Electronic Cigarettes

Subjects: Pathology

Contributor: Serafeim - Chrysovalantis Kotoulas

Electronic cigarettes (EC) are a novel product, marketed as an alternative to tobacco cigarette. Its effects on human health have not been investigated widely yet, especially in specific populations such as patients with asthma.

electronic cigarette asthma review asthma pathogenesis lung function airway inflammation asthma control smoking cessation

1. Introduction

Asthma is a chronic inflammatory airway disease characterized by exacerbations and remissions, affecting 1–18% of the population in different countries [1]. Airway inflammation in asthma is typically eosinophilic, but can also be neutrophilic, mixed, or non-granulocytic [1]. Different factors are involved in aggravating airways inflammation in asthmatic patients, with cigarette smoke being one of the main ones [1][2]. Smoking prevalence in patients with asthma approximates that of the general population [3]. Even in severe asthma, the percentages of asthmatic smokers could reach or even exceed these of the general population [4]. The percentage of severe asthmatics that were using e-cigarettes (ECs) in the same study was 2% and was higher than in the general population in many countries [4]. Asthmatic smokers suffer from more symptoms and exacerbations, develop a more rapid decline in pulmonary function and have a worse prognosis than non-smoking asthmatics [5][6][7]. In addition, they usually present with a higher proportion of neutrophils in induced sputum, reduced pH, and heterogenous inflammatory mediator profiles in exhaled breath condensate (EBC) [8][9][10][11].

Since 2003, the EC has become very popular as it was advertised as a tool for smoking cessation. Clinical experience has shown that smokers attempting to quit smoking use the EC as an alternative [12][13][14][15]. However, ECs' safety has not been scientifically demonstrated, especially in asthmatic patients.

2. The Role of EC Compounds in the Pathogenesis of Asthma

The constitution of EC aerosol is defined by temperature, and by the contents in the heated liquid as propylene glycol (PG), glycerin, flavoring agents, nicotine in variable concentrations and other non-nicotine substances [16]. Laboratory, observational, and clinical studies have revealed that EC aerosols contain numerous respiratory irritants and toxins and that may have a cytotoxic effect on lung tissue, analogous to that of the tobacco cigarette

[17][18]. More than 80 compounds (including known toxins—e.g., formaldehyde, acetaldehyde, metallic nanoparticles, and acrolein) have been found in e-liquid and aerosols and as a result, ECs have been linked with an increase in symptoms in individuals with asthma [16]. Additionally, ECs were found to contain not only formaldehyde but also formaldehyde-forming hemiacetals and potentially toxic particulate matter that deposits on surfaces [19]. The novel-generation high-power electronic nicotine delivery systems (ENDS) which seem to be particularly user-adaptive, produce droplets with a diameter at 0.78 ± 0.03 μm [20][21]. Exposure of the airway epithelial cells to certain liquid flavorings reaches toxicity thresholds. The chocolate flavoring 2,5-dimethypyrazine activates the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel [22]. Work-related inhalation of several usual food-safe flavoring substances has been related with occupational asthma and asthma symptoms deterioration [23]. More specifically, work-related inhalation exposures to the flavoring substance diacetyl was found to cause irreversible obstructive airway disease in healthy workers. The thermal decomposition of PG and vegetable glycerin (VG), the key elements of EC liquids, generates reactive carbonyls, including acetaldehyde, formaldehyde, and acrolein which have well-known lung toxicities [23]. PG vapor has been found to induce respiratory irritation and increase asthma risk, despite the fact that EC use improved home indoor air quality compared with secondhand tobacco smoke [24]. Long-term exposure to EC was found to change the human bronchial epithelial proteome promoting its damage [25]. Heavy EC smoking promotes inflammatory processes (activator of transcription and nuclear factor-κB signaling, Janus tyrosine kinase/signal transducer, and mitogen-activated protein kinase), in a similar way to tobacco smoke. Protracted exposure to some components of EC vapor results in respiratory complications as asthma [26].

Chronic EC exposure also seems to result in increased neutrophil elastase and matrix metalloprotease levels in the lung, abnormal activation of the lung epithelial cells, β-defensins and neutrophilic response (NETosis), activation of transient receptor potential ankyrin 1 (TRAP1), alternations in the normal respiratory microbiota, induced proteolysis and in general impaired respiratory innate immune system, all associated with allergies and asthma [27][28]. Respiratory innate immune cell function has also been found to be impaired by flavored EC liquids and more specifically, by cinnamaldehyde which suppresses phagocytosis by macrophages [29], and provisionally represses ciliary mobility of bronchial epithelial cells through dysregulation of mitochondrial function [30]. These dysregulations of the respiratory immunity by EC could impact asthma development, severity, and/or exacerbations [31].

