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Vaping in the Age of Pandemic – A Narrative Review

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Abstract

Electronic nicotine delivery systems (ENDS) are devices that heat a liquid to create an aerosol that is inhaled by the user. The liquid may contains nicotine, flavorings and other chemicals such as propylene glycol, glycerol or diacetyl. Since their entrance to the market in 2003, e-cigarette use has risen rapidly, especially among young people. Recent studies indicate that e-cigarettes are not harmless and safe alternatives to combustible conventional tobacco, especially with regard to their effects on cardiovascular and lung diseases.

Objective: *This study aimed to explore scientific research on the relationship between SARS-CoV-2 infection rates/ the severity of COVID-19 and vaping.*

Methods: *A bibliometric analysis of articles indexes in PubMed, Scopus and ClinicalKey, published in English from 2020 to 2022 was undertaken.*

Results: *Most of the research revealed the fact that because the COVID-19 virus affects the respiratory tract and has ability to increase angiotensin-converting enzyme 2 (ACE2) expression in the lungs, e-cigarette use may rise the risk of infection or severity of outcomes due to COVID-19.*

Conclusion: *E-cigarette use may have adverse effects and further research is needed to elucidate the impact of e-cigarette consumption on human health in he event of SARS-CoV-2 infection. The significant increase in e-cigarette use in the near future and the impact of COVID-19 may increase the burden of chronic disease.*

Key *words: e-cigarette, adverse health effects, vaping, COVID-19, SARS-CoV-2*

Introduction

Electronic nicotine delivery systems (ENDS) are devices that heat liquid to create an aerosol that is inhaled by the user. The liquid contains nicotine (but not tobacco) and other flavorings and chemicals, such as propylene glycol, glycerol, diacetyl (butter flavor), cinnamaldehyde, benzaldehyde, and metals [1, 2].

There are many different types of e-cigarettes in use, some with nicotine and some without ENDS. Moreover, e-liquid can contain addictive substances other than nicotine. The use of e-cigarettes to administer marijuana has already been reported [3].

Since the first electronic cigarettes were manufactured in Beijing, China, in 2003 and shortly after their introduction to the United States of America (USA) in 2006, their use has become a common phenomenon that has an increasing trend all over the world [4].

In the European Union (EU), the number of users doubled from 2012 to 2017 (7.2–14.6%) [5]. Recent surveys in the USA have shown that the prevalence of e-cigarette use among non-adults increased from 1.5% to 20.8% between 2011 to 2018 [6], with over 5 million middle- and high-school students believed to be e-cigarette users in 2019 [7]. These disturbing consumption data, especially among young people, are associated with more and more recent scientific reports on the harmfulness of e-cigarettes.

The initial longitudinal study that examined the link between e-cigarette usage and the occurrence of respiratory disease in the general population was found that the odds of developing respiratory disease increased by a factor of 1.29 (with a 95% confidence interval between 1.03 and 1.61). It also revealed that dual use, the most common use pattern, poses a greater risk compared to using each product alone [8].

According to certain researchers, using e-cigarettes for a brief period of time may result in outcomes comparable to smoking tobacco, such as cellular inflammation, apoptosis, oxidative stress, and DNA damage [9].

The WHO (World Health Organization) report on the global tobacco epidemic 2021 presents data on ENDS for the first time and highlights its health risk [10].

Several recent studies indicate that e-cigarettes are not safe alternatives to combustible conventional tobacco, especially with regard to their effects on cardiovascular and noncancer lung disease [11, 12].

Using an e-cigarette is typically linked to decreased odds of successfully quitting smoking for the majority of smokers [13, 14]. A review of 38 studies suggests that the likelihood of quitting smoking was 28 percent lower among individuals who used e-cigarettes compared to those who did not. Studies of both smokers using e-cigarettes (irrespective of interest in quitting cigarettes) and those of smokers only interested in quitting indicated similar associations between e-cigarette use and quitting [15].

Moreover, studies show that ENDS users are more likely to become cigarette smokers, which exposes them to the harmful effects of smoking [16]. In addition, dual users use products more frequently than tobacco-only smokers, and this may result in greater nicotine dependence [17]. Young people who experiment with ENDS are two to three times as likely to progress to regular use of conventional cigarettes than those who do not [18].

The WHO suggests that e-cigarettes cannot be considered as a viable method to quit smoking, due to a lack of evidence for the potential role of ENDS as a population-level tobacco cessation intervention [19].

