

E-cigarettes: an aid in smoking cessation, or a new health hazard?

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Abstract: The issue of electronic cigarettes is one of the most controversial topics in public health. There is intense debate and dividing opinions about their use patterns, health effects and association with smoking. This is expected since they were only recently introduced to the market and they refer to a harm-reduction approach and strategy that is not universally accepted for smoking and tobacco use in the public health community. Three main factors determine the public health impact of electronic cigarettes: (1) their safety/risk profile, both relative to smoking and in absolute terms; (2) their effectiveness for smoking reduction and cessation; (3) the patterns of use by different population subgroups, especially never-smokers, and adoption of use by youth. This analysis presents a brief overview of currently available evidence and gaps in research covering these three factors.

Keywords: smoking, tobacco, electronic cigarettes, nicotine, public health

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Introduction

Smoking is a substantial global public health concern. In 2015, the World Health Organization calculated that 22.7% of the global population above the age of 15 was smoking tobacco cigarettes, which represents 1.1 billion people.¹ Most importantly, there are six million deaths annually due to smoking, and it is predicted that one billion people will die prematurely from smoking-related disease during the 21st century. In the United States alone, cigarette smoking causes about one in every five deaths, with the death toll estimated at 480,000 people every year.² In Europe, the number of annual smoking-related deaths is estimated at 700,000.³ As a result, intensive tobacco control efforts to reduce uptake and convince established smokers to quit have been undertaken over the past decades. Measures such as educational campaigns, taxation, restriction of smoking in public places and providing smoking-cessation services have been used widely to combat the smoking epidemic. Globally, the need to reduce smoking prevalence resulted in the creation of the Framework Convention on Tobacco Control (FCTC) by the World Health Organization (WHO). The treaty came into force in 2005 and comprised 168 signatory countries that shared the common dedication to eliminate

the tobacco epidemic. The responsibility of the FCTC was to develop guidelines and policy options and recommendations that can be implemented globally. To this end, the FCTC created MPOWER in 2008, a collection of policies aiming to reduce demand for tobacco. The core principles of MPOWER are to *Monitor* tobacco use and prevention policies, to *Protect* people from tobacco smoke, to *Offer* help to quit tobacco use, to *Warn* about the dangers of tobacco, to *Enforce* bans on tobacco advertising, promotion and sponsorship, and to *Raise* taxes on tobacco. Although these efforts have substantially reduced smoking prevalence in the past, smoking remains the most important preventable risk factor for morbidity and premature mortality.

Smoking-cessation medications have been developed since the 1970s, starting with nicotine replacement therapies and progressing to oral medications. All medications have been proved relatively safe and to increase the odds of smoking cessation compared to placebo,^{4–8} but the long-term success rate is limited. Nicotine replacement therapies have a success rate of less than 7% when assessing the smoking status at 1 year.⁹ Despite the delivery of the main addictive compound of smoking, nicotine, the limited success of nicotine replacement

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therapies can be attributed to the low speed of nicotine delivery and to the absence of the rituals associated with the psycho-behavioral aspect of smoking dependence.^{10–13} Oral medications also have a low success rate even in well-designed controlled trials,¹⁴ while the effectiveness in real-world clinical practice is even lower.¹⁵ Additionally, a substantial proportion of smokers do not seek help from a smoking-cessation service. As a result, the most popular method for smoking cessation is quitting without any aid.^{16,17} To further enhance the tobacco control goal of reducing smoking prevalence, a strategy of harm reduction for smoking has been proposed. Harm reduction is a strategy and policy of reducing the adverse health consequences of recreational drug use to those who cannot or are not willing to achieve complete abstinence. It was developed mainly for psychoactive drugs and has proven effective in reducing health risks and improving quality of life.^{18–20} This approach has been actively endorsed by authorities such as the WHO, and is now officially legislated in several countries worldwide. A harm-reduction strategy for smoking has been proposed for decades, related to the use of lower-risk alternatives to combustible cigarettes. The basis for this approach was first mentioned by Michael A.H. Russell, who noted in 1976 that the combustion process, rather than nicotine, is responsible for smoking-related disease.²¹ Subsequently, smokeless tobacco products were suggested as a harm-reduction approach.^{22,23} A proof of concept about the use of lower-risk alternatives exists in Sweden, where men have a high prevalence of tobacco use, but most of it is snus rather than tobacco cigarettes. Because of this pattern of tobacco use, Sweden has the lowest death rates from cancer and cardiovascular disease in men compared to any other European Union country.²⁴ However, unlike the situation with harm reduction for psychoactive drugs, tobacco harm reduction remains a controversial issue with strong support and opposition within the public health community.^{25–28}

Electronic cigarettes (e-cigarettes) are electronic devices that evaporate a liquid consisting of humectants (mainly propylene glycol and glycerol), flavorings and nicotine, although solutions are also available without nicotine. They were invented in 2004 and both awareness and use has grown exponentially, especially since 2009.^{29–34} This resulted in a heated debate about the potential public health effects of e-cigarette use. One part of the public health community thinks that

e-cigarettes could help smokers to quit and accelerate the smoking decline by supplementing other tobacco control measures, resulting in a net public health benefit.^{35–37} Another part considers e-cigarettes as a threat that could undo the progress made by the tobacco control movement over the past decades by making smoking and nicotine use socially acceptable again.^{38–40} This analysis will discuss the main factors that determine the public health impact of e-cigarettes and present a brief overview on the evidence related to each factor.

