

## **Electronic cigarettes and health with special focus on cardiovascular effects**

Position Paper of the European Association of Preventive Cardiology (EAPC)

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**Word count: 10807**

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## **ABSTRACT**

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 last 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.

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 suggest that the e-cigarette should not be regarded as a cardiovascular safe product. The contribution of e-cigarette use to reduce conventional cigarette use and smoking cessation is complex and the impact of e-cigarette use on long-term cessation lacks sufficient evidence.

This position paper describes the evidence regarding 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. 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 (EAPC) are presented.

## INTRODUCTION

Despite widespread population-based anti-smoking policies, 28% of the adult population (aged ≥15 year) across Europe is still smoking.<sup>1</sup> The use of electronic cigarettes (e-cigarettes) has emerged and gained significant popularity in response to the well-known harmful effects of tobacco smoking,<sup>2</sup> although their safety is questioned.<sup>3</sup> 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.<sup>4</sup> Overall, there are two main types of e-cigarettes: 1) disposable and rechargeable devices that look like cigarettes and 2) refillable vaporizers or tank systems that do not look like cigarettes.<sup>5</sup> 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 carrier, and nicotine and flavors as the active substances.<sup>3</sup>

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 recognized is that an increasing number of children, adolescents, and adults are utilizing e-cigarettes.<sup>6</sup> 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 they are not harmless.<sup>3, 7-10</sup>

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. Whilst 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). The lung injury was associated with adding Vitamin E, which are likely to have a significant public health impact, but

remain outside the scope of our paper and hence not discussed in more detail.<sup>11</sup> 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**

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, that 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.<sup>12</sup> Additionally, response to questionnaires may depend on type and order of the questions asked.<sup>13</sup>

We have considered only the most recent prevalence data from 2015 to 2019. Older data can be found in several reviews.<sup>12, 14-18</sup> Results are summarized in **Table 1**. Prevalence of ever use ranged from 0% (Egypt) to 56.6% (Lithuania); prevalence of past 30-day users ranged from 2.0% (Switzerland) to 35.0% (Poland), and prevalence of daily users 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.<sup>19</sup> The most consistent finding is the increasing prevalence of e-cigarette use in adolescents and young individuals.<sup>20</sup>

### *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 is little 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 increase from 5% to up to 25% between 2013 and 2019.<sup>20-22</sup> **(Figure 1)**

One of the main arguments supporting e-cigarette introduction and uptake was to help with smoking cessation. Whilst this might be a sensible argument for adults, its role in supporting smoking cessation in the young is less well defined.<sup>23</sup> At the same time, while e-cigarette use might be safer compared to tobacco smoking, a worrying increase has been noted in the young who view e-cigarette as a new and safe «trend» and as a part of a «healthy life». Thus, e-cigarette can be easily 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.<sup>24-27</sup> The evidence is based on longitudinal observational studies, because randomized controlled trials to address this research question cannot ethically be performed due to the potential of causing harm.<sup>24-28</sup> Flavors are important when we talk about children and adolescents. They prefer sweet flavors and they believe that sweet flavors are less harmful.<sup>29</sup> Fruit, menthol or mint, and candy, desserts or other sweets are the most commonly reported flavors in e-cigarettes among youth. Therefore, these flavors should be banned.<sup>30</sup>

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.<sup>31</sup> Nicotine is harmful to the developing fetus and has several cardiovascular effects.<sup>32</sup> Maternal active smoking, maternal passive smoking as well as paternal smoking all increase the risk of fetal congenital heart defects in offspring.<sup>33</sup> Nicotine has been shown to increase placental vascular resistance and increase 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 apnea.<sup>34</sup> Likewise, e-cigarette use and secondary exposure have been linked with increased asthma attacks in the young.<sup>35</sup> 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 on in life, however more solid evidence for such a causative effect is awaited.<sup>36</sup>

Similar to the conventional tobacco legislations, selling e-cigarettes to anyone under the age of 18 is illegal in many countries, but the legislation is often ignored. Further, 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 of 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.<sup>37-39</sup>