3.What Is the Effect of EC Use on Lung Function and on Airway Inflammation in Patients with Asthma?

Asthmatic patients exhibited a significant increase in respiratory system total impedance at 5 Hz (Z5), respiratory resistance at 5, 10, and 20 Hz (R5, R10, and R20), resonant frequency and reactance area measured by impulse oscillometry (IOS) after EC use, compared with healthy controls [32]. Mean airway resistance along with the slope of the phase III curve on the single breath nitrogen test increased immediately after short-term EC use in a group of asthmatic smokers, thereby demonstrating airway dysfunction, particularly in small airways [33]. Apart from airway resistance, asthmatic patients also exhibited impaired pulmonary function tests (PFTs) after vaping for five minutes, with the decrease in forced expiratory volume in 1 s to forced vital capacity ratio (FEV1/FVC) and peak expiratory

flow (PEF) being more significant [34]. Furthermore, patients who recovered from electronic vapor acute lung injury (EVALI), a condition more commonly observed in asthmatic patients, exhibited chronic irreversible airflow obstruction, markedly abnormal ^{129}Xe MRI ventilation heterogeneity, abnormal lung clearance index and oscillometry measures and decreased diffusing capacity of the lung for carbon monoxide (DLCO), all persistent after their discharge [35][36]. Studies in animals with allergen-induced airway disease demonstrated not only increased airway hyperresponsiveness after EC vapor inhalation, but also increase in mucus and airway wall thickening which are hallmark features of allergic asthma [37][38][39][40].

The effects of EC use on inflammation have been studied in cell lines, animal models, and humans. In all three, EC use led to inflammation and oxidative stress [41]. However, specifically in asthmatic patients, the studies that evaluate the effects of ECs on airway inflammation are limited [42]. ECs free of nicotine were found to cause heterogenous effects depending on their flavor, while ECs containing nicotine suppressed airway inflammation but not airway remodeling in mice with allergic airway disease [39]. Eosinophilic inflammation is accompanied by an increased fraction of exhaled nitric oxide (FeNO) and correlates with other indices of inflammation in asthmatic patients [43]. FeNO is increased during asthma exacerbations, while it decreases with recovery or inhaled corticosteroids [44][45]. There is conflicting evidence on the effect of EC on the FeNO of asthmatics. There are studies where FeNO significantly decreased after an EC session [32], whereas the opposite result was exhibited in another study [34]. In the latter study, Th2 cytokines such as interleukins (IL) IL-4 and IL-13 in the EBC of asthmatics were found to be significantly increased after vaping for five minutes, reflecting increased eosinophilic inflammation, and supporting the finding of increased FeNO [34]. Apart from Th2 inflammatory mediators, an increase in IL-1β and tumor necrosis factor alpha (TNF-α) was observed. Both are proinflammatory cytokines that amplify and orchestrate the inflammatory response in asthma and determine its severity; IL-10, a cytokine derived from Th2 cells and 8-Isoprostane (ISO8) a biomarker of oxidative stress were also increased [34]. Additionally, in three experimental studies on mice with allergen-induced airway disease, EC inhalation increased infiltration of what by inflammatory cells, including eosinophils, into airways from blood, increased the number of all types of inflammatory cells in Bronchoalveolar lavage fluid (BALF), stimulated the production of Th2 cytokines such as IL-4, IL-5, and IL-13 and allergen-specific immunoglobulin E (IgE) and reduced the levels of transforming growth factor (TGF)-β1 and matrix metalloproteinase (MMP)-2 in lung tissue homogenate [38][40][46].

4. What Is the Effect of EC on the Clinical Characteristics of Asthma?

Thirty-nine observational studies including 2,111,023 participants, six case studies, two opinion articles, eight reviews, and five systematic reviews with four meta-analyses investigated the effects of EC use in asthmatics. Several investigators have concluded that EC could be associated with the development of pulmonary disorders, including asthma and might increase asthma severity and exacerbations [18][31][47][48][49][50]. Numerous cross-sectional studies with a large number of participants have described the significant association between EC use and even secondhand exposure and asthma diagnosis and severity [51][52][53][54][55][56][57][58][59][60], compared to the few studies which found no association [61][62], or even negative association between EC use and asthma [63][64]. A

