



Current E-Cigarette Research in the Context of Asthma

Elise Hickman^{1,2} · Ilona Jaspers^{1,2,3} 

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Abstract

Purpose of Review The purpose of this review is to integrate recent research on the respiratory immune effects of e-cigarettes with the pathogenesis of asthma to better understand how e-cigarettes may affect asthmatics and to note critical knowledge gaps regarding the effects of e-cigarettes on asthmatics.

Recent Findings Human, rodent, and cell culture studies show that key cellular functions of epithelial cells, macrophages, and neutrophils are altered by e-cigarette exposure.

Summary Because respiratory immunity is already dysregulated in asthma, further alteration of cellular function by e-cigarettes could impact asthma development, severity, and/or exacerbations. Future research is needed to more directly investigate this relationship using controlled human exposure studies and exposure of cell culture or animal models of asthma to e-cigarettes.

Keywords E-cigarettes · Vaping · Environmental exposure · Asthma · Immune

Introduction

Approximately 7 million adults and more than 5 million youth are current electronic cigarette, or e-cigarette, users [1–3]. These devices were introduced in the U.S. in 2007 and have since gained popularity both among those trying to quit smoking and never-smokers, particularly teenagers and young adults. E-cigarettes have been touted as smoking cessation devices, but their efficacy for this purpose is still debated [4, 5]. In recent years, there has been a spike in youth use of e-cigarettes, with 27.5% of high schoolers in the U.S. reporting current e-cigarette use [6], reversing the previous decline in youth tobacco use. The rapid evolution and adoption of e-cigarette devices (Fig. 1), the diversity of e-liquids, and the individual variation in e-cigarette use patterns have made e-

cigarette research challenging, and many questions remain regarding the respiratory effects of e-cigarettes.

E-cigarettes heat and aerosolize e-liquids containing flavoring chemicals and nicotine dissolved in humectants propylene glycol (PG) and vegetable glycerin (VG). The composition of e-cigarette aerosol is highly dependent on e-liquid composition, device type, wattage, and coil resistance. Higher power aerosolization generates more aerosol and results in more thermal decomposition of the e-liquid [7–9]. Lower resistance aerosolization is associated with an increase in carbonyl generation, though even higher-resistance devices generate carbonyls [10, 11]. It is clear that flavoring chemicals transfer from the e-liquid to the aerosol, with efficiency estimated to be 40–80% [12, 13•, 14]. Flavoring chemicals can also react with PG in the e-liquid to generate flavorant PG acetals, which may have enhanced biological reactivity [13•, 14, 15•]. However, new designs of e-cigarettes are constantly emerging onto the market, which in turn can influence the chemical composition of the aerosols they generate (Fig. 1).

Pod-based e-cigs, such as JUUL, have become popular, especially among teenagers and young adults, and they now represent the majority of the e-cig market [16]. These sleek and discreet devices are different from previous generations of e-cigs (cig-a-likes, vape pens, and box mods) [17] in their aerosolization parameters, puff topography, and nicotine formulation (use of nicotine salts) [11, 12]. The nicotine salts found in these devices are generated by conjugating free base nicotine with organic acids, which lowers the pH of the e-

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✉ Ilona Jaspers
Ilona_jaspers@med.unc.edu

¹ Curriculum in Toxicology & Environmental Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

² Center for Environmental Medicine, Asthma, and Lung Biology, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

