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REVIEW

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# Chronic airway inflammatory diseases and e-cigarette use: a review of health risks and mechanisms

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## Abstract

Chronic airway inflammatory diseases, which primarily include chronic obstructive pulmonary disease (COPD), asthma, allergic rhinitis, and chronic sinusitis, continue to have a high global prevalence, highlighting their significant public health impact. Concurrently, the use of e-cigarettes (tobacco e-cigarettes) has been rising worldwide, with many users perceiving them as a safer alternative to traditional cigarettes. However, accumulating evidence from international studies suggests that e-cigarettes pose substantial health risks. This review aims to explore recent research on the relationship between e-cigarette use and chronic airway inflammatory diseases. The findings indicate that e-cigarette usage increases the risk of developing these conditions. Specifically, studies have shown that e-cigarettes exacerbate airway inflammatory responses, elevate levels of type 2 inflammatory cytokines such as IL-4, IL-5, and IL-13, increase cellular oxidative stress, and impair lung function. These mechanisms may collectively contribute to an increased risk of chronic airway inflammatory diseases potentially associated with e-cigarette use.

**Keywords** E-cigarettes, Airway inflammation, Chronic obstructive pulmonary disease, Asthma, Inflammatory mediators

## Introduction

### Public health significance of chronic airway inflammatory diseases

Chronic inflammatory airway diseases refer to conditions involving chronic inflammation of the upper and/or lower airways, characterized by airway inflammation, obstruction, and remodeling [1]. Common chronic airway inflammatory diseases include chronic obstructive pulmonary disease (COPD), asthma, allergic rhinitis (AR), non-allergic rhinitis (NAR), chronic rhinosinusitis (CRS), and hypersensitivity pneumonitis (HP), affecting a wide population [1, 2].

According to the 2019 Global Burden of Disease (GBD) report, COPD is the third leading cause of death worldwide, affecting over 210 million people globally in 2019 and resulting in 3.3 million deaths that year [3]. In China, COPD cases and deaths account for 21% and 32% of the global total, respectively [4]. A study published in *The Lancet Global Health* in 2023 estimated the macroeconomic burden of COPD in 204 countries and regions from 2020 to 2050, predicting a global economic loss of $4.326 trillion due to COPD, with China bearing the highest burden at $1.363 trillion [5]. GBD data also show that asthma is the most prevalent chronic airway

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disease, affecting over 260 million people worldwide [3]. The China Pulmonary Health (CPH) study shows a prevalence of asthma of 4.2% among Chinese adults aged 20 years and older [6]. A global epidemiological survey on rhinitis conducted in 2022 indicated a median adult prevalence of 18.1% for AR globally [7]. Another study in 2023 reported a weighted prevalence of 8.1% for AR among Chinese adults [8]. CRS affects people across all age groups, with a 2023 epidemiological survey indicating a national prevalence of 10% in China [9]. HP, also known as extrinsic allergic alveolitis, is a fibrosing interstitial lung disease caused by inhaling various antigens. HP may be induced by a wide and growing variety of antigens, which can be divided into six broad categories: bacteria, fungi, mycobacteria, animal and plant proteins, chemicals, and metals. Among them, *Acinetobacter* spp, *Lichtheimia corymbifera*, *Alternaria alternata*, *Erwinia herbicola* and other bacteria and fungi are microbial derived antigens [10]. A global epidemiological survey in 2024 found an overall occupational HP prevalence of 4.2% [11]. A 2019 study based on a Chinese population showed a high smoking rate among patients with chronic HP ($P=0.004$) [12].

The high prevalence rates of these chronic airway inflammatory diseases highlight their public health importance, necessitating continuous global surveillance, research, and interventions to ensure public health safety and promote sustainable development.

### The rise of e-cigarettes and their status as a substitute for traditional cigarettes

E-cigarettes, also known as Electronic Nicotine Delivery Systems (ENDS), are electronic devices powered by batteries that vaporize a liquid containing nicotine and other components to create an aerosol that is inhaled by the user. E-cigarettes originated in China, with the first modern e-cigarette invented by Chinese pharmacist Hon Lik in 2003 [13]. Since their inception, they have been marketed under labels such as "aids for smoking cessation", "non-addictive", and "healthy and non-toxic" [14–16]. However, with the deepening of research, the current controversy over the safety of e-cigarettes is particularly significant [17, 18]. E-cigarettes have evolved through several generations: the first generation resembled traditional cigarettes in appearance and use; the second generation featured larger batteries with variable voltage and diverse forms; the third generation was similar but larger in size, with more customizable functions for adjusting voltage, wattage, and power; the current fourth generation of e-cigarettes features rapid product changes, with more diverse forms and functions [19]. The fourth-generation e-cigarettes are compact, portable, and user-friendly, featuring closed or open pod designs and nicotine salt e-liquids. Their low-power, low-temperature atomization technology delivers a cigarette-like experience with reduced smoke output, making them ideal for daily use [20].

