



fighting heart disease  
and stroke  
european heart network

## **Electronic cigarettes and cardiovascular disease – an update from the European Heart Network**

*November 2019*

### **Summary**

The role and impact of electronic cigarettes continues to provoke a major public health debate in Europe and beyond.

This paper has a focus on the effects of e-cigarette use on the cardiovascular system. It also presents information on trends in use of e-cigarettes, as well as marketing and regulation, and it discusses the distinction between absolute and relative risk.

The paper does not cover the so-called “heat-not-burn” tobacco devices. EHN will review the evidence of these products and publish it in a separate paper.

### ***Effects of e-cigarettes on the cardiovascular system***

With respect to the short-term impact of e-cigarette use on the cardiovascular system, the evidence is mixed. However, short-term e-cigarette use is likely less harmful to the cardiovascular system than smoking conventional cigarettes.

Long-term effects on the cardiovascular system are unknown. The lack of evidence for long-term effects, however, cannot be interpreted as no effect.

There is an urgent need for more studies to elucidate long-term effects of e-cigarette use on the cardiovascular system as well as whether e-cigarette use is less hazardous to cardiovascular health than conventional cigarette smoking in the longer term.

In the meantime, and based on the evidence that is currently available, it can be concluded that e-cigarette use is of real cardiovascular health concern.

### ***Use of E-cigarettes***

E-cigarettes are promoted as risk-reducing products compared to combustible tobacco cigarettes, and there is conclusive evidence that completely substituting e-cigarettes for combustible tobacco cigarettes reduces users’ exposure to numerous toxicants and carcinogens present in combustible tobacco cigarettes. There is also substantial evidence that completely switching from regular use of combustible tobacco cigarettes to e-cigarettes results in reduced short-term adverse health outcomes in several organ systems. But combustible tobacco cigarettes are arguably the most dangerous products that can be bought legally, and while e-cigarettes lack tar, one of the most toxic and extensively studied components of cigarettes, they

do produce toxic substances, mainly flavours, not found in cigarettes, that are much less well understood.

While a key benefit of e-cigarettes for both individuals and for public health would be to aid smoking cessation among people who smoke conventional cigarettes, there is not sufficient evidence that e-cigarettes are effective as a smoking cessation aid.

Dual users of e-cigarettes and combustible tobacco cigarettes will not reduce their health risks. They may even increase it. A majority of users of e-cigarettes (up to 90%) continue to smoke combustible tobacco cigarettes.

People, and in particular young people who have never smoked, are increasingly taking up e-cigarette use. This is also the case for those who previously quit smoking. Both groups are at substantial risk of (re-)starting smoking. Certain flavours in e-cigarettes are specifically attractive to children and young people.

Interpretation of the evidence of level of risk of e-cigarettes is complicated by extensive conflicts of interest. 95% of papers that did not involve conflicts of interest found potentially harmful effects of e-cigarettes, whereas industry-related conflict of interest was strongly associated with a finding of no harm.

When evaluating the pros and cons of e-cigarettes, it is important to consider their impact on the whole population, not only on the smokers, who are a minority. From a public health point of view, these products may have an unfavourable net effect, especially because of rising uptake by never smokers.

Considering the very high burden of cardiovascular disease in Europe, the mere possibility that e-cigarette use increases the risk of cardiovascular disease is a cause of concern.

All in all, there is every reason to be extremely cautious about e-cigarettes.

### ***Recommendations***

#### New recommendations

- There is a need for longitudinal studies to elucidate long-term effects of e-cigarette use on the cardiovascular system and whether e-cigarette use is less hazardous to cardiovascular health than conventional cigarette smoking in the longer term.
- Medical journals should refrain from publishing studies that are partly or fully funded by entities that have an industry-related conflict of interest.
- Health professionals should inform patients and the public of the risks related to e-cigarette use.
- Flavours should be prohibited. This should certainly be the case for those flavours that may not be safe and those that are likely to attract children and young people.

#### Revised recommendations

- The same buying restrictions and age limits should be set for e-cigarettes as for conventional cigarettes.

- Restrictions on marketing, including advertising, labelling and packaging, of e-cigarettes should be the same as for conventional cigarettes.
- The use of e-cigarettes in public places should be prohibited. Given the fact that second-hand exposure has some impact on bystanders' health, that use of e-cigarettes may make it more complicated to enforce smoke-free legislation, and that use of e-cigarettes may change the norm in terms of use of conventional cigarettes in public places, e-cigarette use in public places should be prohibited.
- Tax measures should be used as appropriate: applying a special excise duty or tax on e-cigarettes has the dual benefit of discouraging use – especially for young people – and raising income for governments. EHN recommends taxing e-cigarettes at a rate high enough to discourage uptake.

## Aim

In November 2016, the European Heart Network (EHN) published a paper presenting data and information with respect to the effect of electronic cigarettes (e-cigarettes) on health, especially cardiovascular health. In its 2016 paper, EHN concluded that it was reasonable to assume that if existing smokers switched completely from conventional cigarettes to e-cigarettes there would be a lower disease burden caused by nicotine addiction. We underlined that e-cigarettes were not harmless, and that the precautionary principle would dictate that it is desirable to limit use and uptake, in particular among children and young people.

Since our 2016 paper, several studies have been published on the impact of e-cigarette use on the cardiovascular system. The aim of this paper is to draw attention to the current body of evidence and provide our recommendations for regulation on e-cigarettes.

