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The evolving landscape of e-cigarettes: a systematic review of recent evidence

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The Evolving Landscape of Electronic Cigarettes: A systematic review of recent evidence

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Abstract

Smoking continues to be a burden to economies and healthcare systems across the world. One proposed solution to the problem has been e-cigarettes; however, as a relatively new product in the market, little is known about their potential health impacts. Furthermore, e-cigarettes continue to evolve at a rapid rate, making it necessary to regularly review and synthesize available studies. Whilst e-cigarettes are marketed as a smoking cessation tool by some manufacturers, the reality is that many non-smokers, including youth, are using them. In this review we focus on two major demographics - smokers and non-smokers, and evaluate the most recent data (2018-2019) regarding the potential health effects of e-cigarettes. We assessed peer-reviewed studies on health impacts of e-cigarettes with particular focus on common questions asked by policy makers, clinicians, and scientists: 1. What are the effects of e-cigarettes compared with air/not-smoking?; 2. Is there any direct evidence of harm or benefit to humans?; 3. Is there a risk from second-hand exposure?; 4. What are the risks and/or benefits of e-cigarettes compared with tobacco cigarette use?; 5. Are there risks or benefits to specific populations – people with COPD or asthma, and pregnant women (and their offspring)?; 6. What are the effects of flavoring chemicals?; 7. What are the effects of including nicotine in e-liquids?; 8. How often is nicotine-level labelling incorrect? and 9. What are the risks when e-cigarettes explode?

Abbreviations

EV = e-cigarette vapor
EVE = e-cigarette vapor extract
CS = cigarette smoke
Cig = cigarette
E-cig = e-cigarette
N-EV = nicotine containing e-cigarette vapor
N-EVE = nicotine containing e-cigarette vapor extract
NF-EV = nicotine free e-cigarette vapor
NF-EVE = nicotine free e-cigarette vapor extract
HR = heart rate
BP = blood pressure
NRT = nicotine replacement therapy
eCO = exhaled carbon monoxide
eNO = exhaled nitric oxide
NNN = nitrosamine N-nitrosonornicotine
NNAL = nicotine-derived nitrosamine ketone (4-(methylnitrosamino)-1-(3-pyridyl)-1-butano
EMT = epithelial–mesenchymal transition
CoI = conflict of interest
ROS = reactive oxygen species
iNOS = inducible nitric oxide synthase

EMT = epithelial–mesenchymal transition

Terminology

Vaper – e-cigarette user
Smoker – tobacco cigarette user
Switcher – tobacco cigarette user who has switched to e-cigarettes
Dual user – user of both tobacco cigarettes and e-cigarettes
Vapor – the cloud of aerosol/mist/fog released by an e-cigarette

Introduction

Modern electronic (e)-cigarettes were commercially developed in 2003 as an alternate nicotine delivery device for tobacco smokers with the aim of smoking abstinence[1]. Since then, the use of e-cigarettes worldwide has grown exponentially, with prevalence particularly high in North America[2,3] and England[3,4], while monthly use among adolescents in Poland was estimated at 35%[5](Table 1). It is generally accepted that e-cigarette vapor contains fewer toxicants than tobacco smoke, however, it still contains numerous toxicants due to the presence of nicotine (in the majority of e-liquids), the humectants propylene glycol and glycerin, flavor additives, and the presence of metal contaminants[6,7]. In the absence of data, tobacco regulatory officials have argued for different positions along a spectrum from promotion of e-cigarettes for harm minimization[8] to a regulatory approach which prevents expansion of the nicotine market and favors proven smoking cessation techniques[9]. This has led to a vastly heterogeneous regulatory approach to e-cigarettes[10], with greater regulatory restriction corresponding to lower prevalence of e-cigarette use amongst tobacco smokers[11].

E-cigarettes are used by non-smokers (including never-smokers), smokers who have switched to e-cigarettes, ex-smokers who have taken up vaping, and those using both conventional cigarettes and e-cigarettes. In regards to e-cigarette use as a smoking cessation tool, a recent randomized controlled trial reported that smoking cessation was achieved in more participants using e-cigarettes than in those using conventional nicotine replacement but with the caveat that participants in both groups had regular face-to-face meetings with clinicians[12], support that is not provided to the majority of those seeking to quit smoking, and in particular medical support and knowledge is not provided for e-cigarette use. Furthermore, only 18% of participants using e-cigarettes achieved smoking abstinence, suggesting that e-cigarettes are not the magic cure for tobacco smoking. Additionally, 80% of the e-cigarette users who were tobacco abstinent were continuing to use e-cigarettes 12 months later, suggesting that e-cigarettes may promote continued nicotine dependence. Evidence also suggests that many e-cigarette users continue to smoke cigarettes[13] and the extent of harm minimization, if any, in dual users is unclear. Even more worrisome, use of e-cigarettes may contribute to relapse of smoking in ex-smokers[14,15] and may encourage initiation of tobacco smoking amongst non-smokers[14]. Systematic reviews on the role of e-cigarettes in smoking cessation have been published previously[16,17].

Much needed clarity was brought to the debate surrounding e-cigarettes by the 2018 report of the National Academies of Sciences, Engineering and Medicine (NASEM)[18] which summarized and drew conclusions based upon the current understanding of e-cigarettes at the time. However, the e-cigarette landscape continues to evolve rapidly, with constant development of new devices and an exponentially growing body of scientific literature. Here, we provide a comprehensive update of data on the potential health effects of e-cigarettes since the NASEM report. We have provided focused discussion of the scientific literature that will help inform the general public, healthcare practitioners and policy makers of the effects of e-cigarette use on health.

Table 1: Prevalence of current e-cigarette use amongst the general population (tobacco smokers and non-smokers) in different regions/countries

Region/Country	Prevalence of current e-cigarette use among general population	Population (date of data collection)	Reference

United States of America	5.5% of adults (>18 years old)[A] 5.2% of youth (16-19 years old)[B]	32,320 adults from Population Assessment of Tobacco and Health (PATH) study (2013-2014) 4,045 youth from International Tobacco Control Youth Tobacco and Vaping Survey (2018)	Kasza 2017[2] Hammond 2019[3]
England	5.5% of adults (≥ 16 years old)[C] 2.2% of youth (16-19 years old)[B]	81,063 adults (2014-2017) 3,902 youth from International Tobacco Control Youth Tobacco and Vaping Survey (2018)	Kock 2019[4] Hammond 2019[3]
Canada	2.9% of adults (≥ 15 years old)[D] 3.6% of youth (16-19 years old)[B]	30,291 adults from The Canadian Tobacco, Alcohol and Drugs Survey (2017) 3,853 youth from International Tobacco Control Youth Tobacco and Vaping Survey (2018)	Reid 2019[19] Hammond 2019[3]
Central & Eastern Europe **Poland only**	2.9% of adults[D] 35% of adolescents (15-19 years old)[E]	14,352 University students in the YoUng People E-Smoking Study (2017-2018) 1,978 secondary and technical school students (2015-2016)	Brozek 2019[20] Smith 2019[5]
Australia	1.2% of adults (≥ 18 years old)[F]	22,354 adults in the National Drug Strategy Household Survey	Chan 2019[21]
New Zealand	2.1% of adults (≥ 15 years old)[E]	3,854 adults in the Health and Lifestyles Survey (2016)	Oakly 2019[22]

China	1.2% of adolescents (11-17 years old)[E]	155,117 middle school students in the Global Youth Tobacco Survey (GYTS) China Project (2013-2014)	Xiao 2018[23]
Japan	1.9% of adults (17–71 years old)[E]	4,217 adults (2017)	Tabuchi 2018[24]
Mexico	1% of adolescents (12-17 years old)[G] 1.1% of adults (18-65 years old)[G]	12,436 adolescents and 44,313 adults from the ENCODAT survey (2016)	Zavala-Arciniega 2018[25]

[A] current use was assessed as use of e-cigarettes every day or some days

[B] current use was assessed as use on ≥ 15 days in the past 30 days

[C] current use was assessed as indication of e-cigarette in response to the question "Can I check, are you using any of the following?"