prospective cohort study also found that EC use was associated with an increased risk of developing respiratory disease, including asthma, independent of cigarette smoking [65]. A study from Korea demonstrated that adolescent EC users presented the highest adjusted odds ratio for severe asthma, which was reflected by the number of days absent from school due to asthma symptoms [66]. EC use was found to be positively correlated with asthma, or even more, to increase the probability of an adolescent being diagnosed with asthma and also enhanced the adverse effects of tobacco cigarettes in asthma [66][67][68]. A study from Sweden which comprised patients with obstructive lung diseases, mostly asthmatics, showed that all respiratory symptoms were most common among dual users (electronic plus tobacco cigarette), former smokers and nonsmokers who used ECs rather than tobacco cigarette smokers-alone [69]. Furthermore, two studies from France and Canada also found that asthma was more commonly associated with EC use [70][71]. A large epidemiological study from the USA including more than 400,000 participants showed that current EC use was associated with 39% higher odds of self-reported asthma, compared to never EC use and that there was a graded increased odds of having asthma with increased EC use intensity, from occasional to daily EC users [72]. Five more studies from the USA also concluded that EC is an independent risk factor for respiratory disease including asthma, after controlling for covariates [73][74][75][76][77]. EC had an additive effect for asthma beyond smoking [77]. Dual use, which is the most common usage pattern, is riskier than using either product alone [73]. Dual use, with even passive exposure to EC, was identified as significant predictor for asthma in two more cross-sectional studies [59][78] and one meta-analysis [79]. A recently published systematic review concluded that evidence up to now suggests that the side effects of ECs may be exaggerated in people with asthma [42]. Additionally, asthma symptoms were among the most frequently reported side effects associated with EC use, second to headaches [80]. Moreover, EC use was associated with lower general health scores, higher breathing difficulty scores and a greater proportion of reporting asthma [81]. A large epidemiological study in USA with a weighted sample size of 31,721,603 adults between 18 and 24 years (2,503,503 with former and 3,200,681 with current asthma) found that the prevalence of EC use was significantly higher among young adults with current or former asthma and that asthma combined with EC use was significantly associated with worse mental health [82], a finding similar to that of another study from Korea [58].

5. Discussion

Most studies indicate the negative effects of vaping on asthma indirectly by the increased likelihood of a vaper being also an asthmatic, with a dose-dependent manner. However, most of the studies were cross-sectional, thus they could not establish a cause-and-effect relationship between EC use and asthma. Nevertheless, they provide excellent epidemiological data to assess trends and note areas where interventions are needed. Studies suggesting that EC improves asthma control presented serious concerns about a possible selection bias, as they were based on online surveys data, or included a small number of asthmatics. Recently published systematic reviews with meta-analyses tally with the above conclusions [79][83][84][85]. More research is needed in order to study the effects of EC on lung function and airway inflammation of asthmatic patients.

As nicotine dependence remains while vaping, most studies reflect the ineffectiveness of EC as a smoking cessation tool by pointing out that patients with asthma could more easily become addicted to EC than non-

asthmatics and that asthmatics who are dual users smoke a greater number of tobacco cigarettes per day, while the most alarming finding on this aspect is the ‘gateway effect’. On the contrary, there are also studies suggesting that EC could in fact promote smoking cessation [86][87]. Nonetheless, the study with the most participants supporting that was based on an online survey [87], thus there are serious concerns of a possible selection bias.

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2021. Available online: www.ginasthma.org (accessed on 4 July 2021).
2. Putcha, N.; Hansel, N.N. All-cause mortality in asthma. The importance of age, comorbidity, and socioeconomic status. Ann. Am. Thorac. Soc. 2014, 11, 1252–1253.
3. Polosa, R.; Thomson, N.C. Smoking and asthma: Dangerous liaisons. Eur. Respir. J. 2013, 41, 716–726.
4. Katsaounou, P.; Ioannou, M.; Hyland, M.E.; Odemyr, M.; Spranger, O.; Lindberg, A.; Gasser, M.; Conde, L.G.; Jaumont, X.; Kasujee, I. Smoking asthmatics, a neglected large phenotype of asthmatic patients. Open J. Asthma 2019, 3, 1–8.
5. James, A.L.; Palmer, L.J.; Kicic, E.; Maxwell, P.S.; Lagan, S.E.; Ryan, G.F.; Musk, A.W. Decline in lung function in the Busselton Health Study: The effects of asthma and cigarette smoking. Am. J. Respir. Crit. Care Med. 2005, 171, 109–114.
6. Aanerud, M.; Carsin, A.E.; Sunyer, J.; Dratva, J.; Gislason, T.; Jarvis, D.; deMarco, R.; Raherison, C.; Wjst, M.; Dharmage, S.C.; et al. Interaction between asthma and smoking increases the risk of adult airway obstruction. Eur. Respir. J. 2015, 45, 635–643.
7. Tommola, M.; Ilmarinen, P.; Tuomisto, L.E.; Haanpää, J.; Kankaanranta, T.; Niemelä, O.; Kankaanranta, H. The effect of smoking on lung function: A clinical study of adult-onset asthma. Eur. Respir. J. 2016, 48, 1298–1306.
8. Prieto, L.; Palop, J.; Llusar, R.; Herrera, S.; Perez-Frances, C.; Lanuza, A.; Aguilar, D. Effects of cigarette smoke on methacholine- and AMP-induced air trapping in asthmatics. J. Asthma 2015, 52, 26–33.
9. Papaioannou, A.I.; Koutsokera, A.; Tanou, K.; Kiropoulos, T.S.; Tsilioni, I.; Oikonomidi, S.; Liadaki, K.; Pournaras, S.; Gourgoulianis, K.I.; Kostikas, K. The acute effect of smoking in healthy and asthmatic smokers. Eur. J. Clin. Investig. 2010, 40, 103–109.
10. Boulet, L.P.; Lemière, C.; Archambault, F.; Carrier, G.; Descary, M.C.; Deschesnes, F. Smoking and asthma: Clinical and radiologic features, lung function, and airway inflammation. Chest 2006, 129, 661–668.