## Cardiovascular disease

Cardiovascular disease (CVD) – the main forms of which are coronary heart disease and stroke – is the main cause of death in Europe as well as in the European Union (EU), where it is responsible for 3.9 million and 1.8 million deaths respectively every year.<sup>1</sup> CVD is also a major cause of disability and a significant economic burden across the EU, estimated to cost the EU economy almost 210 billion euros every year.<sup>2</sup>

Leading risk factors for CVD are tobacco use, high blood pressure, high cholesterol, overweight and obesity, physical inactivity, diabetes, unhealthy diets, and harmful use of alcohol. It is estimated that smoking is responsible for over 19% of all cardiovascular deaths in Europe (almost 750 000 deaths) and 13.6% in the European Union (almost 245 000 deaths).<sup>3</sup>

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<sup>1</sup> Wilkins, E. *et al.* European Cardiovascular Disease Statistics 2017. *European Heart Network* (2017)

<sup>2</sup> Wilkins, E. *et al.* European Cardiovascular Disease Statistics 2017. *European Heart Network* (2017)

<sup>3</sup> Data from the Global Burden of Disease database (2017) <https://vizhub.healthdata.org/gbd-compare/>

## Introduction

The role and impact of electronic cigarettes continues to provoke a major public health debate in Europe and beyond.

In 2015, Public Health England (PHE) published a report presenting an update of the evidence for e-cigarettes. This report concluded, in a nutshell, that e-cigarettes were 95% less harmful to health than conventional cigarettes, and that when supported by a smoking cessation service, they could help most smokers to quit tobacco altogether.<sup>4</sup> The claim by PHE in 2015 that e-cigarettes were 95% less harmful to health than conventional cigarettes has been questioned by several researchers<sup>5</sup> and institutions.<sup>6</sup> Criticisms included how the authors of the paper, on which the claim was derived, conceded that they had little or no empirical evidence, as well as serious concerns about conflicts of interest.

In 2018, PHE published a new review of evidence on e-cigarettes and heated tobacco products. Despite the criticisms, PHE maintained the 95% less harmful claim. In terms of cardiovascular disease, the 2018 PHE report stated that “*comparative risks of cardiovascular disease [and lung disease] have not been quantified...*” but then, despite the absence of any quantification, concluded that these products “*...are likely to be also substantially below the risks of smoking.*”<sup>7</sup> Others have concluded that, on the basis of the short-term effects that have been identified to date, e-cigarettes likely have cardiovascular [and non-cancer lung] disease risks similar to those associated with smoking conventional cigarettes.<sup>8</sup>

This paper has a specific focus on the effects of e-cigarette use on the cardiovascular system, presenting results of studies, many of which were published after publication of our 2016 paper.<sup>9</sup> But we also present developments in use of e-cigarettes, as well as marketing and regulation, and discuss the distinction between absolute and relative risk. We draw extensively on a 2018 report from the National Academies of Sciences, Engineering, and Medicine (NASEM) on *Public health consequences of e-cigarettes*.<sup>10</sup> We have also consulted the separate extensive review by the Australian CSIRO.<sup>11</sup>

The paper does not cover the so-called “heat-not-burn” tobacco devices. EHN will review the evidence of these products and publish it in a separate paper.

## Effects of e-cigarettes on the cardiovascular system

A number of studies suggest harmful cardiovascular effects from e-cigarette use or exposure.

Below we set out how and through which mechanisms e-cigarette use impacts on the cardiovascular system.

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<sup>4</sup> E-cigarettes: an evidence update: a report commissioned by *Public Health England* (2015)

<sup>5</sup> McKee, M. *et al.* Evidence about electronic cigarettes: a foundation built on rock or sand? *British Medical Journal* 351:h4863 (2015)

<sup>6</sup> Editorial. E-cigarettes: Public Health England’s evidence-based confusion. *The Lancet* 386 (2015)

<sup>7</sup> Evidence review of e-cigarettes and heated tobacco products 2018 A report commissioned by *Public Health England* (2018)

<sup>8</sup> Glantz, S.A. *et al.* E-Cigarettes: Use, Effects on Smoking, Risks, and Policy Implications. *Annu Rev Public Health* 39, 215–235 (2018)

<sup>9</sup> Electronic cigarettes and cardiovascular diseases – a European Heart Network paper. *European Heart Network* (2016)

<sup>10</sup> National Academies of Sciences, Engineering, and Medicine. *Public health consequences of e-cigarettes*. Washington, DC: *The National Academies Press*. (2018)

<sup>11</sup> Byrne, S. *et al.* E-cigarettes, smoking and health. A Literature Review Update. *CSIRO Australia* (2018)

We underline that conclusions about insufficient or limited evidence do not necessarily indicate that there is no harm. They are often drawn because too few studies have investigated the particular issues.

### *Heart rate*

A 2018 report from NASEM concluded that there is substantial evidence that heart rate increases shortly after nicotine intake from e-cigarettes.<sup>12</sup>

A systematic review from 2019 published in the *European Journal of Preventive Cardiology* is unclear on the impact on heart rate, stating that findings are inconsistent or conflicting but also that a meta-analysis suggested negative acute effects of e-cigarette use on heart rate.<sup>13</sup>

Studies, not included in either of the two studies referenced above, found significant increases in heart rate and significant increases in pulse wave velocity after e-cigarette use (human studies).<sup>14,15,16</sup>

From this we conclude:

***There is good evidence that heart rate increases shortly after nicotine intake from e-cigarettes.***

### *Blood pressure*

The 2018 NASEM report concluded that there is moderate evidence that diastolic blood pressure increases shortly after nicotine intake from e-cigarettes.<sup>17</sup>

But overall, findings on the impact on blood pressure of e-cigarette use are conflicting<sup>18</sup>, and there is limited evidence on the short-term increase in systolic blood pressure.<sup>19</sup>

From this we conclude:

***There is limited evidence of short-term increases in blood pressure after nicotine intake from e-cigarettes.***

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<sup>12</sup> National Academies of Sciences, Engineering, and Medicine. *Public health consequences of e-cigarettes*. Washington, DC: The National Academies Press. (2018)

<sup>13</sup> Skotsimara, G. *et al.* Cardiovascular effects of electronic cigarettes: A systematic review and meta-analysis. *European Journal of Preventive Cardiology*. (2019) [Epub ahead of print]

<sup>14</sup> Franzen, KF, *et al.* E-cigarettes and cigarettes worsen peripheral and central hemodynamics as well as arterial stiffness: A randomized, double-blinded pilot study. *Vascular Medicine* 23(5),419-425 ( 2018)

<sup>15</sup> Ikonomidis, I. *et al.* Electronic Cigarette Smoking Increases Arterial Stiffness and Oxidative Stress to a Lesser Extent Than a Single Conventional Cigarette: An Acute and Chronic Study. *Circulation* 137, 303–306 (2018)

<sup>16</sup> Chaumont, M. *et al.* Differential Effects of E-Cigarette on Microvascular Endothelial Function , Arterial Stiffness and Oxidative Stress : A Randomized Crossover Trial. *Sci Rep* 8, 1-9 (2018)

<sup>17</sup> National Academies of Sciences, Engineering, and Medicine. *Public health consequences of e-cigarettes*. Washington, DC: The National Academies Press (2018)

<sup>18</sup> Skotsimara, G. *et al.* Cardiovascular effects of electronic cigarettes: A systematic review and meta-analysis. *European Journal of Preventive Cardiology*. (2019) [Epub ahead of print]

<sup>19</sup> Skotsimara, G. *et al.* Cardiovascular effects of electronic cigarettes: A systematic review and meta-analysis. *European Journal of Preventive Cardiology*. (2019) [Epub ahead of print]

## *Oxidative stress, endothelial function and arterial stiffness*

The 2018 NASEM report concluded that there is limited evidence that e-cigarette use is associated with a short-term increase in changes in biomarkers of *oxidative stress*, increased *endothelial dysfunction* and *arterial stiffness*.

The 2019 systematic review published in the European Journal of Preventive Cardiology concluded that there is evidence, though so far limited, that e-cigarette use adversely affects endothelial function and contributes to arterial stiffness.

Individual studies, all but one not included in either of the two studies referenced above, found:

- significant *oxidative stress* after e-cigarette use (human studies).<sup>20,21,22</sup>
- that e-cigarette use is associated with statistically significant changes similar to cigarette smoking in terms of increased *endothelial dysfunction* and cardiovascular morbidity (in vitro study).<sup>23,24,25</sup>
- that e-cigarette use significantly reduced *cell metabolic activity*<sup>26</sup> and increased *barrier disruption*.<sup>27</sup> Normal endothelial metabolic activity is impaired in several cardiovascular pathologies such as heart failure, whilst pro-atherogenic factors may contribute to increased endothelial barrier permeability and consequent increased cardiovascular risk (in vitro study).
- statistically significant increases in pulse wave velocity (a measure of *arterial stiffness* associated with increased risk of cardiovascular disease<sup>28</sup>) in mice after long-term e-cigarette vapour inhalation.

A study from June 2019<sup>29</sup> suggests that acute exposure to *flavoured e-liquids or e-cigarette use* exacerbate *endothelial dysfunction*, which often precedes cardiovascular diseases. The study found that cinnamon and menthol flavours seemed the most toxic.

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<sup>20</sup> Ikonomidis, I. *et al.* Electronic Cigarette Smoking Increases Arterial Stiffness and Oxidative Stress to a Lesser Extent Than a Single Conventional Cigarette: An Acute and Chronic Study. *Circulation* 137, 303–306 (2018)

<sup>21</sup> Chaumont, M. *et al.* Differential Effects of E-Cigarette on Microvascular Endothelial Function, Arterial Stiffness and Oxidative Stress: A Randomized Crossover Trial. *Sci Rep* 8, 1-9 (2018)

<sup>22</sup> Carnevale, R. *et al.* Acute Impact of Tobacco vs Electronic Cigarette Smoking on Oxidative Stress and Vascular Function. *Chest* 150, 606-612 (2016)

<sup>23</sup> Barber, K. *et al.* Endothelial Cell Inflammatory Reactions Are Altered in the Presence of E-Cigarette Extracts of Variable Nicotine. *Cell. Mol. Bioeng* 10, 124–133 (2017)

<sup>24</sup> Yin, W. *et al.* Regulated complement deposition on the surface of human endothelial cells: effect of tobacco smoke and shear stress. *Thromb Res* 122, 221-228 (2008)

<sup>25</sup> Yin, W. *et al.* The combined effect of sidestream smoke and dynamic shear stress on endothelial cell inflammatory responses. *Thromb Res.* 135, 362-367 (2015).