E-cigarette is thus a new potential hazard for children and adolescents. Public health measures should thus be undertaken to minimize 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-cigarette, should encourage better prevention and decrease in the use of e-cigarette, an

«epidemic of youth use».<sup>40</sup> 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 to conventional smoking later in life. Due to the ethical considerations and the potential of causing harm, data from randomized controlled trials on this matter are lacking.
- Robust evidence regarding the influence of e-cigarettes on cognitive, visual and memory performances, and on attention among the youth is lacking. Similarly, no data exist regarding 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.<sup>41</sup> Also in 2016, the American 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.<sup>42</sup> 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 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<sup>43, 44</sup> and one website<sup>45</sup> summarize the existing data regarding legislation on e-cigarettes. Overall, legislation is available for 98 countries and varies considerably (**Table 2 and Table 3**).<sup>46</sup> 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-cigarettes regulation, although some improvements are under way.<sup>46</sup>

Only 13 countries apply a tax to e-cigarettes.<sup>45</sup> Twenty-nine countries ban e-cigarettes completely, and nine ban nicotine-containing liquids only (**Table 3**).<sup>46</sup> It is almost impossible to give updated information, due to quick changes in legislation. Still, the ban of nicotine-containing liquids can be easily circumvented via internet imports or in shops due to lack of enforcement of the ban.<sup>47</sup> Many websites selling e-cigarette products perform no age checking and fail to provide any information regarding use or health warnings.<sup>48</sup> Social media are utilized for promotional strategies and networking purposes, and social media influencers are brand ambassadors for e-liquid marketing.<sup>49</sup> Finally, advertisements for devices resembling e-cigarettes as delivering “nutritional supplements” have been issued, leading consumers to believe that e-cigarettes are health-enhancing.<sup>50</sup>

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.<sup>51</sup> Conversely, a study also

conducted in the US concluded that both higher prices and vaping restrictions are associated with less e-cigarette use.<sup>52</sup> The recent outbreak of lung disease related to e-cigarettes has prompted several US states and countries to ban flavored e-cigarettes and to increase tax on non-flavored cigarettes, and the FDA to issue an enforcement policy regarding flavored e-cigarettes.<sup>8, 53</sup>

The rapid evolution of the e-cigarette market has outpaced the legislator's regulatory capacity, leading to mixed regulations and possibly illegal actions. Harmonization and implementation of existing regulations is necessary, as well as 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 if no evidence of 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 adolescent and young adult are needed.

#### **EFFECT OF E-CIGARETTES ON CARDIOVASCULAR FUNCTION AND CARDIOVASCULAR DISEASE**

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.<sup>54</sup> Therefore, it is generally believed that the physiological effects of e-cigarettes are less harmful compared with tobacco cigarettes.<sup>54, 55</sup> However, e-cigarettes do contain potential toxicants and exert a variety of biologic

effects,<sup>55</sup> such that health-related sequelae linked to the exposure to nicotine as well as other components in the vapor 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 are 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 for myocardial infarction (MI) in e-cigarette users [odds ratio – OR (95% confidence interval – CI=1.79 (1.20, 2.66)], although to a lesser extent than conventional cigarette smoking [2.72(2.29, 3.24)].<sup>56</sup>