An attractive aspect of e-cigarette use among adults and non-adults is that it can be used in smoke-free areas. However, the legal regulations are changing [20–22].

Many studies noted that the air in which e-cigarettes are used contains higher amounts of nicotine, ultrafine particles, and byproducts of heating propylene glycol and glycerin. Moreover, evidence has demonstrated that bystanders can absorb nicotine at levels similar to exposure to secondhand smoke from conventional cigarettes when people around them use e-cigarettes. Nonsmokers exposed to secondhand e-cigarette aerosol or secondhand tobacco smoke from housemates demonstrated elevated nicotine levels in the urine compared with people living in aerosol- and smoker-free homes [23, 24].

Many governments have prohibited the use of e-cigarettes in venues in which conventional cigarette smoking was also prohibited, and vaping has been banned in many countries, including Argentina, Brazil, Colombia,

and Australia (except for therapy). In addition, ENDS are currently illegal in 32 countries worldwide including Japan and Qatar. In places where they are not banned, WHO recommends that ENDS should be regulated [10].

In 2016, the Member States of the European Union banned the promotion, advertising, sponsorship, and use of electronic cigarettes and spare liquids in any place where use of conventional cigarettes is forbidden. The directive also prohibits the sale of electronic cigarettes and refill containers to people under 18 years of age [25]. However, as many countries still demonstrate almost 21.8% prevalence of consumption of traditional tobacco products with electronic cigarettes (i.e., dual use) among teenagers, these restrictions do not appear effective.

Smoking and vaping have received even more attention among researchers, public health institutions, and governments since the outbreak of the pandemic COVID-19.

The 2019 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic has had a considerable impact on physical health, economic, and social behavior, and the psychological impacts and health behavior changes are increasingly being reported [26, 27].

Important issue which has arose during the SARS-CoV-2 pandemic is the role of nicotine from smoke and vapor aerosol in the course of COVID-19. Many studies have attempted to better understand the relationship between combustible tobacco products or non-combustible like a e-cigarettes and COVID-19.

Some early studies identified a lower prevalence of smokers or vapers among hospitalized COVID-19 patients than of non-smokers, leading some to claim that smoking, and nicotine in particular, may act as a protective factor against COVID-19 [28, 29]. Other reports indicated that smokers and vapers are more vulnerable to SARS-CoV-2 infections or more prone to adverse outcomes if they have COVID-19 [30, 31].

There are few systematic reviews or meta-analyses taking into account the COVID-19 pandemic and vaping. Our narrative review is one of the first to attempt to fill this gap. As one of the first literature reviews, it addresses the adverse health effects of COVID-19 and vaping.

Hence, the aim of this narrative review was to investigate the relationship between SARS-CoV-2 infection rates, the severity of the disease, and e-cigarette use.

Methods

This narrative review summarizes recent research on the current state of knowledge regarding vaping during a pandemic. This review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews) [32].

Search Strategy

A comprehensive, systematic literature search was carried out in online databases including PubMed, Google Scholar, Elsevier, Web of Science, and Scopus from March 2020 to August 2022 to identify relevant articles in English. The search included most recent literature published since the announcement of the COVID-19 pandemic. The following keywords were used to search the literature: COVID-19; SARS-CoV-2; adverse health effects, e-cigarette, vaping. These terms are all related to susceptibility to infection, the adverse health effects of e-cigarette use on COVID-19. A total of 134 articles were found (Figure 1).

