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THE IMPACT OF ELECTRONIC CIGARETTES ON THE RESPIRATORY SYSTEM: A NARRATIVE REVIEW

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ABSTRACT

Background: The rapidly increasing global prevalence of e-cigarette use, particularly among adolescents and young adults, has raised significant concern regarding their respiratory safety. E-cigarettes generate an aerosol by heating a liquid mixture containing nicotine, propylene glycol, vegetable glycerin, flavorings, and various toxic and potentially carcinogenic compounds such as aldehydes, acrolein, and heavy metals. The respiratory system, being the primary route of exposure, is especially vulnerable to both acute and chronic toxic effects.

Aims: This review aims to synthesize and critically evaluate current evidence on the respiratory consequences of e-cigarette use, with a focus on acute and chronic pulmonary effects, underlying cellular and molecular mechanisms of injury, and implications for public health and clinical practice.

Methods: A narrative review was conducted following a structured literature search in PubMed, Scopus, Web of Science, and Embase for studies published between 2018 and 2025. The search included the terms "e-cigarette", "vaping", "respiratory system", "lung injury", "EVALI", "oxidative stress", "nicotine", and "pulmonary disease". The initial search identified 246 records; after screening and eligibility assessment, 74 studies were included. Priority was given to systematic reviews, meta-analyses, and large-scale observational or experimental studies. Data were synthesized narratively with emphasis on methodological rigor, quality of evidence, and consistency of findings.

Results: E-cigarette use was shown to cause both acute and chronic respiratory injury. Acute effects include airway inflammation, oxidative stress, and epithelial barrier disruption, while chronic exposure is linked to persistent

inflammation, bronchial remodeling, and increased risk of asthma and chronic obstructive pulmonary disease. The 2019 EVALI outbreak exemplified the acute toxicity potential, particularly from illicit THC-containing products adulterated with vitamin E acetate. Experimental studies confirm mitochondrial dysfunction and DNA damage, indicating genotoxic and pro-carcinogenic mechanisms already in progress. Epidemiological data consistently show higher prevalence of respiratory symptoms and reduced lung function among e-cigarette users compared with non-users, including those who have never smoked combustible cigarettes. However, interpretation must remain cautious due to methodological heterogeneity, self-reported exposure data, and limited long-term follow-up.

Conclusions: Current evidence demonstrates that e-cigarettes are not harmless and should be recognized as independent respiratory risk factors. Although they differ from conventional tobacco products, they induce distinct pathophysiological effects mediated by oxidative stress, inflammation, and epithelial dysfunction. The long-term carcinogenic potential remains uncertain because of limited longitudinal data, yet biomarker evidence indicates possible genotoxicity. Persistent research gaps include the long-term impact of novel flavoring agents, standardized exposure assessment, and dose–response relationships. Continuous high-quality longitudinal research and stronger regulatory measures are essential to mitigate health risks and protect vulnerable populations.

Keywords: e-cigarette, vaping, respiratory system, oxidative stress, EVALI, asthma, COPD, lung injury, nicotine.

INTRODUCTION

Electronic cigarettes (e-cigarettes or vapes) are devices that generate an inhalable aerosol by heating a liquid containing nicotine and other chemicals. Since their introduction, these products have evolved rapidly in design, functionality, and chemical complexity, encompassing disposable, pod-based, and refillable systems [1]. The e-liquids used in these devices typically consist of humectants such as propylene glycol and vegetable glycerin, combined with flavoring agents and, most often, nicotine [2,3]. Their widespread availability, aggressive marketing, and the appeal of flavored disposable products have led to a sharp increase in use, particularly among adolescents and young adults [1,4]. According to the Centers for Disease Control and Prevention (CDC), more than 2.1 million middle and high school students in the United States reported current e-cigarette use in 2023, with disposable flavored products dominating the market [1]. Similar trends are observed in Europe, where recent surveys indicate that up to 29% of individuals aged 15–24 years have tried e-cigarettes, and approximately 11% report current use [5]. This rapid growth underscores the urgent need for a comprehensive evaluation of their health effects.

Although e-cigarettes were initially promoted as a safer alternative to conventional tobacco products and as potential smoking cessation aids, growing scientific evidence contradicts these claims [6]. Numerous studies have demonstrated that e-cigarette aerosols contain toxic and potentially carcinogenic compounds that can cause structural and functional injury to the respiratory system [7–11]. The lungs, as the primary route of exposure, are directly affected by these chemical mixtures, resulting in inflammatory, oxidative, and immune-mediated damage [12,13].

The relevance of this topic lies in the accelerating global prevalence of e-cigarette use and the absence of long-term clinical data clarifying their true safety profile. Despite the widespread perception of reduced harm, emerging evidence indicates that e-cigarettes can induce acute lung injury and contribute to chronic respiratory conditions even in individuals who have never smoked combustible cigarettes [14–16]. These findings challenge the harm reduction paradigm and demand a re-evaluation of current public health strategies.

The novelty of the present review is its integrative approach that combines data from molecular, clinical, and epidemiological studies to delineate the mechanisms and extent of e-cigarette–related respiratory injury. By synthesizing recent systematic reviews and meta-analyses, this work provides an updated, evidence-based overview of the pulmonary consequences of vaping and identifies critical research gaps that must be addressed through future investigation.

AIMS AND RESEARCH OBJECTIVES

The primary aim of this review is to summarize and critically evaluate the current state of knowledge regarding the impact of e-cigarette use on the respiratory system. The specific research objectives are as follows:

1. To analyze the chemical composition of e-cigarette aerosols and identify their toxic constituents.
2. To review clinical and epidemiological evidence describing acute and chronic respiratory effects associated with vaping.
3. To examine the underlying cellular and molecular mechanisms of lung injury induced by e-cigarette exposure.
4. To assess potential long-term risks, including carcinogenic and fibrotic outcomes.
5. To highlight existing knowledge gaps and propose directions for future research and public health policy.

Understanding these aspects is crucial for clinicians, researchers, and policymakers to recognize the full scope of health risks related to e-cigarette use and to develop effective preventive and regulatory strategies [1,5,6,12].

