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Review article

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Nicotine-containing products and the cardiovascular system: mechanisms and global health implications

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Abstract

Tobacco use and emerging nicotine-delivery systems remain major, preventable drivers of cardiovascular disease worldwide. Although tobacco cigarette smoking has declined in some high-income regions, progress is uneven, with persistently high rates across parts of Europe, alongside rapidly expanding global markets for e-cigarettes, heated-tobacco products and oral nicotine formulations. Youth addiction to nicotine-containing products has emerged as an urgent public health challenge, as engineered e-cigarette devices delivering large nicotine doses facilitate early dependence and might establish lifelong exposure trajectories. Regulatory frameworks have not kept pace with this innovation, allowing new platforms to enter markets faster than safety evidence can mature. Leading cardiovascular societies and regulatory authorities agree that no nicotine-containing product can be safe for the cardiovascular system. Nicotine promotes sympathetic activation, haemodynamic stress, oxidative imbalance and inflammation, and endothelial nitric oxide synthase uncoupling and dysfunction, contributing to atherosclerotic plaque instability in animal models and humans. Studies in humans demonstrate adverse vascular responses across all nicotine-containing products, although interpreting studies requires caution and long-term outcome data are lacking. In this Review, we integrate mechanistic, biomarker, preclinical and clinical data to define a cardiovascular continuum of harm from nicotine-containing products, in which eliminating combustion reduces but does not eliminate vascular toxicity.

Sections

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Key points

- Cigarette smoking remains the most harmful form of nicotine use, driving the global burden of cardiovascular morbidity and mortality, with unequivocal evidence linking it to myocardial infarction, stroke, heart failure and premature cardiovascular death.
- No nicotine-delivery system is safe for the cardiovascular system; although e-cigarettes and heated-tobacco and oral nicotine products reduce exposure to combustion toxicants, these products impair endothelial function, increase oxidative stress and arterial stiffness, and activate sympathetic and inflammatory pathways; importantly, long-term outcome data for e-cigarettes and newer oral nicotine products are not available.
- Endothelial dysfunction provides an early and integrative biomarker of vascular harm, with impaired flow-mediated dilatation, increased high-sensitivity C-reactive protein and IL-6 levels, and high pulse wave velocity predicting an increased risk of cardiovascular events; these biomarkers bridge basic, translational and clinical evidence.
- The available evidence reveals a consistent hierarchy of vascular harm: from highest with combustion products (cigarettes and waterpipes), then heating nicotine products, followed by aerosol devices (e-cigarettes), oral nicotine products (chewing tobacco and pouches) and abstinence.
- Mechanistic and experimental studies confirm the biological plausibility of the hierarchy of cardiovascular harm, showing that nicotine, fine particles, metals, aldehydes and flavouring agents induce oxidative stress, uncoupling of endothelial nitric oxide synthase, mitochondrial and circadian dysfunction, and vascular inflammation, replicating the effects observed in human endothelial injury.
- Protection from, and prevention of, initiating nicotine product consumption among young individuals and regulation of nicotine products are urgent priorities; integrating biomarker surveillance, taxation, flavour bans and evidence-based cessation support is also essential to end the evolving epidemic of nicotine-containing product consumption.

Introduction

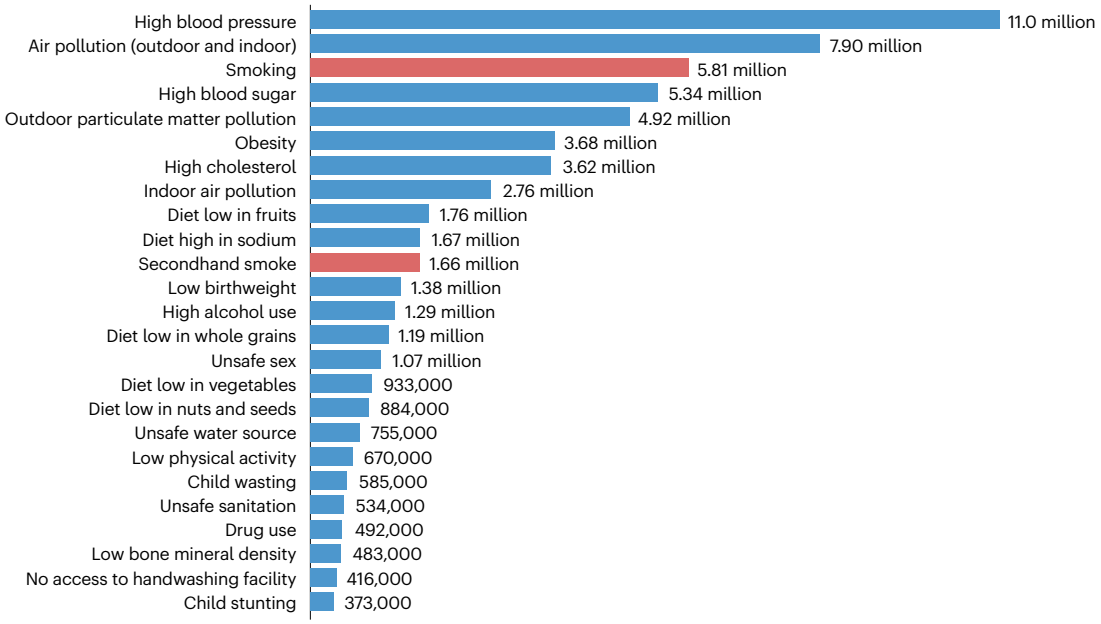
Tobacco smoking is one of the leading preventable causes of premature death worldwide[1]. In 2023, more than 1 billion people globally smoked tobacco, with approximately 5.81 million deaths from direct tobacco use[1] and 1.66 million deaths from secondhand smoke[1,2] (Fig. 1). Moreover, in 2023, tobacco smoking accounted for 15.3% of all deaths among men and 3.1% of all deaths among women, almost 40% due to cardiovascular disease[1]. Despite decades of anti-tobacco campaigns, tobacco cigarette smoking remains the single largest preventable cause of ischaemic heart disease, stroke and heart failure across the globe[3].

The epidemic of consumption of nicotine-containing products has entered a new phase. Over the past decade, novel nicotine-delivery systems, electronic cigarettes (e-cigarettes), heated-tobacco products and smokeless tobacco products (tobacco products that are used without burning, delivering the nicotine through the oral or nasal mucosa rather than by inhaling smoke) have rapidly transformed global markets. E-cigarette use among US high-school students increased from 1.5% in 2011 to 16% in 2015, and up to 40% of European adolescents report ever-use of e-cigarettes[4,5]. Although these products are often marketed as safer alternatives than tobacco cigarettes, robust long-term cardiovascular data are lacking, and dual use with combustible cigarettes is widespread[6]. Pod-based systems deliver high nicotine doses via salt formulations, and the sales of flavoured oral-nicotine pouches have surged by >300% since 2019[7]. Alarmingly, up to 75% of young adults in the USA who use e-cigarettes have never smoked conventional cigarettes, making vaping a gateway, not an exit, from addiction to nicotine-containing products[8]. Heated-tobacco and smokeless nicotine products pose similar concerns to tobacco cigarettes and e-cigarettes (Boxes 1 and 2). Although these products generate fewer or no combustion compounds, their addictive potential remains high, and long-term safety is uncertain. Studies on Swedish snus demonstrated increased mortality after myocardial infarction (MI) and an increased risk of fatal stroke[9,10], underscoring persistent cardiovascular toxicity despite the absence of smoke. Furthermore, exposure to nitrosamines in 24 out of 44 synthetic nicotine pouches and unregulated flavouring agents in certain brands introduces new toxicological uncertainties[11].

The World Heart Federation warns that all nicotine-containing products, including cigarettes, e-cigarettes, heated-tobacco products and emerging oral nicotine products (such as nicotine pouches), can sustain addiction and contribute to cardiovascular harm, underscoring the need for comprehensive regulation[12]. This warning echoes the unified stance of cardiology societies, such as the European Society of Cardiology (ESC)[13] and the American Heart Association (AHA)[6,14], as well as regulatory authorities, such as the US Centers for Disease Control and Prevention (CDC)[15] and the World Health Organization (WHO)[16], that no nicotine-containing product can be considered safe for the cardiovascular system. Beyond direct effects on human health, the WHO underscores the environmental toll of nicotine production, use and disposal, from deforestation and pesticide runoff, to plastic pollution and battery waste from cigarette butts and vaping devices[17]. The combined ecological and medical burden makes nicotine use a trans-sectoral public health challenge.

Progress in tobacco regulation has been slow. Despite modest declines in the age-standardized prevalence of smoking since the 1990s, the absolute number of people who smoke has remained high, being 1.2 billion globally in 2024[18]. Importantly, smoking tobacco cigarettes continues to account for a substantial share of global disability-adjusted life years, remaining one of the leading modifiable causes of disease burden, alongside high systolic blood pressure and particulate matter air pollution[19] (Fig. 1). These data underscore that the reductions in smoking prevalence have not translated into proportional reductions in smoking-related health burden, largely due to global population growth, ageing and persistent high exposure. These trends highlight a paradox: advances in knowledge have not yet translated into adequate behavioural and policy change. Moreover, regional differences in smoking prevalence might reflect variations in the affordability and implementation of control measures for tobacco and other nicotine-containing products, as well as differences in social factors. Comprehensive policy packages, including high excise taxes on nicotine-containing products, smoke-free laws, advertising bans and cessation support, have driven substantial declines when consistently enforced[20]. In parts of Europe, slower progress in the control of tobacco and other nicotine-containing products reflects greater affordability of these products, uneven enforcement of the regulations and

a Global deaths in 2023 according to attributable risk factor



b Change in top level 3 risk factors by DALYs from 2000 to 2021

Leading risks 2000	Percentage of total DALYs, 2000	Leading risks 2021	95% UI for ranking	Percentage of total DALYs, 2021	Percentage change in number of DALYs, 2000–2021	Percentage change in age-standardized rate of DALYs, 2000–2021
1 Particulate matter pollution	10.6 (8.5–12.3)	1 Particulate matter pollution	1–2	8.0 (6.7–9.4)	−17.2 (−25.9 to −6.2)	−41.9 (−47.2 to −35.6)
2 Child growth failure	9.3 (6.4–11.1)	2 High systolic blood pressure	1–2	7.8 (6.4–9.2)	34.3 (26.7–42.3)	−24.3 (−28.4 to −20.0)
3 Low birthweight and short gestation	8.9 (8.3–9.6)	3 Smoking	3–6	5.7 (4.7–6.8)	10.8 (3.2–19.9)	−34.8 (−39.2 to −29.7)
4 High systolic blood pressure	6.3 (5.2–7.4)	4 Low birthweight and short gestation	3–6	5.6 (4.8–6.3)	−32.4 (−41.2 to −22.3)	−33.0 (−41.6 to −22.8)
5 Smoking	5.6 (4.7–6.5)	5 High fasting blood glucose	3–6	5.4 (4.8–6.0)	88.2 (80.5–96.4)	7.9 (3.3–12.9)
6 Unsafe water source	4.0 (2.3–5.2)	6 High body mass index	3–10	4.5 (1.9–6.8)	96.5 (87.1–105.8)	15.7 (9.9–21.7)
7 Unsafe sanitation	3.3 (2.7–3.9)	7 High LDL cholesterol	7–10	3.0 (1.9–4.2)	27.0 (20.8–33.6)	−26.1 (−29.6 to −22.4)
8 High fasting plasma glucose	3.1 (2.8–3.5)	8 Kidney dysfunction	6–10	3.0 (2.6–3.5)	49.5 (42.7–57.0)	−12.4 (−16.5 to −7.9)
9 High LDL cholesterol	2.6 (1.6–3.6)	9 Child growth failure	6–14	2.6 (1.4–3.5)	−69.8 (−77.5 to −62.4)	−71.5 (−78.8 to −64.4)
10 Unsafe sex	2.6 (2.1–3.2)	10 High alcohol use	7–11	2.5 (2.1–3.1)	12.4 (2.6–20.9)	−25.8 (−32.0 to −20.4)

Fig. 1 | Global mortality and disease burden attributable to major risk factors. a, Estimated number of deaths worldwide in 2023 attributable to leading risk factors. High blood pressure was the dominant risk factor, followed by air pollution (combined outdoor and indoor pollution), smoking, high blood glucose levels and outdoor particulate matter pollution[2]. Smoking remains among the top global causes of preventable mortality, exceeding several metabolic and dietary risks. **b**, Top ten level 3 risk factors in the Global Burden of Disease hierarchy ranked by attributable disability-adjusted life years (DALYs) in 2021 compared with 2000, illustrating shifts in the global risk landscape over two decades. In 2021, particulate matter pollution and high systolic blood pressure rank highest, whereas smoking remains a major contributor to global DALYs despite declines in age-standardized rates from 2000 to 2021[19]. Together, these data emphasize the substantial and persistent global health burden imposed by tobacco use and environmental and metabolic risk factors. LDL, low-density lipoprotein; UI, uncertainty interval. Part **a** adapted from ref. 2, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Part **b** adapted from ref. 19, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

persistent socioeconomic inequalities, with higher smoking rates and lower success in smoking cessation among disadvantaged groups[20].

From a cardiovascular perspective, nicotine activates the sympathetic nervous system, increases blood pressure and heart rate, and contributes to systemic oxidative stress and vascular inflammation in experimental animal studies and humans[12]. Among the earliest and most integrative indicators of these effects of nicotine is endothelial function, which is a dynamic barometer of vascular health (Box 3). Moreover, converging data highlight a 'hierarchy of cardiovascular harm' of nicotine-containing products, in which tobacco combustion drives the greatest toxicity compared with a transition to vaping, and incomplete switching from cigarette smoking to e-cigarette vaping nullifies any potential benefits. Importantly, dual use of combustible cigarettes and e-cigarettes represents a heterogeneous exposure spectrum rather than a uniform risk category. Although individuals who predominantly smoke tobacco but also consume other nicotine-containing products (dual users) are likely to have a risk of cardiovascular disease similar to that of exclusive tobacco smokers, those who substantially reduce tobacco cigarette consumption

Box 1 | Definitions of tobacco and nicotine-delivery products

- Electronic nicotine-delivery system or e-cigarette: any battery-operated device that heats a solution, or e-liquid, to generate an aerosolized mixture containing flavoured liquids and nicotine that is inhaled by the user.
- Heated-tobacco products or heat-not-burn systems: products that produce aerosols containing nicotine and toxic chemicals when tobacco is heated or when a device containing tobacco is activated. These aerosols are inhaled by users during a process of sucking or smoking involving a device.
- Secondhand smoke: the combination of 'mainstream' smoke exhaled by the smoker and 'sidestream' smoke emitted into the environment from the burning end of a cigarette or from other smoked tobacco products, usually in combination with the smoke exhaled by the smoker. The terms 'passive smoking' or 'involuntary smoking' are also often used to describe exposure to secondhand smoke.
- Smoke-free policies: 'comprehensive' smoke-free policies completely ban smoking in all indoor public places, with no exceptions for designated smoking rooms.
- Smoked tobacco product: any product made or derived from tobacco through a combustion process. Examples include manufactured cigarettes, roll-your-own tobacco, cigars, shisha (also known as waterpipe), kreteks and bidis.
- Smokeless tobacco: any product that consists of cut, ground, powdered or leaf tobacco and that is intended to be placed in the oral or nasal cavity. Examples include snuff, chewing tobacco, gutka, mishri and snus.

Definitions reused with permission from ref. 3, WHO.

might experience a partial reduction in cardiovascular risk[20,21]. Nevertheless, because the dose–response relationship between smoking and cardiovascular disease is steep and nonlinear[22], even intermittent cigarette exposure might confer considerable vascular risk.