In recent years, the use of e-cigarettes has exploded, with over 68 million users worldwide across more than 60 countries [21]. In the United States, e-cigarette use is most common among adolescents. According to the U.S. Centers for Disease Control and Prevention (CDC), 1.97 million high school students used e-cigarettes in 2023, making e-cigarettes the most commonly used tobacco product among U.S. adolescents and young adults since 2014 [22]. In contrast to the U.S., more than 3.35 million adults use e-cigarettes in China, primarily between the ages of 26 to 35 (57.8%), 36 to 45 (26.9%), and 46 to 55 (7.7%). However, as of 2021, e-cigarette use among Americans aged 50–64 and ≥ 65 years is 2.9% (95% CI 2.3, 3.5) and 0.9% (95% CI 0.6, 1.2), respectively, compared to 10% for those aged 18–34 years [23]. It can be seen that compared with the majority of e-cigarette smokers in the US who are teenagers, the age distribution of e-cigarette smokers in China is more balanced, which may be related to China's electronic cigarette control policy for minors. Approximately 97% of users in China are male, indicating that the overall e-cigarette user base in China is predominantly young and middle-aged men [24]. This may be attributed to the fact that Chinese e-cigarette smokers are mainly male, mainly because the smoking rate of men is much higher than that of women, and e-cigarettes, as a substitute cigarette product, naturally inherit this gender ratio. According to the World Health Organization's (WHO) Framework Convention on Tobacco Control (FCTC) Conference of the Parties (COP6) report, global expenditure on e-cigarettes was $3 billion in 2013, with sales projected to increase 17-fold by 2030 [25].

Alternative tobacco and nicotine products, including nicotine replacement therapy (NRTs), ENDS, e-cigarettes, and low-nitrosamine smokeless tobacco, are self-help and less invasive methods that can help with smoking cessation by reducing withdrawal symptoms [26, 27]. These strategies aid the transition to abstinence by providing lower or no nicotine while significantly reducing exposure to harmful chemicals [28]. Clinical trials suggest that these alternatives are more effective in supporting long-term smoking cessation and are perceived as more pleasant compared to other interventions [29]. Although these harm reduction approaches may offer public health benefits, concerns remain about the potential normalization of addiction behavior and associated risks. Some studies, including a laboratory-based study by Vardavas et al., indicate possible adverse pulmonary effects from alternative nicotine products [30]. However, the overall effectiveness and safety of alternative nicotine

products remain unclear due to limited evidence and the lack of reliable biomarkers [31]. Given these uncertainties, a comprehensive systematic review is necessary to better understand their role in smoking reduction and cessation and to inform tobacco harm reduction policies.

#### Significance of studying the association between e-cigarettes and chronic airway inflammatory diseases

E-cigarette use increases the risk of developing chronic airway inflammatory diseases. An epidemiological study revealed a significant association between adult e-cigarette use and the development of COPD and asthma, independent of other disease-related risk factors. The adjusted odds ratio (aOR) for COPD was 1.49 (95% CI 1.36–1.65) and for asthma was 1.39 (95% CI 1.28–1.51) [32]. Additionally, a cross-sectional study showed that e-cigarette use increases the risk of allergic rhinitis (OR = 1.43, 95% CI 1.22–1.68) and chronic rhinosinusitis (OR = 1.41, 95% CI 1.22–1.63) [33]. Another study of U.S. young adults showed that e-cigarette use was associated with higher odds for any respiratory symptom (aOR, 1.32; 95% CI 1.06–1.65) and wheezing in the chest (aOR, 1.51; 95% CI 1.06–2.14) [34]. Roh et al. conducted a stratified analysis to assess the relationship between e-cigarette use and asthma in adolescents, and they found that e-cigarette use was significantly associated with asthma (OR 1.32, 95% CI 1.06–1.66 and OR 1.18, 95% CI 1.02–1.37, respectively) [35].

Therefore, researchers need to further investigate how e-cigarettes affect airway function and the related inflammatory mechanisms to provide scientific evidence for developing more effective public health strategies and patient education.

## Structure and chemical composition of e-cigarettes

#### Basic structure and working principle of e-cigarette devices

E-cigarettes come in various types, but they all share three fundamental components: a battery, an atomizer, and a cartridge containing the e-liquid. The operating principle involves the battery supplying power to ignite the filament within the atomizer, which heats the e-liquid to generate an aerosol for the user to inhale, mimicking the experience of using traditional cigarettes [36].