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 (NRT), or by estimating the levels of various known harmful substances in e-liquid and vapor/aerosol, 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 randomized trials including 11,647 patients (of which only 2 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.<sup>57</sup> In another meta-analysis of seven trials of NRT (all excluding individuals with known heart disease), only nausea was more common with active NRT vs. placebo.<sup>58</sup> In contrast, some studies have shown that smokeless tobacco use is associated with increased incidence of fatal MI and higher mortality in patients with established coronary artery disease (CAD), suggesting that nicotine may contribute to acute (and potentially fatal) cardiovascular events in the presence of ischemic heart disease.<sup>59</sup> 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 hemodynamic effects of e-cigarettes included 14 non-randomized 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 min after use) and 3 studies after switching from tobacco smoking to chronic e-cigarette use (mean time-point of assessment of 245 days).<sup>60</sup> The meta-analysis showed that exposure to e-cigarettes acutely increased heart rate (HR), systolic and diastolic blood pressure (SBP and DBP). While switching from tobacco smoking to chronic e-cigarette use did not affect HR, it significantly reduced both SBP and DBP.<sup>60</sup> Stimulation of atomized nicotine may also have a harmful long-term impact on vascular wall growth. In an observational study among 24 young smokers in 4 different smoking scenarios, e-cigarette smoking increased arterial stiffness (measured by carotid-femoral pulse wave velocity) 5 min after use.<sup>60</sup> Moreover, smoking e-cigarette for more than 30 minutes had an adverse effect on arterial stiffness that was similar to that of traditional cigarettes.<sup>60</sup> However, e-cigarette use did not lead to increased arterial stiffness (assessed by photoplethysmography method and analysis of pulse wave graph) in another study.<sup>60</sup> Mechanistically, a single dose of e-cigarette aggravates endothelial cell dysfunction. Similar to conventional cigarettes, e-cigarettes have been shown to adversely affect endothelial function and decrease nitric oxide bioavailability.<sup>61</sup> 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.<sup>60</sup> Emerging evidence suggest 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 nonuser controls, habitual e-cigarette use (for at least 1 year) was associated with increased levels of oxidative stress and a shift in cardiac autonomic balance toward sympathetic predominance,<sup>62</sup> both known to be associated with higher cardiovascular risk. In another investigation, acute exposure to e-cigarette containing nicotine was associated with increased cardiac sympathetic nerve activity compared with a sham control or non-nicotine e-cigarette, in a pattern previously linked to increased cardiac risk.<sup>63</sup> In addition to nicotine, other aerosol constituents that may exert adverse cardiovascular effects include oxidizing chemicals and particulate matter (PM).<sup>55</sup> Fine and ultrafine particles (i.e., PM) are solid and liquid particles suspended in the air. PM with a diameter of  $\leq 2.5 \mu\text{m}$  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.<sup>64</sup> It has been shown that PM are not only present in e-cigarette vapors, but are 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-randomized 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 risk of thrombosis and atherosclerosis.<sup>7</sup> Whether the described hemodynamic 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 suggest that the e-cigarette should not be regarded as a cardiovascular safe product.<sup>60</sup> Moreover, on a population level, it is anticipated that the potentially “decreased” harm induced by e-cigarette (versus conventional tobacco smoking) may in part be offset by its increased use, in particular in more vulnerable populations such as the young.<sup>65</sup> A nonlinear dose-response relationship exists between smoking and the risk of CVD and mortality, wherein light smoking (<3 cigarettes per-day), is associated with elevated rates of adverse health outcomes. Hence, it is hypothesized 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-cigarette 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 upon successful smoking cessation has not been comprehensively addressed to date. The most recent Cochrane Systematic Review<sup>66</sup> analyzed 3 randomized 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.<sup>67</sup> 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.<sup>68</sup> 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.<sup>66</sup> 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.<sup>69</sup> 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 behavioral support. It is noteworthy that 80% of the study's participants continued to use e-cigarettes for >12 months.<sup>70</sup>

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.<sup>66</sup> An older systematic review of observational studies and RCTs suggest that adequate nicotine replacement through more frequent use of e-cigarette could reduce nicotine withdrawal symptoms and therefore lead to better smoking cessation rates.<sup>71</sup> 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.<sup>72</sup> 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.<sup>73</sup> 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.<sup>74</sup> 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.<sup>75</sup>

On the other hand, a recent nationwide sample of 1,400 college students showed that baseline e-cigarette users were more likely to report cessation of traditional cigarettes compared to non-users at 6-months' follow-up.<sup>76</sup> Further, a retrospective survey showed that current e-cigarette use was associated with increased past-12-month successful smoking cessation.<sup>77</sup> On 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.<sup>78</sup> Evidence remains conflicting regarding the impact of e-cigarette use on long-term smoking cessation.<sup>79</sup>

Cumulatively, the available evidence seems insufficient to definitively answer the question of whether e-cigarettes help smokers to quit and remain smoke-free in the long term. Imprecision in 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.<sup>80</sup>

The current findings suggest that use of e-cigarettes for smoking cessation might increase abstinence rates in combination with behavioral therapy. The findings might suggest that e-cigarettes ought to be implemented in a clinical setting as part of an 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 randomized trials are urgently needed. Such studies ought to incorporate the frequency of e-cigarette use upon successful long-term smoking cessation.

