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REVIEW

NOVEL INSIGHTS INTO PEDIATRIC ALLERGY AND IMMUNOLOGY

Potential effects of E-cigarettes and vaping on pediatric asthma

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ABSTRACT

Asthma is the most common chronic disease in childhood and exposure to tobacco smoke has been long recognized as a risk factor for its onset as well as for exacerbations and poor disease control. Since the early 2000s, electronic cigarettes have been marketed worldwide as a non-harmful electronic alternative to combustible cigarettes and as a device likely to help stop smoking, and their use is continuously rising, particularly among adolescents. However, several studies have shown that vape contains many different well-known toxicants, causing significant cytotoxic and pro-inflammatory effects on the airways *in-vitro* and in animal models. In humans, a variety of harmful lung effects related to vaping, ranging from bronchoconstriction to severe respiratory distress has been already reported. To investigate the potential effects of vaping in pediatric asthma, we searched relevant published studies in the MEDLINE/PubMed database by combining the adequate Medical Subject Headings terms and key words. At the end of our study selection process, five cross-sectional studies focusing on electronic cigarettes use in adolescents and self-reported asthma and/or other respiratory symptoms, one study focusing on the effects of electronic cigarettes second-hand exposure and one case report were retrieved. These preliminary data support a likely detrimental effect of vaping in asthmatic adolescents. Currently available evidence supports that electronic cigarettes are a potential threat to respiratory health, particularly in adolescents with asthma. High-quality studies on larger population assessing the long-term effects of vape exposure, are urgently needed.

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KEY WORDS: E-cigarette vapor; Smoking; Vaping; Electronic nicotine delivery systems; Asthma.

Electronic cigarettes (EC) and other electronic nicotine delivery systems (ENDS) were introduced into the Chinese market in 2004 (in Europe in 2006 and in the USA in 2007) as a non-harmful electronic alternative to combustible cigarettes (CC) and a device likely to help stop smoking.[1] The aerosol produced by EC is commonly called "*vape*" and appears as denser than that produced by traditional CC. Despite a lack of safety data regarding ENDS, in the last few years a dramatic rise in their diffusion has been registered worldwide, particularly among adolescents:[2] in a recent study from the US, 27.5% of EC users were high school students and 10.5% middle school students[3] and similar data have been reported from other western countries.[4] Adolescents prefer EC to traditional CC mostly because they are discrete and easily concealable, their flavors are attractive and are perceived as a less harmful smoking alternative. Peer and family influence and marketing on the internet also play a significant role.[5] Unfortunately, EC use in adolescents does not decrease the likelihood of CC use, rather, "vaping" is associated with an increased risk of early combustible tobacco use initiation,[6, 7] as confirmed in a recent meta-analysis including more than 8000 adolescents and young adults who were not cigarette smokers at baseline, which demonstrated that those who had ever used EC had a fourfold greater probability of traditional CC smoking initiation.[8] It should also be noted that adolescents are at greater risk to become lifelong tobacco consumers since they are particularly susceptible to nicotine addiction. Moreover, exposure to nicotine in that period of life is particularly dangerous, since nicotine may interfere with the brain development, potentially causing long-term cognitive effects.[9, 10] Even if EC are commonly considered as harmless devices, there is growing evidence of their potential harmful health effects, especially on the lungs. EC-related detrimental effects also include thermal injuries and accidental or suicidal intoxications[11] and the life-threatening risk of EC explosion has been described too.[12] Last but not least, even their efficacy as a smoking cessation device is still controversial since some studies have confirmed their efficacy[13] but others have not.[14] Asthma is defined as a chronic inflammatory disease of the airways characterized by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation.[15] This condition is one of the most common chronic diseases worldwide, affecting more than 300 million people of all ethnic groups and of all ages[16] and is the most common chronic disease in childhood with almost 5-10% of affected children and adolescents.[17, 18] Poor asthma control may be determined by tobacco smoking. Nevertheless, it has been shown that both adult and adolescent asthmatics smoke at least as much as healthy people do[19] or even more so.[20] While a growing amount of evidence has demonstrated *in-vitro* and in animal models a potential cytotoxic as well as the pro-inflammatory effect of vaping on the airway mucosa, such aspects have been scarcely evaluated *in vivo*, especially in asthma. This paper outlines recent data on the topic focusing on adolescents; for the purpose of our work, we will use the general term EC while we will not consider devices characterized by different aerosolization mechanisms such as pod-mods and heat-not-burn devices (Table I).

