



# Reducing the Cardiovascular Risks of Smoking: Insights From the European Society of Cardiology (ESC) Congress 2024 and Two Key Opinion Leaders

Interviewees:



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<b>Disclaimer:</b>	The opinions expressed in this article belong solely to the named interviewees.
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### Interview Summary

Smoking is a major risk factor for cardiovascular disease (CVD) and responsible for around 25% of all CVD-related deaths worldwide. Cigarette combustion releases nicotine and produces thousands of chemicals, many of which are toxic. Complete cessation of smoking is the most effective way of reducing the associated CVD risk. However, many people find it difficult to quit smoking due to nicotine's addictive nature and the ritualistic aspect of smoking. The European Society of Cardiology Congress (ESC) 2024, held in London, UK, between 30<sup>th</sup> August–2<sup>nd</sup> September, included several sessions discussing tobacco harm reduction in relation to CVD, with a particular focus on e-cigarettes and heat-not-burn products (HNBP) as alternatives to cigarettes. EMJ interviewed two key opinion leaders (KOL), who had attended ESC 2024, to obtain their insights into tobacco harm reduction in Europe: Vincenzo Montemurro, Professor and Consultant Cardiologist at the Scilla Hospital of America, Reggio Calabria, Italy; and Emil Toldy-Schedel, Professor, Consultant Cardiologist, and General Director of the St. Francis Hospital, Budapest, Hungary. Montemurro explained that switching from cigarettes to alternative products that

generate fewer toxins would likely reduce CVD risk in people who are unable to quit smoking, which would benefit public health and decrease healthcare expenditure in Europe. Toldy-Schedel agreed with this view but called for well-designed studies to fully characterise the risk profile of these newer products so that healthcare professionals can be better equipped to answer patients' questions about possible long-term effects.

## INTRODUCTION

Tobacco is used by 1.3 billion people (36.7% of men and 7.8% of women) worldwide.<sup>1</sup> Tobacco use is responsible for 8 million deaths annually, including 1.3 million deaths from exposure to second-hand smoke.<sup>1</sup> Cigarette smoking increases the risks of CVD (such as ischaemic heart disease and stroke),<sup>2</sup> chronic obstructive pulmonary disease,<sup>3</sup> and lung cancer,<sup>4</sup> which are the main causes of tobacco-related mortality.<sup>5</sup> Smoking cessation can reduce CVD risk over time to a level similar to that of never smokers,<sup>6</sup> highlighting the health benefits of quitting tobacco use. However, although up to half of adult smokers try to quit each year, only a minority succeed.<sup>7,8</sup>

This year's ESC Congress was the first to include dedicated sessions discussing how tobacco harm reduction might impact CVD. The agenda included an oral presentation evaluating alternatives to cigarettes and differences in tobacco use between European countries;<sup>9</sup> a question-and-answer (Q&A) session focused on the risks of different tobacco/nicotine products;<sup>10</sup> and poster presentations relevant to tobacco harm reduction and CVD.<sup>11-15</sup> For this article, two leading experts in cardiology who attended ESC 2024, Toldy-Schedel and Montemurro, expanded on the insights provided at the Congress and shared their views on how to reduce the cardiovascular risks of tobacco use.

## CIGARETTE SMOKING AND CARDIOVASCULAR DISEASE

The ESC 2024 presentations discussing tobacco harm reduction acknowledged the cardiovascular risks of cigarettes. Montemurro and Toldy-Schedel explained that cigarette smoking

is a major modifiable risk factor for CVD, alongside hypertension, obesity, diabetes, and hypercholesterolaemia.<sup>16</sup> Moreover, cigarette use is associated with increased risks of coronary artery disease/myocardial infarction, cerebrovascular disease/stroke, peripheral vascular disease, and abdominal aortic aneurysm.<sup>2,17</sup> Globally, 2.7 million deaths were attributable to smoking-related CVD in 2019, with Eastern Europe having the highest smoking-related CVD burden.<sup>18</sup> Montemurro commented that nearly 220,000 people die each year from CVD in Italy.<sup>19</sup> Furthermore, Italy has a high smoking prevalence (24.2% in 2022),<sup>20</sup> and around 96,000 people die annually from smoking-related diseases.<sup>21</sup>