³ Department of Pediatrics, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

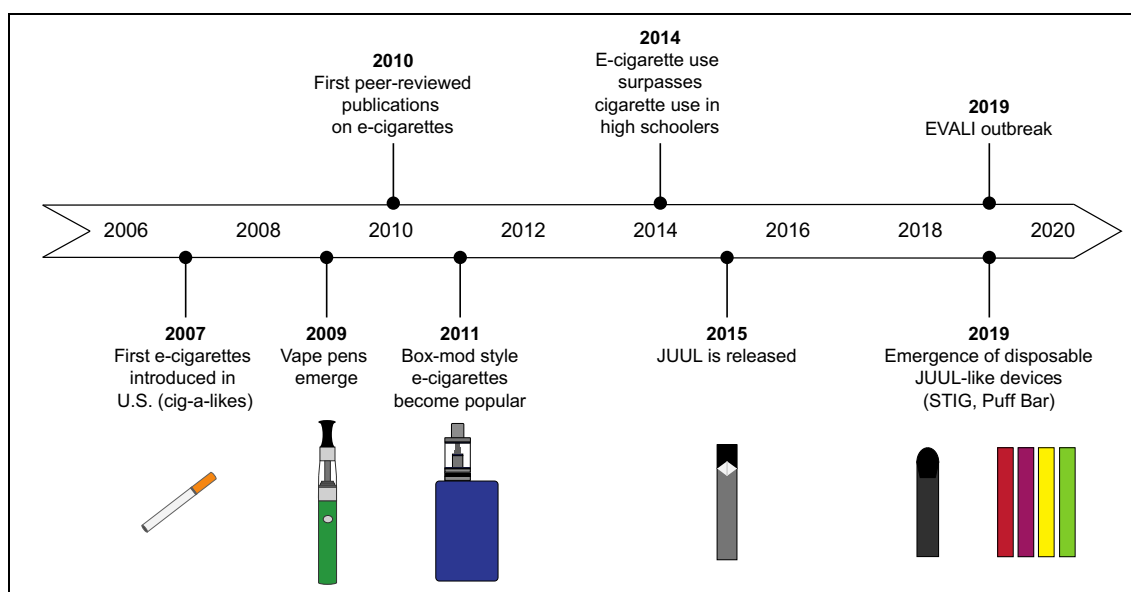


Fig. 1 Timeline representing the evolution of e-cigarette devices and pertinent events related to e-cigarettes

liquid and aerosol, allowing for more comfortable inhalation of high levels of nicotine [11, 18, 19]. Research addressing whether and how the inhalation toxicology of this current generation of e-cigarettes differs from previous generations of e-cigarettes is still ongoing.

While the field of e-cigarette research is less than 10 years old, it has become clear that e-cigarettes significantly affect the respiratory immune system. This has been demonstrated using many different models and experimental approaches [20]. E-cigarettes have also garnered public attention due to the recent outbreak of e-cigarette- and vaping use-associated lung injury (EVALI). The pathology associated with this disease has largely been associated with counterfeit marijuana vaping cartridges and cutting agents and will not be the focus of this review [21]. However, the effects of e-cigarettes on susceptible subpopulations, such as individuals with asthma, have not been well-investigated. This is particularly concerning because there is evidence that young asthmatics may be more likely to use e-cigarettes and may perceive them as less harmful than their non-asthmatic counterparts [22–26, 27, 28]. Furthermore, asthmatics who are current smokers are often advised by their health care providers to switch to e-cigarettes as a safer alternative [29–31] despite lack of thorough inhalation toxicology data to support that recommendation.

This review will focus on integrating the key features and cell types involved in asthma pathogenesis with published research on the effects of e-cigarettes on the respiratory system and respiratory immunity. Through this review, we aim to highlight how e-cigarette use could potentially affect asthmatics and to identify specific

knowledge gaps at the intersection of asthma and e-cigarette research.