#### Chemical composition analysis of e-cigarette liquids and aerosols

The primary difference between e-cigarettes and traditional cigarettes is that traditional cigarettes produce smoke through the combustion of organic matter, whereas e-cigarettes use battery power to heat nicotine-containing liquid to produce an aerosol for inhalation. This process does not involve combustion and therefore does not produce tar and other combustion byproducts [37]. E-cigarette liquid primarily consists of nicotine, organic solvents (such as glycerin and propylene glycol), flavoring agents (such as cinnamaldehyde), and a small number of additives [36]. During the heating process that forms the aerosol, the composition and concentration of its components may change accordingly. E-cigarette aerosol mainly contains nicotine, polycyclic aromatic hydrocarbons, volatile organic compounds, ultrafine particles, heavy metals, and silicates. Glycerin and propylene glycol in the e-liquid can oxidize to form aldehydes (such as formaldehyde, acetaldehyde, butyraldehyde, acrolein, propylene oxide, benzaldehyde, etc.) [21]. Studies have shown that the levels of aldehydes produced by these products exceed occupational safety standards, and they can increase the risk of cancer when they enter the body [38, 39].

## Impact of e-cigarettes on airway immune function

#### Effects of e-cigarettes on cells

E-cigarettes affect both the innate and adaptive immune systems of the body. In innate immunity, e-cigarettes impact various cells, including airway epithelial cells, lung macrophages, neutrophils, eosinophils, and basophils. Common effects include abnormal mucus composition, reduced epithelial barrier function, impaired phagocytic function, and elevated systemic inflammatory markers [40]. Research on how e-cigarettes affect adaptive immunity is limited, but existing studies have confirmed that e-cigarettes increase T cell levels in the body [41].

As structural and immune cells, airway epithelial cells serve as the first line of defense against pathogens and toxins. E-cigarettes can directly damage airway epithelial cells, disrupt tight junctions, and cause epithelial barrier dysfunction [42]. E-cigarettes also affect ciliary motility and mucus clearance functions of the airway epithelium, thereby compromising respiratory mucosal immunity [43, 44]. In vitro studies have shown that e-cigarette aerosol induces stress and inflammation in airway epithelial cells [45]. E-cigarette aerosols are cytotoxic to lung macrophages, causing morphological changes, reduced cell size, and cell death, increased release of chemokines, and weakened phagocytic function [46]. E-cigarettes impair neutrophil chemotaxis, inhibit the formation of neutrophil extracellular traps, increase susceptibility to bacterial infections, and promote neutrophil activation, degranulation, and apoptosis [45, 47]. Moreover, e-cigarettes significantly affect gene expression levels in eosinophils, upregulating airway inflammation-related genes and altering eosinophil metabolic and inflammatory pathways [48]. Long-term use of e-cigarettes increases lung

inflammation levels, including macrophages, neutrophils, eosinophils, and basophils, promotes the migration and infiltration of inflammatory cells from the blood to the respiratory tract, stimulates the production of Th2-related cytokines (IL-4, IL-5, IL-13), and exacerbates inflammation [40, 49].

#### E-cigarettes and inflammatory mediators

Upon inhalation, e-cigarettes initially activate macrophages located in the nasal and pharyngeal epithelium. Activated macrophages participate in phagocytosis and release pro-inflammatory cytokines such as IL-6, IL-10, and IL-1β, leading to B cell and T cell differentiation and downstream signal transduction [50]. IL-6 mediates the JAK–STAT pathway, resulting in STAT3 phosphorylation, promoting neutrophil adhesion and migration to the lungs, releasing neutrophil elastase and matrix metalloproteinase-9, causing emphysema and COPD. E-cigarettes also cause neutrophils to release TNF-α, IL-10, and IL-1β, which activate the p38 and NF-κB signaling pathways, leading to inflammation or apoptosis. Additionally, e-cigarettes stimulate epithelial cells to release β-defensins, which are involved in inflammatory responses [50].

Moreover, e-cigarettes increase eosinophil counts and levels of type 2 inflammation-related cytokines IL-4, IL-5, and IL-13 in asthmatic mice, increasing airway hyperresponsiveness and promoting airway inflammation [51]. Type 2 inflammatory cytokines, along with IL-1β and TNF-α, amplify inflammatory responses in asthma and exacerbate the condition [40]. Mouse models have also confirmed that e-cigarettes increase immune cells like macrophages and neutrophils, as well as multiple COPD-related cytokines, including CCL2, IL-4, IL-13, IL-10, M-CSF, and TNF-α. These increased inflammatory factors and chemokines leads to further infiltration of immune cells into the respiratory tract, resulting in dysfunctions of fibroblasts, goblet cells, and epithelial cells, ultimately leading to emphysema, mucus accumulation, inflammation, and pulmonary fibrosis [52].

