implementing additional taxation. Monitoring the impact of these regulatory changes, and of their variations across the EU, will provide a useful indicator of the impact of different regulatory approaches.

11.5 Harm reduction and the WHO Framework Convention on Tobacco Control

E-cigarettes were not available when the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) was first negotiated. However, the FCTC[41] alludes to harm reduction in Article 1, where tobacco control is defined as including 'harm reduction strategies that aim to improve the health of a population by eliminating or reducing their consumption of tobacco products and exposure to tobacco smoke'. This is further considered in Article 5.2(b), which states that 'each Party shall, in accordance with its capabilities … adopt and implement effective legislative, executive, administrative and/or other measures and cooperate, as appropriate, with other Parties in developing appropriate policies for preventing and reducing tobacco consumption, nicotine addiction and exposure to tobacco smoke'. The FCTC does not have a remit for the regulation of medicinal nicotine, although it has produced guidelines on tobacco dependence and cessation (Article 14 of the FCTC).[42]

The growing popularity of e-cigarettes led to discussions on their role at the biennial FCTC Conference of the Parties (COP), the governing body of the treaty, in 2010 and 2012. At the 2012 COP5, the WHO was asked to produce a report on 'options for prevention and control' of e-cigarettes (referred to as electronic nicotine delivery systems or ENDSs) for consideration at the next COP.[43] The WHO report to COP6[14] focused on three areas of concern: health risks to users and non-users; efficacy in helping smokers to quit smoking and (ultimately) nicotine use; and interference with existing tobacco control efforts and implementation of the FCTC. The main focus of the report was on the latter issues, but, in terms of health risks, the report concluded that 'well-regulated ENDS' would be likely to be less toxic than tobacco cigarette smoking for established adult smokers. In relation to smoking and nicotine cessation, the report concluded that e-cigarettes might have a role in supporting attempts to quit for individuals who had failed treatment, or who were intolerant of or refused conventional treatments. The report discussed and recommended parties to regulate e-cigarettes as either medicines or tobacco products, in accordance with the FCTC.

In response, the Framework Convention Alliance (FCA, a coalition of over 350 non-governmental organisations from over 100 countries) developed a consensus position.[44] The FCA concluded that, because of differences in regulatory systems and national circumstances, it would be difficult to reach consensus at COP6 on specific regulatory approaches to ENDSs. Instead, the FCA position paper set out the following principles as a starting point for reaching agreement on the role and regulation of e-cigarettes, for consideration by the COP:

1 The global burden of death and disease from tobacco is primarily caused by smoking.

2 Although quitting tobacco use is paramount, quitting nicotine use altogether is the best option.

3 For those unable to quit, switching to alternative sources of nicotine that are less harmful than tobacco can reduce, often very substantially, the harm that smoking causes to the individual.

4 The benefits of such an approach would be maximised if uptake were limited to existing smokers who are unable to quit.

5 The risks of such an approach would be minimised by limiting uptake by never-smokers, in particular among young people, and by taking measures to protect non-users and discourage long-term dual use.

6 There could be negative unintended consequences from over-regulation, just as there could be from under-regulation.

7 The involvement of tobacco companies in the production and marketing of e-cigarettes is a matter of particular concern, because there is an irreconcilable conflict of interest between those profiting from the sale of tobacco and public health.

After discussion by the COP, a decision was taken to ask parties to the FCTC to take note of the WHO report, and the WHO was asked to produce a further report with updated intelligence for consideration in time for COP7, which will be held in the last quarter of 2016. The decision also asked parties to the FCTC to consider 'prohibiting or regulating' e-cigarettes, suggesting that this could be as tobacco, or medicinal or consumer products, and to comprehensively monitor their use.[45] E-cigarettes will therefore be discussed again at the next WHO FCTC COP in November 2016 in India.

In the case of tobacco, a range of comprehensive tobacco control measures has been found to be effective and been codified in the FCTC. E-cigarette regulation does not sit appropriately within the context of the FCTC, the explicit objective of which is control of the supply of and demand for a lethal product, tobacco, through the introduction of increasingly restrictive and prohibitive regulatory measures. Furthermore, there is as yet an insufficient evidence base or range of national experience that would enable the development of a detailed set of recommendations for the specific approaches to many of the complicated regulatory issues that these products raise at the global level.