Population-Based Associations Between E-cigarette Use and Asthma

Even though controlled studies of e-cigarette aerosol exposure in the context of asthma susceptibility and pathogenesis have not been conducted, e-cigarette use has been associated with asthma and asthma-like symptoms in population-based studies of both adults and adolescents. The Population Assessment of Tobacco and Health (PATH) study is a longitudinal study of approximately 49,000 people ages 12 and over that evaluates how tobacco use affects health. Bhatta et al. found a significant association between former or current e-cigarette use at wave 1 of the PATH study and having any respiratory disease (COPD, chronic bronchitis, emphysema, asthma) at waves 2 or 3, controlling for factors such as smoking and other demographic and clinical variables [32•]. For asthma specifically, there was a significant association between current e-cigarette use at wave 1 and newly reported asthma at wave 2 [32•]. Furthermore, e-cigarette use was associated with increased odds ratio of self-reported asthma, which was higher in daily as compared to occasional e-cigarette users [33]. In a small pilot study, e-cigarette users had an increase in plasma IgE in comparison with nonsmokers [34], suggesting increased markers of atopy. In adolescents, e-cigarette use has been associated with having asthma, bronchitic symptoms, and days absent for asthmatic high schoolers due to severe asthma, controlling for other substance use and demographic variables [35•, 36, 37]. Increased risk for asthma attacks

following secondhand e-cigarette exposure has also been reported in adolescents [38•]. This body of epidemiological research suggests that there is a link between e-cigarettes and asthma-associated symptoms and morbidity, warranting further controlled and biomolecular investigation of the mechanisms through which e-cigarette exposure affects asthma development, severity, and/or exacerbation and how susceptibility to e-cigarette-induced health effects may be greater in asthmatics.

The Effects of E-Cigarettes on Respiratory Function and General Inflammation

Additional evidence in controlled exposure studies and case reports suggests that e-cigarettes can alter airway function and inflammation and that asthmatics are more susceptible to the effects of e-cigarettes than healthy vapers. Lappas et al. found that both healthy smokers and those with mild asthma experienced bronchoconstriction coupled with a decrease in FeNO following a session of vaping and that mild asthmatics took longer to recover from these effects [39]. However, Boulay et al. found that vaping PG/VG alone does not have acute effects on respiratory function in asthmatics or non-asthmatics [40]. We have described two case reports of adolescent asthmatic vapers who had recently vaped and presented to the emergency room with life-threatening status asthmaticus, necessitating veno-venous extracorporeal membrane oxygenation [41]. Interestingly, the prevalence of underlying asthma in patients who had EVALI was higher than the prevalence of asthma in the general population [42]. Only one study has assessed airway hyperresponsiveness following e-cigarette exposure. Chapman et al. challenged BALB/c mice with either phosphate-buffered saline or house dust mite and then exposed them to aerosols from different flavored e-cigarettes. These mice had varied responses depending on the flavor, with cinnamon-flavored aerosol increasing airway hyperresponsiveness and banana-flavored aerosol increasing lung collagen deposition, indicating that e-cigarettes can induce abnormal lung function in an animal model of allergic airway disease [43]. Collectively, these pieces of evidence from human and animal studies, both controlled exposure and observational clinical studies, indicate that asthmatics may be a susceptible subpopulation for the effects of e-cigarettes; yet, the mechanisms mediating these effects are unknown.

Effects of E-Cigarettes on Epithelial Responses

Airway epithelial cells play critical roles in airway hyperresponsiveness, increased mucus secretion, and altered cytokine secretion, which are all features of asthma [44–46]. E-cigarettes and e-liquid components have been shown to alter mucin composition and mucociliary escalator function.

E-cigarette users had increased levels of MUC5AC in induced sputum and bronchoalveolar lavage fluid [47•, 48•], and aerosolized PG/VG alone increased MUC5AC in primary human bronchial epithelial cells exposed *ex vivo* and in mouse nasal epithelial cells from mice exposed *in vivo* [48•]. E-cigarette aerosols and e-liquid components can impair mucociliary function in primary human bronchial epithelial cells and in sheep [49•, 50•]. Transient receptor potential cation channel subfamily A member 1 (TRPA1), a calcium ion channel, was found to be responsible for initiating these effects in the study by Chung et al., and interestingly, flavoring chemicals and their propylene glycol acetals can also activate TRPA1 [13•, 50•]. These findings are particularly notable given that MUC5AC is often increased in asthmatics and TRPA1 is hypothesized to play a role in asthmatic airway hyperresponsiveness [44, 51, 52].