#### E-cigarettes and oxidative stress

Excessive reactive oxygen species (ROS) in cells can lead to oxidative stress. Glutathione is a key molecule in maintaining cellular redox balance and is involved in scavenging free radicals and ROS. Inhalation of e-cigarette smoke reduces glutathione levels in lung cells, likely leading to oxidative stress and ultimately causing inflammation. In some cases, e-cigarettes stimulate the production of ROS in alveolar macrophages, causing lung epithelial damage and neutrophil influx at injury sites, resulting in aggravated inflammation, mucus production, and destruction of alveolar cells, leading to airway obstruction [53].

A special task force report by the European Respiratory Society points out that oxidative chemicals can damage cell membranes, cause endothelial dysfunction and inflammation, promote atherosclerosis, and activate thrombosis. Oxidative chemicals are considered the main cause of cardiovascular diseases in smokers [51]. Similar findings were observed in a cross-sectional study, where healthy young e-cigarette users showed increased oxidative stress in circulating immune cells, indicating a future risk of cardiovascular diseases [54].

## E-cigarettes and related chronic airway inflammatory diseases

#### E-cigarettes and COPD

One of the primary mechanisms of COPD development is pulmonary immune-inflammatory response, with nicotine being the main factor contributing to this inflammatory response [55]. Nicotine and other chemicals in e-cigarettes may promote COPD development through similar mechanisms. E-cigarette aerosols contain nicotine and degradation products of heated solvents (such as acrolein and propylene oxide), which, along with flavoring agents like cinnamaldehyde, can induce oxidative stress and inflammatory responses. These responses trigger cellular reactions, including impaired respiratory immune cell function, reduced epithelial barrier function, and decreased cell membrane fluidity and protein diffusion [56]. These pathophysiological changes may ultimately lead to airway remodeling, excessive mucus secretion, and fibrosis, thereby contributing to COPD progression [37]. E-cigarettes also induce apoptosis in lung endothelial and epithelial cells, as well as ferroptosis in epithelial cells, further exacerbating COPD development [52]. Ferroptosis is a necrotic form of controlled cell death (RCD) that is closely associated with tissue inflammation. It has been reported in the literature that cigarette smoke induces NCOA4-mediated ferritin phagocytosis, resulting in an increase in free iron and resulting in increased iron death in lung epithelial cells, which exacerbates the progression of COPD [57]. However, another study found that long-term exposure to e-cigarette vapor can disrupt lung lipid balance and impair immune function, and this process is not caused by nicotine, but is related to e-cigarette solvents such as propylene glycol and vegetable glycerin. These changes increase inflammation and tissue damage during influenza infection [58].

Long-term inhalation of e-cigarettes leads to structural changes in lung tissue. Studies on mouse models have shown that prolonged exposure to e-cigarette aerosol increases airway resistance upon acetylcholine stimulation and induces emphysema [59, 60]. Research indicates that e-cigarettes can increase the alveolar space by 17.5 ± 1.4%, and nicotine-containing e-cigarettes can

also increase lung endothelial permeability [61]. The increase of endothelial permeability will increase the probability of immune cells such as monocytes and neutrophils to infiltrate the respiratory tract, further expanding the immune response and aggravating respiratory inflammation [62]. Prolonged use of e-cigarettes may lead to bronchial wall thickening, central airway interstitial fibrosis, bronchial stenosis, and irregular lumens, resulting in airway obstruction and progressive deterioration [63].

E-cigarette use is also associated with a decline in lung function and increased frequency of acute exacerbations in COPD patients. An epidemiological study in the United States showed that e-cigarette users had an 8 ± 2% increase in COPD prevalence ($p < 0.001$). Former e-cigarette users with COPD were more likely to experience disease progression within 5 years, with a faster decline in lung function ($FEV_1$) compared to those who had never used e-cigarettes (43 mL/year vs. 34 mL/year; $p = 0.003$). Additionally, e-cigarette use was associated with an increased number of acute COPD exacerbations ($p = 0.01$) [64]. Long-term use of e-cigarettes can lead to airway failure, decreased lung function, and COPD progression through induced oxidation, rapid reaction, and cell death, while increasing the risk of acute incontinence.