Montemurro explained how tobacco combustion is a major contributor to smoking-related harms. The temperature of a burning cigarette exceeds 800 °C during a puff.<sup>22</sup> Combustion at these high temperatures generates more than 7,000 substances, at least 250 of which are considered harmful (including 69 known carcinogens).<sup>23</sup> The toxic products released by cigarettes include carbon monoxide, oxidising metals/chemicals, and polycyclic aromatic aldehydes.<sup>24</sup> Inhaling combustion products causes detrimental effects such as increases in peripheral vascular resistance and blood pressure, promotion of atherosclerosis, and an elevated CVD risk.<sup>24</sup> Pathophysiological mechanisms implicated in the cardiovascular effects of smoking include oxidative stress, oxidation of low-density lipoprotein-cholesterol, endothelial dysfunction with impaired nitric oxide production, inflammation, and a prothrombotic state.<sup>24</sup>

Toldy-Schedel emphasised the importance of differentiating the effects of combustion from those of nicotine itself, noting that while combustion

generates toxic compounds directly linked to atherosclerosis, nicotine acts more indirectly by stimulating the sympathetic nervous system. Montemurro explained that although nicotine is non-carcinogenic, it maintains the habit of smoking and causes sympathetic nervous system activation,<sup>25</sup> which increases heart rate, blood pressure, and cardiac output.<sup>24,26</sup> Toldy-Schedel added that nicotine can also initiate heart rhythm disturbances such as ventricular arrhythmias.<sup>26</sup> Nevertheless, both specialists agreed that the main drivers of CVD in people who smoke are the toxic byproducts of combustion rather than nicotine. Given these health risks, experts are exploring alternatives to traditional cigarettes.

## CARDIOVASCULAR RISKS ASSOCIATED WITH ALTERNATIVES TO CIGARETTES

Cigarette alternatives, particularly e-cigarettes and HNBPs, were a major focus of the ESC 2024 sessions on tobacco harm reduction.<sup>9,10</sup> Unlike cigarettes, e-cigarettes and HNBPs avoid tobacco combustion. E-cigarettes vaporise a solution containing nicotine, propylene glycol, glycerol, and flavourings to produce an aerosol that is inhaled.<sup>27</sup> HNBPs have a self-regulating temperature system that heats tobacco but prevents its combustion by limiting the temperature to a maximum of 350 °C; this is thought to reduce the production of toxic and carcinogenic substances by around 90%.<sup>28</sup> Nicotine is still released by HNBPs and e-cigarettes, so the psychoactive properties (such as alertness), addictive nature, and cardiovascular effects remain.<sup>24-26</sup> Although several factors can affect nicotine delivery from e-cigarettes,<sup>29</sup> the amount of nicotine absorbed into the bloodstream for e-cigarettes and HNBPs is generally comparable to or lower than that for cigarettes.<sup>30,31</sup>

Experts at the ESC 2024 Q&A session suggested that e-cigarettes and HNBPs likely have fewer detrimental effects on the cardiovascular system than cigarettes,<sup>10</sup> given the reduced number and levels of toxic compounds.<sup>32-34</sup> Montemurro and Toldy-Schedel echoed this viewpoint. Richter's

presentation at ESC 2024 reviewed some of the published evidence suggesting that CVD risk is lower for e-cigarettes and HNBPs than for cigarettes.<sup>9</sup> For example, smoking a cigarette acutely impaired brachial artery flow-mediated dilatation (FMD), a measure of vascular endothelial function, in regular users of cigarettes, whereas vaping an e-cigarette did not impair FMD in regular users of e-cigarettes who refrained from cigarettes.<sup>35</sup> Furthermore, switching from cigarettes to e-cigarettes or HNBPs led to reductions in aortic stiffness, systolic blood pressure, oxidative stress, platelet activation, and the degree of impairment of brachial artery FMD.<sup>36-38</sup> Switching from cigarettes to HNBPs was also associated with improved coronary flow, myocardial function, and vascular function.<sup>39</sup> Richter noted that the above studies were small in scale and provided only indirect evidence that e-cigarettes and HNBPs have a lower CVD risk than cigarettes.<sup>9</sup> However, they went on to describe a study of 5,159,538 adult males in South Korea, which reported that switching from cigarettes to HNBPs was associated with a lower short-term risk of CVD (adjusted hazard ratio: 0.81; 95% CI: 0.78–0.84), although CVD risk was higher for HBNP users than for people who quit cigarettes without HBNP use (adjusted hazard ratio: 1.31; 95% CI: 1.01–1.70).<sup>40</sup> A poster presentation at ESC 2024 provided additional evidence that switching from cigarettes to alternative products might lower cardiovascular harm: endothelial glycocalyx integrity (an indicator of vascular health) was worsened in people who continued to smoke cigarettes for 1 month, maintained in those who switched to e-cigarettes, and improved (for microvessels 20–25 µm in diameter) in persons who switched to HNBPs.<sup>11</sup> However, not all studies have reported lower cardiovascular risks for e-cigarettes than for cigarettes. For example, one investigation found that chronic use of cigarettes and e-cigarettes resulted in similar impairments in vascular endothelial function.<sup>41</sup> Moreover, a study of people who smoked cigarettes demonstrated that using a cigarette or an e-cigarette led to comparable reductions in FMD.<sup>42</sup> Therefore, additional research is needed to definitively establish whether short-term and long-term cardiovascular risks differ between cigarettes, e-cigarettes, and HNBPs.