In this Review, we summarize the available data on the cardiovascular effects of nicotine-containing products, including studies on endothelial function), analyses of large clinical cohorts and translational research in animal models, to establish a hierarchy of harm across all nicotine-delivery systems. By combining mechanistic, biomarker and outcome evidence, we aim to inform cardiovascular clinicians, researchers and policymakers about the magnitude and modifiability of nicotine product-related cardiovascular risk, reinforcing the notion that, although less harmful nicotine-containing products might exist, safe ones do not. The concept of safety in this context should not be interpreted in the same manner as for therapeutic agents with demonstrated medical benefit. Rather, the appropriate public-health benchmark is whether population-level exposure introduces a preventable cardiovascular risk, particularly among adolescents and nicotine-naive individuals.

Nicotine-containing products

Toxic compounds in nicotine-containing products

Although several ISO standards have been developed to monitor emissions from different nicotine products (Box 2), comparing the toxic chemical content in different products remains challenging. In Table 1, we present an overview of the most notable groups of toxic compound originating from different nicotine-containing products, selected on the basis of available literature reporting their concentrations in smoke or aerosol. Smokeless tobacco products are excluded from the table because of the lack of comparable concentrations derived from a 'puff'. Nevertheless, concentration ranges for smokeless tobacco products have been investigated[23]. Of note, high heterogeneity exists among electronic smoking and vaping devices in terms of the temperatures used for volatilization of nicotine, with HNB products usually operating at 250–350 °C (ref. 24) and e-cigarette devices at 150–350 °C with a wet wick and >1,000 °C with a dry wick (when the e-cigarette liquid is depleted)[25].

The pathophysiological effects of nicotine and the involved pathways are discussed in detail in the section on cardiovascular risks. Other toxic compounds in these products, such as tobacco-specific nitrosamines, volatile organic compounds, carbonyl compounds, polycyclic aromatic hydrocarbons, metals, solid particulate matter and other chemical species are listed in Table 1 and discussed in detail in the Supplementary Information.

Tobacco cigarettes. Tobacco and its cigarette smoke contain a large number of chemicals, estimated to exceed 9,000 (ref. 26). Among these constituents, some have been identified as toxic or potentially toxic. For example, a study published in 1998 identified 72 biologically active chemical species that the study investigators suggested should be used as a benchmark for the toxicity of tobacco cigarette smoke[27]. In 2012, the Food and Drug Administration (FDA) modified the list to include a total of 93 harmful and potentially harmful constituents (HPHCs) in tobacco products and tobacco smoke[28], and added 19 additional compounds in 2019. In 2014, the WHO Framework Convention on Tobacco Control (FCTC) provided a mandate for lowering the levels of nine compounds in tobacco products and identified an additional 38 toxicants that should be prioritized for regulation based on toxicity, brand variability and detection feasibility[29].

E-cigarettes. Constituents of e-cigarette liquid and vapour are not as well understood and, therefore, are much less regulated than the constituents of tobacco cigarette smoke. Of note, the meaning of vapour in this context is also uncertain because any heating device produces both an aerosol and a vapour (gas). In this Review, we use the term 'vapour' to denote the inhalable product of heating generated by the specific device, rather than to refer to a physical state. Some products currently on the market use ultrasound to generate true aerosols, but they are not widely used, and research on them is limited. Following the 2015 WHO-commissioned report on e-cigarettes[30], the FCTC provided a report that acknowledged the presence of certain toxic chemicals in e-cigarette aerosol. However, given that a wide range of devices and nearly 8,000 unique e-cigarette liquid flavours are available, what constitutes standard levels of any toxic compound is not clear[31]. The FDA was more definitive, adding electronic nicotine-delivery systems to their tobacco product regulations in 2016, forcing the adherence of e-cigarettes to the same laws and standards as tobacco products.

Waterpipes. Waterpipes (also known as shisha or hookah) burn tobacco in a similar way to cigarettes, producing roughly the same toxic chemicals. Although waterpipes differ from tobacco cigarettes in the addition of glycerine to the tobacco, in the water filtration and in the use of coal as a heat source, the FDA applies the same HPHC framework for both product types[28] and regulates waterpipes according to the 2016 act for tobacco product regulation. Both the FDA and AHA state that waterpipe users

might experience a much higher exposure to toxic chemicals than cigarette smokers owing to the more prolonged smoking sessions[32,33]. The WHO published similar statements on the negative effects of waterpipe smoking but has not emphasized any specific chemical compounds[34].

Heat-not-burn products. HNB cigarettes are recognized and regulated in the same manner as conventional tobacco cigarettes. In 2020, the FDA granted the iQOS system (Philip Morris International) the designation of a 'modified risk tobacco product', acknowledging that this product produces considerably lower levels of certain HPHCs than combustible cigarettes[35]. However, the WHO has raised concerns about the basis of these claims, noting that some of the compounds from the HPHC list had not been reported to the FDA[36]. Moreover, no independent studies quantifying the toxicant profile of HNB aerosol are available, and much of the available evidence originates from industry-sponsored laboratories.

Smokeless oral nicotine products. Smokeless oral nicotine products usually contain the same basic composition as the tobacco used in classic cigarettes or HNB devices. However, these oral nicotine products also contain unregulated flavouring agents, including synthetic

Box 2 | Comparison of consumption patterns of nicotine products

Tobacco cigarettes

The smoking topography shows very little deviation among tobacco cigarette users, allowing for standardized characterization of exposure. This standardized measurement led to the ISO 3308 protocol (2-s puff duration, 35 ml puff volume, 60-s interval between puffs), which is widely used for analytical purposes. An average tobacco cigarette smoker consumes 10–20 cigarettes per day, often with stable puffing patterns. Tobacco combustion reaches temperatures >800 °C, leading to the formation of thousands of toxicants, including nicotine, carbon monoxide and acrolein, many of which contribute to oxidative stress, endothelial dysfunction and cardiovascular disease[323].

E-cigarettes

E-cigarette users exhibit high variability in puffing behaviour, making standardization challenging. The ISO 20768 protocol (3-s puff duration, 55 ml puff volume, 30-s interval) was introduced in 2019 for routine testing, although real-life use often deviates considerably. Daily use frequency ranges widely between users and is influenced by device type (pod systems versus mods), nicotine strength and user behaviour. E-cigarette aerosols, generated at lower temperatures (200–300 °C) than tobacco smoke, avoid combustion but still contain harmful constituents such as formaldehyde, acrolein and fine particles. Nicotine delivery efficiency can be similar to or exceed that of tobacco cigarettes, contributing to addiction potential[324,325]. Importantly, the level of oxidants and volatile organic compounds depends on the device, including the heating temperature and nature of the coil. In pod-like devices, the heating temperature is relatively low, and generation of thermal degradation products is also relatively low compared with tank-style devices. These device characteristics can be optimized to reduce health risks by effective regulation.

Waterpipes

Waterpipe (shisha) smoking typically involves a single, prolonged session per day, often lasting 45–90 min. Puff volume, duration and frequency are all markedly higher than with cigarette smoking, resulting in greater total smoke exposure. An ISO standard for waterpipe smoking is available (ISO 22496; 175 puffs of 530 ml each, taken every 20 s, with puff duration of 2.6 s), but most research groups use the 'Beirut' protocol of 17-s duration between puffs[326]. Charcoal heating creates combustion temperatures sufficient to release large volumes of volatile toxicants and particulate matter, including nicotine, polycyclic aromatic hydrocarbons and heavy metals[220]. A single session can equal or exceed the toxicant intake of up to 100 tobacco cigarettes[326].

Heat-not-burn cigarettes

Heat-not-burn (HNB) sticks have a limited time of use, which forces users to reduce the time duration between puffs[327]. The standardized aerosol collection with HNB products has been provided in the ISO 5501-1 protocol from 2024 (55 ml puff volume, 2 s puff duration, 30 s puff interval). The standard also incorporates mixing with fresh air, given that tobacco cigarettes are typically held between two fingers in a way that can block the holes at the edge of the mouth, which is not the case with HNB cigarettes[328]. Lower heating temperatures and air dilution compared with tobacco cigarettes result in lower exposure to toxic compounds, although all the toxic compounds present in cigarette smoke are also present in HNB smoke (vapour)[220,231].

Smokeless nicotine products

Smokeless nicotine products, such as nicotine pouches, snus, chewing tobacco, chew bags, tobacco bits and moist snuff, deliver nicotine via the oral mucosa without combustion or inhalation. Use typically lasts 20–60 min per session, with frequency ranging from occasional to more than ten uses daily, depending on dependence and product type. Whereas traditional forms such as snus and chewing tobacco contain tobacco and carcinogenic nitrosamines, newer nicotine pouches are tobacco-free but equally addictive. There is no ISO standard for smokeless use, and patterns vary across regions and user habits. These products, although smoke-free, still pose cardiovascular risks and raise public health concerns[6].

Nicotine toothpicks

Nicotine toothpicks are small, flavoured wooden sticks infused with pharmaceutical-grade nicotine for oral absorption via the buccal mucosa. Packaged in pocket-sized dispensers, they provide a discreet, smoke-free and vapour-free nicotine delivery. Typical nicotine content is 1–3 mg per toothpick, with higher strengths reported. Sweeteners (such as xylitol or sucralose), flavourings and alkalizing agents improve taste and absorption. The concealability and youth-appealing flavours of nicotine toothpicks raise concerns about unintended initiation and sustained nicotine dependence.

Box 3 | Endothelial function as a biomarker of vascular harm with prognostic implications

Rationale and limitations

Endothelial function provides a sensitive and clinically validated window into vascular health. Endothelial function is typically assessed by impaired flow-mediated dilatation (FMD), plethysmography and associated methods to assess arterial stiffness such as pulse wave velocity. The endothelium regulates vasomotor tone, inflammation and permeability, as well as platelet activity. Endothelial dysfunction, characterized by reduced nitric oxide bioavailability, oxidative stress and a shift towards vasoconstriction and thrombosis, is one of the earliest processes in atherogenesis[329]. Endothelial dysfunction can arise within hours to days after exposure to cigarette smoke, e-cigarette aerosols or oral nicotine products, as shown in humans[48,124]. Given that endothelial cells deteriorate rapidly after exposure to toxic compounds and recover quickly upon cessation of the exposure, these cells provide a sensitive translational bridge between experimental mechanisms and real-world clinical outcomes. Nevertheless, acute changes in endothelial function, for example, as measured by FMD, should be interpreted as signals of vascular stress rather than direct surrogates for clinical events. Subclinical vascular biomarkers, such as FMD, are intended to inform biological plausibility rather than serve as substitutes for clinical end point data.

Moreover, the prognostic relevance of endothelial dysfunction is greatest when the endothelial impairment is sustained or repeatedly induced[330]. For example, prospective studies confirm that FMD is predictive of an increased risk of myocardial infarction, stroke and cardiovascular death[331], with each 1% higher FMD associated with an 8–13% reduction in the risk of cardiovascular events[332–334]. Increased pulse wave velocity and reduced heart rate variability are similarly predictive of an increased risk of adverse cardiovascular outcomes[335–338].

Importantly, repeated real-world exposures such as daily nicotine consumption or exposure to secondhand smoke generate recurring 'transient' vascular insults, oxidative stress, nitric oxide depletion and arterial stiffening that accumulate into sustained endothelial dysfunction and might thus translate transient endothelial dysfunction into persistent vascular injury. For example, acute environmental triggers, such as nocturnal aircraft noise, have been shown to precipitate cardiovascular events within hours of exposure[102], supporting the concept that acute vascular stressors have clinical consequences when combined with chronic endothelial injury.

Although FMD is a well-established research tool for assessing nitric oxide-dependent vascular function, this measurement has important methodological limitations. Measurements are operator dependent, are sensitive to technical factors and require strict standardization to ensure reproducibility. The spatial resolution relative to arterial diameter and the physiological variability of FMD responses can further influence the results. Accordingly, FMD is not routinely used for clinical risk prediction, but remains valuable for mechanistic and translational research.

Prognostic marker

Findings from animal models and human studies highlight that endothelial dysfunction is not only an integrative and reversible marker of nicotine product-induced vascular injury but also predicts the clinical benefits of smoking cessation in humans. These data also provide a mechanistic foundation to interpret the findings from large, clinical outcome studies. In experimental models, exposure to cigarette smoke, e-cigarette aerosols or waterpipe smoke consistently induces oxidative stress, endothelial NO synthase uncoupling and impaired acetylcholine-mediated vasorelaxation[92,139,175]. These mechanisms have been directly mirrored in human studies, in which acute smoking of a single cigarette or a vaping episode reduces FMD, whereas cessation restores vascular function within weeks[103,114,165]. Supplementation with antioxidants, such as vitamin C, has been shown to reverse endothelial dysfunction in experimental models and controlled clinical trials[125,339], providing compelling evidence for causality.

This mechanistic bridge is crucial for interpreting clinical outcomes (Tables 3–5) and for the proposed biomarkers and pathomechanisms directly related to the exposure to toxic compounds by smoke, aerosols and oral delivery in animal models and human studies (Table 6 and Figs. 2 and 3). Large-scale cohort analyses, including the Cross Cohort Collaboration, demonstrate that cigars, pipes and smokeless tobacco are associated with increased risks of stroke, atrial fibrillation, myocardial infarction and heart failure[97]. Similarly, longitudinal analyses from the PATH and All of Us studies show that dual users of cigarettes and e-cigarettes have cardiovascular risks similar to those of exclusive smokers, whereas exclusive users of e-cigarettes often have intermediate risk profiles[91,95]. However, because most exclusive users of e-cigarettes are former smokers, residual vascular injury and incomplete adjustment for smoking history might contribute to this observation, complicating causal attribution to e-cigarette exposure itself. Therefore, disentangling the independent cardiovascular effects of e-cigarettes from legacy effects of previous smoking remains a central methodological challenge[91,92,95]. Nevertheless, the clinical outcome patterns align with the graded impairments of endothelial function observed in experimental models: cigarettes produce the most pronounced endothelial dysfunction, alternative nicotine products induce intermediate dysfunction levels and dual use largely abolishes any potential vascular benefit.

compounds, and some have been classified in chemical safety databases as respiratory or reproductive toxicants[11]. Smokeless oral nicotine products are mostly regulated through two standards: the WHO Tobacco Product Regulation Group (TobReg)[37] and GOTHIATEK[38] of the tobacco company Swedish Match, which provides limits for toxic compounds in smokeless oral nicotine products. Many of the smokeless tobacco products have been granted a 'modified risk tobacco products' designation by the FDA[39].

Nicotine replacement therapies. Medical nicotine replacement therapies (NRTs) include transdermal nicotine patches, gums and lozenges, as well as pharmacological agents such as bupropion and cytisine that alleviate withdrawal symptoms. These interventions are generally considered to be relatively safe compared with tobacco smoking[40] and occupy the lower end of the cardiovascular risk spectrum in proposed hierarchies of harm of nicotine-containing products[41]. Comparative analyses and systematic reviews confirm the efficacy of NRTs in

promoting cessation across different nicotine-delivery systems and pharmacotherapies[42].

With respect to cardiovascular safety, randomized clinical trials and meta-analyses have not demonstrated a substantial increase in serious cardiovascular events with short-term NRT use compared with non-users[43]. However, these studies were typically of short duration and underpowered for hard cardiovascular end points, particularly in patients with established atherosclerotic disease[44,45]. Importantly, nicotine is a pharmacologically active sympathomimetic compound that acutely increases heart rate, blood pressure and myocardial oxygen demand, and can promote vasoconstriction and endothelial stress[46]. Therefore, although NRTs are an evidence-based and substantially safer alternative to continued smoking, the cardiovascular effects of this approach should not be regarded as biologically inert.

Use patterns of different nicotine products

One of the important points of disagreement between scientists studying the consequences of tobacco smoke exposure is the use of smoking protocols, known as smoking topographies, to model smoke exposure. Smoking topography describes the frequency and volume of smoke that the user inhales during one smoking session. Due to the nature of different smoking products and their patterns of use, the topographies vary widely (Box 2). Different strategies have been developed with the aim of standardizing the exposure protocols used for chemical analysis and animal studies. These standards are primarily based on data acquired from trials in humans, but some of the standards are disputed as being too strict and not reflecting real-world use[47].