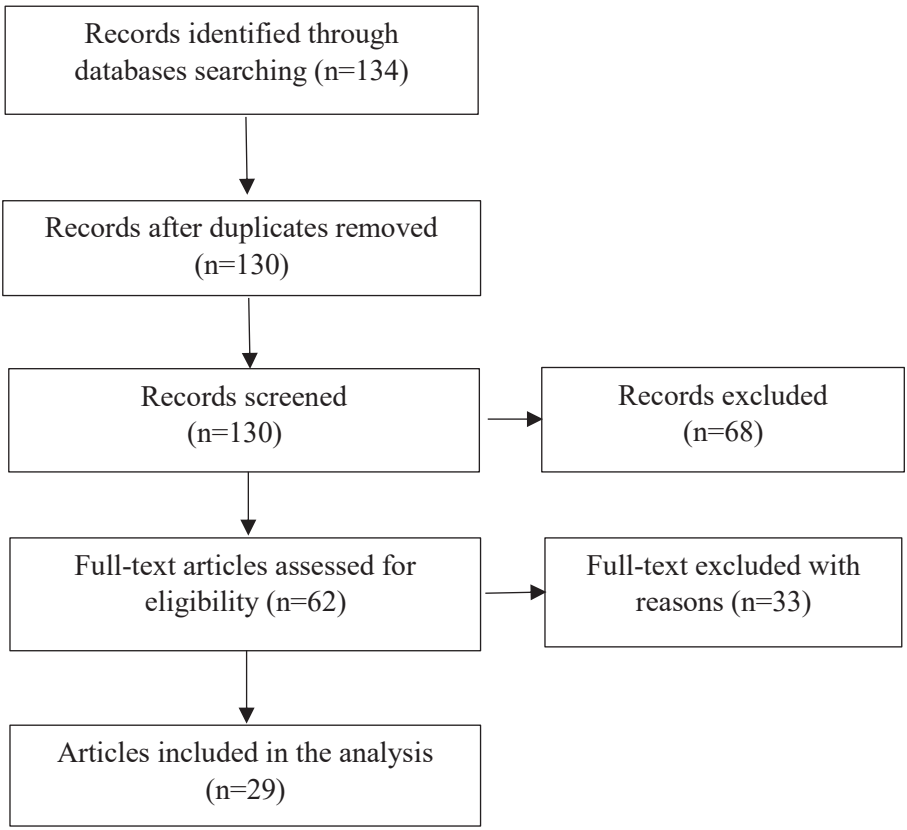

Figure 1. PRISMA Diagram of Study Selection

The titles, abstracts, and full text of the articles were then independently checked by two researchers (MZ and ML). The reference lists were then screened to identify other potentially eligible articles for review. All disputes were resolved by another researcher (DK).

Selection Criteria

The inclusion criteria for the articles were as follows: (1) The study designs included cross-sectional studies, case-control studies, cohort studies, meta-analyses, as well as case reports of the relationship between e-cigarette use and adverse health effects, (2) at least one result reported from demographics, comorbidities, clinical

symptoms, or laboratory tests was from e-cigarette users during the COVID-19 pandemic; (3) the research sample was greater than 20; (4) they were available in English; (5) they have been published in a peer-reviewed journal as a pre-print or public health report. *In vitro, in vivo, in silico* studies were also included.

Study Criteria

When selecting the studies, various factors were considered including the authors and publication year, the primary objective of the study, the findings, and the type of research (whether it was an epidemiological, *in silico, in vitro*, or *in vivo* study). Only original articles with both human and *in vitro* impact assessments were included. Finally, for the purposes of this review, the following information was extracted from each study: study population; type of outcome (cardiovascular disease, respiratory disease, COVID-19), and results.

As a result, 29 publications on adverse health effects of COVID-19 and e-cigarette use were selected. Their inclusion was approved by two reviewers with excellent agreement (k = 0.80). The exclusion criteria comprised duplicate reports, conference abstracts and commentaries issued before 2020, and publication in a language other than English.

In this paper, the term ENDS/ ECIG/e-cigarette is used to define electronic cigarettes.

Results

An initial search found 134 articles of potential interest. Of these, 29 articles met the full eligibility criteria (according to PRISMA). The studies included in the review were conducted after the announcement of the COVID-19 pandemic in 2020, 2021, and 2022.

The impact of e-cigarette use on susceptibility to SARS-CoV-2 infection

Summarizing the results of the review on this topic, five studies indicated no link between e-cigarette use and the risk of contracting COVID-19 [33–37],

and seven showed that vapers are at a higher risk of catching COVID-19 [38–44].

Two articles on the correlation between vaping and COVID-19 concluded that the evidence for e-cigarette use as a risk factor for infection is mixed [45, 46] (Table 1).

Table 1. The impact of e-cigarette use on susceptibility to SARS-CoV-2 infection

Authors, Year of Publication	Type of Study/ material	Country	Main objective	Results/conclusion
Chen, 2021	cohort/human	UK	assessing the relationship between different groups of tobacco users and symptoms of COVID-19	the act of using both conventional cigarettes and e-cigarettes concurrently was linked to a 2.15-fold increase in the likelihood of reporting a COVID-19 infection
Gao, 2022	cohort/human	UK	assessing whether smoking and e-cigarette use has been associated with severe COVID-19	the risk of severe COVID-19 was found to be lower among current smokers, but the link between e-cigarette use and the disease was uncertain; possible that smoking may have protective mechanisms against SARS-CoV-2 infection
Merianos, 2021	cross-sectional/ human	US	current e-cigarette use and reported COVID-19 symptoms	given use of two or more tobacco products (e-cigarettes, combustible cigarettes, and cigars) increased COVID-19-related risks
Gaiha, 2020 (2)	cross-sectional/ human	US	is the use of electronic cigarettes (e-cigarettes) related to the symptoms, testing, and diagnosis of COVID-19	COVID-19 diagnosis was five times more likely among ever-users of e-cigarettes only, seven times more likely among ever-dual-users, 6.8 times more likely among past 30-day dual-users