Expression of certain cytokines and chemokines by epithelial cells mediates the recruitment and activation of immune cells such as lymphocytes and dendritic cells, which are involved in the pathogenesis of asthma [53]. E-cigarettes and e-liquid flavoring chemicals can alter cytokine expression in airway epithelial cells [7, 54, 55]. We have shown that e-cigarette users have suppressed immune gene expression in the nasal epithelia [56], and Park et al. found that flavoring chemicals alone can induce changes in cytoskeletal- and cilia-related gene expression in airway epithelial cells [57]. Additionally, both unflavored e-cigarette aerosol and e-cigarette flavoring chemicals have been shown to impair airway epithelial cell barrier function [54, 58•]. These data convincingly show that epithelial cell function and cytokine expression is altered by e-cigarettes; however, an important knowledge gap remains in that it is unknown how cytokine expression is altered by e-cigarettes in the asthmatic epithelium. Hence, it will be important for future studies to investigate how e-cigarette exposure affects epithelial cells from asthmatics specifically.

The Effects of E-Cigarettes on Macrophage Function

Macrophages are the most highly abundant immune cells in the airways, and they are responsible for a wide range of pro- and anti-inflammatory functions to maintain host defense and respiratory immune homeostasis. In asthma, macrophages exhibit impaired phagocytosis and efferocytosis, which can contribute to impaired bacterial clearance, increased neutrophils in the airways, and excess inflammation [59, 60]. Macrophages from asthmatics also release more pro-inflammatory cytokines, yet are not responsive to stimulation with lipopolysaccharide [59]. It has been hypothesized that shifts in macrophage polarization along the M1/M2 spectrum may play a role in asthma and differentiation of asthma subtypes, but due to the complexity of both asthma and macrophage polarization, this relationship is still being explored [59,

61]. Additionally, macrophages can play a role in regulating airway hyperresponsiveness and in recruitment and function of T cells, which are important components of asthma pathogenesis [59, 60, 62]. Because macrophages are constantly responding to diverse signals from the environment around them, they are likely to be affected by exposures to toxicants, and it is possible that impairment of respiratory macrophage function by inhaled toxicants could worsen macrophage dysfunction already observed in asthmatics, thereby contributing to increased disease severity.

Studies on the effects of e-cigarettes and e-liquid components suggest that e-cigarettes can alter macrophage function. Multiple studies have shown that *in vitro* exposure of macrophages to e-cigarette condensate, flavoring chemicals, and nicotine can modulate cytokine release. For example, IL-8 release from macrophages is increased following exposure to flavored and unflavored condensate, as well as many e-cigarette flavoring chemicals alone, and one study found that this response was nicotine dependent [63–65]. Other cytokines that have been shown to be modulated by e-cigarette exposure include IL-6 and TNF- α , though whether their release is increased or decreased in response to e-cigarette exposure is not consistent between studies [63, 65]. Phagocytosis, another key macrophage function, is decreased following both *in vitro* and *in vivo* exposure to e-cigarettes and e-liquid components [65, 66, 67], and this impairment can be reversed or partially reversed by treatment with dithiothreitol or N-acetylcysteine, suggesting that oxidant imbalance contributes to impaired phagocytic function [65, 67]. E-cigarettes have also been shown to increase reactive oxygen species production, increase protease release, alter surface marker expression, and dysregulate lipid homeostasis in macrophages [63, 65, 68, 69]. As macrophages are such central regulators of respiratory immunity and are already dysregulated in asthma, alterations of their function by e-cigarette use will likely have additional implications for asthmatics.