METHODS

This narrative review was conducted to summarize and critically evaluate current scientific evidence on the respiratory effects of e-cigarette use. The review focused on data from systematic reviews, meta-analyses, and large-scale observational or experimental studies published between 2018 and 2025 to ensure the inclusion of the most recent and reliable findings.

A systematic search was performed in the PubMed, Scopus, Web of Science, and Embase databases using combinations of the following keywords and Medical Subject Headings (MeSH): "e-cigarettes", "vaping", "respiratory system", "lung injury", "EVALI", "oxidative stress", "nicotine", "pulmonary disease", "systematic review", and "meta-analysis". Additional publications were identified through manual searches of reference lists and official reports from the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and the European Respiratory Society (ERS).

The initial search yielded 246 publications. After screening titles, abstracts, and full texts according to predefined inclusion criteria, 74 studies were selected for detailed analysis. Eligible studies included peer-reviewed articles addressing acute and chronic respiratory effects, cellular and molecular mechanisms of injury, and epidemiological trends associated with e-cigarette use. Non-peer-reviewed reports, conference abstracts, and studies unrelated to respiratory health were excluded.

The data were synthesized narratively, emphasizing methodological quality, consistency of findings, and strength of evidence. Particular attention was given to distinguishing between nicotine-containing and THC-containing products, identifying independent respiratory outcomes, and outlining gaps that require further investigation.

RESULTS

AEROSOL COMPOSITION

E-cigarettes are diverse in their design, but most models share fundamental components: a reservoir or cartridge for the e-liquid, a heating element (atomizer), a power source (typically a battery), and a mouthpiece for inhalation . The e-liquid, the core consumable, is primarily composed of humectants such as propylene glycol (PG) and vegetable glycerin (VG), which serve as solvent carriers to produce the aerosol [12]. These base liquids are mixed with concentrated flavorings and, in the vast majority of products, varying concentrations of nicotine [2]. The market offers a wide array of device types, including disposable units that come pre-filled and may be rechargeable, refillable systems with tanks, and devices that utilize pre-filled cartridges or pods. Some devices are designed to resemble everyday items like USB drives or pens, further contributing to their appeal, particularly among youth [1].

Beyond these primary constituents, the act of heating and aerosolizing the e-liquid generates or releases numerous other substances, many of which are known to be harmful or potentially harmful when inhaled [17].

- **Aldehydes:** Toxic aldehydes such as formaldehyde, acetaldehyde, and acrolein are formed through the thermal degradation of humectants and flavorings during the vaping process [11,18]. Formaldehyde is classified as a human carcinogen, and acrolein is a potent irritant that can cause significant lung damage [19–21].
- **Heavy Metals:** E-cigarette aerosols have been found to contain various heavy metals, including nickel, tin, lead, chromium, and manganese [22]. These metals can leach from the metallic heating coils, other device components, or even be present as contaminants in the e-liquid itself, especially when exposed to acidic e-liquids [12]. Exposure to lead is associated with neurotoxicity and cardiovascular disease [23,24], while chromium(VI) and nickel are recognized risk factors for respiratory diseases, including lung cancer [25].
- **Ultrafine Particles:** E-cigarettes are a significant source of fine and ultrafine particulate matter, which are generated when the humectants are aerosolized [12]. These microscopic particles are capable of penetrating deep into the pulmonary system, potentially causing widespread damage upon inhalation [1].
- **Flavorings:** The e-cigarette market boasts over 7,000 unique flavors, many of which are derived from compounds "generally recognized as safe" (GRAS) for ingestion in food products [12]. However, the safety of these compounds when inhaled is largely unstudied and distinct from their oral safety [1]. Specific flavorings such as diacetyl, acetylpropionyl, and acetoin, used to impart creamy or buttery tastes, have been strongly linked to severe respiratory conditions like bronchiolitis obliterans, commonly known as "popcorn lung". Other flavor chemicals like cinnamaldehyde, vanillin, and menthol have demonstrated cytotoxicity and can contribute to inflammation and impaired cellular processes within the lungs [12].

- **Vitamin E Acetate:** This compound, primarily used as a thickening agent, gained notoriety for its strong implication in the E-cigarette, or Vaping, Product Use-Associated Lung Injury (EVALI) outbreak [26,27]. It was found predominantly in illicit tetrahydrocannabinol (THC)-containing vaping products [27]. When inhaled, vitamin E acetate is believed to interfere with pulmonary surfactant function, leading to alveolar collapse and inflammation, and can decompose into harmful compounds upon heating [6].
- **Reactive Oxygen Species (ROS) and Free Radicals:** The heating element and the aerosolization process itself lead to the production of reactive oxygen species and free radicals. These highly reactive molecules induce oxidative stress, which damages cellular components such as proteins, lipids, and DNA, contributing to a range of respiratory and other systemic disorders [12].
- **Other Toxicants:** Additional harmful substances detected in e-cigarette aerosols include volatile organic compounds (VOCs) like benzene and toluene, phenolic compounds, polycyclic aromatic hydrocarbons (PAHs), and minor tobacco alkaloids. The presence and concentration of these various substances can vary significantly depending on the specific product, device characteristics, and user behavior [12].

To provide a clear and organized overview of the diverse chemical landscape of e-cigarette aerosols and their known or potential respiratory effects, Table 1 is presented below. It summarizes the principal chemical constituents of e-cigarette aerosols, their sources or formation pathways, and their documented or potential respiratory effects as reported in experimental and clinical studies published between 2018 and 2025.