#### *Knowledge gaps*

- 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

1. Health professionals should be cautious in recommending use of e-cigarettes to their patients and the general public as: 1) mounting evidence suggests that e-cigarettes are harmful to health, including to the heart, 2) smokers might end up using e-cigarettes as a supplement to smoking without cutting back their tobacco consumption, 3) there is lack of robust evidence that e-cigarettes are effective as smoking cessation tool, 4) e-cigarettes seem to be used instead of evidence-based smoking cessation products and smoking cessation clinics.
2. E-cigarette should only be considered to aid tobacco cessation alongside a formal tobacco cessation program.
3. Decision makers should regulate e-cigarettes strongly or forbid their use as: 1) an epidemic rise in 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, 2) there is evidence that non-smoking children/youth using e-cigarettes might have an increased risk of uptake of smoking of conventional cigarettes, 3) at population level, it seems that e-cigarettes may have an unfavorable net effect on smoking.
4. 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.
5. 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 particular aim to protect the young. Strong age verification procedures are needed to prevent adolescents from accessing tobacco and e-cigarettes websites.
6. Similar to traditional cigarette smoking, abstinence of e-cigarette during pregnancy should be recommended.

7. Awaiting further scientific research, caution is needed when consuming e-cigarettes. Hence, the population should be made aware of potential adverse effects. Media and social media campaigns with effective messages/testimonials should be utilized to prevent initiation of new e-cigarette smokers. In particular, the knowledge of the negative effects of e-cigarette should be included during specific healthy lifestyle education programs at school.
8. 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.
9. Researchers should apply standardized methodologies in studies assessing surrogate or clinical effects of e-cigarettes to allow direct comparisons between the studies.
10. 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 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.

## FIGURE LEGENDS

**Figure 1.** Longitudinal trend in e-cigarette and tobacco use in pupils aged 11-18 years in the United States between 2011 and 2018.

**Figure 1.** Data used with permission from Cullen KA, Ambrose BK, Gentzke AS et al. Notes from the field: use of electronic cigarettes and any tobacco product among middle and high school students - United States, 2011-2018. *MMWR Morb Mortal Wkly Rep.* 2018;67:1276-7.<sup>20</sup>

## TABLES

**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
<b>Americas</b>					
Brazil <sup>81</sup>	2015	Students of the Federal University of Mato Grosso	489	NR	2.7% ever users 0.61% current users
Canada <sup>82</sup>	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 <sup>83</sup>	2015	Canadian Tobacco Alcohol and Drugs	15,154	15+	13.2% ever users 3.2% past 30-day users 0.8% daily users
Mexico <sup>84</sup>	2015	Stratified random sampling of schools in Mexico City, Guadalajara, and Monterrey	10,146	12-13	10% ever users
Mexico <sup>85</sup>	2016	National Survey of Drugs, Alcohol and Tobacco Use	12,436	12-17	7.0% ever users 1.1% current users
Mexico <sup>85</sup>	2016	National Survey of Drugs, Alcohol and Tobacco Use	36,966 non-smokers	18+	3.0% ever users 0.3% current users
Mexico <sup>85</sup>	2016	National Survey of Drugs, Alcohol and Tobacco Use	7,347 smokers	18+	18.0% ever users 5.0% dual users
USA <sup>86</sup>	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 <sup>87</sup>	2015		17,711	<18	4.8% (middle school) and 12.8% (high school) past 30-day users
USA <sup>88</sup>	2015	National Youth Tobacco Survey Tobacco Products and Risk Perceptions Survey	6,008	18+	17.0% ever users 7.4% current users 1.7% daily users
USA <sup>89</sup>	2015	Health Information National Trends Survey	3,738	18+	22.4% ever users
USA <sup>90</sup>	2016	Behavioral Risk Factor Surveillance System	466,842	18+	4.5% current users 1.5% daily users
USA <sup>91</sup>	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 <sup>92</sup>	2016	National Health Interview Survey	32,931	18+	15.3% ever users 3.2% current users
USA <sup>93-95</sup>	2018	Monitoring the Future	13,850	NR	Past 30-days users 25.0% (12 <sup>th</sup> grade) 20.3% (10 <sup>th</sup> grade) 8.1% (8 <sup>th</sup> grade)
<b>Eastern Mediterranean</b>					
Egypt <sup>96</sup>	2015	Cross-sectional community survey	1239	15-75	0% ever users
Saudi Arabia <sup>97</sup>	Nov-Dec 2017	Three universities in Jeddah	1007	15+	27.7% ever users 4.1% daily users 4.4% mixed smoker/vaper
<b>Western Pacific</b>					
Australia <sup>98</sup>	Feb 2016	New South Wales	3,188	18+	13.0% ever users 4.0% past 30-day users

