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MINIREVIEWS

E-cigarettes and arterial health: A review of the link between vaping and atherosclerosis progression

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Abstract

Recent studies have suggested an evolving understanding of the association between vaping, specifically electronic cigarette (e-cigarette) use, and the progression of atherosclerosis, a significant contributor to cardiovascular disease. Despite the prevailing perception of vaping as a safer alternative to traditional tobacco smoking, accumulating evidence suggests that the aerosols emitted by e-cigarettes contain harmful constituents that may promote endothelial dysfunction, oxidative stress, inflammation, and dyslipidemia—key mechanisms implicated in atherosclerosis pathogenesis. While past research, including experimental studies and clinical investigations, has shed light on the potential cardiovascular risks associated with vaping, gaps in knowledge persist. Future research endeavors should focus on interpreting the long-term effects of vaping on atherosclerosis development and progression, exploring the impact of different e-cigarette formulations and user demographics, and identifying effective strategies for mitigating the cardiovascular consequences of vaping. By identifying and addressing these research gaps, we can enhance our understanding of the cardiovascular implications of vaping and inform evidence-based interventions and policies to safeguard public health.

Key Words: E-cigarettes; Vaping; Atherosclerosis; Cardiovascular disease; Dyslipidemia; Oxidative stress; Nicotine

Core Tip: E-cigarette use has been linked to various cardiovascular risks, including the progression of atherosclerosis. Despite the perception of vaping as a safer alternative to smoking, evidence suggests that e-cigarette aerosols contain harmful substances that contribute to endothelial dysfunction, oxidative stress, inflammation, and dyslipidemia. These mechanisms are crucial in the development and progression of atherosclerosis. This review explores multiple facets of e-cigarettes and arterial health, focusing on the connection between vaping and atherosclerosis progression. It presents up-to-date evidence on pathophysiology and significant clinical implications, the impact of various constituents, and discusses contemporary public health strategies.

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INTRODUCTION

Electronic cigarettes, also known as e-cigarettes, have rapidly emerged as a popular alternative to traditional tobacco cigarettes since their introduction in the mid-2000s[1]. The rise in popularity of e-cigarettes can be attributed to the perception that e-cigarettes are less harmful compared to conventional smoking, as well as the appealing variety of flavors and the convenience of use, not requiring combustion. Their lack of smoke and the absence of a lingering odor make them more socially acceptable. Additionally, their small, handheld design makes them easy to carry and use discreetly in various settings, without attracting the negative attention often directed at conventional smokers. E-cigarettes have been marketed both as smoking cessation tools and as recreational products, further boosting their use among different age groups and demographics. These battery-operated devices vaporize a liquid solution (e-liquid) containing nicotine, flavorings, and other additives to create an inhalable aerosol, which users then inhale in a process commonly referred to as "vaping"[2]. Advancements in technology and design have made e-cigarettes more user-friendly and efficient, contributing to their widespread adoption. These improvements include longer battery life, customizable settings, and a variety of flavors that can make e-cigarettes an appealing alternative to traditional cigarettes. The global e-cigarette market has experienced exponential growth, with an estimated 68 million users worldwide in 2020, a figure projected to reach 84.4 million by 2025[3]. This surge in popularity is particularly evident among youth and young adults, with a 78% increase in e-cigarette use among high school students in the United States from 2017 to 2018[4].

Proponents of e-cigarettes argue that these devices offer a less harmful alternative to conventional smoking and may aid in smoking cessation efforts[1]. This is because e-cigarettes can reduce exposure to many harmful chemicals found in traditional cigarettes. However, the rapid rise in e-cigarette use has raised significant public health concerns. Critics argue that while e-cigarettes may contain fewer toxic substances compared to traditional cigarettes, they are not without health risks[5]. Because the use of e-cigarettes is relatively new, the long-term health effects of e-cigarette use is largely unknown and necessitates further research. However, prevailing concerns include the potential for nicotine addiction, respiratory issues, and emerging evidence of cardiovascular harm[6,7]. Furthermore, the prevalent use among youth has sparked fears of a new generation addicted to nicotine, potentially leading to a gateway effect where users transition to conventional cigarettes. Public health officials also worry about the insufficient regulation of these e-cigarette products, which can vary widely in terms of quality and safety. Understanding the full spectrum of health implications is crucial for developing appropriate regulatory policies and public health strategies.

Understanding the cardiovascular implications of vaping is of paramount importance, given that cardiovascular disease (CVD) remains the leading cause of death globally. In 2019, an estimated 17.9 million people died from CVDs, representing 32% of all global deaths[8]. This staggering statistic underscores the critical need to identify and mitigate all potential risk factors for CVD, including emerging threats like e-cigarette use. Central to the pathogenesis of CVD is atherosclerosis, a progressive condition characterized by the accumulation of lipids, inflammatory cells, and fibrous elements in the arterial walls[9]. This buildup, known as atherosclerotic plaque, can narrow the arteries, reduce blood flow, and, if ruptured, lead to life-threatening events such as myocardial infarction and ischemic stroke[10]. Over time, the plaque can harden and further restrict blood flow, exacerbating cardiovascular issues. The development and progression of atherosclerosis are influenced by various factors, including endothelial dysfunction, oxidative stress, inflammation, and dyslipidemia[11]. Lifestyle factors such as diet and physical activity in addition to smoking, play significant roles in the onset and severity of atherosclerosis. This comprehensive review examines the link between vaping and arterial health, aiming to inform evidence-based policies, guide public health strategies and regulatory policies, and ultimately work towards reducing the global burden of CVD.