<sup>26</sup> Barber, K. *et al.* Endothelial Cell Inflammatory Reactions Are Altered in the Presence of E-Cigarette Extracts of Variable Nicotine. *Cell. Mol. Bioeng* 10, 124–133 (2017)

<sup>27</sup> Schweitzer, KS. *et al.* Endothelial disruptive proinflammatory effects of nicotine and e-cigarette vapor exposures. *Am J Physiol Lung Cell Mol Physiol.* (2015)

<sup>28</sup> Ohkuma, T. *et al.* Brachial-Ankle Pulse Wave Velocity and the Risk Prediction of Cardiovascular Disease: An Individual Participant Data Meta-Analysis. *Hypertens (Dallas, Tex 1979)* 69, 1045-1052 (2017)

<sup>29</sup> Lee, HW. *et al.* Modeling Cardiovascular Risks of E-Cigarettes With Human-Induced Pluripotent Stem Cell-Derived Endothelial Cells. *Journal of the American College of Cardiology* 73 (21), 2722-2737 (2019)

From this we conclude:

***There is limited, but increasing, evidence that e-cigarette use is associated with a short-term increase in changes in biomarkers of oxidative stress, increased endothelial dysfunction and arterial stiffness.***

### *Platelets*

Individual studies have found:

- Significant increases in platelet aggregation, adhesion, activation and complement interactions after e-cigarette use (i.e. exposure of cells to e-cigarette aerosol extract (eCAE)). These changes have been invoked as a mechanism for increased risk of thrombosis after cigarette smoking (in vitro study).<sup>30</sup>
- Statistically significant increases in platelet aggregation, alpha particle secretion, dense particle secretion, platelet-integrin activation and platelet resistance to inhibition by prostacyclin but not platelet count following eCAE exposure (animal study).<sup>31</sup>
- Statistically significant decreases in bleeding time (increased haemostasis) and occlusion time (increased thrombogenesis) and statistically significant increases in markers of *vascular inflammation* after e-cigarette vapour inhalation (animal study).<sup>32</sup>
- Statistically significant decreases in circulating thrombomodulin in mice – a molecule that is protective against thrombosis (animal study).<sup>33</sup>
- Significant increases in platelet microparticle secretion<sup>34</sup> and statistically significant increases in platelet aggregation after e-cigarette use (human studies).<sup>35</sup>

From this we conclude:

***There is evidence, although so far limited, that e-cigarette exposure affects the function of platelets.***

### *Cardiac function*

The 2018 NASEM report concluded that there is no available evidence on whether e-cigarette use is associated with clinical cardiovascular outcomes (coronary heart disease, stroke, and peripheral artery disease) and subclinical atherosclerosis (carotid intima-media thickness and coronary artery calcification).

<sup>30</sup> Hom, S. *et al.* Platelet activation, adhesion, inflammation, and aggregation potential are altered in the presence of electronic cigarette extracts of variable nicotine concentrations. *Platelets* 27, 694-702 (2016)

<sup>31</sup> Qasim H, *et al.* Short-Term E-Cigarette Exposure Increases the Risk of Thrombogenesis and Enhances Platelet Function in Mice. *J Am Heart Assoc* 7(15):e0092642018 (2018)

<sup>32</sup> Qasim H, *et al.* Short-Term E-Cigarette Exposure Increases the Risk of Thrombogenesis and Enhances Platelet Function in Mice. *J Am Heart Assoc* 7(15):e0092642018 (2018)

<sup>33</sup> Kaiser, MA. *et al.* Offsetting the impact of smoking and e-cigarette vaping on the cerebrovascular system and stroke injury: Is Metformin a viable countermeasure?. *Redox Biol* 13, 353-362 (2017)

<sup>34</sup> Kerr, DMI. *et al.* Acute effects of electronic and tobacco cigarettes on vascular and respiratory function in healthy volunteers: a cross-over study. *J Hypertens* 37(1), 154-166 (2018)

<sup>35</sup> Nocella, C. *et al.* Impact of Tobacco Versus Electronic Cigarette Smoking on Platelet Function. *Am J Cardiol* 122, 1477-1481 (2018)

Individual studies not included in the 2018 NASEM report found:

- Statistically significant increases in left ventricular mass of mice after chronic exposure to e-cigarette vapour but not in those exposed to cigarette smoke. Moreover statistically significant decreases were observed in fractional shortening and ejection fraction in mice exposed to cigarette smoke but there were no significant decreases in ejection fraction in mice exposed to e-cigarette vapour (animal study).<sup>36</sup> The clinical implication from the study is that chronic use of e-cigarettes, even at relatively low exposure levels, induces cardiovascular dysfunction. The study also found that the urine cotinine (a nicotine biomarker) level in mice exposed to e-cigarette vapour was approximately half that of those exposed to cigarette smoke, yet vascular damage was similar, suggesting a role for mechanisms other than those involving nicotine.
- Statistically significant increases in two cardiac mutagens in the cardiac tissue of mice exposed to eCAE (animal study).<sup>37</sup>

A study from March 2019 on *The impact on cardiovascular outcomes among e-cigarette users*<sup>38</sup> found that e-cigarette users have higher odds of heart attacks, stroke, depression/anxiety/emotional problems, circulatory problems but lower risk of hypertension and diabetes compared to non-e-cigarette users. The researchers acknowledge that there is a need for cohort studies to establish causation of the cardiovascular outcomes described.

From this we conclude:

***There is insufficient evidence to date that e-cigarette use is associated with impairment of cardiac function and risk of heart attack and stroke.***

### ***Conclusions on the effects of e-cigarettes on the cardiovascular system***

Evidence on the short-term impact of e-cigarette use on the cardiovascular system is mixed. However, short-term effects are likely less harmful to the cardiovascular system than smoking conventional cigarettes. This is not to say that e-cigarette use, even in the short-term, is harmless.

Currently, it is not known what the cardiovascular effects are after long-term use of e-cigarettes. Most studies exposed participants to vaping for only a few minutes. Lack of evidence cannot, however, exclude that there is no long-term impact on cardiovascular disease of e-cigarette use. Similarly, with respect to short-term exposure, it is important to note that conclusions about insufficient or limited evidence do not necessarily indicate that there is no harm; such conclusions may merely indicate that there are too few studies to draw a final conclusion.

Also, several studies examined specific mechanisms (as listed above), whereas what matters is their combined effects in real life.