Secondhand smoke

Passive smoking, or secondhand smoke exposure, refers to the involuntary inhalation of smoke by non-smokers and remains a major global public health concern. Exposure to secondhand smoke is associated with approximately 1.66 million deaths globally each year[1]. Data from animal models and humans indicate that even a brief exposure to secondhand smoke can acutely impair endothelial function, increase platelet aggregation and trigger vascular inflammation, all early steps in the development of atherosclerotic and other cardiovascular diseases[48]. Secondhand smoke consists of both mainstream smoke (inhaled and

Table 1 | Toxic compounds in tobacco cigarettes, e-cigarettes, waterpipes and heat-not-burn cigarettes

Toxic compound type	Toxic compound	Concentration range per puff (refs.)			
		Tobacco cigarette	E-cigarette	Waterpipes	Heat-not-burn cigarettes
Carbonyls[a]	Formaldehyde	7–10 µg ([27,215,216])	0.12–82.00 µg ([162,217–219])	0.21–0.65 µg ([220,221])	0.53–2.10 µg ([222,223])
	Acetaldehyde	50–140 µg ([27,215,216])	0.2–53.0 µg ([162,217–219])	2.0–5.5 µg ([220,221])	12.8–21.0 µg ([222–224])
	Acrolein	6–14 µg ([27,215,216])	0.12–3.30 µg ([162,217–219,225])	0.06–1.19 µg ([220,221])	0.40–0.99 µg ([222,223,226])
	Propionaldehyde	0.4–5.9 µg ([27,215,216])	0.057–1.790 µg ([162,217])	0.05–1.06 µg ([215])	0.96–1.18 µg ([223])
	Crotonaldehyde	1–2 µg ([27,215,216])	ND to 0.04 µg ([227])	0.78–1.39 µg ([228])	0.24–0.64 µg ([222,223])
N-nitrosamines	*N*′-nitrosonornicotine	0.5–370.0 ng ([27,215,216])	ND to 0.029 ng ([218,229,230])	0.2 ng ([220,231])	0.5–1.0 ng ([223,226])
	N′-nitrosoanabasine	ND–15 ng ([27,215,216])	ND to 0.01 ng ([229,230])	0.05 ng ([220,231])	0.26–0.56 ng ([223,226])
	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone	1.2–77.0 ng ([27,215,216])	ND to 0.019 ng ([218,229,230])	0.27 ng ([220,231])	0.34–0.73 ng ([223,226])
	N′-nitrosoanatabine	0.8–16.0 ng ([27,215,216])	ND to 0.085 ng ([229,230])	0.6 ng ([220,231])	0.6–1.8 ng ([223,226])
Volatile organic compounds	Toluene	0.8–6.9 µg ([27,215,216])	ND to 1.53 µg ([232])	0.058 µg ([220,233])	0.08–0.25 µg ([222,223,226])
	Benzene	0.6–4.5 µg ([27,215,216])	ND to 0.41 µg ([232])	1.58 µg ([220,233])	0.01–0.06 µg ([222,223,226])
	Carbon monoxide	1.0–2.3 mg ([27,215,216])	NA	1.15–1.67 mg ([220,221,234])	0.02–0.05 mg ([223])
Inorganic compounds	Nickel	ND–60 ng ([27,215,216])	0.1–6.4 ng ([235])	9.9 ng ([220,236])	5.3 ng ([237])[b]
	Cobalt	0.013–0.020 ng ([27,215,216])	0.05–0.58 ng ([238])	0.7 ng ([220,236])	ND
	Chromium	0.4–7.0 ng ([27,215,216])	0.05–9.00 ng ([235])	13.4 ng ([220,236])	1.1 ng ([237])[b]
	Lead	3.4 – 8.5 ng ([27,215,216])	0.16–3.80 ng ([239])	68.7 ng ([220,236])	0.16 ng ([237])[b]
Heterocyclic and polycyclic aromatic hydrocarbons	Benz[*a*]anthracene	2–7 ng ([27,215,216])	NA[c]	1.3–1.6 ng ([220,231,234])	0.18 ng ([224])
	Benzo[*b*]fluoranthene and benzo[*k*]fluoranthene	1.0–3.4 ng ([27,215,216])	NA[c]	0.13–2.16 ng ([220,231,234])	0.09 ng ([224])
	Benzo[*a*]pyrene	2–4 ng ([27,215,216])	NA[c]	0.78–1.79 ng ([220,231,234])	0.08–0.10 ng ([224,240])
	Dibenzo[*a*,*h*]anthracene	0.06–0.40 ng ([27,215,216])	NA[c]	0.86 ng ([220,231,234])	ND
Nicotine	Nicotine	0.1–0.3 mg ([27,215,216])	0–0.142 mg ([238])	0–0.058 mg ([215,221,241])	0.05–0.13 mg ([222,223,226])
Particulate matter	Total particulate matter	0.1–1.7 mg, mostly solid ([216])	0.87–5.80 mg, mostly liquid ([217,242])[d]	1.8–9.3 mg ([234,241,243])	2.5–5.5 mg ([222,223,226])

NA, not applicable; ND, not detectable. [a]Most toxic carbonyls found in smoke, aerosol or vapour of tobacco or nicotine-delivery products are volatile compounds and could be termed volatile organic compounds. However, some long-chain or branched carbonyls are not volatile, which is why we present them as a separate class of toxic compound. [b]Industry-associated study. [c]Only a few studies have described concentrations of polycyclic aromatic hydrocarbons in e-cigarette aerosol that are close to the limit of quantification. For heat-not-burn cigarettes, most of the values were originally given per stick and are converted in this table to per puff quantities, assuming ten puffs per stick. [d]Liquid aerosol droplets.

exhaled by the smoker) and sidestream smoke (which is emitted from the burning tip of a cigarette or other tobacco products). The latter is especially harmful because it is generated at a lower combustion temperature (for example, at ~400 °C versus ~900 °C for mainstream smoke), resulting in higher levels of toxic substances such as ammonia, benzene, carbon monoxide, polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines[49]. Compared with mainstream smoke, sidestream smoke contains finer particles and higher concentrations of several toxicants, which penetrate more deeply into the lungs and systemic circulation. Because sidestream smoke is unfiltered and undiluted at its source, non-smokers exposed to it are subjected to a chemically distinct and, for some compounds, more concentrated toxicant profile than smokers experience from mainstream smoke alone[50,51].

The risks of passive exposure to smoke extend to other tobacco products such as waterpipes. During a single 45–60-min session, a person who smokes a waterpipe inhales about 90,000 ml of smoke, which is 100–200 times more than a person who smokes a single cigarette (about 500–600 ml), and the smoke can affect both users and bystanders[33,52]. Despite passing through water, the smoke retains high levels of carbon monoxide, tar, volatile organic compounds and heavy metals[53]. In addition, the charcoal used for heating introduces additional carbon monoxide and polycyclic aromatic hydrocarbons into the air[54], with documented effects including endothelial dysfunction and systemic inflammation in passive shisha smokers[55].

Although e-cigarettes do not rely on combustion, the exhaled aerosols contain fine and ultrafine particles, nicotine, volatile organic compounds, aldehydes (such as formaldehyde and acrolein) and metal nanoparticles[56]. However, this composition applies mostly to the previous generation of e-cigarettes, which used a high wattage that generated high volumes of aerosol. Studies show that passive exposure to these aerosols impairs endothelial function and increases oxidative stress in non-smokers[57]. Reflecting this evidence, the WHO, CDC and ESC now recommend including e-cigarettes in indoor smoking bans to protect bystanders[58]. However, modern pod-type e-cigarette devices with liquids containing high nicotine concentrations produce little or no exhaled aerosol, thereby decreasing the risk of secondhand exposure.

Smokeless nicotine products, such as snus, pouches, lozenges and gums, do not produce aerosols or sidestream smoke and thus pose no direct inhalation risk to bystanders[59]. However, concerns persist about indirect nicotine exposure through contaminated surfaces, saliva and product waste. Current evidence suggests that these risks are minimal compared with inhaled tobacco or consumption of nicotine products[6].

Nicotine-containing products and cardiovascular risk

Pathophysiological effects of nicotine

The stimulating effects of nicotine on the sympathetic nervous system, short-term stimulatory physical and cognitive effects, particularly on increasing attention and arousal[60], and its addictiveness are the main reasons why humans smoke tobacco[12]. Nicotine-induced sympathetic activation results in acute increases in heart rate, blood pressure and myocardial workload, and directly induces coronary artery vasoconstriction via α_1-adrenergic stimulation[61]. The resulting increase in cardiac output transiently raises flow-mediated dilatation (FMD) through haemodynamic mechanisms, such as increased shear stress, rather than through improved endothelial nitric oxide (NO) bioavailability[62]. In general, activation of the sympathetic nervous system is also linked to oxidative stress and inflammation, as occurs with mental stressors such as immobilization and traffic noise[63,64]. Sympathetic nervous system activation leads to systemic oxidative stress and inflammation through multiple interconnected pathways. β_1-Adrenergic receptor stimulation increases renin release and angiotensin II formation, which activates vascular NADPH oxidases (NOX1 and NOX2) via type 1 angiotensin II receptor signalling, generating reactive oxygen species (ROS)[65]. Catecholamines further promote ROS production directly by α_1-adrenergic receptor and protein kinase C-dependent activation of NOX enzymes[66] and through elevated Ca^{2+} flux and metabolic workload[67]. Catecholamines also uncouple endothelial NO synthase (eNOS; also known as NOS3)[64] and stimulate immune cells to release cytokines and oxidants[68], all of which converge to sustain vascular oxidative stress and inflammation during sympathetic overdrive.

Nicotine has also been implicated in promoting cardiac remodelling and fibrosis[69]. Moreover, a central and often underestimated finding is that nicotine itself is a direct vascular toxin, independent of combustion-derived constituents. A study using in vivo and in vitro models demonstrated that nicotine alone induces endothelial dysfunction and accelerates atherosclerosis by disrupting endothelial NO signalling[70]. Nicotine exerts direct vascular toxicity by downregulating GTP cyclohydrolase 1 (GCH1), the rate-limiting enzyme for tetrahydrobiopterin (BH_4) synthesis, thereby inducing eNOS uncoupling and leading to reduced NO bioavailability and increased ROS production[70]. In *Apoe*$^{-/-}$ mice, nicotine exposure induced endothelial dysfunction and accelerated atherosclerotic lesion formation, effects that were reversed by BH_4 supplementation or GCH1 overexpression[70]. These findings demonstrate a causal role for nicotine in redox imbalance and atherogenesis in these models. In addition to disrupting NO signalling, nicotine interferes with several other endothelial pathways that regulate vascular tone. Nicotine stimulates the release of endothelin 1 from human endothelial cells and increases circulating endothelin 1 levels[46]. Endothelin 1 is a potent vasoconstrictor that acts through the endothelin receptor type A and type B on vascular smooth muscle cells to promote vasoconstriction and vascular remodelling[46]. Chronic exposure to cigarette smoke or nicotine-containing products has also been associated with upregulation of endothelin receptors in experimental animals and humans, thereby amplifying vasoconstrictor signalling pathways[46]. Nicotine further alters the endothelial balance of vasoactive mediators by reducing the synthesis of prostacyclin (also known as prostaglandin I_2)[46], an important endothelium-derived vasodilator and inhibitor of platelet aggregation. Reduced prostacyclin bioavailability contributes to increased vasoconstriction and a prothrombotic vascular environment[46].

Nicotine also interferes with ATP-sensitive potassium channels in vascular smooth muscle cells[46]. These channels normally promote membrane hyperpolarization and vascular relaxation by facilitating potassium efflux and reducing calcium influx through voltage-gated calcium channels. Experimental studies demonstrate that nicotine blunts vasodilatory responses mediated by ATP-sensitive potassium channel activation, thereby favouring vasoconstriction and impairing endothelium-independent vasodilatation[46].

Taken together, the acute sympatho-excitatory effects of nicotine could trigger MI via increases in heart rate and blood pressure, either by inducing atherosclerotic plaque rupture, vasospasm or acute thrombosis. In support of this concept, smoking cessation has been associated with an immediate decrease in the risk of adverse cardiovascular events, even though the underlying coronary plaques remain in the short term[71]. In addition, NRT increases the risk of MI[72] (Fig. 2). Of note, the potential health effects of nicotine remain controversial due to the

phenomenon known as the 'smoker's paradox'. This term refers to the observation that tobacco cigarette smokers have better outcomes after MI than never-smokers (although the MI occurs at younger ages among people who smoke)[73], as well as to reported positive effects of nicotine from transdermal delivery via patches on ulcerative colitis[74] and of tobacco smoking and oral nicotine-delivery products on Parkinson disease and Alzheimer disease[75]. However, the so-called smoker's paradox reflects confounding by age, comorbidities and coronary anatomy rather than any protective effects of smoking. When long-term outcomes are assessed, the paradox vanishes: continued smoking after MI markedly increases the risk of recurrent events and death[76], whereas smoking cessation improves survival[71], underscoring the role of smoking cessation as an essential therapeutic intervention. However, these registry-based studies on continued smoking and cessation are mainly based on observational data, and thus undetected bias, particularly confounding by indication, cannot be excluded.

Although heated-nicotine products are generally accepted to be safer than products involving nicotine burning[62], these products still have harmful effects. For example, the angiogenic effect of nicotine, although potentially protective in the coronary circulation, might promote tumour growth and metastasis formation mediated by prothrombotic effects, promotion of tumour cell proliferation and increased DNA damage[77]. The angiogenic effect of nicotine can also foster vascularization of atherosclerotic plaques, thereby increasing the risk of plaque rupture[78]. Direct pro-inflammatory effects of tobacco-free nicotine products have also been reported in human gingival and bronchial epithelial cells in vitro[79].

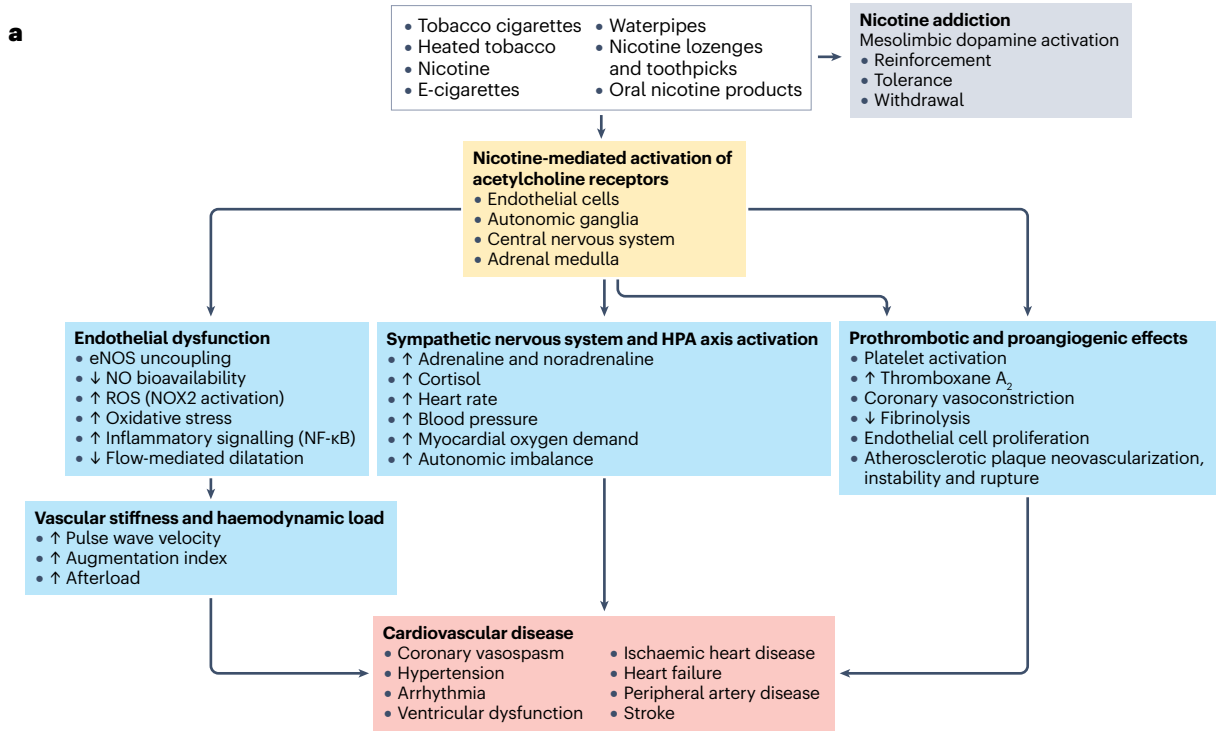
Clinical studies of nicotine-containing products and cardiovascular risk