Factors determining the public health impact of electronic cigarettes

Electronic cigarettes could have intended and unintended public health consequences, depending on several factors (Table 1). It is possible to present the calculation of the public health impact of e-cigarettes (and any other tobacco harm-reduction product) with the formula:

$$\text{Public health impact}_{EC} = (\text{hazard}_{SM-EC} \times \text{smoking cessation}) - (\text{hazard}_{EC} \times \text{use among non-smokers}) - (\text{hazard}_{SM} \times \text{smoking initiation})$$

where EC = e-cigarette, SM = smoking, $SM-EC$ = difference in hazard between smoking and e-cigarettes use, hazard_{SM} = smoking initiation due to e-cigarettes (gateway to smoking effect).

The safety/risk profile of e-cigarettes is particularly important. Tobacco cigarette smoke contains thousands of compounds, many of which are officially classified as toxic and carcinogenic. Smoking is a major risk factor for a plethora of diseases, particularly cardiovascular disease, respiratory disease and cancer of the lungs and other organs. The 10-year fatal cardiovascular risk is approximately doubled in smokers compared to non-smokers, while the relative risk for myocardial infarction in smokers aged less than 50 years is four-fold higher compared to non-smokers of similar age.^{41,42} Smokers also have 3–5-fold higher risk for developing chronic obstructive pulmonary disease compared to non-smokers.⁴³ Additionally, one in nine smokers develop cancer, having a 20-fold higher risk compared to non-smokers.^{44,45} Importantly, smoking cessation lowers the risk for developing disease or halts disease progression and improves future prognosis.^{46–48} Therefore, it is very important to assess the relative safety of e-cigarettes compared to tobacco cigarettes.

Table 1. Main factors determining the public health impact of electronic cigarettes.

Factor	Details
Safety/risk profile	The safety/risk profile of e-cigarettes should be determined both relative to smoking, to inform smokers about the relative risks, and in absolute terms to inform never-smokers about potential risks from adoption of use.
Effectiveness on smoking cessation and reduction	The intended use of e-cigarettes (from a public health perspective) would be as smoking substitutes. Studies need to assess their real-world effectiveness in this aspect as well as any possible unintended consequences such as delaying or hindering smoking cessation.
Patterns of use by population subgroups	Ideally, e-cigarettes should be used only by current and former smokers. Their popularity among never-smoking adults needs to be monitored. Additionally, monitoring use by adolescents is important to determine how it affects smoking initiation and prevalence at a young age, which is a major predictor of long-term sustained smoking.

Additionally, their safety/risk profile in absolute terms (i.e. compared to not using any other product) is important in determining the residual risk for smokers compared to quitting without the use of any substitute and the risk of e-cigarettes users who were never smokers. This may be of particular interest for smokers with pre-existing smoking-related disease, since smoking cessation in this population is a very effective secondary prevention measure,⁴⁹ but many smokers fail to quit even after they develop such disease.⁵⁰

A second factor that determines the public health impact of e-cigarettes is their effect on the smoking status and consumption of smokers. The intended role (from a public health perspective) of e-cigarettes is to be used as smoking substitutes. Therefore, their success in achieving smoking abstinence is a major determinant of their public health impact. Reduction in smoking consumption is also expected to result in some benefit, although it will certainly be less pronounced compared to complete abstinence. It should be noted that although there seems to be a dose-response relationship between smoking consumption and duration and disease risk as well as all-cause mortality,⁵¹⁻⁵³ there are conflicting data about the effects of smoking reduction on disease risk.⁵⁴⁻⁵⁷ Since reduction in smoking consumption can vary widely, it will be difficult to quantify the risk reduction among smokers who lower their

smoking consumption. Due to this and for simplification, the effect of smoking reduction is not displayed in the formula above.

The third factor that needs to be considered is the prevalence and patterns of e-cigarettes use in different population subgroups. E-cigarette use is an inhalational habit that closely resembles the act of smoking and can deliver nicotine. These characteristics could create dependence and sustained long-term use by never-smokers, which would result in added health risk compared to not using any inhalational product. Therefore, it is important to assess which population subgroups are using e-cigarettes, with particular attention to the smoking status before initiation of e-cigarette use. Additionally, the adoption of use by adolescents needs to be monitored. Most long-term smokers start at a young age and early initiation predicts regular smoking in adulthood.⁵⁸⁻⁶³ Adolescents are more prone to test things and engage in risky behaviors. In that respect, e-cigarettes could attract their attention and curiosity but could also theoretically serve as a 'distraction' from use of tobacco cigarettes. Another reason for monitoring the prevalence of use among never-smokers is the possibility that e-cigarettes might have a gateway effect to smoking. This means that people who have never and would have never smoked become addicted to e-cigarettes and then transition to tobacco cigarette use. Finally, it is

