LITERATURE REVIEW

Current Developments of Smoking and Vaping, Is Vaping Safer?

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ABSTRACT

Vape fans claim that vaping is the solution to smoking cessation, but this is still debatable. Even if vape is still considered new, numerous studies show that vaping is associated with lung injury (EVALI). Despite this, the trend of vaping is still increasing. This study aimed to review the current understanding of conventional smoking and vaping and compare both. Is vaping safer than smoking? Smoking has health risks for lung cancer, chronic obstructive pulmonary disease (COPD), stroke, and others, while vaping has been linked with EVALI. Local perfusions were decreased in tobacco smokers after exposure. However, perfusion increased in vaping after exposure. Bronchoalveolar lavage (BAL) in vape users showed an increase of vitamin E acetate, possibly causing impairment in lung structure and functionality of surfactant. This is the potential mechanism of EVALI in vape users. Smoking uses the Brinkman Index to determine the severity of smoking, but there is no index for vaping because it depends not on how many sticks but on how many e-liquids were used. It seems that vape is "safer" than smoking, but smoking and vaping both have their own health risks, and it is safe to assume that neither is safe for use. "Vape is the solution for smoking cessation" needs further research because it takes years to understand conventional smoking in relation to other diseases. Prospective follow-up studies to determine the risk of vaping on other diseases are needed in the future.

INTRODUCTION

It is predicted that the number of smokers worldwide will increase, and the risk of disease that will be caused is also of concern. A study by Mallol, *et al.* (2021) in determining the prevalence of tobacco smoking in low-income urban populations in 2021 showed that 24% of 2,747 adolescent participants were smokers, with no significant difference for girls and boys.[1] A systematic analysis conducted to determine the prevalence of tobacco smoking in 204 countries from 1990 to 2019 showed that 7.69 million deaths and 200 million disability-adjusted life-years attributable to smoking would increase over the coming decades. The study also found that the increasing population also increased the number of smokers from 0.99 billion in 1990 to 1.14 billion in 2019. This shows that the number of smokers is increasing to date.[2]

There are many ways to deliver nicotine into the body (Table 1). Cigarettes are the most popular, and e-cigarette users will increase. A claim that also offers a way for smoking cessation is vaping. Vaping or e-cigarettes is basically inhaling and exhaling vapor containing nicotine with a modern device. Vaping fans claim it is safe and that people do not have to struggle more with smoking cessation because they provide nicotine in the vapor. Hence, it will be easy to stop smoking. Some studies showed that vaping has an impact related to lung injury, and the latest information concerns the effect of vaping related to bronchitis

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obliterans.[3,4] A study by Oliver, *et al*. (2021) looked at the risks of e-cigarette use in youth and found that 18% of youth were e-cigarette users.[5] From 2015 to 2021, there was no linear change in e-cigarette use, but there was an increase in female users. Another study also examined e-cigarette use in medical students at Saudi University and showed that 49 of 401 students (12.2%) were e-cigarette users.[6] France (6%), Poland (6%), and the Netherlands (5.9%) are the European Union (EU) member states with the highest vaping rates when daily and occasional use is included.[7] Against the backdrop of the debate that vaping is safer than smoking, there is unclear information about the effects of vaping on health. A literature review is needed to discuss this matter. This review aimed to explore more about the current developments of smoking (cigarette) and vaping (e-cigarette) and compare both.

Current Developments Regarding Smokers

It is well-known that smoking increases the risk of developing cancer. Nevertheless, cancer is not the only thing clinicians are concerned about. There is also hypertension, respiratory infection, osteoporosis, diabetes, etc. Meta-analysis in 2019 showed that smoking increased the risk of stroke by 12% for each increment of five cigarettes per day.[8] Active and passive smoking could also impact the increased risk of stroke. Nicotine can enhance neuroinflammation due to increased mitochondrial oxidative stress, and it will worsen if followed by diabetes (Figure 1). Chronic exposure to nicotine could exacerbate transient focal cerebral ischemia-induced brain injury caused by pre-existing oxidative stress.[9] Other gaseous and particulate in cigarettes other than nicotine can also play a role in vascular reactivity and endothelial dysfunctions. Carbon monoxide plays a role in inhibiting the production of platelet-derived growth factor and endothelin-1 by endothelial cells.[9]