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E-CIGARETTES AND CARDIOVASCULAR HEALTH

As e-cigarette use increases, understanding its potential role in exacerbating each of these conditions is essential to inform both public health and clinical interventions. Given the current gaps in knowledge regarding the long-term cardiovascular effects of vaping, this narrative review was designed to synthesize and analyze the existing literature to fully understand and interpret the risks of this common recreational activity. A comprehensive search strategy was employed on May 13, 2024 using the terms: "e-cigarettes," "vaping," "arterial health," "atherosclerosis," and "cardiovascular effects." PubMed, Scopus, and Web of Science databases were utilized for the search. Inclusion criteria comprised of peer-reviewed articles, most published within the last ten years, and other articles centered on e-cigarette usage.

Conventional cigarette smoking is a well-established risk factor for atherosclerosis and CVD. The toxic constituents in tobacco smoke, including nicotine, carbon monoxide, and oxidative compounds, contribute to endothelial damage, platelet activation, and a prothrombotic state, accelerating atherosclerotic plaque formation and increasing the risk of acute cardiovascular events[12]. Given these established risks, the cardiovascular safety of e-cigarettes has come under scrutiny. While e-cigarettes are often marketed as a safer alternative to traditional smoking, emerging research suggests that the aerosols produced by these devices may not be as benign as initially thought. Studies have shown that e-cigarette aerosols contain harmful substances such as ultrafine particles, diacetyl (a chemical linked to "popcorn lung," a severe lung disease characterized by scarring and narrowing of the small airways), volatile organic compounds (VOCs), and heavy metals like nickel, tin, and lead[13,14]. These constituents have the potential to induce oxidative stress, inflammation, and endothelial dysfunction-all of which are key processes in the initiation and progression of atherosclerosis[15,16].

Moreover, the nicotine content in e-cigarettes, often comparable to or higher than that in traditional cigarettes, raises additional concerns. Nicotine is known to increase heart rate, blood pressure, and myocardial contractility, which can exacerbate existing cardiovascular conditions[17]. It also stimulates the release of catecholamines, which can further stress

the cardiovascular system. Nicotine has been shown to promote angiogenesis and contribute to the growth and destabilization of atherosclerotic plaques, increasing the risk of acute cardiovascular events[18]. These effects make nicotine a significant concern for individuals with or at risk for CVD. The flavoring agents and other additives in e-cigarettes also undergo chemical changes during the heating process, producing potentially harmful byproducts. For instance, the formation of formaldehyde and other aldehydes during vaping have been linked to cellular damage and inflammation [19]. The stakes are high, and as the prevalence of e-cigarette use continues to rise, particularly among younger populations who may not have otherwise used tobacco products, understanding the comprehensive impact of these products on health becomes increasingly critical. This includes not only the immediate physiological effects but also the long-term consequences of sustained use and the potential for increased susceptibility to other cardiovascular risk factors.

The belief that vaping is a safer alternative to traditional smoking is largely driven by aggressive marketing strategies that highlight e-cigarettes' reduced harmful chemicals compared to conventional cigarettes and promote them as smoking cessation tools. The initial regulatory landscape for e-cigarettes was relatively lenient, enabling rapid market penetration without extensive health impact assessments, which further fueled these misconceptions. Although e-cigarettes may lack many of the harmful components of tobacco smoke, they still contain addictive substances like nicotine and pose substantial risks to cardiovascular health. A nationally representative cross-sectional survey of young individuals (ages 11-18) in Great Britain revealed that while 63% of respondents had accurate perceptions of e-cigarettes, only 9% had accurate perceptions of nicotine. The study by East *et al*[20] found that neither smoking nor e-cigarette use was associated with accurate perceptions of nicotine harm, highlighting a significant gap in knowledge about the dangers of nicotine dependence and the overall risks associated with e-cigarettes use.

E-cigarette or vaping use-associated lung injury (EVALI) is well documented in the literature. E-cigarettes heat nicotine extracted from tobacco to create an aerosol with a multitude of other flavors and chemicals. While often regarded as less harmful than smoking, the use of e-cigarettes, or vaping, is not considered to be safe. The chemicals in e-cigarettes, such as propylene glycol, vegetable glycerin, acetaldehyde, acrolein, and formaldehyde, are attributed to irreversible lung damage and disease, and have caused tremendous harm in cases of explosions and burns[19]. In February 2020, the CDC confirmed over 2800 cases of EVALI and 68 deaths attributed to e-cigarette or vaping use[21].

CARDIOVASCULAR RISKS: E-CIGARETTES *VS* TRADITIONAL TOBACCO

Conventional tobacco products contain over 7000 chemicals, many of which are highly toxic to both the lungs and heart [22]. Among these, tar, nicotine, carbon monoxide, formaldehyde, ammonia, and benzene are particularly harmful. Cardiovascular risks associated with the use of tobacco products include immediate and long-term increases in both heart rate and blood pressure, vasoconstriction, reduced blood flow to the heart thereby impeding blood flow to the tissues, blood clots, arterial damage, and arrhythmias. These changes are directly related to coronary artery disease, heart attacks, hypertension, and strokes. Tobacco inhalation, primarily due to nicotine and carbon monoxide found in traditional tobacco products, is a main risk factor for atherosclerotic CVD. Nicotine stimulates the release of catecholamines, which increases heart rate and blood pressure, while carbon monoxide reduces oxygen delivery to the heart muscle[23].