						0.5% daily users
China <sup>99</sup>	2015	Mobile app-based survey	2,042	12-18	26.4% ever users	
Japan <sup>100</sup>	2015	Japan "Society and New Tobacco" Internet Survey	8,240	15-69	1.3% past 30-day users	
Korea <sup>101</sup>	2015	middle and high school students from Seoul, Incheon, Gyeonggi, and Cheongju	2,744	13-18	12.6% ever users 6.3% past 30-day users 4.9% past 30-day dual users	
Korea <sup>101</sup>	2015	University students from fourteen universities	2,167	19-29	21.2% ever users 7.2% past 30-day users 5.9% past 30-day dual users	
Malaysia <sup>102</sup>	2016	National E-cigarette survey	4,288	18+	11.9% ever users 3.2% current 2.3% dual users	
New Zealand <sup>103, 104</sup>	2016	Health and Lifestyles Survey	3,854	15+	17.0% ever users 1.8% current users 1.0 daily users	
Taiwan <sup>105</sup>	2014-2016	Taiwan Global Youth Tobacco Survey	NR	12-18	3.1% past 30-day users 1.6% dual users	
Taiwan <sup>106</sup>	2015	Adult Smoking Behavior Survey.	26,021	15+	2.7% ever users	
<b>Europe</b>						
Belarus <sup>107</sup>	2017-2018	University students	3,895	19.3±2.1	42.7% ever users 2.7% current users 2.0% dual users	

France <sup>108</sup>	2014-2015	Cross-sectional study on two major campuses	1,134	20.8 years	23.0% ever users 5.7% current users
Germany <sup>109</sup>	2015	Epidemiological Survey of Substance Abuse	9,204	18-64	14.3% ever users 2.9% past 30-day users 2.1% dual users
Germany <sup>110</sup>	2016	Representative surveys on substance use conducted by the Federal Center for Health Education	2,462	18-25	7.6% (male) and 3.4% (female) past 30-day users <sup>5</sup>
Germany <sup>110</sup>	2016	Representative surveys on substance use conducted by the Federal Center for Health Education	2,459	12-17	4.2% (male) and 2.5% (female) past 30-day users <sup>5</sup>
Germany <sup>111</sup>	2016	Random sample	4,002	14+	11.8% ever users 1.4% regular users
Greece <sup>112</sup>	2017	adults living in Attica prefecture	4,058	18+	27.2% ever users 5.0% current use
Lithuania <sup>107</sup>	2017-2018	University students	1,128	19.8±1.3	56.6% ever users 3.5% current users 2.1% dual users
Poland <sup>70</sup>	2015-2016	National Adult Tobacco Survey	1,978	15-19	35.0% past 30-day users 24.0% past 30-day dual users
Poland <sup>107</sup>	2017-2018	University students	7,324	21.9±2.1	45.0% ever users 2.8% current users 1.5% dual users
Russia <sup>48</sup>	2015	Students of the Republic of Bashkortostan	716	15+	28.6% ever users 2.2% past 30-day users