How do e-cigarettes work?

EC are electronic portable devices that simulate the act of smoking a traditional cigarette without burning tobacco. Several different types of EC are available on the market, all made up of the same three main components: 1) a power source (usually a rechargeable lithium battery); 2) a heating element that vaporizes the solution (the atomizer), including a wick that absorbs the EC liquid (e-liquid) together with a metallic resistance that heats up when the electric current flows through it; 3) a liquid storage unit[21] (Figure 1). EC are activated by the user's inhalation or by manual activation through a button: once activated, the atomizer heats and vaporizes the e-liquid and the resulting aerosol is inhaled by the user through a mouthpiece. Since their introduction on the market, EC have undergone many major structural and functional changes, so that it is possible to identify four EC generations (Figure 2):[22] newer generation EC allow the user to control the composition of the e-liquid, as well as the aerosolization process, by customizing the settings for resistance and power and, consequently, the aerosol temperature.[23] Increasing the aerosol temperature results in a higher amount of generated vape, so that the user can feel a stronger "throat hit" (the sensation felt in the oropharynx during vape inhalation).[24] However, a higher temperature can also change the chemical composition of the inhaled aerosol, potentially increasing the number of toxic substances.[21] Moreover, there is no universal regulation or standards related to EC contents or technical issues. Therefore, many different ENDS and flavors are currently available to the point that, in 2016, 433 EC brands and over 15.500 unique flavors were described.[25] Generally, e-liquids consist of solutions mainly composed by a stabilizing humectant, such as propylene glycol (PG) and/or vegetable glycerin (also known as glycerol) (VG) (80-97% of the e-liquid by weight) and one or more flavoring additives which are used to provide a distinctive

TABLE I.—*Glossary.*

Dabbing	The term comes from "dabs", which indicates cannabis concentrates that can be aerosolized using ENDS
Dripping	Users inhaling vapors not from the electronic cigarette's mouthpiece but directly (the vapor is produced by manually dripping e-liquids onto the device's heating coils, to obtain denser vape)
Dual user	User of both electronic cigarettes and traditional combustible cigarette
E-cigar, e-pipe, e-hookah	ENDS essentially working as electronic cigarettes, but resembling cigars, pipes and hookah respectively
E-cigarette	Electronic cigarettes (EC) are portable battery-powered electronic devices that simulate the act of smoking a traditional cigarette without burning tobacco. Four generations of EC are currently available; newer generations allow the power and resistance settings to be customized and, therefore, the characteristics of the resulting aerosol
ENDS	"Electronic Nicotine Delivery Systems" (ENDS) is a generic term used to identify all the available electronic devices used to deliver nicotine or nicotine-free liquids by inhalation, such as e-cigarettes, e-pipes, e-cigars, pod-mods
EVALI	EVALI stands for "E-cigarette or Vaping use-Associated Lung Injury". Previously known as VAPI (Vaping Associated Pulmonary Illness) or VALI (Vaping Associated Lung Injury), this acronym was introduced in 2019, when many cases of unusual respiratory distress potentially connected to vaping and associated with gastrointestinal and/or constitutional symptoms, were registered in the US, mostly among young college or high school students. Most patients present with respiratory symptoms such as cough, chest pain, and shortness of breath that usually worsen over one to two weeks, with progressive hypoxemia requiring high flow oxygen and, in some cases, mechanical ventilation. EVALI is a diagnosis of exclusion in patients presenting with respiratory distress and a recent history of vaping or dabbing, abnormal chest CT (mainly ground-glass opacities), absence of pulmonary infection or any other alternative plausible diagnoses. EVALI seems to be linked to the use of e-liquids containing THC and vitamin E acetate
Heat-not-burn devices	Electronic devices which generate aerosol, heating up tobacco without burning it
JUUL	Pod-mod resembling a USB flash drive, particularly appreciated by young people
Juuling	The act of using the JUUL pod-mod device; some people use this term as a synonym for vaping
Pod-mods	Miniaturized USB rechargeable vape devices, delivering high concentration of nicotine
Smoker	Combustible cigarette user
Vape	The aerosol produced by ENDS, usually appearing denser than that produced by combustible cigarettes
Vaper	Electronic cigarette user
Vaping	The act of inhaling and exhaling the vapor produced by an electronic cigarette

