All Dugoni School of Dentistry Faculty Articles                    All Faculty Scholarship

1-1-2020

# Effects of electronic cigarette aerosol exposure on oral and systemic health

Cássio Luiz Coutinho Almeida-da-Silva
*University of the Pacific*, csilva2@pacific.edu

Harmony Matshik Dakafay
*University of the Pacific*, hmatshikdakafay@pacific.edu

Kenji O'Brien
*University of the Pacific*

Dallin Montierth
*University of the Pacific*

Nan Xiao
*University of the Pacific*, nxiao@pacific.edu

*See next page for additional authors*

Follow this and additional works at: https://scholarlycommons.pacific.edu/dugoni-facarticles

 Part of the Dentistry Commons

## Recommended Citation

## Authors

Cássio Luiz Coutinho Almeida-da-Silva, Harmony Matshik Dakafay, Kenji O'Brien, Dallin Montierth, Nan Xiao, and David M. Ojcius

Review Article

# Effects of electronic cigarette aerosol exposure on oral and systemic health

*Cássio Luiz Coutinho Almeida-da-Silva* [a], *Harmony Matshik Dakafay* [a], *Kenji O'Brien* [b], *Dallin Montierth* [b], *Nan Xiao* [a], *David M. Ojcius* [a,*]

[a] *Department of Biomedical Sciences, University of the Pacific, Arthur Dugoni School of Dentistry, San Francisco, CA, USA*
[b] *Dental Surgery Program, University of the Pacific, Arthur Dugoni School of Dentistry, San Francisco, CA, USA*

ARTICLE INFO

ABSTRACT

Conventional cigarette smoke harms nearly every organ of the body and is the leading cause of death in the United States and in the world. Decades of research have associated conventional cigarette smoke with several diseases and death. Heavily marketed, electronic nicotine delivery systems such as electronic cigarettes (e-cigarettes) are available in a variety of flavors and high nicotine concentrations. In 2019, a severe lung disease outbreak linked to e-cigarette use led to several deaths, which was called electronic-cigarette or vaping product use-associated lung injury (EVALI). Even though the trend of e-cigarette use among teens continues to increase, information on the effects of e-cigarette smoke on oral and overall health are still scarce. This review discusses the possible health effects due to unregulated e-cigarette use, as well as the health effects of second-hand smoke and third-hand smoke on non-smokers.

Tobacco leaves are the major materials used to make cigarettes, cigars, and pipe tobacco. Cigarette consumption and exposure is a worldwide issue that has devastating health, social, economic, and environmental consequences. Despite years of efforts to reduce tobacco consumption, the World Health Organization has estimated that tobacco use and exposure is currently responsible for the death of about six million people across the world each year [1]. According to information from the U.S. Department of Health and Human Service, the total economic cost of smoking is over $300 billion a year, which includes the direct cost of medical care and indirect cost of lost productivity [2].

Cigarette smoke contains a deadly mix of more than 7000 chemicals, including hundreds that are toxic and approximately 70 that are known cancer-causing substances [3]. Decades of studies have associated chemicals in tobacco smoke with higher risks of cardiovascular disease, cancer, pneumonia, diabetes mellitus, rheumatoid arthritis, impaired immune functioning, and genetic diseases of the fetus [2,3]. Cigarette smoking also increases the risk of developing

Fig. 1 Examples of different electronic nicotine delivery system (ENDS) commercially available.

orofacial clefts in infants, and alveolar bone loss, periodontal disease, and oral mucosa cancer in adults [3]. In addition, there is increasing evidence showing that smoking increases dental caries in permanent teeth and is a risk factor for dental implant failure [4,5].

Although electronic cigarettes (e-cigarettes) have been described as a healthier substitute to tobacco smoking, the aerosol of e-cigarettes still contains a wide range of deleterious products [6]. Chronic exposure to these substances at a much higher level than in the air remains a great health risk for smokers and people passively exposed to the e-cigarette vapor [7].

## Electronic cigarettes and their impact on smokers' health

E-cigarettes are classified as electronic nicotine delivery system (ENDS) by the U.S. Food and Drug Administration. They are battery-operated devices that were primarily designed to heat nicotine and flavoring containing chemical substances to produce a smokeless vapor called aerosol, which is inhaled by the user [8,9]. The e-cigarette solution in the cartridge is referred to as e-liquid or e-juice and is generally comprised of nicotine, flavor ingredients in propylene glycol, and vegetable glycine. In addition, some vaping devices contain cannabis, which further broadens the composition and appeal of aerosols [10]. The cartridge may also contain heavy metals such as nickel, tin, lead or chrome [11,12]. Even though there are fewer components in e-cigarettes compared to conventional cigarettes, e-cigarettes still contain toxic and cancer-causing residues, such as formaldehyde, acetaldehyde, and acrolein [6].

E-cigarettes are operated by a battery that generates an electrical current that ignites a filament located on an atomizer. The ignited filament evaporates the e-liquid in the cartridge to produce an aerosol. However, ignition of the filament also causes transfer of heavy metals and nanoparticles to the aerosol that can infiltrate the lungs and damage health [11]. Some brands of e-cigarettes contain a sensor that detects the drag and initiates a cascade of events to activate the e-cigarette. When a sensor is not built in, a button that closes the system on the battery and generates the electrical current to power the filament is usually supplied. Depending on the

brand, some devices have a LED light that shows when the device is activated or needs to be recharged [9,13]. Some examples of ENDS devices are shown in Fig. 1.