Russia <sup>107</sup>	2017-2018	University students	1,290	20.4±2.2	33.4% ever users 4.0% current users 2.6% dual users
Serbia <sup>113, 114</sup>	December 2017	three stage, random, nationally representative survey	1,045	18+	10.7% ever users 0.2% daily users
Slovakia <sup>107</sup>	2017-2018	University students	715	22.5±1.8	34.4% ever users 2.3% current users 2.6% dual users
Spain <sup>115</sup>	2015	Sistema de Información sobre Conductas de Riesgo	7,908	15+	5.3% ever users 0.7% current users
Spain <sup>116</sup>	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
Sweden <sup>117</sup>	2016	Schools of the Scania region	13,835	14-21	9 <sup>th</sup> grade 32% (males) and 27% (females) ever users 10.8% (males) and 7.0% (females) past 30-day users 2 <sup>nd</sup> grade 43% (males) and 31% (females) ever users 11.1% (males) and 5.0% (females) past 30-day users
Switzerland <sup>118</sup>	July-Dec 2015	Continuous Rolling Survey of Addictive Behaviours and Related Risks	5,252	15+	14.0% ever users 2.0% past 30-day users 0.3% daily users

The Netherlands <sup>119</sup>	2014-2015	19 secondary schools randomly selected across the Netherlands	6,819	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 <sup>119</sup>	2016-2017	Traditional and Novel Substance use among Adolescents study	2,758	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) <sup>120</sup>	2015	87 Secondary schools in Wales.	32,479	11-16	18.5% ever users 1.4% daily users
UK <sup>121</sup>	2015-2016	Smoking Toolkit Study	81,063	16+	5.5% current users
UK <sup>106</sup>	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

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

Current use is defined as either daily or occasionally.

Abbreviations: NR, not reported.

**Table 2.** Details of the legislation regarding e-cigarettes, as of April 2019. Countries who have a complete ban are not represented.

Country	Advertising	Minimum age	Child proof packaging	Health warning label	Nicotine vol./concentr.	Vape-free public places
<b>Europe</b>						
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

**Africa**

South Africa	-	-	-	-	-	-	-
Togo	Yes	Yes					Yes

**Americas**

Barbados, Jamaica							Yes
Canada, Mexico	Yes						
Chile	-	-	-	-	-	-	-
Costa Rica, Ecuador, Haiti, Honduras	Yes	Yes					Yes
USA	Yes	Yes	Yes	Yes			
Venezuela	Yes						Yes

**South-East Asia, Eastern Mediterranean, Western Pacific**

Australia	Yes						Yes
Fiji, Republic of Korea, Viet Nam	Yes	Yes					Yes
Japan, New Zealand	Yes						
Malaysia		Yes					
Philippines			Yes				Yes

DPR Korea, Tunisia,  
China, Hong Kong

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-, no data available. Empty cell indicates no such topic.

Countries are categorized according to the WHO geographical areas, with a further division for European countries. <sup>43-45</sup>

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.

**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	Authorization required
Belgium	Existing		Medicinal, consumer good	Authorization required
Bulgaria				Authorization required
Croatia	Existing	Tobacco (imitation)	Consumer good, chemical product	Authorization required
Cyprus				Authorization required
Czech Republic	Existing	Tobacco (imitation)	Medicinal, consumer good, hazardous substance	Authorization required
Denmark	Existing & new	E-cigarette	Medicinal	Authorization required
Estonia	New	Tobacco-related product E-cigarette		Authorization required
Finland	New	Tobacco (imitation), tobacco-related product, E-cigarette	Medicinal	Authorization required
France	Existing & amended	E-cigarette	Medicinal, consumer good	Authorization required
Germany	New	Tobacco-related product E-cigarette	Consumer good	Authorization required
Greece	Amended	Tobacco-related product	Consumer good	Authorization required

		E-cigarette		
Hungary	Amended		Consumer good	Authorization required
Ireland	Existing & new	E-cigarette	Medicinal, consumer good	Authorization required
Italy	Amended	Tobacco-related product E-cigarette		Authorization required
Latvia	New	Tobacco-related product E-cigarette		Authorization required
Lithuania	New	Tobacco-related product E-cigarette		Authorization required
Luxembourg	Existing		Poison, electrical appliance	Authorization required
Malta	Legal notice	Tobacco-related product E-cigarette		Authorization required
Netherlands	Existing	Tobacco-related product E-cigarette	Medicinal, consumer good	Authorization required
Poland	New		Chemical mixture, Consumer good	Authorization required
Portugal	Existing	E-cigarette		Authorization required
Romania				Authorization required
Slovakia	Amended	Tobacco	Tobacco-free product intended to smokers	Authorization required
Slovenia				Authorization required