[D] current use was assessed as the answers "Yes, I use e-cigarettes" or "Yes, I smoke traditional cigarettes and e-cigarettes"

[E] current use was assessed as e-cigarette use (including dual use) within the past 30 days

[F] current use was assessed as 'less than monthly' or more regularly

[G] current use was assessed as e-cigarette use on a "daily or less than daily" basis

Methods

The authors conducted a PubMed search in the title or abstract for “electronic cigarette” OR “e-cigarette” OR “electronic nicotine delivery system” OR “personal vaporiser” OR “personal vaporizer”’ published between Feb 2017 until end of May 2019 as well as “e-liquid” AND “nicotine content” until end of May 2019 as these were not covered in the NASEM report. This initial series of searches identified 2687 unique results. Items were removed if they were a duplicate, not in English, meeting abstracts, reviews, editorials, or comments on articles. The authors then screened for articles that specifically answered these common questions: 1 What are the effects of e-cigarettes compared with air/not-smoking?; 2. Is there any direct evidence of harm or benefit to humans?; 3. Is there a risk from second-hand exposure?; 4. What are the risks and/or benefits of e-cigarettes compared with tobacco cigarette use?; 5. Are there risks or benefit to specific populations –people with COPD or asthma, and pregnant women (and their offspring)?; 6. What are the effects of flavoring chemicals? 7. What are the effects of including nicotine in e-liquids?, 8. How often is nicotine-concentration labelling incorrect? and 9. What are the risks when e-cigarettes explode? A total of 225 unique results were included in this review. The authors conducted reviews of the literature and categorized the study types as: 0 – Chemical analysis of e-liquid or vapor; 1 – *in vitro* work; 2 – *ex vivo* work from human samples; 3 – animal model; 4 – case study; or 5 – human study. The authors had a specific focus on elucidating study design for reproducibility in future studies, study results, and any limitations to the studies including any stated conflict of interest. Where authors had authored an article to be assessed, an author who did not participate in the study independently reviewed the study.

The harms of vaping to non-smokers

Numerous studies have investigated the health effects of using e-cigarettes compared with breathing air/not-smoking as well the effects of secondhand exposure to people, animals or cells naïve to tobacco smoke (Table 2 and Supplementary Tables 1-2).

Progression to tobacco smoking

When addressing the role of e-cigarettes in harm minimization for smokers consideration must also be given to any effect e-cigarettes may have in promoting the uptake of tobacco cigarettes among non-smokers i.e. the "gateway effect"[14]. An early meta-analysis of nine studies containing data from 17389 adolescents and young adults showed that e-cigarette use was associated with an increased risk of subsequent initiation of tobacco smoking (odds ratio = 3.5)[26]. The evidence from more recent studies is conflicting. Temporal analysis of youth tobacco smoking and e-cigarette use suggested that at a population level, increasing prevalence of e-cigarette use in the US was associated with a faster decline in tobacco smoking[27]. In contrast, Barrington-Trimis et al[28] and Chaffee et al[29] reported that among never smokers, adolescents who used e-cigarettes were more likely to transition to tobacco cigarette smoking, whether as a dual user or sole tobacco cigarette smoker. This suggests that the effect of e-cigarettes may be different at the population level and the individual level.

Inflammation and immune response

E-cigarette induced toxicity in a range of cells (including lung cells) was well established in the NASEM report[18] and recent studies have reinforced these findings[30-34] with many studies suggesting increased oxidative stress as a cause of toxicity[30,35-37]. Studies have begun to explore beyond toxicity, many with a focus on inflammation. This has proven an interesting area of research as some *in vitro/ex vivo* studies have shown that e-cigarettes can cause the release of pro-inflammatory cytokines[38-41], whilst others have shown that the levels of some cytokines can decrease with certain flavors or exposure times[33,34,42-44]. Mouse studies also showed conflicting cytokine data[45,46]. Human studies showed unchanged cytokines in the gingival crevicular fluid[47] or saliva[48] of e-cigarette users whilst several cytokines were increased in the sulcular fluid of e-cigarette users[49,50].
E-cigarette exposure also impaired *in vitro/ex vivo* viral responses[33] and bacterial clearance by macrophages[39,51] and neutrophils[43,52]. Additional studies showed increased adhesion and colonization of bacteria[52,53]. These findings suggest that use of e-cigarettes may impair the ability to fight infection.

Clinical analysis of cardio-respiratory changes

E-cigarette users have an increased risk of respiratory symptoms compared to never-smokers, and there is a significantly increased risk in ex-smokers who currently use e-cigarettes compared to ex-smokers who do not[54]. Although lung function, as assessed by spirometry, has been shown to be impaired in tobacco naïve e-cigarette users compared to never-smokers[55], a prospective study (with a CoI) of tobacco smoking naïve e-cigarette users showed no change in lung function, respiratory symptoms, and inflammation over 3.5 years of use[56]. The airways of e-cigarette users appear more friable and erythematous during bronchoscopy compared to non-users[57]. Short-term e-cigarette use elevated HR in humans[58,59], while in mice chronic exposure decreased HR and elevated BP[40]. There are conflicting reports as to whether e-cigarette use is associated with cardiovascular disease in population studies[60,61]. Although a very small study in humans (n=9) suggested that e-cigarette use does not affect the metabolic activity of aortic wall tissue[62], another showed that e-cigarette use increased arterial stiffness[63]. Murine models have shown that e-cigarette exposure leads to increased aorta stiffness and constrictor responses[64], increased angiogenesis in heart tissue[65], increased endothelial cell markers[63] and decreased vasodilation[64]. In rodents, long-

term e-cigarette exposure leads to emphysematous lung destruction, loss of pulmonary capillaries[66], reduced small airway function and airway hyperresponsiveness[67]. Furthermore, acute exposure in guinea pigs causes transient bronchoconstriction due to activation of vagal bronchopulmonary C-fiber afferents[68]. There has also been a number of case studies where e-cigarette use is thought to be the cause of respiratory disease (Table 2). Recently, there has been an outbreak of lung injuries associated with e-cigarette use in the United States which has been named EVALI (e-cigarette, or vaping, product use associated lung injury) / VAPI (vaping associated pulmonary illness). Almost 2300 cases of EVALI) had been reported to CDC by late November 2019 with 47 deaths confirmed[69,70]. Cases including one death have now been reported from Canada, Britain, Malaysia, Argentina and Malaysia. Many of the respiratory case reports in Table 2, may also have been early cases of EVALI. Whilst the specific chemical/s responsible for these injurie are yet to be determined with proof of causation, these reports highlight the fact that heating and inhalation of the wrong substance into the lungs can cause serious lung damage and even death[70-72].