The design of e-cigarettes rapidly evolved since they were originally manufactured in China in 2003 by the pharmacist Hon Lik. There are four generations of e-cigarettes so far with differences including shape, size and prices [14]. The first generation of e-cigarettes resembled closely conventional cigarette and were made of three components: the battery, and the atomizer which was either combined with or separated of the cartridge. The second generation, called cleoatomizers, operated via a multi-voltage battery, a removable filament and had a larger tank capacity that could be removed to refill with e-liquid [15]. The third-generation devices, called "mods", are characterized by a modified battery with varying voltages, wattage, and power capacity. The fourth generation devices operate with a fixed voltage battery and can have different battery styles and shapes, such as a USB flash drive [13].

E-cigarettes are considered to be safer and healthier compared to conventional cigarettes [16]. Consequently, ENDS use has drastically increased among smokers, including among U.S. youth. Among middle school and high school students, the use of e-cigarettes has continued to increase from 48% to 78% (from 2017 to 2018) [17]. According to a survey with 45,971 U.S. adults and youth, 81% of youth who smoked tobacco products (aged 12–17 years old) reported that their first e-cigarette was flavored [18]. Another study with 150,000 participants showed that 27% of individuals who have ever tried e-cigarettes continued to smoke at least once every 30 days [19]. Regular e-cigarette use was higher in U.S. states with lower cigarette taxes compared with states that have higher cigarette taxes [19].

### Nicotine and its effects on smokers

Nicotine is found in conventional cigarettes and e-cigarettes and is the major chemical component responsible for addiction in tobacco products [3]. According to e-cigarette manufacturers, a single e-cigarette device may contain as much nicotine as a pack of 20 conventional cigarettes [20]. A recent CDC study demonstrated that 99% of the e-cigarettes sold in the U.S. contain nicotine, some labels do not disclose whether they contain nicotine, and some of them contain nicotine

even though they are marketed as 0% nicotine [21]. Using devices that contain nicotine during adolescence can impair parts of the brain responsible for attention, learning, mood, and impulse control. The brain continues to develop until approximately age 25 and every time a new memory is created, or a new skill is learned, stronger synapses are built between neurons. Nicotine can affect the way in which these synapses are formed. Using nicotine during adolescence may also increase the risk for future addiction to other drugs [22]. In fact, a study with 1312 teenagers in Southern California showed that e-cigarette users were more likely to smoke conventional cigarettes after a one-year follow-up. Additionally, participants who used mods smoked >6 times as many cigarettes at follow-up compared with vape pen smokers [23].

### Effects of e-cigarettes on oral health and the oral microbiome

The oral microbiome is the second most abundant and one of the most diverse microbiomes in the body, comprising over 600 species, with distinct subsets predominating at different microenvironments [24]. Under normal and healthy conditions, the oral microbiota is considered as a commensal because it exists in harmony with the individual host [25]. However, under dysbiotic conditions, some bacterial species such as *Porphyromonas gingivalis* can lead to periodontal disease and others, such as *Streptococcus mutans*, can promote dental caries [25]. There is a large body of evidence showing that conventional cigarette smoking is a risk factor for periodontal disease and dental caries [26–29]. However, studies on whether e-cigarettes are risk factors for dental caries and periodontal diseases are still scarce.

The salivary microbiome analysis from 119 participants showed that the abundance of the Gram-negative bacteria *Porphyromonas* and *Veillonella* was higher among e-cigarette users compared with conventional cigarette smokers or never smokers [30]. A pilot study with 20 recruited participants showed statistically significant increase in gingival inflammation when participants switched from smoking conventional cigarettes to e-cigarettes [31]. However, the same study showed that high levels of variation in the levels of the pro-inflammatory cytokines IL-8 and IL-1β made these measurements not conclusive. A more controlled study involving 135 participants evaluated pro-inflammatory markers (IL-1β, IL-6, IFN-γ, TNF-α and MMP-8) in the oral cavity and showed increased levels of these markers in conventional cigarette-smokers compared with never-smokers; however, there were no differences between e-cigarette users and never-smokers [32]. Regarding dental caries, an *in vitro* study shows that the combination of the viscosity of e-liquids and some classes of chemicals in sweet flavors may increase the risk of cariogenic potential. The data available so far must be interpreted with extreme caution, especially because different studies use different brands of e-cigarettes that may have large differences in composition.

### Electronic-cigarette or vaping product use-associated lung injury (EVALI)

It is likely that e-cigarette users can also experience systemic effects due to e-cigarette aerosol components. In recent investigations, the U.S. CDC, U.S FDA and U.S. state health authorities have linked hospitalizations to the use of vaping products [33–35]. An outbreak with many patients showing acute and severe respiratory symptoms has compelled health agencies to conduct studies on e-cigarette or vaping product use-associated lung injury (EVALI).