E-cigarette use contributes to CVD in multiple ways. In addition to flavoring, nicotine, and metal particles, e-cigarettes also contain glycerol and propylene glycol, which undergo thermal decomposition. This process leads to the formation of potentially toxic compounds such as acrolein and acetaldehyde. These compounds can subsequently cause macrophage activation, DNA damage, sympathetic dominance, hyperlipidemia, and endothelial dysfunction, leading to proinflammatory phenotypes and oxidative stress, ultimately contributing to CVD[24]. Another example is the effect of nicotine on adipocytes and the cardiovascular system. As Espinoza-Derout *et al*[24] portray in their review, nicotine from e-cigarettes produces the release of free fatty acids (FFAs) and adipokines. This results in macrophage activation as well as the activation of an inflammatory phenotype which substantially diminishes cardiovascular system function. Nicotine also directly affects the vascular system by promoting angiogenesis and smooth muscle cell proliferation, which can destabilize atherosclerotic plaques and increase the risk of thrombotic events[25].

The cardiovascular effects of dual users of both e-cigarettes and combustible cigarettes are evident in medical literature. An analysis by Osei *et al*[26] identified a 36% increased risk of CVD in those who use both e-cigarettes and combustible cigarettes, compared to those who only use combustible cigarettes. These findings reinforce the harm of e-cigarettes, not only when used alone, but also in conjunction with traditional cigarettes. Dual use can result in higher overall nicotine exposure and exposure to a broader spectrum of toxic substances from both traditional and e-cigarettes, which compounds the adverse effects. Results from the Framingham Heart Study corroborate these findings and demonstrate a positive association between aortic stiffness and cardiovascular events as a result of regular e-cigarette use [24]. Aortic stiffness, as measured by pulse wave velocity, is an indicator of vascular aging and a predictor of cardiovascular events. These findings demonstrate how arterial stiffening, as a result of e-cigarette use, leads to not only increased risk of myocardial infarction, but also increased risk of heart failure and mortality[24]. The cardiovascular risks associated with both conventional tobacco and e-cigarette use are summarized in Table 1.

CONSTITUENTS OF E-CIGARETTE AEROSOLS

The perception of e-cigarettes as a safer alternative to traditional smoking largely stems from the absence of combustion in the vaping process. Unlike conventional cigarettes, which burn tobacco to produce smoke containing thousands of chemicals, e-cigarettes heat a liquid solution (e-liquid) to generate an inhalable aerosol, commonly referred to as "vaping"

Table 1 Comparison of e-cigarettes and traditional cigarettes

Category	E-cigarettes	Traditional cigarettes
Key components	Nicotine, flavorings, metal particles, glycerol, propylene glycol	Nicotine, tar, carbon monoxide, formaldehyde, ammonia, benzene
Toxic compounds	Acrolein, acetaldehyde (formed through thermal decomposition)	> 7000 chemicals, including tar and carbon monoxide, many of which are highly toxic
Immediate cardiovascular effects	Increases in heart rate and blood pressure due to nicotine; causes DNA damage, endothelial dysfunction, and oxidative stress	Immediate increases in heart rate and blood pressure; vasoconstriction, reduced blood flow to the heart, blood clots, and arrhythmias
Long-term cardiovascular effects	Aortic stiffness, proinflammatory phenotypes, hyperlipidemia, endothelial dysfunction, increased risk of myocardial infarction, heart failure, and mortality	Coronary artery disease, heart attacks, hypertension, strokes; arterial damage, reduced oxygen delivery to the heart muscle
Mechanism of cardiovascular harm	Nicotine causes macrophage activation and release of FFAs and adipokines, promoting inflammatory responses and oxidative stress	Nicotine stimulates catecholamine release, increasing heart rate and blood pressure; carbon monoxide reduces oxygen delivery to the heart muscle
Impact of dual use	Increases overall nicotine exposure and exposure to a broader spectrum of toxic substances, compounding adverse effects; 36% increased risk of CVD	Similar risks compounded by additional exposure to harmful chemicals when combined with e-cigarette use
Additional risks	Potential exposure to metal particles and other contaminants from e-cigarette devices	Exposure to tar and numerous carcinogenic substances not present in e-cigarettes

CVD: Cardiovascular disease; FFAs: Free fatty acids.

[1,6]. However, the composition of this aerosol is far from benign, containing a complex mixture of potentially harmful substances that may contribute to cardiovascular risk. It is important to note that the levels of harmful constituents can vary widely depending on the e-liquid composition, device characteristics, and user behavior (*e.g.*, device power settings, puffing patterns)[27].

Nicotine

The primary psychoactive component in most e-liquids, nicotine, is a highly addictive substance with well-documented cardiovascular effects. Nicotine stimulates the sympathetic nervous system, leading to increased heart rate, blood pressure, and myocardial contractility[17]. These hemodynamic changes can exacerbate existing cardiovascular conditions and increase the workload on the heart. Moreover, nicotine has been implicated in endothelial dysfunction, a critical initiating event in atherosclerosis. It impairs endothelium-dependent vasodilation, promotes oxidative stress, and enhances the expression of adhesion molecules, facilitating the adhesion and migration of inflammatory cells into the arterial wall[28]. Nicotine also contributes to the progression of atherosclerotic plaques. It stimulates the proliferation and migration of vascular smooth muscle cells (VSMC) and enhances the release of growth factors like basic fibroblast growth factor, which can accelerate plaque growth[18]. Furthermore, nicotine has been shown to promote angiogenesis within plaques, increasing their vulnerability to rupture and subsequent thrombotic events[25].