Table 1. Key Constituents of E-Cigarette Aerosol and Their Known or Potential Respiratory Effects

Constituent Category	Specific Constituent	Source / Formation	Known or Potential Respiratory Effects	References
Humectants	Propylene glycol (PG)	Base liquid used for aerosol generation	Causes airway irritation, epithelial damage, and impaired mucociliary clearance	[12]
	Glycerol (VG)	Base liquid used for aerosol generation	Increases mucus viscosity, disrupts nasal epithelial barrier, promotes inflammation	[12]
Aldehydes	Formaldehyde	Thermal degradation of PG/VG and flavorings	Classified human carcinogen; causes airway irritation and cytotoxicity	[11]
	Acetaldehyde	Thermal degradation of e-liquid components	Possible human carcinogen; damages respiratory epithelium	[11]
	Acrolein	Thermal degradation of glycerol and flavorings	Potent irritant; causes oxidative stress and lung tissue injury	[11]
Heavy Metals	Nickel	Released from metallic heating coils	Causes respiratory inflammation and allergic sensitization; linked to	[22]

			carcinogenesis	
	Lead	Contamination from device components	Neurotoxic and cardiotoxic; impairs pulmonary antioxidant defenses	[22–24]
	Chromium (Cr VI)	Leaching from heating elements	Causes oxidative DNA damage and increases risk of lung cancer	[22]
Ultrafine Particles	PM2.5 and nanoparticles	Formed during aerosolization of PG/VG	Penetrate alveoli, induce inflammation and oxidative stress	[1,12]
Flavorings	Diacetyl, acetylpropionyl	Added for creamy or buttery taste	Induce bronchiolitis obliterans and chronic airway fibrosis ("popcorn lung")	[6,12]
	Cinnamaldehyde	Flavoring compound	Cytotoxic to epithelial cells; inhibits immune cell function	[12]
	Menthol	Cooling agent	Increases nicotine absorption; alters ciliary motility; pro-inflammatory	[12]
Other Additives	Vitamin E acetate	Thickening agent in illicit THC products	Causes alveolar collapse and inflammation; identified cause of EVALI	[6,26,27]
Reactive Species	Reactive oxygen species (ROS), free radicals	Generated during heating of e-liquids	Cause oxidative stress, lipid peroxidation, DNA strand breaks	[12]
Volatile Organic Compounds (VOCs)	Benzene, toluene, xylene	Byproducts of incomplete vaporization	Benzene is a known carcinogen; toluene causes airway irritation	[12]
Polycyclic Aromatic Hydrocarbons (PAHs)	Naphthalene, phenanthrene	Produced by overheating e-liquid components	Contribute to DNA adduct formation and carcinogenic risk	[12]

ACUTE EFFECTS

The most striking acute respiratory consequence attributed to e-cigarette use is the severe condition known as E-cigarette, or Vaping, Product Use-Associated Lung Injury (EVALI). This illness emerged as a public health crisis in the United States, with a significant surge in hospitalizations peaking in late 2019 and early 2020 [6,28]. Patients

afflicted with EVALI typically present with a constellation of symptoms, prominently featuring respiratory complaints such as cough, shortness of breath, and chest pain [26]. Beyond pulmonary manifestations, gastrointestinal symptoms, including nausea, vomiting, and abdominal pain, are frequently observed, alongside constitutional symptoms like fever, chills, fatigue, and rapid heartbeat [6]. The severity of EVALI can vary widely, ranging from mild presentations to life-threatening acute respiratory failure, often necessitating hospitalization, intensive care unit admission, and mechanical ventilation in severe instances [6].

Strong epidemiological and laboratory evidence has definitively linked the EVALI outbreak to the presence of vitamin E acetate, a thickening agent found predominantly in illicit tetrahydrocannabinol (THC)-containing vaping products [27,29]. Studies have consistently detected vitamin E acetate in the bronchoalveolar lavage (BAL) fluid of a significant majority of EVALI patients, solidifying its role as a key etiological agent [14]. While THC-containing products were implicated in over 80% of reported EVALI cases, it is important to note that many affected individuals also reported concurrent use of nicotine-containing products [6]. Conversely, the risk of EVALI is considered low among users of commercially available nicotine-only e-liquids, suggesting that the adulteration of illicit products was the primary driver of the epidemic [6].

Radiological assessment, typically via chest computed tomography (CT) scans, frequently reveals bilateral ground-glass opacities, often accompanied by consolidations and subpleural sparing, which are indicative of diffuse alveolar injury and inflammation [27,30,31]. Histopathological examination of lung biopsies from EVALI patients often shows non-specific patterns such as organizing pneumonia, acute fibrinous pneumonitis, or diffuse alveolar damage [32]. A common, though not exclusive, finding is the presence of lipid-laden alveolar macrophages, also known as "foam cells" [32]. However, it is crucial to recognize that the presence of lipid-laden macrophages is not pathognomonic for EVALI, as these cells can be observed in various other pulmonary conditions [33].

Moreover, studies found that using e-cigarettes may be concerned with a decrease of lung function parameters and fractional exhaled nitric oxide, which reflects the level of airway inflammation [34].

The diagnosis of EVALI is one of exclusion, requiring a thorough clinical evaluation. The Centers for Disease Control and Prevention (CDC) criteria emphasize a history of e-cigarette use within 90 days preceding symptom onset, the presence of pulmonary infiltrates on chest imaging, and the rigorous exclusion of other potential etiologies, particularly infectious causes [35,36]. Management of EVALI is primarily supportive, focusing on respiratory assistance, which can range from supplemental oxygen to mechanical ventilation for severe cases [37]. Corticosteroids are frequently administered to reduce lung inflammation, though optimal dosing and duration remain variable and require careful clinical judgment [6]. Critically, cessation of all e-cigarette use is a cornerstone of treatment and is essential to prevent recurrence of the illness [37].

The rapid emergence and subsequent decline of EVALI cases, directly tied to an adulterant in unregulated products, highlights a profound public health vulnerability. This sequence of events demonstrates how quickly a novel, severe illness can manifest when product safety is compromised outside of established regulatory channels. The crisis underscored the significant challenge in controlling rapidly evolving consumer products, particularly when illicit markets thrive. This situation forces a re-evaluation of the public discourse surrounding e-cigarettes. While they were initially presented as a "safer way to consume nicotine" or a harm reduction tool compared to traditional combustible cigarettes, the emergence of EVALI revealed a distinct and acute health threat not directly analogous to smoking-related illnesses [6]. This necessitates a shift in public health messaging from comparative harm to emphasizing the inherent dangers of e-cigarette use itself, particularly concerning unregulated products. This also implies that even if one avoids EVALI, other chronic harms may still exist, demanding continued vigilance and research.