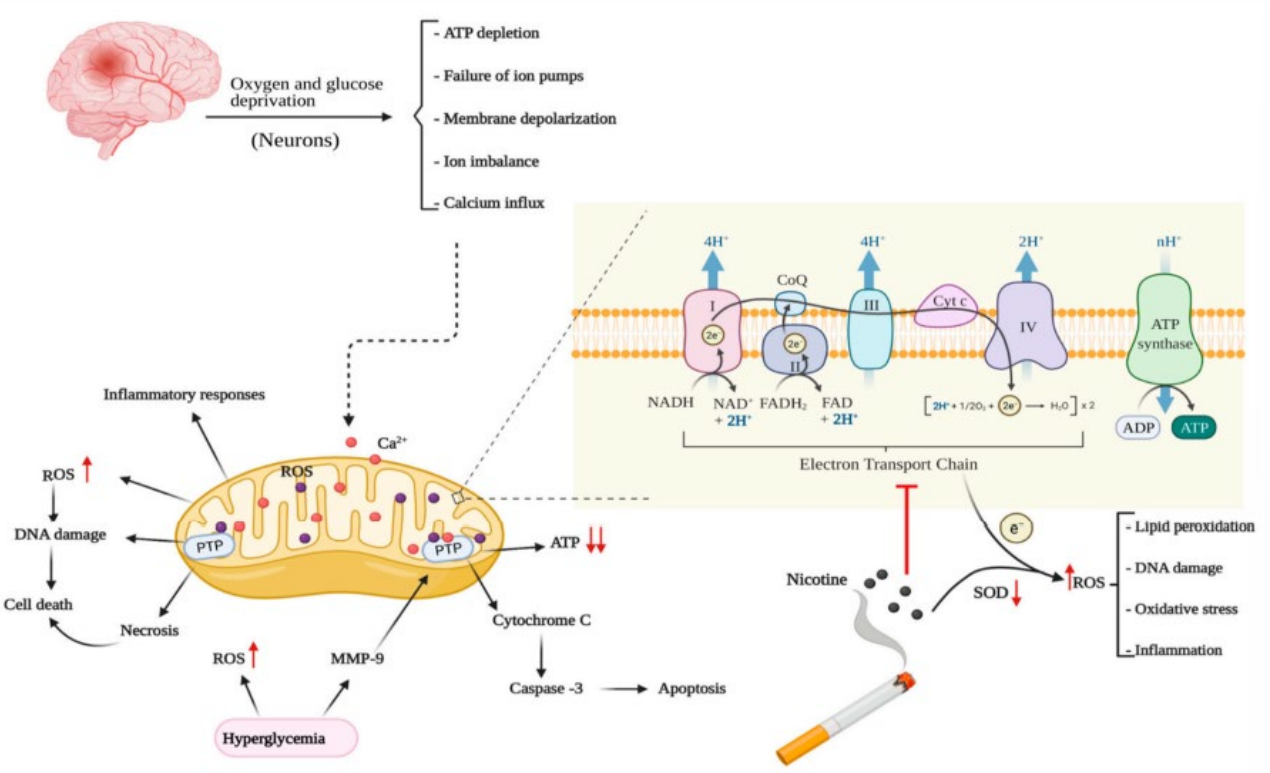

Figure 1. Effects of nicotine and diabetes in ischemic stroke[9]

Active and passive smoking could also impact pregnancy. Soneji, *et al*. (2021) found that among 25 million pregnant women, an estimated 1 in 4 women who smoked before pregnancy quit throughout the pregnancy, and 1 in 2 pregnant women smoked 10 or more cigarettes per day during their pregnancy.[10] A case-control study by Hamadneh, *et al*. (2021) showed significantly lower gestational age at delivery in active smokers than in passive and non-smoking women ($p = 0.038$ and $p = 0.003$), significantly lower weight in neonates ($p = 0.016$ and $p = 0.019$), and significantly lower first-minute APGAR score than non-smoking women ($p = 0.023$).[11] Carbon monoxide (CO) causes abnormal placental vascularization, placental hypertrophy, and/or hypoxia and reduces uterine blood flow.[12] This mechanism could increase the risk of intrauterine growth restriction. Nicotine plays a role as a vasoconstrictor and causes withdrawal in newborn

infants.[12] Smoke cessation at the start of pregnancy is associated with a lower risk of preterm birth even for high-frequency cigarette smokers (9% (95%CI: 8.8% - 9.1%)).[10]