11.6 Summary

- A variety of different approaches to tobacco harm reduction and regulation of e-cigarettes, including extension of regulations for alternative products to e-cigarettes and including complete prohibition, have been adopted in different countries around the world.
- The prevalence of use of e-cigarettes is rising or already significant in some countries that have attempted to prohibit use, suggesting that prohibition is not an effective approach to regulation.
- Surveillance data are limited in most countries, as are the use of consistent terminology and standardised measures of e-cigarette use, so between-country differences are difficult to assess.
- There is general recognition that comprehensive monitoring and surveillance of the evidence and national regulatory experience of e-cigarettes are essential.
- The WHO recognises a role for e-cigarettes as part of a harm-reduction strategy for smokers, but in the context of a recommendation by the FCTC COP that they be regulated to minimise any potential risks.
- However, currently there is no consensus about what this regulatory framework should be, and as yet an insufficient evidence base, or range of national experience, that would justify the development of a regulatory structure at a global level.

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12 Ethics and conclusions

12.1 Moral and ethical considerations of harm-reduction strategies

This report has made the case for applying harm-reduction principles to tobacco smoking, principally to prevent avoidable harm to smokers. There is, however, a strong ethical dimension to the use of harm-reduction strategies in tobacco control that were discussed in some detail in our earlier report;[1] these strategies include a duty to ensure that options to reduce harm are made available to smokers, and provision of a substitute for tobacco to smokers, particularly those on low incomes, to protect them from the hardship that might otherwise arise from applying tax increases to provide a stronger fiscal disincentive to smoke. There are, however, wider considerations arising from concerns over the broader effects of applying harm-reduction strategies in society.

The central ethical concern is with harm, and whether the harm-reduction strategies identified and adopted will, in practice, reduce it. However, there are also wider questions relating to the ethos of harm reduction itself, over and above any examination of the effectiveness of particular strategies. In some areas of public health (particularly in drug control, alcohol control and sex work control, for example), there is a societal concern that the behaviour being targeted is inherently wrong. Drug addiction, prostitution and drunkenness, it is sometimes thought, are inherently bad, and the proper focus of public health should not be on making the use of drugs, or sex work, or excess alcohol consumption safer; it should be on eradicating these behaviours. In tobacco control, however, this argument is rarely made: few people acknowledge smoking as a behaviour that is immoral. Its harms are real and serious, and inflicting these on unwilling third parties is wrong, but these concerns fit quite naturally within the harm-reduction model.

A second concern is with the distribution of harm. A harm-reduction strategy could be considered to have failed if the net harm were reduced, but the distribution of harm changed in a way that was unjust, eg if, as a result of the harm-reduction strategy, some socially or economically vulnerable group

became *more* at risk of harm, or systematically less able to benefit from smoking cessation and prevention strategies. The benefit to existing smokers of switching to e-cigarettes is clear, but, if large numbers of never-smokers were to take up e-cigarette use, they would be exposing themselves to health risks that would otherwise be avoided, and financial costs, which are of particular detriment to poorer smokers, that they would not otherwise incur. At present this does not appear to be happening, but it could occur, for example, if the addictive potential of e-cigarettes and other non-tobacco nicotine products increases over time.

A third concern relates to social responsibility: if engaging in harm reduction involves working with corporate actors with a track record of deceit or other socially irresponsible business practices, and particularly of undermining public health, then there is a concern that doing so may have wider ramifications than the harm-reduction strategy itself. Such engagement might, for example, discredit other public health interventions or institutions that are focused on ending these bad practices. We can think of this as 'reputational harm'. Conversely, it may be that such corporate actors acquire some perverse benefit from such engagement: by appearing to be responsible in one area (the provision of reduced-harm products) they might be able to reclaim a good reputation in other areas, however undeservedly. From a 'harm-reduction' point of view, these factors must be considered, but these harms may be inchoate and hard to measure, certainly compared with the real benefits accruing to harm-reduction products in terms of reductions in mortality and morbidity.