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<sup>36</sup> Olfert, IM. *et al.* Chronic exposure to electronic cigarette (E-cig) results in impaired cardiovascular function in mice. *J Appl Physiol* 124(3), 573-582 (2018)

<sup>37</sup> Lee, HW. *et al.* E-cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells. *Proc Natl Acad Sci USA* 13, 115(7) (2018)

<sup>38</sup> Mohinder, R. *et al.* Impact on cardiovascular outcomes among e-cigarette users: a review from national health interview surveys. *Journal of the American College of Cardiology* 73, (9 Supplement 2) 11 (2019)



***Based on the evidence that is currently available, it can be concluded that documented risks to the cardiovascular system are of concern. Several issues remain unexplored and there is a need for longitudinal studies. Such studies need to elucidate not only the long-term effects of e-cigarette use on the cardiovascular system but also if e-cigarette use is less hazardous to cardiovascular health than conventional cigarette smoking in the longer term.***

## **Use of E-cigarettes**

The evidence set out in the above section on risks to the cardiovascular system of e-cigarette use suggests that individuals should abstain from using e-cigarettes. This is even more the case for children, adolescents and pregnant women as there is sufficient evidence related to the potential long-term consequences for brain development of foetal and adolescent nicotine exposure.<sup>39</sup>

But what if the alternative to e-cigarette use is smoking combustible tobacco? The 2018 NASEM report<sup>40</sup> states that “*while e-cigarettes are not without health risks, they are likely to be far less harmful than conventional cigarettes*”. According to this report, e-cigarettes contain fewer numbers and lower levels of toxic substances than conventional cigarettes and it concludes that:

- there is conclusive evidence that completely substituting e-cigarettes for conventional cigarettes reduces users’ exposure to many toxicants and carcinogens present in conventional cigarettes.
- there is substantial evidence that completely switching from regular use of conventional cigarettes to e-cigarettes results in reduced short-term adverse health outcomes in several organ systems.

Nevertheless, the NASEM report cautions that long-term health effects of e-cigarette use are not known, and it states that the possibility that e-cigarettes may increase the risk of cardiovascular disease must be evaluated carefully given the high burden of cardiovascular disease.

***Our 2016 paper concluded that it was reasonable to assume that if existing smokers switched completely from conventional cigarettes to e-cigarettes there would be a lower disease burden caused by nicotine addiction. We underlined that e-cigarettes were not harmless, and that the precautionary principle would dictate that it is desirable to limit use and uptake, in particular among children and young people. Studies published since increasingly highlight risks of using e-cigarettes, especially for cardiovascular disease. Continued application of the precautionary principle is warranted.***

### ***E-cigarettes as a smoking cessation aid***

The key benefit of e-cigarettes for both individuals and for public health would be to aid smoking cessation among people who smoke conventional cigarettes. It is, therefore, essential to establish if e-cigarette use has been proven effective as a smoking cessation aid.

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<sup>39</sup> The health consequences of smoking – 50 years of progress. A report of the Surgeon General. Rockville (MD); US Department of Health and Human Services (2014)

<sup>40</sup> National Academies of Sciences, Engineering, and Medicine. *Public health consequences of e-cigarettes*. Washington, DC: The National Academies Press (2018)

The 2018 NASEM report<sup>41</sup> concludes that there is general agreement that, due to the number, size, and quality of studies, the evidence on effectiveness of e-cigarettes as cessation aids in comparison with cessation aids of proven efficacy is limited. The report found that there is insufficient evidence from randomised controlled trials (RCTs) about the effectiveness of e-cigarettes as cessation aids compared with no treatment (or to U.S. Food and Drug Administration (FDA)–approved smoking cessation treatments). But the report also found that within the current body of evidence, different study designs have produced conflicting findings with moderate evidence from *RCTs* that e-cigarettes with nicotine are more effective than e-cigarettes without nicotine for smoking cessation. One major *RCT* did not find sufficient evidence to conclude that e-cigarette use was effective as a cessation aid.<sup>42</sup> A *meta-analysis* of longitudinal real-life studies, included in the NASEM report, showed that use of e-cigarettes significantly undermined smoking abstinence.<sup>43</sup> The NASEM report also found that while the overall evidence from *RCTs* is mixed, there is moderate evidence from *observational studies* that more frequent use of e-cigarettes is associated with an increased likelihood of cessation.

A *cohort study* from the US published in 2018 (not included in the 2018 NASEM report) found no evidence that e-cigarette use helped adult smokers quit at rates higher than cigarette smokers who did not use these products.<sup>44</sup> An *RCT*, also from 2018, (not included in the 2018 NASEM report) found that financial incentives added to free cessation aids resulted in a higher rate of sustained smoking abstinence than free cessation aids alone. Among cigarette smokers who received usual care (information and motivational text messages), the addition of free cessation aids or e-cigarettes did not provide a benefit.<sup>45</sup>

An *RCT* of e-cigarettes versus nicotine replacement therapy accompanied by behavioural support reported an almost two-fold increase in 12-month quit rates with e-cigarettes.<sup>46</sup> The authors of the study, in which the results of the trial were published in 2019, acknowledged that the effects of e-cigarettes were stronger than in previous studies. The abstinence rate, achieved in the intervention group, was similar to that achieved with varenicline (a nicotine replacement) in other trials. It is important to note that it was a trial of two forms of nicotine replacement in a population that had a strong motivation to quit smoking, as acknowledged by the authors, and who were also receiving a behavioural intervention. Hence, it provides no evidence on effectiveness of e-cigarettes used in the absence of such support. It is also important to note that 80% of people who used e-cigarettes in the trial continued to use them after one year, and there were more adverse events with conditions plausibly linked to e-cigarettes in the group allocated to them.