Ultrafine particles

E-cigarette aerosols contain high concentrations of ultrafine particles (UFPs), defined as particles less than 100 nanometers in diameter. These particles are of particular concern because their small size allows them to penetrate deep into the lungs and even enter the systemic circulation[29]. UFPs have been associated with increased oxidative stress, inflammation, and alterations in heart rate variability, all of which can contribute to atherosclerosis[30]. In the context of atherosclerosis, UFPs can directly interact with endothelial cells, causing mitochondrial damage, increased production of reactive oxygen species (ROS), and activation of pro-inflammatory pathways[31]. They can also translocate into the bloodstream and interact with circulating immune cells, promoting a systemic inflammatory response that exacerbates atherosclerotic processes[32].

Flavorings and additives

The wide array of flavors available for e-cigarettes is a major factor in their appeal, especially among youth. However, these flavoring compounds, often considered "generally recognized as safe" for ingestion, may pose risks when inhaled. For instance, diacetyl, a butter-flavored chemical, has been linked to bronchiolitis obliterans, or "popcorn lung," when inhaled in high concentrations[33]. In terms of cardiovascular effects, certain flavoring compounds have been shown to impair endothelial function. A study by Fetterman *et al*[34] found that flavoring chemicals like vanillin and cinnamaldehyde, the major flavor components of vanilla and cinnamon, respectively, induced oxidative stress and inflammatory responses in endothelial cells, impaired nitric oxide (NO) production, and reduced cell viability. NO is crucial for maintaining vascular homeostasis, and its reduction is a hallmark of endothelial dysfunction in atherosclerosis.

Free radicals and ROS

The heating process in e-cigarettes can lead to the formation of free radicals and ROS, highly reactive molecules that can cause cellular damage. Vaping has been shown to increase markers of oxidative stress in humans, such as 8-isoprostane, a product of lipid peroxidation[16]. Oxidative stress is a key driver of atherosclerosis, contributing to endothelial dysfunction, VSMC proliferation, and oxidation of low-density lipoprotein (LDL) cholesterol, which is more readily taken up by macrophages to form foam cells in atherosclerotic lesions[35]. The chronic exposure to ROS and the resulting oxidative stress can also lead to vascular remodeling, characterized by the thickening of the arterial wall and loss of elasticity, which are hallmarks of hypertension and atherosclerosis. Additionally, ROS-mediated damage to mitochondrial DNA and proteins can impair cellular energy metabolism, further exacerbating cardiovascular dysfunction[36].

Heavy metals

Analysis of e-cigarette aerosols has revealed the presence of toxic metals such as lead, nickel, tin, and copper, likely originating from the heating coils or other device components[14]. These metals can accumulate in the body and have been associated with cardiovascular toxicity. For example, lead exposure has been linked to hypertension, coronary heart disease, and peripheral arterial disease, partly due to its ability to induce oxidative stress and inflammation[37]. Several studies have confirmed the presence of these heavy metals in e-cigarette aerosols. One study by Goniewicz *et al*[38] demonstrated that the concentrations of cadmium and nickel in e-cigarette aerosols were similar to those found in traditional cigarette smoke. A later study by Olmedo *et al*[39] found significant levels of chromium, nickel, and lead in these aerosols, often at concentrations higher than those found in conventional cigarettes, raising concerns about the effects of exposure to these various toxic metals.

Carbonyls

When e-liquids are heated at high temperatures, they can produce carbonyls like formaldehyde, acetaldehyde, and acrolein. These compounds are known cardiovascular toxicants. Acrolein, in particular, has been shown to modify apolipoprotein A-I (ApoA-I), the major protein component of high-density lipoprotein (HDL), impairing its cardioprotective functions[40]. Acrolein can also induce endothelial dysfunction, platelet activation, and vascular inflammation [41]. Meanwhile, acetaldehyde forms adducts with proteins and lipids to disrupt their normal function. These acetaldehyde-protein adducts can impair the function of crucial enzymes involved in cellular metabolism and antioxidant defense, leading to inflammation[42].

PATHOPHYSIOLOGY

Atherosclerosis, the primary underlying cause of CVD, is a complex, multifaceted process involving the accumulation of lipids, inflammatory cells, and fibrous elements in the arterial walls[9]. This accumulation leads to the formation of atherosclerotic plaques, which can narrow arteries, reduce blood flow, and, if ruptured, cause life-threatening events like myocardial infarction and stroke[10]. The pathogenesis of atherosclerosis involves several interrelated mechanisms, including endothelial dysfunction, oxidative stress, inflammation, and dyslipidemia. Emerging evidence suggests that e-cigarette use may contribute to each of these mechanisms, thereby potentially accelerating atherosclerosis progression.