CHRONIC EFFECTS

Beyond the acute syndrome of EVALI, accumulating evidence points to independent associations between e-cigarette use and the development or exacerbation of chronic respiratory conditions. This growing body of data challenges the perception of e-cigarettes as a benign alternative to traditional tobacco products.

Epidemiological studies have consistently demonstrated a significant association between e-cigarette use and asthma, even after accounting for the confounding effects of combustible cigarette smoking [38,39]. A meta-analysis of 15 studies reported a pooled adjusted odds ratio for asthma of 1.39 (95% CI 1.28–1.51) among e-cigarette users [40]. Some investigations have revealed an "inverse interaction," where the association of e-cigarette use with asthma was particularly pronounced among never-smokers, suggesting an independent etiological role for e-cigarettes in asthma development [40]. Furthermore, e-cigarette use has been linked to an increased incidence of asthma exacerbations, indicating not only a potential for disease initiation but also a worsening of pre-existing conditions [41].

Similarly, e-cigarette use is significantly associated with chronic obstructive pulmonary disease (COPD) [15,42] and chronic bronchitis [43]. A pooled adjusted odds ratio of 1.49 (95% CI 1.36–1.65) for COPD has been reported based on nine studies [40]. Prospective analyses provide compelling evidence that e-cigarette use at baseline can predict the new onset of chronic bronchitis, emphysema, or COPD in individuals who were initially disease-free [40]. Of particular concern is the impact on dual users—individuals who concurrently use both e-cigarettes and combustible

cigarettes. These individuals consistently exhibit an even higher likelihood of developing respiratory disease compared to exclusive users of either product, underscoring an additive or synergistic detrimental effect [40]. Moreover, studies have shown that passive exposure to e-cigarette aerosol can induce inflammation in the lungs of individuals with pre-existing COPD, highlighting risks even for bystanders [44].

Beyond these more common conditions, case reports have documented a spectrum of other severe lung pathologies associated with e-cigarette use. These include diffuse alveolar hemorrhage, eosinophilic pneumonia and acute respiratory bronchiolitis interstitial lung disease [45,46]. Such varied presentations suggest a broad range of injurious mechanisms at play within the respiratory system.

The impact on lung function parameters, as measured by spirometry, presents a more complex picture. Some studies indicate an association between e-cigarette use and the development of obstructive lung physiology, characterized by lower forced expiratory volume in 1 second (FEV1) and reduced FEV1/FVC ratios [47]. However, spirometric findings can be inconsistent across studies. While some investigations report no significant difference in spirometry measurements, others have detected increased pulmonary airflow resistance through impulse oscillometry, suggesting early obstructive changes that may not yet be apparent on standard spirometry [6]. This indicates that subtle physiological impairments may precede overt clinical or spirometric manifestations of disease.

The consistent association of e-cigarette use with asthma and COPD, even in individuals who have never smoked combustible cigarettes, and the observed additive effects with combustible smoking, carry profound implications. This body of evidence indicates that e-cigarettes are not merely a "less bad" habit or a benign smoking cessation tool. Instead, they represent an independent risk factor for chronic respiratory diseases. The additive effects seen in dual users are particularly concerning, as they negate any perceived harm reduction benefits and highlight a significantly increased burden of respiratory morbidity. This understanding challenges the narrative that e-cigarettes are a harmless alternative and underscores their unique contribution to pulmonary pathology.

Furthermore, the nature of many chronic lung diseases, such as COPD, is that they develop over decades [5]. Given that e-cigarettes have only been widely used for a relatively short period, the current epidemiological data, while concerning, likely represent only the initial manifestations of a much larger latent disease burden. The observed associations with asthma and early obstructive changes may be merely the tip of an iceberg regarding the full spectrum of chronic lung diseases that could emerge with prolonged e-cigarette use, especially among younger cohorts who initiate vaping early in life [6]. This suggests a significant future public health challenge that is currently underestimated, necessitating urgent, long-term surveillance and a precautionary principle in public health policy.

Table 2 presented below summarizes the main acute and chronic respiratory conditions associated with e-cigarette use, based on evidence from clinical, epidemiological, and experimental studies published between 2017 and 2025. This table is valuable for clinicians and public health practitioners, offering a quick reference to the range of pathologies and their associated evidence.

Table 2: Summary of Acute and Chronic Respiratory Conditions Associated with E-Cigarette Use

Condition Type	Specific Condition	Evidence Type	Key Findings	References
Acute Effects	**E-cigarette or Vaping Product Use-Associated Lung Injury (EVALI)**	**Case series, CDC reports**	**Characterized by acute respiratory distress, hypoxemia, and bilateral infiltrates; strongly linked to use of THC-containing products adulterated with vitamin E acetate; histopathology shows diffuse alveolar damage and organizing pneumonia.**	[6,37]
	Acute bronchial irritation	**Human exposure studies**	**Short-term exposure induces cough, throat**	[12,48]

			irritation, and increased airway resistance; symptoms often appear after first vaping episodes.	
	Airway inflammation	**Clinical and animal studies**	**Elevated cytokines (IL-6, IL-8, TNF-α), increased neutrophil influx, and epithelial barrier disruption observed after aerosol exposure.**	[12,40]
	Oxidative stress	**Experimental studies**	**Increased production of reactive oxygen species and reduced antioxidant enzyme activity in epithelial cells and bronchoalveolar lavage fluid.**	[12,40]
Chronic Effects	**Asthma exacerbation and development**	**Epidemiological and longitudinal studies**	**Higher prevalence of wheezing, cough, and asthma diagnosis among e-cigarette users compared to non-users; risk persists after adjusting for combustible tobacco exposure.**	[12,49,50]
	Chronic bronchitis	**Cross-sectional and cohort studies**	**Associated with chronic cough and sputum production; inflammatory profiles resemble those in conventional smokers.**	[43]
	Chronic obstructive pulmonary disease (COPD)	**Population-based studies**	**E-cigarette use linked to accelerated decline in FEV1, impaired gas exchange, and increased COPD prevalence, especially among dual users.**	[15,42]
	Impaired mucociliary clearance	**In vitro and in vivo studies**	**Propylene glycol and glycerol exposure slows ciliary beat**	[12,40,48]

			frequency and increases mucus viscosity, contributing to mucus stasis and infection risk.	
	Structural lung damage	**Histopathological studies**	**Long-term exposure leads to epithelial metaplasia, alveolar wall thickening, and signs of early emphysematous changes.**	[12]
	Potential carcinogenicity	**Biomarker and toxicological studies**	**Detection of DNA strand breaks, oxidative DNA damage, and mutagenic aldehydes in airway cells; long-term risk remains under investigation.**	[12,51]