Dental Health

Reports suggest that, compared to never-smokers, e-cigarette users are more likely to have gum disease, bone loss around teeth and broken teeth[73-76]. In people with dental implants, e-cigarette use was associated with bone loss around the implant, increased inflammation and higher plaque index and probing depth[49,50]. However, other studies report no difference in tooth health or oral inflammation[47,77]. Conflicting results are also reported regarding the effect of e-cigarette use on the oral microbiome with studies showing higher oral *Candida* carriage rates[78] and greater *Streptococcus mutans* colonization on the enamel surface[79], or no difference in the oral microbiome[80].

Developmental Effects

E-cigarette exposure reduced proliferation and altered morphology in healthy human bone marrow-derived mesenchymal stem cells[37] as well as reducing placental trophoblast invasion and tube formation[81]. In a frog model, flavored e-cigarette exposure with and without nicotine during embryonic development led to craniofacial defects[82]. Similarly, exposure of pregnant mice to e-cigarettes without nicotine led to heavier offspring with more fat mass and body fat percentage suggesting that in utero exposure may lead to metabolic dysfunction in the offspring[83]. In addition, maternal e-cigarette exposure also increased brain neuropeptide Y and iNOS in offspring [84], leading to impaired short-term memory and hyperactivity[85].

Table 2. Studies addressing research question 2: Is there any direct evidence of harm or benefit to humans?

Study types are categorized as: 0 – Chemical analysis of e-liquid or vapor; 1 – *in vitro* work; 2 – *ex vivo* work from human samples; 3 – animal model; 4 – case study; or 5 – human study

REFERENCE	Study type	Text Summary *Methodology, findings, conclusions*	Limitations	Summative data – No of participants, pooled ODDS RATIOS ETC.
Abafalvi 2019[86]	5 General Health	**Survey** Self-reported health effects of vaping among Hungarian adults. Participants were either current smokers (tobacco cigarettes only), ex-smokers that had switched to exclusive e-cig use, or dual-users of both tobacco and e-cigarettes. Smoking and e-cig use was graded according to frequency of use and nicotine content. Exclusion criteria: < 18 years old, never-smokers, invalid/incomplete responses. Less than a quarter of e-cig users (single + dual) reported adverse events related to use but the majority perceived improvements in several health outcomes, such as breathing, quality of sleep and general physical status. Dual users were more likely to report adverse events than exclusive e-cig users (26.2% vs 11.8%). Over 80% of exclusive e-cig users reported improved breathing and overall physical status. Over 65% of dual users reported improvements in breathing and overall physical status. Self-reported improvements were significantly higher among individuals exclusively using e-cigarettes more than a year and people who were past heavy smokers (smoked ≥20 cigarettes per day)	Self-reported effects. Recruited through online e-cig forum websites which may add bias. Confined to 14 specified Acute Events and 10 physiological functions. No data on generation/type of e-cigarette No assessment of health effects in e-cig users who have never smoked.	1042 unique responders. Dual users = 183 E-cig only users = 858 E-cig only users had higher odds of reporting benefits in breathing (OR [95% CI] 3.39 [2.15–5.33]), general physical status (2.28 [1.56–3.32]), mood (2.09 [1.48–2.96]) and quality of sleep (1.70 [1.21–2.41]).
Ahmed 2018[87]	4 Cardiovascular	**Case report** A 41-year-old woman with no significant medical history except daily e-cigarette use developed spontaneous coronary artery dissection (SCAD) while breastfeeding after an uncomplicated delivery. Patient recovered after treatment.	No mention of device, e-juice, or nicotine level used. Postpartum hormonal changes are a known risk factor for SCAD and the use of e-cigarettes may only "potentially" increase the risk.	n = 1
Al-Aali 2018[49]	5 Oral Health \	**Human study** Group 1: Current vapers who reported e-cig use for ≥ 1 year. Group 2: Never smokers (no tobacco in any form) Exclusion: current cigarette smokers, waterpipe smokers, smokeless tobacco smokers. Comparison of dental health around dental implants in male E-cig users vs non-users (no tobacco of any form). E-cig users had more bone loss around the implant but had less bleeding on probing. Inflammation (TNF-α and IL-1B) was considerably higher in sulcular fluid from e-cig users.	Participants in vaper group may have previously smoked. Only studied males. Less than half in each group brushed twice/day. No mention of nicotine or flavors.	E-cig users = 47 Non-users = 45
AlQahtani 2018[50]	5 Oral Health	**Human study** Group 1: Current e-cigarette users. Group 2: Current cigarette users. Group 3: Never-smokers (control). Participants had ≥ one dental implant which had been in service for ≥ 3 years. Plaque index, probing depth, mesial and distal bone loss were all higher in e-cig users than controls, whilst bleeding on probing was lower than in controls. Bone loss and probing depth were higher in cigarette users than e-cig users. Peri-implant sulcular fluid,	Lack of information on what defined an e-cig user. May have been dual users rather than exclusive e-cig users. Although full-mouth periodontal examination was performed, their recordings are not presented in the study.	n = 40 per group

		TNFα, IL-6, and IL-1β were increased in e-cig users compared with non-users. IL-6 was higher in cigarette users than e-cig users.		
Ang 2018[88]	5 Poisonings	**Analysis of telephone enquiries** The UK National Poisons Information Service received 278 enquiries relating to e-cigarette liquid exposure in children between April 2008 and March 2016. There has been a consistent and substantial increase in calls regarding e-liquid exposure in children since 2012, with over 100 calls in 2018. 80% of cases involved children under four. Most cases were minor and asymptomatic and there were no fatalities. In symptomatic cases, the most common symptoms were vomiting and tachycardia.	Complete follow-up data unavailable.	278 enquiries Symptoms present in 63/278 cases
Arter 2019[89]	4 Respiratory	**Case report** An 18-year-old female presented with fever, cough, difficulty breathing and pleuritic chest pain. She developed hypoxic respiratory failure as was diagnosed with acute eosinophilic pneumonia. Cause was attributed to e-cigarettes use as she had begun using e-cigarette with nicotine (6%) two months prior. She vaped for 30min, 5 times/day.	No clear link between e-cigs and AEP. E-cig use was implicated because there was a lack of other causative irritants.	n = 1
Augustin 2018[90]	4 Respiratory	**Case report** A 33-year-old male presented with hemoptysis and subacute respiratory failure. He was later diagnosed with diffuse alveolar hemorrhage syndrome, likely induced by aggressive vaping. Blood found in BAL but little inflammation in serum. No microbiological growth. The patient recovered after steroid treatment and has ceased using e-cigarettes. E-juice used in this case was predominantly PG-based, with nicotine (quantity not specified) and flavorings.	Was treated with antibiotics for pneumonia 2 weeks before visit with minimal improvement. Implied that it was caused by "experiment[ing] with new flavors" but no causality. No mention of flavors used or nicotine level.	n = 1
Bardellini 2018[91]	5 Oral Health	**Human study** Group 1: Former smokers (daily/almost daily use, ≥100 lifetime cigarettes, quit between 6 months and 2 years ago). Group 2: Current e-cigarette users (≥ 6 months of use) E-cigarette was associated with more oral mucosal lesions than former cigarette use. Significant increases in rates of nicotine stomatitis, hairy tongue, and hyperplastic candidiasis were seen in e-cig users compared to former smokers. One case of squamous cell carcinoma was seen in former smokers, but none in e-cig users. No differences in terms of precancerous OMLs (lichen planus, leukoplakia) were found between the two groups.	Definition of smokers is only 'smoked more than 100 cigarettes in lifetime', not very representative of real smokers, could include people who smoked for a short period against heavy e-cig users. No details of use frequency of participants. E-cig users weren't restricted to same device/ E-liquid, which could contribute to variation. E-cig group was almost all men.	n = 45 former smokers, 45 e-cig users
Cant 2017[92]	4 Oral Health	**Case report** A 72-year-old male presented with a severe, necrotic looking oral ulcer attributed to a severe burn caused by electronic cigarette use. He gave a history of a painful area appearing after inhaling strongly on his e-cigarette and suffered extreme discomfort immediately afterwards. The area eventually healed completely.	Patient had smoked 20 conventional cigarettes per day for 30 years.	n = 1
Caponnetto 2017[93]	5 Neurological	**Human study**	**COI: Research supported by Happy Liquid**	34 regular tobacco smokers