Setting aside these objections to harm reduction in principle, we turn instead to the objections that might be raised against particular harm-reduction strategies from within a focus on harm. Obviously, the most important consideration is whether the harm-reduction intervention actually does reduce harm, in terms of reduction of lives (and life years) lost, increase in numbers of smokers who successfully quit smoking tobacco, reductions in the numbers of new smokers, etc. However, as for any other medical or public health intervention, we need to consider any particular strategy in the light of available alternatives: in particular, if we focus on regulation of a tobacco harm-reduction product, we need to ask whether the regulatory mechanism is the most effective in reducing harm, or whether some other approach would be more effective. We need to ask whether adoption of a particular regulatory approach makes the production of some products more likely than others, and whether the products favoured by this approach are, in fact, better from a harm-reduction and public health point of view than those disfavoured. As within the harm-reduction model, the least harmful intervention is the most ethical intervention, we need always to keep in mind that choice of regulatory approach must be seen in ethical terms. The evidence summarised in this report goes some way towards addressing these questions.

12.2 Smoking and public health

Tobacco smoking is the biggest avoidable cause of death and disability in the UK. In 2014, 21% of men and 16% of women were smokers,[2] which in absolute terms represents almost 9 million people. Half these smokers, or 4.5 million people, alive in the UK today will have their lives cut short by smoking and, if their smoking continues unabated, their total loss of life will amount to nearly 90 million years.[3,4] Their smoking will also cause thousands of fetal deaths and cases of childhood illness, and deaths in non-smoking adults, and cost our health services and wider society billions of pounds. This massive burden of death, disability and lost opportunity has been entirely avoidable, and much of it can still be prevented by measures that encourage as many smokers as possible, as soon as possible, to stop smoking. As the biggest beneficiaries of preventing smoking are individuals who are disadvantaged, marginalised or have mental health problems, prevention of smoking will make society both healthier and more equal. Smoking may be less prevalent today than when the RCP published its first report on smoking and health in 1962,[5] but it is still our biggest health problem. All measures that can be deployed to prevent smoking should therefore be applied, as quickly as possible, and to their maximum effect.

12.3 The effect of conventional tobacco control approaches

The UK is a world leader in tobacco control policy. Since the late 1990s, a comprehensive package of policies, including an advertising ban, smoke-free legislation, high taxes, minimum purchase age, mass media campaigns, a point-of-sale display ban and clinical services to help smokers to quit, has been introduced, and will be enhanced in 2016 by standardised packaging legislation. The result in the UK has been the same as in other countries that have followed this approach: smoking prevalence has fallen steadily, but slowly. However, the decline in smoking prevalence that has occurred over recent decades appears to owe more to success in preventing the uptake of smoking: quit rates among established smokers have changed relatively little. However, it is the adults smoking today, particularly those in middle and older age, who will generate most of the burden of death and disability caused by smoking in the short- and near-term future, and it is these adults whom tobacco control policies need to target in particular if this burden of harm is to be reduced. All existing and new policies with the potential to promote smoking cessation, particularly among disadvantaged groups, should therefore be applied to their fullest extent.

12.4 Priorities for conventional tobacco control policy implementation

Of the range of policies available, the UK has already achieved a relatively high level of prohibition of tobacco advertising and smoke-free policy. Opportunities to promote tobacco brands will be further reduced by the introduction of mandatory standardised packaging in May 2016, although a great deal more could be done to reduce exposure of children and young people to the normalising effect of smoking imagery in the media, including films, television programmes, music videos and computer games. Children may also be less likely to grow up thinking that smoking is a normal or aspirational adult behaviour if they were exposed less to smoking behaviour among adults in their everyday lives, which could be achieved by extending smoke-free policies to outdoor areas, eg at school gates, play areas, town centres and other areas where smokers congregate in view of children. Making hospital premises completely smoke free generates an opportunity to initiate and support cessation among the many smokers, and their visitors, who use hospital services. Similarly, making prisons smoke free will provide an opportunity to reduce the very high prevalence of smoking among prisoners. More could also be done to reduce retail availability of tobacco to children, particularly in areas close to schools, and the requirement that tobacco retailers be licensed would be a useful step towards making enforcement of regulations easier. Mass media campaigns are effective in motivating smokers to try to quit, but require funding to achieve and sustain the necessary intensity and salience for success. Cessation services also need to be adequately funded, and in clinical settings integrated much more systematically into routine health service delivery. Large increases in tobacco prices, particularly in the lower cost range of products preferred by low-income smokers, have a particular potential to reduce smoking among disadvantaged groups. Proper funding of enforcement measures against illicit tobacco and measures to curtail the tobacco industries' own involvement in this trade are crucial. All these measures would be likely to help to achieve further reductions in smoking prevalence. However, almost all would be complemented by promoting harm-reduction approaches that encourage smokers, who otherwise prove unwilling or unable to quit smoking, to switch to an alternative, low-hazard source of nicotine.