Toldy-Schedel emphasised that, although e-cigarettes and HNBPs likely cause less harm than cigarettes, they still probably increase CVD risk to a level above that in people who do not use tobacco/nicotine products. Furthermore, they made the point that no data are currently available regarding the long-term effects of these products on CVD risk. Other potential safety issues with e-cigarettes should be noted. First, the heating coil temperature of e-cigarettes is affected by numerous factors, including user settings and heating element ageing, and higher temperatures can increase the levels of potentially toxic carbonyl compounds.<sup>43</sup> Second, although open-system e-cigarettes are designed to be refilled manually with customised vape fluid, Montemurro explained that the addition of substances not intended by the manufacturer could potentially result in additional adverse effects. Third, discussions at ESC 2024 highlighted several cases of e-cigarette-related lung injury and death in the USA 4–5 years ago.<sup>10,44</sup> These deaths were linked to the use of illicit e-cigarettes containing tetrahydrocannabinol oil and vitamin E acetate as a thickening agent.<sup>44</sup>

## TOBACCO USE TRENDS ACROSS EUROPE

Richter's presentation at ESC 2024 described wide variations in cigarette smoking rate between European countries,<sup>9</sup> ranging from <10% in Sweden, Iceland, and Finland to >25% in Serbia, Turkey, and Bulgaria in 2019.<sup>45</sup> Richter also mentioned differences in the prevalence of e-cigarette use across Europe (ranging from 0.6% in Spain to 7.2% in England during 2017–2018)<sup>46</sup> and the lower level of current HNBPs use ( $\leq 0.5\%$  during 2017–2018).<sup>47</sup>

Montemurro, Toldy-Schedel, and Richter all highlighted that Sweden has a lower prevalence of cigarette smoking than other European countries due to the widespread use of snus (an oral tobacco product placed under the upper lip),<sup>9</sup> mainly among men.<sup>48</sup> The experts emphasised that the prevalence of lung cancer and smoking-related mortality in men are much lower in Sweden than in

other EU countries, despite comparable levels of overall tobacco consumption.<sup>48</sup> Montemurro pointed out that, in contrast to the situation in men, lung cancer rates among women in Sweden are comparable to those in women from other European countries because tobacco use by Swedish women is predominantly through cigarette smoking rather than snus.<sup>48</sup> Toldy-Schedel considered the findings in Sweden to represent real-world evidence that cigarette smoke is the predominant cause of tobacco-related harm. Montemurro concluded that Sweden's experience illustrates how replacing cigarettes with a non-combustion alternative can reduce tobacco-related harm. Nevertheless, snus is not without adverse effects, which include oral mucosal changes and increased risks of hypertension, death after myocardial infarction, oesophageal cancer, pancreatic cancer, Type 2 diabetes, and metabolic syndrome.<sup>49</sup>

Montemurro and Toldy-Schedel gave the UK as an example of a country that has had recent success in reducing the smoking rate among its population, which fell from 20.2% in 2011 to 12.9% in 2022.<sup>50</sup> According to Richter's presentation at ESC 2024,<sup>9</sup> the decrease in smoking prevalence in the UK was likely related to a series of measures, including public health awareness campaigns, implementation of plain packaging, high taxation on tobacco products, a ban on indoor smoking in public places, and the promotion of e-cigarettes as an aid to stopping smoking.<sup>51</sup> The increasing use of e-cigarettes by young people in the UK may also have contributed to the fall in cigarette smoking rate.<sup>52</sup> Notably, the current UK government appears committed to introducing legislation to ban the sale of cigarettes to anyone born on or after 1<sup>st</sup> January 2009,<sup>53</sup> legislation that Toldy-Schedel suggested should be extended to other European countries. Richter's presentation at ESC 2024 cited a recent Cochrane review showing that e-cigarettes were more effective than nicotine replacement therapy in helping people quit smoking.<sup>9,54</sup> Consistent with this, a poster presentation at ESC 2024 reported that the smoking abstinence rate among people with obesity who used e-cigarettes as a smoking cessation aid was 53% at 3 months and 42%



at 6 months.<sup>12</sup> Both Richter's presentation and Montemurro highlighted the success of e-cigarettes as a tool to facilitate smoking cessation in the UK,<sup>9</sup> with Montemurro emphasising that reducing tobacco-related harm would free up resources for allocation to sectors other than health.