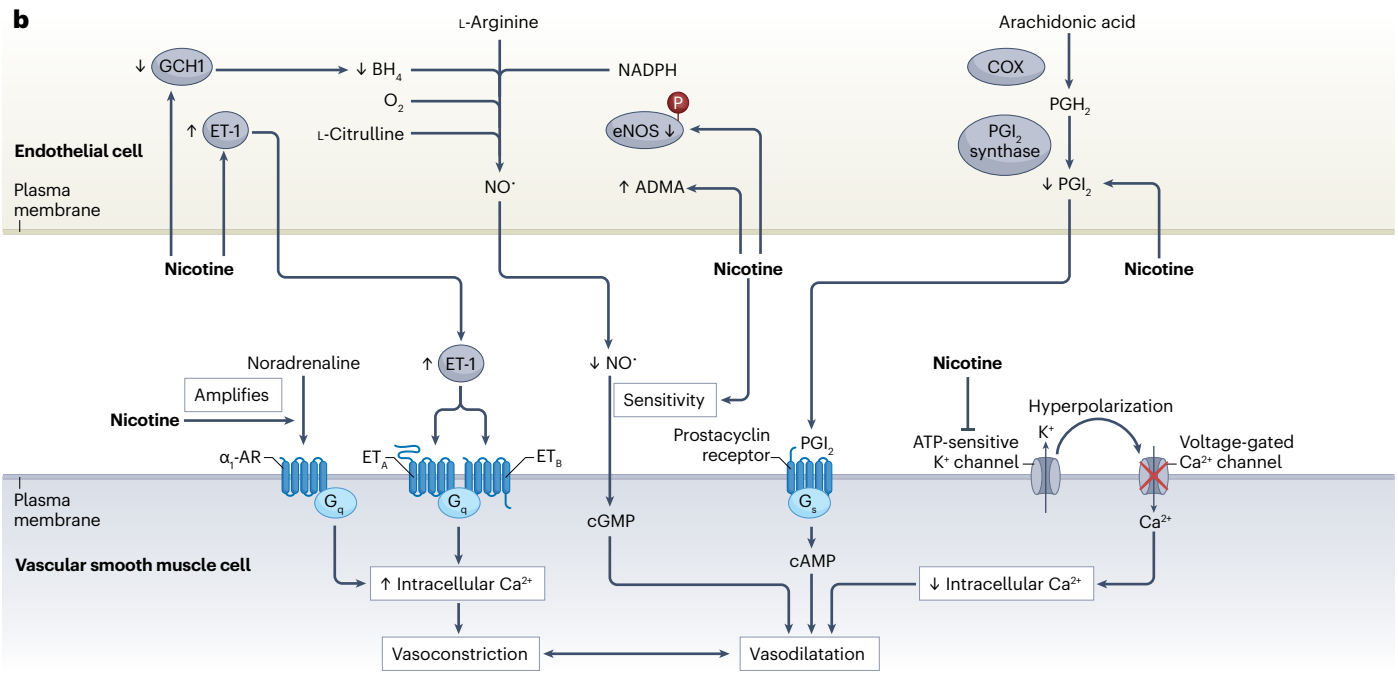
Tobacco cigarettes and waterpipes. Robust evidence from clinical studies links tobacco cigarette smoking with cardiovascular events, including coronary artery disease (CAD), MI, stroke, heart failure and cardiovascular death[48] (Tables 2 and 3). This link was first demonstrated in the British Doctors Study[80] and the Framingham Heart Study[81], and later confirmed globally in the INTERHEART study[82], which included 27,089 participants from 52 countries and showed an odds ratio of 2.95 for non-fatal MI in current smokers versus those who had never smoked. The ARIC study[83], which included 13,355 individuals and 26 years of follow-up, showed a dose–response between pack-years and an increased risk of peripheral artery disease, CAD and stroke. A meta-analysis of 25 cohorts (approximately 500,000 individuals) reported a hazard ratio of 2.07 for cardiovascular death in current smokers and 1.37 in former smokers compared with never-smokers[84].

Other nicotine products also have been associated with an increased risk of cardiovascular disease. A systematic review and meta-analysis of waterpipe smoking reported an odds ratio of 1.67 for CAD and heart failure[85]. A large Bangladeshi cohort demonstrated higher CAD-related mortality in individuals who smoked waterpipe compared with non-smokers (of any form of tobacco)[86]. Cross-sectional angiographic studies indicate a threefold higher risk of coronary stenosis in heavy users of waterpipes compared with individuals who did not smoke any tobacco product[87]. Mechanistic research has confirmed the presence of endothelial dysfunction and systemic inflammation in animal models and humans, similar to that observed with cigarette smoking[88].

E-cigarettes. The cardiovascular effects of e-cigarettes remain debated. Analyses of the US National Health Interview Survey found associations between daily use of e-cigarettes and an increased risk of MI compared with people who had never used e-cigarettes or smoked tobacco (odds ratio 1.79 for daily users and 2.11 for some-days users)[89,90]. However, the causality is uncertain. An analysis of the PATH cohort suggested no significant excess risk of cardiovascular events in exclusive e-cigarette users, but the study was underpowered owing to the small numbers of events[91]. Importantly, the PATH data revealed that the cardiovascular risk among dual users (tobacco cigarettes and e-cigarettes) was similar to that in exclusive tobacco cigarette smokers[91]. Biomarker studies showed that dual users had inflammatory and oxidative stress profiles similar to those in tobacco cigarette smokers, whereas exclusive e-cigarette users had similar (for some parameters, intermediate) levels compared with non-users (neither e-cigarettes nor tobacco cigarettes)[92]. In 2025, large, pooled datasets demonstrated a dose–response relationship between smoking exposure and vascular biomarkers, with high-sensitivity C-reactive protein values of 3.0 mg/l in exclusive e-cigarette users, which were close to the levels in never-smokers (2.6 mg/l), compared with 4.8 mg/l in smokers and dual tobacco cigarette and e-cigarette users[93,94]. These findings indicate a partial benefit in improving biomarker profiles only with complete substitution of tobacco cigarettes with e-cigarettes (Table 2). An analysis of the All of Us study (249,190 participants) found a positive association between e-cigarette use and hypertension, although no associations were observed for MI or stroke, which could have been due to the short follow-up (3.7–3.9 years)[95]. However, the lack of consistent associations between e-cigarette vaping and the risk of MI or stroke should be viewed as inconclusive rather than reassuring, given the limited availability of longitudinal data and the identification of mechanistic pathways that link nicotine to atherogenesis independently of the presence of chronic hypertension[96].

Smokeless nicotine products. Smokeless tobacco and snus are also associated with an increased cardiovascular risk. A pooled cohort analysis including 103,642 individuals reported that smokeless tobacco was associated with a hazard ratio of 1.2–1.3 for stroke, atrial fibrillation or heart failure, and was also associated with a higher risk of MI and coronary heart disease death compared with never using smokeless tobacco[97]. A Swedish registry cohort study including 43,389 patients with recent MI found that continued use of snus after the MI was associated with increased all-cause and cardiovascular mortality compared with quitting snus (hazard ratio ~1.28)[9]. An analysis of eight Swedish cohort studies (n = 169,103) showed higher all-cause and cardiovascular mortality in current users of snus (hazard ratio 1.27–1.28) compared with never-users of any tobacco product[10]. In a Swedish cohort study of 118,395 non-smoking men (almost 30% had used snuff), long-term use of snus was linked to an elevated risk of MI compared with never-users of any tobacco product[98]. A pooled analysis including 130,485 participants showed a higher incidence of stroke and stroke-related death in snus users compared with individuals who had never consumed any tobacco product[99]. A systematic review concluded that smokeless tobacco increases the risk of MI (relative risk 1.13) and stroke (relative risk 1.40) compared with people who had never used any tobacco product[100]. Data from the US NHANES and ARIC studies show that smokeless tobacco use is associated with a higher risk of hypertension and peripheral artery disease compared with never-users of any tobacco product[101]. Taken together, these findings show that although snus and smokeless tobacco confer a lower cardiovascular risk than tobacco cigarettes, these products are still associated with measurable cardiovascular morbidity and mortality, which depends also on the quality standards of the product.





Summary of evidence. Large-scale, observational studies provide important population-level insights into the cardiovascular risk associated with nicotine products; however, the interpretation requires caution. Most cohorts of exclusive users of e-cigarettes consisted predominantly of former smokers of combustible tobacco. Carryover risk from previous exposure to combustible tobacco, including persistent endothelial dysfunction, arterial stiffness and vascular inflammation as well as established atherosclerosis, might confound the associations and limit causal attribution. Cross-sectional designs further preclude reliable temporal sequencing and might underestimate cumulative risk. Tobacco cigarettes and dual use (combustible tobacco plus alternative nicotine product) are associated with the highest cardiovascular

Fig. 2 | Nicotine as a central driver of cardiovascular injury in nicotine-containing products. Schematic overview of the pathophysiological mechanisms by which nicotine, independently of the delivery system (combustible tobacco cigarettes, e-cigarettes, heat-not-burn products, waterpipes and oral nicotine formulations), contributes to cardiovascular disease. **a**, Nicotine activates nicotinic acetylcholine receptors in the autonomic nervous system, adrenal medulla and vascular endothelium, triggering sympathetic nervous system activation with increased catecholamine release. These changes result in elevated heart rate, blood pressure, myocardial contractility, cardiac output and peripheral vasoconstriction, thereby increasing myocardial oxygen demand and promoting autonomic imbalance. **b**, At the vascular level, nicotine induces endothelial dysfunction, characterized by reduced flow-mediated dilatation, increased oxidative stress and decreased nitric oxide (NO) bioavailability due to uncoupling of endothelial nitric oxide synthase (eNOS), partly driven by downregulation of GTP cyclohydrolase 1 (GCH1) and reduced tetrahydrobiopterin (BH_4) availability. Nicotine exposure also disrupts endothelial vasoactive balance through reduced prostacyclin (also known as prostaglandin I_2; PGI_2) synthesis and increased endothelin 1 (ET-1) production, promoting vasoconstriction and vascular inflammation. These mechanisms contribute to arterial stiffness and increased haemodynamic load, including elevated pulse wave velocity and augmentation index, thereby facilitating the progression to hypertension and heart failure. In parallel, nicotine activates prothrombotic and vasoconstrictive pathways, including platelet activation, thromboxane A_2 signalling, impaired fibrinolysis and coronary vasoconstriction, increasing the risk of acute ischaemic events. Proangiogenic effects of nicotine on endothelial cells promote atherosclerotic plaque neovascularization and instability, whereas chronic exposure contributes to adverse cardiac remodelling, myocardial fibrosis and impairment of systolic and diastolic function. Addiction to nicotine further amplifies exposure frequency and duration through mesolimbic dopamine activation, reinforcing cumulative vascular injury. Together, these interconnected mechanisms link exposure to nicotine to a continuum of cardiovascular harm that culminates in overt cardiovascular disease. α_1-AR, α_1-adrenergic receptor; ADMA, asymmetric dimethylarginine; COX, cyclooxygenase; ET_A, endothelin receptor type A; ET_B, endothelin receptor type B; HPA, hypothalamic–pituitary–adrenal; NF-κB, nuclear factor-κB; NOX2, NADPH oxidase 2; ROS, reactive oxygen species.

burden (Table 2). Cigar and pipe smoking, as well as smokeless tobacco (including snus), are in an intermediate, but clinically meaningful, risk category. Exclusive use of e-cigarettes seems to be less toxic than combustible tobacco products in short-term biomarker studies, with the levels of some toxicants approaching those found in never-users; nevertheless, normalization of biomarker profiles does not equate to proven cardiovascular safety. Across all product categories, complete abstinence remains the lowest-risk strategy. Tables 3–5 summarize the hierarchy of evidence: robust longitudinal and mechanistic data support the cardiovascular harm of tobacco cigarettes and smokeless tobacco; evidence for e-cigarettes is moderate and largely based on biomarker studies; and much of the survey literature remains cross-sectional with inherent methodological limitations. Crucially, the main evidence gap is the lack of long-term, adjudicated cardiovascular outcome data, particularly for individuals who exclusively use e-cigarettes or oral nicotine products. Well-powered, prospective studies in nicotine-naive populations are urgently required to define absolute cardiovascular risk and inform regulatory decision-making.

Clinical studies of nicotine-containing products and vascular function

Endothelial dysfunction provides the most sensitive and integrative measure of the hierarchy of harm of nicotine-containing products, reflecting oxidative, inflammatory and autonomic pathways that converge on vascular injury and adverse cardiovascular outcomes. Endothelial function represents a mechanistically proximal intermediate phenotype linking exposure to cardiovascular risk[102] (Box 3) and, therefore, in this Review, we use this parameter as the primary biomarker of the cardiovascular effects of nicotine-containing products (Supplementary Table 1).

Tobacco cigarettes. Among all forms of tobacco use, conventional cigarette smoking remains the most extensively studied. Early work established a robust dose-dependent relationship between cumulative tobacco exposure and impaired FMD of the brachial artery[103]. This association was observed in later studies, showing that chronic smokers had impaired endothelium-dependent coronary vasodilatation[104]. Importantly, cessation of cigarette smoking seems to allow partial vascular recovery: improvement in FMD by 1% was found after 1 year of smoking abstinence[105]. However, smoking light cigarettes (which have less nicotine and more efficient filters and, therefore, less toxic compounds in the smoke than regular cigarettes) did not confer a lower vascular risk than smoking regular cigarettes[106].

Acute exposure to cigarette smoking causes rapid deterioration of endothelial function. Smoking a single cigarette has been shown to transiently impair FMD compared with the FMD in never-smokers or in paired analysis of individuals before and after the smoking session[107,108]. Exposure to secondhand smoke also induced dose-dependent reductions in vascular function among healthy young individuals[109]. Encouragingly, the vascular dysfunction induced by passive smoke might be partially reversible after cessation of exposure[110].

Mechanistic insights reveal that oxidative stress and eNOS uncoupling are pivotal mediators of smoking-induced endothelial injury[111]. Vitamin C supplementation and BH_4 administration restore endothelial responsiveness in chronic smokers, confirming the role of oxidative perturbations in smoking-induced endothelial dysfunction[112].

Early exposure to tobacco smoke compounds the risk of vascular dysfunction. An analysis of the ALSPAC cohort identified additive deleterious effects of tobacco smoking and alcohol consumption on vascular function during adolescence[113]. A 2024 meta-analysis of 14 cohort studies found a pooled mean difference of −3.15% (95% confidence interval −3.84% to −2.46%) in FMD in current tobacco smokers compared with non-smokers[107]. Available data indicate a graded alteration in FMD, with lower vasodilatation among current smokers compared with non-smokers and intermediate FMD values among former smokers, and a favourable response in FMD with smoking cessation that also corresponds to the duration and dose of exposure to tobacco smoking[103,107,114]. These findings highlight both the legacy of tobacco use on vascular harm and the potential for recovery. The dose–response effect of tobacco smoking has also been observed in other ethnic groups, such as in Japanese individuals, with progressively worsening FMD across increasing pack-year categories[115].

Tobacco smoking also impairs microvascular function, as evidenced by reductions in reactive hyperaemia index and reflection index compared with never-smokers reported in the Gutenberg Health Study[116]. Another study suggests a diminished myocardial stress perfusion response to cold pressor testing in current tobacco smokers compared with non-smokers[117].