MECHANISMS OF INJURY

The deleterious effects of e-cigarettes on the respiratory system are mediated by a complex interplay of direct cellular injury, inflammatory responses, oxidative stress, and immune system dysregulation. Inhaled e-cigarette aerosols, laden with various chemicals, deposit directly onto the delicate lung epithelium, initiating a cascade of pathological events.

Direct cellular injury and inflammatory responses are fundamental mechanisms. Components such as menthol, ethyl maltol, and volatile organic compounds present in e-liquids trigger immediate inflammatory reactions upon deposition in the airways [37]. This inflammatory cascade is further amplified by the generation of reactive oxygen species (ROS) by the e-cigarette aerosols, which can lead to cellular apoptosis through ROS-mediated autophagy [52]. Studies have consistently reported increased levels of pro-inflammatory cytokines, including interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α), in response to e-cigarette exposure. These cytokines recruit immune cells and perpetuate the inflammatory cycle, contributing to lung tissue damage [40].

Oxidative stress plays a central role in the cellular damage and dysfunction observed. E-cigarette aerosols significantly increase oxidative stress, which is an imbalance between the production of oxidants and the body's antioxidant defenses. This imbalance leads to damage to critical cellular components such as proteins, lipids, and DNA [53]. The generation of ROS and free radicals, stemming from the heating element and the aerosolization of e-liquid, is a primary driver of this oxidative damage. Specific flavorings and the high temperatures involved in the vaping process further contribute to ROS generation, exacerbating the oxidative burden on lung cells [12]. This oxidative stress is a known contributor to a wide array of respiratory, cardiovascular, and neurodegenerative disorders, as well as certain cancers [53].

The pathogenesis of severe conditions like bronchiolitis obliterans and other fibrotic changes is also linked to chronic airway-centric inflammation. Specific flavorings, notably diacetyl, are implicated in this process [6]. Bronchiolitis obliterans is a severe and often irreversible condition characterized by hypertrophy of bronchiolar smooth muscle, persistent peribronchiolar inflammation, accumulation of intraluminal mucus, and ultimately, fibrotic scarring. These changes lead to a progressive and often irreversible decline in pulmonary function [37].

The toxicity of heavy metals present in e-cigarette aerosols is another significant mechanism of injury. Metals such as chromium, nickel, and lead, which leach from the device components, are known risk factors for various respiratory diseases, including chronic bronchitis, asthma, COPD, and lung cancer [37]. In vitro studies have demonstrated that even copper nanoparticles derived from e-cigarette aerosols can increase mitochondrial oxidative stress and induce DNA fragmentation, highlighting the direct cellular toxicity of these metallic components [54].

Acute lung injury, as seen in EVALI, involves the disruption of the alveolar-capillary barrier. Damage to both the alveolar epithelial cells and the pulmonary vascular endothelial cells compromises the integrity of this crucial barrier.

This disruption leads to fluid accumulation in the alveoli, resulting in pulmonary edema, significant neutrophil infiltration, and the release of cytotoxic and pro-inflammatory mediators. These events collectively culminate in severe respiratory distress [37].

Furthermore, e-cigarette components can impair respiratory immune cell function, leading to immune dysregulation and an increased susceptibility to respiratory infections [37]. Studies have indicated reduced antimicrobial activity of alveolar macrophages [55] and an increase in bacterial virulence following e-cigarette exposure [56]. The suppression of host defense mechanisms, including a reduction in the motility and beat frequency of lung cilia, further compromises the lung's ability to clear pathogens [57]. Human studies have revealed differential gene expression patterns in e-cigarette users consistent with immune suppression, suggesting a systemic impact on respiratory immunity [58].

Specific roles of flavorings and other additives in pulmonary toxicity are increasingly recognized. Many flavorants, while considered safe for ingestion, exert direct toxic effects when inhaled, causing cytotoxicity, ROS generation, and impaired cellular clearance mechanisms [37]. Vitamin E acetate, strongly implicated in EVALI, interferes with pulmonary surfactant function, leading to alveolar collapse and inflammation [26,27]. Additionally, THC, often added to e-liquids, can degrade into highly toxic substances like methacrolein and benzene when heated, adding another layer of chemical insult [59].

The various mechanisms of lung injury—direct cellular damage, inflammation, oxidative stress, heavy metal toxicity, barrier disruption, immune dysregulation, and specific additive effects—are not isolated but rather highly interconnected. For instance, direct cellular injury can trigger an inflammatory response, which in turn generates more reactive oxygen species, exacerbating oxidative stress and causing further cellular damage. Heavy metals can contribute to both oxidative stress and immune dysfunction. This intricate web of interactions suggests a complex, multi-hit model of lung injury rather than a single causative agent or pathway. This complexity helps explain the varied clinical presentations observed, ranging from acute EVALI to more insidious chronic obstructive changes. Consequently, effective interventions and public health strategies must adopt a comprehensive approach, addressing multiple facets of e-cigarette exposure and their downstream effects, rather than focusing on a singular "bad" ingredient.