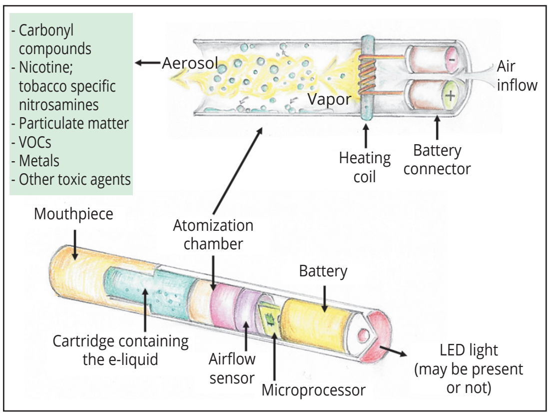
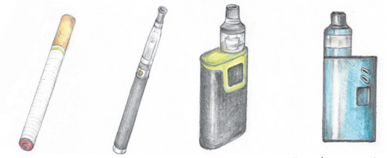


Figure 1.—Schematic of an Electronic Cigarette. Several different types of EC are available on the market. However, every device is provided with at least a battery, an atomizer and a liquid storage unit. In the atomization chamber a wick absorbs the e-liquid and a resistance, connected to the battery, heats and vaporize the liquid, creating a final aerosol, which contains well-known toxic agents. Some of the particles of the aerosol condensate and deposit on the chamber walls.

vape aroma: for example, they can mimic the traditional cigarette flavor (tobacco) or make the vape taste like foods (fruits, sweets, candies) or drinks (coffee, alcoholic drinks). Nicotine may or may not be included in ENDS[21] and, when present, its concentration may range up to more than 50 mg/mL, while a traditional standard cigarette contains 10-14 mg of nicotine. Nevertheless, there is evidence of a discrepancy between the nicotine levels declared on the labels and those experimentally measured.[26-28] Inconsistencies between the real and declared amounts of nicotine as well as those of other e-liquid components have been observed not only in products from different companies but also in liquids from the same brand or batch.[29] Notably, the presence of nicotine in the so-called nicotine-free liquids has also been reported.[30] Moreover, some of the ENDS allow the consumer to add other substanc-



	First generation (Cig-a-Like)	Second generation (Vape-Pen)	Third generation (Box Mod)	Fourth generation (Temperature control Box Mod)
Design	CC Style	Pen Style	Tank Style	Tank Style
Battery Voltage	~ 3,7 - 4,2 V	~ 3,7 - 6 V	~ 6 - 8 V	~ 3 - 8 V
Disposable	✓	×	×	×
Refillable cartridge	×	✓	✓	✓
Components customization	×	×	✓	✓
Voltage-Wattage setup	×	×	✓	✓
Temperature control system	×	×	×	✓

Figure 2.—Features of the four generations of Electronic Cigarettes. Different designs and features of the four generations of EC are shown in the figure. As for the fourth generation, we included only updated versions of the third-generation devices with increased customizability and a temperature control system. We did not include more recent pods resembling flash drives such as the JUUL, since they have a different aerosolization mechanism.

es, such as marijuana and cannabis derivatives. Newer generation "pod-mod" ENDS (such as the "JUUL" device, which looks like a USB flash drive) are becoming increasingly popular among adolescents and the term "*juuling*" is becoming synonymous for "vaping" for some youths:[31] such devices are particularly dangerous, since they use a nicotine formulation derived from nicotine salts, delivering a higher concentration of nicotine with less airway irritation than old generation EC (Table I).[32, 33]

What are the effects of vaping components on the airways?

