


Electronic cigarettes and health with special focus on cardiovascular effects: position paper of the European Association of Preventive Cardiology (EAPC)

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Abstract

Background: Tobacco use is the single largest preventable risk factor for premature death of non-communicable diseases and the second leading cause of cardiovascular disease. In response to the harmful effects of tobacco smoking, the use of electronic cigarettes (e-cigarettes) has emerged and gained significant popularity over the past 15 years. E-cigarettes are promoted as safe alternatives for traditional tobacco smoking and are often suggested as a way to reduce or quit smoking. However, evidence suggests they are not harmless.

Discussion: The rapid evolution of the e-cigarette market has outpaced the legislator's regulatory capacity, leading to mixed regulations. The increasing use of e-cigarettes in adolescents and young individuals is of concern. While the long-term direct cardiovascular effects of e-cigarettes remain largely unknown, the existing evidence suggests that the e-cigarette should not be regarded as a cardiovascular safe product. The contribution of e-cigarette use to reducing conventional cigarette use and smoking cessation is complex, and the impact of e-cigarette use on long-term cessation lacks sufficient evidence.

Conclusion: This position paper describes the evidence regarding the prevalence of e-cigarette smoking, uptake of e-cigarettes in the young, related legislations, cardiovascular effects of e-cigarettes and the impact of e-cigarettes on smoking cessation. Knowledge gaps in the field are also highlighted. The recommendations from the population science and public health section of the European Association of Preventive Cardiology are presented.

Keywords

Electronic cigarette, cardiovascular, tobacco, blood pressure, heart rate, myocardial infarction

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Introduction

Despite widespread population-based anti-smoking policies, 28% of the adult population (aged ≥ 15 years) across Europe is still smoking.¹ The use of electronic cigarettes (e-cigarettes) has emerged and gained significant popularity in response to the well-known harmful effects of tobacco smoking,² although their safety is questioned.³ The initial inception of the modern device is credited to Hon Lik, a Chinese pharmacist, who in 2003 discovered this method of vaping which gained a patent in 2007.⁴ Overall, there are two main types of e-cigarettes: (a) disposable and rechargeable devices that look like cigarettes; and (b) refillable vaporisers or tank systems that do not look like cigarettes.⁵

E-cigarettes deliver a heated aerosol into the mouth and lungs. The main ingredients of e-cigarettes are propylene glycol and/or vegetable glycerine as a carrier, and nicotine and flavours as the active substances.³

In many countries e-cigarettes do not undergo the same strict regulations as conventional tobacco. Therefore, promotion via media and the internet is often allowed, reaching adults but also the young. Although the popularity of each type of e-cigarette can vary over time and between countries, what is universally recognised is that an increasing number of children, adolescents and adults are utilising e-cigarettes.⁶ E-cigarettes are promoted as safe alternatives for traditional tobacco smoking and are often suggested as a method to reduce or quit smoking. However, some evidence suggests that they are not harmless.^{3,7–10}

Hence, there is a need for an overview of the evidence for perceived benefits and harms of e-cigarettes. This position paper describes the prevalence of e-cigarette smoking, uptake of e-cigarettes in the young, related legislations, cardiovascular effects of e-cigarettes and impact of e-cigarettes on smoking cessation in adults. While our paper focuses on the cardiovascular effects of e-cigarettes, we are becoming increasingly aware of non-cardiac effects including the many cases of deaths associated with vaping and lung injury in the United States (US). Lung injury was associated with adding vitamin E, which is likely to have a significant public health impact, but remains outside the scope of our paper and hence is not discussed in more detail.¹¹ We do not review other adverse health effects in detail. We further highlight the knowledge gaps in the field. Finally, we present the recommendations from the population science and public health section of the European Association of Preventive Cardiology (EAPC) concerning e-cigarette usage.

Prevalence of e-cigarette smoking

The prevalence of e-cigarette use is complex to define and three important aspects need to be considered.

Firstly, definition of e-cigarette usage varies. Most studies in the literature describe ever use, which ranges from single-time experimentation to active, regular use and/or use in the past 7 or 30 days that is sometimes used as a surrogate of 'current use'. Secondly, independent of definition, there is heterogeneity in prevalence across countries and sometimes even within a country. Thirdly, patterns of e-cigarette use evolve over time, with a rise in prevalence in more contemporary versus older surveys.¹² In addition, response to questionnaires may depend on the type and order of the questions asked.¹³

We have considered only the most recent prevalence data from 2015 to 2019. Older data can be found in several reviews.^{12,14–18} The results are summarised in Table 1. The prevalence of ever use ranged from 0% (Egypt) to 56.6% (Lithuania); the prevalence of past 30-day use ranged from 2.0% (Switzerland) to 35.0% (Poland), and the prevalence of daily use ranged from 0.2% (Serbia) to 1.7% (USA). Dual use (i.e. e-cigarettes and classic cigarettes) ranged between 1.5% and 24.0% (both for Poland). Studies targeting youth or students consistently reported higher prevalence rates.

Overall, the available data show a wide variation in the prevalence of ever and current users between and even within countries. A plausible explanation is the role of the regional legislative and social environment in supporting or deterring e-cigarette use.¹⁹ The most consistent finding is the increasing prevalence of e-cigarette use in adolescents and young individuals.²⁰

Knowledge gaps

- Data on prevalence, determinants and motivations to use e-cigarettes in adolescents and young adults are lacking in many countries.
- Prospective studies assessing the impact of occasional e-cigarette use on becoming a current e-cigarette user or a dual (e-cigarette and traditional tobacco) user are lacking.
- There are few data available regarding trends in e-cigarette consumption and how people start with and quit e-cigarettes.