## THE POTENTIAL ROLES OF CIGARETTE ALTERNATIVES IN TOBACCO HARM REDUCTION

Primary and secondary prevention measures can reduce tobacco-related harms. In terms of primary prevention, the experts at the ESC 2024 Q&A session emphasised that people who have never smoked should be discouraged from taking up any form of tobacco/nicotine use, including e-cigarettes and HNBPs, because none of these products can be considered safe due to the associated health risks and addictive nature of nicotine.<sup>10</sup> Some of the KOLs at the Q&A session were concerned by the high rate of e-cigarette use among adolescents.<sup>10</sup> The experts suggested various methods to limit e-cigarette use among younger people, including stricter legislation to reduce the levels of flavourings and other compounds that promote addiction, banning the sale of e-cigarettes to the general public (but leaving the products available on prescription for those attempting to quit smoking), and increasing the taxation level.<sup>10</sup> However, it was also recognised that the latter two options might disincentivise some people from using e-cigarettes as a smoking cessation tool.<sup>10</sup> Richter's presentation mentioned that several countries have approved (UK, Belgium, and France) or announced (Poland and Germany) a ban on disposable e-cigarettes.<sup>9</sup> Furthermore, there are flavour restrictions in the UK, Denmark, Estonia, Finland, Lithuania, the Netherlands, Slovenia, and Ukraine.<sup>9</sup> Montemurro and Toldy-Schedel concurred that the main smoking-related public health advice should be not to use any type of tobacco/nicotine product because of the negative health effects. This view agrees with the current ESC guidelines mentioned at the ESC 2024 Q&A session.<sup>10</sup> Given that

many people take up smoking when they are teenagers, Montemurro suggested that the effective delivery of primary prevention strategies will necessitate the co-ordinated involvement of healthcare professionals, schools, and families.

Secondary prevention methods provide advice, medical support, and psychological support to help people quit smoking. Experts at the ESC 2024 Q&A session recommended a personalised approach that gradually reduces the dependence on nicotine and helps to overcome the ritualistic/social drivers of smoking.<sup>10</sup> There is strong evidence that smoking cessation is associated with health benefits.<sup>6</sup> For example, poster presentations at ESC 2024 reported that smoking cessation lowers inflammatory marker levels at 3 months and reduces the long-term risks of ischaemic heart disease,<sup>13</sup> peripheral arterial disease, and aortic aneurysm.<sup>14</sup> However, Montemurro argued that healthcare professionals need to be realistic and accept that many current smokers will not be able to stop smoking cigarettes in the absence of an alternative form of nicotine that partly replicates the smoking ritual. Montemurro went on to explain that nicotine patches, gums, and sprays have a high failure rate when used as a smoking cessation aid.<sup>55,56</sup> Italy has 'no-smoking centres' that offer advice, medical support, and psychological support to help smokers quit. However, their numbers have fallen in recent years despite an increase in the total number of employees, and they are visited by only a small proportion of the smoking population.<sup>57</sup> Although about 35% of smokers attempt smoking cessation in Italy each year, only 10% are successful.<sup>58</sup> The experience in Italy is reflected elsewhere: despite tobacco use declining since 2010, only 56 countries are predicted to achieve the WHO's global goal of a 30% reduction in tobacco use between 2010–2025.<sup>59</sup> Montemurro stressed that this failure to substantially reduce smoking prevalence translates into cases of CVD that are treated at the state's expense.