Even if exposure to EC should be less harmful than conventional cigarette smoke, considering that vaping contains less than the 7000 compounds (at least 70 recognized carcinogens) found in traditional cigarettes,[10] there is growing evidence of the presence of potentially harmful compounds and their detrimental effects by inhalation. PG, VG and EC flavors are included in the FDA "Generally Recognized as Safe" (GRAS) list, but it should be noted that for that purpose those compounds have been tested for ingestion as food additives, while their effects when repetitively inhaled have not been clarified yet.[21]

Apart from the components which are present in e-liquids, other compounds are produced during the heating and atomization process, the safety of which, particularly in the long term, is still under study. Wang *et al.* observed that when PG and VG are heated at a temperature higher than 215 °C, a significant amount of formaldehyde and acetaldehyde is produced, while heating VG to a temperature higher than 270° VG results in acrolein production:[34] these reactive carbonyls are already known for their toxic, irritant and potentially cancerogenic effect on the airways when inhaled, provoking airway constriction, direct damage to airway epithelium and alterations in gene expression.[35, 36] The outcomes of this study have been questioned since the compounds were identified in a significant amount only when the device was overheated, and those temperatures should not be commonly reached with normal usage of EC.[37] Nonetheless, these preliminary data underline the importance of using EC supplied with temperature-control systems ensuring that predefined heat levels of the resistance and the e-liquid are not exceeded. However, Klager *et al.* evaluated the components of vape under typical usage conditions, showing that all the EC emissions tested contained at least one potentially harmful aldehyde.[38] Interestingly, theatrical and other entertainment industry workers exposed to fog produced by heating VG and PG often complain of acute cough and dry throat in the short term, while chronic exposure has been shown to cause chronic work-related chest tightness and wheezing, as well as a lung function reduction in the long term.[39] As far as flavors are concerned, evidence of lung damage has been reported in relation to the inhalation of diacetyl (2,3-butanedione), which is one the most prevalent of the flavoring chemicals found in EC,[38] commonly used to provide a "buttery" or "creamy/sweet" flavor. This compound has been linked to the pathogenesis of irreversible bronchiolitis obliterans in microwave pop-corn producing factory workers exposed to its aerosol ("popcorn worker's lung").[40, 41] Other flavors are considered as potentially harmful when inhaled: some flavors are well-known allergens[42] as in the case of eugenol (clove aroma) and cinnamaldehyde (cinnamon aroma), which are skin sensitizers potentially linked to asthma pathogenesis,[21, 43] others may lead to ocular and airway irritation when inhaled, as in the case of benzaldehyde (fruity aromas such as cherry).[44] Vape contains other toxic agents such as ultra-fine particles, volatile organic compounds (VOCs) (*e.g.* benzene and toluene),[45] and tobacco-specific nitrosamines and metals (such as aluminum, iron, lead, nickel, chromium).[46, 47] Even if the levels of some of these compounds in CC smoke are from 9 to 450-fold higher compared to those in the EC vapor, others like metals are detectable in similar amounts.[46] It is important to take into account that these studies are performed on specific amounts of vapor produced in a standardized process, while real individual exposition to different compounds depends on a wide range of variables such as the voltage of the device, the heat reached by the e-liquid and the user's vape habits.[48] As an example, Talih *et al.* evaluated the amount of nicotine in the aerosol produced by EC puffs with different lengths and speeds and using different voltages, showing that the detected levels of nicotine varied up to 50-fold using different settings.[49] In other words, if on one hand, the same e-liquid may produce different vapes depending on the EC settings and features, on the other, the type of exposure depends also on the smoking behavior of the vaper, making the studies exploring health effects of vaping extremely heterogeneous and far from real-life exposure. Most of the available studies have been carried out *in-vitro* or in animal models, while studies *in vivo* have been focused mainly on adult vapers. Overall, the available evidence agrees on the fact that vaping can exert negative effects on the respiratory system at multiple levels, including direct cytotoxic effect, proinflammatory effects and pathogens defense impairment.[50, 51] Several studies on animal models have shown that exposure to vape causes lung inflammation with increased levels of pro-inflammatory cytokines and enhanced pulmonary oxidative stress.[52, 53] Other studies in mice have shown that EC aerosols may also reduce lung function and cause hyperresponsiveness to methacholine even without significant pulmonary inflammation,[54] as well as promote protease-mediated lung tissue damage similar to what has been found in COPD.[55] Vaping has also been shown to predispose to respiratory infections, mainly by: 1) impairing ciliary function;[56] 2) reducing cough sensitivity;[57] 3) suppressing alveolar macrophage phagocytosis;[58] 4) impairing neutrophil functioning;[59] 5) modifying the expression of immune-related genes and molecules.[60] Notably, Ghosh *et al.* recently performed a proteomic investigation on bronchial brush biopsies and lavage samples from healthy adult non-smokers, CC smokers, and EC users, showing that 300 proteins are differentially expressed in smokers and vapers, with 78 proteins altered in both groups and 113 uniquely altered in vapers (*e.g.* increased levels of CYP1B1, MUC5AC and MUC4 in vapers).[61] Few studies on adult healthy smokers have shown that exposure to EC smoke exerts acute effects on the lungs, resulting in increased total respiratory impedance, respiratory flow resistance, overall peripheral airway resistance and reduced fractional exhaled nitrogen oxide (FeNO).[62] Similar effects have also been reported in never smokers.[63] Concerning lung function as assessed by spirometry, the available data show mixed results, with some studies reporting airflow obstruction and others not: Flouris *et al.*, for example, compared the effects of CC smoke and active and passive EC smoking in a small group of patients (15 never-smokers and 15 smokers), finding airflow obstruction in terms of acute reduction in FEV_1/FVC only in subjects with active CC smoke exposure.[64] In contrast, Ferrari *et al.* found that active nicotine-free EC smoking significantly reduced FEV_1 and $FEF_{25\%}$ in 10 healthy CC smokers but not in 10 non-smokers.[65] Moreover, severe acute lung injury has been reported in relation to EC: a recent meta-analysis collected all vaping-related clinical cases reported in the literature, finding many different acute clinical pictures,[11] the majority of which are referred to previously healthy adolescents and young adults, including hypersensitivity pneumonitis, organizing pneumonia, acute eosinophilic pneumonia, lipoid pneumonia and diffuse alveolar hemorrhage. In 2019 a new condition mainly affecting adolescent and young adult vapers, characterized by severe respiratory distress together with a prevalent lipoid pneumonia pattern, bilateral ground-glass opacities and gastrointestinal and constitutional symptoms,[66] was described in the United States. This condition, actually known as E-Vaping Acute Lung Injury (EVALI), seems to be linked to the inhalation of vitamin E acetate, which is used as a diluent in e-liquids containing tetrahydrocannabinol. However, the role of other possible toxic agents has not been ruled out.[67, 68] Data on the long-term health effects of active EC smoking are not available and the same is true for second and third-hand EC smoke exposure. Nevertheless, it is already known that EC use impairs indoor air quality, with increased concentration of ultrafine particles, 1,2-propanediol, VOCs, polycyclic aromatic hydrocarbons and nicotine, even if at lower levels than in the case of CC smoking.[69, 70] Unsurprisingly, evidence of acute effects of exposure to second-hand EC smoke has already been reported in adults, such as symptoms of nasal and ocular irritation, sore throat, cough, breathlessness and headache[71] with serum cotinine levels equivalent to those seen after CC smoke,[64] but nothing is known about possible effects in children. It should be also considered that nicotine delivered by EC smoke in pregnant women may interfere with fetal lung development,[72] predisposing the upcoming baby to respiratory diseases such as asthma.