The Effects of E-Cigarettes on Neutrophil Function

Both eosinophilic and neutrophilic inflammation play important roles in asthma pathophysiology. Neutrophilic asthma, which can be both allergic and non-allergic, is characterized by accumulation of neutrophils in the airways, which are typically highly activated [70–72]. Increased numbers of neutrophils in the airways have been associated with increased airflow obstruction, more severe asthma, and asthma exacerbations [73, 74]. Neutrophils also contribute to airway remodeling and hypersensitivity through secretion of serine proteases such as matrix metalloproteinase 9 and neutrophil elastase [73–76]. Further modulation of neutrophil function via toxicant exposure could negatively impact disease severity by shifting neutrophils to an even more dysregulated state. E-cigarette users have significantly elevated markers of

neutrophil activation in induced sputum and bronchoalveolar lavage fluid in comparison with nonsmokers, and peripheral blood neutrophils from e-cigarette users are more susceptible to PMA-induced NETosis [47, 68], indicating that chronic e-cigarette use may cause neutrophils to become even more reactive. However, exposure of human peripheral blood neutrophils from non-vaping subjects to e-cigarette aerosol condensate *ex vivo* decreases chemotaxis, reactive oxygen species production, NETosis, and phagocytosis [77]. We have shown that exposure of human peripheral blood neutrophils to flavoring chemicals alone can suppress phagocytosis and oxidative burst, and that flavored e-liquids can modulate NETosis [15, 67]. Though these *in vivo* and *in vitro* findings may seem to be contradictory, they are likely the result of different routes, lengths, and chemical compositions of exposure. Together, they indicate that e-cigarettes can dysregulate neutrophil function and that acute exposure to e-cigarette aerosol or specific flavorings could impair key neutrophil functions, resulting in decreased host defense. Interestingly, nicotine alone can elicit a dose-dependent increase in protease release [68], which could have implications for the development or exacerbation of asthma due to the connection between proteases and airway remodeling in asthma.

Effects of E-Cigarettes on Immune Responses to Infection

Viral infections are the leading cause for asthma exacerbations, and asthmatics are at increased risk for viral infections [78, 79]. Anything that perturbs the natural antiviral host defense response could affect susceptibility to viral infections and asthma exacerbations. Two studies in mice have shown that exposure to e-cigarette aerosol impairs antiviral responses to influenza [66, 69], and as compared to nonsmokers, bronchial expression of toll-like receptor 3, which recognizes double-stranded RNA and is important for antiviral defense responses, was decreased in vapers [48]. These studies are all in agreement that e-cigarettes can suppress antiviral responses; therefore, asthmatics who use e-cigarettes may be even more susceptible to viral infections, which could lead to additional or more severe asthma exacerbations.

Altered bacterial colonization of the respiratory tract and increased risk for bacterial infections are also a feature of asthma [78, 79]. The respiratory microbiome is an important component in respiratory mucosal homeostasis, and respiratory microbiome dysbiosis has been associated with asthma, asthma exacerbations, and asthma severity [80–83]. Although the respiratory microbiome in e-cigarette users has not been compared to that of nonsmokers, smoking has been shown to be associated with changes in the nasal microbiome, and e-cigarette use has been associated with changes in the oral microbiome [84, 85], indicating that it is likely that the respiratory microbiome is also altered by e-cigarette use.

Table 1 Summary of reviewed studies evaluating the effects of e-cigarettes on the function of epithelial cells, macrophages, and neutrophils