equally important to assess the popularity of e-cigarettes among smokers. To result in significant public health benefit, any smoking cessation aid needs to be not only effective but also acceptable and popular among the intended population subgroup (smokers). A product that is more attractive for smokers will result in a higher proportion of them quitting or reducing smoking. A characteristic example of how popularity affects the public health outcome comes from the use of snus by men in Sweden. Ramström and colleagues presented aggregate data from Your Country and Your Life (YCYL) 2003–11 studies and reported that the overall prevalence of daily tobacco use among Swedish men was 30.8%.⁶⁴ However, the prevalence of daily smoking was 12.3%, while the prevalence of daily snus use was 20.2% (15.5% non-smoking, 3.0% occasionally smoking and 1.7% daily smoking snus users). Additionally, snus was reported as the most popular smoking-cessation aid among men. The high prevalence of snus and low prevalence of tobacco cigarette use among tobacco users is at least partly responsible for the lowest death rates from cancer and cardiovascular disease that are observed in Sweden compared to any other European Union country.²⁴

An overview of the main findings and challenges in e-cigarette research is presented in Table 2.

Safety of electronic cigarettes

Smoking causes disease after a period of several years. This means that in order to assess the health impact of e-cigarettes compared to smoking in the clinical setting, long-term epidemiological studies are needed. With e-cigarettes being available mostly in the past 10 years, it is not unexpected that long-term epidemiological evidence of their health effects is still not available. However, there is extensive preclinical research, mostly on chemistry and toxicology of e-cigarettes. Tobacco cigarette smoke is a complex mixture of thousands of chemicals, with many of them being linked to cancer and others being linked to cardiotoxicity, respiratory toxicity and genotoxicity.^{65–67} Tobacco cigarette smoke also contains inorganic compounds such as heavy metals. The main pathophysiological mechanisms of causing disease are through inflammation, oxidative stress and DNA damage.^{68–72} Most of these toxins are derived from the combustion process,^{73–75} while some are inherently present in the

tobacco plant or are produced during the curing process of tobacco leaves.^{75–77} The combustion process is critical in the generation of toxic chemicals, with the tobacco cigarette reaching up to 900°C during a puff and burning at more than 400°C between puffs.⁷⁸

The main differences between e-cigarettes and tobacco cigarettes that are expected to largely determine the potential risk discrepancies are the lack of combustion and tobacco in the former. E-cigarettes function by evaporating a liquid, which is rapidly condensed into an aerosol and is then inhaled by the user. The main ingredients in e-cigarette liquids are compounds that have been used extensively in food, pharmaceutical and cosmetic products. In fact, to the best of my knowledge, there is no chemical which was specifically developed to be used in e-cigarettes. Propylene glycol (1,2 propanediol) is a diol (a polyhydric alcohol with a 2-hydroxyl group) that was discovered in 1859,⁷⁹ was recognized as safe for use in food products by the US FDA in 1982⁸⁰ and is also used in pharmaceuticals, including intravenous and inhalational preparations.^{81–83} In the human body, it is mainly metabolized to lactate and then to pyruvate and glucose. Glycerol (1,2,3-propanetriol) is a polyol (a polyhydric alcohol with a 2-hydroxyl group) that exists in nature, is essential for living organisms, was first discovered in 1783 and has been approved for use in food products since 1959.⁸⁴ It is also widely used in cosmetic, pharmaceutical and food products. Propylene glycol and glycerol are mainly used in e-cigarettes as solvents and for the production of visible aerosol. Flavorings are, in most cases, also chemicals approved for use in food products. It should be noted, however, that e-cigarettes introduce a new route of long-term daily exposure to these compounds, through inhalation. There is limited evidence from clinical studies about the effects of inhaling these compounds. This creates uncertainty mainly for the local effects in the respiratory tract, while the metabolic and excretion pathways once absorbed have been clearly determined, raising little concern about potential risks. Studies on exposure to propylene glycol aerosol through inhalation were performed in the 1940s because of observations that it had bacteriostatic and virostatic properties in animals and humans.^{85,86} A study exposing primates to propylene glycol aerosol for 12–18 months showed no adverse effects on any organ.⁸⁷ More recently,

Table 2. Overview of main findings and challenges in e-cigarette research.