Endothelial dysfunction

Endothelial dysfunction refers to the impairment of the normal physiological functions of the endothelium, the single layer of cells lining blood vessels. Healthy endothelium plays a crucial role in vascular homeostasis by regulating vasodilation, inflammation, thrombosis, and smooth muscle cell proliferation[43]. Endothelial dysfunction is considered the earliest detectable change in the development of atherosclerosis, preceding the formation of visible plaques[44]. It is characterized by a reduction in the bioavailability of NO, which is produced by endothelial cells, and serves as an essential molecule for vascular health. Several studies have demonstrated that e-cigarette use can impair endothelial function. Chatterjee *et al*[16] exposed healthy, non-smoking young adults to e-cigarette aerosol and found acute impairment in flow-mediated dilation (FMD), a measure of endothelium-dependent vasodilation. The reduction in FMD was comparable to that observed with traditional cigarette smoking, suggesting that vaping can acutely impair endothelial function even in young, healthy individuals[16]. This impairment in endothelial function is a critical early step in the development of atherosclerosis. *In vitro* studies have also provided insights. Fetterman *et al*[34] exposed human endothelial cells to e-cigarette flavorings and found that certain compounds, such as vanillin and cinnamaldehyde, increased oxidative stress, reduced NO production, and impaired angiogenesis. NO is a potent vasodilator and inhibitor of platelet aggregation, inflammation, and smooth muscle cell proliferation—all protective against atherosclerosis. The nicotine in e-cigarettes may also contribute to endothelial dysfunction. Nicotine has been shown to increase endothelial cell apoptosis, decrease NO synthase activity, and upregulate the expression of adhesion molecules like vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, which facilitate the recruitment of inflammatory cells into the arterial wall[18].

Oxidative stress

Oxidative stress occurs when there is an imbalance between the production of ROS and the body's ability to neutralize them with antioxidants. ROS can damage cellular components, including DNA, proteins, and lipids. In the context of atherosclerosis, oxidative stress plays a pivotal role by promoting endothelial dysfunction, oxidizing LDL into toxic

oxLDL, stimulating VSMC proliferation, and activating inflammatory pathways[35,45]. E-cigarette aerosols contain a variety of compounds that can induce oxidative stress, significantly contributing to the pathogenesis of poor cardiovascular health. A study by Anderson *et al*[46] found that e-cigarette use increased levels of 8-isoprostane, a marker of lipid peroxidation and oxidative stress, in the urine of users. This increase was comparable to that seen in traditional cigarette smokers, indicating that e-cigarettes can generate similar oxidative burdens. The heating process in e-cigarettes can also lead to the formation of reactive carbonyl species (RCS) such as formaldehyde, acetaldehyde, and acrolein[47]. These RCS can deplete cellular glutathione, a key antioxidant, and form protein adducts that disrupt cellular function. Glutathione is essential for neutralizing ROS and maintaining redox balance within cells. When depleted, cells are more susceptible to damage. Acrolein has been shown to react with and deplete glutathione leading to further cellular injuries [48]. Moreover, e-cigarette aerosols contain the UFPs that penetrate deep into the lungs and even enter the systemic circulation[29]. UFPs have been shown to induce oxidative stress in endothelial cells by increasing mitochondrial ROS production and activating NADPH oxidase[31]. This oxidative stress can stimulate the migration of vascular smooth muscle cells to form plaques.

Inflammation

Inflammation is a key driver of atherosclerosis at all stages, from initiation to progression and complications. The inflammatory response in atherosclerosis involves the recruitment and activation of various immune cells, including monocytes, macrophages, and T-cells, within the arterial wall[9]. These cells release pro-inflammatory cytokines, chemokines, and growth factors that amplify the inflammatory milieu, promote plaque growth, and contribute to plaque instability[49]. Several studies have demonstrated that e-cigarette use can induce both local and systemic inflammation. A study by Reidel *et al*[50] found that acute e-cigarette exposure in mice led to increased pulmonary inflammation, as evidenced by elevated levels of pro-inflammatory cytokines [interleukin (IL)-6, IL-1β] and increased macrophage infiltration in the lungs. These pulmonary effects could contribute to systemic inflammation, a key factor in atherosclerosis progression. In humans, Moheimani *et al*[51] observed increased levels of soluble intercellular adhesion molecule-1 (sICAM-1) in the serum of e-cigarette users. sICAM-1 is a marker of endothelial activation and inflammation, and its elevation suggests that vaping may promote a pro-inflammatory state conducive to atherosclerosis.

The nicotine in e-cigarettes may also contribute to inflammation. Nicotine has been shown to activate nuclear factor kappa-B (NF-κB), a key transcription factor that regulates the expression of pro-inflammatory genes[52]. Activation of NF-κB leads to increased productions of cytokines such as tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-6, which further enhance the inflammatory process[18]. Additionally, nicotine can stimulate the release of pro-inflammatory cytokines from immune cells and increase leukocyte-endothelial cell adhesion, such as macrophages and T cells, facilitating the infiltration of inflammatory cells into the arterial wall, another key step in plaque development[18].

Dyslipidemia

Dyslipidemia refers to abnormal levels of lipids in the blood, typically characterized by elevated LDL cholesterol, reduced HDL cholesterol, and/or increased triglycerides. Dyslipidemia is a major risk factor for atherosclerosis because LDL particles can penetrate the arterial wall, become oxidized, and trigger an inflammatory response that promotes plaque formation[53]. Conversely, HDL plays a protective role by promoting reverse cholesterol transport and exerting anti-inflammatory and antioxidant effects[54]. While research on the lipid-altering effects of e-cigarettes is still emerging, several studies suggest that vaping may contribute to an atherogenic lipid profile. A study by Majid *et al*[55] found that e-cigarette use was associated with lower levels of HDL cholesterol and higher levels of triglycerides in a population-based study. This lipid pattern is consistent with increased cardiovascular risk. The mechanisms by which e-cigarettes may induce dyslipidemia are multifaceted. Nicotine has been shown to increase lipolysis and FFA release, leading to increased hepatic triglyceride synthesis[17]. These FFAs are taken up by the liver and converted to triglycerides, contributing to hypertriglyceridemia[17]. Additionally, oxidative stress and inflammation induced by e-cigarette constituents can impair HDL function. When acrolein modifies ApoA-I, its ability to promote cholesterol efflux from macrophages is inherently reduced[40]. Furthermore, flavorings in e-cigarettes may also contribute to dyslipidemia. Farsalinos *et al*[33] found that certain flavoring compounds contained high levels of diacetyl and acetyl propionyl. While these compounds are primarily associated with respiratory risks, they may also have systemic effects, including lipid metabolism disruption, although more research is needed to understand these mechanisms. These findings challenge the notion that vaping is a safe alternative to traditional smoking and underscore the need for further research to fully understand the long-term cardiovascular implications of e-cigarette use.