E-CIGARETTES AND CANCER RISK

The assessment of cancer risk associated with e-cigarette use presents a unique challenge due to the relatively recent introduction and widespread adoption of these products. Current epidemiological evidence, as of recent systematic reviews, has not yet demonstrated a significant incident or prevalent risk of lung cancer or other types of cancer specifically in the population of "never smoker current vapers" [51]. This absence of observed long-term cancer outcomes in epidemiological studies is largely attributable to the short period e-cigarettes have been on the market. Many cancers, particularly lung cancer, are characterized by a long latency period, often requiring two decades or more of exposure before clinical manifestation. Therefore, the current follow-up periods in available studies are generally insufficient to definitively assess long-term cancer risk in e-cigarette users [51].

Despite the limitations in long-term epidemiological data, there is substantial biomarker-based evidence indicating a significant association between e-cigarette exposure and biological processes reflective of cancer disease risk. This evidence is particularly compelling following acute exposure in cell and animal studies [51,60]. E-cigarette aerosols have been shown to induce oxidative stress, cellular apoptosis (programmed cell death), DNA damage, genotoxicity, and even promote tumor growth in various experimental models [51]. For example, acute exposure to nicotine e-cigarettes has led to significant reductions in cell viability and increased apoptosis in multiple studies [51]. Furthermore, significant increases in oxidative stress and DNA damage or strand breaks have been observed following exposure to both nicotine and non-nicotine e-cigarettes [40]. These findings underscore the biological plausibility that long-term e-cigarette use could increase cancer risk [61].

The identification of potential carcinogens within e-cigarette aerosols further supports concerns regarding their carcinogenic potential. While nicotine itself is not classified as a carcinogen, e-cigarette aerosols contain known or suspected carcinogens such as formaldehyde, acrolein, and various heavy metals (e.g., chromium, nickel) [1]. Volatile organic compounds, also present in the aerosols, can contribute to this carcinogenic burden [12]. These chemicals are capable of causing DNA damage and mutagenesis, which are critical steps in the initiation and progression of cancer [51]. Formaldehyde, in particular, can lead to the binding of reactive molecules to DNA, a key mechanism in chemical carcinogenesis, with specific concerns for DNA damage in the upper airways that could contribute to nasopharyngeal and lung cancers [60].

The current absence of significant epidemiological evidence for cancer risk in exclusive e-cigarette users should not be interpreted as an absence of risk. Rather, this situation reflects the relatively short follow-up periods available for e-cigarette users compared to the long latency period characteristic of most cancers [51]. The strong biomarker evidence of DNA damage, genotoxicity, and cellular apoptosis, coupled with the presence of known carcinogens in the aerosols, strongly indicates a latent carcinogenic potential. This potential is likely to manifest in future decades,

particularly among youth who initiate vaping early in life. This understanding emphasizes the critical need for a strong precautionary principle in public health policy, advocating for stringent regulation and public education even in the absence of definitive long-term epidemiological data on cancer outcomes.

RISK GROUPS

The widespread adoption of e-cigarettes has significant implications for various populations, with distinct health risks and behavioral patterns emerging, particularly among adolescents, young adults, and those engaged in dual use of nicotine and cannabis e-cigarettes.

E-cigarette use is notably prevalent among adolescents and young adults [62–66]. This demographic is particularly vulnerable to the effects of nicotine, a highly addictive substance that can detrimentally impact adolescent brain development [67]. Nicotine affects brain circuits that control attention and learning, and establishing nicotine dependence earlier in life may predispose individuals to poorer mental health outcomes, including anxiety and depression [68,69], and can lead to greater nicotine dependence and escalation in substance use later in life [2]. Adolescents also face susceptibility to acute lung injuries like EVALI, with 15% of reported cases occurring in individuals under 18 years old [49].

A concerning behavioral pattern is the dual use of nicotine and cannabis e-cigarettes. This practice is observed more frequently among younger men, White and Hispanic populations, and individuals with higher socioeconomic status and educational levels [70]. Dual vapers exhibit a heightened susceptibility to both respiratory and systemic symptoms when compared to those who exclusively vape nicotine or cannabis. Respiratory complaints such as cough, chest pain, wheezing, and shortness of breath are more common, as are constitutional symptoms like headache, fatigue, and weight fluctuations [71].

The risk of EVALI is significantly increased with THC vaping, and dual vapers accounted for a substantial proportion of both fatal and non-fatal EVALI cases [70]. The rapid and higher quantity of THC delivery via vaping devices, which can deliver up to 50 mg of THC in a single session compared to approximately 12 mg from a typical marijuana joint [72], significantly increases the risk of acute adverse effects such as hallucinations, psychosis, cannabinoid hyperemesis syndrome, and other mental health and behavioral disorders [70].

Beyond acute risks, combined use of nicotine and cannabis e-cigarettes is associated with a greater overall risk of physical and mental health problems, increased dependence on both substances, and greater difficulty in achieving cessation [70]. A notable prevalence of psychiatric disorders, including various substance use disorders, anxiety, and depression, has been observed among dual vapers [73]. Behavioral patterns suggest that the use of one substance often predisposes individuals to the use of the other, leading to concurrent use [70]. Peer influence and positive expectations regarding e-cigarettes are significant predictors of this dual use [74].

The popularity of e-cigarettes among youth, coupled with the potential for nicotine dependence, creates a pathway that extends beyond combustible cigarettes, leading to broader poly-substance use, particularly involving cannabis. The observed behavioral patterns, driven by peer influence and perceived benefits, contribute to a higher burden of respiratory, systemic, and mental health issues in these vulnerable populations. This highlights a critical public health concern regarding the long-term addiction and health trajectories of young individuals, suggesting that e-cigarettes may act as a gateway not just to traditional tobacco but to a wider spectrum of substance use.

KNOWLEDGE GAPS AND FUTURE RESEARCH DIRECTIONS

Despite the rapidly expanding body of research on e-cigarettes, significant knowledge gaps persist, particularly concerning their long-term respiratory effects and the comprehensive toxicological profile of their diverse constituents. Addressing these gaps is paramount for developing robust public health strategies and regulatory frameworks.