Symptoms associated with EVALI include chest pain, shortness of breath, fever, nausea, and vomiting. According to the CDC, as of February 18, 2020, a total of 2807 hospitalized cases or deaths were reported from all 50 states, the District of Columbia, Puerto Rico and U.S. Virgin Islands [33–35]. Prevalence among cases of EVALI patients were: 15% were under 18 years of age, 78% (the majority) were between the age of 18 and 34, and 23% were over 34 years old. Hospitalized patients reported using vaping products that contained either nicotine or THC that they obtained from an informal source, shop or a dispensary [33–35]. Screening bronchoalveolar lavage of EVALI patients have pointed to alpha tocopherol, otherwise known as vitamin E, as the potential cause of the disease due to its detection in 94% of patients with EVALI [36]. Analysis by mass spectrometry of vaping products cartridges and pods received from patients showed that vitamin E was present in 80% of THC cartridges [37,38]. As a supplement or an ointment, vitamin E is usually administered orally or applied on the skin and is harmless. However, when used as a diluent of vaping products, it could have toxic effects in the lungs, such as inducing strong inflammation [38]. Fortunately, hospital admissions for patients with EVALI have significantly decreased since the peak of the outbreak in September 2019. In February 2020, the CDC has low numbers of hospitalizations on their database [33–35].

## Second-hand and third-hand smoke and their health impacts in non-smokers

Second-hand smoke is the smoke accidently inhaled by a non-smoker. Smoke and aerosols directly from conventional cigarettes, e-cigarettes, marijuana, hookahs, and the smoke exhaled by smokers are considered second-hand smoke and aerosols. Second-hand smoke and aerosols from cigarettes, e-cigarettes, marijuana, and hookah are toxic and contains cancer-causing agents. Data from 192 countries worldwide showed that 40% of children, 33% of male non-smokers and 35% of female non-smokers were exposed to second-hand smoke in 2004 [39]. In addition, 603,000 deaths were attributed to second-hand smoke, which corresponded to 1% of worldwide fatalities [39]. According to the California Department of Public Health, over 50% of Californians were still exposed to second-hand tobacco smoke in 2018 [40].

Second-hand smoke is harmful to the overall health and can lead to death by ischemic heart disease, lower respiratory infections, asthma and lung cancer [39]. Chemicals from e-cigarette aerosols, such as nicotine and cancer-causing alkaloids, were found to be transferred from a vape shop to a nearby business in a multiple-tenant retail building [41]. Exposure to second-hand marijuana smoke can lead to accumulation of cannabinoid metabolites in bodily fluids, and people experiencing psychoactive effects after such exposure [42]. Second-hand smoke is also dangerous to the general

**Table 1 Harmful health effects due to the use of conventional cigarettes and e-cigarettes.**

| Smoking device | Health effects | References |
|---|---|---|
| Conventional cigarette | **Oral conditions** | |
| | Bad breath, stained teeth and tongue, dulled sense of taste and smell, slow healing after tooth extraction or surgery | [3] |
| | Dental caries | [61,62] |
| | Periodontitis | [63,64] |
| | Cleft lip and palate | [65,66] |
| | Oral cancer | [67] |
| | **Systemic conditions** | |
| | Heart disease and coronary heart disease | [3,68—70] |
| | Stroke | [71] |
| | Cancer (breast, colon, head and neck, lung) | [72—77] |
| | Diabetes | [78] |
| | Chronic obstructive pulmonary disease | [3,79] |
| | Inflammation and decreased immune function | [23,80—82] |
| | Preterm delivery, low birth weight, birth defects, ectopic pregnancy, reduced fertility | [3,83,84] |
| | Rheumatoid arthritis and lupus erythematosus | [85] |
| | Second-hand smoke exposure | [39,40,86,87] |
| | Third-hand smoke exposure | [44,45,88,89] |
| E-cigarette | **Oral conditions** | |
| | Dental caries, toothache, periodontal disease | [90—92] |
| | Oral lacerations, teeth fractures and avulsions due to e-cigarette explosions | [90] |
| | **Systemic conditions** | |
| | Reduced control of attention, learning, mood, and impulse | [22] |
| | EVALI | [36—38] |
| | Second-hand smoke exposure | [41] |
| | Third-hand smoke exposure | [46] |

population but especially children. Some harmful effects to children involve increasing risks of respiratory symptoms, obesity, disorders of the ear, nose, throat and sleep-disorder breathing [43]. Second-hand smoke can infiltrate into other units in a building [3]; therefore it is important to maintain as much smoke-free space as possible. Because second-hand smoke is visible, extensive research has been conducted approaching this issue. However, third-hand smoke is an understudied public health concern and the potential risks to human health are rising.

Third-hand smoke is a relatively new phenomenon that was first described in 2009 [44]. Third-hand smoke is the residue from tobacco smoke gases and particles (from conventional cigarettes, e-cigarettes, and other tobacco products) that cling to nearby surfaces such as clothing, bags, skin, hair and furniture after tobacco product consumption. The residual tobacco smoke pollutants can persist for minutes to months in indoor environments and on surfaces [45]. The exposure to third-hand smoke present in dust, air and surfaces can occur through dust ingestion, dermal absorption and inhalation [45]. Young children are especially vulnerable due to their crawling, hand-to-mouth and exploratory habits. E-cigarettes were shown as a source of third-hand exposure to nicotine that was recovered from windows, walls, floor, wood and metals [46]. Exposure to these residues can cause DNA damage and increase the risk for short-term and long-term health problems, including asthma and cancer [47—49].