Table 2 | Health risks associated with different nicotine-containing products

Condition	Tobacco cigarettes	Waterpipes	E-cigarettes	Heated-tobacco products	Oral nicotine products
All-cause mortality	HR 1.40 (1.06–1.86) for men; HR 1.65 (1.16–2.36) for women [86]	OR 1.15 (0.93–1.43); HR 1.47 (1.23–1.76)[85,244]	HR 1.30 (1.01–1.66)[21]	NA	HR 1.39 (1.22–1.58); HR 1.46 (1.34–1.60)[97]; HR 1.28 (1.20–1.35)[10]
	Evidence grade: high	Evidence grade: high	Evidence grade: moderate	–	Evidence grade: high
Arterial stiffness	AIx+5.5%[245,a]	AIx+8.8%[246,b]	AIx+11.2%[247,a]	AIx+6.2%[248,b]	AIx+7.2%[59,a]
	Evidence grade: moderate	Evidence grade: low	Evidence grade: low	Evidence grade: low	Evidence grade: low
Chronic obstructive pulmonary disease	OR 2.90 (2.22–3.80)[249]	OR 3.18 (1.25–8.08)[85]	OR 1.55 (1.26–1.84); HR 2.29 (1.42–3.71)[95,250]	NA	NA
	Evidence grade: moderate	Evidence grade: high	Evidence grade: high	–	–
Cardiovascular disease mortality	HR 2.07 (1.82–2.36); HR 1.87 (1.08–3.24)[84,86]	HR1.23 (1.01–1.50)[244]	HR 1.30 (1.01–1.67)[21]	NA	HR 1.41–1.54 (1.20–1.65, 1.24–1.91); HR 1.27 (1.15–1.41)[10,97]
	Evidence grade: high	Evidence grade: high	Evidence grade: moderate	NA	Evidence grade: high
Coronary artery disease	RR 2.34 (1.96–2.79)[251]	OR 1.56 (1.36–1.79)[244]	OR 1.89 (1.01–3.53)[90]	NA	HR 1.41 (1.21–1.64)[97]
	Evidence grade: high	Evidence grade: high	Evidence grade: moderate	–	Evidence grade: high
Erectile dysfunction	OR 1.51 (1.34–1.71)[252]	NA	OR 2.24 (1.50–3.34)[253]	NA	NA
	Evidence grade: moderate	–	Evidence grade: moderate	–	–
Heart failure	RR 1.75 (1.54–1.99)[254]	HR 1.23 (1.01–1.49)[97]	HR 1.35 (0.75–2.42)[91,c]	NA	HR 1.41 (1.22–1.64)[97]
	Evidence grade: high	Evidence grade: moderate	Evidence grade: moderate	–	Evidence grade: high
Lung cancer	HR 13.1 (9.90–17.3)[255]	RR 3.25 (2.01–5.25)[256]	NA	–	RR 1.53 (1.09–2.14)[256]
	Evidence grade: high	Evidence grade: moderate	–	–	Evidence grade: moderate
Myocardial infarction	OR 2.95 (2.77–3.14); OR 4.34 (3.68–5.12)[82,257]	OR 1.33 (1.04–1.68); HR 1.43 (1.17–1.74)[97,258]	OR 1.44 (1.22–1.74); OR 1.79 (1.20–2.66)[89,96]	NA	RR 1.13 (1.06–1.21); HR 1.20 (1.03–1.39); RR 1.96 (1.08–3.58)[97,98,100]
	Evidence grade: high	Evidence grade: moderate	Evidence grade: high	–	Evidence grade: high
Perceived addictiveness[d]	PP 60.6–87.3%[259]	PP 45.2%[259]	PP 49.8%[259]	NA	NA
	Evidence grade: moderate	Evidence grade: moderate	Evidence grade: moderate	–	–
Peripheral endothelial dysfunction[e]	FMD –50.5%[133]	FMD –63.3%[144]	FMD –39.3%[144]	FMD –41.4%[260]	FMD –12.6%[154]
	Evidence grade: low	Evidence grade: low	Evidence grade: low	Evidence grade: moderate	Evidence grade: low
Stroke	OR 1.90 (1.55–2.34)[261]	OR 2.79 (1.74–3.84)[262]	OR 1.52 (1.17–1.97)[263]	NA	OR 1.17 (1.04–1.30)[264]
	Evidence grade: high	Evidence grade: moderate	Evidence grade: high	–	Evidence grade: moderate

The strength of clinical evidence has been graded as low (single cohort study of <500 individuals), moderate (single cohort study of 500–10,000 individuals) or high (large-scale, meta-analysis or cohort study of >10,000 individuals). The values are from selected representative studies with different quality levels of evidence, highlighting the need for more research. Some studies actively adjusted for dual use of nicotine products. However, in chronic-exposure studies, individuals classified as users of one specific nicotine-delivery method might have consumed two or more different nicotine products in the past or during the study period, either frequently or occasionally. For example, users of e-cigarettes or heated-tobacco products are often former tobacco cigarette smokers. AIx, augmentation index; FMD, flow-mediated dilatation; HR, hazard ratio; NA, not available; OR, odds ratio; PP, proportion of participants; RR, relative risk. [a]Absolute increase in AIx in response to exposure. [b]Acute effects on AIx. [c]Combined end point of risk of myocardial infarction, heart failure or stroke. [d]Proportion of participants who believe that smoking or vaping is addictive. [e]Change based on healthy control values.

Collectively, these data reaffirm that smoking induces profound endothelial dysfunction across vascular beds, with restoration of endothelial function after smoking cessation that is partly contingent on dose and duration of exposure. This observation might imply that, although cessation initiates vascular repair, a residual risk might persist for years, reflecting the enduring hazard of tobacco exposure.

Besides FMD, three other methods can be used to assess endothelial function: carotid intima–media thickness (cIMT), which is used as an early marker of atherosclerosis; pulse wave velocity (PWV), a marker of arterial stiffness and vascular health; and heart rate variability, a readout for sympatho-vagal balance and cardiovascular fitness. Studies using these methods have shown overall similar results to those obtained with FMD-based assessment. A meta-analysis including 34,025 men and women from 15 cohorts found that cIMT was increased in smokers compared with never-smokers[118]. However, two smaller studies found no effect of smoking on cIMT[119,120]. A meta-analysis on tobacco smoking and PWV reported increased PWV especially when measured immediately after smoking[121]. However, other studies have found no effects of tobacco smoking on PWV[122]. Finally, a large study of 4,751 participants found that heart rate variability was lower in current smokers than in past smokers[123].

E-cigarettes. The growing prevalence of e-cigarette use has sparked intense investigation into its potential vascular consequences. Early optimism about the safety of e-cigarettes has waned given

the evidence of their association with endothelial impairment. One study found that short-term exposure to e-cigarettes or to conventional tobacco cigarettes induced similar plasma levels of markers of oxidative stress, reduced NO bioavailability and impaired FMD to those in people who had never smoked[124]. A small clinical trial showed that exposure to nicotine-containing, but not nicotine-free, aerosols from e-cigarettes induced endothelial dysfunction (measured by acetylcholine-dependent microvascular perfusion and PWV) in individuals who were occasional tobacco smokers[125]. Acute vascular stiffening (higher PWV) following e-cigarette use has also been confirmed in current tobacco smokers in other clinical studies[126,127], with concomitant acute alterations in peripheral and central aortic blood pressure that were often persistent for 1–2 h after e-cigarette use[127]. One study including 15 healthy female individuals who smoked suggested lower impairment of arterial stiffness and reflection index with acute e-cigarette use compared with tobacco smoking, although the study was not a controlled trial and thus the finding needs verification[128]. A study including 16 healthy individuals who seldomly smoked showed that short-term (10-min) vaping was associated with increases in the number of circulating endothelial progenitor cells[129], which is indicative of vascular injury. Single-session exposure of healthy individuals who were tobacco smokers to e-cigarettes, HNB devices or tobacco cigarettes all acutely impaired FMD and several parameters of oxidative stress, antioxidant reserve and platelet function, albeit to varying degrees, with tobacco cigarettes having the most effect on many of these measures[130].

Chronic users of e-cigarettes also show reduced endothelium-dependent vasodilatation compared with people who had never smoked or vaped, with more pronounced effects observed among female individuals[131]. Microvascular dysfunction is also evident in healthy non-smokers after acute use of e-cigarettes, caused by impaired vascular smooth muscle cell reactivity following nicotine-containing vaping[132]. These findings are mirrored by diminished NO release from human cultured endothelial cells incubated with sera from tobacco cigarette or e-cigarette users versus sera from never-smokers[133]. A study including individuals who consumed e-cigarettes or tobacco cigarettes reported increases in arterial stiffness after acute use of JUUL devices (Juul Labs) compared with baseline[134]. In addition, another study found that chronic use of e-cigarettes confers arterial stiffness levels similar to those associated with tobacco cigarette use[57].

However, not all studies have consistently detected acute endothelial impairment following e-cigarette use. A controlled clinical trial found that acute tobacco cigarette smoking (one cigarette) impaired FMD compared with sham control in chronic smokers of tobacco cigarettes[135]. By contrast, acute vaping of a similar e-cigarette dose (as estimated by change in plasma nicotine levels) did not decrease FMD in chronic users of e-cigarettes[135]. Similarly, variable effects on vascular function have been reported after exposure to nicotine-free aerosols[136,137]. Nevertheless, e-cigarette aerosol is not inert. Data from cell and animal models show that exposure to e-cigarette aerosol promotes vascular inflammation and oxidative stress, potentially contributing to thrombosis and atherosclerosis[138,139]. Overall, reports on increased PWV and cIMT in exposed mice[140] and humans[121], as well as impaired heart rate variability in e-cigarette users[141] support the conclusion that e-cigarette use damages the endothelium and impairs cardiovascular health.

Waterpipes. Vascular impairments associated with waterpipe use have been reported. Acute sessions of waterpipe smoking elevate vascular resistance and diminish forearm blood flow[142]. Acute use of waterpipes also decreased heart rate variability in a crossover study with 32 participants[143]. Chronic smokers of waterpipes have been reported to have lower FMD than chronic smokers of tobacco cigarettes or than individuals who never smoked[144]. Of note, the individual's fitness level modulates the susceptibility to vascular impairments[145], and waterpipe smoking potentially has variable effects across vascular beds[55].

The advent of electronic waterpipes or e-hookahs has expanded the landscape of potential vascular effects. For example, electrically heated waterpipes acutely reduce FMD, whereas charcoal-heated waterpipes might transiently increase FMD owing to carbon monoxide-mediated vasodilatation and augmented shear stress[54]. However, this response reflects an acute haemodynamic effect and

Table 3 | Clinical studies of tobacco cigarettes and cardiovascular risk

Study design (year)	*n*	Exposure assessment	Primary CVD end point or biomarker	Effect estimates	Key limitations	Evidence grade	Rationale for grade
Prospective cohort, British Doctors Study, UK (1954)[80]	34,439	Baseline questionnaires; mortality follow-up 2.5 years	All-cause and CVD death	↑ Mortality in smokers; dose–response	Male physicians, early exposure capture	High	Prospective, long follow-up, hard outcomes
Prospective cohort, Framingham Study, USA (1962)[81]	5,209	Clinic exams; standardized questionnaires	CHD incidence	Smoking strongly associated with CHD	Limited diversity, early methods	High	Adjudicated events, foundational cohort
Case–control, INTERHEART, 52 countries (2006)[82]	27,089	Standardized interview	Non-fatal MI	OR 2.95 for current smoking versus never smoked	Recall bias, case–control design	Moderate–high	Global, very large cohort
Prospective cohort, ARIC, USA (2019)[83]	13,355	Detailed smoking history (pack-years)	Incident PAD, CAD, stroke	Clear dose–response	Residual confounding possible	High	Longitudinal, adjudicated outcomes
Meta-analysis of 25 cohorts, global (2015)[84]	503,905	Cohort-level exposure data	Cardiovascular mortality	HR 2.07 current smoking versus never smoked	Heterogeneity across cohorts	High	Robust synthesis
Prospective pooled cohorts, USA (2025)[93]	182,364	Detailed dose and intensity	hsCRP, fibrinogen, carotid IMT	Clear dose–response gradient	Observational confounding possible	High	Robust gradient across cohorts

CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; hsCRP, high-sensitivity C-reactive protein; IMT, intima–media thickness; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio; PAD, peripheral artery disease.

does not indicate improved endothelial function or reduced cardiovascular risk[54]. A study in hookah users showed that e-hookah vaping containing nicotine impaired FMD compared with sham control, whereas nicotine-free e-hookah aerosols had no effect[146]. E-hookah use acutely elevated the PWV and augmentation index — a measure of arterial stiffness and wave reflection that is used to assess cardiovascular risk and vascular health — indicating greater arterial stiffening, and was associated with systemic inflammation, as determined by elevated plasma C-reactive protein levels, compared with traditional waterpipes[147]. Pretreatment with antioxidants attenuates the FMD impairment following e-hookah vaping[148], implicating oxidative stress as a key mediator. Waterpipe use might also be associated with early vascular ageing, as suggested by higher augmentation indices among habitual smokers of waterpipes compared with individuals who had never used a waterpipe, although central arterial stiffness (carotid–femoral PWV) was similar to that of non-smokers[149]. These findings underscore that the use of either traditional or electronic waterpipes is deleterious to vascular health, with nicotine having a central pathological role.

Heat-not-burn and smokeless nicotine products. Vascular studies also suggest potential adverse vascular effects of HNB products.

Table 4 | Clinical studies of e-cigarettes and cardiovascular risk

Study design (year)	*n*	Exposure assessment	Primary CVD end point or biomarker	Effect estimates	Key limitations	Evidence grade	Rationale for grade
Cross-sectional, NHIS, USA (2018)[89]	69,452	Self-reported use	Self-reported MI (ever)	OR 1.79 for MI in daily e-cigarette versus never-users	Reverse causation, self-reported	Low	Hypothesis-generating
Randomized trial, UK (2019)[165]	114	Assigned switch from tobacco cigarettes to e-cigarettes versus continue tobacco cigarettes	FMD, PWV	↑ FMD by 1.5%; ↓ PWV by 0.5 m/s at 1 month after switching	Short duration, selected sample	Moderate–high	Randomized, mechanistic end points
Cross-sectional, NHIS, USA (2019)[90]	59,770	Self-reported use	Self-reported MI	OR 2.11 for MI in some-days e-cigarette users versus never-users; no differences for daily users	Cross-sectional, definitions vary	Low	Design limitations
Cross-sectional, PATH, USA (2021)[92]	7,130	Self-reported, clinical blood parameters	hsCRP, IL-6, F2-isoprostanes	Dual use[a] similar to exclusive tobacco use; exclusive e-cigarette use similar to never smoked	Cross-sectional, no outcomes	Moderate	USA-only sample, objective biomarkers
Longitudinal, PATH waves 1–5, USA (2022)[91]	24,027	Self-reported patterns	Incident CVD (self-reported)	Exclusive e-cigarette use OR 1.16 (wide CI, NS) versus never-smokers; dual use[a] similar to exclusive tobacco use	Few events in exclusive e-cigarette group, outcome self-reported	Moderate	Prospective but underpowered
Cross-sectional surveillance, BRFSS, USA (2023)[265]	414,755	Self-reported	Use prevalence, demographics	E-cigarette use prevalence 6%; dual use[a] was common	No outcomes	Low	Contextual denominator only
Longitudinal data, All of Us, USA (2025)[95]	249,190	Self-reported exposure, EHR-linked outcomes	Incidence of ASCVD, COPD, HF, hypertension and T2DM	E-cigarette: COPD HR 2.29, hypertension HR 1.39 in those aged 30–70 years, no association with ASCVD, HF or T2DM; tobacco-only and dual use[a] increased risk of all outcomes	Short follow-up (3.7–3.9 years); e-cigarette group small (*n*=3,164), limited power for rarer outcomes	Moderate	Large, diverse cohort; objective EHR-confirmed end points, adjusted Cox regression; exclusive combustible cigarette use used as positive control to validate methodology
Randomized, crossover, patients with HIV, mechanistic, USA (2025)[266]	28	Verified exposure, e-cigarette versus tobacco cigarette	Monocyte migration, foam cells	E-cigarette similar to never smoked; tobacco worse than e-cigarette	Specific population, surrogate end points	Moderate	Mechanistic insight
Cross-sectional, Cross Cohort Collaboration, USA (2025)[94]	18,797	Self-reported across cohorts	hsCRP	Never-use similar to exclusive e-cigarette use (1.2 mg/l versus 1.3 mg/l); tobacco use 2.5 mg/l; dual use[a] 3.2 mg/l	Cross-sectional; device, dose unknown	Moderate	Consistent gradient

ASCVD, atherosclerotic cardiovascular disease; BRFSS, Behavioral Risk Factor Surveillance System; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; EHR, electronic health record; FMD, flow-mediated dilatation; HF, heart failure; HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; MI, myocardial infarction; NS, not significant; OR, odds ratio; PWV, pulse wave velocity; T2DM, type 2 diabetes mellitus. [a]Dual use refers to consumption of both tobacco cigarettes and e-cigarettes.