Uptake of e-cigarettes in the young

E-cigarette use has shown an exponential expansion of uptake in the young, with studies reporting an increase from 5% to up to 25% between 2013 and 2019 (Figure 1).^{20–22}

One of the main arguments supporting e-cigarette introduction and uptake was to help with smoking cessation. While this might be a sensible argument for adults, its role in supporting smoking cessation in the

Table 1. Prevalence e-cigarette consumption, stratified by WHO region and country, among studies conducted from 2015 onwards.

| Country/reference | Study period | Setting | Sample size | Age | Results |
|----------------------|--------------|---|-------------|-------|---|
| Americas | | | | | |
| Brazil ⁸¹ | 2015 | Students of the Federal University of Mato Grosso | 489 | NR | 2.7% ever users 0.61% current users |
| Canada ⁸² | 2014–2015 | Canadian Student Tobacco, Alcohol and Drugs Survey (336 schools from 128 school boards) | 42,094 | NR | 17.7% ever users 5.7% past 30-day users |
| Canada ⁸³ | 2015 | Canadian Tobacco Alcohol and Drugs | 15,154 | 15+ | 13.2% ever users 3.2% past 30-day users 0.8% daily users |
| Mexico ⁸⁴ | 2015 | Stratified random sampling of schools in Mexico City, Guadalajara and Monterrey | 10,146 | 12–13 | 10% ever users |
| Mexico ⁸⁵ | 2016 | National Survey of Drugs, Alcohol and Tobacco Use | 12,436 | 12–17 | 7.0% ever users 1.1% current users |
| Mexico ⁸⁵ | 2016 | National Survey of Drugs, Alcohol and Tobacco Use | 36,966 | 18+ | 3.0% ever users 0.3% current users |
| Mexico ⁸⁵ | 2016 | National Survey of Drugs, Alcohol and Tobacco Use | 7347 | 18+ | 18.0% ever users 5.0% dual users |
| USA ⁸⁶ | 2014–2015 | Tobacco Use Supplement – Current Population Survey | 225,413 | 18+ | 9.4% (rural) and 7.0% (urban) ever users 2.8% (rural) and 2.1% (urban) current users |
| USA ⁸⁷ | 2015 | National Youth Tobacco Survey | 17,711 | <18 | 4.8% (middle school) and 12.8% (high school) past 30-day users |
| USA ⁸⁸ | 2015 | Tobacco Products and Risk Perceptions Survey | 6008 | 18+ | 17.0% ever users 7.4% current users 1.7% daily users |
| USA ⁸⁹ | 2015 | Health Information National Trends Survey | 3738 | 18+ | 22.4% ever users |
| USA ⁹⁰ | 2016 | Behavioral Risk Factor Surveillance System | 466,842 | 18+ | 4.5% current users 1.5% daily users |
| USA ⁹¹ | 2016 | Behavioral Risk Factor Surveillance System | 477,665 | 18+ | 16.2% (DC) to 28.4% (Arkansas) ever users 2.4% (DC) to 6.7% (Oklahoma) current users |
| USA ⁹² | 2016 | National Health Interview Survey | 32,931 | 18+ | 15.3% ever users 3.2% current users |
| USA ^{93–95} | 2018 | Monitoring the Future | 13,850 | NR | Past 30-days users 25.0% (12th grade) 20.3% (10th grade) 8.1% (8th grade) |

(continued)

Table I. Continued.

| Country/reference | Study period | Setting | Sample size | Age | Results |
|--------------------------------|--------------|--|-------------|------------|---|
| Eastern Mediterranean | | | | | |
| Egypt ⁹⁶ | 2015 | Cross-sectional community survey | 1239 | 15–75 | 0% ever users |
| Saudi Arabia ⁹⁷ | Nov–Dec 2017 | Three universities in Jeddah | 1007 | 15+ | 27.7% ever users 4.1% daily users 4.4% mixed smoker/vaper |
| Western Pacific | | | | | |
| Australia ⁹⁸ | Feb 2016 | New South Wales | 3188 | 18+ | 13.0% ever users 4.0% past 30-day users 0.5% daily users |
| China ⁹⁹ | 2015 | Mobile app-based survey | 2042 | 12–18 | 26.4% ever users |
| Japan ¹⁰⁰ | 2015 | Japan ‘Society and New Tobacco’ Internet Survey | 8240 | 15–69 | 1.3% past 30-day users |
| Korea ¹⁰¹ | 2015 | middle and high school students from Seoul, Incheon, Gyeonggi, and Cheongju | 2744 | 13–18 | 12.6% ever users 6.3% past 30-day users 4.9% past 30-day dual users |
| Korea ¹⁰¹ | 2015 | University students from 14 universities | 2167 | 19–29 | 21.2% ever users 7.2% past 30-day users 5.9% past 30-day dual users |
| Malaysia ¹⁰² | 2016 | National E-cigarette survey | 4288 | 18+ | 11.9% ever users 3.2% current 2.3% dual users |
| New Zealand ^{103,104} | 2016 | Health and Lifestyles Survey | 3854 | 15+ | 17.0% ever users 1.8% current users 1.0 daily users |
| Taiwan ¹⁰⁵ | 2014–2016 | Taiwan Global Youth Tobacco Survey | NR | 12–18 | 3.1% past 30-day users 1.6% dual users |
| Taiwan ¹⁰⁶ | 2015 | Adult Smoking Behavior Survey | 26,021 | 15+ | 2.7% ever users |
| Europe | | | | | |
| Belarus ¹⁰⁷ | 2017–2018 | University students | 3895 | 19.3±2.1 | 42.7% ever users 2.7% current users 2.0% dual users |
| France ¹⁰⁸ | 2014–2015 | Cross-sectional study on two major campuses | 1134 | 20.8 years | 23.0% ever users 5.7% current users |
| Germany ¹⁰⁹ | 2015 | Epidemiological Survey of Substance Abuse | 9204 | 18–64 | 14.3% ever users 2.9% past 30-day users 2.1% dual users |
| Germany ¹¹⁰ | 2016 | Representative surveys on substance use conducted by the Federal Center for Health Education | 2462 | 18–25 | 7.6% (men) and 3.4% (women) past 30-day users ⁵ |

(continued)

Table 1. Continued.