Traditional cleaning methods may not be effective in removal of third-hand smoke compounds due to their ability to strongly adhere to surfaces [50]. In fact, it is estimated that

vacuuming and wiping strategies may help to release the residual compounds from surfaces to the air as aerosols [50]. To remove these third-hand smoke residues from surfaces, fabrics and other materials, regular cleaning and/or laundry should be performed.

## Can e-cigarettes help adults quit smoking?

Outside of the U.S. (particularly in the United Kingdom and other parts of Europe), e-cigarettes are viewed very differently. The National Health Services in the UK have embraced e-cigarettes as a harm-reduction strategy and safer alternative to the thousands of chemicals found in conventional cigarettes [51,52]. The UK places limits on the amount of nicotine allowed in their e-cigarettes (up to 20 mg/mL of nicotine [53], whereas the U.S. has no limit (some brands currently have up to 87 mg/mL [54]). These different approaches to e-cigarettes have resulted in a dramatically different teenage e-cigarette rate in the UK, which is only 2% [55,56] compared to 20% in the US [57]. These differences raise obvious questions for the US: Should nicotine levels in e-cigarettes be regulated? Should e-cigarettes be advocated as a safer alternative to traditional cigarettes?

Several studies and systematic reviews support the view that e-cigarettes may be used as a harm-reduction strategy. Hajek et al. [58] conducted a randomized control trial that showed adults who were given e-cigarettes had double the abstinence rate after 1 year (18.8% compared to 9.9%) [58]. In this study patients were randomly assigned to use e-cigarettes
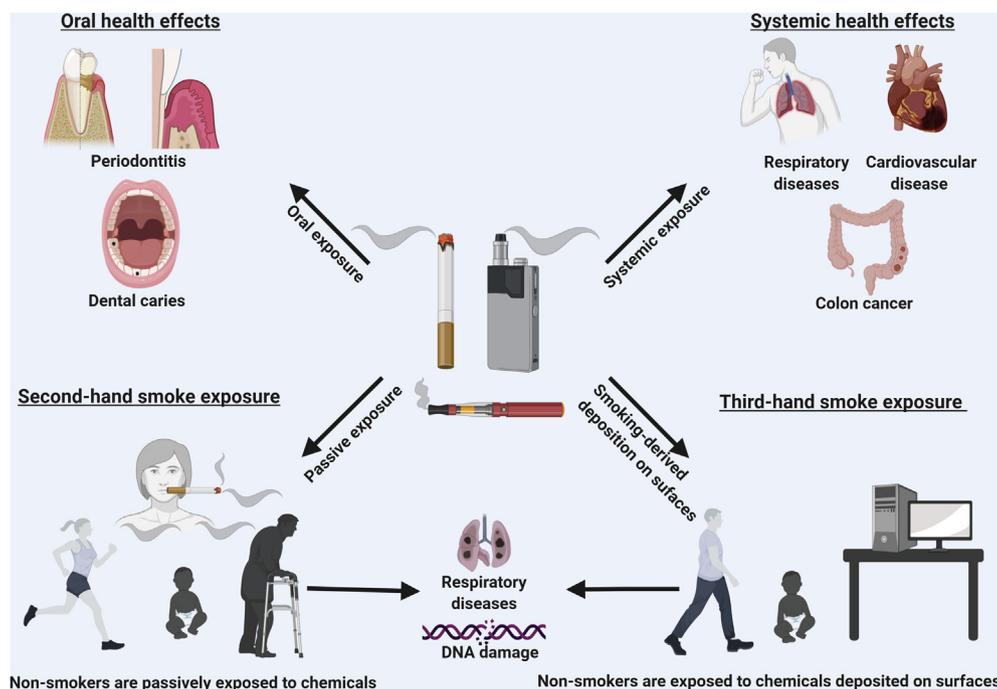
Fig. 2 Scheme illustrating the different ways that smoking or vaping can affect overall health. The figure shows examples of smoking causing harm to oral health and systemic health, as well as second-hand smoke and third-hand smoke being harmful to non-smokers. Smoking is associated with higher risks of developing periodontal disease, caries, and oral cancer. It is also associated with systemic diseases such as respiratory and cardiovascular disease, adverse pregnancy outcomes and cancer. Second-hand smoke can affect non-smokers and may cause asthma and lung cancer. Third-hand smoke (pollutants that cling to furniture and overall surroundings) is dangerous especially to children due to their hand-to-mouth and exploratory habits. This image exemplifies a smoker using a common computer and leaving third-hand smoke to the next user. This image was created in BioRender.com.

or a traditional nicotine-replacement product of their choice (patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strip, and microtabs), and the patients on e-cigarettes had a higher cessation rate, lower levels of nausea, lower levels of phlegm production, but higher throat irritation. Liu et al. [59] conducted a systematic review of 14 different studies and 35,665 participants, finding that the efficacy rate of e-cigarettes ranged from 48.3% to 58.7% for smoking reduction and from 13.2% to 22.9% for smoking cessation [59]. As a cautionary note, Hendlin et al. [60] warned that studies that disclosed financial support from the tobacco industry had higher rates of support for e-cigarettes as a smoking-cessation device (58% compared to 50% [60]). While these results are promising, most of the studies are still limited, and several studies commented that there is a lack of longitudinal data for e-cigarettes due to their short time on the market.