11. St-Laurent, J.; Bergeron, C.; Pagé, N.; Couture, C.; Laviolette, M.; Boulet, L.P. Influence of smoking on airway inflammation and remodelling in asthma. Clin. Exp. Allergy 2008, 38, 1582–1589.
12. Rom, O.; Pecorelli, A.; Valacchi, G.; Reznick, A.Z. Are E-cigarettes a safe and good alternative to cigarette smoking? Ann. N. Y. Acad. Sci. 2015, 1340, 65–74.
13. Löhler, J.; Wollenberg, B. Are electronic cigarettes a healthier alternative to conventional tobacco smoking? Eur. Arch. Otorhinolaryngol. 2019, 276, 17–25.
14. Notley, C.; Ward, E.; Dawkins, L.; Holland, R.; Jakes, S. Vaping as an alternative to smoking relapse following brief lapse. Drug Alcohol Rev. 2019, 38, 68–75.
15. Jackson, S.E.; Shahab, L.; Kock, L.; West, R.; Brown, J. Expenditure on smoking and alternative nicotine delivery products: A population survey in England. Addiction 2019, 114, 2026–2036.
16. Thirión-Romero, I.; Pérez-Padilla, R.; Zabert, G.; Barrientos-Gutiérrez, I. Respiratory Impact of Electronic Cigarettes And “Low-Risk” Tobacco. Rev. Investig. Clin. 2019, 71, 17–27.
17. Ratajczak, A.; Feleszko, W.; Smith, D.M.; Goniewicz, M. How close are we to definitively identifying the respiratory health effects of e-cigarettes? Expert Rev. Respir. Med. 2018, 12, 549–556.
18. Traboulsi, H.; Cherian, M.; Abou Rjeili, M.; Preteroti, M.; Bourbeau, J.; Smith, B.M.; Eidelman, D.H.; Baglole, C.J. Inhalation Toxicology of Vaping Products and Implications for Pulmonary Health. Int. J. Mol. Sci. 2020, 21, 3495.
19. Cooke, A.; Fergeson, J.; Bulkhi, A.; Casale, T.B. The Electronic Cigarette: The Good, the Bad, and the Ugly. J. Allergy Clin. Immunol. Pract. 2015, 3, 498–505.
20. Pourchez, J.; de Oliveira, F.; Perinel-Ragey, S.; Basset, T.; Vergnon, J.M.; Prévôt, N. Assessment of new-generation high-power electronic nicotine delivery system as thermal aerosol generation device for inhaled bronchodilators. Int. J. Pharm. 2017, 518, 264–269.
21. Casula, L.; Sinico, C.; Valenti, D.; Pini, E.; Pireddu, R.; Schlich, M.; Lai, F.; Maria Fadda, A. Delivery of beclomethasone dipropionate nanosuspensions with an electronic cigarette. Int. J. Pharm. 2021, 596, 120293.
22. Sherwood, C.L.; Boitano, S. Airway epithelial cell exposure to distinct e-cigarette liquid flavorings reveals toxicity thresholds and activation of CFTR by the chocolate flavoring 2,5-dimethypyrazine. Respir. Res. 2016, 17, 57.
23. Clapp, P.W.; Jaspers, I. Electronic Cigarettes: Their Constituents and Potential Links to Asthma. Curr. Allergy Asthma Rep. 2017, 17, 79.
24. Oh, A.Y.; Kacker, A. Do electronic cigarettes impart a lower potential disease burden than conventional tobacco cigarettes? Review on E-cigarette vapor versus tobacco smoke.

Laryngoscope 2014, 124, 2702–2706.