Authors, Year of Publication	Type of Study/ material	Country	Main objective	Results/conclusion
Jose, 2021	retrospectively screening study/human	US	whether current e-cigarette use was associated with an increased risk of SARS-CoV-2 infection in patients seeking medical care	e-cigarettes do not appear to increase susceptibility to SARS-CoV-2 infection
Kale, 2021	cross-sectional/ human	UK	to investigate the link between e-cigarette use and self-reported diagnosed/suspected cases of Covid-19	self-reported diagnosed/suspected Covid-19 was not associated with vaping status
Li, 2020	Behavioral Risk Factor Surveillance System (BRFSS) survey data/ human	US	present research findings on the correlation between vaping and COVID-19 infections and fatalities among the population in the United States.	the GEE models showed significant correlations between the percentage of vapers and both the number of confirmed COVID-19 cases and deaths in the US, after adjusting for the percentage of smokers and other important factors
Mallis, 2022	cross-sectional/ human	US	identification of risk factors associated with SARS-CoV-2 infection among students	current high and low frequency e-cigarette users were 2.76 and 2.27 more likely to report SARS-CoV-2 infection than non-users
Kashyap, 2020	review/human	US	the review of the current knowledge on the effects of smoking on clinical symptoms, disease progression, inflammatory reactions, immuno-pathogenesis, racial and ethnic differences, and the incidence of COVID-19 (e-cigarette, vaping, Hooka, and COVID-19)	active smoking is significantly linked with the risk of greater severity of COVID-19. E-cigarettes are brought to the mouth and face to inhale repeatedly, and many users have an increased urge to cough or expectorate which can increase the transmission of COVID-19

Authors, Year of Publication	Type of Study/ material	Country	Main objective	Results/conclusion
Sharma, 2021	review/human	US	the review assesses the evidence of pulmonary effects of electronic vaping products from pathophysiological and epidemiological studies and explores electronic vaping product (EVP) use as a risk factor for COVID-19	the evidence for EVP use as a risk factor for COVID-19 is mixed: some studies showed that ever-EVP-nicotine users were several times more likely to be diagnosed with COVID-19, some studies conversely, found no difference in self-reported COVID-19 infection between never, current, and past EVP users
McFadden, 2022	cohort/human	US	to evaluate that vapers are at greater risk for contracting COVID-19	no evidence to suggest that vapers are more likely to contract COVID-19, but vapers who do contract the virus experience a higher frequency of COVID-19 related symptoms compared to non-vapers who are matched for age and gender
Burnett-Hartman, 2022	cohort/human	US	determining the risk of SARS-CoV-2 infection and severe COVID-19 disease associated with the use of e-cigarettes	vapers are not susceptible to infection
Merianos, 2022	cross-sectional/ human	US	to determine whether using electronic cigarettes and cannabis in the past 30 days is linked to COVID-19 symptoms, testing, and diagnosis.	the more often e-cigarettes and cannabis were used concurrently, the greater the likelihood of experiencing COVID-19 symptoms and being diagnosed with the disease, with higher odds observed in groups that reported more frequent use

Authors, Year of Publication	Type of Study/ material	Country	Main objective	Results/conclusion
Duszynski, 2021	cross-sectional/ human	US	to examine how overall health status, as well as nicotine consumption and smoking behaviors (including vaping), are associated with current (identified by viral PCR) and previous infection (identified by antibody) with SARS-CoV-2	the use of vaping/e-cigarettes was not associated with infection, positive smoking status was inversely associated with SARS-CoV-2 infection

These surveys were mainly based on cross-sectional or cohort study on adolescents and young adults and examined the susceptibility to SARS-CoV-2 infection in both exclusive vaping and dual-use (e-cigarette with traditional smoking or cannabis).

Harmful health effects of COVID-19 and the use of e-cigarettes

Among studies describing the harmful health effects of COVID-19 and vaping, 13 have shown that e-cigarettes cause complications due to SARS-CoV-2 infection [37, 47–58]. Conversely, two studies, *in silico*, conducted at the beginning of the pandemic, revealed a binding tendency in nicotine with the ACE2 receptor, which may lead to the blocking of the ACE2 receptor against SARS-CoV-2 [59, 60].