## Final considerations

Smoking can harm nearly every organ of the body [3] and is considered the leading cause of death in the U.S. and the world. Several decades of research have demonstrated the harmful effects of conventional cigarettes. Although there have been several recent reports on the damaging health effects related to e-cigarette use, more research in the future will reveal the full extent of harm due to e-cigarette use. The harmful effects of conventional cigarettes and e-cigarettes use are summarized in Table 1, and a summary of the harmful effects of smoking are shown in Fig. 2. There is no safe level of tobacco smoke, and a better understanding of the risks imposed by tobacco smoke can help in prevention of tobacco-related diseases. Furthermore, second-hand and third-hand smoke are public health issues that should be taken into consideration in order to improve the overall health of the general population.

## Conflict of interest

The authors declare no conflict of interest.

## Acknowledgements

## REFERENCES

[1] Bilano V, Gilmour S, Moffiet T, d'Espaignet ET, Stevens GA, Commar A, et al. Global trends and projections for tobacco use, 1990–2025: an analysis of smoking indicators from the WHO Comprehensive Information Systems for Tobacco Control. Lancet 2015;385:966–76.

[2] Warren GW, Alberg AJ, Kraft AS, Cummings KM. The 2014 surgeon general's report: "The health consequences of smoking–50 years of progress": a paradigm shift in cancer care. Cancer 2014;120:1914–6.

[3] HHS-(Department-of-Health-and-Human-Services). The health consequences of smoking–50 years of progress: a report of the surgeon general. Atlanta, GA: National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.

[4] Jette AM, Feldman HA, Tennstedt SL. Tobacco use: a modifiable risk factor for dental disease among the elderly. Am J Public Health 1993;83:1271–6.

[5] Holmen A, Stromberg U, Magnusson K, Twetman S. Tobacco use and caries risk among adolescentsa longitudinal study in Sweden. BMC Oral Health 2013;13:31.

[6] Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. Circulation 2014;129:1972–86.

[7] Hess IM, Lachireddy K, Capon A. A systematic review of the health risks from passive exposure to electronic cigarette vapour. Public Health Res Pract 2016;26:2621617.

[8] Food-and-Drug-Administration. Vaporizers, E-cigarettes, and other Electronic Nicotine Delivery Systems (ENDS). 2020. [Accessed 19 June 2020].

[9] Breland A, Soule E, Lopez A, Ramoa C, El-Hellani A, Eissenberg T. Electronic cigarettes: what are they and what do they do? Ann N Y Acad Sci 2017;1394:5–30.

[10] Varlet V, Concha-Lozano N, Berthet A, Plateel G, Favrat B, De Cesare M, et al. Drug vaping applied to cannabis: is "Cannavaping" a therapeutic alternative to marijuana? Sci Rep 2016;6:25599.

[11] Hwang C, O'Neil J. E-cigarette use among adolescents. J Nurse Pract 2016;16:453–6.

[12] Nayir E, Karacabey B, Kirca O, Ozdogan M. Electronic cigarette (e-cigarette). J Oncol Sci 2016;2:16–20.

[13] Williams M, Talbot P. Design features in multiple generations of electronic cigarette atomizers. Int J Environ Res Public Health 2019;16:2904.

[14] Clapp PW, Jaspers I. Electronic cigarettes: their constituents and potential links to asthma. Curr Allergy Asthma Rep 2017;17:79.

[15] Zhu SH, Sun JY, Bonnevie E, Cummins SE, Gamst A, Yin L, et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. Tob Control 2014;23(Suppl 3):iii3–9.

[16] Beaglehole R, Bates C, Youdan B, Bonita R. Nicotine without smoke: fighting the tobacco epidemic with harm reduction. Lancet 2019;394:718–20.

[17] Cullen KA, Ambrose BK, Gentzke AS, Apelberg BJ, Jamal A, King BA. Notes from the field: use of electronic cigarettes and any tobacco product among middle and high school students - United States, 2011–2018. MMWR Morb Mortal Wkly Rep 2018;67:1276–7.

[18] Villanti AC, Johnson AL, Ambrose BK, Cummings KM, Stanton CA, Rose SW, et al. Flavored tobacco product use in youth and adults: findings from the first wave of the PATH study (2013–2014). Am J Prev Med 2017;53:139–51.

[19] Levy DT, Yuan Z, Li Y. The prevalence and characteristics of E-cigarette users in the U.S. Int J Environ Res Public Health 2017;14:1200.

[20] Willett JG, Bennett M, Hair EC, Xiao H, Greenberg MS, Harvey E, et al. Recognition, use and perceptions of JUUL among youth and young adults. Tob Control 2019;28:115–6.