		34 smokers (using ≥ 15 cigarettes per day for ≥ 10 years) abstained from smoking for ≥ 12 hours before using one of four e-cigarettes or their usual tobacco cigarette. 1st and 2nd generation devices tested, 0 or 24mg/mL nicotine, mint or tobacco flavor. An initial 15-minute session was followed by ad libitum use throughout the day. No effect was seen on cognitive performance (attention, executive function and working memory).	Current smokers so no true control session was available due to nicotine withdrawal. .	
Carter 2017[94]	4 Respiratory	**Case report** A 35-year-old female presented to the emergency department with sudden-onset dyspnea, extensive pattern of suspected chemical injury was noted in her airways, her injuries were likely suffered secondary to use of an ENDS. Reported daily use of ENDS with 25 mg/mL nicotine.	Case report Patient had several chronic conditions associated with obesity.	n = 1
Chatterjee 2019[95]	3 Vascular 5 Systemic/Blood Marker	**Human Study** 10 Healthy non-smokers Device name: E-puffer eco-disposable Device power settings: 3.7 V 2.7Ω Puff length in seconds: 2s Puff frequency: Puff volume in ml: No of puffs:16-17 Total exposure time: Nicotine concentration (if any): 0 mg/mL List flavors tested: PG/VG ratio: 70:30 Increased serum CRP and ICAM1 after single vape session (blood from participants) Decreased Nitric Oxide was also found in serum (sign of endothelial dysfunction). Increased ROS in HPMVEC treated with EVE	Cell lines used for ROS experiments, would've been better to measure ROS in participants, although maybe not enough oxidant?	N = 10
Chaumont 2018[96]	5 Cardiovascular Systemic/Blood Marker	**Human study** 25 occasional smokers used an e-cigarette containing 50:50 PG:VG, 0 or 3 mg/mL nicotine for ~12 minutes. A "last-generation high-power vaping device" was used with the following settings: Power settings: 60 W (0.4 Ω dual coil). Puff number and frequency: 25 x 4 s puffs, at 30 s intervals. Vaping nicotine free PG/VG mix did not alter microcirculatory function, arterial stiffness, or oxidative stress. Using the nicotine-containing e-cig decreased microcirculatory endothelial-dependent function, increased arterial stiffness, increased blood pressure and heart rate, and increased plasma myeloperoxidase (oxidative stress).	All participants were occasional smokers. Blinding not possible. Nicotine level low, not representative of common levels.	25 participants
Cho 2017[97]	5 Oral Health	**Survey** Responses from the Twelfth Korean Youth Risk Behavior Web-based Survey were analyzed. Responses were divided into never-, former-, past month- and daily E-cig users. E-cig users were further divided into nicotine and nicotine-free groups. Compared to never-users, daily E-cig use was associated with an increased odds of having a cracked or broken tooth in the past 12 months and tongue/inside-cheek pain. Odds were adjusted for potential confounders such as tobacco smoking, economic status, obesity and carbonated drink consumption. ORs were only significant in nicotine e-cig users.	Low numbers of non-nicotine e-cig users gave very wide confidence intervals	65,528 students Daily users = 297 Past month users = 1259 Former users =3484 Cracked tooth Never Use No = 53605, yes = 6519 Former No = 3202, Yes = 646 OR 1.16 (1.04-1.30) * Past Month No = 1005, Yes = 254 OR 1.26 (1.06-1.51) *

				Daily user No = 216, Yes = 81 OR 1.65 (1.19-2.27) ** <u>Tongue/inside-cheek pain</u> Never Use No = 53549, yes = 6575 Former No = 3417, Yes = 431 OR 0.98 (0.86±1.11) Past Month No = 1087, Yes = 172 OR 1.26 1.08 (0.88±1.33) Daily user No = 238, Yes = 59 OR 1.54 (1.05±2.26) *
Demir 2018[98]	4 Auditory	**<u>Case report</u>** A 6-year-old female presented to the emergency clinic after ingesting a bottle of e-liquid (1.2 mg/mL nicotine) 3 – 4 hours previously. The patient was experiencing nausea and vomiting. Her estimated nicotine intake was 8.4 mg. She experienced sudden sensorineural hearing loss (defined as 30+ dB bilateral or unilateral sensorineural hearing loss at 3 consecutive frequencies within 72 hours) 24 hours after consuming the e-liquid. In the absence of any other significant previous history or abnormal test results the authors theorize that the hearing loss is related to the ingestion of e-liquid. The patient's hearing did not recover, and now uses bilateral hearing devices.	Case report Only subjective evidence of normal hearing loss prior to exposure. Methylprednisolone was given yet it is unclear as to whether immunological causes were ruled out.	n = 1
Flower 2017[99]	4 Respiratory	**<u>Case report</u>** A 33-year-old male experienced respiratory bronchiolitis interstitial lung disease (RB-ILD). The patient was a dual user of tobacco and electronic cigarettes, vaping 10 – 15 times per day in addition to smoking 10 tobacco cigarettes. After 3 months of e-cigarette use the patient had poorly defined pulmonary nodules with fluffy parenchyma opacification along the terminal bronchovascular units on their chest CT. The abnormalities resolved after the patient ceased use of e-cigarettes.	No mention of nicotine. Patient "continued to smoke 10 cigs per day" suggests tobacco smoking did not change with e-cig. Therefore, could be caused by increased exposure. Diagnosis of mixed germ cell cancer may reduce generalizability to all e-cig users.	n = 1
Franzen 2018[100]	5 Cardiovascular	**<u>Human study</u>** Crossover study of 15 smokers using an e-cigarette with nicotine, an e-cigarette without nicotine, and tobacco cigarettes in three separate sessions (48 h washout between). Device name: DIPSE, eGo-T CE4 vaporizer Device power settings: 3.3 V, 1.5 Ω 7.26 W Puff length in seconds: 4 s Puff frequency: 1 puff per 30 s Puff volume in ml: N/A No of puffs: 10 puffs Duration and frequency of exposure: Nicotine concentration (if any): 0 and 24 mg/mL nicotine List flavors tested (if any): tobacco flavor PG/VG ratio: 55/35 Participants were followed up for 2 hours after smoking a cigarette or vaping an electronic cigarette. Nicotine-containing EV had similar effects to cigarettes. N-EV increased systolic BP for 45 minutes after exposure. CS increased SBP for 15 minutes after exposure. NF-EV did not affect SBP.	Small group sizes Only used 10 puffs of e-cigarette	n = 4 – 6 per group