PRE-CLINICAL, CLINICAL, AND OBSERVATIONAL EVIDENCE

Several key findings have been found when examining animal models in pre-clinical experimental studies assessing the cardiovascular effects of e-cigarettes. E-cigarette aerosols show milder impacts on cardiovascular health such as less severe vascular impairment and aortic stiffness in mice when compared to traditional cigarette smoke. Additionally, atherosclerosis-prone mice did not develop atherosclerotic plaques when exposed to e-cigarette aerosols as they did when exposed to cigarette smoke. However, both human and animal studies reveal that vaping can still lead to inflammation, endothelial dysfunction, and oxidative stress albeit to a lesser extent than traditional smoking[56]. Both e-cigarette aerosols and liquids have also been found to induce oxidative stress and cytotoxicity in vascular and myocardial endothelial cells during *in vitro* studies. These effects are exacerbated by the activation of heating elements in e-cigarettes which could potentially be linked to the presence of metals such as copper nanoparticles in the aerosols[57].

More recent *in vivo* studies emphasize the potential risks of vaping on cardiovascular health by revealing increased cytokine levels, inflammation, oxidative stress, platelet activation, and thrombogenesis risk following exposure to e-cigarette aerosols[57]. Observations of decreased cardiac ejection fraction and increased oxidative stress in mice exposed to e-cigarette aerosols highlight the potential impact vaping can have on cardiac function[56]. Observational and clinical studies investigating the cardiovascular effects of vaping provide insights into the potential risks that are associated with e-cigarettes. Although the cardiovascular toxicity caused by traditional cigarettes and nicotine are well-documented, the potential long-term cardiovascular effects of vaping are unclear. Epidemiological studies suggest an increased incidence of adverse cardiovascular outcomes among e-cigarette users such as myocardial infarctions, coronary heart disease, chest pain and arrhythmias. The frequency of e-cigarette use correlates with the severity of these outcomes, with severity diminishing as usage decreases. Individuals with known polytobacco use face a higher cardiovascular risk compared to individuals who exclusively use e-cigarettes, complicating the interpretation of study findings in the presence of polytobacco use[56].

Studies have found that even short-term use of e-cigarettes can lead to increased heart rate, elevated blood pressure, and arterial stiffness, effects that can all occur independently of the presence of nicotine in e-liquids. Additionally, acute exposure to e-cigarettes has been shown to prefer sympathetic dominance which may lead to potential disruption of cardiovascular function due to e-cigarette use. While e-cigarettes may produce similar cardiovascular changes as traditional cigarettes, these studies suggest that the range and type of these effects can vary[56]. E-cigarette aerosols contain metals like lead, chromium, nickel and manganese as well as low levels of polycyclic aromatic hydrocarbons, VOCs, and phenolic compounds. Although these levels are generally lower than what is found in traditional cigarette smoke, certain parameters such as high battery voltage can increase the production of toxic substances in e-cigarette aerosols to levels comparable to cigarettes. These toxic substances have the ability to induce pathological mechanisms such as inflammation and oxidative stress which raises concerns about their potential cardiotoxic effects[17].

GAPS IN KNOWLEDGE AND FUTURE RESEARCH DIRECTIONS

Much of the current evidence comes from short-term studies, *in vitro* experiments, or animal models. Long-term epidemiological studies are needed to definitively establish the impact of chronic e-cigarette use on atherosclerosis progression and cardiovascular events in humans. Given the diversity of e-cigarette devices, e-liquid formulations, and user behaviors, future research should consider these variables to provide a more nuanced understanding of the cardiovascular risks associated with vaping. This approach would provide a more thorough understanding of the cardiovascular risks associated with vaping, considering the complexity and variability of use.

The variability of the device in power settings, puffing patterns, and e-liquid compositions can significantly influence the levels of harmful chemicals inhaled by users. While some studies have examined individual toxicants such as nicotine, heavy metals, VOCs, and carbonyl compounds, they often do not capture the combined and potentially synergistic effects of these components[5,58]. While these individual constituents have been studied, the combined and possibly synergistic effects of these components in the unique matrix of an e-cigarette aerosol remain largely unexplored. The unique matrix of an e-cigarette aerosol creates a complex interplay between these elements, which could lead to health effects that are not predictable from studying each component in isolation. This underscores the need for research that assesses the overall cardiovascular impact of e-cigarette aerosols rather than focusing on individual constituents alone.

Current research frequently relies on biomarkers of oxidative stress and systemic inflammation, such as C-reactive protein and IL-6, to infer potential cardiovascular risks associated with e-cigarette use[59]. Although these biomarkers are correlated with atherosclerosis, they provide only indirect evidence of actual disease progression. The lack of longitudinal studies specifically examining vascular changes in e-cigarette users means that the link between vaping and atherosclerosis progression remains speculative. Direct measurements of arterial health, such as carotid intima-media thickness or coronary artery calcium scans, are necessary to draw more definitive conclusions about the role of e-cigarettes in CVDs [60]. By addressing these knowledge gaps, we can inform evidence-based policies and interventions to protect public health in the face of the evolving e-cigarette landscape.