| Country/reference | Study period | Setting | Sample size | Age | Results |
|---------------------------|---------------|--|-------------|----------|--|
| Germany ¹¹⁰ | 2016 | Representative surveys on substance use conducted by the Federal Center for Health Education | 2459 | 12–17 | 4.2% (men) and 2.5% (women) past 30-day users |
| Germany ¹¹¹ | 2016 | Random sample | 4002 | 14+ | 11.8% ever users 1.4% regular users |
| Greece ¹¹² | 2017 | Adults living in Attica prefecture | 4058 | 18+ | 27.2% ever users 5.0% current use |
| Lithuania ¹⁰⁷ | 2017–2018 | University students | 1128 | 19.8±1.3 | 56.6% ever users 3.5% current users 2.1% dual users |
| Poland ⁷⁰ | 2015–2016 | National Adult Tobacco Survey | 1978 | 15–19 | 35.0% past 30-day users 24.0% past 30-day dual users |
| Poland ¹⁰⁷ | 2017–2018 | University students | 7324 | 21.9±2.1 | 45.0% ever users 2.8% current users 1.5% dual users |
| Russia ⁴⁸ | 2015 | Students of the Republic of Bashkortostan | 716 | 15+ | 28.6% ever users 2.2% past 30-day users |
| Russia ¹⁰⁷ | 2017–2018 | University students | 1290 | 20.4±2.2 | 33.4% ever users 4.0% current users 2.6% dual users |
| Serbia ^{113,114} | December 2017 | Three stage, random, nationally representative survey | 1045 | 18+ | 10.7% ever users 0.2% daily users |
| Slovakia ¹⁰⁷ | 2017–2018 | University students | 715 | 22.5±1.8 | 34.4% ever users 2.3% current users 2.6% dual users |
| Spain ¹¹⁵ | 2015 | Sistema de Información sobre Conductas de Riesgo | 7908 | 15+ | 5.3% ever users 0.7% current users |
| Spain ¹¹⁶ | 2015–2016 | Students of the University of Almeria | 745 | 21.9±3.9 | 22.5% ever users 2.5% current users 1.7% daily users |

(continued)

Table I. Continued.

| Country/reference | Study period | Setting | Sample size | Age | Results |
|--------------------------------|---------------|---|-------------|-------|--|
| Sweden ¹¹⁷ | 2016 | Schools of the Scania region | 13,835 | 14–21 | 9th grade 32% (men) and 27% (women) ever users 10.8% (men) and 7.0% (women) past 30-day users 2nd grade 43% (men) and 31% (women) ever users 11.1% (men) and 5.0% (women) past 30-day users |
| Switzerland ¹¹⁸ | July–Dec 2015 | Continuous Rolling Survey of Addictive Behaviours and Related Risks | 5252 | 15+ | 14.0% ever users 2.0% past 30-day users 0.3% daily users |
| The Netherlands ¹¹⁹ | 2014–2015 | 19 secondary schools randomly selected across The Netherlands | 6819 | 11–17 | With nicotine 13.7% ever users 6.7% past 30-day users Without nicotine 29.4% ever users 13.2% past 30-day users |
| The Netherlands ¹¹⁹ | 2016–2017 | Traditional and Novel Substance use among Adolescents study | 2758 | 14–21 | With nicotine 12.3% ever users 2.5% past 30-day users Without nicotine 27.6% ever users 2.6% past 30-day users |
| UK (Wales) ¹²⁰ | 2015 | 87 Secondary schools in Wales | 32,479 | 11–16 | 18.5% ever users 1.4% daily users |
| UK ¹²¹ | 2015–2016 | Smoking Toolkit Study | 81,063 | 16+ | 5.5% current users |
| UK ¹⁰⁶ | 2015–2017 | The Youth Tobacco Policy Survey; the Schools Health Research Network Wales survey; two Action on Smoking and Health (ASH) Smokefree Great Britain-Youth Surveys; and the Scottish Schools Adolescent Lifestyle and Substance Use Survey | 60,201 | 11–16 | 7% to 32% ever users 1% to 3% weekly users |

Only studies conducted from 2015 to 2018 are included in this table.

Current use is defined as either daily or occasionally.

NR: not reported.

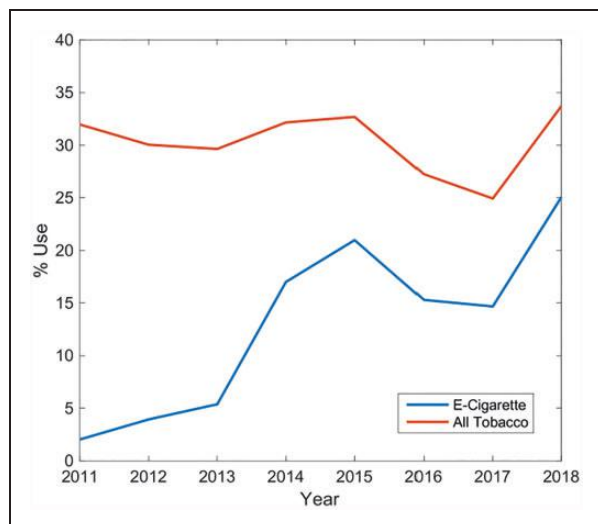


Figure 1. Longitudinal trend in e-cigarette and tobacco use in pupils aged 11–18 years in the United States between 2011 and 2018. Data used with permission from Cullen et al.²⁰

young is less well defined.²³ At the same time, while e-cigarette use might be safer compared with tobacco smoking, a worrying increase has been noted in the young who view e-cigarettes as a new and safe ‘trend’ and as a part of a ‘healthy life’. Thus, e-cigarettes can easily be taken up in the young without health-related considerations. There is a growing body of evidence that never-smoker minors who use e-cigarettes might double their chance of starting to smoke cigarettes later in life.^{24–27} The evidence is based on longitudinal observational studies, because randomised controlled trials to address this research question cannot ethically be performed due to the potential of causing harm.^{24–28} Flavours are important when we talk about children and adolescents. They prefer sweet flavours and they believe that sweet flavours are less harmful.²⁹ Fruit, menthol or mint, and candy, desserts or other sweets are the most commonly reported flavours in e-cigarettes among youth. Therefore, these flavours should be banned.³⁰

Furthermore, specific health-related conditions in the young, including pregnancy and asthma, are adversely affected by e-cigarettes. There is actually no evidence proving e-cigarettes to be safe during pregnancy.³¹ Nicotine is harmful to the developing fetus and has several cardiovascular effects.³² Maternal active smoking, maternal passive smoking as well as paternal smoking all increase the risk of fetal congenital heart defects in offspring.³³ Nicotine has been shown to increase placental vascular resistance and increase the risk of hypertension throughout childhood and later in life. Possible mechanisms include

endothelial injury, kidney abnormalities and increased cholesterol levels. Fetal nicotine exposure can impair the development of neurons and brain circuits and can increase the risk of preterm birth, stillbirth and neonatal apnoea.³⁴ Likewise, e-cigarette use and secondary exposure have been linked to increased asthma attacks in the young.³⁵ Moreover, there is circumstantial evidence that nicotine from e-cigarette use in the young might affect brain maturation leading to problems with cognition and emotional regulation later in life; however, more solid evidence for such a causative effect is awaited.³⁶

Similar to the conventional tobacco legislations, selling e-cigarettes to anyone under the age of 18 years is illegal in many countries, but the legislation is often ignored. Furthermore, the young often get or buy their supplies from relatives and friends or even directly from the stores and online. Where legal, e-cigarette advertising is a powerful inducer, with television advertising having the highest recall. Peer pressure and specialty retailer presence near schools may have an environmental influence on students’ e-cigarette experimentation, where it looks like an ‘adult candy store’. Passive smoking from adults inside the same home and the tolerance of e-cigarettes at home in the young is also of concern.^{37–39}

E-cigarettes are thus a new potential hazard for children and adolescents. Public health measures should thus be undertaken to minimise e-cigarette use in the young. The increased awareness and education of the young, in particular relating to the potential negative health effects of e-cigarettes, should encourage better prevention and decrease in the use of e-cigarettes, an ‘epidemic of youth use’.⁴⁰ It is important to ensure minimal risk to the adverse effects of potential nicotine addiction.