A meta-analysis in 2018 examined the sex-specific association between smoking and lung cancer. It showed a similar risk of lung cancer in women (RR:6.99) compared to men (RR:7.33).[13] In a comparative modeling approach by simulation of smoking patterns in the United States (US), the population showed lung cancer mortality, adjusted for age, was predicted to decrease by 79% between 2015 and 2065. The predicted annual number of lung cancer fatalities would drop from 135,000 to 50,000 (a 63% decrease). With an expected 20 million smokers between the ages of 30 and 84 still smoking in 2065, there will still be 4.4 million lung cancer deaths in the US from 2015 until that year.[14] Smoking has harmful consequences that are dose- and time-dependent. Smoking exposure may enhance lung damage susceptibility, increase lung barrier permeability, and cause epithelial and endothelial cell injuries.[15] The chemicals in cigarettes affect cells and make it more difficult to repair any genetic damage. Cancer develops later in people when genetic damage builds up in one cell over time.

In tobacco-smoking users, nicotine is a strong alkaloid and main component. Thus, peripheral vasoconstriction, tachycardia, and increased blood pressure could occur after smoking. Therefore, smoking will show ventilation and perfusion mismatch by measuring blood flow in pulmonary capillaries.[16,17] Low perfusion was also shown by Nyilas, *et al*. (2022) for-tobacco smokers by measuring impairment of lung perfusion from 8.6% to 9.1%.[18]

Current Knowledge Regarding Vaping

E-cigarettes or vaping is one of many ways to deliver nicotine "without" tobacco smoke but with boiling nicotine liquid (Table 1). It has a common function with conventional smoking but with a different technique. Conventional smoking works by burning tobacco. Meanwhile, e-cigarettes use a synthetic liquid converted to steam/vaporized. E-cigarettes have been a trend from their introduction in 2004 until now. A study by Karuniawati (2019) tried to determine factors related to vape users in Purbalingga. It showed that family environments (parenting style), lifestyle, and social environments play important roles in teenagers trying to use vape and becoming addicted to it.[19]

The E-cigarette structure comprises an atomizing, battery, and cartridge (Figure 2).[20] To date, there are three generations of e-cigarettes, cigar-like (1st generation), pen-like (2nd generation), and tank systems & mods (3rd generation). Liquid is the fuel for e-cigarettes. There are two types of liquid: freebase and salt nicotine. Freebase has a low dose of nicotine with more steam. Meanwhile, salt nicotine has less steam but with a higher dose of nicotine. Propylene glycol (PG) and vegetable glycerine (VG) are the main liquid components. VG/PG ratio is stated on the bottle label. There is also additional "essence" that plays a role in giving a certain flavor to the liquid.

Table 1. Nicotine delivery system[20]

Smoked tobacco (combustible)	Smokeless tobacco (non-combustible)	Nontobacco nicotine delivery	
		Medicinal nicotine	Other nicotine products
Cigarettes	Chewing tobacco	Transdermal patch	E-cigarettes
Cigars	Dry snuff	Gum	Nicotine gel
Pipes	Moist snuff	Nasal Spray	Nicotine water
Water pipes	Swedish-style snus	Inhaler	Nicotine wafer
Bidis	Tobacco strips	Sublingual tablet	Nicotine lollipop
Kreteks	Dissolvable tobacco products	Nicotine lozenge	Nicotine lip balms

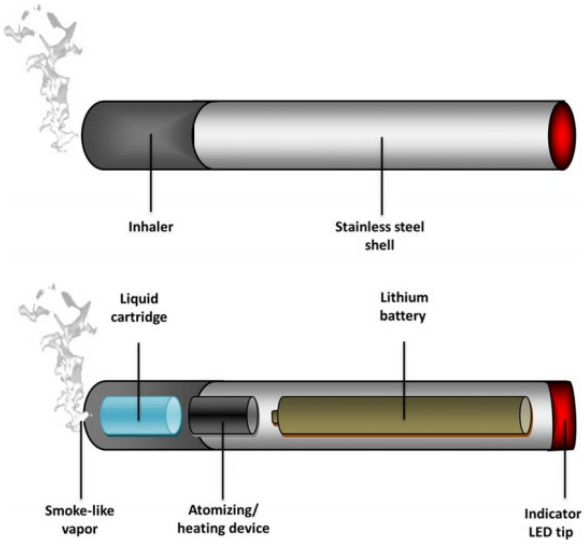

Figure 2. E-cigarette structure[20]