12.5 Nicotine addiction and its effects

Nicotine is the main addictive component of tobacco smoke. Although other tobacco smoke components probably contribute to the development of nicotine addiction, it is the capacity to achieve rapid increases in systemic arterial levels through pulmonary absorption that makes tobacco smoking particularly addictive, as well as lethal, although factors such as the taste and smell of

cigarette smoke, and the behavioural action of smoking, can reinforce nicotine use and hence themselves become important drivers of continued smoking. At low doses, nicotine is a stimulant, which in the short term increases heart rate and may improve attention, memory and fine motor skills. Although potentially lethal at very high doses, at the blood levels typically achieved by smoking nicotine does not result in clinically significant short- or long-term harms. Nicotine is not a carcinogen; there is no evidence that sustained human use of nicotine alone increases the risk of cancer. It is possible that nicotine exposure during the fetal and/or adolescent periods causes cognitive impairment, but in all other respects, and certainly in relation to tobacco smoke, the real and potential hazards of sustained nicotine use are negligible. The harm of smoking is therefore caused not by nicotine, but by other constituents of tobacco smoke. Non-tobacco nicotine products that reproduce the nicotine delivery and behavioural characteristics of smoking, without the many other toxins in tobacco smoke, therefore have the potential to allow smokers to continue to use nicotine and avoid the significant harm to themselves and others that smoking causes.

12.6 Non-tobacco nicotine products

A wide range of nicotine replacement therapy (NRT) products, licensed as medicines to reduce symptoms of nicotine withdrawal among people trying to quit smoking, is available. In clinical trials, NRT has been shown consistently to be effective in helping smokers to quit smoking. Although initially developed to help people give up all smoking and nicotine use, NRT licences have been extended to include short-term use to relieve withdrawal symptoms during temporary abstinence from smoking, and long-term use as a partial or complete substitute for smoking (harm reduction).[6] These licensed applications of NRT, which are endorsed by the National Institute for Health and Care Excellence (NICE),[7] promote dual use of NRT and tobacco on the grounds that smokers who learn to use NRT in this way are more likely to quit smoking completely.[7] NRT products have to date been produced by pharmaceutical companies and offer high levels of purity and hence safety, such that a smoker who switches from tobacco to NRT use, but continues to use NRT in the long term, probably achieves much the same in health terms as a smoker who quits all tobacco and nicotine use.

The choice of non-tobacco nicotine products in the UK has been substantially extended by the emergence of e-cigarettes, which have to date been marketed as consumer alternatives to smoking. E-cigarettes offer a behavioural experience that is much closer to smoking than is the case with NRT products, and later-generation e-cigarettes appear able to achieve venous nicotine levels similar to those of tobacco smoking. The extent to which inhalation of e-cigarette vapour results in rapid pulmonary absorption remains uncertain, but it seems likely that,

as the technology improves, the degree of pulmonary absorption will increase, making the products more effective as smoking substitutes, but also increasing addictiveness, and hence posing the new ethical problems highlighted above. E-cigarettes generate vapour from a solution that typically contains nicotine, propylene glycol and glycerine, but, in addition to these constituents, e-cigarette vapour contains a variable range of compounds arising from impurities in the solutions or generated by the heating process that produces vapour. There appear to be few, if any, significant short-term adverse effects of e-cigarette use, but adverse health effects from long-term exposure to constituents of vapour cannot be ruled out. Although unknown, the hazard to health arising from long-term vapour inhalation is unlikely to exceed 5% of the harm from tobacco smoke. Switching from tobacco to e-cigarettes is therefore likely to be almost as effective in preventing harm as switching to NRT. However, the recent award of a medicines licence to an e-cigarette product raises the prospect of e-cigarettes with safety profiles similar to NRT becoming available in the near future.