Table 5 | Clinical studies of waterpipes, cigars, pipes and smokeless tobacco and cardiovascular risk

Study design (year)	*n*	Exposure assessment	Primary CVD end point or biomarker	Effect estimate	Key limitations	Evidence grade	Rationale for grade
Waterpipe							
Prospective cohort, Bangladesh (2013)[86]	20,033	Questionnaires, mortality at 7.6 years	CAD mortality	↑ CAD mortality among waterpipe users versus never-smokers	Exposure misclassification	Moderate–high	Prospective, hard outcomes
Cross-sectional clinical, Lebanon (2014)[87]	1,210	Questionnaires, clinical angiography	Coronary stenosis	≥40 years of waterpipe smoking associated with threefold higher risk of stenosis	Cross-sectional, selection bias	Low–moderate	Association strong, design limits
Systematic review and meta-analysis, multiple countries (2017)[85]	NA	Cross-sectional and cohort studies (pooled)	Prevalent CAD	OR 1.67 and 3.75 in two cross-sectional studies, both waterpipe smokers versus never-smokers	Cross-sectional design limits causal inference; only two primary studies, with heterogeneous effect sizes	Moderate	Synthesis limited by small number and heterogeneity of the primary studies
Cigars, pipes, smokeless tobacco							
Prospective cohort, Sweden (2007)[98]	118,395	Registers; snus status	MI incidence	HR 1.3 for MI in long-term users of snus versus never-smokers or snus users	Confounding by lifestyle, alcohol consumption, men only	Moderate–high	Large cohort, hard end points
Systematic review and meta-analysis, USA and Sweden (2009)[100]	NA	Observational cohort, case–control studies (pooled); smokeless tobacco	Fatal MI and fatal stroke	RR 1.13 for fatal MI; RR 1.40 for fatal stroke	Heterogeneity across studies	Moderate	Synthesis limited by inability to distinguish risk from North American or Swedish products
Prospective study of eight cohorts, Sweden, (2012)[267]	130,361	Self-report and mortality registry; snus	Incident acute MI and 28-day case–fatality after acute MI	No association between current snus use and incident acute AMI or 28-day case–fatality after acute MI	Residual confounding by socioeconomic status	Moderate	Low number of outcome events; male-only cohort; self-reported exposure
Prospective pooled analyses, Sweden (2014)[99]	130,485	Registers; snus status	Stroke incidence and survival	OR ~1.4 for 28-day mortality after stroke	Residual confounding, few data from women	Moderate–high	Large, pooled dataset, registry outcomes
Prospective cohort, Sweden (2014)[9]	43,389 patients with MI	Registers; snus status	All-cause and CVD mortality	Increased mortality after MI in snus group	Confounding by disease severity	Moderate–high	Large registry, hard outcomes
Prospective cohort, Sweden (2021)[10]	169,103	Registers; snus status	All-cause and CVD mortality	Increased mortality in subgroups	Exposure changes over time	Moderate–high	Large cohort; registry outcomes
Cross-sectional, NHANES, USA (2023)[101]	16,336	Self-reported plus exams; smokeless chewing tobacco, snuff	Hypertension, PAD, metabolic markers	Higher risk of hypertension and obesity in users	Cross-sectional	Low–moderate	National sample, design limitations
Prospective pooled cohorts; USA (2025)[97]	103,642	Baseline self-report, outcomes follow-up 13.8 years; cigars, pipes, smokeless tobacco	Stroke, atrial fibrillation, heart failure, MI, CHD death	HR ~1.2–1.3 with any of the three products versus never consumed	Residual confounding, misclassification	High	Large, prospective; hard outcomes
Cross-sectional, USA (2025)[157]	98,450	Self-reported use; laboratory and imaging markers; tobacco cigarettes versus cigars, pipes, smokeless tobacco	hsCRP, fibrinogen, carotid IMT	All products associated with all adverse markers, but non-cigarette products less pronounced than cigarettes	Cross-sectional design; no assessment of exposure intensity or pack-years for non-cigarette products; dual or poly use not evaluated	Moderate	Biomarker plausibility

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; MI, myocardial infarction; NA, not available; OR, odds ratio; PAD, peripheral artery disease; RR, relative risk; SES, socioeconomic status.

Children exposed to passive HNB product emissions had impaired FMD, reduced NO bioavailability and heightened oxidative stress, paralleling the effects seen in children exposed to passive tobacco cigarette smoke, compared with children not exposed to either product[150]. Among adult users of HNB products, switching from tobacco cigarettes to HNB products might lead to some vascular recovery, as indicated by improved FMD[151]. Nevertheless, acute use of HNB products has been associated with impaired endothelial function and reduced NO bioavailability after a single exposure session in healthy smokers and vapers[152,153], with acute FMD impairments similar to those seen with e-cigarette use[130].

Smokeless tobacco products similarly impair vascular function. Chronic use of snus is associated with increased arterial stiffness and impaired endothelial responsiveness compared with non-users[59], findings that are consistent with the lower FMD observed among snuff users[154]. Even a single administration of moist snuff leads to acute endothelial dysfunction[155]. Moreover, habitual users of snuff have vascular profiles similar to those in tobacco cigarette smokers[156].

Therefore, although HNB products and smokeless tobacco avoid the exposure to combustion-related toxins, they still have potential to harm vascular health via oxidative stress, sympathetic activation and endothelial dysfunction. Smokeless tobacco is also associated with increased cIMT[157] and augmentation index[158]. Acute exposure to HNB products also increases the PWV and augmentation index[159,160] and reduces heart rate variability[161]. The convergence of these mechanisms provides biological plausibility for vascular injury even when epidemiological risk differs across product categories. Accordingly, similar short-term effects on FMD should be interpreted as evidence of shared pathophysiological pathways rather than as a direct indicator of equivalent long-term cardiovascular risk, which is likely to be shaped by the broader toxicant profile and exposure intensity associated with each product. Overall, these data support pro-atherosclerotic effects and impaired endothelial integrity by smokeless tobacco and HNB products.

Switching from combustion to aerosol products. Translational and clinical data provide insights into the cardiovascular effects of switching from combustible tobacco to electronic nicotine-delivery systems. Toxicological comparisons show that e-cigarettes emit considerably fewer harmful substances than combustible tobacco cigarettes[162]. This notion has led public health authorities, such as the National Health Service in the UK, to cautiously support the use of e-cigarettes in smoking cessation, particularly among patients with cardiovascular disease who have failed with other strategies for smoking cessation[163]. Some evidence suggests that transitioning might yield partial vascular benefits. PWV improved in tobacco smokers who switched to e-cigarettes compared with values before switching and those in individuals who continued tobacco smoking[164]. Another study found improvements in endothelial function and arterial stiffness just 1 month after switching from tobacco cigarettes to vaping[165]. This finding has potential implications for patients with CAD, who are prone to pro-atherosclerotic effects triggered by endothelial dysfunction and vascular stiffness. In the VESUVIUS trial[165], tobacco smokers who replaced cigarettes with e-cigarettes for just 4 weeks had meaningful improvements in endothelial function compared with values before switching and those in individuals who continued tobacco smoking, with FMD and arterial stiffness values approaching those seen in non-smokers. Blood pressure levels and oxidative stress markers also declined[124], suggesting that removing combustion compounds from nicotine-containing products yields rapid vascular benefit. Notably, these improvements occurred regardless of nicotine content, underscoring that combustion, rather than nicotine, is the main source of acute vascular toxicity with these products.

In a 2024 study including nearly 18,000 patients undergoing percutaneous coronary intervention, both the patients who completely quit smoking and those who switched to exclusively use e-cigarettes experienced fewer major adverse cardiovascular events (MACE) during a median follow-up of 2.4 years than those who continued to smoke[166]. However, dual users (those who continued to smoke while vaping) derived no such benefit[166], confirming that harm reduction depends on complete substitution. These findings offer the first large-scale evidence that switching to exclusive use of e-cigarettes might lower the risk of cardiovascular events for secondary prevention, even if switching does not fully match the benefit of cigarette and e-cigarette abstinence. Mechanistically, this benefit might stem from reduced vascular oxidative stress, a central driver of endothelial dysfunction and MACE[111,167]. In an accompanying editorial, we welcomed these data as a sign of progress but cautioned against complacency[168]. Studies on endothelial function and biomarkers reveal persistent oxidative stress, sympathetic activation and vascular inflammation across all non-medical nicotine products, albeit at lower intensity without combustion, as outlined in previous sections. Together, these studies convey a consistent message: eliminating combustion clearly reduces vascular injury and can improve prognosis, but ongoing exposure to nicotine products sustains a residual cardiovascular risk and addiction. Vaping might serve as a transitional step for some tobacco cigarette smokers unable to quit, but the ultimate goal of public health and cardiology remains complete nicotine-product cessation.

Summary of evidence. The available data allow a comparative ranking of the effects of nicotine-containing products on endothelial function in humans. Across all modes of nicotine delivery, whether combustible or not, evidence consistently demonstrates adverse effects on vascular function. At the top of the harm spectrum, tobacco cigarettes consistently produce the most substantial impairment of endothelial function, with robust evidence for both acute and chronic use. Waterpipe and e-hookah products also acutely impair endothelial function, although results vary by device and nicotine content. E-cigarettes seem to be less harmful than tobacco cigarettes and might confer partial vascular benefit when used exclusively in place of tobacco smoking, but still cause endothelial changes. HNB devices similarly show partial benefit compared with tobacco cigarettes, but cause minor endothelial dysfunction. Finally, smokeless tobacco, despite the absence of combustion, also produces measurable endothelial abnormalities and arterial stiffness. In summary, the evidence supports a coherent model: removing combustion reduces but does not abolish endothelial harm, and thus nicotine-containing products of all types cannot be regarded as risk-free for vascular health.

Experimental studies of nicotine-containing products and vascular function

Experimental studies in animal models provide crucial mechanistic insights into how tobacco and nicotine products impair vascular health (Supplementary Table 2). These types of study are essential because they allow controlled exploration of exposure–response relationships that cannot be ethically performed in humans.

Tobacco cigarettes. In rats and rabbits, prolonged exposure to cigarette smoke disrupts acetylcholine-induced vasorelaxation, reduces

coronary perfusion and causes structural endothelial injury, together with increased plasma cholesterol and lipid peroxidation levels[169,170]. Even short-term (approximately 2-week) exposure to cigarette smoke induced endothelial dysfunction and mild hypertension in mice, mediated by downregulation of sirtuin 3 expression and increased mitochondrial oxidative stress, a phenotype that was reversed by overexpression of catalase[171]. Exposure of Sprague–Dawley rats to sidestream smoke compromised femoral artery FMD, an effect that was reproduced by inhalation of synthetic aldehydes, such as acrolein and acetaldehyde, a finding that identifies these compounds as major vasoactive toxicants[172]. In BALB/c mice, exposure to cigarette smoke induced dysfunction of the thoracic aorta, attributed to suppression of eNOS activity and increased oxidative stress in endothelial cells, both of which were reversible with administration of the antioxidant ebselen[173].

C57BL/6 mice exposed to cigarette smoke also show elevated expression of inducible NO synthase, NLRP3 inflammasome and caspase 1 p20 in the aorta, leading to vascular pyroptosis[174]. Knockdown of genes encoding these mediators preserved endothelial function[174]. Long-term (48-week) exposure of mice to cigarette smoke depletes BH_4 and causes eNOS uncoupling, leading to superoxide rather than NO production[175]. In mice exposed to tobacco smoke, deletion of the gene encoding the detoxifying enzyme glutathione S-transferase P amplifies the accumulation of acrolein adducts in the lung, plasma and aorta, as well as endothelial injury, confirming the role of aldehyde detoxification pathways in the smoke-induced endothelial harm[176]. These findings establish oxidative and nitro-oxidative stress as central mechanisms of tobacco smoke-related vascular damage.

E-cigarettes. E-cigarette studies consistently reveal similar, although generally less intense, vascular toxicity as tobacco cigarettes. In mice, 3 days of whole-body exposure to e-cigarette vapour induced endothelial dysfunction through NOX2 activation, eNOS uncoupling and acrolein–protein adduct formation, effects that were preventable by NOX2 inhibition, endothelin receptor blockade or *Nox2* deletion[139]. Chronic (8–13 months of) whole-body exposure of mice to e-cigarette vapour produces arterial stiffening, endothelial dysfunction, higher blood pressure, diminished NO bioavailability and increased 3-nitrotyrosine levels compared with unexposed mice, indicating persistent nitro-oxidative stress, with effects increasing with higher nicotine concentrations in the vapour[177,178]. A mouse study using the same exposure protocol reported similar detrimental effects of e-cigarette aerosol with high nicotine content and tobacco cigarette smoke on endothelial function, blood pressure and oxidative stress[179]. In rats, short-term exposure to high-nicotine aerosols (such as those in JUUL devices) caused greater FMD impairment than low-nicotine formulations[180]. Remarkably, even nicotine-free aerosol provokes endothelial dysfunction via TRPA1-dependent oxidative pathways in mice, whereas inhibition of the receptor for advanced glycation end-products (RAGE) prevents these effects in rats[181,182]. These results highlight that not only nicotine but also carrier solvents and flavouring chemicals contribute to endothelial injury.

Waterpipes. In mice, 1 month of exposure to waterpipe smoke (30 min per day) upregulated endothelial adhesion molecules and pro-apoptotic markers and reduced sirtuin 1 expression compared with unexposed mice, indicating accelerated endothelial ageing[183]. Longer exposure further elevated oxidative stress markers, suppressed antioxidant defences and impaired NO signalling in mice[184,185]. Because waterpipes use charcoal as a heat source, high levels of polycyclic aromatic hydrocarbons compound their vascular toxicity, and carbon monoxide contributes to tissue hypoxia owing to carboxyhaemoglobin formation[186], despite the general vasculo-protective effects of carbon monoxide[187].

Heat-not-burn products. Among all nicotine-containing products, HNB products produce an intermediate but still substantial degree of vascular dysfunction. In rats and mice, exposure to HNB products impaired acetylcholine-dependent relaxation and FMD, lowered plasma levels of NO metabolites and raised arterial stiffness and systolic blood pressure compared with unexposed animals[188–190]. Long-term exposure to HNB aerosols altered lung architecture and reduced pulmonary function in mice[191], and induced intestinal inflammation, oxidative stress and microbiome shifts in rats[192]. Although not strictly cardiovascular, these systemic inflammatory responses probably amplify vascular oxidative stress. In vitro data support these findings. Aerosols and smoke extracts from all nicotine-delivery systems increased the expression of genes related to oxidative stress (*Gsta1*, *Hmox1* and *Nqo1*) in rat epithelial cells[193], induced ROS generation mediated by calcium/calmodulin-dependent protein kinase kinase in human oral squamous cell carcinoma[194], and upregulated inflammatory cytokines and adhesion molecules in human peripheral blood mononuclear cells and dermal fibroblasts[195,196]. These cell study results confirm that both particulate and aerosol (including vapour) phase components directly damage the vascular endothelium.