		N-EV increased heart rate for 45 minutes after exposure. CS increased SBP for 30 minutes after exposure. NF-EV did not affect SBP. Elevation of pulse wave velocity was independent from mean arterial pressure as well as HR in the N-EV and CS groups.		
Fuller 2018[101]	5 Urine marker	**Human study** 13 non-smoking (≥ 6 months) e-cigarette users (> 24 times per week) 10 non-smoking, non- e-cigarette using controls Analysis of e-cigarette user urine revealed the presence of two carcinogenic compounds, o-toluidine and 2-naphthylamine, at a mean 2.3- and 1.3-fold higher concentration.	Small group sizes Not all participants in e-cig group were long term non-smokers (>12m) No comparison with levels in current smokers. Limited information about e-cigarette use.	Non-smoker non-vaper = 10 E-cig user = 13
Goniewicz 2018[102 514]	5 Systemic/Blood Marker	**Human study** Population Assessment of Tobacco and Health (PATH) Study data were used. Exclusive e-cigarette users, tobacco-only users, and dual users were identified and biomarkers of nicotine exposure and other tobacco-related toxicants (PAHs, VOCs, metals etc.) were assessed. Concentrations of nicotine and toxicants were lower among exclusive e-cigarette users compared to tobacco smokers. Dual users exhibited higher concentrations of exposure to almost all the biomarkers compared to exclusive cigarette smokers and exclusive e-cigarette smokers.	No data on generation/type of e-cigarette	The final analytic sample size was 5105 participants. Smokers = 2411 E-cig– only users = 247 Dual users = 792 Never-users = 1655
Govindarajan 2018[103]	5 Poisonings	**E-cigarette exposure report analysis** Reports of liquid nicotine exposure data from the US National Poison Data System for January 2012 through April 2017 were analyzed. 8269 exposures occurred among children < 6 years. The number of exposures has fallen since Jan 2015 which may be related to introduction of child resistant packing (federal law requiring child-resistant packaging was introduced after July 26, 2016). 20.3 % of children experienced a minor effect, 1.67 % a moderate effect and 0.1 % a major effect. 35.1 % were treated and/or evaluated and released; 1.4 % were admitted to hospital. There was one death of a child aged one year.	Calls to poisons centers are voluntary therefore the NPDS likely underestimates the true incidence of exposures to liquid nicotine. Differentiation of liquid nicotine exposures due to e-cigs themselves versus e-liquids was uncertain –thus limiting the ability to assess impact of child resistant packaging laws that only apply to e-cig liquid containers.	
Hughes 2019[104]	4 Poisonings	**Review of case reports** 265 calls to the Oregon Poison Centre related to e-cigarettes were assessed. Cases were followed up in 4 hours to re-evaluate symptoms of the affected individual. Of the 265 incidents, 193 involved children and 72 involved adults. 72% of the pediatric cases and 61% of the adult cases involved e-liquid refill containers or liquid. 56% of pediatric exposures involved ingestion of refill liquid. Of these, 32% exhibited symptoms after ingesting e-liquid. Only 2 children who were asymptomatic during the initial call became symptomatic on follow-up. Most symptomatic patients were no longer symptomatic on follow-up. 71 specific products/brands were identified as being involved in the incidents. These products had nicotine concentrations ranging from 0 to 60 mg/mL. A variety of flavors of e-liquid were involved, many of which with names that may be attractive to children.	Not all patients or practitioners were able to identify the brand of e-cigarette solution or the concentration. Poison center reporting is voluntary, their data likely underestimates the total number of e-cigarette exposures and associated adverse clinical effects.	n = 265
Itoh 2018[105]	4 Respiratory	**Case report** A 46-year-old healthy male developed respiratory distress, night sweats, fever, and weight loss after 1-month e-cigarette use. He was admitted to hospital after 2 months and diagnosed with acute alveolitis (intra-alveolar fibrosis accompanied with exudate	Single case report, not representative of how all patients would respond, although the author cites two other	n = 1

		containing abundant lipid-laden macrophages, eosinophils, and neutrophils). This was attributed to e-cig induced acute lung injury (ALI) after other testing. Glycerin could be attributed to the abundant lipid-laden macrophages. The patient ceased e-cig use and after pharmacological treatment ALI was resolved.	case studies of acute eosinophilic pneumonia related to e-cig use.	
Khan 2018[106]	4 Respiratory	**Case report** 40 -year-old African American female patient who presented with acute hypoxemic respiratory failure and was diagnosed with organizing pneumonia secondary to e-cigarette use after 1 month of symptoms. History: smoked half a pack a day for more than 10 years, 1 month ago, when she switched to e cigarettes to help her quit.	No evidence given as to why e-cigarettes were decided to be the cause beyond coincidental timing of symptom onset and switching from tobacco cigarettes to E-cigs.	
Lappas 2018[107]	5 Respiratory	**Human study** Participants (current duel e-cigarette and cigarette users) with and without mild asthma used an e-cigarette. Device name: N/A Device power settings: 1.6 Ω, 3.7V Puff length in seconds: 4 s Puff frequency: 30 s puff interval Puff volume in ml: N/A No of puffs: 10 Duration and frequency of exposure: Nicotine concentration (if any): 12 mg/mL List flavors tested (if any): tobacco PG/VG ratio: 46:34 PG:VG **Asthmatics** Both 'healthy' and 'mild asthmatic' groups exhibited increased total impedance and resistance immediately after e-cigarette session. 'Mild asthmatic' group had higher baseline values and more prominent effects immediately after e-cigarette session. FeNO decreased significantly in both groups, 'asthmatic' group took additional 15 minutes to return to baseline levels (≥ double 'healthy' group time).	Participants were all dual e-cigarette and cigarette users. Participants were all smokers No smoke group comparison	Single study of 54 smokers
Marasco 2018[108]	4 Respiratory	**Case report** A 17-year-old male experienced dyspnea, shortness of breath and painful swallowing and was found to have spontaneous pneumomediastinum (mediastinal emphysema) from e-cigarette use. The patient claimed this was his first and only e-cigarette use. Patient was discharged and referred to general thoracic surgery department outpatient clinic after discharge as 48 hr. chest radiograph showed no progression/complication. At 2 months follow up condition appeared to have resolved and patient had stopped vaping.	Single case report, very rare condition, hasn't been reported before from e-cig use.	
Meo 2019[109]	5 Respiratory	**Human study** E-cigarette users defined as using nicotine-containing e-liquid daily for ≥ the past 6 months with current or former cigarette smokers, shisha smokers, and users of other tobacco products excluded. Non-users defined as never tried e-cigarettes, regular cigarettes, or shisha The lung function test parameters that were found to be significantly decreased in e-cigarette users compared to their control group were FEV_1, FEV_1/FVC, FEF25%, FEF50%, FEF75%, FEF25%–75%, FEF75%–85%. No significant difference in FeNO, FVC and PEF between the two groups. The reduced pattern of lung function test parameters exhibits peripheral obstructive airway impairment	Only males assessed Only 6 months of E-cig exposure Were not able to calculate the dose response of e-cigarettes as there was no set "dose" for use	Non-users = 30 Daily users = 30