[21] National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. Preventing tobacco use among youth and young adults: a report of the surgeon general. In: Department of Health and Human Services CfDCaP. Atlanta (GA): Centers for Disease Control and Prevention (US); 2012.

[22] National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. E-cigarette use among youth and young adults: a report of the surgeon. Atlanta (GA): Centers for Disease Control and Prevention (US); 2016.

[23] Barrington-Trimis JL, Yang Z, Schiff S, Unger J, Cruz TB, Urman R, et al. E-cigarette product characteristics and subsequent frequency of cigarette smoking. Pediatrics 2020;145:e20191652.

[24] Dewhirst FE, Chen T, Izard J, Paster BJ, Tanner AC, Yu WH, et al. The human oral microbiome. J Bacteriol 2010;192:5002–17.

[25] Wade WG. The oral microbiome in health and disease. Pharmacol Res 2013;69:137–43.

[26] Borojevic T. Smoking and periodontal disease. Mater Sociomed 2012;24:274–6.

[27] Leite FRM, Nascimento GG, Scheutz F, Lopez R. Effect of smoking on periodontitis: a systematic review and meta-regression. Am J Prev Med 2018;54:831–41.

[28] Jiang X, Jiang X, Wang Y, Huang R. Correlation between tobacco smoking and dental caries: a systematic review and meta-analysis. Tob Induc Dis 2019;17:34.

[29] Benedetti G, Campus G, Strohmenger L, Lingstrom P. Tobacco and dental caries: a systematic review. Acta Odontol Scand 2013;71:363–71.

[30] Pushalkar S, Paul B, Li Q, Yang J, Vasconcelos R, Makwana S, et al. Electronic cigarette aerosol modulates the oral microbiome and increases risk of infection. iScience 2020;23:100884.

[31] Wadia R, Booth V, Yap HF, Moyes DL. A pilot study of the gingival response when smokers switch from smoking to vaping. Br Dent J 2016;221:722–6.

[32] BinShabaib M, ALHarthi SS, Akram Z, Khan J, Rahman I, Romanos GE, et al. Clinical periodontal status and gingival crevicular fluid cytokine profile among cigarette-smokers, electronic-cigarette users and never-smokers. Arch Oral Biol 2019;102:212–7.

[33] Chatham-Stephens K, Roguski K, Jang Y, Cho P, Jatlaoui TC, Kabbani S, et al. Characteristics of hospitalized and nonhospitalized patients in a nationwide outbreak of E-cigarette, or vaping, product use-associated lung injury - United States, November 2019. MMWR Morb Mortal Wkly Rep 2019;68:1076–80.

[34] Ellington S, Salvatore PP, Ko J, Danielson M, Kim L, Cyrus A, et al. Update: product, substance-use, and demographic characteristics of hospitalized patients in a nationwide outbreak of E-cigarette, or vaping, product use-associated lung injury - United States, August 2019–January 2020. MMWR Morb Mortal Wkly Rep 2020;69:44–9.

[35] Krishnasamy VP, Hallowell BD, Ko JY, Board A, Hartnett KP, Salvatore PP, et al. Update: characteristics of a nationwide outbreak of E-cigarette, or vaping, product use-associated lung injury - United States, August 2019–January 2020. MMWR Morb Mortal Wkly Rep 2020;69:90–4.

[36] Duffy B, Li L, Lu S, Durocher L, Dittmar M, Delaney-Baldwin E, et al. Analysis of cannabinoid-containing fluids in illicit vaping cartridges recovered from pulmonary injury patients: identification of vitamin E acetate as a major diluent. Toxics 2020;8:8.

[37] Blount BC, Karwowski MP, Shields PG, Morel-Espinosa M, Valentin-Blasini L, Gardner M, et al. Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. N Engl J Med 2020;382:697–705.

[38] Heinzerling A, Armatas C, Karmarkar E, Attfield K, Guo W, Wang Y, et al. Severe lung injury associated with use of e-cigarette, or vaping, products-California, 2019. JAMA Intern Med 2020;180:861–9.

[39] Oberg M, Jaakkola MS, Woodward A, Peruga A, Pruss-Ustun A. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. Lancet 2011;377:139–46.

[40] California-Tobacco-Control-Program. Online California adult tobacco survey, 2018. In: Health. CDoP, editor; 2018. Sacramento, CA.

[41] Khachatoorian C, Jacob Iii P, Benowitz NL, Talbot P. Electronic cigarette chemicals transfer from a vape shop to a nearby business in a multiple-tenant retail building. Tob Control 2019;28:519–25.

[42] Holitzki H, Dowsett LE, Spackman E, Noseworthy T, Clement F. Health effects of exposure to second- and third-hand marijuana smoke: a systematic review. CMAJ Open 2017;5:E814–22.

[43] Jimenez-Ruiz CA. Children's second-hand tobacco smoke exposure: the silent killer. Rev Port Pneumol (2006) 2017;23:175–6.

[44] Winickoff JP, Friebely J, Tanski SE, Sherrod C, Matt GE, Hovell MF, et al. Beliefs about the health effects of "thirdhand" smoke and home smoking bans. Pediatrics 2009;123:e74–9.