As electronic cigarette use continues to rise, there is increasing importance to explore the short-term and long-term risks, including the potential effects of electronic cigarette use associated with increased cardiovascular risk. To date, little information is known regarding the role electronic cigarettes may have in perpetuating CVDs, including progression to atherosclerosis. Current studies attempting to connect e-cigarette use to atherosclerotic progression are limited due to the majority of studies assessing short-term effects, conducting *in vitro* experiments, or using animal models, restricting application of results to human models. Additionally, the precise mechanisms by which components of e-cigarettes might exert their effects remain poorly understood, particularly given the constantly evolving composition of these products as new flavors and additives are introduced to the market.

However, proinflammatory mediators have been identified, serving as a basis for further exploration. In a cross-sectional study analyzing the risk of atherosclerosis in young people with chronic electronic cigarette use, users of electronic cigarette products for greater than one year were found to have increased levels of monocyte-derived foam cell formation (MDFCF) and monocyte transendothelial migration (MTEM) when compared to nonusers[61]. Both MDFCF and MTEM serve as key facilitators in the development of atherosclerosis. The increase in pro-atherosclerotic markers in electronic cigarette users emphasizes the need for further investigation of the association between vaping and atherosclerotic development through longitudinal studies. Efforts to bridge the current gaps in literature are necessary to mitigate current public health policy regarding electronic cigarette use and advance cardiovascular health in the general

public.

While future research should aim at better understanding the cardiovascular risks electronic cigarette use can impose, there are significant challenges in conducting such studies. Aside from nicotine, there has been very little studies that assess the potential health effects of the various chemical additives in vaping liquids[62]. Additionally, electronic cigarettes are relatively new, having been introduced to the U.S. less than 20 years ago[63]. The exploitation of long-term electronic cigarette use will take years to uncover, limiting researchers to controlled studies within human populations. Further consideration should be given to the potential effects of electronic cigarette use in populations with comorbidities compared to healthy populations, including the risks of second-hand exposure to electronic cigarette aerosols.

Impact of different e-cigarette formulations

The variation in e-cigarette formulations presents a significant challenge to public health understanding and regulatory oversight. These formulations range widely in terms of nicotine concentrations, types of solvents (such as propylene glycol and vegetable glycerin), and flavoring chemicals, each of which can have distinct toxicological profiles. Notably, research indicates that certain flavor additives can undergo thermal degradation during vaping to produce compounds with known toxicity, such as formaldehyde and acrolein, which are both implicated in CVDs[64-67]. Thus, the type and concentration of ingredients in e-cigarettes can significantly influence the risk of atherosclerosis by affecting endothelial cell function, promoting oxidative stress, and triggering inflammatory pathways.

Given the rapid pace of product innovation in the vaping industry, regulatory bodies face the challenge of keeping up with the introduction of new products. This situation calls for adaptive regulatory strategies that can swiftly respond to new evidence regarding the safety of these products. Comprehensive toxicological assessments and standardized testing methods for new and existing e-cigarette formulations are essential to ensure consumer safety and to guide consumers towards less harmful options.

User demographics

Another gap within our current knowledge is the role that user demographics play in the relationship between vaping and cardiovascular health. Emerging evidence suggests that the cardiovascular effects of vaping may vary significantly across different age groups, genders, and individuals with varying health conditions. For instance, adolescents and young adults, who are at a critical stage of cardiovascular development, might be more susceptible to the negative effects of nicotine and other e-cigarette constituents. Additionally, women may experience different effects compared to men, possibly due to differences in body fat distribution, hormonal levels, and metabolic processes, which can influence how substances like nicotine are metabolized and affect the body. Furthermore, individuals with pre-existing health conditions such as hypertension or diabetes may experience accelerated progression of atherosclerotic conditions when exposed to e-cigarette aerosols. These insights underscore the importance of demographic-specific studies that can provide tailored risk assessments and help develop targeted public health interventions. Such research is crucial for crafting effective health advisories and preventive measures that consider the diverse susceptibilities and risk factors present in the general population.

E-cigarette use and regulation across the globe

The regulation of e-cigarettes varies significantly across different countries, impacting their usage patterns and public health outcomes. In the United States, e-cigarettes are regulated by the Food and Drug Administration as tobacco products under the Family Smoking Prevention and Tobacco Control Act. Regulations focus primarily on restricting youth access by limiting the sale of flavored products and enforcing age verification. Despite these efforts, e-cigarette use has surged, particularly among adolescents and young adults[4]. In contrast, the United Kingdom has taken a more permissive approach, viewing e-cigarettes as harm-reduction tools for adult smokers seeking to quit traditional tobacco use. Public Health England even endorses e-cigarettes as being 95% less harmful than conventional cigarettes, integrating them into smoking cessation programs[68]. These divergent regulatory frameworks reflect differing public health strategies, influencing the extent and nature of e-cigarette use in each country.

Across Europe, approaches to e-cigarette regulation vary, with the European Union's Tobacco Products Directive providing a common regulatory framework that includes advertising bans, product content limitations, and warning labels. Some countries, such as France and Germany, have adopted strict regulations, while others, like Sweden, allow more liberal access[69]. These differing approaches have resulted in wide variations in usage rates across the continent, with some nations reporting high levels of adult use for smoking cessation, while others see more recreational use among younger populations. Meanwhile, in countries like Australia and Japan, e-cigarettes containing nicotine are largely banned unless prescribed by a doctor, reflecting a much more restrictive stance. This has led to an underground market in some regions, where unregulated products potentially pose even greater health risks due to a lack of quality control.