Knowledge gaps

- There is an increasing use of e-cigarettes in the young. A growing body of evidence from longitudinal observational studies suggest that never-smoker minors who use e-cigarettes might double their chance of starting conventional smoking later in life. Due to the ethical considerations and the potential of causing harm, data from randomised controlled trials on this matter are lacking.
- Robust evidence regarding the influence of e-cigarettes on cognitive, visual and memory performance, and on attention among youth is lacking. Similarly, no data exist regarding the potential depressive effects and the influence of e-cigarettes on the quantity and the quality of sleep.

Legislation

In 2016, the World Health Organization (WHO) submitted a report on e-cigarettes for the seventh session of the Conference of the Parties to the WHO Framework Convention on Tobacco Control (FTCT). WHO suggested regulatory measures to prohibit or restrict the manufacture, importation, distribution, presentation, sale and use of e-cigarettes, as appropriate to national laws and public health objectives.⁴¹ Also in 2016, the US Food and Drug Administration (FDA) issued a rule on tobacco products, including e-cigarettes. Products marketed for therapeutic purposes 'to help people quit smoking' are regulated through the Center for Drug Evaluation and Research.⁴² In the EU, article 20 of the Tobacco Products Directive (2014/40/EU) regulates e-cigarettes as consumer products, but allows EU member states to classify e-cigarettes as medicines if conditions are fulfilled. The legislation that regulates the manufacture, import, packaging, labelling, advertising, promotion, sale and distribution, including components and parts was implemented in 2015, establishing a common format for the notifications of e-cigarettes and refill containers and in 2016 regarding technical standards for the refill mechanism.

Legislation regarding e-cigarettes is relatively new and there is no consensus on how to legislate the sales, packaging, taxes and public use. While most nicotine-dispensing e-cigarettes might be included under existing legislation regarding tobacco products, the legal fate of non-nicotine dispensing e-cigarettes is more complex. Two recent reviews^{43,44} and one website⁴⁵ summarise the existing data regarding legislation on e-cigarettes. Overall, legislation is available for 98 countries and varies considerably (Table 2 and Table 3).⁴⁶ Even within a country such as the USA, regulations regarding e-cigarettes vary by state. The issue is further complicated by the fact that e-cigarettes can also be considered as consumer products or medicinal products. Worryingly, most African countries and populous countries such as India, Indonesia, China and Russia lack e-cigarette regulation, although some improvements are under way.⁴⁶

Only 13 countries apply a tax to e-cigarettes.⁴⁵ A total of 29 countries ban e-cigarettes completely, and nine ban nicotine-containing liquids only (Table 3).⁴⁶ It is almost impossible to give updated information, due to quick changes in legislation. Still, the ban of nicotine-containing liquids can easily be circumvented via internet imports or in shops due to lack of enforcement of the ban.⁴⁷ Many websites selling e-cigarette products perform no age checking and fail to provide any information regarding use or health warnings.⁴⁸ Social media are utilised for promotional strategies

and networking purposes, and social media influencers are brand ambassadors for e-liquid marketing.⁴⁹ Finally, advertisements for devices resembling e-cigarettes as delivering 'nutritional supplements' have been issued, leading consumers to believe that e-cigarettes are health-enhancing.⁵⁰

Due to its relatively recent implementation, the effect of legislation on e-cigarette use has seldom been assessed. A US study suggested that higher excise taxes decrease e-cigarette purchases, while e-cigarette smoke-free laws do not affect e-cigarette purchases.⁵¹ Conversely, a study also conducted in the USA concluded that both higher prices and vaping restrictions are associated with less e-cigarette use.⁵² The recent outbreak of lung disease related to e-cigarettes has prompted several US states and countries to ban flavoured e-cigarettes and to increase tax on non-flavoured cigarettes, and the FDA to issue an enforcement policy regarding flavoured e-cigarettes.^{8,53}

The rapid evolution of the e-cigarette market has outpaced the legislator's regulatory capacity, leading to mixed regulations and possibly illegal actions. Harmonisation and implementation of existing regulations is necessary, as well as the setting of swift procedures to adapt regulations and taxation to incoming evidence regarding the benefits and harms of e-cigarettes. Countries lacking a legal framework for e-cigarettes should rapidly create one.

Knowledge gaps

- There is no information at general population level regarding their acceptance of different measures to legislate e-cigarette use.
- There is little or no evidence on the impact of different regulatory measures on the uptake and prevalence of e-cigarette use.
- Longitudinal studies to understand the role of social media on e-cigarette use initiation among adolescents and young adults are needed.

Effect of e-cigarettes on cardiovascular function and CVD

While the association of conventional tobacco smoking with cardiovascular disease (CVD) is well established, research on the impact of e-cigarettes on CVD is limited. The harmful effects of tobacco are largely caused by the exposure to combustion products. There is substantial evidence that except for nicotine, under typical conditions of use, exposure to potentially toxic substances from e-cigarettes is significantly lower compared with combustible cigarettes.⁵⁴ Therefore, it is generally believed that the physiological effects of e-cigarettes are less harmful compared with tobacco

Table 2. Details of the legislation regarding e-cigarettes, as of April 2019; countries that have a complete ban are not represented.