In Montemurro's opinion, HNBPs and e-cigarettes provide an opportunity for harm reduction in people who are unable

to stop smoking cigarettes. With this in mind, both Montemurro and Toldy-Schedel highlighted the experience of Japan, where the current restrictions on HNBP are more lenient than those on cigarettes: in the 10 years following the introduction of HNBP in 2014, there has been a 50% reduction in cigarette consumption as smokers have switched to HNBP, with little change in the overall use of tobacco-containing products.<sup>60</sup> The experiences of Japan and the UK (see above) illustrate how an individual country's policies can influence the success of harm reduction strategies. According to Montemurro, although e-cigarettes and HNBP do not eliminate risk, the lower risks relative to cigarettes would reduce harm in those who are unable/unwilling to stop smoking completely. This view was also highlighted at the ESC 2024 Q&A session,<sup>10</sup> although the point was made that there are currently insufficient data to demonstrate this effect directly. Richter's presentation at ESC 2024 pointed out that two heated tobacco products have recently obtained a reduced toxicity claim in Greece, suggesting that Greece may be moving toward a harm reduction strategy.<sup>9</sup> By contrast, other countries in Europe, such as Italy, have yet to adopt such an approach.

Agreeing with views aired by experts at the ESC 2024 sessions,<sup>9,10</sup> Toldy-Schedel stated that, in their opinion, CVD rates will likely be lower for e-cigarette and HNBP users than for cigarette users. They suggested that switching to a non-combustion alternative would reduce harm in people who are unable to stop using nicotine. Nevertheless, Toldy-Schedel stressed that a limitation of the studies published to date is that they have been small-scale, short-term investigations evaluating indirect measures of CVD risk. Furthermore, there is evidence that young adults who use e-cigarettes have elevated risk factors for CVD development.<sup>41,61,62</sup> Therefore, independent, large-scale, long-term studies are needed to establish the health risks of e-cigarettes and HNBP more clearly.

Montemurro also discussed how switching from cigarettes to alternative products might impact the harms of second-hand smoke. An analysis presented at ESC 2024 found

that the number of cardiovascular deaths caused by second-hand smoke worldwide had increased by 38% between 1990–2019, with cardiovascular disease accounting for 46% of these deaths in 2019.<sup>15</sup> Prenatal tobacco smoke exposure is also associated with harms including cardiovascular defects.<sup>63,64</sup> Montemurro suggested that switching from cigarettes to e-cigarettes or HNBP might reduce the detrimental effects of second-hand smoke. They explained that combustion cigarettes produce particulate matter (PM) in addition to other toxins. Notably, smoking a conventional cigarette in a car with its windows closed generates peak levels of PM<sub>10</sub> (PM with a diameter  $\leq 10 \mu\text{m}$ ) that are more than 10-fold higher than the EU limit for outdoors (the EU has legislated that the daily mean level of PM<sub>10</sub> outdoors should not exceed 50  $\mu\text{g}/\text{m}^3$  more than 35 times in a year).<sup>65,66</sup> HNBP and e-cigarettes release less PM<sub>10</sub>,<sup>34,67</sup> as well as fewer toxins and carcinogens than cigarettes.<sup>32–34</sup> Therefore, Montemurro concluded that the effects of second-hand smoke would likely be less harmful for e-cigarettes and HNBP than for cigarettes.

A final concern raised by Toldy-Schedel was that the widespread uptake of non-combustion alternatives might lead to a renormalisation of smoking indoors in public places because of the perceived lower risk. Toldy-Schedel argued that the ban on smoking in public spaces should be extended to include e-cigarettes and HNBP, since the aerosol from these products contains nicotine as well as other substances. Indeed, it has been reported that nicotine from second-hand smoke exposure results in substantial nicotinic acetylcholine receptor occupancy in the brain, which might contribute to the initiation and maintenance of smoking behaviour.<sup>68</sup>

## CONCLUSION

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Sessions at ESC 2024 dedicated to tobacco harm reduction highlighted potential opportunities for lowering CVD risk in people who smoke cigarettes, paving the way for further research and discussion regarding the impact of cigarette alternatives on long-term

cardiovascular health. Despite the current limited availability of evidence on long-term CVD risk, Montemurro and Toldy-Schedel agreed that healthcare professionals may need to accept that switching to a less harmful product might be a positive result in many people who smoke cigarettes, even if risk is only reduced rather than eliminated. An important question that remains unanswered is whether

alternatives to cigarettes offer a sustainable long-term reduction in cardiovascular risk. Therefore, long-term studies are needed to determine the full extent of any harm reduction, not only in people who switch entirely from cigarettes to e-cigarettes or HNBPs, but also in dual users who incorporate these alternatives as a strategy to reduce their cigarette consumption.