In the area of harmful effects examined by the reviews, seven *in vivo*, seven *in vitro*, two *in silico* studies, two reviews, and one cohort study were analyzed [37, 47–60] (Table 2).

Table 2. Vaping and COVID-19 – harmful effects and complications

Type of Outcome	Type of Study	Results
Changes in angiotensin-converting enzyme 2 expression in the lungs	in vivo/mice lung tissue in vivo in silico in silico in vitro/human bronchial epithelial cells (HBECs) in vivo/mice in vivo/mice in vivo/mice	+ ↑ Lallai, 2021 + ↑ Zhang, 2022 +↓ Mohammadi, 2022 +↓ Wan, 2020 +↑ Ghosh, 2022 + ↑ Naidu, 2021 + ↑ Wang, 2020 + ↑ Masso-Sliva, 2021
Vulnerability to acute respiratory distress syndrome (ARDS)/ Exacerbated pulmonary disease severity of coronavirus disease Changes in viral proteases	review in vivo, in vitro/mice, epithelial cell lines review/human in vitro/human bronchial epithelial cells (HBECs) in vitro/human cells	+ ↑ Brar, 2021 + ↑ Sivaraman, 2021 + ↑ Pino, 2020 +↑ Ghosh, 2022 + ↑ Kelesidis, 2022
Dysregulation of proinflammatory cytokines/ inflammatory response	in vitro/human cell in vivo/mice in vitro/ mice in vitro/murine model	+ ↑ Lee, 2020 + ↑ Wang, 2020 + ↑ Masso-Sliva, 2021 + ↑ Muthumalage, 2020
Evaluating in the generation of reactive oxygen species	in vitro, human bronchial epithelial cell lines and human monocytic leukemia-derived cell lines	+ ↑ Muthumalage, 2020
More severe course of COVID-19 (chest pain, chills, myalgia, headaches, anosmia/dysgeusia, nausea/ vomiting/abdominal pain diarrhea non-severe light-headedness	cohort/human	+↑ McFadden, 2022

+ effect (↓ decrease of the effect, ↑ increase of the effect)

Most of the reports linking smoking or vaping to the adverse outcome of COVID-19 are based on their ability to increase angiotensin-converting enzyme 2 (ACE2) expression in the lungs [47–52, 56, 57]. It appears that smoking or vaporizing nicotine may have a negative effect on COVID-19 score.

Wang et al. found that chronic exposure to e-cigarettes with or without nicotine modified the abundance of extracellular matrix collagen and fibronectin with gender being a significant factor here, but the nAChR*a7 gene* was not directly involved. Subchronic exposure to electronic cigarette vaping (ECIG) with or without nicotine influenced pneumonia and nAChR*a7 mediated repair/remodeling responses by* nAChR*a7 in a gender-specific manner*. Type 1 collagens chain 1 (COL1A1) protein abundance was reduced in wild-type male mice exposed to propylene glycol with or without nicotine, and nAChR*a7 deficiency further decreased the baseline of COL1A1 levels in male mice. Decreased level of fibronectin protein was also observed in the propylene glycol-exposed wild-type male mice* [50]. In a study by Naidu et al., subchronic exposure to e-cigarette caused significant increase in immune cell influx into respiratory tracts, development of inflammation of the airways, impaired lung function, and upregulation of ACE-2 expression in the lungs of male and female mice [51].

This result suggests that certain vaping devices and e-liquid components may influence ACE2 expression and increase susceptibility to SARS-CoV-2. Exposure to e-cigarette aerosols, regardless of nicotine content, was found to result in changes in the eicosanoid lipid profiles present in the bronchoalveolar lavage (BAL). Daily inhalation of e-cigarette aerosols fundamentally alters lung inflammatory and immune status [52].

Sivaraman et al. demonstrated in an *in vitro* study that vaping may significantly exacerbate the severity of coronavirus infection, resulting in increased lung infiltrate of inflammatory cells. An increase in cytotoxicity has also been observed with the increasing amounts of e-liquid vaporized. When mice were exposed to intranasal vaporized e-liquid, the levels of acute inflammation were found to increase, but insignificantly. Vaping appeared to deregulate cytokine activation, suggesting that vape-associated Ca^{2+} translocation has a complex and intricate role in the development of inflammation and ultimately respiratory disease [53].