A randomized controlled trial (RCT) by Nyilas, *et al*. (2002) evaluated lung function by measuring impairment of lung perfusion (Rq) for nicotine-free e-liquids and nicotine-containing e-liquids. Local perfusion was increased after exposure to nicotine-containing e-liquids (Rq, 9.7% to 8%; p = 0.01), and no changes were observed in nicotine-free e-liquids.[18]

Even if vaping is considered new and needs future research to find its relation with other diseases, it is known to be related to lung injury.[3,4] Many cases of e-cigarette and vaping-associated lung injury (EVALI) have been reported. A case report by Aftab, *et al*. (2019) found a 46-year-old female who recently started vaping and presented to the hospital with dyspnoea and with dry cough for two days.[21] The patient had been using e-cigarettes one month before hospital admission and required intubation and temporary paralysis. Computed tomography (CT) angiography revealed diffuse patchy alveolar opacities in both lungs.[21] A review study by Callaghan, *et al*. (2022) sought to determine EVALI cases and found 24 studies evaluated EVALI and reported EVALI cases.[4] Most patients that use e-cigarettes and develop EVALI will have abnormal chest imaging, such as bilateral lung opacities with ground-glass changes and sometimes subpleural sparing by CT (Figure 3).[4]

Figure 3. CT of EVALI in 18-year-old patient. Axial CT imaging (A–C) showed extensive bilateral centrilobular and peri-bronchial ground glass opacification with subpleural sparing.[4]

Studies have attempted to compare toxic exposures from e-cigarettes to conventional cigarettes and found that levels of two nitrosamines and CO were lower in e-cigarettes.[22–24] However, toxic exposure was mostly found in dual users (vaping and smoking).[25] A study by Scott, *et al*. (2018) found that exposure to e-cigarette vapor macrophages can cause cellular and functional changes in alveolar macrophages, similar to those in conventional smokers and COPD patients.[26] Commonly used in e-cigarettes, reports have associated it with increased wheezing and coughing, and exacerbation of asthma.[27]

The exact mechanism of EVALI is still debatable and under investigation. Bronchoalveolar lavage (BAL) in EVALI patients shows a high level of vitamin E acetate.[28] In animal studies, mice exposed to aerosols of vitamin E acetate showed increased levels of macrophages containing BAL lipids on Oil-Red-O staining, consistent with the BAL findings in EVALI patients (Figure 4).[29] The increase in vitamin E acetate may have impaired the surfactant's physical structure and phase behavior. Therefore, surfactants impair the ability to maintain alveolar surface tension and cause respiratory failure.[29–32]

Diacetyl ($C_4H_6O_2$) is also commonly identified in e-cigarettes. It naturally occurs in tea, coffee, beer, and others. Diacetyl in e-cigarettes, on the other hand, is actually a toxicant and plays a role as a flavoring component and enhancer of e-juices.[33] A study by White, *et al*. (2021) showed a significantly higher non-carcinogenic risk in e-cigarette users.[33] Exposure to diacetyl is known to cause subclinical changes in lung function, which can cause life-threatening airway obstruction. It is known as a causative agent for obliterative bronchiolitis (Figure 5).[33–35] Exposure to diacetyl was actually found in several cases like workers at food-flavoring factories, microwave popcorn plants, fragrance companies, and others, which showed a cluster of bronchiolitis obliterans syndrome among workers.[33] In this case, diacetyl is also commonly found in e-cigarettes, potentially causing harm in the future.

The largest components in e-liquid are solvents, which could be propylene glycol (PG) and vegetable glycerine (VG), also known as glycerol or glycerin.[36] These solvents act as humectants or stabilizing agents, keeping the other chemical components (nicotine) and flavorants in suspension form.[37] PG is generally considered safe (GRAS) for ingestion but not in aerosol form.[36] As the largest component in e-liquid, it presents in varying ratios but is commonly accepted for 80-94.9% of total e-liquid volume for PG and glycerol.[36] PG and glycerol are both airways irritants. Occupational exposure to PG in aerosol form is documented in theatrical workers.[36–40] Those exposed to PG described wheezing and chest tightness at work proportionate to their estimated cumulative exposure. Moreover, PG irritates mucosal membranes, the respiratory system, the eye, and the throat and causes peripheral airways to contract.[41]