Miler 2017[110]	4 Oral Health/ Infection	**Case report** A never-smoker who became a vaper experienced a complete resolution of chronic tonsillitis and a marked improvement in tonsil stones after 8 months of e-cigarette use.	Self-reported diagnosis and improvement rather than medical records.	n = 1
Miler 2018[111]	4 Respiratory/Infection	**Case report** A never-smoker adopted an e-cigarette that his wife was using. After a few weeks of vaping liquids containing vegetable glycerin with low levels of nicotine (3 mg/mL) experienced a complete resolution of chronic nasal Staphylococcus aureus infections. Patient periodically exhaled the vapor through nostrils. No VG in E-liquids.	Single patient with no investigation as to what changed in the nasal passages, and no discussion about what else was ruled out as the cause. Authors admit it could be merely coincidental.	n = 1
Mokeem 2018[78]	5 Oral Health/Infection	**Human study** Group 1: Cigarette smokers (≥ 100 cigarettes during their lifetime and reported smoking daily) Group 2: Waterpipe smokers (smoked waterpipe daily for ≥ 15 min for 12 months and had never smoked other tobacco products) Group 3: E-cig users (vaping ≥ 6 times daily since 12 months) Group 4: never-smokers (never used any form of tobacco product). Determination of oral *Candida* species was carried out, followed by identification of yeast species. Microbial colonies were subcultured and then on each sample, PCR was performed without DNA extraction to generate PCR products for 3 different *Candida* species – *C. tropicalis, C. parapsilosis, C. guilliermondii*. Overall oral *Candida* carriage rate was the highest among cigarette smokers, waterpipe smokers and E-cig users compared to never-smokers, with *C. albicans* being the most commonly isolated oral yeast species from all groups. The percentage of patients colonized by *C. albicans* was the highest for cigarette smokers, followed by waterpipe smokers, E-cig users and never-smokers. Prevalence of *C. albicans* was significantly higher in cigarette smokers, waterpipe smokers and E-cig users compared to never-smokers. After stratification for age and among individuals with up to 6 missing teeth, there was no significant differences in oral yeasts carriage between cigarette smokers, waterpipe smokers and E-cig users, but the oral yeasts carriage for these groups was significantly higher than never-smokers. After stratification for daily frequency of tooth brushing and UWSFR, there was no significant differences in oral yeasts carriage between individuals in all groups.	Only male participants. Narrow range of nicotine concentrations in E-liquids. No comparison with nicotine-free E-liquid. Self-perceived oral symptoms taken into account – may not be accurate. Mean number of missing teeth was >4 across all groups suggesting low dental hygiene in this population. No assessment of oral health/hygiene done by a dental clinician. History of oral health not known.	Smokers = 24 Waterpipe smokers = 33 E-cig users = 30 Never-smokers = 32
Morely 2017[112]	4 Poisonings	**Case report** A 32-year-old male ingested nicotine-containing e-liquid while under the influence of alcohol. His ingested approximately 1440 mg of nicotine by drinking 20 mL of e-liquid. The patient suffered brain hypoxia caused by prolonged cardiopulmonary resuscitation. He died after 3 days in intensive care.	Single case report.	n = 1
Motooka 2018[113]	4 Respiratory/General Health	**Case report analysis** Authors analyzed 7,348,357 cases of Adverse Events (AE) in the Food and Drug Administration Adverse Event Reporting System. 27 cases were identified where e-cigs were designated as the primary source of the AE. Causes of AE included dizziness, dyspnea, nausea, chest pain, cough and wheeze. Other, non- MDRA labels included chills, VIIth nerve paralysis and productive cough (1 each).	May be limited by under-reporting and/or miss-classification in the Reporting System. No adjustment for confounding and/or patient medical history.	Reporting Odds Ratios not calculated for e-cigs.
Noble 2017[114]	4 Poisonings	**Case report** A 6-year-old girl with severe toxicity who required intubation after ingestion of e-cigarette liquid containing nicotine. It was estimated that the child ingested approximately 703 mg (35 mg/kg) of nicotine. The patient survived.	The e-cigarette liquid was stored in an Ibuprofen bottle and was (unknowingly) given to the girl by her father.	n = 1

Paik 2018[115]	4 Poisonings/Cardiovascular	**Case report** A male orally ingested a high concentration of liquid bought for e-cigarette use with the intention to commit suicide. The patient presented with bradycardia and hypotension, together with impaired consciousness. He recovered following treatment with atropine and a vasopressor.		n = 1
Park 2018[116]	4 Poisonings/Cardiovascular	**Case reports** A 27-year-old male who ingested about 23 mg/kg of nicotine and a 17-year-old female who ingested about 30 mg/kg of nicotine. Both patients presented seizure-like movement and cardiac arrest. They had metabolic acidosis and transient cardiomyopathy. They were ultimately discharged with a cerebral performance category of 2 and 4, respectively.		
Polosa 2017[117]	5 Respiratory	**Human study** Prospective study of vapers (regular daily for greater than or equal to 3 months) (who had previously not smoked cigarettes) to assess a range of health outcomes including respiratory parameters over 3.5 yrs. No sig differences in lung function including eNO and eCO over 3.5 years in vapers and in vapers compared with non-smokers. no worsening in spirometry (i.e. lung function); No development of respiratory symptoms; No changes in markers of lung inflammation in exhaled air; No signs of early lung damage on high resolution computed tomography (HRCT)	**COI: RP has previously received funding or fees from Philip Morris and other pro-e-cigarette associations.** Only 9 subjects completed study. Young subjects, short term follow-up. Potential for selection bias if those who failed to return for follow-up may have been experiencing adverse effects.	n = 9
Pywell 2018[118]	5 Vascular	**Human study** Measured hand microcirculation in smokers/non-smokers using a Doppler probe, after using a 0 or 24 mg/mL nicotine e-cig (5-minute session). Quitting smoking attributed to 41% reduction in complications post hand surgery, therefore the group did this study. Nicotine containing e-cig significantly reduces hand microcirculation of smokers, no change in non-smokers, thus should be used as a safe replacement prior to surgery	No info on E-cig used. Smoking protocol was not *ad-lib*, followed a 10-inhalation protocol over 5 minutes, with no reference to why these times were chosen other than more sessions made some participants feel nauseous. N is low	Smoker = 7 Non-smoker = 8
Richmond 2018[119]	5 Poisonings/Respiratory	**Survey** 220 cases of harm to children and adolescents reported by survey 135 cases of adolescents seeking treatment for nausea, vomiting, cough, throat irritation or acute nicotine toxicity after inhalation of e-cigarette vapor 85 cases of children presenting to emergency department with nausea, vomiting cough or respiratory irritation after e-liquid ingestion.	Data are self-reported, from survey **Conflict of interest reported "AM reports grants from Canadian Institutes of Health Research during the conduct of the study."**	
Samburova 2018[120];	5 Respiratory/Cancer Markers	**Human study** Measured exhaled aldehydes in breath and retention of aldehydes in respiratory tract (RT) of 12 e-cig users. All participants used BLU e-cigs, and their own personal devices for comparison (CE4, V2, Sigelei, Aspire Cleito). Menthol, Classic, Red tobacco, Bubble-gum, Watermelon, Fruit mix, Butterspot, Vanilla, Snozberry, Vanilla + Fruit flavors used. Puff durations for participants were 3 ± 1 s for each participant. Aldehydes were measured in straight mainstream extracts from e-cig minus exhaled aldehydes to determine RT retention. Results showed increased concentrations of exhaled carbonyls post e-cig use (i.e. Formaldehyde, acetaldehyde, propionaldehyde, benzaldehyde, glyoxal, methyl ethyl ketone). Also showed approx. 97% formaldehyde retention and 91.6±10% acetaldehyde retention in participants.	No smoking histories listed, participants were asked to abstain from e-cig for 2 hours prior, no mention of smoking abstinence. Small sample size Method for determining retention is not accurate, topography of all participants would be different so can't assume they all inhale the same amount as a mainstream sample.	n = 12 participants, 19 samples