25. Ghosh, A.; Coakley, R.C.; Mascenik, T.; Rowell, T.R.; Davis, E.S.; Rogers, K.; Webster, M.J.; Dang, H.; Herring, L.E.; Sassano, M.F.; et al. Chronic E-Cigarette Exposure Alters the Human Bronchial Epithelial Proteome. Am. J. Respir. Crit. Care Med. 2018, 198, 67–76.
26. Kaur, G.; Pinkston, R.; Mclemore, B.; Dorsey, W.C.; Batra, S. Immunological and toxicological risk assessment of e-cigarettes. Eur. Respir. Rev. 2018, 27, 170119.
27. Ghosh, A.; Coakley, R.D.; Ghio, A.J.; Muhlebach, M.S.; Esther, C.R., Jr.; Alexis, N.E.; Tarran, R. Chronic E-Cigarette Use Increases Neutrophil Elastase and Matrix Metalloprotease Levels in the Lung. Am. J. Respir. Crit. Care Med. 2019, 200, 1392–1401.
28. Quinones Tavarez, Z.; Li, D.; Croft, D.P.; Gill, S.R.; Ossip, D.J.; Rahman, I. The Interplay Between Respiratory Microbiota and Innate Immunity in Flavor E-Cigarette Vaping Induced Lung Dysfunction. Front. Microbiol. 2020, 11, 589501.
29. Clapp, P.W.; Pawlak, E.A.; Lackey, J.T.; Keating, J.E.; Reeber, S.L.; Glish, G.L.; Jaspers, I. Flavored e-cigarette liquids and cinnamaldehyde impair respiratory innate immune cell function. Am. J. Physiol. Lung Cell Mol. Physiol. 2017, 313, L278–L292.
30. Clapp, P.W.; Lavrich, K.S.; van Heusden, C.A.; Lazarowski, E.R.; Carson, J.L.; Jaspers, I. Cinnamaldehyde in flavored e-cigarette liquids temporarily suppresses bronchial epithelial cell ciliary motility by dysregulation of mitochondrial function. Am. J. Physiol. Lung Cell Mol. Physiol. 2019, 316, L470–L486.
31. Hickman, E.; Jaspers, I. Current E-Cigarette Research in the Context of Asthma. Curr. Allergy Asthma Rep. 2020, 20, 62.
32. Lappas, A.S.; Tzortzi, A.S.; Konstantinidi, E.M.; Teloniatis, S.I.; Tzavara, C.K.; Gennimata, S.A.; Koulouris, N.G.; Behrakis, P.K. Short-term respiratory effects of e-cigarettes in healthy individuals and smokers with asthma. Respirology 2018, 23, 291–297.
33. Palamidas, A.; Tsikrika, S.; Katsaounou, P.A.; Vakali, S.; Gennimata, S.A.; Kaltsakas, G.; Gratziou, C.; Koulouris, N. Acute effects of short-term use of e-cigarettes on airways physiology and respiratory symptoms in smokers with and without airway obstructive diseases and in healthy non-smokers. Tob. Prev. Cessat. 2017, 3, 1–8.
34. Kotoulas, S.C.; Pataka, A.; Domvri, K.; Spyratos, D.; Katsaounou, P.; Porpodis, K.; Fouka, E.; Markopoulou, A.; Passa-Fekete, K.; Grigoriou, I.; et al. Acute effects of e-cigarette vaping on pulmonary function and airway inflammation in healthy individuals and in patients with asthma. Respirology 2020, 25, 1037–1045.
35. Eddy, R.L.; Serajeddini, H.; Knipping, D.; Landman, S.T.; Bosma, K.J.; Mackenzie, C.A.; Dhaliwal, I.; Parraga, G. Pulmonary Functional MRI and CT in a Survivor of Bronchiolitis and Respiratory Failure Caused by e-Cigarette Use. Chest 2020, 158, e147–e151.