Similarly, Ghosh et al. demonstrated that nicotine from e-cigarette increases cellular Ca^{2+} *concentrations*, which are important in viral entry, gene and protein processing, and subsequent viral release [56].

Some studies focused on the fact that e-cigarettes can upregulate pro-inflammatory cytokines and inflammasome-related genes. Release of

inflammasome products such as IL-1B and cytokine storms are hallmarks of COVID-19 infection. As a result, these findings suggest that vaping may worsen inflammation related to COVID-19 or increase the risk of contracting the virus [49, 50, 52, 55].

Furthermore, Muthumalage et al. revealed that cells exposed to ECIG aerosols produced reactive oxygen species, induced epithelial barrier dysfunction and caused cytotoxicity [55].

Archie et al. summarized in a review that vaping increases the expression of the mediator of ACE2 virus entry in endothelial cells, glial cells, and neurons. In addition, elevated von Willebrand factor levels in the blood and decreased thrombomodulin levels in users of e-cigarettes disrupt blood circulation, promote blood clotting and thrombus formation, significantly increasing the risk of cerebral stroke and other cardiovascular events [61].

It has been shown that exposure to inhalation of nicotine and other stimulants from ECIG disrupts renin-angiotensin homeostasis. Inhibition of local compensatory mechanisms may result in susceptibility to cardiovascular and respiratory disorders, hypothetically increasing the risk of severe COVID-19 [54].

In a cohort study, patients who contracted and developed COVID-19 infection had an increased risk of experiencing symptoms such as chest pain or tightness in the chest, muscle aches, headache, loss of smell, nausea/vomiting/abdominal pain, diarrhea, and non-severe lightheadedness. An analysis of clinical data collected from patients infected with COVID-19 showed a higher frequency of COVID-19 symptoms among e-cigarette users compared to those of non-users [37].

Discussion

ENDS are relatively new products and the long-term health effects of their use are still unknown, but there is growing evidence which demonstrates that they are not harmless [11, 12]. A cross-sectional study conducted in the United States found that there was a higher likelihood of having experienced a heart attack among individuals who used e-cigarettes daily. As biochemical studies have shown, ultrafine particles created by e-cigarettes are biologically active,

inducing inflammatory processes, and having a direct role in the development of cardiovascular disease and acute cardiovascular events [62, 63].

Aerosol also induces platelet activation, aggregation, and adhesion and all these changes increase the risk of cardiovascular disease as well. Moreover, e-cigarette users experience increased oxidative stress [64, 65].

Evidence indicates that exposure to e-cigarette aerosol has adverse effects on the lungs and pulmonary function. Moretto et al. report that the production of acrolein through heating of propylene glycol and glycerin in e-liquids has been shown to cause various pulmonary issues such as inflammation, reduction of host defense, neutrophil inflammation, mucus hypersecretion, and protease-mediated lung tissue damage. These factors are linked to the development of obstructive pulmonary disease [66].

Chaumont et al. conducted a study which showed that acute exposure to vaping aerosols, with or without nicotine, can cause airway epithelial injury and sustained decrement in TcpO2 (transcutaneous oxygen tension) in young tobacco smokers. They also found that intense vaping conditions can transiently impair arterial oxygen tension in heavy smokers, and that this effect is primarily driven by propylene glycol/glycerol rather than nicotine [67].

Studies indicate that using an e-cigarette is associated with twice the risk of experiencing symptoms of chronic bronchitis [68] and an increased diagnosis of asthma among high school students [69].

Additionally, case reports have linked e-cigarette use to various pulmonary diseases such as asymptomatic and incidental radiographic findings [70], lipoid pneumonia, acute eosinophilic pneumonia [71], hypersensitivity pneumonitis [72], and diffuse alveolar hemorrhage [73].

Regarding the impact on cancer, e-cigarettes have been found to deliver 9 to 450-fold lower levels of carcinogens than conventional cigarettes [74]. However, Fuller et al. detected two carcinogenic compounds in the urine of e-cigarette users [75]. Although nicotine itself is not a carcinogen, it can facilitate the neovascularization that provides nourishment to tumors and accelerates tumor growth [76]. Preclinical data show that the activation of the sympathetic nervous system by nicotine in e-cigarettes could promote cancer development and growth through various mechanisms [77].

The term E-cigarette and Vaping Associated Lung Injury (EVALI) was introduced by The Centers for Disease Control and Prevention (CDC) in 2019. The CDC defines EVALI as a condition characterized by the occurrence of pulmonary infiltrates in an individual who has used e-cigarettes within the previous 90 days, and for whom no other explanation for the illness, such as infection, cardiac, rheumatologic, or oncologic causes, can be identified [78].