		Highest total aldehyde exposure was (14.2 µg·puff−1), (53.2 µg·puff−1), and (12.8 µg·puff−1). Range of Formaldehyde and Acetaldehyde exposure was 0.33–24.4 µg·puff−1. Acrolein exposure was seen in 12 of 19 samples at a range of 0.01 and 1.4 µg·puff.		
Sommerfeld 2018[121]	4 Respiratory	**Case report** An 18-year-old girl with mild intermittent asthma experienced hypersensitivity pneumonia and acute respiratory distress syndrome. She had started to use e-cigarettes over preceding 2 – 3 weeks and had been using them 1 – 2 days prior to onset of symptoms. She was intubated and required vasopressor support but responded rapidly to corticosteroids.	Suggestive but not confirmed diagnosis	
Spindle 2017[58]	5 Cardiovascular	**Human study** Experienced e-cigarette users used an e-cigarette (either *ad libitum* or directed) with or without a "mouthpiece-based computerized systems" used to measure puff topography. Researchers assessed whether presence of the mouthpiece influenced nicotine delivery and other acute effects of e-cig use (heart rate etc.). E-cig use altered heart rate, plasma nicotine content and had subjective effects. Mouthpiece-based computerized systems had no effect on outcomes.		N = 29 experienced e-cigarette users – each with a session with and without mouthpiece addition
Van der Meer 2017[122]	4 Poisonings	**Case report** A 42-year-old male was admitted to the intensive care ward due to cardiac arrest. The patient had ingested highly concentrated liquid nicotine, originating from a vial with liquid for e-cigarettes. When the ambulance personnel found the patient, he did not have a pulse; following CPR and administration of adrenaline his pulse returned. Upon admission, the plasma nicotine level was high at 3.0 mg/L (reference values for a smoker are 0.01-0.05 mg/L) and the patient's neurological function was poor. The patient was treated symptomatically, but eventually died of a postanoxic encephalopathy.	Case report	n = 1

The harms and/or benefits of vaping for smokers

E-cigarettes are proposed as a harm reduction tool for tobacco smokers wishing to quit. Systematic reviews suggest a lack of clear efficacy of e-cigarettes in smoking cessation[16,17]. Although a recent randomized controlled trial demonstrated a higher quit rate-with e-cigarettes compared with nicotine replacement in committed quitters, 80% of those in the e-cigarette group were still vaping at 12 months[123]. Therefore it is vital to determine the potential risks and/or benefits of transitioning to e-cigarettes from tobacco cigarettes (see Supplementary Table 3). Studies have compared the toxicant exposure between e-cigarettes and tobacco cigarettes, assessed by systemic and salivary tobacco-specific nitrosamines, toxicants and metals [102,125-127]. Levels of NNN, carbon monoxide and NNAL were all lower in e-cigarette users than in smokers, suggesting a reduced risk of harm from toxicant exposure if smokers were to switch to e-cigarettes. Goniewicz *et al.* found that toxicant exposures were highest in dual users, but were reduced in e-cigarette users compared to smokers[102]. Smokers and e-cigarette users both had increased toxic metals in urine and blood, but the metals detected in each group were different[102,126,128]. Data from the Behavioral Risk Factor Surveillance System (BRFSS) study showed that smokers and dual users, but not e-cigarette only users, were at increased risk of cardiovascular disease compared to non-smokers[129]. Alzahrani et al. analyzed data from the 2014 and 2016 National Health Interview Surveys and found that daily e-cigarette use resulted in an increased odds of myocardial infarction, suggesting that switching to e-cigarettes may not alleviate risk of cardiovascular disease[130]. In contrast, studies have suggested that switching from tobacco cigarettes to e-cigarettes may improve oral health[131-136] as well as improving blood pressure, HR, eCo, eNO and voice shimmer[137-140]. However, it should be noted that in the majority of the studies where healthy controls were compared to e-cigarette users, these markers were higher than non-smoking, highlighting that long term switching to e-cigarettes instead of smoking may not be superior to smoking cessation using NRT (Supplementary Table 3). Furthermore, numerous studies have shown e-cigarettes to be pro-inflammatory *in vitro* and *in vivo* suggesting that lung pathology in smokers related to a dysregulated inflammation would not necessarily be resolved by switching to e-cigarettes. Therefore, studies comparing e-cigarettes with the more traditional NRT should be considered to identify the best methods to begin the healing process that has been shown to occur in smokers who quit entirely as soon as possible and avoid further damage.

The harms and or benefits of e-cigarette use in high-risk populations

Populations that are especially vulnerable to the effects of tobacco smoking include people with COPD and asthma, and pregnant women and their offspring. Therefore we reviewed recent studies on the effects of e-cigarettes in these vulnerable populations (Supplementary Table 4).

People with COPD

People with COPD who are struggling to quit smoking may consider e-cigarette use as an alternative smoking cessation tool, and some patients with COPD may have already transitioned to dual use or e-cigarette only use. The NASEM review concluded that results were unclear regarding whether e-cigarette use in COPD patients would be beneficial, neutral, or harmful. Recent studies have not further elucidated whether switching to e-cigarettes from traditional tobacco cigarettes would reduce lung inflammation or disease progression in these patients. Traditional NRT is currently the safest option for COPD patients as research to date suggests that e-cigarettes dysregulate inflammation and have adverse effects on the airways of users[124], thus

a negative impact on COPD patients cannot be ruled out. Furthermore, COPD patients are at significant risk of cardiovascular comorbidity which may be worsened by e-cigarette use given its known association with increased cardiovascular events[129,130].

People with Asthma

The prevalence of e-cigarette use in adults with asthma has continued to increase[141]. Currently, some clinicians and researchers advocate that smokers with asthma switch to e-cigarettes to ameliorate the effect of smoking on asthma exacerbations[142,143]. However, the health outcomes of e-cigarette use in people with asthma are unclear. E-cigarette use is more prevalent in adolescents with asthma than without asthma[144-147]. E-cigarette use has been associated with asthma diagnosis and exacerbations[141,148,149], even with second-hand exposure [150]. A recent study in dual users, non-atopic smokers and smokers with mild, intermittent and well-controlled asthma, showed that even a single session of e-cigarette use (using standardized puffing settings) induced pro-inflammatory markers and impaired respiratory mechanics[107]. Importantly, the effects were exaggerated in smokers with asthma[107]. These findings suggest that the negative effects of e-cigarettes may be exaggerated in people with asthma[147] and highlight an important area for further research.

Pregnant woman and their offspring

Many women perceive e-cigarettes to be safer than tobacco smoking during pregnancy[151]. However, there are currently no human experimental or epidemiological studies which assess the potential for maternal e-cigarette use to impact the health of the developing human fetus. Recent research using animal models[152-155] has shown that maternal exposure to e-cigarette vapor can have significant impacts on offspring health, particularly with respect to neurodevelopment[153-155]. In most animal studies, exposures continue after the offspring are born, so clear conclusions regarding *in utero* effects alone are impossible. Regardless, studies have shown that exposure to e-cigarette vapor during pregnancy can alter behavior and cognition in offspring[153,154], and that these changes are often unrelated to the nicotine content of the e-cigarette used.