36. Reddy, A.; Jenssen, B.P.; Chidambaram, A.; Yehya, N.; Lindell, R.B. Characterizing e-cigarette vaping-associated lung injury in the pediatric intensive care unit. Pediatr. Pulmonol. 2021, 56, 162–170.
37. Marczylo, T. How bad are e-cigarettes? What can we learn from animal exposure models? J. Physiol. 2020, 598, 5073–5089.
38. McAlinden, K.D.; Naidu, V.; Sohal, S.S.; Sharma, P. In utero Exposure to Nicotine Containing Electronic Cigarettes Increases the Risk of Allergic Asthma in Female Offspring. Am. J. Physiol. Lung Cell Mol. Physiol. 2020, 319, L1061.
39. Chapman, D.G.; Casey, D.T.; Ather, J.L.; Aliyeva, M.; Daphtary, N.; Lahue, K.G.; van der Velden, J.L.; Janssen-Heininger, Y.M.W.; Irvin, C.G. The Effect of Flavored E-cigarettes on Murine Allergic Airways Disease. Sci. Rep. 2019, 9, 13671.
40. Lim, H.B.; Kim, S.H. Inhallation of e-cigarette Cartridge Solution Aggravates Allergen-induced Airway Inflammation and Hyper-responsiveness in Mice. Toxicol. Res. 2014, 30, 13–18.
41. Bals, R.; Boyd, J.; Esposito, S.; Foronjy, R.; Hiemstra, P.S.; Jiménez-Ruiz, C.A.; Katsaounou, P.; Lindberg, A.; Metz, C.; Schober, W.; et al. Electronic cigarettes: A task force report from the European Respiratory Society. Eur. Respir. J. 2019, 53, 1801151.
42. Bozier, J.; Chivers, E.K.; Chapman, D.G.; Larcombe, A.N.; Bastian, N.; Masso-Silva, J.A.; Byun, M.K.; McDonald, C.F.; Alexander Crotty, L.E.; Ween, M.P. The Evolving Landscape of Electronic Cigarettes: A Systematic Review of Recent Evidence. Chest 2020, 157, 1362–1390.
43. Riise, G.C.; Torén, K.; Olin, A.C. Subjects in a Population Study with High Levels of FENO Have Associated Eosinophil Airway Inflammation. ISRN Allergy 2011, 2011, 792613.
44. Harkins, M.S.; Fiato, K.L.; Iwamoto, G.K. Exhaled nitric oxide predicts asthma exacerbation. J. Asthma 2004, 41, 471–476.
45. Kharitonov, S.A.; Barnes, P.J. Effects of corticosteroids on noninvasive biomarkers of inflammation in asthma and chronic obstructive pulmonary disease. Proc. Am. Thorac. Soc. 2004, 1, 191–199.
46. Taha, H.R.; Al-Sawalha, N.A.; Alzoubi, K.H.; Khabour, O.F. Effect of E-Cigarette aerosol exposure on airway inflammation in a murine model of asthma. Inhal. Toxicol. 2020, 32, 503–511.
47. St Claire, S.; Gouda, H.; Schotte, K.; Fayokun, R.; Fu, D.; Varghese, C.; Prasad, V.M. Lung health, tobacco, and related products: Gaps, challenges, new threats, and suggested research. Am. J. Physiol. Lung Cell Mol. Physiol. 2020, 318, L1004–L1007.
48. Casey, A.M.; Muise, E.D.; Crotty Alexander, L.E. Vaping and e-cigarette use. Mysterious lung manifestations and an epidemic. Curr. Opin. Immunol. 2020, 66, 143–150.