A critical need exists for robust, long-term longitudinal studies. Many chronic lung diseases, including various cancers and chronic obstructive pulmonary diseases, develop over decades [5]. The relatively short period during which e-cigarettes have been widely used means that current epidemiological data, while suggestive of harm, often lack the extended follow-up necessary to observe the full lagged effects on these disease endpoints [51]. Future research must commit to multi-decade observation periods, especially tracking youth and young adults who are early adopters of e-cigarettes into older adulthood.

Precise exposure measurement and comprehensive characterization of product variability are also crucial areas for future investigation. The toxins emitted from e-cigarettes are highly variable, influenced by device characteristics, e-liquid composition, and individual user behavior (e.g., puff duration, frequency, depth of inhalation) [5]. Many existing studies inadequately capture these nuances, which limits the generalizability and time sensitivity of their conclusions. Future research must employ more sophisticated methodologies to characterize e-cigarette use intensity and exposure more precisely.

The development of e-cigarette-specific biomarkers of exposure is another vital research frontier. Currently, there is a lack of unique biomarkers that can accurately quantify exposure levels specifically to e-cigarette constituents, making it challenging to establish clear dose-response relationships and assess health impacts [5]. Identifying and validating such biomarkers would significantly enhance the precision of future epidemiological and clinical studies.

Further investigation into the inhalation toxicology of flavorants and novel compounds is urgently required. The e-cigarette market is characterized by rapid innovation, with thousands of new products, flavors, and chemical combinations constantly emerging [1]. While many flavorants are deemed safe for ingestion, their health impact when inhaled at the levels found in e-cigarettes over prolonged periods remains largely uncertain [5]. E-liquids often involve complex mixtures of chemically unstable compounds that may undergo novel toxicological reactions upon heating, necessitating dedicated research into these unique interactions.

Finally, strategies to address confounding by combustible tobacco use and potential publication bias are essential for robust evidence generation. Associations between e-cigarette use and health outcomes are frequently confounded by concurrent or prior combustible tobacco use, making it challenging to isolate the independent effects of e-cigarettes [5]. Future research designs must employ rigorous methodologies to disentangle these effects. Additionally, the potential for publication bias, particularly in studies funded by manufacturers, needs to be acknowledged and mitigated through transparent reporting and collaborative research frameworks.

There is a fundamental mismatch between the rapid pace of product development and market innovation in the e-cigarette industry and the inherently slower pace of rigorous scientific inquiry. With thousands of new products and flavors constantly emerging [1], by the time definitive long-term data on one generation of products becomes available, the market has often already shifted to new formulations and devices. This creates a perpetual state of incomplete knowledge, posing a significant challenge for regulatory bodies attempting to keep pace with evolving health risks.

This persistent knowledge gap, coupled with the widespread use of e-cigarettes, particularly among vulnerable populations like youth and dual users [1], highlights a critical regulatory lag. The current frameworks struggle to keep pace with the rapid evolution of e-cigarette products and the emerging evidence of harm. This delay in scientific understanding directly translates to a delay in effective public health interventions and regulations. Consequently, a proactive, precautionary approach to regulation becomes imperative, one that prioritizes public health protection over market innovation in the absence of clear safety data. This situation also underscores the ethical imperative for transparent, independent research and the need for enhanced global collaboration to address this dynamic and complex public health challenge effectively.

DISCUSSION

The analyzed literature demonstrates that e-cigarette use produces measurable and clinically relevant effects on the respiratory system. The evidence consistently shows that inhalation of e-cigarette aerosol exposes the lungs to complex mixtures of toxic and potentially carcinogenic substances, including aldehydes, acrolein, formaldehyde, heavy metals, ultrafine particles, and various flavoring chemicals [11,12,22]. Although e-cigarettes were initially promoted as less harmful alternatives to traditional tobacco products, current research does not confirm their safety [1,6].

Experimental studies have demonstrated that exposure to e-cigarette aerosol leads to airway inflammation, oxidative stress, mitochondrial dysfunction, and impairment of epithelial integrity [37,40,52,53]. These mechanisms explain clinical findings such as cough, wheezing, decreased forced expiratory volume, and an increased risk of bronchitis and chronic obstructive pulmonary disease [5,37,40]. Importantly, these effects occur not only in individuals who switched from smoking to vaping but also in people who never smoked, indicating that the observed toxicity is not merely a residual effect of prior tobacco use [12,61].

Epidemiological research supports these findings. Several meta-analyses report a significantly higher prevalence of asthma and COPD among e-cigarette users compared with non-users [15,38,40]. However, interpretation must remain cautious due to heterogeneity in study design, duration, and exposure assessment. Many studies rely on self-reported vaping history, with limited adjustment for confounding factors such as dual use, environmental exposure, or underlying health conditions. Short observation periods also limit assessment of chronic disease progression. Despite these constraints, the overall direction of results remains consistent and biologically plausible, suggesting a real causal relationship between e-cigarette use and respiratory pathology [37,50,65].

The EVALI outbreak has confirmed the acute toxicity potential of e-cigarettes, particularly those containing vitamin E acetate and THC additives [27,29]. Although this epidemic was primarily linked to illicit products, it demonstrated that aerosols from vaping devices can provoke severe lung injury characterized by diffuse alveolar damage and organizing pneumonia [27]. The similarity between histopathological findings in EVALI and chronic epithelial damage observed in habitual users indicates that acute and chronic toxicity represent different degrees of the same pathogenic process.

The carcinogenic potential of e-cigarettes remains uncertain because of the short history of product use and limited longitudinal data [51]. Nevertheless, experimental studies show DNA strand breaks, oxidative DNA damage, and apoptosis in airway epithelial cells after e-cigarette exposure [53]. Detection of aldehydes, metals, and nitrosamines in aerosols supports a biologically plausible link to carcinogenesis [12,48]. These results justify long-term monitoring of users and the inclusion of vaping exposure in cancer risk surveillance programs.

From a public health standpoint, the growing popularity of e-cigarettes among adolescents and young adults is alarming [62–66]. Early initiation of nicotine use fosters dependence and may lead to dual consumption or transition to other substances [70]. The perception of vaping as harmless undermines tobacco control policies and contributes to the normalization of nicotine use in the general population.