The health effects of flavor additives in e-cigarettes

The “generally recognized as safe” classification of flavorings is based on ingestion into the gastrointestinal system, not heating until vaporization and inhalation into the lungs[156]. Fruit, candy/dessert, and tobacco-based flavorings are the most popular amongst e-cigarette users[157]. Additional chemical compounds are generated during the vaporization process, and studies suggest adducts may form over time[158], complicating the issue further. Much of the flavoring research to date has focused on toxicity in a range of cells with cinnamon in particular being singled out for its toxic effects[44,159-163] (Supplementary Table 5). Several *in vitro/ex vivo* studies have shown that flavors could also affect cellular function including phagocytosis[162,164,165] and cytokine production[44,162,164,166].

One of the biggest flaws to date with studies into flavorings is the lack of clarity regarding the components of each e-liquid, making reproducibility an issue. The specific ingredients and quantities are rarely listed on the bottles, and are often not accurate when they are listed (Supplementary Table 7). It is therefore important for future research to include identification of the flavor compounds in the tested e-liquids. Studies that have utilized mass spectrometry have identified up to 28 mg/mL of total flavoring in some e-liquids and found that the total amount of flavoring correlated to toxicity[167,168].

The effects of nicotine vs nicotine-free e-cigarettes

Most commercial e-cigarettes/e-liquids include nicotine. The morerecent e-cigarettes utilize nicotine salts to deliver high nicotine levels up to 59 mg/mL Therefore it is important to understand the contribution of nicotine to the health effects of e-cigarettes (Supplementary Table 6). In a large-scale population-based sample, depressive symptoms were associated with e-cigarette use and nicotine concentration[170]. Several human studies have shown that e-cigarettes containing nicotine have greater effects than nicotine-free e-cigarettes. In particular, inhaled vaporized nicotine via an e-cigarette was shown to increase HR, arterial stiffness and flow resistance[171] and in another study to decrease microcirculatory endothelial-dependent function, increase arterial stiffness, increase BP, HR, and plasma myeloperoxidase[96] in occasional smokers. In healthy non-smokers, inhalation of unflavored, nicotine containing vapor increased heart rate variability, a measure of cardiac sympathetic nerve activity[172]. However, in these and other *in vitro, ex vivo*, and animal studies showed other effects regardless of whether nicotine was present or not [152,160,162,164]. In conclusion, future studies should continue to investigate the effects of heated vaporized nicotine as it has been shown to have effects outside of the other ingredients in e-cigarettes.

Incorrect nicotine concentration labeling

Many studies have demonstrated that nicotine concentrations in e-liquids are often considerably different to the concentrations listed on the labels[169,173-184] (Supplementary Table 7). There is no consistent trend in measured concentrations being higher or lower than on the label, yet variation beyond 10% is commonplace[185]. These inaccuracies are unsurprising due to lack of quality control in the e-liquid manufacturing industry, which already suffers from the entrance to the market of poor quality counterfeit versions of major brands. Most alarmingly, in numerous instances, nicotine has been detected in e-liquids that are labeled as "nicotine-free"[169,173-176,181,182,184]. Nicotine in these e-liquids is often at trace amounts, although levels in excess of 20 mg/mL have been reported[169,181,184]. This has implications for health, from a legal standpoint, whereby nicotine containing e-liquids are sold in jurisdictions where the practice is illegal (*eg*. Australia[174]) and, from an addiction standpoint, whereby "vapers" may unwittingly be exposing themselves to an addictive substance.

Harm from exploding e-cigarettes

Another concern regarding e-cigarette use is the potential of these devices to spontaneously explode and cause harm to users with one reported death[186]. Currently, the frequency of e-cigarette explosions remains unclear although many cases have been reported (Supplementary Table 8). These explosions are largely attributed to the overheating of lithium ion batteries in e-cigarettes[187], which could be due to faulty batteries or user modification of batteries. Furthermore, storing the battery in contact with metal objects could create an external short circuit which could also lead to explosions. Case studies have reported e-cigarette explosions in the mouth during use, resulting in oral and facial injuries including tooth avulsions and fractured facial bones[188-191]. Numerous case studies have also reported significant burns due to e-cigarette explosions while being held[192,193] or while in pants or breast pockets[187,194-199]. In some cases, the severity of burns required surgery or skin grafts to aid wound healing.

Relationship between e-cigarette use and cancer risk

Many questions exist about whether e-cigarettes pose a similar, lesser, or greater cancer risk than cigarette smoking. Known carcinogens, formaldehyde and acrolein have been found in e-cigarette vapor[200-202] at lower levels than cigarette smoke[203,204], but it remains unclear if the levels produced are enough to contribute to cancer development. Decreased levels of carcinogens were observed in e-cigarette users *vs* smokers in two studies, however no healthy controls were assessed[127,205]. Schaal *et al*., found increased EMT markers, increased spheroid formation, increased wound healing, proliferation, and increased Sox2 expression in NSCLC cells[206] whilst Tommasi *et al*., found a similar downregulation of tumor suppressor genes in oral cells of both e-cigarette users and smokers[207]. Previous animal studies into the effects of nicotine on cancer development found no evidence of tumorogenicity[208-210], however, the delivery methods used did not involve inhalation of heated nicotine, and existing e-cigarette animal studies were too acute for tumorigenicity studies. Dodemane *et al*., found that nicotine ingestion caused changes which could lead to bladder cancer[211] whilst Fuller *et al*., found bladder carcinogenic compounds were increased in the urine of e-cigarette users vs healthy controls (many were ex-smokers)[101]. Canistro *et al.*, showed urine from e-cigarette-exposed rats caused bacterial mutagenicity using the Ames assay[212]. Further studies are clearly needed to determine the effects of inhalation of heated nicotine, glycerine, glycols, and flavors on cancer development.

Conclusions

The findings in this review established via *in vitro, ex vivo,* and animal models that e-cigarette exposure/use leads to distinct immunological alterations which may contribute to an increased susceptibility to infection. While the presence of nicotine contributes to the detrimental effects of e-cigarettes, recent research has highlighted the potential toxicity of flavor additives. Furthermore, flavor specific findings highlight the need for human studies to consider whether varied flavor use amongst e-cigarette users may unwittingly conceal outcomes. E-cigarette use in humans has been shown to affect the cardiopulmonary system with evidence for reduced lung function and increased BP, HR, and arterial stiffness in comparison with never-smoker/never-vapers. This review did find evidence suggesting that smokers who switch to e-cigarettes may experience harm reduction particularly in relation to cardiopulmonary health but we were unable to find evidence suggesting that these clinical measures returned to the levels of a non-smoker. Additionally, there remains much we do not know about the effects of e-cigarette use, in particular in the long-term, and there is evidence that smokers do not “quit” with e-cigarettes, but rather “switch” to e-cigarette use. Of great concern are the latest studies which show that dual use of e-cigarettes and tobacco cigarettes may put users at increased cardiovascular disease risk over smoking or e-cigarette use alone. There is currently a lack of evidence as to the effects of e-cigarette use in vulnerable populations, such as people with respiratory disease and pregnant women. However, the evidence to date suggests that e-cigarette use may worsen asthma and that maternal use may negatively affect the development of the child. Additional studies are needed in both humans and animal models to determine what health impacts e-cigarettes may have on the many groups who may use them. Overall, this review adds to the conclusion of the NASEM report which indicated that there is increasing emerging evidence that e-cigarette use is not risk free for non-smokers, and that use in smokers as a cessation aid is not preferential to NRT from a health impact perspective.

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