12.7 How smokers in the UK try to quit, and their chances of success

Around one in three smokers in the UK tries to quit each year, but only around one in every six of those who try to quit is successful. Those who try are slightly more likely to be younger and female, and to be in non-manual occupations; those in non-manual occupations are also more likely to succeed. Most of those who try to quit do so without help, or until recently by using NRT bought over the counter. Over the past 3 years, however, e-cigarettes have become the most widely used aid to quitting.

The observational data on quitting used in this report suggest that those who use prescribed medication and behavioural support from a qualified stop smoking adviser (typically through NHS Stop Smoking Services (SSSs)) are two to three times more likely to succeed than those using no help. However, the use of NHS SSSs has declined significantly in recent years, such that they are now accessed by only a small minority of smokers. For reasons that are not clear, those who use over-the-counter NRT appear to be no more likely to succeed in quitting smoking than those using no help, whereas those who use e-cigarettes, or NRT or other pharmacotherapy provided by a healthcare professional, are around 50% more likely to succeed than those using no help at all.

The popularity of e-cigarettes has thus resulted in a substantial increase in the proportion of smokers using effective help to quit. It is probable that adding behavioural support would increase the likelihood of quitting with e-cigarettes still further, and this is an important area for new research. Possible explanations for the popularity of e-cigarettes, and their effectiveness relative to NRT, include

their ability to replace some of the behavioural components of smoking, their relatively high nicotine delivery, the fact that smokers tend to try them for longer and with more frequent dosing than NRT, and their cultural acceptability.

Smokers are motivated to make a quit attempt in particular by cost and health concerns. Price rises, media campaigns and health professional advice are therefore likely to increase the numbers of smokers trying to quit.

12.8 Use of e-cigarettes by smokers and non-smokers

E-cigarettes are used almost exclusively by smokers who are trying to cut down or quit smoking, or who have quit smoking. Among adults, use by non-smokers is extremely rare. A higher proportion of non-smoking children than adults have experimented with e-cigarettes, but most of those who do have smoked in the past, or are current smokers. More than experimental use among children who are not also experimenting with tobacco is rare. Among regular users, whether children or adults, second- and third-generation devices are now much more widely used than first-generation 'cigalike' devices. Fruit flavours are popular among e-cigarette users, whether adults or children.

12.9 Harm reduction and population health

The emergence and consumer success of e-cigarettes, as a partial or complete substitute for smoking, reflects significant potential to reduce the harm caused by smoking to society by encouraging as many smokers as possible to use e-cigarettes, or indeed other non-tobacco nicotine products, rather than tobacco cigarettes. There are many, however, who retain significant concerns over the potential risks and adverse effects of this approach, for both individuals and wider society.

Concerns that e-cigarettes are not hazard free are justified, but this hazard could be minimised by a combination of technological development and appropriate regulation. Concerns that e-cigarettes will be used dually by smokers are inconsistent with current guidance and licence indications for NRT, which encourage dual use as a step towards quitting smoking and of protecting those around the smoker from the harmful effects of second-hand smoke. All the UK evidence, and almost all the international evidence, on the use of e-cigarettes by children and young people to date indicates that concerns about e-cigarettes helping to recruit a new generation of tobacco smokers through a gateway effect are, at least to date, unfounded, although vigilant surveillance is required to ensure that the emergence of any such effect is detected and reversed promptly. Renormalisation concerns, based on the premise that e-cigarette use encourages

tobacco smoking among others, also have no basis in experience to date. Exploitation of e-cigarette advertising as a means of promoting tobacco smoking by tobacco companies is perhaps a more real concern, but will largely be prevented by impending controls on advertising in the EU Tobacco Products Directive (TPD).[8]

12.10 Regulation and harm reduction

It is difficult to determine, and more difficult still to apply, the right level of regulation for reduced-harm products. The wide range of different regulatory approaches adopted in different countries in relation to e-cigarettes, which spans a spectrum from freedom to market as a consumer product to complete prohibition, reflects a desire, on the one hand, to encourage as many smokers as possible to switch from tobacco to e-cigarettes and, on the other, to prevent harm to users or others from e-cigarette use. A risk-averse, precautionary approach to e-cigarette regulation can be proposed as a means of minimising the risk of avoidable harm, eg exposure to toxins in e-cigarette vapour, renormalisation, gateway progression to smoking, or other real or potential risks. However, if this approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer friendly or pharmacologically less effective, or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking. Getting this balance right is difficult.