Spain	Amended	ENDS		Permitted, regulated
Sweden				Authorization 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 E-cigarette	Medicinal	Authorization required
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	Authorization required
Africa				
Gambia				Complete ban
Mauritius	Existing	Tobacco (imitation)		Complete ban

Seychelles	Existing	Tobacco (imitation)		Complete ban
South Africa	Ruling		Medicinal	Authorization 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

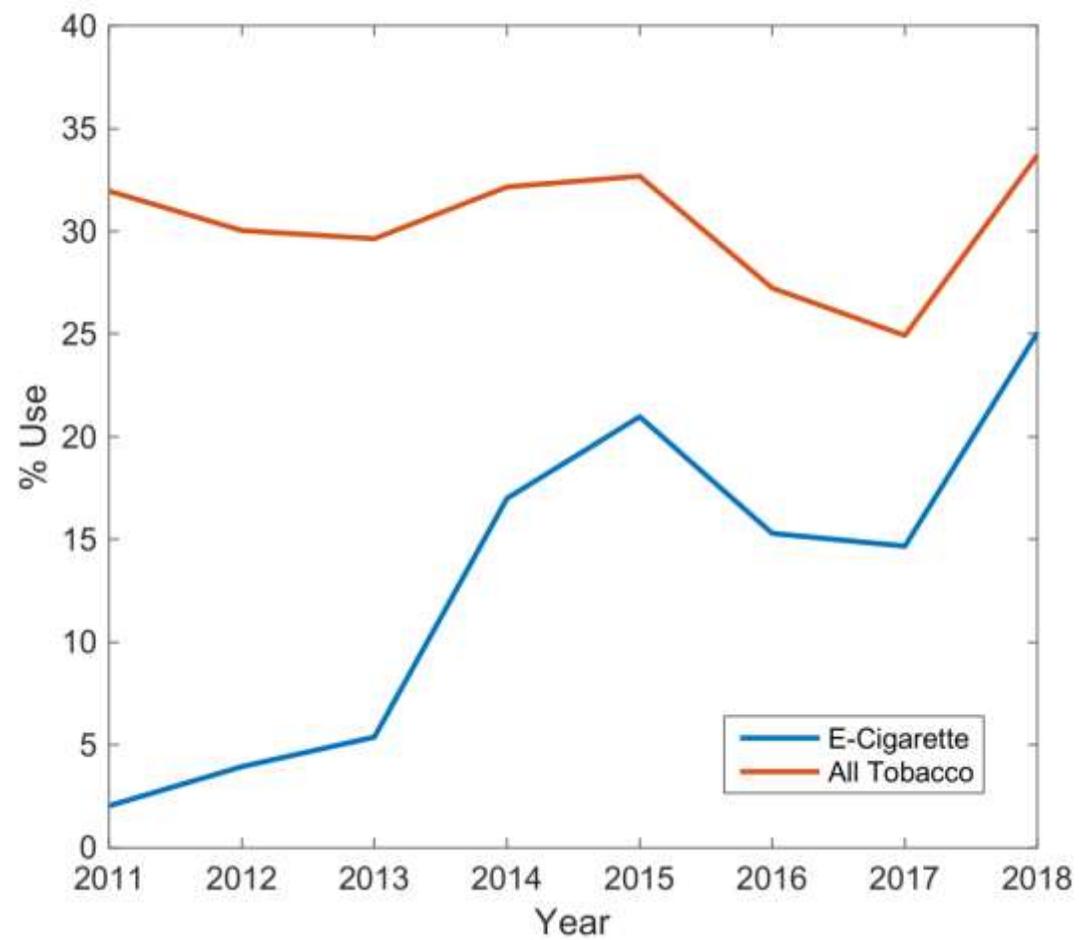
USA	New	Tobacco product		Permitted, regulated
Uruguay	Amendment/decreed	Electronic smoking device		Complete ban
Venezuela	Existing	Tobacco (derivative)	Medicinal, consumer good	Permitted, regulated
South-East Asia				
DPR Korea				Permitted, regulated
Nepal	Notification	ENDS		Complete ban
Thailand	Existing	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				Authorization 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		Authorization 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	Authorization required
Republic of Korea	Existing & amended	Tobacco	Consumer good	Unclear
Singapore	Existing	Tobacco (imitation)		Complete ban
Timor-Leste	New	E-cigarette		Complete ban
Viet Nam	Existing	Tobacco		Permitted, regulated