Metals/metalloids could be found in e-cigarettes that originate from the coil, soldered joints, and other parts of the device (Figure 3).[42–44] Alloys such as kanthal (iron, chromium, and aluminum), and high-purity metals (titanium) are commonly used for coils.[43,44] The metal/metalloid contamination in e-liquids also relies on how the liquid is stored, which can be either a tank or a refillable cartridge.[43] Thus, contamination of metal/metalloids potentially causes metal toxicity in e-cigarette users. Metal/metalloid in aerosol form is a major concern that could give serious health effects, including cancer,[45,46] cardiovascular disease,[45,47] renal damage,[48] and neurotoxicity.[49] With the exception of cadmium, most meta/metalloid levels in e-cigarette users' BioSamples were comparable to or even greater than those of regular cigarette smokers. The idea that aerosol metals/metalloids are breathed and absorbed by vape users has been supported by a comparison of meta/metalloid aerosols levels to human BioSample levels.[50]

E-liquid comes in many different flavors, with over 670 flavored e-liquids identified, including ethyl maltol, ethyl vanillin, vanillin, cinnamaldehyde, and others.[36,37,39] Between 5 and 1.55 x 105 ppm of taste, chemical concentrations were found when 476 e-liquids from seven studies were compared.[36] There is no proof that flavoring substances found in vape goods are safe to inhale as aerosols, although they are typically considered safe for oral consumption. Contrarily, the scant information suggests that they present a serious inhalation threat.[36,37] For instance, Erythropel, *et al*. (2019) recently reported that flavor aldehydes, including benzaldehyde, cinnamaldehyde, citral, ethylvanillin, and vanillin, rapidly reacted with the e-liquid solvent PG after mixing with >40% of flavor aldehyde content converted to flavor aldehyde PG acetals which, in turn, activated aldehyde-sensitive TRPA1 irritant receptors and aldehyde insensitive TRPV1 irritant receptors in vitro.[51] Nearly all aldehydes are respiratory irritants when inhaled at significant concentrations.[39]

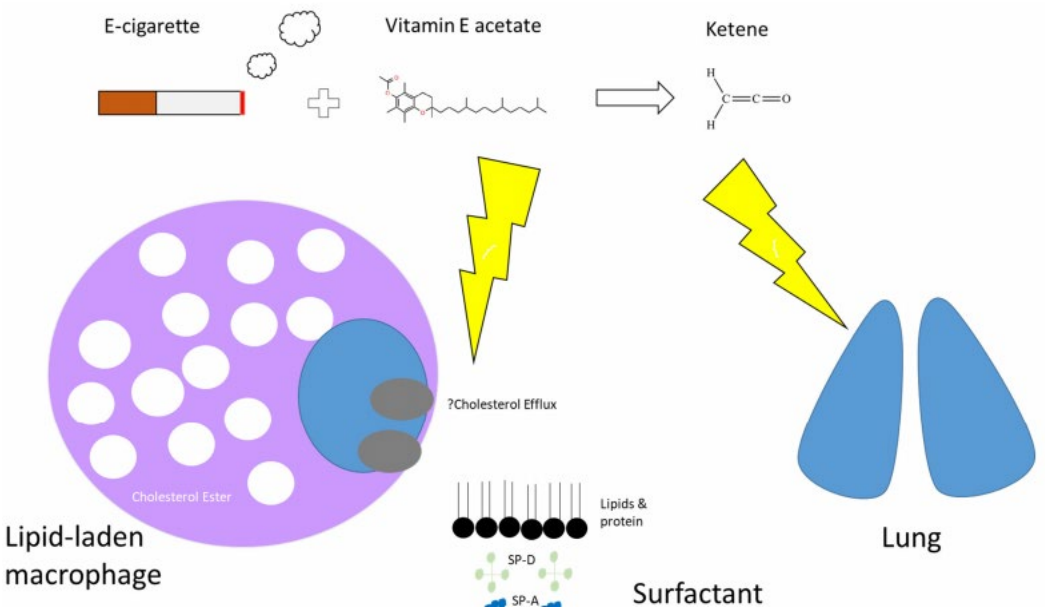

Figure 4. Proposed mechanism of e-cigarettes causing lung injury. Tetrahydrocannabinol (THC) found in e-cigarettes has been shown to commonly contain high levels of vitamin E acetate as a thickening agent. This vitamin E affects the structure and phase of surfactants, interfering with their ability to maintain surface tension and possibly causing shortness of breath and reverse cholesterol transport or efflux.[4]