| Country | Advertising | Minimum age | Child-proof packaging | Health warning label | Nicotine volume/concentration | Vape-free public places |
|--|-------------|-------------|-----------------------|----------------------|-------------------------------|-------------------------|
| <i>Europe</i> | | | | | | |
| Austria, Belgium, Bulgaria, Croatia, Cyprus, Denmark, Estonia, Finland, France, Germany, Italy, Lithuania, Luxembourg, Poland, Portugal, Slovakia, Slovenia, Spain | Yes | Yes | Yes | Yes | Yes | Yes |
| Czech Republic, Greece, Netherlands, Sweden, United Kingdom | Yes | Yes | Yes | Yes | Yes | |
| Malta | Yes | | Yes | Yes | Yes | Yes |
| Ireland, Latvia, Romania | Yes | | Yes | Yes | Yes | |
| Georgia | | Yes | | Yes | | Yes |
| Norway | Yes | Yes | | | | |
| Hungary, Iceland, Serbia | Yes | | | | | |
| Azerbaijan, Ukraine | | | | | | Yes |
| Belarus, Bosnia & Herzegovina, FYR, Macedonia, Israel, Switzerland | – | – | – | – | – | – |
| <i>Africa</i> | | | | | | |
| South Africa | – | – | – | – | – | – |
| Togo | Yes | Yes | | | | Yes |
| <i>Americas</i> | | | | | | |
| Barbados, Jamaica | | | | | | Yes |
| Canada, Mexico | Yes | | | | | |
| Chile | – | – | – | – | – | – |
| Costa Rica, Ecuador, Haiti, Honduras | Yes | Yes | | | | Yes |
| USA | Yes | Yes | Yes | Yes | | |
| Venezuela | Yes | | | | | Yes |
| <i>South-East Asia, Eastern Mediterranean, Western Pacific</i> | | | | | | |
| Australia | Yes | | | | | Yes |
| Fiji, Republic of Korea, Vietnam | Yes | Yes | | | | Yes |
| Japan, New Zealand | Yes | | | | | |
| Malaysia | | Yes | | | | |
| Philippines | | | Yes | | | Yes |
| DPR Korea, Tunisia, China, Hong Kong | – | – | – | – | – | – |

–: no data available.

Empty cell indicates no such topic.

Countries are categorised according to the WHO geographical areas, with a further division for European countries.^{43–45}

Advertising: most countries include advertising, promotion or sponsorship of all types of e-cigarettes, while others restrict advertisement of nicotine-containing e-cigarettes; minimum age is usually set at 18 years, with some exceptions (i.e. 16 years for Belgium and 19 years in the Republic of Korea); child-proof packaging: in the EU, packages should also be tamper-proof and have a mechanism that allows refilling without spillage to protect consumers; health warnings: usually indicating that the product contains nicotine, which is an addictive product; nicotine volume or concentration: in the EU, maximum concentration is 20 mg/ml; vape-free public places: vaping in vehicles with minors and/or pregnant women is also prohibited in several countries.

cigarettes.^{54,55} However, e-cigarettes do contain potential toxicants and exert a variety of biological effects,⁵⁵ such that health-related sequelae linked to the exposure to nicotine as well as other components in the vapour produced by the devices cannot be excluded. Although nicotine-free e-cigarette liquids are available, those containing nicotine are used much more commonly.

Currently, direct evidence from clinical trials and long-term cohort studies regarding the clinical

cardiovascular effects of e-cigarettes is not available and the consequences of their chronic use are largely unknown. The only available epidemiological evidence is based on the observational data from two studies. The National Health Interview Surveys of 2014 ($N=36,697$) and 2016 ($N=33,028$) suggest an increased risk of myocardial infarction (MI) in e-cigarette users (odds ratio 1.79, 95% confidence interval 1.20, 2.66), although to a lesser extent than conventional cigarette smoking (2.72, 2.29, 3.24).⁵⁶

Table 3. Available legislation regarding e-cigarettes.

| Country | Legislation | Product classification | | Sales |
|----------------------|-------------------------|---|---|------------------------|
| | | Tobacco-related product | Other | |
| European Union | | | | |
| Austria | Existing, amended & new | Tobacco-related product | Medicinal, medical device, consumer good | Authorisation required |
| Belgium | Existing | | Medicinal, consumer good | Authorisation required |
| Bulgaria | | | | Authorisation required |
| Croatia | Existing | Tobacco (imitation) | Consumer good, chemical product | Authorisation required |
| Cyprus | | | | Authorisation required |
| Czech Republic | Existing | Tobacco (imitation) | Medicinal, consumer good, hazardous substance | Authorisation required |
| Denmark | Existing & new | E-cigarette | Medicinal | Authorisation required |
| Estonia | New | Tobacco-related product | | Authorisation required |
| Finland | New | Tobacco (imitation), tobacco-related product, E-cigarette | Medicinal | Authorisation required |
| France | Existing & amended | E-cigarette | Medicinal, consumer good | Authorisation required |
| Germany | New | Tobacco-related product | Consumer good | Authorisation required |
| Greece | Amended | Tobacco-related product | Consumer good | Authorisation required |
| Hungary | Amended | | Consumer good | Authorisation required |
| Ireland | Existing & new | E-cigarette | Medicinal, consumer good | Authorisation required |
| Italy | Amended | Tobacco-related product | | Authorisation required |
| Latvia | New | E-cigarette | | Authorisation required |
| Lithuania | New | Tobacco-related product | | Authorisation required |
| Luxembourg | Existing | | Poison, electrical appliance | Authorisation required |
| Malta | Legal notice | Tobacco-related product | | Authorisation required |
| Netherlands | Existing | E-cigarette | Medicinal, consumer good | Authorisation required |
| Poland | New | | Chemical mixture, Consumer good | Authorisation required |
| Portugal | Existing | E-cigarette | | Authorisation required |
| Romania | | | | Authorisation required |
| Slovakia | Amended | Tobacco | Tobacco-free product intended to smokers | Authorisation required |
| Slovenia | | | | Authorisation required |
| Spain | Amended | ENDS | | Permitted, regulated |
| Sweden | | | | Authorisation required |
| Europe, other | | | | |
| Azerbaijan | | | | Permitted, regulated |
| Belarus | | | | Permitted, regulated |
| Bosnia & Herzegovina | | | | Permitted, regulated |
| FYR Macedonia | | | | Permitted, regulated |
| Iceland | Existing | | Medicinal, consumer product | Permitted, regulated |
| Israel | | | | Permitted, regulated |
| Georgia | | | | Permitted, regulated |
| Norway | Existing | Tobacco surrogate | Medicinal | Authorisation required |
| | | E-cigarette | | |
| Serbia | | | | Permitted, regulated |
| Switzerland | Existing | E-cigarette | Consumer good | Nicotine ban |
| Turkey | Amended | Tobacco, e-cigarette | | Complete ban |
| Turkmenistan | | | | Complete ban |
| Ukraine | Amended | E-cigarette | | Permitted, regulated |
| United Kingdom | Existing & new | E-cigarette | Medicinal, consumer good | Authorisation required |