Summary of evidence. Collectively, these preclinical data define a unified mechanistic pathway of nicotine product-related endothelial injury: oxidative stress, inflammation, eNOS uncoupling, nitro-oxidative imbalance and NO depletion (Table 6 and Fig. 3). Combustion markedly amplifies these processes, but non-combusted and even nicotine-free aerosols are not benign, given that they trigger similar signalling cascades to those induced by combustion products, through reactive carbonyls, metals and volatile organic compounds. Therefore, these animal studies provide causal evidence that complements data on human endothelial function and biomarkers, reinforcing a translational picture: all nicotine-delivery systems can disrupt vascular homeostasis, differing mainly in intensity rather than in kind. This mechanistic foundation underpins the hierarchy of cardiovascular harm described in this Review and justifies the emphasis on endothelial dysfunction as a sensitive early biomarker of nicotine product-induced vascular injury.

Global policy on nicotine products

Global health authorities increasingly recognize the urgent need to address the rapidly evolving nicotine-product landscape. What began as a fight against combustible tobacco now encompasses e-cigarettes, heated-tobacco products, waterpipes and smokeless oral formulations, such as nicotine pouches, each posing distinct public-health and cardiovascular challenges. In the USA, the FDA regulates tobacco and nicotine products under the 2009 Family Smoking Prevention and Tobacco Control Act, later extended to regulate e-cigarettes and heated-nicotine devices[197,198]. Under current FDA regulation, few products qualify as 'modified risk tobacco products', reflecting the limited available evidence of reduced harm of non-combustible tobacco compared with combustible tobacco products[39]. The CDC complements the FDA regulation through surveillance of the markets and education of the general population and health-care professionals,

Table 6 | Adverse effects of toxic compounds present in nicotine products

Pathway	Tobacco cigarettes	Waterpipes	E-cigarettes	Heated-tobacco products	Oral nicotine products
Oxidative stress	↑ OxLDL and isoprostane plasma levels in humans[268–270]. ↑ Aortic NOX2 and ROS, eNOS uncoupling, BH_4 depletion in mice[271] and humans[112]. ↑ TBARs, 3-NT in serum in *Apoe*$^{-/-}$ mice[272]. NOX activation and ROS in white blood cells in mice[273]. ↑ Cardiac mtROS, decreased SIRT3 expression in heart and vessels in hypertensive mice[171].	↑ Lipid peroxidation in lungs[274] and ↑ urinary 8-isoprostane levels[275] in humans. ↑ MDA in lungs in mice[276]. ↑ TBARs in heart[184] and kidneys[277] in mice. ↓ SOD, GPX1, catalase in lungs[276,278] and plasma[279] in mice. ↓ Vitamin C, GSH reductase in plasma in mice[279].	↑ Soluble NOX2-derived peptide[124], ↑ NO and isoprostane[124,280], ↓ vitamin E[124], ↑ oxLDL[281] in plasma in humans. ↑ NOX2 and ROS, eNOS uncoupling in mouse aorta and human endothelial cells in vitro[139].	↑ ROS, MDA, protein carbonyls, NRF2, SOD, catalase and XO, and ↓ SIRT1 in rat testes[282]. ↑ Oxidative stress markers in various species[283].	↑ Protein-carbonyls and antioxidant defence proteins SIRT1 and NRF1 in rat aorta[284].
Inflammation	↑ CRP[285] and WBCs[286] in humans. ↑ *IL1B*, *IL6*, *TNF*, *NOS2* in ECs and VSMCs[287,288] and serum[289] in mice. ↑ *Vcam1*, *Icam1*, *Cyba* (encodes p22^{phox}) in aorta in *Apoe*$^{-/-}$ mice[290].	↑ MMP9 and MPO activity in lung lavage[274] and plasma[275] in humans. ↑ ICAM1 and PGE2 in plasma in humans[275]. ↑ IL-1β, IL-6, IL-8, TNF, CRP, WBCs in plasma in mice[279,291] and in lung lavage[274,278,292] and plasma[275], in humans. ↑ iNOS and NO in lungs in mice[291].	↑ IL-1β, IL-6, IL-8, IFNγ, MMP9 in plasma in humans[280]. ↑ Angiopoietin 1, EGF, IL-8 in human airway epithelial cells in vitro[293]. ↑ ICAM1, PECAM1, VCAM1 in brain in mice[294].	↑ IL-6, IL-1β, phosphorylated NF-κB, TNF, COX2 in rat testes[282]. ↑ Inflammation markers in various species[283].	↓ CD19$^+$ B cells, CD4$^+$ T cells, CD8$^+$ T cells, CD11b$^+$ monocytes, EPCs in mice[295]. ↑ IFNγ, IL-1α, IL-5, IL-6, IL-8, IL-1RA, TNF MIF, FGF, VEGF, M-CSF in mouse embryonic stem cell lines[296]. ↑CRP, TNF in serum in rats[284].
Thrombosis	↑ Fibrinogen and D-dimer in plasma in humans[285].	↑ Fibrinogen and PAI-1 in mice[291].	↑ Integrin, phosphatidylserine, platelet activation and tail bleeding time in mice[297].	Platelet thrombus formation[260].	No changes in mice[295,298].
DNA damage	↑ Methylguanine[299] and γ-hydroxypropano-deoxyguanosine in humans[300]. ↑ 8-Hydroxy-2′-deoxyguanosine in humans and mice[301,302].	↓ Expression of DNA repair-related genes (*OGG1*, *XRCC1*) in humans[303,304]. ↑ DNA strand breaks, 8-hydroxy-2′-deoxyguanosine in lungs[274] and heart[184] in mice and plasma in humans[303,304].	↓ Expression of DNA repair-related genes (*OGG1*, *OGG2* and *XPC*) in mice[305]. ↑ O^6-methyldeoxyguanosine, γ-hydroxy-1,*N*-propano-deoxyguanosine[305], 8-hydroxy-2′-deoxyguanosine in mice[306] and humans[280].	↑ DNA repair proteins OGG1, p-H2AX and PARP1, and ↑ 8-hydroxy-2′-deoxyguanosine in rat testes[282].	↑ Ames test showed minor mutagenic effects[296,298].
Adverse effects	Atherosclerosis[286], cancer[255], cerebral aneurysm[288], COPD[307], emphysema[301], hypertension in mice[171] and humans (especially passive smoking)[308], ischaemic heart disease[82,251]. ↑ LDL and total cholesterol levels in humans[309,310]. Impaired endothelial function in humans[124,311,312]. ↑ Collagen deposition in the aorta in rats[271]. Circadian clock dysregulation in rats and mice[313,314].	Cancer[315], COPD[85], ischaemic heart disease[87,258] and impaired endothelial function[145] in humans. Thrombosis[291], ↑ heart weight, cardiac troponin I, BNP[184], and circadian clock dysregulation[316] in mice.	COPD[85], ischaemic heart disease[90], impaired endothelial function[124] in humans. Cancer[305], fibrosis in multiple organs[293], aggravated ischaemic brain damage[294], circadian clock dysregulation[316] in mice.	Thrombosis in humans[260]. Impaired endothelial function in humans and rats[188,260]. ↑ Systolic blood pressure, ↓ systolic function, ↓ heart rate variability in rats[190].	Impaired endothelial function in humans[154]. Impaired cardiovascular health[284] and ↑ 5-HT1B and 5-HT2A receptor-mediated cardiac contraction[317] in rats.
Potential therapies and targets	Resveratrol[311], vitamin E[318], NOX inhibition by apocynin[288], *Ncf1* (encodes p47^{phox}) deletion[288], catalase overexpression[171], *Nrf2* knockout aggravates damage[301].	Betaine[291], selenium[276].	Metformin[294], *Nox2* deletion[139].	Unknown.	Pterostilbene, resveratrol[284,319].

3-NT, 3-nitrotyrosine; 5-HT1B, 5-hydroxytryptamine receptor 1B; 5-HT2A, 5-hydroxytryptamine receptor 2A; CRP, C-reactive protein; COPD, chronic obstructive pulmonary disease; COX2, cyclooxygenase 2; EC, endothelial cells; EGF, epidermal growth factor; eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cell; FGF, fibroblast growth factor; GPX1, glutathione peroxidase 1; GSH, glutathione; ICAM1, intercellular adhesion molecule 1; IFNγ, interferon-γ; iNOS, inducible nitric oxide synthase; LDL, low-density lipoprotein; M-CSF, macrophage colony-stimulating factor; MDA, malondialdehyde; MIF, macrophage migration inhibitory factor; MMP9, matrix metalloproteinase 9; MPO, myeloperoxidase; mtROS, mitochondrial reactive oxygen species; NCF1, neutrophil cytosol factor 1; NF-κB, nuclear factor-κB; NOX, NADPH oxidase; NO, nitric oxide; NRF1, nuclear respiratory factor 1; NRF2, nuclear factor erythroid 2-related factor 2; OGG1, 8-oxoguanine DNA glycosylase; oxLDL, oxidized LDL; p22^{phox}, cytochrome b-245 light chain; PAI-1, plasminogen activator inhibitor 1; PARP1, poly(ADP-ribose) polymerase 1; PECAM1, platelet endothelial cell adhesion molecule 1; PGE2, prostaglandin E_2; p-H2AX, phospho-histone H2A.X; ROS, reactive oxygen species; SIRT, sirtuin; SOD, superoxide dismutase; TNF, tumour necrosis factor; VCAM1, vascular cell adhesion protein 1; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cells; TBAR, thiobarbituric acid-reactive substances; WBC, white blood cells; XO, xanthine oxidase.

warning that flavoured products are attractive to youths and reaffirming that e-cigarettes and heated-tobacco products are not approved tobacco-cessation aids[52,199]. Although cigarette smoking by youths in the USA has fallen to <2%, e-cigarette use remains substantial at 5.9% in 2024[200], one-third of the peak usage observed in 2019[201], prompting calls from the AHA for e-cigarette flavour bans and stricter oversight[6].

Across the European Union, regulation is guided by the Tobacco Products Directive (2016) and advertising bans, with the 2025 Tobacco Taxation Directive extending excise duties to e-cigarettes, heated tobacco and nicotine pouches[202,203]. The ESC maintains that safety data on novel nicotine products are so far insufficient and, thus, novel nicotine products should be included in comprehensive smoke-free policies[58,204]. The UK has adopted a more permissive harm-reduction approach by recommending e-cigarettes to aid in smoking cessation, even considering covering the costs by public health systems[205]. However, the prevalence of youth vaping in the UK now exceeds the prevalence of cigarette smoking, intensifying calls for tighter e-cigarette flavour and marketing restrictions[206,207].

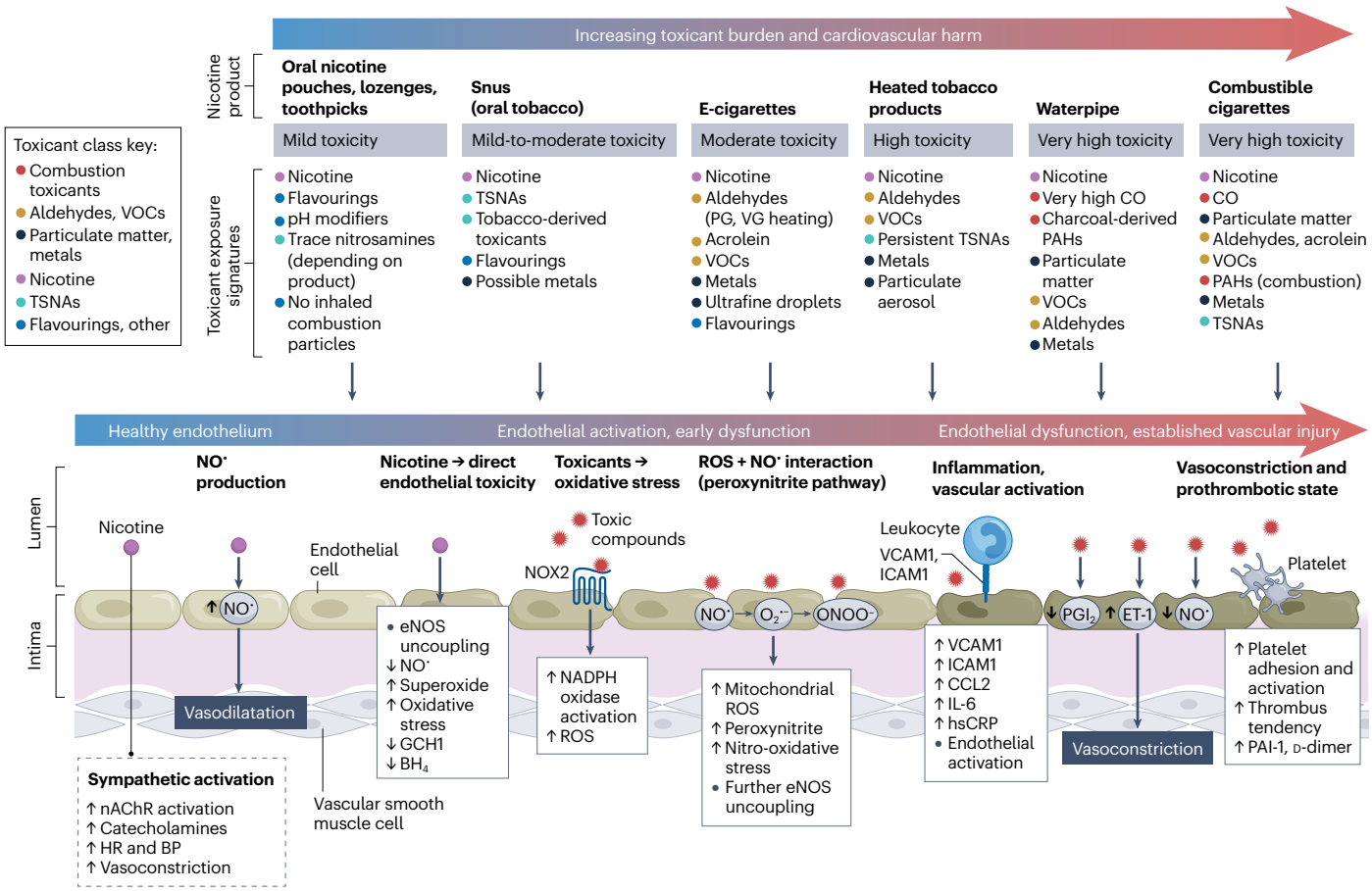


Fig. 3 | Toxicant burden of nicotine and tobacco products and associated adverse effects on endothelial cells. Nicotine and tobacco products span a graded continuum of toxicant burden and cardiovascular harm. Each product class has a distinct signature of toxicant exposure that includes nicotine, aldehydes and volatile organic compounds (VOCs), particulate matter and metals, tobacco-specific nitrosamines (TSNAs), polycyclic aromatic hydrocarbons (PAHs), carbon monoxide (CO) and flavouring constituents. The toxicity classification increases from mild or mild-to-moderate for oral nicotine products, to moderate for e-cigarettes, high for heated-tobacco products and very high for waterpipes and combustible tobacco cigarettes. These graded toxicant exposures converge on a common cascade of vascular injury (lower part). Nicotine acts on nicotinic acetylcholine receptors (nAChRs) to drive sympathetic activation, which increases catecholamine release, heart rate, blood pressure and vasoconstrictive tone. By contrast, endothelial nitric oxide (NO) maintains vasodilatory tone in the healthy vessel. Direct exposure to nicotine uncouples endothelial nitric oxide synthase (eNOS), which reduces GTP cyclohydrolase 1 (GCH1) and tetrahydrobiopterin (BH_4) availability (for more details, see Fig. 2), thereby lowering $NO^{\cdot}$ bioavailability and increasing superoxide ($O_2^{\cdot-}$) production. Combustion-derived and aerosol-derived toxicants activate NADPH oxidase 2 (NOX2), which amplifies the generation of reactive oxygen species (ROS). The reaction between $NO^{\cdot}$ and $O_2^{\cdot-}$ yields peroxynitrite ($ONOO^-$), which drives mitochondrial ROS production, nitro-oxidative stress and further eNOS uncoupling in a self-amplifying loop. This oxidative and nitrosative injury promotes endothelial activation, marked by upregulation of adhesion molecules (vascular cell adhesion molecule 1 (VCAM1) and intercellular adhesion molecule 1 (ICAM1)), CC-motif chemokine 2 (CCL2), IL-6 and high-sensitivity C-reactive protein (hsCRP), all of which facilitate leukocyte adhesion and vascular inflammation. In established vascular injury, loss of prostaglandin I_2 (PGI_2) and $NO^{\cdot}$, together with increased levels of endothelin 1 (ET-1), shift the endothelium towards a vasoconstrictive, prothrombotic phenotype, characterized by platelet adhesion and activation, elevated levels of plasminogen activator inhibitor 1 (PAI-1) and D-dimer, and increased thrombus tendency. Together, this schematic illustrates a dose-dependent continuum linking toxicant exposure across the spectrum of nicotine and tobacco products to progressive endothelial dysfunction and cardiovascular risk. BP, blood pressure; HR, heart rate; PG, propylene glycol; VG, vegetable glycerin.