What are the potential effects of vaping in asthma?

To further investigate the potential effects of vaping in pediatric asthma, we searched relevant published studies in the MEDLINE/PubMed database by combining the following MeSH (Medical Subject Headings) terms and keywords: “e-cigarettes” or “electronic cigarettes” or “vaping” AND “asthma” or “wheezing.” The original search was run in April 2020 and updated in June 2020. The search strategy included filters for language (English), year of publication (last 10 years) and age of study subjects (0-18 years). All studies had to be published in peer-reviewed journals; we excluded studies not related to the field of interest as well as specific types of articles such as editorials, letters, comments and meeting abstracts. Two authors (MDC and PC) independently screened titles and abstracts and analyzed the full-text version of the selected studies to assess their eligibility. Our first searched retrieved 2047 references; after screening by title and by abstract, 1943 records and 91 records were respectively excluded. Therefore, 13 full-text articles were assessed for eligibility, together with four references not included during the first search and which were selected by fully and accurately scanning the reference list of the selected studies. At the end of our study selection process, five cross-sectional studies focusing on EC use in adolescents and self-reported outcomes (chronic/recurrent respiratory symptoms and/or asthma), one study focusing on second-hand exposure to aerosols from ENDS and one case report were included. Considering the shortage of data in children and adolescents, in the following section we present also the main data coming from *in-vitro* and in-animal models’ studies as well as in adult asthmatics.