(continued)

Table 3. Continued.

| Country | Legislation | Product classification | | Sales |
|------------------------------|--------------------|------------------------------------|---------------------------|------------------------|
| | | Tobacco-related product | Other | |
| Africa | | | | |
| Gambia | | | | Complete ban |
| Mauritius | Existing | Tobacco (imitation) | | Complete ban |
| Seychelles | Existing | Tobacco (imitation) | | Complete ban |
| South Africa | Ruling | | Medicinal | Authorisation required |
| Togo | New | Tobacco (derivative) | | Permitted, regulated |
| Uganda | | | | Complete ban |
| Americas | | | | |
| Argentina | Existing | ENDS, tobacco | | Complete ban |
| Barbados | | | | Unknown |
| Brazil | Decree; resolution | E-cigarette, tobacco | | Complete ban |
| Canada | Existing | | Drug, consumer good | Nicotine ban |
| Chile | Resolution | | Medicinal | Unclear |
| Colombia | Existing | Tobacco (imitation) | | Complete ban |
| Costa Rica | Existing | ENDS, tobacco (derivative) | | Nicotine ban |
| Ecuador | Existing | ENDS, tobacco (derivative) | | Permitted, regulated |
| El Salvador | Decree | E-cigarette | | |
| Haiti | Existing | Tobacco (derivative) | | Unclear |
| Honduras | | | | Permitted, regulated |
| Jamaica | Existing & amended | ENDS | Medicinal | Nicotine ban |
| Mexico | Existing | Tobacco (imitation) | | Nicotine ban |
| Nicaragua | Existing | Tobacco (imitation) | | Complete ban |
| Panama | Decree | ENDS, tobacco (imitation) | | Complete ban |
| Suriname | New | ENDS | | Complete ban |
| USA | New | Tobacco product | | Permitted, regulated |
| Uruguay | Amendment/decree | Electronic smoking device | | Complete ban |
| Venezuela | Existing | Tobacco (derivative) | Medicinal, consumer good | Permitted, regulated |
| South-East Asia | | | | |
| DPR Korea | | | | Permitted, regulated |
| Nepal | Notification | ENDS | | Complete ban |
| Thailand | Existing | Tobacco (imitation) E-cigarette | 'Modern' medicinal | Complete ban |
| Eastern Mediterranean | | | | |
| Bahrain | Existing | ENDS, tobacco | | Complete ban |
| Iran | Amended | Tobacco product | | Complete ban |
| Jordan | Official letter | E-cigarette | | Complete ban |
| Kuwait | Decision | E-cigarette | | Complete ban |
| Lebanon | Decision | E-cigarette | | Complete ban |
| Oman | Decision | E-cigarette | | Complete ban |
| Qatar | Circular; decision | E-cigarette | | Complete ban |
| Saudi Arabia | Decision | E-cigarette | | Complete ban |
| Syria | Circular | E-cigarette | | Complete ban |
| Tunisia | | | | Authorisation required |
| United Arab Emirates | Decision | E-cigarette | | Complete ban |
| Western Pacific | | | | |
| Australia | Existing | | Poison, consumer good | Nicotine ban |
| Brunei Darussalam | Existing | Tobacco (imitation) | Poison | Complete ban |
| Cambodia | Circular | E-cigarette | | Complete ban |
| China | | | | Permitted, regulated |
| Fiji | Amended | E-cigarette | | Authorisation required |
| Hong Kong | | | | Permitted, regulated |
| Japan | Existing | | Medicinal | Nicotine ban |
| Malaysia | | | | Nicotine ban |
| New Zealand | Existing | Tobacco | Medicinal, consumer good | Nicotine ban |
| Philippines | Order | | Medicinal, medical device | Authorisation required |
| Republic of Korea | Existing & amended | Tobacco | Consumer good | Unclear |
| Singapore | Existing | Tobacco (imitation) | | Complete ban |
| Timor-Leste | New | E-cigarette | | Complete ban |
| Vietnam | Existing | Tobacco | | Permitted, regulated |

ENDS: electronic nicotine delivery systems.

Countries are categorised according to the WHO geographical areas, with a further division for European countries.^{43–45}

In the absence of robust long-term evidence regarding the impact of e-cigarettes on CVD, only indirect estimates can be made. These are based on smoking cessation trials that used nicotine replacement therapies (NRTs), or by estimating the levels of various known harmful substances in e-liquids and vapours/aerosols, as well as by experimental animal and human studies and *in vitro* studies investigating responses to exposure that are known to increase cardiovascular risk.

A meta-analysis of 21 randomised trials including 11,647 patients (of which only two trials included patients with known CVD) found that NRT was associated with an increased risk of any cardiovascular event (driven by a higher risk of less serious events, namely palpitations and arrhythmias) but not with a higher risk of major adverse cardiac events compared with placebo.⁵⁷ In another meta-analysis of seven trials of NRT (all excluding individuals with known heart disease), only nausea was more common with active NRT versus placebo.⁵⁸ In contrast, some studies have shown that smokeless tobacco use is associated with an increased incidence of fatal MI and higher mortality in patients with established coronary artery disease, suggesting that nicotine may contribute to acute (and potentially fatal) cardiovascular events in the presence of ischaemic heart disease.⁵⁹ Of note, because nicotine is absorbed more slowly from NRT delivery systems compared with the rapid absorption from conventional or e-cigarettes, and in view of slower absorption and lower peak nicotine levels in e-cigarette users compared with tobacco cigarette smokers, the results of NRT studies cannot be directly extrapolated to e-cigarette users. It should also be noted that the amount of nicotine delivered by e-cigarettes may vary substantially depending on several factors such as nicotine concentration in the e-cigarette liquid; user experience; puffing intensity and device characteristics (less nicotine delivered by first-generation compared with more recent devices).