#### E-cigarettes and asthma

Chronic inflammation and airway hyperresponsiveness are key pathophysiological features of bronchial asthma, characterized by increased reactivity of the airways to non-specific stimuli, leading to airway smooth muscle contraction, increased airway resistance, and airflow limitation [65]. Research shows that nicotine in e-cigarettes increases the infiltration of inflammatory cells, including eosinophils, from the blood into the airways, stimulates the production of type 2 inflammatory cytokines such as IL-4, IL-5, and IL-13, and promotes mucin secretion, exacerbating airway inflammation and hyperresponsiveness, ultimately worsening asthma [66, 67]. Mouse models have demonstrated that nicotine and propylene glycol/vegetable glycerin (PG/VG) in e-cigarettes increase airway hyperresponsiveness in mice, while acrolein in e-cigarettes leads to increased proliferation of inflammatory cells and airway hyperresponsiveness ($P < 0.05$) [68, 69]. In a mouse model of ovalbumin (OVA)-induced asthma, the researchers found that formaldehyde in e-cigarettes activated the TRPV4-p38 MAPK pathway, further aggravating airway hyperreactivity [70].

Asthma patients are susceptible to impaired respiratory mucosal immunity, and e-cigarettes further damage the immune function of the respiratory mucosa, including the functions of epithelial cells, macrophages, and neutrophils, affecting the development, severity, and acute exacerbations of asthma [71]. Studies have found a significant association between e-cigarette use and asthma exacerbations [72–74]. Moreover, e-cigarette use significantly reduces lung function in asthma patients (reduced $FEV_1$/FVC ratio and peak expiratory flow (PEF)), and increases the fraction of exhaled nitric oxide (FeNO) and the pH of exhaled breath condensate (EBC) by 3.60 ppb ($p = 0.001$) and 0.15 ($p = 0.014$), respectively [75]. Non-invasive techniques such as the assessment of FeNO and EBC are increasingly used to analyze airway inflammation, and these measures are positively associated with airway inflammation and poor prognosis [76].

It can be seen that e-cigarettes enhance airway irritation and hyperresponsiveness through nicotine and harmful chemicals, impairing respiratory immune function, leading to disease, decreased lung function, and increasing the risk of preventive custody.

#### E-cigarettes and respiratory infections

The airway epithelium serves as the first line of defense against external harmful stimuli, and e-cigarettes can reduce respiratory mucosal immunity and defense by affecting ciliary motility, mucus clearance, and disrupting tight junctions of the epithelium. Studies have shown that long-term exposure to e-cigarettes can alter the human bronchial epithelial proteome. Mucin levels, including MUC5AC (mucin 5AC) and MUC4, are elevated [77]. In addition, e-cigarettes downregulate the expression of genes related to ciliary assembly and motility (*DNAH10* and *FOXJ1*), leading to a reduction in airway epithelial ciliated cells [78]. Nicotine in e-cigarettes can induce dysfunction in the cystic fibrosis transmembrane conductance regulator (CFTR), delaying ciliary clearance and impairing mucociliary defense function [43]. Research has shown that e-cigarettes alter mucin expression levels in airway epithelium (e.g., increased MUC1 expression), leading to mucus plug formation, which accumulate in the airway lumen and affect airway airflow [44]. Various compounds in e-cigarettes, such as nicotine and flavoring agents, cause epithelial damage, affect tight junctions and adhesive junctions of epithelial cells, and compromise the integrity of the airway epithelial barrier [42].

After damaging the airway epithelium, e-cigarettes weaken the respiratory tract's defense against bacterial and viral infections, leading to increased pathogen load and heightened susceptibility to respiratory pathogens. Alveolar macrophages play a crucial role in the innate immune response in the lungs. E-cigarettes induce the production of pro-inflammatory mediators and proteases, damaging lung connective tissue and parenchymal cells, suppressing alveolar macrophage phagocytic and defensive capabilities, and further increasing susceptibility to respiratory infections [78]. Lung proteolytic

enzymes are a key component of the innate immune system. The study found that protease levels (such as neutrophil elastase, MMP-2 and MMP-9) were elevated in both e-cigarette users and smokers, similar to those in smokers, while anti-protease levels remained unchanged. The nicotine in e-cigarettes triggers immune cells such as neutrophils and macrophages to release proteases, leading to an imbalance between proteases and anti-proteases. These findings suggest that long-term vaping increases proteolysis in the lungs, possibly increasing the risk of chronic lung disease, and suggest that vaping may not be safer than smoking [79]. An animal study found that e-cigarette exposure increased oxidative stress and caused macrophage-mediated inflammation. Mice exposed to e-cig vapor had impaired bacterial clearance and reduced phagocytosis by alveolar macrophages, resulting in worse outcomes after Streptococcus pneumoniae infection. Additionally, e-cigarette-exposed mice exhibited higher viral titers and increased morbidity and mortality after Influenza A infection [80]. Early preclinical findings suggest that e-cigarette exposure increases bacterial and viral toxicity in the airway epithelium. Preclinical mouse models have confirmed that e-cigarettes increase the infectivity of *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, human rhinovirus (HRV), and respiratory syncytial virus (RSV) [42, 47]. An epidemiological study in the United States found that for every 1% increase in the weighted proportion of e-cigarette users, the number of COVID-19 cases increased by 0.3139 (95% CI 0.0554–0.5723) [81].