In the UK, consumer product regulation supported by advertising codes of practice has worked well to date, but does not guarantee that products actually deliver nicotine to a degree that smokers will find satisfying or, more importantly, that vapour is as toxin free as is reasonably possible. Medicines regulation guarantees efficacy and safety, but imposes high manufacturing, compliance and opportunity costs. That even the streamlined Medicines and Healthcare products Regulatory Agency (MHRA) 'right touch' medicines regulation has to date awarded a licence to only one e-cigarette, and none that has come to market, indicates that mandatory medicines regulation of e-cigarettes, although valuable as a complement to other regulatory approaches, is not ideal as a single regulatory approach. EU TPD regulation, if implemented as planned, offers a compromise between these two approaches by requiring emission reporting that will enable consumers to identify the best and cleanest nicotine delivery systems, but includes much, such as health warnings and nicotine content limits (see Chapter 10), that is potentially counterproductive. None of these approaches is therefore ideal, and experience in other countries does not offer better alternatives. The UK needs a nicotine regulatory system that applies controls on products in proportion to their potential harm, to promote innovation and diversity, ensure reasonable levels of protection for consumers and, above all, discourage tobacco use.

The use of reduced-harm products, and hence the health gains that they generate, is also influenced by other regulatory policies. Applying low levels of tax to non-tobacco nicotine products, as, for example, the 5% VAT rate levied on NRT, helps to make reduced-harm products attractive to smokers and offset the potentially regressive effect of tobacco tax increases. Allowing messages on harm relative to smoking in commercial and government media campaigns could help to reverse the growing misconception that e-cigarettes and tobacco cigarettes are similarly harmful (see Chapter 10). Prohibition of use of e-cigarettes where smoking is also prohibited may discourage smokers from trying e-cigarettes, and may also contribute to a false impression that they are similarly harmful. The inclusion of recommendations on use of unlicensed (and, in due course, licensed) e-cigarettes in NICE guidance is another example of an area where policies can change to encourage more smokers to switch from smoking to a non-tobacco nicotine product.

12.11 The tobacco industry and e-cigarettes

Tobacco companies make their money by selling tobacco, and the industry's recent programme of investment and acquisitions in e-cigarettes perhaps indicates recognition that these products represent a disruptive technology that should be harnessed to protect the core business of selling tobacco, exploited to expand tobacco markets or developed as an opportunity to make nicotine products attractive to non-smokers. There is little likelihood that the industry sees e-cigarettes as a route out of the tobacco business, but it is highly likely that e-cigarettes will be exploited to enhance claims of corporate social responsibility, and to undermine implementation of Article 5.3 of the World Health Organization Framework Convention on Tobacco Control.[9] There is no firewall between a 'good' tobacco industry that is marketing harm-reduction products in the UK and a 'bad' one that promotes smoking, or undermines tobacco control activities, in low- and middle-income countries.

12.12 Conclusions

Harm reduction was proposed by the RCP in 2007[1] as a means of reducing still further the vast burden of death and disability that tobacco smoking causes in our society. The evidence summarised in this report demonstrates that the emergence of e-cigarettes has generated a massive opportunity for a consumer- as well as a healthcare-led revolution in the way that nicotine is used in society. As the technology of these and other non-tobacco nicotine products improves, so the vision of a society that is free from tobacco smoking, and the harm that smoking causes, becomes more realistic. Experience to date suggests that, as predicted in principle in the 2007 report,[1] the availability of e-cigarettes has been beneficial to UK public health. There is, however, no room for complacency and

it is particularly important that patterns of use of tobacco and non-tobacco nicotine continue to be monitored closely, and prompt remedial measures applied to deal with changes that are counterproductive to health. The potential for the tobacco industry to exploit and appropriate harm reduction, to undermine public health and bolster sales of tobacco, is a real problem that is likely to become more acute as tobacco companies move into the licensed, as well as unlicensed, nicotine market, but that problem can be managed with vigilance and care. Large-scale substitution of e-cigarettes, or other non-tobacco nicotine products, for tobacco smoking has the potential to prevent almost all the harm from smoking in society. Promoting e-cigarettes, NRT and other non-tobacco nicotine products as widely as possible, as a substitute for smoking, is therefore likely to generate significant health gains in the UK.