However, the interpretation of current evidence must consider several limitations. Most available studies cover a relatively short observation period, often less than five years. The diversity of e-cigarette devices and liquids complicates comparisons across research results, and there is no standardized exposure metric that would allow for consistent dose–response assessment [12]. Furthermore, many clinical and epidemiological studies depend on self-reported vaping data, which may introduce recall bias and underreporting. These methodological issues restrict the precision and generalizability of conclusions.

Taken together, existing evidence indicates that e-cigarette use should be regarded as an independent risk factor for respiratory morbidity. The consistency of findings across cellular, clinical, and epidemiological levels supports this interpretation. Nevertheless, further long-term, standardized, and independent studies are required to quantify the magnitude of risk, clarify dose relationships, and determine the full extent of chronic and oncological consequences associated with vaping.

CONCLUSIONS

The current state of knowledge unequivocally demonstrates that e-cigarettes are not harmless products. While they may present a different risk profile compared to combustible cigarettes, they pose distinct and significant acute risks, exemplified by the severe E-cigarette, or Vaping, Product Use-Associated Lung Injury (EVALI). Furthermore, growing epidemiological evidence establishes independent associations between e-cigarette use and chronic respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD). The underlying mechanisms of injury are complex, involving direct cellular damage, widespread inflammation, oxidative stress, disruption of the delicate alveolar-capillary barrier, and immune dysregulation, all driven by a diverse array of toxic constituents present in e-cigarette aerosols. Although long-term cancer risk remains to be fully elucidated due to the relatively short history of widespread e-cigarette use, biomarker data indicate a concerning genotoxic and pro-carcinogenic potential that warrants serious consideration.

This review demonstrates that e-cigarette exposure represents a distinct and emerging category of inhalation-induced respiratory injury requiring specific clinical awareness. The evidence summarized here confirms that vaping products, regardless of nicotine content, can induce measurable toxic effects on airway epithelium, immune responses, and pulmonary function. These findings highlight the urgent need for ongoing clinical vigilance, improved diagnostic criteria for vaping-related lung injury, and reinforcement of preventive strategies targeting young users and dual consumers.

CLINICAL RECOMMENDATIONS

Based on the accumulated evidence, the following recommendations are put forth for healthcare professionals, public health initiatives, and regulatory bodies:

For Healthcare Professionals:

- Routine Screening: It is imperative to routinely inquire about e-cigarette use in all patients, with particular emphasis on adolescents and young adults, as part of a comprehensive medical history.
- Patient Education: Healthcare providers must educate patients on the known and potential harms of e-cigarettes, emphasizing that these devices are not benign and carry their own unique risks that are distinct from those of combustible cigarettes. Misconceptions about e-cigarette safety must be actively dispelled.
- Counseling Against Dual Use: Patients engaging in dual use of e-cigarettes and combustible tobacco must be counseled on the exacerbated health risks associated with this practice, as it negates any perceived harm reduction benefits and compounds respiratory and systemic damage.
- Vigilance for Lung Injury: Clinicians should maintain a high index of suspicion for symptoms of EVALI and other e-cigarette-related lung injuries, especially in patients presenting with respiratory distress and a history of vaping, particularly illicit THC products.
- Cessation Support: For patients expressing a desire to quit e-cigarettes, healthcare professionals should offer

or refer them to evidence-based cessation services, recognizing the addictive nature of nicotine delivered by these devices.

For Public Health Initiatives:

- Targeted Public Education Campaigns: Implement robust public education campaigns, specifically designed to reach and resonate with youth, to counter pervasive misconceptions about e-cigarette safety and to highlight the documented harms.
- Enhanced Surveillance: Strengthen and expand surveillance systems to continuously monitor e-cigarette use trends and associated health outcomes, enabling timely identification of emerging risks and patterns of disease.
- Support for Independent Research: Prioritize and allocate substantial funding for long-term, independent research to address critical knowledge gaps, particularly concerning the chronic disease development pathways, the impact of novel products and flavorings, and the development of e-cigarette-specific biomarkers.

For Regulatory Bodies:

- Strengthened Product Regulations: Implement and enforce stringent regulations on e-cigarette products, including comprehensive restrictions on flavors that appeal to youth and limits on nicotine concentration to reduce addiction potential.
- Pre-Market Review: Mandate comprehensive pre-market review of all e-cigarette products and their constituent ingredients, with a rigorous focus on inhalation toxicology and long-term safety data before products are allowed on the market.
- Combat Illicit Markets: Intensify efforts to combat the illicit e-cigarette market, which has demonstrably posed significant and immediate public health dangers, as tragically evidenced by the EVALI outbreak.
- Precautionary Principle: Adopt a proactive, precautionary principle in policy-making, prioritizing public health protection in the face of evolving scientific evidence and regulating products where long-term safety remains uncertain. This approach is essential given the rapid pace of product innovation outstripping scientific understanding.

The conclusions presented in this review are limited by the relatively short duration of available longitudinal studies, the heterogeneity of e-cigarette devices and formulations, and the lack of standardized exposure metrics. These factors may influence the comparability and generalizability of results across studies. However, the consistency of evidence from cellular, clinical, and epidemiological research strongly supports the assertion that e-cigarettes cause measurable harm to the respiratory system and cannot be considered a safe alternative to smoking.

The presented synthesis provides a scientific foundation for evidence-based clinical management, preventive health education, and the formulation of regulatory policies addressing e-cigarette use. Continued international cooperation, transparent reporting, and long-term cohort research are essential to further clarify the full spectrum of health consequences associated with vaping and to guide the development of effective public health interventions.

DISCLOSURE

AUTHORS' CONTRIBUTIONS

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USE OF AI

Artificial intelligence tools, such as ChatGPT and other OpenAI systems, were used to support language refinement, structural improvement, and the development of certain text sections (including results and conclusions). All AI-

generated contributions were thoroughly reviewed and verified by the authors.

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