Box 4 | Evidence-based approaches to tobacco cessation

The 2024 World Health Organization guidance highlights several complementary approaches to support tobacco cessation[211]. These interventions should ideally be embedded in health-care systems and made broadly accessible to all population groups.

Core behavioural and clinical interventions

- Brief advice from health-care providers during routine clinical encounters.
- Intensive behavioural counselling for individuals requiring structured support.
- Quit lines offering telephone-based counselling and follow-up.
- Digital cessation interventions, including Internet-based programmes.
- Text-message support programmes to reinforce motivation and adherence.
- Mobile applications providing interactive cessation tools.
- Group-based behavioural therapy to increase peer support and accountability.

Pharmacological cessation therapies

- Varenicline as an effective first-line pharmacotherapy.
- Nicotine replacement therapy, including patches, gum, lozenges, inhalers or sprays.
- Bupropion as an additional evidence-based pharmacological option.

Integrated cessation strategies

- Combination of behavioural and pharmacological treatment, an approach that is generally more effective than either approach alone.
- Health-system integration, ensuring that cessation support is routinely offered, affordable and equitable.

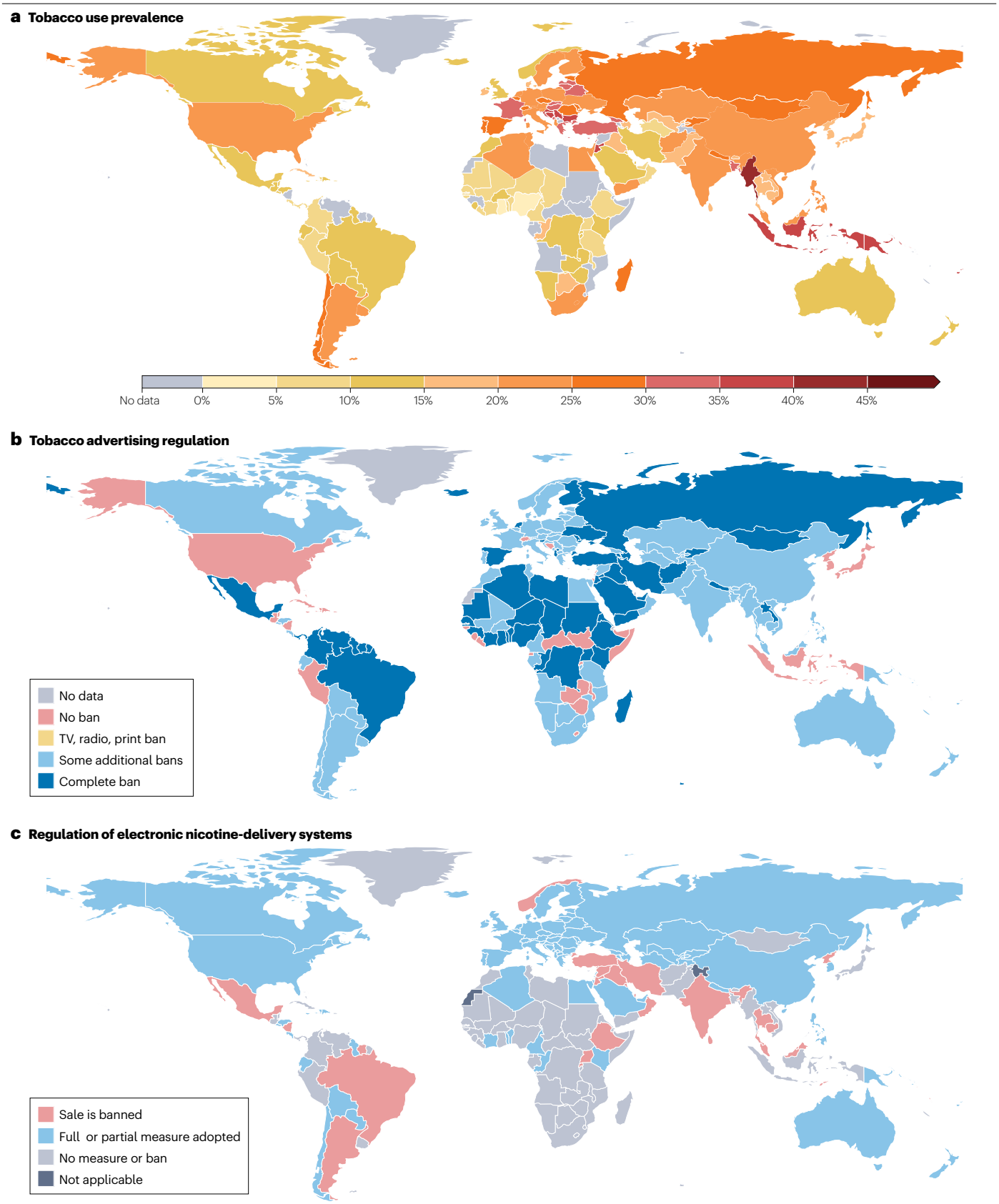
Important caution

- E-cigarettes are not recommended as tobacco cessation tools, because evidence remains insufficient and concerns persist regarding dual use with tobacco cigarettes, long-term safety and youth uptake.
- Traditional or non-evidence-based therapies (including acupuncture, hypnotherapy, Chinese herbal medicines, mindfulness and yoga) alone should not replace established cessation strategies.

Globally, the WHO FCTC remains the cornerstone of regulation, warning that dual use (tobacco cigarettes plus heated-tobacco products) undermines harm reduction with complete cessation and that current evidence is insufficient to classify heated tobacco as much safer than combustion tobacco products[208,209]. Despite national differences, consensus is emerging: no nicotine product is risk-free for cardiovascular health; combustion amplifies toxicity, but non-combusted forms remain harmful; stronger control to prevent youth uptake is needed; and nicotine addiction warrants preventing the initiation of nicotine-containing product consumption and higher taxation of all nicotine-containing products. Of note, not all tobacco-control professionals agree with the WHO FCTC guidelines[210]. In 2024, the WHO issued new tobacco-cessation guidelines, advising that every tobacco user receive brief advice (30 s to 3 min) during health-care visits[211]. The use of digital tools, especially text messaging, is encouraged, although smartphone apps and artificial intelligence-based chatbots show variable effectiveness[211] (Box 4). First-line medications include varenicline, NRT and bupropion, alone or in combination; cytisine is an alternative where available[211]. Smokeless-tobacco users should also receive behavioural and pharmacological support. Crucially, the WHO states that e-cigarettes and heated-tobacco products should not be recommended for smoking cessation owing to insufficient safety evidence[211]. However, emerging reviews add nuance: a 2025 Cochrane analysis found higher quit rates with e-cigarettes versus NRT[42], and a meta-analysis reported a 52% greater likelihood of abstinence with structured vaping programmes[212,213]. These findings suggest potential benefit under clinical supervision but reinforce the WHO's precautionary stance given ongoing concerns about dual use, relapse and youth uptake.

Regulation has struggled to keep pace with rapid product innovation. Novel nicotine devices frequently enter markets faster than independent safety data can accumulate and faster than legislation can adapt, which creates regulatory gaps that manufacturers could exploit through product redesign, the use of synthetic nicotine, flavour diversification and targeted marketing. This lag has resulted in fragmented oversight, inconsistent taxation and uneven youth-protection measures across jurisdictions. Given the pace of innovation, a reactive, tobacco-centred regulatory model might no longer be sufficient. Transitioning from tobacco-specific legislation towards a nicotine products directive that regulates nicotine itself, irrespective of source or delivery platform, could close regulatory loopholes, harmonize product standards and taxation, strengthen youth protection and better anticipate future technological developments. This framework would also address a growing regulatory inconsistency: medicinal

Fig. 4 | Global tobacco use, advertising restrictions and sales regulation. **a**, Tobacco use prevalence. Global distribution of tobacco consumption (including smoking, chewing and snuffing, but excluding e-cigarette vaping) among adults, shown as a percentage of the national population[320]. **b**, Status of tobacco advertising regulation worldwide. Countries are categorized by the degree of implemented advertising bans: from no ban (red) to complete bans across all media platforms (dark blue)[321]. **c**, Global overview of legal approaches to regulate electronic nicotine-delivery systems (such as e-cigarettes). Countries with a complete ban on sales are shown in red, those with partial or full regulatory measures are shown in blue, and countries with no measures are shown in light grey[322]. TV, television. Part **a** map adapted from ref. 320, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Part **b** map adapted from ref. 321, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Part **c** map adapted from ref. 322, CC BY NC SA 3.0 (https://creativecommons.org/licenses/by-nc-sa/3.0/).


a Tobacco use prevalence
No data
0%
5%
10%
15%
20%
25%
30%
35%
40%
45%
b Tobacco advertising regulation
No data
No ban
TV, radio, print ban
Some additional bans
Complete ban
c Regulation of electronic nicotine-delivery systems
Sale is banned
Full or partial measure adopted
No measure or ban
Not applicable

NRTs are tightly regulated and administered at low doses for smoking cessation, whereas high-dose oral nicotine products, such as pouches, are widely marketed as consumer goods despite delivering substantially greater nicotine exposures and carrying a substantial addiction potential. Therefore, aligning regulation with pharmacological activity rather than product category would be a more coherent public-health strategy. Taken together, these developments underscore the need to extend nicotine control beyond tobacco cigarettes because cardiovascular and environmental harms are intertwined, and no nicotine-containing product can be regarded as risk-free for vascular health.

In summary, global frameworks increasingly align on one message: nicotine control must extend beyond tobacco cigarettes, which is reflected by the higher current use of tobacco and the lack of national bans and regulatory measures (Fig. 4).

Clinical implications and knowledge gaps

All major nicotine-delivery systems, whether combusted (tobacco cigarettes and waterpipes), heated (HNB products), aerosolized (e-cigarettes and e-hookahs) or orally absorbed (snus and nicotine pouches), exert measurable, deleterious effects on vascular and endothelial function. This dysfunction, often occurring rapidly after exposure, serves as an early and reversible marker of cardiovascular injury and is strongly predictive of adverse clinical outcomes, such as MI, stroke and heart failure. Although smoking cessation yields partial vascular recovery, the persistence of residual endothelial dysfunction even in former smokers underscores the long-term vascular legacy of tobacco exposure, associated with an increased risk of MACE and cardiovascular death[22].

E-cigarettes and HNB devices, initially marketed as reduced-risk alternatives to combustible cigarettes, have not demonstrated an absence of cardiovascular adverse effects and should, therefore, be considered to be on a continuum of cardiovascular risk. Acute and chronic exposures to these products are associated with impaired FMD, increased arterial stiffness, heightened oxidative stress and reduced NO bioavailability. Randomized clinical trials and meta-analyses indicate that e-cigarettes increase short-term smoking cessation rates compared with the use of NRT[42], suggesting a potential role of these products in smoking-related harm reduction for adult smokers who are unable to quit by other means. However, the long-term safety of e-cigarettes is unproven, dual use with combustible tobacco is frequent[21], and nicotine itself is a driver of sympathetic activation and endothelial injury[46]. Consequently, major cardiovascular societies, including the ESC and AHA, caution against considering e-cigarettes as safe or as validated tobacco-cessation tools. Notably, female individuals might have heightened vulnerability to the adverse vascular effects of e-cigarettes compared with male individuals[131].

Waterpipe and e-hookah use, deeply rooted in cultural traditions and part of social activity in the Middle East, are widely, but mistakenly, perceived as less harmful than cigarette smoking. However, evidence suggests that their cardiovascular toxicity is at least similar to, and in some cases can exceed, that of cigarette smoking[48]. Particularly worrisome is the uptake of waterpipe and e-hookah among younger adults and adolescents, who might be unaware of the cardiovascular burden induced by these devices. Given that the risk of cardiovascular disease is directly correlated with the frequency of use[33], waterpipe-related cardiovascular risk is more pronounced in the Middle East and regions where waterpipes are part of daily cultural life, and is lower in Western countries, where waterpipe use is occasional[214]. Smokeless oral nicotine products, including snus and synthetic nicotine pouches, are an emerging threat in European regions other than Scandinavia, where their use is quite established. These products bypass inhalation but can still confer substantial cardiovascular risk through sympathetic stimulation, endothelial dysfunction and potential toxic exposures via flavouring agents and unregulated additives[79]. Long-term data on these products are scarce, especially for synthetic formulations, and their widespread use among nicotine-naive youths raises pressing concerns[14].

Key gaps in current knowledge persist. Long-term prospective studies evaluating cardiovascular outcomes in e-cigarette and smokeless-tobacco users, both exclusive and dual use with tobacco cigarettes, are needed. Sex-based differences in vascular response to exposure to nicotine-containing products warrant further investigation. More sensitive and standardized techniques are required to assess microvascular function in users across all nicotine device types. Finally, regulatory responses must keep pace with the rapid evolution of product designs and marketing strategies. For example, non-nicotine-containing products include nicotine analogues in their composition, such as 6-methylnicotine, or metatine (SPREE BAR), for which published safety data are limited. Therefore, further research is needed to raise awareness and education about these constituents and the hurdles that limit their regulation.

Conclusion

Evidence from experimental models, biomarker studies and population data supports a hierarchy of cardiovascular harm for nicotine-containing products, with a higher risk for combustion products (cigarettes and waterpipes), then heating products, followed by aerosol devices (e-cigarettes), oral nicotine products (pouches or chewing tobacco) and tobacco abstinence. Exclusive users of e-cigarettes often have a lower inflammatory burden than cigarette smokers. However, dual use abolishes any biomarker-related benefit. In addition, the lack of long-term, adjudicated cardiovascular outcome data for vaping and oral nicotine use remains a crucial evidence gap. Importantly, because most exclusive users of e-cigarettes are former tobacco cigarette smokers, carryover effects from previous exposure to combustible tobacco, such as persistent endothelial dysfunction, arterial stiffness and established atherosclerosis, cannot be excluded, which complicates causal attribution to e-cigarette use alone. Accordingly, 'less harmful' must not be conflated with 'harmless'.

From a public-health and clinical perspective, preventing the initiation of nicotine-product consumption, particularly among youths, remains paramount, given the high addictive potential of modern nicotine products and the risk of lifelong exposure trajectories. Clinicians and policymakers should prioritize smoke-free and vape-free environments, evidence-based cessation, and regulation that curbs youth-targeted flavourings and marketing. The rapid evolution of nicotine-containing technologies argues for a shift from tobacco-specific regulation towards a comprehensive nicotine products directive that regulates nicotine itself across all delivery platforms. Integrating vascular and inflammatory biomarkers into surveillance of public use of nicotine-delivery products and clinical trials might accelerate risk assessment. However, until definitive outcome data are available, complete nicotine cessation remains the strategy associated with the greatest cardiovascular benefit.

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Author contributions
T.M. conceptualized the article. T.M., M.K., J.L. and A.D. researched data for the article. T.M., M.K., J.F.K., J.L., F.C. and A.D. provided substantial contribution to discussion of content. T.M., M.K., J.F.K., T.F.L., S.R. and A.D. wrote the manuscript. T.M., M.K., F.C., T.F.L., S.R. and A.D. reviewed and edited the manuscript before submission.

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