Factor	Findings	Challenges
Safety/risk profile		
Chemistry	Most potentially toxic compounds are either absent or substantially lower compared to tobacco cigarettes. Some studies show extremely high levels of some toxic compounds (mainly aldehydes). E-cigarettes emit a lot of small particles that easily penetrate deep into the lungs and are absorbed.	Many studies do not ensure realistic use conditions and avoidance of 'dry puffs'. Lack of standardized testing conditions. The amount of exposure determines the risk. Particle size and number have little value in assessing harm without considering the composition of the particles.
Toxicology	Potential mechanisms for adverse health effects identified (e.g. inflammation and oxidative stress). Comparison with smoking almost always shows reduced toxicological effects.	Difficult to interpret absolute effects in the context of clinical risk. Toxicological studies have more value when comparing e-cigarettes with tobacco cigarettes at equivalent exposure levels, to examine relative effects.
Clinical	Limited studies show some clinical benefit (asthma, blood pressure). Other studies show adverse effects, mostly relevant to sympathetic stimulation. Biomarkers of exposure studies show reduced exposure among e-cigarette users, similar to smoking cessation.	Acute effects rarely predict long-term harm. Sympathetic activation has been observed in caffeine intake or post-exercise, with no prognostic value. Long-term epidemiological studies are needed to accurately quantify the absolute and relative risk.
Efficacy in smoking cessation		
	Randomized controlled trials show limited efficacy. Cohort studies show mixed results. Reviews have identified positive, no or negative effects of e-cigarettes in smoking cessation. Cross-sectional studies show e-cigarettes help smokers quit.	Low quality of available evidence. Randomized controlled trials need to use new-generation products and allow product choice to participants. Cohort studies until now suffer from strong bias. Ever or current use is a poor measure to assess efficacy in smoking cessation.
Use by population subgroups		
Adults	Experimentation has grown among adults, including non-smokers. Regular use is largely confined in current and former smokers. Dual use of tobacco and e-cigarettes is the most common pattern with few exceptions (UK).	Regular use is an important factor in estimating public health effects. Dual use is vaguely defined and includes people with very diverse use patterns; better definition needed. The health effects of dual use will be determined by the amount of smoking reduction.
Youth	Experimentation has grown among youth, including non-smokers. Regular use is largely confined in current and former smokers; poly-tobacco use is common. Ever e-cigarette use at baseline predicts ever smoking at follow up in youth.	Among youth, e-cigarette use predicts tobacco cigarette use and vice versa. Regular use, nicotine use and smoking status of users are important determinants of potential harm. Smoking prevalence decreases considerably in youth, but how this is affected by e-cigarettes is unknown.

studies of short-term exposure in animals and humans did not find any significant adverse health effects.^{88,89} Concerns exist for flavorings because

some compounds, although safe to be ingested, might be harmful when inhaled. Examples of this include the food-approved additives diacetyl and

acetylpropionyl. These compounds have been associated with respiratory dysfunction and linked with rare cases of bronchiolitis obliterans, an irreversible obstructive lung disease involving the respiratory bronchioles.^{90–92} A study evaluating 159 sweet-flavored e-cigarette liquids found either or both of these compounds in 74.2% of the tested samples.⁹³ These chemicals are also present in tobacco cigarette smoke at levels 1 to 2 orders of magnitude higher compared to the e-cigarette liquids tested; however, in e-cigarettes they represent an avoidable risk since they are added as ingredients, while in tobacco cigarette smoke they are formed due to combustion.⁹⁴ It should be mentioned that no documented cases of bronchiolitis obliterans due to smoking or e-cigarette use have been reported, but smoking is a major risk factor for respiratory dysfunction and chronic obstructive lung disease, and these chemicals could contribute to this high risk.

The chemistry profile of e-cigarette liquid and aerosol is substantially less harmful compared to tobacco cigarettes for a variety of potentially toxic compounds such as tobacco-specific nitrosamines, phenols, nitrates, polycyclic aromatic hydrocarbons, aromatic amines and carbon monoxide.^{95–100} Many of the toxins present in tobacco cigarette smoke are absent from e-cigarettes, while others are present in substantially lower levels. For example, traces of tobacco-specific nitrosamines are present in e-cigarette liquids, resulting in non-detectable levels to the aerosol unless the samples are spiked with standard nitrosamine solutions.⁹⁹ Concern has been recently raised about the emissions of carbonyl compounds from e-cigarettes. While several studies have shown substantially lower levels of formaldehyde, acetaldehyde and acrolein compared to smoking,^{96,98,100–103} some recent studies have found levels similar to or higher than in tobacco cigarette smoke.^{104–106} Carbonyls can be derived from thermal degradation of the main ingredients of e-cigarette liquids.¹⁰⁷ However, a major sensory parameter of e-cigarettes is that liquid overheating creates a strong unpleasant taste that users avoid. This phenomenon, called ‘dry puffs’ has been presented in the literature since 2013 and has been explained in detail.^{101,108,109} Being an organoleptic (sensory) characteristic, it is by definition subjectively defined by e-cigarette users who try the e-cigarettes at the power settings and puffing patterns used in the laboratory. None of the studies finding very high levels of carbonyl