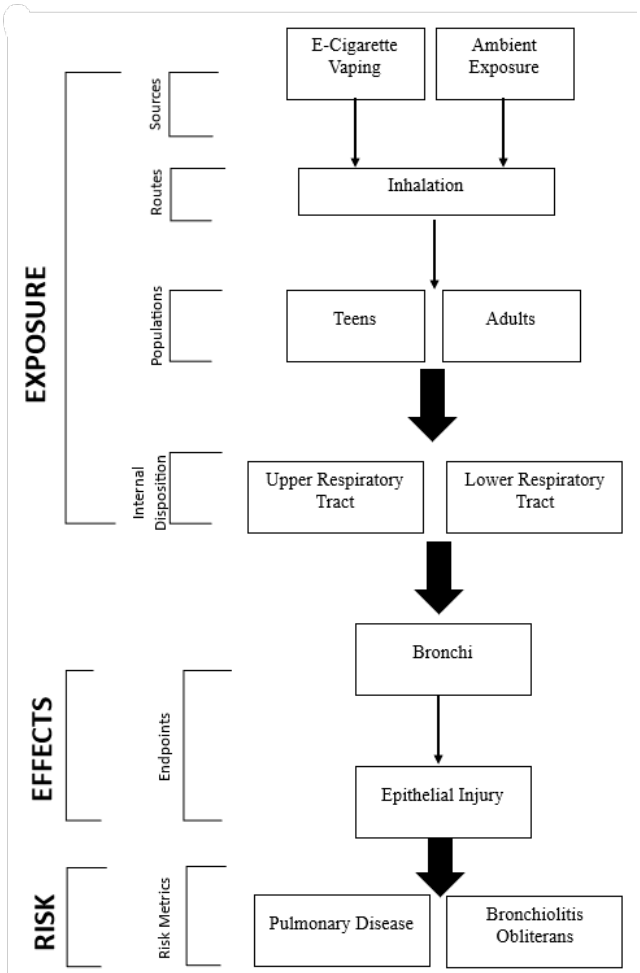

Figure 5. Conceptual model of diacetyl impact on humans and risk that could happen[33]

Comparison between Smoking and Vaping

Until now, vaping has been claimed to be the solution and safer for smoking cessation. Comparisons between smoking and vaping in some aspects are compiled in Table 2.

Table 2. Comparing smoking and vaping

Aspect	Smoking	Vaping	General Comments
Health Risk	● Cancer[14] ● COPD[15] ● Stroke[8] ● Others	● EVALI[4] ● Bronchiolitis obliterans[3,52]	● Conventional smoking seems to have more risk rather than vaping. This is because vaping is still considered new and needs future prospective research to determine the risk of vaping. ● Currently, regular smoking uses the Brinkman Index to determine the severity of smoking. On the other hand, vaping does not have an index to determine the severity. This makes it hard to determine the severity of vaping related to health risks.
Environmental Aspects[22,39,50]	● Second-hand exposure to combustion ● Waste from cigarette butts (from plastics)	● No second-hand exposure to combustion toxicants ● Potential waste from batteries	● Smoking and vaping potentially cause environmental harm. Cigarette butts contribute more than 766 million kgs every year. ● Batteries from vapes that are not used and disposed of carelessly can pollute the environment.
Social Aspects[5]	● Looks cool, calm, and manly	● Looks cool and modern	● Cigarette users rather than e-cigarettes dominate the current prevalence. Potentially e-cigarette users will be increased, especially among teenagers, due to looking cool and modern.[53]
Price[54,55]	**Indonesia**		Vaping seems more expensive than conventional smoking, but e-liquid can be used for up to one month (depending on usage). Vaping is considered cheaper than smoking because it lasts longer, and the mode is reusable, with users only needing to buy e-liquid.
	Cheapest: 1.07USD/pack Expensive: 2.27USD/pack	Ranges from 7.69USD to 60.21USD (exclude e-liquid, 5.82USD–30.10 USD)	
	United Kingdom[56]		
	14.20USD/pack	Between 24.80USD and 55.81USD (for a starter kit)	
	United States[57]		
	8USD/pack	10USD-30USD (pod system)	

A recent RCT from 2022 investigated the effects of e-cigarettes and smoking on pulmonary ventilation and blood flow (changes in lung function and assessment of lung function by MRI). This study showed that regional perfusion (Rq, a measured impairment of lung perfusion) was decreased in cigarette smokers after exposure (Rq, 8.6% to 9.1%; p = 0.03). However, blood flow during vaping increased after exposure (Rq 9.7% to 9%; p = 0.01).[18]

Future Prospective of E-Cigarettes: Are E-Cigarettes Safer?