A 2019 study<sup>47</sup> found that vaping more than one year after quitting cigarette smoking was associated with smoking relapse. The study acknowledged that further studies are needed to evaluate whether this association is causal.

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<sup>41</sup> National Academies of Sciences, Engineering, and Medicine. *Public health consequences of e-cigarettes*. Washington, DC: The National Academies Press (2018)

<sup>42</sup> El Dib, R. *et al.* Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: A systematic review and meta-analysis. *BMJ Open* 7(2), e012680 (2017)

<sup>43</sup> Kalkhoran, S. *et al.* E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *Lancet Respir Med* 4(2), 116-28 (2016)

<sup>44</sup> Weaver, SR. *et al.* Are electronic nicotine delivery systems helping cigarette smokers quit? Evidence from a prospective cohort study of U.S. adult smokers, 2015–2016. *Plos One* (2018)

<sup>45</sup> Halpern, S.D. *et al.* A Pragmatic Trial of E-cigarettes, Incentives, and Drugs for Smoking Cessation. *N Engl J Med* 378(24), 2302-2310 (2018)

<sup>46</sup> Hajek, P. *et al.* A randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med* 380, 629-637 (2019)

<sup>47</sup> Dai, H. *et al.* Association of electronic cigarette vaping and subsequent smoking relapse among former smokers. *Drug Alcohol Depend* 199, 10-17 (2019)

From this we conclude:

***There is not sufficient evidence that e-cigarettes are effective smoking cessation aids.***

### ***Dual use***

The 2018 NASEM report found that dual use of combustible tobacco cigarettes and e-cigarettes is highly prevalent among both adults and youth. The report concluded that there is no available evidence whether or not long-term dual use changes morbidity or mortality compared with those who only smoke combustible tobacco cigarettes. The report also found insufficient evidence that e-cigarette use would confer a short-term benefit (“*change short-term adverse health outcomes in several organ systems*”) in smokers who continue to smoke combustible tobacco cigarettes.<sup>48</sup> More worrying is that a large study from 2018 (not included in the 2018 NASEM report) found that toxicant exposure was higher among dual users than among smokers of conventional cigarettes only (exclusive cigarette users showed 10% to 36% lower concentrations of several biomarkers than dual users).<sup>49</sup>

A systematic review<sup>50</sup> on the dual use of e-cigarettes and classic cigarettes from 2017 (not included in the 2018 NASEM report) found that dual users make use of e-cigarettes for smoking reduction, smoking cessation, reduction of health risks and that they perceive e-cigarettes to be safer and less addictive than tobacco cigarettes. Dual users are more likely to use tobacco cigarettes when there is no restriction of use, or when stressed and/or anxious. Situations such as these might be the most difficult circumstances to dissuade dual users from smoking conventional cigarettes.

A study from 2019 found no evidence of any association between dual use and eventual abstinence from all tobacco products.<sup>51</sup>

Moreover, a US study found that the majority (up to 90%) of dual users consume e-cigarettes as a supplement to conventional cigarettes, not as an alternative to smoking.<sup>52</sup> Therefore, there will be no health benefit for the majority of smokers.

From this we conclude:

***Smokers of combustible tobacco cigarettes who do not succeed in quitting smoking completely using e-cigarettes and end up as ‘dual users’ will not reduce their health risks. They may even increase it.***

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<sup>48</sup> National Academies of Sciences, Engineering, and Medicine. *Public health consequences of e-cigarettes*. Washington, DC: The National Academies Press (2018)

<sup>49</sup> Goniewicz, M.L. *et al.* Comparison of Nicotine and Toxicant Exposure in Users of Electronic Cigarettes and Combustible Cigarettes. *JAMA network open* 1(8), e185937 (2018)

<sup>50</sup> Maglia, M. *et al.* Dual use of electronic cigarettes and classic cigarettes: a systematic review. *Addiction Research & Theory* 26:4, 330-338 (2018)

<sup>51</sup> Sweet, L. *et al.* Quitting Behaviors Among Dual Cigarette and E-Cigarette Users and Cigarette Smokers Enrolled in the Tobacco User Adult Cohort. *Nicotine TobRes* 21(3), 278-284 (2019)

<sup>52</sup> Glantz, S.A. *et al.* E-Cigarettes: Use, Effects on Smoking, Risks, and Policy Implications. *Annu Rev Public Health* 39, 215–235 (2018)

## ***Gateway to smoking***

A 2016 review of longitudinal studies *Is vaping a gateway into smoking?* concluded that e-cigarette use is associated with higher rates of smoking initiation amongst adolescents, even among those who would otherwise have no inclination to smoke.<sup>53</sup>

The 2018 NASEM report also states that there is very strong evidence from longitudinal cohort studies of high plausibility that e-cigarette use may be a catalyst for smoking initiation and that e-cigarette use may increase the risk and speed of progression to more frequent, heavy, and chronic cigarette smoking after first trying combustible tobacco cigarettes. It concludes that there is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults.<sup>54</sup>

A 2019 report *Vaping in England: an evidence update (2019)* from Public Health England<sup>55</sup> notes that trends in smoking and vaping need to be monitored, particularly in the light of concerns in North America about youth smoking and vaping. The report calls for more research on how young people move from e-cigarettes to smoking and vice versa.

Another 2019 study found that among (Italian) e-cigarette users, those starting or re-starting cigarette smoking after using e-cigarettes outnumbered those who stopped smoking after using e-cigarettes. So even if ‘stick by stick’ e-cigarette use is less harmful than conventional cigarettes, their use may not have a favourable net public health effect.<sup>56</sup>

From this we conclude:

***There is substantial risk that young people using e-cigarettes will become smokers and that from a public health point of view e-cigarette use may have an unfavourable net effect.***

## **Marketing and regulation**

### ***Product***

Some e-cigarettes are designed to resemble regular cigarettes, while others look more like cigars, pipes, pens and even USB flash drives.