emissions checked for the generation of dry puffs; as a result, the laboratory testing setup could have represented unrealistic conditions and be irrelevant to true human exposure. One study already showed that a previous report about high aldehyde emissions¹⁰⁴ was indeed associated with dry puff conditions that regular users identified.¹¹⁰ Further research into carbonyl emissions from e-cigarettes is warranted, as well as into the dry puff phenomenon, to understand inter- and intra-individual differences in detecting the unpleasant taste. In any case, it is very important to ensure that realistic use conditions are adopted during aerosol collection. Another issue that has been raised is the emission of metals.^{96,111,112} Electronic cigarettes are metallic structures that are expected to emit metals to the aerosol. Some metals have been found at levels higher compared to tobacco cigarettes.¹¹¹ Although, in general, the levels detected are below safety limits for inhalational medications or for occupational exposure and do not seem to represent any substantial health risk, emissions can be further reduced by using appropriate materials.¹¹³ There is a lot of discussion about the number and size of particles emitted from e-cigarettes.^{114–116} Although particle size determines the penetration into the respiratory tract and subsequent absorption potential, it is misleading to assess the risk profile without taking into account the composition of the particles. The potential toxicity of the emitted compounds is the major determinant of adverse health effects, while particle size will affect the potential for penetration and exposure of tissues. Therefore, if toxic compounds are transferred in small particles into the lungs, the health risk will be increased compared to larger particles. No adverse effects are expected if small particles are composed of inert and harmless compounds. In general, it is important to note that a basic principle in toxicology, as defined centuries ago, is that ‘nothing is a poison and everything is poisonous; solely the dose determines that a thing is not a poison (*Sola dosis facit venenum*)’.¹¹⁷ Therefore, finding potentially toxic emissions from e-cigarettes is only a marker of *potential* toxicity but is not enough to quantify the risk. The accurate determination of amount of exposure under realistic use conditions is an absolute requirement to determining the potential health effects of any product.

Toxicological studies have detected several mechanisms through which e-cigarettes could cause adverse health effects, including oxidative stress,

inflammation and gene expression.^{118–121} Other studies have found minimal effects when compared with smoking.^{122,123} It is difficult to interpret *in vitro* studies in the context of clinical effects, mainly because the *in vitro* response depends on the level of exposure, and the dose that could better represent realistic clinical effects has not been determined. Such studies have more value in evaluating comparative effects between different products, especially when similar levels of exposure are examined. The majority of the studies comparing e-cigarette aerosol with tobacco cigarette smoke have found lower toxicity for e-cigarettes. However, these studies explore potential mechanisms of harm that need to be further examined.

Limited clinical studies assessing the effects of e-cigarettes have been performed. Some evaluated the acute effects of use and found elevated blood pressure and aortic stiffness,^{124,125} which are related to the sympathetic effects of nicotine. Similar effects have been observed immediately after use of medicinal nicotine,¹²⁶ after short- or long-term use of caffeine^{127,128} or after exercise,¹²⁹ but none of these factors have any long-term adverse health implications. Therefore, their value is limited concerning the long-term effects. One study identified increased cardiac sympathetic activity in e-cigarette users after abstaining from nicotine intake for several hours.¹³⁰ Although the study did not include a smoking group for comparison, the effects seem to be lower compared to other studies evaluating smokers, and this effect needs to be further explored. Other clinical studies have shown objective improvement in respiratory function of asthmatics after switching from smoking to e-cigarette use which was sustained for 2 years, and improvement in blood pressure and hypertension control.^{131–133} Of particular importance are studies evaluating biomarkers of exposure to toxic chemicals. Such studies have long been performed to assess smokers' exposure and now assess the exposure of e-cigarette users. The studies have shown substantial reductions in biomarkers of exposure, which are similar to non-smokers or former smokers who use pharmaceutical nicotine products.^{134,135}

Reviews of the evidence on the safety/risk profile of e-cigarettes agree that current evidence suggests e-cigarettes are less harmful than smoking, although the level of risk reduction is an area of disagreement and intense debate.^{136–138} A recent

risk assessment analysis of the carcinogenic potential of e-cigarettes based on emissions to the aerosol calculated that they have 0.4% of the cancer risk from smoking,¹³⁹ although more research on the chemistry is needed. Another area of agreement is that e-cigarettes are unlikely to be absolutely safe. In the UK, two major health organizations, Public Health England and the Royal College of Physicians, published reports reviewing the evidence on the e-cigarette safety/risk profile and estimated that the health risks of e-cigarettes are at least 95% reduced compared to the risks of smoking. Therefore, although not risk-free, they can substantially reduce the exposure of smokers to harmful toxins. Recently, the UK government officially included e-cigarettes as a harm-reduction approach that will contribute to the elimination of smoking by 2030. However, there is also criticism for the position of the UK authorities concerning the estimates of risk and the endorsement of e-cigarette use,^{140–142} with the authors of the Public Health England report responding that their intention was to communicate to the public the difference in relative risk and their estimate was based on the difference in the chemistry profile between tobacco cigarette smoke and e-cigarette aerosol.¹⁴³