The respiratory microbiota affects the innate immune response in the lungs, and these play a critical role in maintaining respiratory health and fighting infections [82]. Using 16S rRNA gene sequencing to analyze nasal samples from adult e-cigarette users, smokers, and nonsmokers, researchers uncovered distinct patterns of respiratory microbiome dysbiosis associated with both e-cigarette use and smoking. Notably, significant sex-dependent differences were observed, particularly among e-cigarette users. The findings revealed that *Staphylococcus aureus*, a common respiratory pathogen, was more prevalent in both e-cigarette users and smokers compared to nonsmokers. In contrast, *Lactobacillus iners*, a species often regarded as protective, was more abundant in smokers but notably reduced in e-cigarette users relative to nonsmokers [83]. Another study found that while the oral microbiota α-diversity increased similarly over time across all three groups, each maintained distinct microbial characteristics. The microbiota of e-cigarette users exhibited similarities to both traditional smokers and nonsmokers, yet their subgingival microbiota remained uniquely distinct, characterized by an enrichment of *Fusobacterium* and *Bacteroidales G-2*. These findings suggest that e-cigarette use fosters a distinct periodontal microbial environment, positioning it as an intermediate state between that of traditional smokers and nonsmokers, while also presenting unique oral health challenges [84].

### E-cigarettes and other related airway inflammatory diseases

Allergic rhinitis (AR) is a chronic, non-infectious inflammatory disease of the nasal mucosa, primarily mediated by immunoglobulin E (IgE) in atopic individuals exposed to allergens [85]. Some studies suggest that new tobacco products such as e-cigarettes may increase the risk of allergic rhinitis in adolescents [86]. However, which components in e-cigarettes are related to AR need to be further explored in the future.

Chronic rhinosinusitis (CRS) is characterized by immune disorders and mucociliary dysfunction, and e-cigarette-induced nasal epithelial cell dysregulation may be a fundamental basis for CRS development [33]. Additionally, e-cigarettes affect mucociliary clearance, suggesting a potential association between e-cigarettes and CRS [43].

Hypersensitivity pneumonitis (HP) is an inflammatory disease caused by inhaling organic dust or, in rare cases, chemical substances that trigger hypersensitivity reactions. Chemicals in e-cigarette aerosols can bind to human proteins, inducing excessive immune responses in susceptible individuals, leading to HP [87]. Particulate matter and volatile organic compounds present in e-cigarette secondhand smoke may also induce excessive immune responses in cells, leading to HP [88].

Studies also indicate that propylene glycol/vegetable glycerin (PG/VG) in e-cigarettes may induce goblet cell hyperplasia and trigger excessive airway mucus secretion in vivo. PG/VG can upregulate MUC5AC expression and downregulate MUC5B expression, resulting in an elevated MUC5AC/MUC5B ratio. A higher MUC5AC/MUC5B ratio is associated with the severity of mucus-obstructive diseases, such as cystic fibrosis, bronchiectasis, and primary ciliary dyskinesia [89]. The potential mechanism of e-cigarette regulating chronic airway inflammation is shown in Fig. 1.

## Conclusion and future directions

E-cigarettes contain various harmful substances, including propylene glycol, glycerin, formaldehyde, acetaldehyde, heavy metals, and more. Although the harmful substances released by e-cigarettes are generally less than those from traditional cigarettes, they still cause respiratory irritation and inflammation [90]. E-cigarettes can damage cells related to innate and