[45] Acuff L, Fristoe K, Hamblen J, Smith M, Chen J. Third-hand smoke: old smoke, new concerns. J Community Health 2016;41:680–7.

[46] Goniewicz ML, Lee L. Electronic cigarettes are a source of thirdhand exposure to nicotine. Nicotine Tob Res 2015;17:256–8.

[47] Franks AS, Sando K, McBane S. Do electronic cigarettes have a role in tobacco cessation? Pharmacotherapy 2018;38:555–68.

[48] Kioi Y, Tabuchi T. Electronic, heat-not-burn, and combustible cigarette use among chronic disease patients in Japan: a cross-sectional study. Tob Induc Dis 2018;16:41.

[49] Kruse GR, Kalkhoran S, Rigotti NA. Use of electronic cigarettes among U.S. adults with medical comorbidities. Am J Prev Med 2017;52:798–804.

[50] Kuo HW, Rees VW. Third-hand smoke (THS): what is it and what should we do about it? J Formos Med Assoc 2019;118:1478–9.

[51] Campbell K, Coleman-Haynes T, Bowker K, Cooper SE, Connelly S, Coleman T. Factors influencing the uptake and use of nicotine replacement therapy and e-cigarettes in pregnant women who smoke: a qualitative evidence synthesis. Cochrane Database Syst Rev 2020;5:CD013629.

[52] Wilson S, Partos T, McNeill A, Brose LS. Harm perceptions of e-cigarettes and other nicotine products in a UK sample. Addiction 2019;114:879–88.

[53] GOV.UK. E-cigarettes: regulations for consumer products, 2016. https://www.gov.uk/guidance/e-cigarettes-regulations-for-consumer-products/. [Accessed 19 June 2020].

[54] National Academies of Sciences E, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice; Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems. Chapter 4: Nicotine. Washington (DC): National Academies Press (US); 2018.

[55] Booth P, Albery IP, Cox S, Frings D. Survey of the effect of viewing an online e-cigarette advertisement on attitudes towards cigarette and e-cigarette use in adults located in the UK and USA: a cross-sectional study. BMJ Open 2019;9:e027525.

[56] Conner M, Grogan S, Simms-Ellis R, Scholtens K, Sykes-Muskett B, Cowap L, et al. Patterns and predictors of e-cigarette, cigarette and dual use uptake in UK adolescents: evidence from a 24-month prospective study. Addiction 2019;114:2048–55.

[57] Miech R, Johnston L, O'Malley PM, Bachman JG, Patrick ME. Adolescent vaping and nicotine use in 2017–2018 - U.S. national estimates. N Engl J Med 2019;380:192–3.

[58] Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, et al. A randomized trial of E-cigarettes versus nicotine-replacement therapy. N Engl J Med 2019;380:629–37.

[59] Liu X, Lu W, Liao S, Deng Z, Zhang Z, Liu Y, et al. Efficiency and adverse events of electronic cigarettes: a systematic review and meta-analysis (PRISMA-compliant article). Medicine (Baltimore) 2018;97:e0324.

[60] Hendlin YH, Vora M, Elias J, Ling PM. Financial conflicts of interest and stance on tobacco harm reduction: a systematic review. Am J Public Health 2019;109:e1–8.

[61] Iida H, Kumar JV, Kopycka-Kedzierawski DT, Billings RJ. Effect of tobacco smoke on the oral health of U.S. women of childbearing age. J Publ Health Dent 2009;69:231–41.

[62] Krall EA, Abreu Sosa C, Garcia C, Nunn ME, Caplan DJ, Garcia RI. Cigarette smoking increases the risk of root canal treatment. J Dent Res 2006;85:313–7.

[63] Pinto KP, Ferreira CM, Maia LC, Sassone LM, Fidalgo TKS, Silva E. Does tobacco smoking predispose to apical periodontitis and endodontic treatment need? A systematic review and meta-analysis. Int Endod J 2020;53:1068–83.

[64] Aminoshariae A, Kulild J, Gutmann J. The association between smoking and periapical periodontitis: a systematic review. Clin Oral Invest 2020;24:533–45.

[65] Ericson A, Kallen B, Westerholm P. Cigarette smoking as an etiologic factor in cleft lip and palate. Am J Obstet Gynecol 1979;135:348–51.

[66] Martelli DR, Coletta RD, Oliveira EA, Swerts MS, Rodrigues LA, Oliveira MC, et al. Association between maternal smoking, gender, and cleft lip and palate. Braz J Otorhinolaryngol 2015;81:514–9.

[67] Nocini R, Lippi G, Mattiuzzi C. The worldwide burden of smoking-related oral cancer deaths. Clin Exp Dent Res 2020;6:161–4.

[68] de Groh M, Morrison HI. Environmental tobacco smoke and deaths from coronary heart disease in Canada. Chron Dis Can 2002;23:13–6.

[69] Khan RJ, Stewart CP, Davis SK, Harvey DJ, Leistikow BN. The risk and burden of smoking related heart disease mortality among young people in the United States. Tob Induc Dis 2015;13:16.