Efficacy in smoking cessation and reduction

A major determinant of the public health effects of e-cigarettes depends on whether they promote or hinder and delay smoking reduction. Surveys of e-cigarette users suggest that e-cigarettes are used as smoking-cessation aids, while a large proportion of e-cigarette users manage to quit smoking or substantially reduce smoking consumption.^{144–147} However, these studies use convenience samples, suffer from selection bias and cannot represent the general population. A study of vapeshop customers objectively assessed the smoking status of participants by measuring exhaled carbon monoxide and identified that 66% of participants had quit smoking.¹⁴⁸ Again, this study did not assess a random sample of users and could over-represent more advanced and dedicated consumers. Randomized controlled trials represent the gold-standard in assessing the efficacy of any medical intervention. Three such studies assessed the efficacy of e-cigarettes and showed modest results for first-generation devices and somewhat better results for newer-generation devices.^{149–151} Several cohort studies have shown mixed results, with some showing that e-cigarette use increases the odds of quitting

while others show the opposite effect.^{152–157} Several meta-analyses have also shown mixed results. Cochrane reviews reported that e-cigarettes help smokers to quit.^{158,159} However, both analyses indicated that the confidence in the result was rated ‘low’ by GRADE standards due to the small number of trials, low event rates and wide confidence intervals around the estimated means. Similar results and limitations were reported in another meta-analysis.¹⁶⁰ Another systematic review found that e-cigarette use was associated with 28% reduced chances of quitting,¹⁶¹ while the most recent one found limited evidence for a positive or negative effect of e-cigarettes on smoking cessation, again rating the evidence as low or very low certainty.¹⁶²

Although the systematic reviews were of good quality, there were major problems in the studies that were included to the analyses. The two randomized controlled trials used outdated and poor-quality products that were already withdrawn and replaced by more advanced products at the time of the studies’ publication.^{149,150} The third study provided nicotine-containing e-cigarette liquids for a limited period of time, while for the rest of the study follow up participants could not easily obtain such liquids because they were banned in that country at the time of the study.¹⁵¹ Several cohort studies suffered from very strong bias, such as failure to examine motivation to quit smoking and reasons for using e-cigarettes and no differentiation between regular *versus* occasional use and experimentation. Many studies included subjects who had already failed to quit smoking with the use of e-cigarettes at baseline, resulting in bias of the outcome being present at the start of the study.^{153,155,156} Additionally, they usually assessed ever or current (past 30-day) use, definitions that include a lot of experimenters rather than regular users.¹⁶³ As expected, it has been shown that frequency of use is positively associated with both quit attempts and quit success.¹⁶⁴ There are also inherent problems in randomized controlled trials, such as the long duration for trial planning, recruitment, implementation and analysis,¹⁶⁵ which become more important when you consider the dynamic and rapidly evolving nature of the e-cigarette market. Additionally, the classical implementation of randomized controlled trials, using a single product and evaluating the effects compared to placebo, is largely inapplicable to e-cigarette research. Switching from smoking to

e-cigarette use represents a behavioral change, with the large variability of devices and liquid flavors serving mainly to substitute a positive experience from smoking with another positive experience from use of a less harmful substitute.¹⁶⁶ Thus, although randomized controlled trials are undoubtedly valuable tools, they need to be performed in an ‘unconventional’ way, allowing participants for product choice based on self-preference and use of new-generation devices that appear to be better in satisfying smokers’ needs. Finally, these trials do not consider that smoking-cessation medications are unpopular among smokers, with most quit attempts done without the use of any aids.¹⁶⁷ These problems raise questions about the ability to generate valid and useful conclusions from the meta-analyses performed until now.

Population studies have shown that e-cigarettes have helped people quit smoking, with increasing proportions of e-cigarette users being former smokers. In the UK, there has been an increase in prevalence of e-cigarette use from 700,000 in 2013 to 2.9 million in 2017.¹⁶⁸ The proportion of e-cigarette users who were former smokers also rose from 33% in 2012 to 52% in 2017. In the European Union, an estimated 6.1 million smokers have managed to quit with the help of e-cigarettes, while an additional 9.2 million smokers have reduced their smoking consumption.¹⁶ Reported smoking cessation and reduction rates were by far higher when current and daily e-cigarette use was assessed separately from ever-use,^{16,169} which emphasizes the importance of differentiating between experimentation and regular use. A cross-sectional survey assessing use of e-cigarettes as part of a quit attempt found that their use was associated with 60% higher odds of quitting compared to pharmaceutical nicotine products.¹⁷⁰ A time series analysis also reported a significant direct association between e-cigarette use and successful quitting.¹⁷¹ Of course, cross-sectional studies also have serious limitations, such as the lack of temporal association and causality, self-report bias and no objective assessment of the smoking status or the duration of smoking cessation. Also, these studies fail to explore how many of those who claim that they have stopped with the aid of e-cigarettes would have stopped anyway and how many of those who used an e-cigarette but failed to stop would have stopped had they used another method.¹⁷²