The harmful cardiovascular effects of e-cigarettes have also been assessed indirectly, based on the documented toxicity of various constituents as well as on mechanistic studies investigating surrogate markers that are known to increase cardiovascular risk (Figure 2). A recent meta-analysis regarding haemodynamic effects of e-cigarettes included 14 non-randomised clinical studies of moderate quality ($N=441$ participants) among which 11 studies examined the acute effects of e-cigarettes on the cardiovascular system (5–30 minutes after use) and three studies after switching from tobacco smoking to chronic e-cigarette use (mean time point of assessment of 245 days).⁶⁰ The meta-analysis showed that exposure to e-cigarettes acutely increased heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure

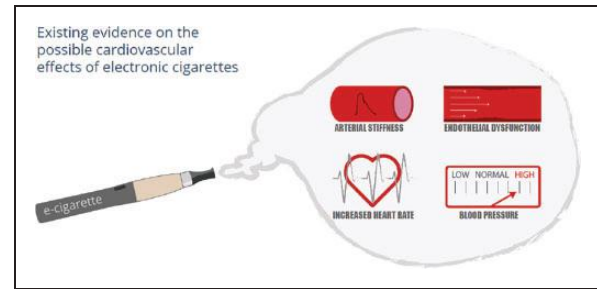


Figure 2. Existing evidence on the cardiovascular effects of e-cigarettes.

(DBP). While switching from tobacco smoking to chronic e-cigarette use did not affect HR, it significantly reduced both SBP and DBP.⁶⁰ Stimulation of atomised nicotine may also have a harmful long-term impact on vascular wall growth. In an observational study among 24 young smokers in four different smoking scenarios, e-cigarette smoking increased arterial stiffness (measured by carotid-femoral pulse wave velocity) 5 minutes after use.⁶⁰ Moreover, smoking e-cigarettes for more than 30 minutes had an adverse effect on arterial stiffness that was similar to that of traditional cigarettes.⁶⁰ However, e-cigarette use did not lead to increased arterial stiffness (assessed by a photoplethysmography method and analysis of pulse wave graph) in another study.⁶⁰ Mechanistically, a single dose of e-cigarettes aggravates endothelial cell dysfunction. Similar to conventional cigarettes, e-cigarettes have been shown to affect endothelial function adversely and decrease nitric oxide bioavailability.⁶¹ Relative to cigarette smoking, e-cigarette use has been associated with a comparable and rapid increase in the number of circulating endothelial progenitor cells, which could be attributed to acute endothelial dysfunction and/or vascular injury.⁶⁰ Emerging evidence suggests that nicotine, irrespective of its source, could impair vascular function and lead to vascular calcification. With respect to myocardial function, one study assessing left ventricular diastolic function and strain found a delay in myocardial relaxation following acute smoking inhalation, but no significant effects in daily users of e-cigarettes. In a case-control study among 23 apparently healthy, habitual e-cigarette users and 19 non-user controls, habitual e-cigarette use (for at least one year) was associated with increased levels of oxidative stress and a shift in cardiac autonomic balance toward sympathetic predominance,⁶² both known to be associated with higher cardiovascular risk. In another investigation, acute exposure to e-cigarettes containing nicotine was associated with increased cardiac sympathetic nerve activity compared with a sham control or non-nicotine e-cigarettes, in a pattern previously linked to

increased cardiac risk.⁶³ In addition to nicotine, other aerosol constituents that may exert adverse cardiovascular effects include oxidising chemicals and particulate matter (PM).⁵⁵ Fine and ultrafine particles (i.e. PM) are solid and liquid particles suspended in the air. PM with a diameter of approximately less than 2.5 µm can penetrate the airways and reach the circulation. Exposure to PM from ambient air pollution and tobacco smoking has been linked to higher risk of cardiovascular and all-cause mortality.⁶⁴ It has been shown that PM is not only present in e-cigarette vapours, but is also exhaled in significant levels by e-cigarette users. Thereby, although direct evidence regarding cardiovascular consequences of e-cigarette-derived PM is missing, it is likely that e-cigarettes pose a potential risk to users and represent a source of second-hand exposure to PM.

The available indirect evidence regarding the cardiovascular effect of e-cigarettes is currently based mainly on non-randomised observational studies of small sample sizes, overall moderate quality and short-term follow-up. A systematic review of cardiovascular effects from e-cigarettes included 38 studies. The review concluded that most studies suggest potential cardiovascular harm from e-cigarettes through mechanisms that increase the risk of thrombosis and atherosclerosis.⁷ Whether the described haemodynamic changes translate to a clinical risk of CVD remains uncertain, and interpretation of these findings requires caution. Collectively, while the long-term cardiovascular effects of e-cigarettes remain largely unknown, the existing evidence suggests that the e-cigarette should not be regarded as a cardiovascular safe product.⁶⁰ Moreover, on a population level, it is anticipated that the potentially 'decreased' harm induced by e-cigarettes (versus conventional tobacco smoking) may in part be offset by its increased use, in particular in more vulnerable populations such as the young.⁶⁵ A non-linear dose-response relationship exists between smoking and the risk of CVD and mortality, wherein light smoking (less than three cigarettes per-day), is associated with elevated rates of adverse health outcomes. Hence, it is hypothesised that increased e-cigarette use may ultimately not result in proportional harm reduction of cardiovascular mortality. At the population level, such adverse health effects are expected to increase by the widespread adoption of e-cigarettes for both active smoking and smoking cessation. The long-term effects of ever-increasing e-cigarette use rates particularly in adolescents and youth, together with potential lag time effects upon attributable CVD and mortality rates, ought to be closely monitored and preemptively addressed by public health authorities.

Knowledge gaps

- Prospective studies assessing the effects of e-cigarettes on clinical cardiovascular outcomes are lacking.
- Whether different patterns of e-cigarette smoking (with respect to age of onset, frequency and cumulative duration of use) exert differential cardiovascular effects is largely unknown.

Effects of e-cigarettes on smoking cessation in adults

E-cigarettes have been employed for facilitating smoking cessation attempts. However, their impact on successful smoking cessation has not been comprehensively addressed to date. The most recent Cochrane Systematic Review⁶⁶ analysed three randomised clinical trials (RCTs) and 21 cohort studies (combined sample size 662) regarding the effect of e-cigarette use on smoking cessation. One RCT compared nicotine patches, nicotine-releasing e-cigarettes and nicotine-free e-cigarettes. E-cigarettes, with or without nicotine, were modestly effective at helping smokers to quit, with similar achievement of abstinence as with nicotine patches.⁶⁷ One-year abstinence rates were higher in the e-cigarette users (smokers not intending to quit) compared with users of non-nicotine e-cigarettes in another RCT.⁶⁸ The RCTs were deemed to be at low risk of bias; however, overall quality of evidence was 'low' or 'very low' as a result of the small number of trials included.⁶⁶ Since then, two other RCTs have been performed. In a pragmatic RCT including more than 6000 smokers, free e-cigarettes were not superior to usual care or to free smoking cessation medication after one year.⁶⁹ On the other hand, a smoking cessation clinic based RCT found e-cigarettes to be more effective than NRT for smoking cessation, when both products were accompanied by intensive behavioural support. It is noteworthy that 80% of the study's participants continued to use e-cigarettes for more than 12 months.⁷⁰