**References**

1. World Health Organization (WHO). Tobacco. Fact sheet. 2023. Available at: <https://www.who.int/news-room/fact-sheets/detail/tobacco>. Last accessed: 27 September 2024.
2. Banks E et al. Tobacco smoking and risk of 36 cardiovascular disease subtypes: fatal and non-fatal outcomes in a large prospective Australian study. *BMC Med.* 2019;17(1):128.
3. Forey BA et al. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. *BMC Pulm Med.* 2011;11:36.
4. O'Keefe LM et al. Smoking as a risk factor for lung cancer in women and men: a systematic review and meta-analysis. *BMJ Open.* 2018;8(10):e021611.
5. GBD 2019 Tobacco Collaborators. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019. *Lancet.* 2021;397(10292):2337-60.
6. Duncan MS et al. Association of smoking cessation with subsequent risk of cardiovascular disease. *JAMA.* 2019;322(7):642-50.
7. Centers for Disease Control and Prevention. Smoking cessation: fast facts. 2024. Available at: <https://www.cdc.gov/tobacco/php/data-statistics/smoking-cessation/index.html>. Last accessed: 27 September 2024.
8. Cheung CM et al. Factors associated with abstinence after a recent smoking cessation attempt across 28 European Union member states. *Tob Prev Cessat.* 2020;7:5.
9. Richter D. Is vaping better than smoking? Differences between the UK and European countries. Symposium presentation. ESC Congress, 30 August-2 September, 2024.
10. Biondi-Zoccai G et al. The floor is yours: bring your questions on the risks of other tobacco products (i.e. vaping, snus). Expert panel session. ESC Congress, 30 August-2 September, 2024.
11. Ikonomidis I et al. Differential effects of heat-not-burn, electronic cigarettes and conventional cigarettes on endothelial glycocalyx. Poster presentation ehae666.3388. ESC Congress, 30 August-2 September, 2024.
12. Kouroutzoglou A et al. Smoking cessation medicines and e-cigarettes in smokers with obesity. Poster presentation ehae666.2955. ESC Congress, 30 August-2 September, 2024.
13. Komiyama M et al. Immunoglobulin free light chain-kappa, a novel biomarker of inflammation and cardiovascular risk, decreases after smoking cessation in association with NT-proBNP. Poster presentation ehae666.2877. ESC Congress, 30 August-2 September, 2024.
14. Van Den Bogaart M et al. Associations of smoking status with long-term cardiovascular events in different arterial territories: the EPIC Norfolk prospective population cohort. Poster presentation ehae666.2878. ESC Congress, 30 August-2 September, 2024.
15. Jiang H et al. The Cardiovascular Disease Burden Associated with secondhand smoke, 1990-2019: an age-period-cohort analysis of the Global Burden of Disease study. Poster presentation ehae666.2623. ESC Congress, 30 August-2 September, 2024.
16. Global Cardiovascular Risk Consortium; Magnussen et al. Global effect of modifiable risk factors on cardiovascular disease and mortality. *N Engl J Med.* 2023;389(14):1273-85.
17. Tonstad S, Andrew Johnston J. Cardiovascular risks associated with smoking: a review for clinicians. *Eur J Cardiovasc Prev Rehabil.* 2006;13(4):507-14.
18. Khan Minhas AM et al. Global burden of cardiovascular disease attributable to smoking, 1990-2019: an analysis of the 2019 Global Burden of Disease Study. *Eur J Prev Cardiol.* 2024;31(9):1123-31.
19. Eurostat. Cardiovascular diseases statistics. 2024. Available at: [https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Cardiovascular\\_diseases\\_statistics#Deaths\\_from\\_cardiovascular\\_diseases](https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Cardiovascular_diseases_statistics#Deaths_from_cardiovascular_diseases). Last accessed: 27 September 2024.
20. Istituto Superiore di Sanità. Press Release N°39/2022 -Smoking: Italy reports almost 800,000 smokers more than in 2019 and the consumption of heated tobacco products has tripled. 2022. Available at: <https://www.iss.it/en/-/no-tobacco-day-2022-iss-en#:~:text=ISS%2C%2030%20May%202022%20-%20Almost,carried%20out%20before%20the%20pandemic>. Last accessed: 27 September 2024.
21. OECD/European Observatory on Health Systems and Policies. Italy: Country Health Profile 2021. State of Health in the EU. OECD Publishing, Paris. 2021. Available at: <https://www.oecd-ilibrary.org/docserver/5bb1946e-enpdf?expires=1727742103&id=id&acname=guest&checksum=2C668721D32BEC87F0BB85E59C6C32AC>. Last accessed: 27 September 2024.
22. Baker R. Temperature distribution inside a burning cigarette. *Nature.* 1974;247:405-6.
23. National Cancer Institute. Harms of cigarette smoking and health benefits of quitting. 2017. Available at : <https://www.cancer.gov/about-cancer/causes-prevention/risk/tobacco/cessation-fact-sheet>. Last accessed: 27 September 2024.
24. Salahuddin S et al. Pathophysiological mechanisms of tobacco-related CVD. *Glob Heart.* 2012;7(2):113-20.
25. Wittenberg RE et al. Nicotinic acetylcholine receptors and nicotine addiction: a brief introduction. *Neuropharmacology.* 2020;177:108256.

26. Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. *Trends Cardiovasc Med*. 2016;26(6):515-23.
27. Rom O et al. Are E-cigarettes a safe and good alternative to cigarette smoking? *Ann N Y Acad Sci*. 2015;1340:65-74.
28. Mallock N et al. Heated tobacco products: a review of current knowledge and initial assessments. *Front Public Health*. 2019;7:287.
29. DeVito EE, Krishnan-Sarin S. E-cigarettes: impact of e-liquid components and device characteristics on nicotine exposure. *Curr Neuropharmacol*. 2018;16(4):438-59.
30. Rabenstein A et al. Usage pattern and nicotine delivery during ad libitum consumption of pod e-cigarettes and heated tobacco products. *Toxics*. 2023;11(5):434.
31. Marsot A, Simon N. Nicotine and cotinine levels with electronic cigarette: a review. *Int J Toxicol*. 2016;35(2):179-85.
32. Yayan J et al. Comparative systematic review on the safety of e-cigarettes and conventional cigarettes. *Food Chem Toxicol*. 2024;185:114507.
33. Bekki K et al. Comparison of chemicals in mainstream smoke in heat-not-burn tobacco and combustion cigarettes. *J UOEH*. 2017;39(3):201-7.
34. Simonavicius E et al. Heat-not-burn tobacco products: a systematic literature review. *Tob Control*. 2019;28(5):582-94.
35. 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*. 2018;137(3):303-6.
36. Biondi-Zoccai G et al. Acute effects of heat-not-burn, electronic vaping, and traditional tobacco combustion cigarettes: the Sapienza University of Rome-Vascular assessment of proatherosclerotic effects of smoking (SUR-VAPES) 2 randomized trial. *J Am Heart Assoc*. 2019;8(6):e010455.
37. Haptonstall KP et al. Differential effects of tobacco cigarettes and electronic cigarettes on endothelial function in healthy young people. *Am J Physiol Heart Circ Physiol*. 2020;319(3):H547-56.
38. Ioakeimidis N et al. Acute effect of heat-not-burn versus standard cigarette smoking on arterial stiffness and wave reflections in young smokers. *Eur J Prev Cardiol*. 2021;28(11):e9-11.
39. Ikonomidis I et al. Differential effects of heat-not-burn and conventional cigarettes on coronary flow, myocardial and vascular function. *Sci Rep*. 2021;11(1):11808.
40. Choi S et al. Combined associations of changes in noncombustible nicotine or tobacco product and combustible cigarette use habits with subsequent short-term cardiovascular disease risk among South Korean men: a nationwide cohort study. *Circulation*. 2021;144(19):1528-38.
41. Mohammadi L et al. Chronic e-cigarette use impairs endothelial function on the physiological and cellular levels. *Arterioscler Thromb Vasc Biol*. 2022;42(11):1333-50.
42. Ben Taleb Z et al. Pod-based e-cigarettes versus combustible cigarettes: the impact on peripheral and cerebral vascular function and subjective experiences. *Tob Induc Dis*. 2023;21:71.
43. Chen W et al. Measurement of heating coil temperature for e-cigarettes with a "top-coil" clearomizer. *PLoS One*. 2018;13(4):e0195925.
44. Krishnasamy VP et al. Update: characteristics of a nationwide outbreak of e-cigarette, or vaping, product use-associated lung injury -United States, August 2019-January 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(3):90-4.
45. Eurostat. Tobacco consumption statistics. 2022. Available at: [https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Tobacco\\_consumption\\_statistics](https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Tobacco_consumption_statistics). Last accessed: 27 September 2024.
46. Gallus S et al. Electronic cigarette use in 12 European countries: results From the TackSHS survey. *J Epidemiol*. 2023;33(6):276-84.
47. Gallus S et al. Use and awareness of heated tobacco products in Europe. *J Epidemiol*. 2022;32(3):139-44.
48. Clarke E et al. Snus: a compelling harm reduction alternative to cigarettes. *Harm Reduct J*. 2019;16(1):62.
49. Norwegian Institute of Public Health. Health risks from snus use. 2019. Available at: <https://www.fhi.no/en/publ/2019/health-risks-from-snus-use2/>. Last accessed: 20 November 2024.
50. Harker R. Research briefing: Statistics on smoking. 2023. Available at: <https://commonslibrary.parliament.uk/research-briefings/cbp-7648/#:~:text=Smoking%20is%20a%20leading%20cause,adults%20aged%2035%20and%20over>. Last accessed: 27 September 2024.
51. Bafunno D et al. Impact of tobacco control interventions on smoking initiation, cessation, and prevalence: a systematic review. *J Thorac Dis*. 2020;12(7):3844-56.
52. Office for National Statistics. Adult smoking habits in the UK: 2022. Available at: <https://backup.ons.gov.uk/wp-content/uploads/sites/3/2023/09/Adult-smoking-habits-in-the-UK-2022.pdf>. Last accessed: 21 November 2024.
53. The King's Speech 2024. 2024. Available at: [https://assets.publishing.service.gov.uk/media/6697f5c10808eaf43b50d18e/The\\_King\\_s\\_Speech\\_2024\\_background\\_briefing\\_notes.pdf](https://assets.publishing.service.gov.uk/media/6697f5c10808eaf43b50d18e/The_King_s_Speech_2024_background_briefing_notes.pdf). Last accessed: 3 October 2024.
54. Lindson N et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev*. 2024;1(1):CD010216.
55. Sivasankari T et al. Comparative evaluation of the efficacy of nicotine chewing gum and nicotine patches as nicotine replacement therapy using salivary cotinine levels as a biochemical validation measure. *Indian J Psychiatry*. 2023;65(6):635-40.
56. Caldwell BO et al. Combination rapid-acting nicotine mouth spray and nicotine patch therapy in smoking cessation. *Nicotine Tob Res*. 2014;16(10):1356-64.
57. Beatrice F, Albera A. No smoke centers in Italy: critical issues & perspectives. *J Community Med Public Health Care*. 2022;9:117.
58. Gorini G et al. Disuguaglianze regionali e socioeconomiche nella cessazione del fumo in Italia, 2014-2017 [Socioeconomic and regional inequalities in smoking cessation in Italy, 2014-2017]. *Epidemiol Prev*. 2019;43(4):275-85.
59. World Health Organization. Tobacco use declines despite tobacco industry efforts to jeopardize progress. News release. 2024. Available at: <https://www.who.int/news/item/16-01-2024-tobacco-use-declines-despite-tobacco-industry-efforts-to-jeopardize-progress>. Last accessed: 27 September 2024.
60. Global State of Tobacco Harm Reduction. Cigarette sales halved: heated tobacco products and the Japanese experience. Briefing paper. 2024. Available at: <https://gsth.org/resources/briefing-papers/cigarette-sales-halved-heated-tobacco-products-and-the-japanese-experience/>. Last accessed: 3 October 2024.
61. Halstead KM et al. Sex differences in oxidative stress-mediated reductions in microvascular endothelial function in young adult e-cigarette users.