Electronic cigarette use by population subgroups

Since e-cigarettes are supposed to be used as smoking substitutes, the intended population group target is smokers. Use by never-smokers could be associated with health effects considering that current evidence suggests they are not absolutely harmless. Population studies have been reassuring, showing that current regular use of e-cigarettes is largely confined to current and former smokers. In the UK in 2017, only 2–3% of current adult users report being never-smokers, with the proportion remaining stable between 2012 to 2017 despite the increased awareness and popularity of e-cigarettes over this period.¹⁶⁸ In the European Union, although 2.3% of never-smokers reported ever e-cigarette use, current use was limited to 0.2%.¹⁶ Current or past daily nicotine use was confined to 0.09% of never-smokers,¹⁶ while current daily nicotine use was even more infrequent (0.04%).¹⁶⁹ In the US, the situation is similar, with e-cigarette use being more prevalent among current and recent former smokers while being rare among never-smokers.^{173–175} Daily use was also rare in both never-smokers and former smokers who had quit more than 4 years ago.¹⁷⁴ Similar patterns of use have been observed in other countries.^{176–181} Several studies raised the issue of accurately defining regular e-cigarette use.^{16,167,182} A detailed analysis of frequency of e-cigarette use among ‘current’ users (defined as any past 30-day use) identified that this definition includes a lot of infrequent users, including 89.5% of never-smoking past 30-day e-cigarette users.¹⁶³ Therefore, it is important to determine the frequency of use in order to accurately examine the impact of e-cigarettes on the smoking status of users. In any case, current evidence suggests that the patterns of e-cigarette use in the adult population is favorable for public health, clearly showing that e-cigarettes are not attractive for the vast majority of adult never-smokers. Obviously, continuous monitoring is needed in order to rapidly identify any changes in the use patterns.

Another aspect that has generated a lot of concern is dual use of tobacco and e-cigarettes. In the UK, almost 50% of e-cigarette users are current smokers (i.e. dual users).¹⁶⁸ In Europe in 2014, more than 53% of current daily e-cigarette users were dual users.¹⁶⁹ The PATH study in the US found that, among adult tobacco users, the prevalence of multiple product use was 37.8%, with

69.7% of current e-cigarette users being current smokers.¹⁸³ Dual use of tobacco and e-cigarettes is a vague definition with a large variety of different patterns of use. For example, both an occasional e-cigarette user who takes a few e-cigarette puffs per week and smokes daily, and a daily e-cigarette user who also smokes but reduced tobacco cigarette consumption from 20 to 2 cigarettes per day are considered dual users. However, the health-risk profile of these people is substantially different. Thus, a better definition is needed, especially by presenting the frequency of use of each product and the smoking reduction in those who were smokers before initiating e-cigarette use. Dual use is unlikely to increase harm since e-cigarette use represents an alternative source for smokers to obtain the nicotine they need; thus, no added exposure is expected. Studies on biomarkers of exposure have shown that dual use is associated with either no increase or reduction in toxin exposure, depending on the level of smoking reduction.^{135,184,185} In terms of effects on smoking cessation, dual use represents an expected transition period, which could lead to smoking cessation, although frequently dual users abandon e-cigarette use because they find them unsatisfactory as smoking substitutes. However, long-term dual use is associated with higher quit attempt rates and cessation rates.¹⁸⁶ Additionally, frequent e-cigarette use is associated with reduced rates of dual use.¹⁸³ Available evidence suggests that it is reasonable to encourage, rather than discourage, dual use of tobacco and e-cigarettes unless the motivation for such use is purely recreational and not an attempt to quit or substantially reduce smoking.

There is an intense debate, especially in the US, about the adoption of e-cigarette use by adolescents and subsequent gateway effects to smoking. In late 2016, the Surgeon General published a report about e-cigarette use among youth and young adults, presenting an explosive rise in ever-use from 2011 to 2016 and declaring this to be a major public health concern.¹⁸⁷ The report was mainly based on two large surveys of adolescents, the National Youth Tobacco Survey (NYTS) and the Monitoring the Future Study (MTF).^{188–191} It is accurate that ever and current (past 30-day) e-cigarette use have increased over the past few years among US youth. However, the report provides little discussion on frequent regular use, use of nicotine-containing e-cigarettes and the smoking status of e-cigarette users. These are expected

to be important determinants of the effects of e-cigarettes on this population subgroup. Experimentation is unlikely to result in long-term regular use at the same rate as regular use and is not expected to meaningfully increase health risks. Use of nicotine with e-cigarettes is expected to increase the likelihood of dependence in non-smokers, while use by the latter determines if e-cigarettes are recruiting new users to an inhalational habit and nicotine intake. An analysis of the NYTS 2014 found that the majority of past 30-day e-cigarette users were ever-users of tobacco products, while less than 0.1% of tobacco never-users had used e-cigarettes for 10 or more days in the past month.¹⁹² That study also presented the issue of poly-tobacco use among youth, which has also been detected in an analysis of the MTF 2014.¹⁹¹ A secondary analysis of the latter survey showed that never-smoking high-school students were highly unlikely to use e-cigarettes in the past 30-days while most of those who used them reported use for 1–2 of the past 30 days.¹⁹³ Additionally, most adolescent users were not using nicotine-containing e-cigarettes.¹⁹⁴ Surveys in the UK also show that there is considerable experimentation among youth but little regular use.^{195,196} A recent analysis of five studies in the UK concluded that there is a consistent pattern in terms of e-cigarette use among adolescents, with most e-cigarette experimentation not turning into regular use and levels of regular use in young people who have never smoked remaining very low.¹⁹⁷ Similar patterns are observed in the US. The alarming increase in ever and past 30-day use is, fortunately, not accompanied by elevated regular use among never-smoking US adolescents.¹⁹⁸ Despite these findings, the temporal association between smoking and e-cigarette use cannot be determined through such cross-sectional surveys. Additionally, the rapidly evolving e-cigarette market and technology could potentially change the patterns of use by adolescents. Therefore, it is important to continuously assess the use of e-cigarettes among youth. The latest data from NYTS 2016 and MTF 2016, which were released after the Surgeon General report, showed a substantial decline in e-cigarette ever and past 30-day use in youth, which is a positive sign.^{199,200}