Cell type	Study	Experimental system	Results
Epithelial cells	Chung et al. (2019) [50•]	Primary human bronchial epithelial cells exposed in vitro to e-cigarette aerosol and nebulized nicotine	↑ mucus viscosity
		Sheep exposed in vivo to e-cigarette aerosol and nebulized nicotine	↓ tracheal mucus velocity
	Clapp et al. (2019) [49•]	Primary human bronchial epithelial cells and BEAS2Bs exposed in vitro to cinnamon-flavored e-liquids and aerosols and to cinnamaldehyde alone	↓ cilia beat frequency ↓ mitochondrial respiration
	Crotty Alexander et al. (2018) [58•]	Primary human bronchial epithelial cells exposed in vitro to e-cigarette aerosol	↓ barrier function
	Escobar et al. (2020) [7]	Primary human bronchial cells and 16HBEs exposed in vitro to e-cigarette aerosol	↑ IL-6, IL-8, HMOX-1, NQO1
	Gerloff et al. (2017) [54]	BEAS-2Bs and 16HBEs exposed in vitro to flavoring chemicals	↑ IL-8 release ↓ barrier function
	Ghosh et al. (2018) [48••]	Bronchial brush biopsies from nonsmokers, e-cigarette users, and smokers	↑ MUC5AC expression
		Primary human bronchial epithelial cells exposed in vitro to e-cigarette aerosol with PG/VG only	↑ MUC5AC expression
		Mice exposed in vivo to e-cigarette aerosol with PG/VG only	↑ MUC5AC expression
	Lerner et al. (2015) [55]	H292 cells exposed in vitro to e-cigarette aerosols	↑ IL-8 and IL-8 release
		C57BL/6 J mice exposed in vivo to e-cigarette aerosol	↑ IL-6 and MCP-1 in bronchoalveolar lavage fluid
	Martin et al. (2016) [56]	Human nasal epithelial cells from nonsmokers, e-cigarette users, and smokers	↓ expression of immune-related genes
	Park et al. (2019) [57]	Human bronchial epithelial cells exposed to flavoring chemicals diacetyl and 2,3-pentanedione	↓ expression of cytoskeletal- and cilia-related genes
Macrophages	Reidel et al. (2017) [47••]	Induced sputum from nonsmokers, e-cigarette users, and smokers	↑ MUC5AC expression
	Clapp et al. (2017) [67•]	Alveolar macrophages from healthy subjects exposed in vitro to flavored e-liquids and cinnamaldehyde	↓ phagocytosis ↑ ↓ IL-6, ↓ IL-8
	Ghosh et al. (2019) [68••]	Alveolar macrophages from healthy subjects exposed in vitro to nicotine	↑ protease release
	Madison et al. (2019) [69••]	C57BL/6 J mice exposed in vivo to e-cigarette aerosol	↑ phospholipid ↓ M1 polarization ↓ interferon response to poly I:C
	Muthumalage et al. (2017) [64]	MM6 and U937 (monocytic) cells exposed in vitro to flavoring chemicals	↑ IL-8 release
	Scott et al. (2018) [65•]	Alveolar macrophages and THP-1 cells exposed in vitro to e-cigarette condensate	↑ reactive oxygen species ↑ proinflammatory cytokine release ↓ phagocytosis
	Sussan et al. (2015) [66]	C57BL/6 J mice were exposed in vivo to e-cigarette aerosol	↓ phagocytosis
	Ween et al. (2017) [63]	THP-1 cells exposed in vitro to e-cigarette condensate	↑ IL-8 release ↓ other proinflammatory cytokine release ↓ phagocytosis
Neutrophils	Clapp et al. (2017) [67•]	Peripheral blood neutrophils from healthy subjects exposed in vitro to flavored e-liquids and cinnamaldehyde	↓ phagocytosis, ↑ ↓ NETosis, ↑ IL-8 release
	Ghosh et al. (2019) [68••]	Peripheral blood neutrophils from healthy subjects exposed in vitro to nicotine	↑ protease release
	Hickman et al. (2019) [15•]	Peripheral blood neutrophils from healthy subjects exposed in vitro to flavoring chemicals	↓ phagocytosis ↓ oxidative burst
	Hwang et al. (2016) [77]	Peripheral blood neutrophils from healthy subjects exposed in vitro to e-cigarette condensate	↓ phagocytosis ↓ oxidative burst ↓ chemotaxis, ↓ NETosis
	Reidel et al. (2017) [47••]	Peripheral blood neutrophils from nonsmokers, e-cigarette users, and smokers	↑ NETosis in cells from e-cigarette users

Table 1 (continued)

Cell type	Study	Experimental system	Results
		Induced sputum from nonsmokers, e-cigarette users, and smokers	↑ markers of neutrophil activation in e-cigarette users