Tobacco smoke has long been described as a factor involved in asthma pathogenesis and as a trigger for exacerbation[73] in both adults and children. Moreover, exposure to CC smoke accelerates the decline in lung function and reduces the efficacy of inhaled and oral steroids, and is associated with increased asthma severity.[74, 75] Furthermore, it is known that CC smoking provokes more airway inflammation in smokers with asthma compared to healthy smokers.[76] Considering the available evidence of the effects of vaping on the airways (Table II), as well as the characteristic airway inflammation in asthma, it is likely that exposure to EC may exert similar

TABLE II.—*Main effects of vaping exposure on the airways documented* in-vitro *and in-animal model studies.*

Effects of vaping exposure
• Recruitment of immune cells to the site of exposure
• Inhibition of ciliary beating
• Impaired macrophage and neutrophil function
• Altered host-defense gene expression
• Direct cytotoxicity
• Decreased cough sensitivity
• Promotion of protease-mediated lung tissue
• Increased:
• airway hyperreactivity
• airflow resistance
• pro-inflammatory cytokines secretion
• mucosal secretions
• oxidative stress

effects,[77] and that is what some studies carried out *in-vitro* and in-animal models have tried to analyze. For example, Lim *et al.* showed, in a mice model of asthma induced by sensitization to ovalbumin, that the intratracheal instillation of e-liquid containing nicotine for 10 weeks worsened asthmatic symptoms and increased airway hyperresponsiveness and inflammation by increasing the mucosal infiltration of inflammatory cells including eosinophils and the production of Th-2 cytokines, such as IL-4, IL-5, IL-13[78] and ovalbumin specific IgE. Interestingly, Chapman *et al.* have recently studied the effects of different flavors on the airways in another murine asthma model showing that all EC containing nicotine suppressed airway inflammation without altering airway hyperresponsiveness and remodeling, while flavored EC without nicotine had heterogeneous effects on airway inflammation and airway hyperresponsiveness, dependent upon the specific flavor.[79] As far as studies in humans are concerned, Lappas *et al.* have shown that even a single EC session causes immediate inflammatory and mechanical obstructive effects on peripheral and central airways as assessed by impulse oscillometry impedance, resistance and reactance and FeNO, both in 27 healthy adult smokers and 27 adult smokers with intermittent asthma. The effect was more prominent and long-lasting in smokers with asthma.[80] Regarding the potential role of EC as a device to stop smoking or reduce the detrimental effects of CC on asthma, beneficial effects of EC have been reported in asthmatics smokers switching from traditional cigarettes to EC. A small study on 16 adult smokers with mild to moderate asthma followed for 24 months has suggested that significant and stable improvements in respiratory symptoms, lung function and airway hyperresponsiveness, but not in exacerbation rates, may be achieved after the switch.[81] Similar results were found in dual users.[81] A larger study confirmed a significant improvement in asthma control and quality of life in those switching from CC to EC, but with no significant effect on pulmonary function tests.[82] Our search showed that studies on the effects of active and passive EC smoke exposure in children and adolescents with asthma are still lacking. However, in 2019, Bradford *et al.* reported two cases of asthmatic adolescents with a history of recent and past ENDS use and severe status asthmaticus with hypercarbic respiratory failure who required veno-venous extracorporeal membrane oxygenation (VV-ECMO), suggesting a possible role of ENDS in contributing to the onset of severe exacerbations.[83] It should be noted that both patients had primary and secondary exposure to ENDS, in agreement with preliminary data suggesting that second-hand exposure to ENDS may cause respiratory symptoms, lung dysfunction and bronchoconstriction.[84] As far as the other papers included in our final qualitative synthesis, we retrieved 5 cross-sectional studies with self-reported outcomes, linking EC use to chronic or recurrent respiratory symptoms in adolescents. In particular, in a large survey by Cho *et al.* involving 35,904 South Korean high school students, increased odds of self-reported diagnosis of asthma by a physician in the past 12 months were found in current EC users (in the previous 30 days) compared with never users (OR 2.36; 95% CI, 1.89-2.94; considering three CC smoking categories, within the "never CC" category, OR for "current EC" users was 3.41; 95% CI, 1.79-6.49).[85] In current EC users, increased odds were also found for school absences due to asthma symptoms.[85] In another survey on more than 45.000 adolescents in Hong Kong, Wang *et al.* demonstrated that EC use in the previous month was associated with increased odds of reporting chronic cough or phlegm for three consecutive months (OR 1.28; 95% CI, 1.06-1.56).[86] Similarly, McConnell *et al.* evaluated 2.086 high school students in Southern California, showing that those who were past EC users (those who had used EC, but not in the last 30 days) had nearly twice the risk of reporting chronic cough, phlegm, and/or bronchitis (OR 1.85; 95% CI, 1.37-2.49) while the risk of bronchitic symptoms was increased by 2.02-fold in current users (CI, 1.42-2.88).[87] Moreover, Choi and Bernat reported data from a survey on 36.085 high school students in Florida, showing a higher prevalence of current asthma among EC users as well as an association between past-30-day EC and having an asthma attack in the past 12 months among participants with asthma.[88] In another survey conducted on 6.089 high school students in Hawaii, Schweitzer *et al.* confirmed that current EC use was associated with currently having asthma (OR 1.48; 95% CI 1.26-1.74) and with previously having asthma (OR 1.22; 95% CI 1.07-1.40), independently of cigarette smoking, marijuana use, and other covariates.[89] However, all these studies are limited by their design, which does not allow us to evaluate a causality relationship between respiratory symptoms and vape exposure. It is also unclear whether the reported respiratory symptoms are secondary to chronic airway inflammation and/or to increased susceptibility to infections. Even if we have found no study evaluating the role of vaping in asthma pathogenesis, a significant amount of literature is available on the possible role of many of the toxic agents found in the vape, such as formaldehyde,[90] acrolein,[91] acetaldehyde[92] and benzaldehyde.[93] Last but not least, a higher-than-expected occurrence of EVALI in asthmatic patients has recently been reported,[94] suggesting a synergic effect between airway inflammation due to asthma and lung damage caused by EC smoke exposure.