First generation e-cigarettes closely resemble cigarettes and are disposable. Second generation e-cigarettes are larger, usually pen-shaped devices that can be recharged. Third generation e-cigarettes refer to devices that do not resemble a combustible cigarette and often have very large and sometimes customizable batteries. Some parts may be replaced. These devices are refillable.

More recently, e-cigarettes that have a sleek, high-tech design and easily rechargeable batteries have entered the market.

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<sup>53</sup> Alzghoul, B. *et al.* Is vaping a gateway to smoking: A review of the longitudinal studies. *International journal of adolescent medicine and health* (2016)

<sup>54</sup> National Academies of Sciences, Engineering, and Medicine. *Public health consequences of e-cigarettes*. Washington, DC: The National Academies Press (2018)

<sup>55</sup> Vaping in England: an evidence update February 2019. A report commissioned by *Public Health England*

<sup>56</sup> Liu, X. *et al.* Electronic cigarettes in Italy: a tool for harm reduction or a gateway to smoking tobacco? *Tob Control* (2019)

Nicotine levels in e-cigarettes are highly variable, with some reaching levels near combustible cigarettes.<sup>57</sup> One product, JUUL e-cigarettes, is supposed to have nicotine content like traditional cigarettes, and deliver the nicotine up to 2.7 times faster than other e-cigarettes.<sup>58</sup> While that may make them more attractive to smokers as an alternative to combustible tobacco cigarettes, it may also increase the potential for youth addiction.

In the section above on ‘Effects of e-cigarettes on the cardiovascular system’, we referred to emerging evidence about risk of acute exposure to flavoured e-liquids or e-cigarette use. Apart from this potential risk, flavoured e-cigarettes are considered to appeal especially to young people.<sup>59</sup>

In March 2019, the US FDA announced it would go ahead with efforts to restrict sales of some types of flavoured vaping products to minors. Under the rules, most forms of flavoured e-cigarettes would only be sold in stores that verify a customer's age when s/he enters the store, or the store should have a special age-restricted area set aside for vaping products (federal law currently bans use of e-cigarettes by people under the age of 18).

### ***Trends in use and uptake***

Use of e-cigarettes (use on one or more days in the past 30 days) by US high school students rose from 1.5 percent in 2011 to a high of 16.0 percent in 2015, before declining to 11.3 percent in 2016.<sup>60</sup> The FDA has declared that e-cigarette use is an epidemic in youth in the US.

A study from 2019 found increases in the prevalence of vaping among adolescents aged 16-19 in Canada in 2018 to be the highest levels recorded to date.<sup>61</sup>

In England, the 2019 report from PHE on vaping found that as a whole, experimentation with e-cigarettes has steadily increased in recent years. However, regular use remains low, with 1.7% of 11 to 18 year olds in Great Britain reporting at least weekly use in 2018 (0.4% among 11 year olds and 2.6% among 18 year olds).<sup>62</sup> The report also found that the proportion of young people who have not smoked but have tried vaping, is increasing even if it remains very low (0.2% of 11-18 year olds).

The trend towards an increase in use of e-cigarettes among young people, including in young people who have never smoked, at least in the US and Canada, would indicate that the marketing of e-cigarette products is effective.

### ***Market***

The e-cigarette market was worth USD 11.26 billion (~ euros 8.56 billion) in 2018.<sup>63</sup> The source providing this information foresees a growth in the market to USD 18.16 billion (~ euros 13.84 billion) in 2024 with Europe being the fastest growing market.

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<sup>57</sup> National Academies of Sciences, Engineering, and Medicine. *Public health consequences of e-cigarettes*. Washington, DC: The National Academies Press (2018)

<sup>58</sup> <https://truthinitiative.org/news/e-cigarettes-facts-stats-and-regulations> (Last access on 19 August 2019)

<sup>59</sup> The Flavor Trap: How tobacco companies are luring kids with candy-flavored e-cigarettes and cigars. *American Academy of Pediatrics, Cancer Action Network/American Cancer Society, American Heart Association/ American Stroke Association, American Lung Association, Campaign for Tobacco Free Kids* (2017)

<sup>60</sup> National Academies of Sciences, Engineering, and Medicine. *Public health consequences of e-cigarettes*. Washington, DC: The National Academies Press (2018)

<sup>61</sup> Hammond, D. *et al.* Prevalence of vaping and smoking among adolescents in Canada, England, and the United States: repeat national cross sectional surveys. *BMJ* 365:12219 (2019)

<sup>62</sup> Vaping in England: an evidence update February 2019. A report commissioned by *Public Health England*

<sup>63</sup> <https://www.mordorintelligence.com/industry-reports/global-e-cigarettes-market-industry> (Last access on 19 August 2019)

## ***Regulation***

Across the world, there is a patchwork of regulations on e-cigarettes. Regulations include completely banning e-cigarettes (40 countries in the world have banned them), banning marketing, banning flavours (see above reference to the FDA), and banning use in public places.

In the EU, the Tobacco Products Directive (TPD)<sup>64</sup>, which entered into force in May 2016, contains rules for e-cigarettes sales and use. The TPD covers all consumer electronic cigarettes placed on the EU market (medicinal e-cigarettes are not covered by the TPD). It sets maximum nicotine concentration level for e-cigarettes of no more than 20 mg/ml, and maximum volumes for cartridges, tanks and containers of nicotine liquids.