EVALI is characterized by a range of symptoms, including shortness of breath, chest pain, cough, and hemoptysis. Patients may also experience gastrointestinal symptoms like nausea, vomiting, and abdominal pain, as well as constitutional symptoms such as fever and malaise. Commonly observed physical signs at presentation include tachycardia, tachypnea, fever, and hypoxemia. The severity of respiratory failure can vary, with as many as one-third of patients requiring mechanical ventilation. Demographic studies of EVALI patients have shown that the condition is more prevalent in males (67%) with a median age of 24 years, and up to 86% of cases are linked to the use of e-cigarettes containing tetrahydrocannabinol [79, 80]. However, there is now growing concern about the potential intersection of vaping and its effects with COVID-19 infection, particularly among young people [81].

Most of these reports linking smoking or vaping with the harmful effects of COVID-19 are based on their capability of changing the expression of ACE2 which is present in different organs including lung, heart, kidney, testis, as well as the neurons and glial cells of the brain. ACE2 is widely recognized as the point of entry for SARS-CoV-2 [47–52, 56, 57].

Firstly, some studies have reported that nicotine bonds with the ACE2 receptor, which may block this receptor and prevent SARS-CoV-2 from entering the host cells [59, 60].

Furthermore, nicotine was suggested as a preventive agent against COVID-19 and a new potential therapy for CRS (cytokine release syndrome) in patients with severe SARS-CoV-2 [82].

Recently, most studies suggested that nicotine-based e-cigarettes or vaping may contribute to the upregulation of ACE2, which may also perform an important role in the progression and outcome of COVID-19 [57, 83].

Brar et al. reported that e-cigarette use by adolescents can compromise their pulmonary defenses against SARS-CoV-2 by increasing the number of ACE2 receptors, making them particularly vulnerable to COVID-19-related multisystem inflammatory syndrome (MIS-C). This puts them at a higher risk of developing acute respiratory distress syndrome (ARDS) and related complications. The authors arrived at these conclusions by noting that 70% of adolescents with MIS-C also had ARDS, and e-cigarette use may be a common factor that links the two conditions [58].

The impact of vaping was examined by Lee et al., who have noted that flavored and nicotine-containing e-cigarettes caused significant dysregulation of cytokines and potential activation of inflammasomes, whereas non-flavored and non-nicotine-containing e-cigarettes did not produce these effects [49].

Gaiha et al. have shown that smokers, especially dual users (ECIG and combustible tobacco) over the last 30 days, were nine times more likely to be tested for COVID-19 [39].

Gunge et al. found adverse associations between nicotine-based inhalants and sleep quality [84]. These data seem to be provided by *in vivo* studies in mice [51–53, 56]. All of these have revealed that e-cigarette vapor (both with and without nicotine) exposure increases airway inflammation, impairs lung function, and significantly upregulates ACE-2 expression in the lung.

Summarizing the results of this review, five studies indicated no link between e-cigarette use and the risk of contracting COVID-19 [33–36, 38], and 20 (with 10 *in vitro* and *in vivo* on mice) showed that vapers are at a higher risk of COVID-19 [31, 37, 39, 40, 42,43, 47–56, 58, 61, 83, 85].

Two articles of correlation between vaping and COVID-19 concluded that the evidence for e-cigarette use as a risk factor for infection is mixed [45, 46]. Sharma et al. suggested that large-scale epidemiological studies and meta-analysis would be helpful to confirm theoretical models to examine this association and to better guide clinicians [46].

Gao et al., in their cohort study, noticed that there was no conclusive evidence linking e-cigarette use to a difference in the risk of severe COVID-19. However, the estimates were imprecise, ranging from potential modest protection to a significant increased risk [45].

At present, there is limited information available regarding the connection between e-cigarette use and COVID-19. Nonetheless, the current evidence suggests that e-cigarettes are harmful and can elevate the risk of heart disease and lung disorders.

Due to the fact that vaping epidemic may have contributed to a significant part of COVID-19 hospitalizations of young adults, there is a need for clinicians to screen for EVP use among them and to educate them about potential harms associated with vaping, during lung infections, not only COVID-19. E-cigarette vapor studies have demonstrated that it can amplify the virulence and inflammatory profile of pathogens like Streptococcus pneumoniae, in addition to other harmful biological effects. Vaping has been found to increase pneumococcal adherence by upregulating the expression of the platelet-activating factor receptor [19, 83].