49. Galderisi, A.; Ferraro, V.A.; Caserotti, M.; Quareni, L.; Perilongo, G.; Baraldi, E. Protecting youth from the vaping epidemic. Pediatr. Allergy Immunol. 2020, 31, 66–68.
50. Hernandez, M.L.; Burbank, A.J.; Alexis, N.E.; Rebuli, M.E.; Hickman, E.D.; Jaspers, I.; Guidos, G. Electronic Cigarettes and Their Impact on Allergic Respiratory Diseases: A Work Group Report of the AAAAI Environmental Exposures and Respiratory Health Committee. J. Allergy Clin. Immunol. Pract. 2021, 9, 1142–1151.
51. Entwistle, M.R.; Valle, K.; Schweizer, D.; Cisneros, R. Electronic cigarette (e-cigarette) use and frequency of asthma symptoms in adult asthmatics in California. J. Asthma 2020, 28, 1–7.
52. Clawson, A.H.; Ruppe, N.M.; Nwankwo, C.N.; Blair, A.L. Profiles of Nicotine and Cannabis Exposure among Young Adults with Asthma. Behav. Med. 2020, 23, 1–13.
53. Xie, L.; Rao, D.R.; Harrell, M.B.; Vidot, D.C.; Gelfand, A.; Sterling, K.; Messiah, S.E. Ethnic disparities in the e-cigarette use epidemic and childhood asthma in the US. Pediatr. Pulmonol. 2020, 55, 2498–2500.
54. Han, C.H.; Chung, J.H. Factors associated with electronic cigarette use among adolescents asthma in the Republic of Korea. J. Asthma 2020, 4, 1–9.
55. Alnajem, A.; Redha, A.; Alroumi, D.; Alshammasi, A.; Ali, M.; Alhussaini, M.; Almutairi, W.; Esmaeil, A.; Ziyab, A.H. Use of electronic cigarettes and secondhand exposure to their aerosols are associated with asthma symptoms among adolescents: A cross-sectional study. Respir. Res. 2020, 21, 300.
56. Parekh, T.; Owens, C.; Fay, K.; Phillips, J.; Kitsantas, P. Use of e-Cigarettes and Development of Respiratory Conditions in Women of Childbearing Age. South. Med. J. 2020, 113, 488–494.
57. Han, Y.Y.; Rosser, F.; Forno, E.; Celedón, J.C. Electronic vapor products, marijuana use, smoking, and asthma in US adolescents. J. Allergy Clin. Immunol. 2020, 145, 1025–1028.e6.
58. Kim, C.W.; Jeong, S.C.; Kim, J.Y.; Lee, J.S.; Lee, J.H.; Jo, S.H.; Kim, S.H. Associated factors for depression, suicidal ideation and suicide attempt among asthmatic adolescents with experience of electronic cigarette use. Tob. Induc. Dis. 2020, 18, 85.
59. Ebrahimi Kalan, M.; Bursac, Z.; Behaleh, R.; Jebai, R.; Osibogun, O.; Gautam, P.; Li, W.; Anderson, T.; Rahman, A.; Ward, K.D.; et al. Nicotine-naive adolescents who live with tobacco products users, 2018 Florida Youth Tobacco Survey. J. Addict. Dis. 2021, 39, 265–269.
60. Alqahtani, M.M.; Alanazi, A.M.; Pavela, G.; Dransfield, M.T.; Wells, J.M.; Lein, D.H., Jr.; Hendricks, P.S. Binge Drinking Moderates the Association Between Chronic Lung Disease and E-Cigarette Use. Respir. Care 2021, 66, 936–942.
61. Tran, L.; Tran, P.; Tran, L. A cross-sectional analysis of electronic cigarette use in US adults by asthma status. Clin. Respir. J. 2020, 14, 991–997.

62. Walker, C.J.; Christian, W.J. Estimating the Population Attributable Fraction of Asthma Due to Electronic Cigarette Use and Other Risk Factors Using Kentucky Behavioral Risk Factor Survey Data, 2016–2017. Subst. Use Misuse 2021, 56, 353–358.
63. Gibson-Young, L.; Martinasek, M.; Tamulevicius, N.; Fortner, M.; Alanazi, A.M. Examining electronic nicotine delivery system use and perception of use among college students with and without asthma across the South. J. Am. Coll. Health 2020, 5, 1–7.
64. Alanazi, A.M.M.; Alqahtani, M.M.; Lein, D.H.; Ford, E.W. The relationship between asthma diagnosis and E-Cigarette use among youth and young adults: The mediation effects of anxiety, depression, and impulsivity and the moderation effects of substance use. J. Asthma 2021, 12, 1–9.
65. Xie, W.; Kathuria, H.; Galiatsatos, P.; Blaha, M.J.; Hamburg, N.M.; Robertson, R.M.; Bhatnagar, A.; Benjamin, E.J.; Stokes, A.C. Association of Electronic Cigarette Use with Incident Respiratory Conditions Among US Adults From 2013 to 2018. JAMA Netw. Open 2020, 3, e2020816.
66. Cho, J.H.; Paik, S.Y. Association between Electronic Cigarette Use and Asthma among High School Students in South Korea. PLoS ONE 2016, 11, e0151022.
67. Chung, S.J.; Kim, B.K.; Oh, J.H.; Shim, J.S.; Chang, Y.S.; Cho, S.H.; Yang, M.S. Novel tobacco products including electronic cigarette and heated tobacco products increase risk of allergic rhinitis and asthma in adolescents: Analysis of Korean youth survey. Allergy 2020, 75, 1640–1648.
68. Kim, S.Y.; Sim, S.; Choi, H.G. Active, passive, and electronic cigarette smoking is associated with asthma in adolescents. Sci. Rep. 2017, 7, 17789.
69. Hedman, L.; Backman, H.; Stridsman, C.; Bosson, J.A.; Lundbäck, M.; Lindberg, A.; Rönmark, E.; Ekerljung, L. Association of Electronic Cigarette Use With Smoking Habits, Demographic Factors, and Respiratory Symptoms. JAMA Netw. Open 2018, 1, e180789.
70. Aljandaleh, H.; Bolze, C.; El-Khoury Lesueur, F.; Melchior, M.; Mary-Krause, M. Factors Associated with Electronic Cigarette Use among Young Adults: The French Trajectoires EpidéMiologiques en POpulation (TEMPO) Cohort Study. Subst. Use Misuse 2020, 55, 964–972.
71. Larsen, K.; Faulkner, G.E.J.; Boak, A.; Hamilton, H.A.; Mann, R.E.; Irving, H.M.; To, T. Canadian Respiratory Research Network. Looking beyond cigarettes: Are Ontario adolescents with asthma less likely to smoke e-cigarettes, marijuana, waterpipes or tobacco cigarettes? Respir. Med. 2016, 120, 10–15.
72. Osei, A.D.; Mirbolouk, M.; Orimoloye, O.A.; Dzaye, O.; Uddin, S.M.I.; Dardari, Z.A.; DeFilippis, A.P.; Bhatnagar, A.; Blaha, M.J. The association between e-cigarette use and asthma among never combustible cigarette smokers: Behavioral risk factor surveillance system (BRFSS) 2016 & 2017. BMC Pulm. Med. 2019, 19, 180.