In Asia, many countries have imposed outright bans on e-cigarettes due to concerns over public health, safety, and youth uptake. Singapore, India, and Thailand are among the countries that have implemented such measures, with authorities emphasizing the potential dangers of unregulated products and nicotine addiction[70]. As of December 2021, e-cigarettes are completely banned in Singapore, Thailand, Bhutan, India, Sri Lanka, and Timor-Leste[71]. In Japan, Cambodia, and Australia, e-cigarettes containing nicotine are also prohibited. However, the effectiveness of these bans has been mixed; some reports suggest an increase in black-market sales of e-cigarettes and related products. The lack of proper labeling on most e-cigarette devices further complicates efforts by authorities to regulate them effectively. These disparities in regulatory and enforcement practices across the globe reflect differing perspectives on the risks and benefits of e-cigarettes, with significant implications for public health and atherosclerosis progression research.

Strategies to reduce cardiovascular risks of vaping

To effectively mitigate the cardiovascular risks posed by vaping, a multi-faceted approach is required. This approach should include both regulatory measures and public health interventions tailored to the unique challenges posed by e-cigarettes. Regulations might involve setting standards for maximum allowable concentrations of harmful constituents, banning particularly dangerous flavoring chemicals, and enforcing stricter controls over product labeling and marketing practices. Additional age restrictions could be implemented by raising the minimum purchase age for e-cigarette purchase to 25 years. It would be essential for businesses selling these products to strictly enforce this age restriction, potentially in collaboration with local law enforcement, to prevent younger individuals from obtaining e-cigarettes. Furthermore, marketing restrictions could require enhanced warning labels beyond the current nicotine warnings. These labels could highlight potential risks, such as the development of CVD and other cardiovascular effects. By adding these warnings, consumers may be more cautious when considering e-cigarette products, particularly if they have a family history of related health issues.

Public health interventions could include education campaigns that specifically address the risks of e-cigarettes and encourage cessation among current users, particularly focusing on high-risk demographic groups. Thorough screening of patients' usage status, along with counseling on the risks of both tobacco and e-cigarettes, should be emphasized during all medical visits, regardless of specialty or current usage status. Community-wide campaigns, particularly targeting younger and high-risk populations, can be launched to educate the public about the dangers of electronic cigarettes. Additional public health interventions could involve programs that offer social and medical support to assist current e-cigarette users in their efforts to quit. Continued innovation in developing safer e-cigarette technologies, such as alternative nicotine delivery systems that minimize harmful byproducts, is also necessary. Collaboration between scientists, manufacturers, and policymakers is crucial to align product development with public health goals, ultimately reducing the burden of CVD associated with vaping.

These implications for public health are significant, emphasizing the importance of evidence-based interventions and policies to educate youth on the dangers of e-cigarettes and advocate for further regulation of all tobacco-based products. A systematic review by Mylocopos *et al*[72], investigates non-regulatory interventions at different stages, from interactive video games tailored to children and youth at an individual level, to educational sessions in schools and campus bans. It also evaluates mass media campaigns in the community and advocates for further research on school-based peer leader programming and best practices when it comes to community public health education. The impact of these research findings underscores the importance of ensuring up-to-date public health guidelines and regulations at various levels. Currently, the United States Food and Drug Administration (FDA) authorizes the sale of 23 e-cigarette devices with a disclaimer to clarify that the products are not safe or "FDA approved"[73]. The disclaimer also notes the harm and addictive potential of nicotine products and discourages anyone from starting tobacco use, however, more public health education is needed to reach groups at higher risk of tobacco use, including youth and even younger children.

CONCLUSION

While vaping is often perceived as a safer alternative to traditional tobacco smoking, emerging literature underscores the dangers of e-cigarette aerosols. Vaping can influence atherosclerosis development through mechanisms such as endothelial dysfunction, oxidative stress, inflammation, and dyslipidemia. In summarizing findings from experimental, clinical, and observational studies to highlight a consensus on the cardiovascular risks associated with e-cigarette use, it is clear that significant gaps in knowledge remain and challenge the notion of its safety. These knowledge gaps highlight the imperative of public health education and regulation of these products in order to promote long-term cardiovascular health.

Understanding the long-term effects of e-cigarette use on atherosclerosis and overall cardiovascular health remains critical. Longitudinal studies are needed to assess these impacts fully. Additionally, the diversity of e-cigarette devices, formulations and user behaviors complicate risk assessment, underscoring the need for comprehensive research that accounts for all variables. These future studies must understand how age, gender, and pre-existing health conditions influence the cardiovascular effects of vaping to enable more precise and relevant health recommendations. Addressing these research gaps will provide a more complete picture of the risks and guide the development of effective interventions.

Informed public health strategies are essential to mitigate the cardiovascular risks associated with vaping. Evidence-based interventions and policies must be developed and evaluated to regulate e-cigarette use and reduce harm. Public health guidelines should be routinely updated to reflect novel research findings, and further emphasize the potential cardiovascular dangers of e-cigarette use. Educational campaigns can raise awareness about these risks, and should particularly target vulnerable populations such as youth and individuals with pre-existing health conditions. By prioritizing informed strategies and continuing rigorous research, public health authorities can better protect individuals from the cardiovascular risks of vaping and e-cigarette use.

FOOTNOTES

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