Studies have shown that exposure to e-cigarettes can increase bacterial burden of *Streptococcus pneumoniae* in mice [66, 86••] and decrease survival of mice infected with methicillin-resistant *Staphylococcus aureus* (MRSA) [77]. Additionally, e-cigarette condensate can have direct effects on MRSA, including increasing cellular invasion, virulence gene expression, and resistance to killing by antimicrobial peptide LL-37 [77]. These pieces of evidence suggest that e-cigarette use can both directly and indirectly modulate bacterial colonization in the respiratory tract, and future studies seeking to understand how this affects respiratory microbial communities in both asthmatics and non-asthmatics will be highly relevant.

Effects of E-Cigarettes on the Development of Asthma

In addition to exacerbation of asthma, understanding how e-cigarette use could enhance the development of asthma needs to be better understood. For example, an important consideration is that maternal smoking has been linked to asthma development, and nicotine is thought to drive this effect through the nicotinic acetylcholine receptor [87]. Pregnant women who are smokers are sometimes advised to switch to e-cigarettes, particularly in the United Kingdom, despite lack of toxicological data supporting their safety for use during pregnancy and disregarding the potential for effects of nicotine [88]. In utero exposure to both cigarette smoke and nicotine alone in animal models impacts pulmonary function, respiratory illness, airway anatomy, and cellular changes (reviewed in [87]). Although there are no studies yet investigating whether *in utero* e-cigarette exposure increases risk for offspring airway disease, e-cigarettes typically contain nicotine, sometimes at very high concentrations. Therefore, we hypothesize that use of nicotine-containing e-cigarettes during pregnancy could increase risk for asthma development in offspring.

Conclusions

Current research clearly demonstrates that e-cigarettes can affect respiratory mucosal immunity, including the functions of epithelial cells, macrophages, and neutrophils (Table 1). These effects can be attributed both to whole e-cigarette

aerosol and to some of the individual components of e-liquids. Importantly, respiratory mucosal immunity is already altered in asthma, making asthmatics a susceptible subpopulation to perturbations in these cellular functions. Given the overlap between the biological processes affected by e-cigarette exposure and those affected by asthma, there is the possibility that e-cigarettes could induce asthma-like symptoms in non-asthmatics and exacerbate asthma in people who already have it. A significant amount of additional research will be required to understand whether and how e-cigarettes differentially affect asthmatics and to identify specific components of e-cigarette aerosols mediating these effects. It is important to note that most of the research reviewed here was conducted with model systems or subjects exposed to older generation e-cigarettes (vape pens and box mods). Whether and how exposure to pod-based devices, such as JUUL, differently affects respiratory mucosal immune responses represents a critical knowledge gap. It is unclear whether inhalation of nicotine salts as compared to freebase nicotine poses unique health risks. Future studies will also need to investigate the effects of exposure of cell culture or animal models of asthma to e-cigarettes on asthma-specific endpoints and biological mechanisms to identify clear cause-and-effect relationships. For example, the effects of e-cigarette exposure on the function of eosinophils, basophils, dendritic cells, mast cells, and T cells will need to be studied in order to more directly understand the underlying mechanisms of how e-cigarette exposure could affect asthmatics. Additionally, there is a need for e-cigarette research that focuses on whether and how the respiratory biology of teenagers and adolescents who use e-cigarettes is differentially affected, as most current e-cigarette research uses adult subjects, animals, and cells. To further support these research questions, better documentation of e-cigarette use (device, flavor, nicotine concentration, amount of e-liquid consumed) in electronic medical records needs to be implemented. This will facilitate population-based studies and improve linking e-cigarette use and clinical outcomes, including the development or exacerbation of asthma. Finally, there is an urgent need for health care providers to obtain the most up-to-date information about respiratory effects of e-cigarettes so they can inform their patients, asthmatics and non-asthmatics, about the potential health risks associated with e-cigarette use.

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