73. Bhatta, D.N.; Glantz, S.A. Association of E-Cigarette Use with Respiratory Disease among Adults: A Longitudinal Analysis. Am. J. Prev. Med. 2020, 58, 182–190.
74. Wills, T.A.; Pagano, I.; Williams, R.J.; Tam, E.K. E-cigarette use and respiratory disorder in an adult sample. Drug Alcohol Depend. 2019, 194, 363–370.
75. Schweitzer, R.J.; Wills, T.A.; Tam, E.; Pagano, I.; Choi, K. E-cigarette use and asthma in a multiethnic sample of adolescents. Prev. Med. 2017, 105, 226–231.
76. Fedele, D.A.; Barnett, T.E.; Dekevich, D.; Gibson-Young, L.M.; Martinasek, M.; Jagger, M.A. Prevalence of and beliefs about electronic cigarettes and hookah among high school students with asthma. Ann. Epidemiol. 2016, 26, 865–869.
77. Wills, T.A.; Choi, K.; Pagano, I. E-Cigarette Use Associated With Asthma Independent of Cigarette Smoking and Marijuana in a 2017 National Sample of Adolescents. J. Adolesc. Health 2020, 67, 524–530.
78. Leavens, E.L.S.; Ford, B.R.; Ojo-Fati, O.; Winkelman, T.N.A.; Vickery, K.D.; Japuntich, S.J.; Busch, A.M. Electronic cigarette use patterns and chronic health conditions among people experiencing homelessness in MN: A statewide survey. BMC Public Health 2020, 20, 1889.
79. Xian, S.; Chen, Y. E-cigarette users are associated with asthma disease: A meta-analysis. Clin. Respir. J. 2021, 15, 457–466.
80. Hua, M.; Sadah, S.; Hristidis, V.; Talbot, P. Health Effects Associated with Electronic Cigarette Use: Automated Mining of Online Forums. J. Med. Internet Res. 2020, 22, e15684.
81. Wang, J.B.; Olgin, J.E.; Nah, G.; Vittinghoff, E.; Cataldo, J.K.; Pletcher, M.J.; Marcus, G.M. Cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms in the Health eHeart Study. PLoS ONE 2018, 13, e0198681.
82. Alanazi, A.M.M.; Alqahtani, M.M.; Pavela, G.; Ford, E.W.; Leventhal, A.M.; Hendricks, P.S. Mental Health and the Association between Asthma and E-cigarette Use among Young Adults in The United States: A Mediation Analysis. Int. J. Environ. Res. Public Health 2020, 17, 8799.
83. Goniewicz, M.L.; Miller, C.R.; Sutanto, E.; Li, D. How effective are electronic cigarettes for reducing respiratory and cardiovascular risk in smokers? A systematic review. Harm Reduct. J. 2020, 17, 91.
84. Gugala, E.; Okoh, C.M.; Ghosh, S.; Moczygemba, L.R. Pulmonary Health Effects of Electronic Cigarettes: A Scoping Review. Health Promot. Pract. 2021, 4, 1524839920985506.
85. Wills, T.A.; Soneji, S.S.; Choi, K.; Jaspers, I.; Tam, E.K. E-cigarette use and respiratory disorders: An integrative review of converging evidence from epidemiological and laboratory studies. Eur. Respir. J. 2021, 57, 1901815.

86. Polosa, R.; Campagna, D.; Sands, M.F. Counseling patients with asthma and allergy about electronic cigarettes: An evidence-based approach. Ann. Allergy Asthma Immunol. 2016, 116, 106–111.

87. Farsalinos, K.E.; Romagna, G.; Tsiapras, D.; Kyrzopoulos, S.; Voudris, V. Characteristics, perceived side effects and benefits of electronic cigarette use: A worldwide survey of more than 19,000 consumers. Int. J. Environ. Res. Public Health 2014, 11, 4356–4373.