- Hypertension. 2023;80(12):2641-9.
62. Matheson C et al. Evidence of premature vascular dysfunction in young adults who regularly use e-cigarettes and the impact of usage length. *Angiogenesis*. 2024;27(2):229-43.
63. Braun M et al. Influence of second-hand smoke and prenatal tobacco smoke exposure on biomarkers, genetics and physiological processes in children -an overview in research insights of the last few years. *Int J Environ Res Public Health*. 2020;17(9):3212.
64. Hackshaw A et al. Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls. *Hum Reprod Update*. 2011;17(5):589-604.
65. Pitten L et al. TAPaC-tobacco-associated particulate matter emissions inside a car cabin: establishment of a new measuring platform. *J Occup Med Toxicol*. 2022;17(1):17.
66. European Environment Agency. Particulate matter (PM10) -Annual limit value for the protection of human health. 2024. Available at: <https://www.eea.europa.eu/en/analysis/maps-and-charts/particulate-matter-pm10-annual-limit-value-for-the-protection-of-human-health-3>. Last accessed: 27 September 2024.
67. Savdie J et al. Passive exposure to pollutants from a new generation of cigarettes in real life scenarios. *Int J Environ Res Public Health*. 2020;17(10):3455.
68. Brody AL et al. Effect of secondhand smoke on occupancy of nicotinic acetylcholine receptors in brain. *Arch Gen Psychiatry*. 2011;68(9):953-60.