[70] Heidrich J, Wellmann J, Heuschmann PU, Kraywinkel K, Keil U. Mortality and morbidity from coronary heart disease attributable to passive smoking. Eur Heart J 2007;28:2498–502.

[71] Oshunbade AA, Yimer WK, Valle KA, Clark 3rd D, Kamimura D, White WB, et al. Cigarette smoking and incident stroke in Blacks of the Jackson Heart Study. J Am Heart Assoc 2020;9:e014990.

[72] Hsiao JRHC, Ou CY, Chang CC, Lee WT, Tsai ST, Huang JS, et al. Investigating the health disparities in the association between lifestyle behaviors and the risk of head and neck cancer. Cancer Sci 2020;111:2974–86.

[73] Shimatani K, Ito H, Matsuo K, Tajima K, Takezaki T. Cumulative cigarette tar exposure and lung cancer risk among Japanese smokers. Jpn J Clin Oncol 2020;50:1009–17.

[74] Yu LCJ, Cui X, Wang J. Province-specific smoking-attributable cancer mortality in China 2013. Tob Induc Dis 2020;18:49.

[75] Yoshida K, Gowers KHC, Lee-Six H, Chandrasekharan DP, Coorens T, Maughan EF, et al. Tobacco smoking and somatic mutations in human bronchial epithelium. Nature 2020;578:266—72.

[76] Gram IT, Park SY, Wilkens LR, Haiman CA, Le Marchand L. Smoking and risk of colorectal cancer may differ by anatomical subsite and sex. Am J Epidemiol 2020;189:543—53.

[77] Kispert S, McHowat J. Recent insights into cigarette smoking as a lifestyle risk factor for breast cancer. Breast Cancer 2017;9:127—32.

[78] Szwarcbard N, Villani M, Earnest A, Flack J, Andrikopoulos S, Wischer N, et al. The association of smoking status with glycemic control, metabolic profile and diabetic complications — results of the Australian National Diabetes Audit (ANDA). J Diabetes Complicat 2020;34:107626.

[79] Eisner MD, Balmes J, Katz PP, Trupin L, Yelin EH, Blanc PD. Lifetime environmental tobacco smoke exposure and the risk of chronic obstructive pulmonary disease. Environ Health 2005;4:7.

[80] Mossina A, Lukas C, Merl-Pham J, Uhl FE, Mutze K, Schamberger A, et al. Cigarette smoke alters the secretome of lung epithelial cells. Proteomics 2017;17.

[81] Gaschler GJ, Zavitz CC, Bauer CM, Skrtic M, Lindahl M, Robbins CS, et al. Cigarette smoke exposure attenuates cytokine production by mouse alveolar macrophages. Am J Respir Cell Mol Biol 2008;38:218—26.

[82] Ballweg K, Mutze K, Konigshoff M, Eickelberg O, Meiners S. Cigarette smoke extract affects mitochondrial function in alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol 2014;307:L895—907.

[83] Perry MF, Mulcahy H, DeFranco EA. Influence of periconception smoking behavior on birth defect risk. Am J Obstet Gynecol 2019;220:588.e1—7.

[84] Nakamura A, Pryor L, Ballon M, Lioret S, Heude B, Charles MA. Maternal education and offspring birth weight for gestational age: the mediating effect of smoking during pregnancy. Eur J Publ Health 2020:ckaa076.

[85] Harel-Meir M, Sherer Y, Shoenfeld Y. Tobacco smoking and autoimmune rheumatic diseases. Nat Clin Pract Rheumatol 2007;3:707—15.

[86] DiGiacomo SI, Jazayeri MA, Barua RS, Ambrose JA. Environmental tobacco smoke and cardiovascular disease. Int J Environ Res Publ Health 2018;16:96.

[87] Ahn A, Edwards KM, Grijalva CG, Self WH, Zhu Y, Chappell JD, et al. Secondhand smoke exposure and illness severity among children hospitalized with pneumonia. J Pediatr 2015;167:869—874.e1.

[88] Matt GE, Quintana PJ, Zakarian JM, Fortmann AL, Chatfield DA, Hoh E, et al. When smokers move out and non-smokers move in: residential thirdhand smoke pollution and exposure. Tob Control 2011;20:e1.

[89] Matt GE, Quintana PJE, Zakarian JM, Hoh E, Hovell MF, Mahabee-Gittens M, et al. When smokers quit: exposure to nicotine and carcinogens persists from thirdhand smoke pollution. Tob Control 2016;26:548—56.

[90] Isik Andrikopoulos G, Farsalinos K, Poulas K. Electronic Nicotine Delivery Systems (ENDS) and their relevance in oral health. Toxics 2019;7:61.

[91] Kim SA, Smith S, Beauchamp C, Song Y, Chiang M, Giuseppetti A, et al. Cariogenic potential of sweet flavors in electronic-cigarette liquids. PLoS One 2018;13:e0203717.

[92] Jeong W, Choi DW, Kim YK, Lee HJ, Lee SA, Park EC, et al. Associations of electronic and conventional cigarette use with periodontal disease in South Korean adults. J Periodontol 2020;91:55—64.