There is a lack of information on any link between e-cigarettes and other diseases like cancer. Conventional smoking needs years of experiments to determine a relation to cancer, Brinkman Index (sticks each day x duration of smoking (years)) exists to determine how severe the smoking experience is for the patients. Meanwhile, to date, there is no "index" to determine the severity of vape users because it is not based on how many sticks are consumed per year but on how much volume in millimeters (mL) of e-liquid is used. Therefore, further research is needed to determine the degree of severity of vape users and the relationship between vape and vaping. Determining severity in vape users is tricky because it has different variables. Not only does the volume (mL) of e-liquid needs to be considered for severity, but also ingredients, solvents, and other mixed chemicals that could be different from one to another. Various problems could arise from different chemical compounds. However, it is possible to generalize for severity by using how many mL of e-liquid a person uses per day multiplied by how long they have been vaping (volume (mL) x duration of vaping (years)) in order to assess additional health risks.

In order to determine or make a degree of severity of vape users, it should also be noted whether the patient has a previous history of tobacco smoking. Hence, they are considered a dual user. Clinicians must develop a severity scale for vaping and determine how it relates to other diseases in order to provide clear information about the risk of vaping. As it has been projected that the number of vape users will rise in the next years, health impact awareness should be increased and evaluated.

Although traditional smoking has a greater risk than vaping, it takes years of research and experience to grasp how smoking affects other diseases fully. Regarding the time experiment to establish the risk of vaping, vaping is still relatively new and cannot be compared directly to other forms of tobacco use. Yet, it has been noted in numerous studies that vaping can cause lung damage even if a patient uses e-cigarettes for only one month. In the previous section, factors associated with vaping that can be harmful such as flavors, metals, and solvent ingredients, were presented.

Vaping is the new way and new wave for nicotine addiction. Particularly at risk are young people. An increase from 1.5% in 2011 to 20.8% of high school students reporting using e-cigarettes on at least one day in the previous 30 days is significant.[53] It is predicted that vape users will increase and be dominated by youth. Smoking effects cannot be seen in just a year, but need years to expect any effect on health. It is prospectively estimated that youths that start smoking early are at risk of having health issues later on. Thus, it will be a burden due to spending on costs.

The risk of vaping is considered potentially fatal, and it is safe to assume that vaping is not safer than conventional smoking. Vape fans' claims that e-cigarettes are the solution for smoking cessation, provide better nicotine, and are safer are still questionable. Nevertheless, at the end of the day, it is better to prevent rather than wait for more serious conditions to happen if the vaping trend increases. Large-scale prospective studies are needed regarding the relationship between vaping and other diseases that may occur. It is predicted that, in the coming years, the health effects of vaping will emerge, and studies like this will be a major topic of discussion.

A limitation of this study is that few studies directly show the health effects of vaping. Very few observational studies determine the risk of vaping and the degree of the effects. This study is also limited by the lack of relevant articles that directly discuss the differences between cigarettes and vaping, which is an advantage of this article, providing a more detailed comparison. The limitations of the study should not be misinterpreted to mean that the impact of vaping is lower than tobacco smoking. Therefore, readers should be cautious in concluding. With the lack of knowledge on the health effects of vaping to date, it is recommended that the public be educated against vaping due to its potentially more harmful effects in the future.

SUMMARY

Both smoking and vaping have risks to one's health. Thus, it is safe to infer that neither should be utilized. Although vape fans assert that "vaping is the solution for quitting smoking," this is still debatable and uncertain. Therefore, more research is necessary because it will take time to understand how conventional smoking affects other diseases. Even though vaping is still a "new" trend, several reports have linked it to lung damage, demonstrating the potential for future health risks associated with the practice. The e-cigarette trend should be stopped before it worsens. It can be concluded that vaping cannot be considered safer than smoking and could prove potentially more dangerous.

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Authors' Contribution
Conceiving the ideas: AMS, YPN, IES. Performing literature collection: AMS, AH, BST, SB, YPN. Analyzing literature: AMS, AH, BST, SB, YPN, IES, SS. Manuscript writing: AMS, AH, BST, SB, YPN, SS. Revising: AMS, AH, BST, SB, YPN, IES, SS. All authors contributed and approved the final version of the manuscript.

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