Conclusions

EC are no longer considered as harmless devices, since it is now well known that vape may contain harmful or potentially harmful constituents, including nicotine. Even if EC globally expose smokers to fewer toxic compounds than CC, considering the growing evidence on EC smoke exposure health risks as well as youth susceptibility to nicotine addiction,[95] in a recent position statement the Forum of International Respiratory Societies (FIRS) strongly recommended that EC should be considered and regulated as tobacco products and included in smoke-free policies, prohibiting their sale to youth worldwide. Also, flavoring should be prohibited in EC and advertising accessible by youths and young adults should be banned.[96] Research on potential harmful health effects of vaping is hampered by the heterogeneity in EC devices, e-liquid composition, the customizable setting for EC use and smoking behavior of the vaper, with different produced aerosols and exposures.[97] Moreover, the long-term effects of vape exposure are not known, therefore the so-called precautionary principle should be considered when regulating the sale and distribution of EC.[98] As far as asthma is concerned, the data on animal models have evidenced a role of vaping in inducing lung inflammation and in reducing lung function, while studies in adults considered only acute effects, showing an immediate obstructive effect after vaping. As far as children and adolescents are concerned, several cross-sectional studies on self-reported studies have shown an association between EC use and chronic bronchitis and/or asthma in adolescents, but more studies are needed to confirm and better elucidate this relationship. Data on the effects of vaping in asthma pathogenesis are lacking, as well as on the effect of second and third-hand exposure in childhood. Notwithstanding the potential threat for children and adolescents represented by EC use epidemics, clinicians treating adolescent asthmatics are not well aware of the potential harmful health effects of vaping and do not discuss the subject with patients and their relatives, nor do they ask questions about EC use at all when evaluating patients with respiratory distress, especially when they are teenagers.[98] In the near future it will be important to improve the education of health care professionals accordingly,[99] involving also pediatricians, who have a fundamental role in smoking habit prevention and counselling, particularly in asthmatic patients. Speaking of which, it should be noted that even children aged 12-14 years are reported to have tried their first EC.[100]

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