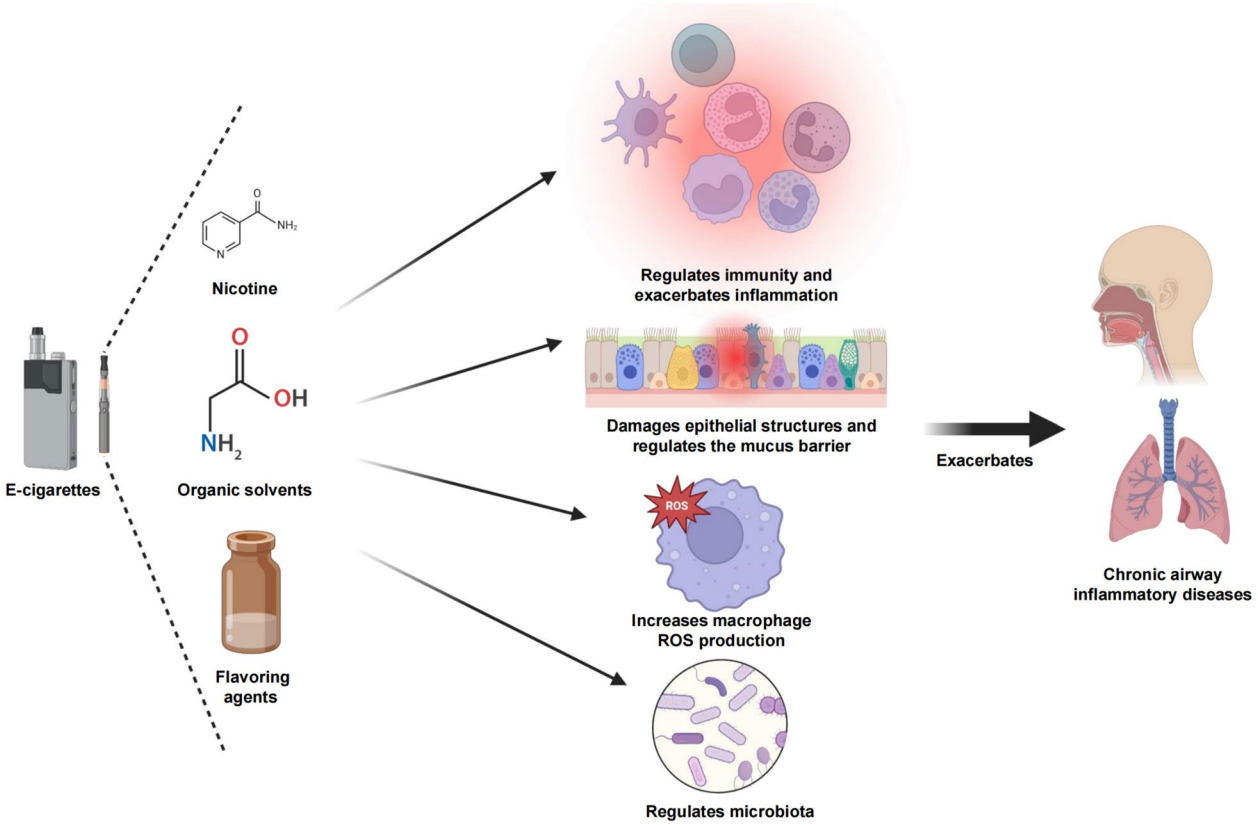


**Fig. 1** Mechanism diagram of regulation of chronic airway inflammation by e-cigarette

adaptive immunity in the respiratory tract, resulting in abnormal mucus composition, reduced epithelial barrier function, impaired phagocytic function, and elevated systemic inflammatory markers (especially type 2 inflammatory cytokines IL-4, IL-5, IL-13). They also increase the adhesion of bacteria and fungi, as well as the virulence of pathogens such as the influenza virus [81]. E-cigarettes can lead to changes in gene expression within lung immune and structural cells, reducing innate and adaptive immune defenses in the lungs and increasing susceptibility to infections. The altered immune status in the lungs due to inhaled aerosols may involve effects on healing (lung fibrosis), inflammatory responses (hypersensitivity pneumonitis, acute eosinophilic pneumonia, and acute interstitial pneumonia), and the regulation of genetically damaged cells (potentially leading to lung cancer) [91]. The increased oxidative stress induced by e-cigarettes stimulates the production of reactive oxygen species (ROS) in alveolar macrophages, causing lung epithelial damage and neutrophil influx at the injury site, leading to aggravated inflammation, mucus production, destruction of alveolar cells, and airway obstruction, potentially increasing future cardiovascular risks [53, 54].