Another important research question is to assess whether e-cigarettes act as a gateway to or a gateway from smoking in the never-smoking youth population. Several studies have shown that e-cigarette use at baseline predicted tobacco cigarette

use at follow up.^{201–205} A recent meta-analysis estimated that e-cigarette use at baseline was associated with 3–4-fold higher odds of subsequent tobacco cigarette use.²⁰⁶ The authors mentioned that several criteria suggested a causal link between e-cigarette use and cigarette smoking, such as association, consistency, specificity, temporality and biological and behavioral plausibility. The studies and subsequent meta-analysis provide sufficient and worrying evidence that there is a temporal transition from e-cigarette to tobacco cigarette experimentation among never-smoking adolescents. The causal link was based on the Branton Hill criteria to establish the link between previous exposure and future development of disease.²⁰⁷ While temporality was established through these studies for baseline never-smokers, it should be noted that a reverse temporal association has also been established. Leventhal and colleagues found that baseline ever-use of a combustible tobacco product was positively associated with e-cigarette use at both 6- and 12-month follow up.²⁰¹ In reality, e-cigarettes seem to have both a ‘cause’ and an ‘effect’ role depending on the population studied. Therefore, not only does use of e-cigarettes ‘cause’ use of conventional cigarettes, but also use of conventional cigarettes ‘causes’ use of e-cigarettes.²⁰⁸ Additionally, the biological plausibility would normally require the establishment of addiction to e-cigarettes and then transition to regular smoking. However, the studies that were included in the meta-analysis assessed ever or past 30-day use of e-cigarettes at baseline, and ever, past year or past 30-day smoking at follow up. Additionally, none of the studies assessed nicotine use with e-cigarettes. Specificity also requires that no other likely causes can explain the effect. However, an alternative explanation is that common factors could lead to both e-cigarette and tobacco cigarette use. Factors such as impulsivity, sensation seeking and tendency toward risky behavior could predispose some adolescents to trying e-cigarettes and tobacco cigarettes.²⁰⁸ Therefore, other confounding factors could explain this association. In any case, the most crucial factor for public health is the prevalence of smoking, especially regular smoking, in adolescents. Data consistently show a substantial decline in tobacco cigarette use from 2010 until 2016, despite the huge rise in e-cigarette use experimentation.^{199,200} This probably suggests that the association between e-cigarette use at baseline and future tobacco cigarette use is affecting a small proportion of adolescents. Indeed, a secondary

analysis of the 2014 NYTS showed that only 3.3% of adolescents were past 30-day exclusive e-cigarette users, with two-thirds (2.1%) being ever tobacco users.¹⁹² Of course, it cannot be excluded that the decline in smoking prevalence would have been stronger if e-cigarettes did not exist. Therefore, continuous monitoring is needed and it remains to be seen whether e-cigarettes represent a source of harm. At the same time, however, the possibility that e-cigarettes might have a primary preventive role, promoting a decline in tobacco cigarette use, should also be considered and research should also focus on this issue.

Conclusions

E-cigarettes are one of the most controversial issues in public health today. There is little doubt that they are less harmful than smoking, but there is disagreement on the level of risk reduction. However, there is agreement that they are not absolutely harmless. Epidemiological evidence of long-term health effects is unavailable for now, and it will take years to generate final conclusions about the clinical effects of switching from tobacco to e-cigarette use. However, it is reasonable to communicate to smokers the relative risks of smoking and e-cigarette use based on current knowledge, keeping in mind that the ideal pathway is to quit without using any alternative products. While population studies suggest that smokers can successfully quit smoking with the help of e-cigarettes, randomized controlled trials and cohort studies have failed to show substantial effects. This is, at least in part, due to both methodological problems in studies and the complexity and dynamic evolution of the e-cigarette market, as well as the time-consuming research methods. While there is clear evidence that e-cigarettes are not attracting adult never-smokers, there is considerable experimentation among adolescents, including never-smokers. Recent evidence shows a trend for reduction of experimentation among youth while regular use appears to be largely confined to smokers, and smoking prevalence is continuously declining. More research is needed to evaluate the complex interactions between smoking and e-cigarette use in adolescents and the impact of e-cigarettes on adolescent smoking prevalence, and to examine whether e-cigarettes are a source of harm or harm reduction in this population. It appears that e-cigarettes will remain a controversial topic and heated debate will continue for many more years.

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Conflict of interest statement

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