RCTs are superior to observational studies with respect to internal validity. However, RCTs measure the relative effectiveness of e-cigarettes in specific groups of smokers under controlled circumstances. As e-cigarettes are readily available consumer products without clear instructions for use, observational studies could provide insight into the impact of e-cigarettes on smoking cessation as they are being used in real-world settings. The review of longitudinal studies regarding the impact of e-cigarette use on smoking cessation provides conflicting evidence.⁶⁶ An older systematic review of observational studies and RCTs suggests that adequate nicotine replacement through more frequent use

of e-cigarette could reduce nicotine withdrawal symptoms and therefore lead to better smoking cessation rates.⁷¹ However, a meta-analysis of 15 longitudinal real-world studies assessing smoking in e-cigarette users compared with those who did not use e-cigarettes reported a negative association between e-cigarette use and cessation.⁷² A more recent cohort of young Swiss men confirmed that e-cigarette use was not associated with beneficial smoking reduction and/or cessation effects at 15 months follow-up.⁷³ An American natural environment observational study found that dual users of e-cigarettes and cigarettes were more likely than cigarette smokers to quit cigarettes in the short term at 6 months, but no more likely to quit cigarettes over time at 12 or 18 months.⁷⁴ A large Italian survey comparing smoking abstinence rates for different quitting methods showed that e-cigarette users were as likely to report abstinence as those using no aid but less likely to report abstinence than users of established quitting methods.⁷⁵

On the other hand, a recent nationwide sample of 1400 college students showed that baseline e-cigarette users were more likely to report cessation of traditional cigarettes compared with non-users at 6 months' follow-up.⁷⁶ Furthermore, a retrospective survey showed that current e-cigarette use was associated with increased past 12-month successful smoking cessation.⁷⁷ At a population level, findings from an Italian cohort of e-cigarette users revealed that in the long term those reverting to smoking outnumbered those who successfully ceased smoking.⁷⁸ Evidence remains conflicting regarding the impact of e-cigarette use on long-term smoking cessation.⁷⁹

Cumulatively, the available evidence seems insufficient definitively to answer the question of whether e-cigarettes help smokers to quit and remain smoke-free in the long term. Imprecision in the measurement of e-cigarette exposure, inclusion of smokers not using e-cigarettes to quit, limited adjustment for confounding factors and variable outcome measures of cessation are among the limitations of the current studies.⁸⁰

The current findings suggest that the use of e-cigarettes for smoking cessation might increase abstinence rates in combination with behavioural therapy. The findings might suggest that e-cigarettes ought to be implemented in a clinical setting as part of intensive repeated counselling to have an effect but might undermine cessation for the clear majority of adult smokers who use e-cigarettes outside a smoking cessation clinic. Additional studies of high quality and in particular pragmatic randomised trials are urgently needed. Such studies ought to incorporate the frequency of e-cigarette use upon successful long-term smoking cessation.

Knowledge gap

- There is a lack of robust longitudinal data regarding the impact of e-cigarettes on smoking cessation.

Recommendations from the EAPC population science and public health section

- Health professionals should be cautious in recommending the use of e-cigarettes to their patients and the general public as: (a) mounting evidence suggests that e-cigarettes are harmful to health, including to the heart; (b) smokers might end up using e-cigarettes as a supplement to smoking without cutting back their tobacco consumption; (c) there is a lack of robust evidence that e-cigarettes are effective as a smoking cessation tool; (d) e-cigarettes seem to be used instead of evidence-based smoking cessation products and smoking cessation clinics.
- E-cigarette should only be considered to aid tobacco cessation alongside a formal tobacco cessation programme.
- Decision-makers should regulate e-cigarettes strongly or forbid their use as: (a) an epidemic rise in the use of e-cigarettes among non-smoking adolescents has been observed in some parts of the world, and we cannot rule out that this will spread to the rest of the world; (b) there is evidence that non-smoking children/youth using e-cigarettes might have an increased risk of the uptake of smoking of conventional cigarettes; (c) at population level, it seems that e-cigarettes may have an unfavourable net effect on smoking.
- Because of the rapidly evolving market, a regular update of the e-cigarette legislation is needed. Tobacco legislation revision, update and adaptation is needed in countries with legislation written before e-cigarettes came on the market.
- There should be strict regulation of e-cigarette marketing and advertising to youth. E-cigarette marketing and advertising in public places, all media, internet and social media should be governed by the same regulations as for tobacco, with the particular aim to protect the young. Strong age verification procedures are needed to prevent adolescents from accessing tobacco and e-cigarette websites.
- Similar to traditional cigarette smoking, abstinence of e-cigarettes during pregnancy should be recommended.
- Awaiting further scientific research, caution is needed when consuming e-cigarettes. Hence, the population should be made aware of the potential adverse effects. Media and social media campaigns

with effective messages/testimonials should be utilised to prevent the initiation of new e-cigarette smokers. In particular, the knowledge of the negative effects of e-cigarettes should be included during specific healthy lifestyle education programmes at schools.

- Government and non-government funding should be encouraged to support ethically and appropriately designed research investigating multiple subclinical and clinical effects of e-cigarette smoking on various systems, including the cardiovascular system.
- Researchers should apply standardised methodologies in studies assessing the surrogate or clinical effects of e-cigarettes to allow direct comparisons between the studies.
- Countries should be encouraged to follow the WHO Framework Convention on Tobacco Control (FCTC).

Conclusions

The prevalence of e-cigarette smoking is increasing, particularly in the young, and evidence suggests that this will increase the likelihood of conventional smoking. Some studies have found e-cigarettes to have harmful cardiovascular effects, but more studies in particular on long-term effects of e-cigarettes on cardiovascular outcomes are needed. Currently, there is a lack of robust longitudinal data on the impact of e-cigarettes on smoking cessation, and more research is warranted. Nonetheless, health professionals should inform their patients and the general public of the possible cardiovascular and other risks of e-cigarette smoking. Continued monitoring and legislation to limit use is important.

Author contribution

MLL and EBP contributed to the conception of the work. MK and MLL drafted the manuscript. All authors contributed to the design, acquisition, analysis and interpretation of the work. All authors critically revised the manuscript, gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

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