### Limitations of current e-cigarette research

Current research on e-cigarettes may face limitations in experimental design, such as insufficient sample size, lack of long-term follow-up studies, and difficulty in fully simulating real smoking environments [92]. These limitations may affect the representativeness and predictive capability of research findings. Animal models and cell models are primarily used to assess the toxicity and potential health impacts of e-cigarettes. However, due to physiological and anatomical differences between animals and humans, these models may not accurately reflect the true responses to e-cigarettes in the human body [93]. Research based on cell models is often conducted in vitro with isolated single cells, lacking co-culture with other cells to simulate real physiological conditions in vivo [94]. At present, clinical studies are the main research means to reveal e-cigarettes and chronic respiratory diseases. For example, one clinical study found that that fourth-generation e-cigarette users exhibited signs of airway injury and immune suppression, with lower levels of key inflammatory and immune markers compared to other groups. Predictive modeling indicated distinct biological effects, suggesting that fourth-generation e-cigarettes uniquely disrupt immune homeostasis [20]. Another

clinical study revealed the effects of e-cigarettes in fighting infections. Study found that e-cigarette use impairs immune responses to influenza infection, including reduced anti-LAIV IgA levels and altered gene expression in nasal tissues. Cytokine levels (IFN-γ, IL-6, and IL-12p40) associated with antiviral defense were also lower in e-cigarette users, suggesting that e-cigarettes may disrupt nasal immune function and weaken respiratory antiviral defenses [95]. However, most current studies focus predominantly on Caucasian populations, with limited research on adolescents, who may have different e-cigarette usage patterns compared to adults [96]. Studies on adolescents largely focus on American youth, which may not be applicable to adolescents in other countries [97].

#### Future directions: e-cigarette and microbiome

Many studies have demonstrated that e-cigarettes altered the microbiome composition of respiratory tracts such as the nasal passages, mouth, and lungs, as well as the gut microbiota [83, 84, 98–100]. In the mouth microbes of e-cigarette smokers, the abundance of *Saccharibacteria* (TM7) (G-1 and G-5), *Selenomonas*, *Campylobacter*, *Prevotella*, *Actinomyces*, and *Corynebacterium* was significantly upregulated. In addition, the abundance of *Prevotella* and *Saccharibacteria* (TM7) (G-1) was also positively correlated with serum IFN-γ, IL-10, IL-12p70, IL-13, IL-1β, IL-2, IL-4 and TNF-α levels of e-cigarette smokers. *Prevotella* is a symbiotic bacterium that promotes Th17 differentiation, activates the IL-23/IL-17A axis, increases the inflammatory response, and aggravates chronic inflammation of the airway [101, 102]. Another study similarly showed a higher abundance of Saccharibacteria in the mouth of e-cigarette users, suggesting a role in airway inflammation [103]. There is no specific study on how Saccharibacteria regulates host immunity, but it has been reported that it is positively associated with pneumonia in Norwegians, suggesting its role in regulating respiratory inflammation [104]. Although there is a large amount of evidence to prove the relationship between e-cigarette use and microbiota and respiratory inflammation, there is a lack of systematic research on the mechanism. Chen et al. reported that nicotine accumulates in the gut during smoking, activates AMPKα and promotes the inflammatory progression of NAFLD. *Bacteroides xylanisolvens* can degrade nicotine, reduce the concentration of nicotine in the intestine and reduce nicotine-induced NAFLD. Mechanistically, AMPKα stabilizes SMPD3, increases ceramide formation and promotes disease progression [105]. These findings highlight the critical role of gut microbes in nicotine metabolism and underscore the importance of investigating the intricate relationship between smoking, the microbiome, and respiratory inflammation in future e-cigarette research.

#### Future directions: mechanism of e-cigarette and chronic airway inflammation

Some studies have attempted to elucidate the immune mechanism of airway inflammation caused by e-cigarettes through animal experiments. Researchers compared the effects of combustible cigarettes (CC) and ENDS on infiltrating immune cells in the lungs of mice. They found that sustained exposure to CC or ENDS caused a severe systemic inflammatory response, with increased activation of the NLRP3 inflammasome in neutrophils and macrophages, and enhanced dendritic cell-dependent activation of Th1 and Th17 cells in the lungs. While both cause lung damage driven by immune cells, ENDS aerosols are less harmful to respiratory function than CC smoke [106]. Another study showed that e-cigarette exposure combined with ovalbumin (OVA) sensitization significantly increased airway hyperreactivity, inflammatory cell infiltration, and Th2 cytokine production (IL-4 and IL-5) in mice. MUC5AC mucin levels increased in all exposed groups, while MUC5B levels increased in OVA-sensitized groups. These findings suggest that e-cigarette vapor can exacerbate allergic inflammation [67]. However, these studies lack deep mechanism exploration, and it is not clear that the specific components in e-cigarettes regulate the host immune system and aggravate airway inflammation. In the future, we can use metabolomics, proteomics and other means, combined with gene editing and genetic manipulation, to explore the specific mechanism of e-cigarette regulation of airway inflammation.

## Material and code availability

Not applicable.

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#### Author contributions

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#### Data availability

No datasets were generated or analysed during the current study.

### Declarations

#### Ethics approval

Not applicable.

**Consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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