12.13 Summary

- Smoking is the biggest avoidable cause of death and disability, and social inequality in health, in the UK.
- Most of the harm to society and to individuals caused by smoking in the near-term future will occur in people who are smoking today.
- Vigorous pursuit of conventional tobacco control policies encourages more smokers to quit smoking.
- Quitting smoking is very difficult and most adults who smoke today will continue to smoke for many years.
- People smoke because they are addicted to nicotine, but are harmed by other constituents of tobacco smoke.
- Provision of the nicotine that smokers are addicted to without the harmful components of tobacco smoke can prevent most of the harm from smoking.
- Until recently, nicotine products have been marketed as medicines to help people to quit.
- NRT is most effective in helping people to stop smoking when used together with health professional input and support, but much less so when used on its own.
- E-cigarettes are marketed as consumer products and are proving much more popular than NRT as a substitute and competitor for tobacco cigarettes.
- E-cigarettes appear to be effective when used by smokers as an aid to quitting smoking.
- E-cigarettes are not currently made to medicines standards and are probably more hazardous than NRT.
- However, the hazard to health arising from long-term vapour inhalation from the e-cigarettes available today is unlikely to exceed 5% of the harm from smoking tobacco.
- Technological developments and improved production standards could reduce the long-term hazard of e-cigarettes.

- There are concerns that e-cigarettes will increase tobacco smoking by renormalising the act of smoking, acting as a gateway to smoking in young people, and being used for temporary, not permanent, abstinence from smoking.
- To date, there is no evidence that any of these processes is occurring to any significant degree in the UK.
- Rather, the available evidence to date indicates that e-cigarettes are being used almost exclusively as safer alternatives to smoked tobacco, by confirmed smokers who are trying to reduce harm to themselves or others from smoking, or to quit smoking completely.
- There is a need for regulation to reduce direct and indirect adverse effects of e-cigarette use, but this regulation should not be allowed significantly to inhibit the development and use of harm-reduction products by smokers.
- A regulatory strategy should, therefore, take a balanced approach in seeking to ensure product safety, enable and encourage smokers to use the product instead of tobacco, and detect and prevent effects that counter the overall goals of tobacco control policy.
- The tobacco industry has become involved in the e-cigarette market and can be expected to try to exploit these products to market tobacco cigarettes, and to undermine wider tobacco control work.
- However, in the interests of public health it is important to promote the use of e-cigarettes, NRT and other non-tobacco nicotine products as widely as possible as a substitute for smoking in the UK.

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Harnessing tobacco harm reduction

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Harm reduction is a successful public health strategy, for example, in minimising the harms of drug use.[1] Tobacco harm reduction[2] should, therefore, be a central strategy of the WHO Framework Convention on Tobacco Control (FCTC) in addition to the measures for demand and supply reduction which are necessary, but not sufficient. WHO FCTC has been influential in encouraging a global response to tobacco control,[3,4] but it has been challenging to show a strong and consistent association between the implementation of FCTC measures and smoking prevalence and cigarette consumption outcomes.[5,6] The FCTC does not prohibit harm reduction approaches but leaves it up to countries to decide how to regulate e-cigarettes and other novel nicotine products.[3] WHO's lack of endorsement of tobacco harm reduction limits healthier choices for the 1·3 billion people globally who smoke and who are at an increased risk of early death.[4]

There is no scientific justification for WHO's position that e-cigarettes and other novel nicotine products should be treated in the same way as tobacco products.[7,8] This position overlooks a risk-proportionate approach. We believe WHO needs to provide positive leadership and technical support to countries as they consider the use of e-cigarettes and other nicotine delivery devices, including snus, pouches, and heated and smokeless tobacco.[9] WHO's current approach to these lower-risk products[10] is to reward countries, such as India, for banning e-cigarettes;[11] 34 countries, primarily low-income and middle-income countries, now ban e-cigarettes.[10]