We strongly recommend that countries take action and accelerate their efforts to decrease the prevalence of vaping.

Healthcare professionals should be ready to have a conversation with their patients about the dangers associated with vaping during the COVID-19 pandemic, which includes the adverse impact on respiratory health and increased vulnerability to the virus, as well as the likelihood of developing severe symptoms and complications.

As COVID-19 primarily affects the respiratory system, using e-cigarettes may heighten the risk of contracting the virus or experiencing more severe symptoms [19].

The lack of information about e-cigarettes underscores the need for action from parents, educators, youth advocates, and healthcare providers to protect young people from the harmful effects of tobacco products. Healthcare providers should screen patients for tobacco product use, including e-cigarettes, and provide assistance to those who want to quit.

The perception of higher risks of infection and severe complications due to COVID-19 is associated with an increased motivation to quit smoking, indicating that the pandemic may provide an opportunity to encourage smoking cessation.

Several studies have investigated the relationship between e-cigarette use and the severity of COVID-19, but the findings have been conflicting. Some

studies have proposed the "nicotinic hypothesis", which suggests that nicotine found in e-cigarettes could have a protective effect against SARS-CoV-2 infection. However, other research have found no association between e-cigarette use and COVID-19, while others have reported a strong link between vaping and COVID-19 symptoms and complications.

Although toxicological analyses suggest that e-cigarettes may be less harmful than conventional cigarettes, most public health institutions and governments view them as a new type of tobacco product that is perpetuating and worsening the tobacco epidemic. Therefore, from a health policy standpoint, it is crucial to regulate the use of e-cigarettes during and after the pandemic, as well as to distribute COVID-19 prevention messages targeted at e-cigarette and dual users, particularly the youth. Development of effective strategies (e.g., banning the sale of ENDS to individuals under 18 and online sales) to prevent the use of these products should be implemented in the countries where e-cigarettes are legal.

There is no doubt that more data are needed from prospective longitudinal studies with the purpose of researching the burden of vaping-associated health consequences on the diagnosis and course of COVID-19.

Publishing this information will contribute to a better understanding of the impact of e-cigarette use on public health, both in the context of the COVID-19 pandemic and overall. The information in our narrative review is an important step toward protecting public health and informing the public about the potential risk associated with e-cigarette use. It will allow effective regulatory, educational, and preventive actions to be taken, ensuring a safe and healthy environment for everyone.

Limitations

Due to the design and other methodological limitations of the studies we analyzed in our review, the results of this review should be treated with some caution.

Most of the studies presented are cross-sectional studies where exposure and effect are measured over the same period, using cross-sectional designs.

Several studies used a cohort design and longitudinal designs, performance measures varied, and any observations were of limited duration.

Conclusion

In the light of new health threats such as Covid-19, conducting research and analyses of the interaction between the incidence of infections and the use of e-cigarettes is extremely important. E-cigarettes or nicotine-based vaporization may contribute to an increase in ACE2 activity, which may perform an important role in the progression and outcome of COVID-19. Additional research is required to elucidate the effects of e-cigarette use on pulmonary and cardiovascular complications from SARS-CoV-2 infection. The significant increase in e-cigarette use in the near future and the impact of COVID-19 may increase the burden of chronic disease. Some essential measures for protecting public health and mitigating the potential risks associated with e-cigarette use, both in the context of COVID-19 and in the long term should be implemented: prohibiting the sale of electronic nicotine delivery systems to individuals under 18 and implementing restrictions on online sales. Healthcare providers should screen patients, especially young people for not only tobacco product use but for e-cigarettes too.

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Abbreviations

WHO	World Health Organization
COVID-19	Coronavirus disease 2019
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
EU	the European Union
USA	the United States of America
ENDS	electronic nicotine delivery systems
EVALI	electronic cigarette or vaping product use-associated lung injury
ACE2	the angiotensin-converting enzyme 2
EVP	electronic vaping product
nAChRα7	the α7 nicotinic acetylcholine receptor
ECIG	electronic cigarette vaping
TcpO2	transcutaneous oxygen tension
BAL	bronchoalveolar lavage
IL-1B	interleukin (IL)-1B
CDC	Centers for Disease Control and Prevention
BRFSS	Behavioral Risk Factor Surveillance System
CRS	cytokine release syndrome
MIS-C	multisystem inflammatory syndrome
ARDS	acute respiratory distress syndrome
PRISMA	Preferred Reporting Items for Systematic Reviews
HBECs	human bronchial epithelial cells

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