It also stipulates that e-cigarette manufacturers must notify EU Member States before placing new products on the market. Notification must include information on the manufacturer; the ingredients used and emissions; nicotine dose and uptake; product and production process and a declaration that the manufacturer takes full responsibility for the quality and safety of the product under normal use. Manufacturers are also required to report annually to EU Member States on the sales volumes of the products, types of users and their preferences and trends.

A report from the European Commission on the implementation and impact of this Directive is due in May 2021. The report should include information on market developments concerning consumer perception of electronic cigarettes and refill containers.

## **Conclusions and recommendations**

### ***Conclusions***

With respect to the effect of e-cigarettes, there is mixed evidence for effects on the cardiovascular system from short-term exposure. While some studies found a higher risk compared to smoking combustible tobacco cigarettes, short-term e-cigarette use is likely less harmful to the cardiovascular system than smoking conventional cigarettes. But it is by no means harmless. The long-term effects on the cardiovascular system are still unknown. The fact that there is no evidence for long-term effects cannot be interpreted as no effect, and findings from recent studies suggest that use may pose a higher risk than so far assumed. Several issues remain unexplored and there is a need for long-term follow-up studies.

E-cigarettes are promoted as risk-reducing products compared to combustible tobacco cigarettes. There is conclusive evidence that completely substituting e-cigarettes for combustible tobacco cigarettes reduces users' exposure to numerous toxicants and carcinogens present in combustible tobacco cigarettes.<sup>65</sup> There is substantial evidence that completely switching from regular use of combustible tobacco cigarettes to e-cigarettes results in reduced short-term adverse health outcomes in several organ systems.<sup>66</sup> But combustible tobacco cigarettes are arguably the most dangerous products that can be bought legally. As e-cigarettes lack tar, one of the most toxic and extensively studied components of cigarettes, it is possible that they may be somewhat safer. However, e-cigarettes produce toxic substances, mainly

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<sup>64</sup> [http://ec.europa.eu/health/tobacco/docs/dir\\_201440\\_en.pdf](http://ec.europa.eu/health/tobacco/docs/dir_201440_en.pdf) (Last access on 19 August 2019)

<sup>65</sup> National Academies of Sciences, Engineering, and Medicine. *Public health consequences of e-cigarettes*. Washington, DC: The National Academies Press (2018)

<sup>66</sup> National Academies of Sciences, Engineering, and Medicine. *Public health consequences of e-cigarettes*. Washington, DC: The National Academies Press (2018)

flavours, not found in cigarettes, which are much less well understood. The long-term effects of e-cigarette use on the cardiovascular system are still unknown.

There is not sufficient evidence that e-cigarettes are effective as a smoking cessation tool. In addition, dual use of e-cigarettes and combustible tobacco cigarettes does not provide any (short-term) health benefits. Unfortunately, most people (up to 90%) use e-cigarettes as a supplement to conventional cigarettes, not as an alternative to smoking. Therefore, there will be no health benefit for the majority of smokers.

People, and in particular young people, who have never smoked, are increasingly taking up e-cigarette use, and they are at substantial risk of becoming cigarette smokers. Certain flavours in e-cigarettes make them specifically attractive to children and young people. Whether these young people would have started smoking conventional cigarettes had e-cigarettes not existed is a question that we cannot answer. Nevertheless, it is a problem when a product that is far from risk-free is being used increasingly by a population of non-smokers. Especially as there is strong evidence that e-cigarette use is a gateway to smoking.

There is also an issue of impact of conflict of interest in studies on health effect of e-cigarettes. Such impact was documented in a study published in 2019.<sup>67</sup> This study demonstrated that 95% of papers without conflicts of interest found potentially harmful effects of e-cigarettes, whereas industry-related conflict of interest was strongly associated with a finding of no harm.

When evaluating the pros and cons of e-cigarettes, we must consider their impact on the whole population, not only on the smokers, who are a minority. From a public health point of view, these products may have an unfavourable net effect.

Considering the very high burden of cardiovascular disease in Europe, the mere possibility that e-cigarette use increases the risk of cardiovascular disease is a cause of concern.

All in all, it is crucial to be extremely cautious about e-cigarette use.

## ***Recommendations***

### New recommendations

- There is a need for longitudinal studies to elucidate long-term effects of e-cigarette use on the cardiovascular system and whether e-cigarette use is less hazardous to cardiovascular health than conventional cigarette smoking in the longer term.
- Medical journals should refrain from publishing studies that are partly or fully funded by entities that have an industry-related conflict of interest.
- Health professionals should inform patients and the public of the risks related to e-cigarette use.
- Flavours should be prohibited. This should certainly be the case for those flavours that may not be safe and those that are likely to attract children and young people.

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<sup>67</sup> Pisinger, C. *et al.* A conflict of interest is strongly associated with tobacco industry – favourable results, indicating no harm of e-cigarettes. *Preventive Medicine* 119, 124-131 (2019)

## Revised recommendations

- The same buying restrictions and age limits should be set for e-cigarettes as for conventional cigarettes.
- Restrictions on marketing, including advertising, labelling and packaging, of e-cigarettes should be the same as for conventional cigarettes.
- The use of e-cigarettes in public places should be prohibited. Given the fact that second-hand exposure has some impact on bystanders' health, that use of e-cigarettes may make it more complicated to enforce smoke-free legislation, and that use of e-cigarettes may change the norm in terms of use of conventional cigarettes in public places, e-cigarette use in public places should be prohibited.
- Tax measures should be used as appropriate: applying a special excise duty or tax on e-cigarettes has the dual benefit of discouraging use – especially for young people – and raising income for governments. EHN recommends taxing e-cigarettes at a rate high enough to discourage uptake.

For more information visit the European Heart Network at <http://www.ehnheart.org/>

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