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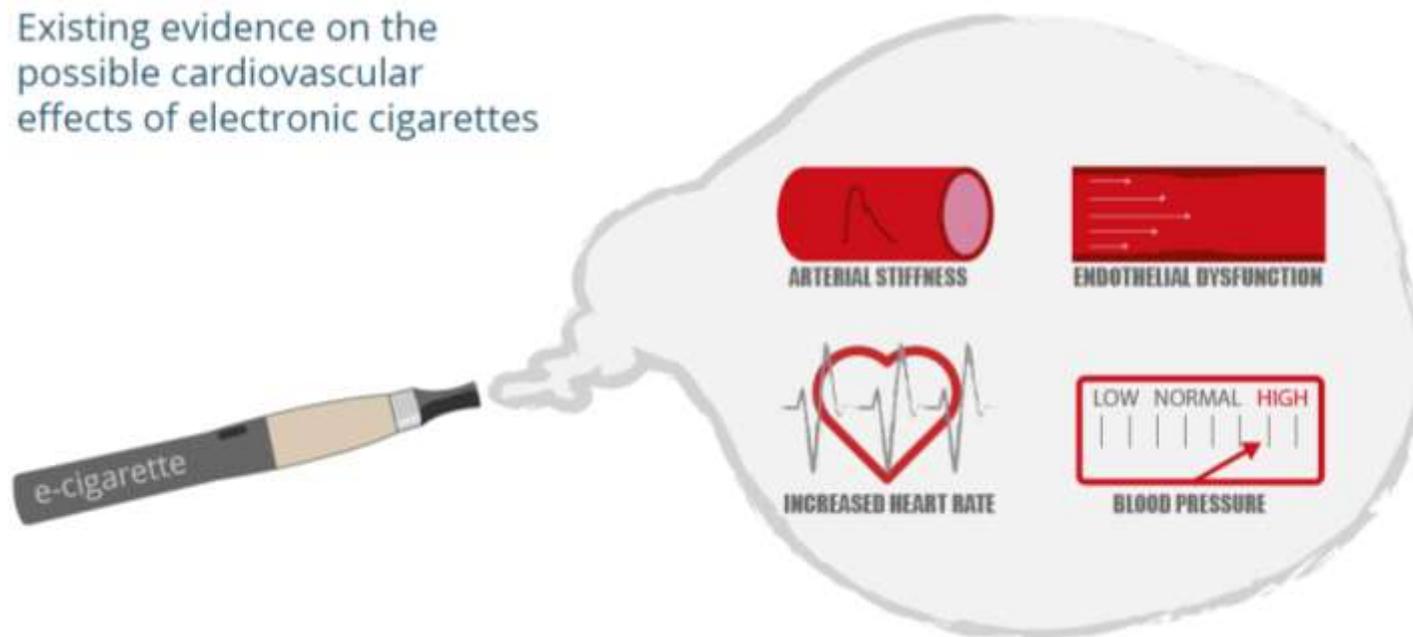
ENDS, electronic nicotine delivery systems. Countries are categorized according to the WHO geographical areas, with a further division for European countries.<sup>43-45</sup>

**Figure 1.** Longitudinal trend in e-cigarette and tobacco use in pupils aged 11-18 years in the United States between 2011 and 2018.



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

Existing evidence on the possible cardiovascular effects of electronic cigarettes



**AUTHOR CONTRIBUTION**

MLL and EBP contributed to the conception of the work. MK and MLL drafted the manuscript. All authors contributed to 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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