In some countries, substantial reductions in smoking prevalence have coincided with the uptake of novel nicotine products. In New Zealand, for example, the prevalence of adult daily smoking plummeted from 13·3% in 2017–18 to 6·8% in 2022–23[12] after e-cigarettes became widely available, a 49% decline in 5 years. In the same period, and with the support of the government and regulation of vaping,[13] the prevalence of adult daily vaping increased from 2·6% to 9·7%.[12] New Zealand's recent decline in smoking occurred in the absence of any other major tobacco control policy, apart from the annual cost-of-living price increases.[14] The decrease in smoking during this period in New Zealand shows what can be achieved and exceeds the WHO smoking prevalence reduction goals of 30% over 15 years from 2010 to 2025.[15] The New Zealand 2022 smoke-free legislation includes a "tobacco-free generation", a 90% reduction in smoked tobacco retail outlets, and compulsory denicotinisation of retail tobacco.[16] The New Zealand Government, elected in November, 2023, is committed to reaching the Smokefree 2025 goal of 5% (or less) smoking prevalence for the adult population, but intends to repeal the 2022 smoke-free legislation.[17] However, because of the implementation timelines, fears that this repeal would jeopardise the Smokefree 2025 goal can be allayed; none of the three headline measures would be expected to have an impact before 2025 and might have had negative unintended consequences.[18] Based on recent progress, New Zealand's Smokefree 2025 goal looks likely to be reached by consent rather than coercion and by further support for switching to smoke-free nicotine products.[19]

Other high-income countries have also succeeded in reducing smoking prevalence in association with the use of a range of lower-risk nicotine delivery devices to complement FCTC demand and supply reduction measures. Sweden, with a long tradition of snus use, has the lowest prevalence of adult daily smoking in the world, down to 6% in 2022, accompanied by low mortality from tobacco-related diseases.[20] Norway has had similar success with reducing smoking prevalence in the context of increased use of snus and e-cigarettes,[21] and in England vaping is helping adults to quit smoking.[7,22] The substantial decline in cigarette consumption in Japan is associated with the rapid uptake of products that heat, rather than burn, tobacco.[23] Less progress has been made in low-income and middle-income countries where tobacco control capacity and political will to advance tobacco control measures are weaker, and the potential of tobacco harm reduction is not being realised.[5]

Two concerns suggest why tobacco harm reduction is not more actively embraced, despite its association with reduced smoking prevalence. The first is that, compared with cigarettes, where the damage has been known for more than half a century, the long-term effects of e-cigarettes are unknown. Although vaping may not be risk-free, especially for people who do not smoke,[22] the risks of there being substantial long-term harm from the constituents of e-cigarettes are likely to be low, especially when compared with the damage caused by smoked tobacco.[7]

The second concern is that the widespread availability of e-cigarettes in the absence of adequate controls and regulations encourages youth nicotine dependence and enables the vaping industry to act unethically.[24] There is little evidence to suggest that vaping leads to smoking among youth, and although the proportion of non-smoking youth who vape is increasing, it remains at a fairly low level.[25,26] Stricter regulations, including enforcing sales restrictions, and appropriate health-promoting campaigns are needed to prevent vaping by young people, but these measures must be balanced with the health needs of older adults who smoke and require support to quit.

There is understandable scepticism about the motives of the tobacco industry in selling smoke-free products while continuing to expand tobacco markets in low-income and middle-income countries.[24] To remain profitable, the tobacco industry will eventually need to migrate its global business to less harmful alternatives since cigarettes will no longer monopolise the delivery of nicotine.

The WHO FCTC Conference of the Parties 10 (COP10), the governing body of the FCTC, will be held in Panama on Feb 5–9, 2024. The critical background papers to COP10 recommend treating nicotine products as equivalent to cigarettes and regulating them in a similar way.[27,28] This approach is a retrograde step because they are not comparable products in terms of the damage they cause; after all, it is the burning of tobacco that causes harm, not nicotine.[29] Worse, such a strategy would ultimately favour the global cigarette market and may discourage vaping.

The focus must remain on the central public health problem—the damaging health effects of tobacco consumption. Reducing cigarette smoking is the most effective way to prevent tobacco-related deaths[15] and tobacco harm reduction is the fastest and fairest way to lower smoking prevalence. WHO needs to embrace these innovations in nicotine delivery. Countries that are reaping the benefit of tobacco harm reduction, such as New Zealand, Sweden, Norway, England, and Japan, should encourage participating countries at COP10 to support proposals that will quickly reduce smoking rates. The world's 1·3 billion people who smoke, half of whom will die early, deserve this leadership.

We declare no competing interests. RBe is the Chair of ASH, Action for Smokefree 2025, an incorporated society that campaigns to eliminate the death and harm caused by tobacco. The views expressed in this Comment are those of the authors.

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