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The oral health impact of electronic cigarette use: a systematic review

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ABSTRACT

Introduction: Electronic cigarette (e-cigarette) use is becoming more prevalent and is particularly popular among adolescents and conventional smokers. While the oral health sequelae of conventional smoking are well-established, the impact of e-cigarettes on oral health is still unknown. This study aims to systematically review the available research evidence on the oral health impact of e-cigarette use.

Methods: This systematic review was conducted according to PRISMA guidelines and used the Effective Public Health Practice Project Quality Assessment Tool to evaluate the evidence. Three electronic databases (PubMed, Web of Science, and Embase) were systematically searched for studies including case reports. Two independent reviewers extracted data and synthesized the findings.

Results: Ninety-nine articles were included in this systematic review. Analyses of the articles yielded seven categories based on symptom similarity and/or focus: mouth effects, throat effects, periodontal effects, dental effects, cytotoxic/genotoxic/oncologic effects, oral microbiome effects, and traumatic/accidental injury. The majority of mouth and throat symptoms experienced by e-cigarette users were relatively minor and temporary, with some evidence that conventional smokers who switched to e-cigarettes experienced mitigation of these symptoms. E-cigarette exposure increased the risk for deteriorating periodontal, dental and gingival health as well as changes to the oral microbiome. Extensive dental damage as a result of e-cigarette explosions were described in case reports. Components of e-cigarette vapor have known cytotoxic, genotoxic, and carcinogenic properties.

Conclusions: Although switching to e-cigarettes may mitigate oral symptomatology for conventional smokers, findings from this review suggest that a wide range of oral health sequelae may be associated with e-cigarette use. Well-designed studies to investigate oral health outcomes of e-cigarette use are needed.

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KEYWORDS

ENDS; e-cigarettes; vaping; oral health; systematic review

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<i>Mouth effects</i>	98	Electronic cigarettes, also known as e-cigarettes, are battery-powered electronic devices designed to heat and aerosolize liquids with constituents like propylene glycol, glycerol as humectants, varied flavors, and in most cases, nicotine (McRobbie et al. 2015). Since becoming commercially available in the United States and Europe in 2006 (Rahman et al. 2014), e-cigarette usage has rapidly increased in certain global markets including the United States, Russia, and Germany (Gordon and MacGuill 2012). In the United States, over 15% of adults have ever used an e-cigarette, with the majority being between the ages of 18 and 44 years of age (Schoenborn and Clarke 2017). The products are particularly popular among conventional cigarette users (Syamlal et al. 2016) who may be drawn to the marketing of e-cigarettes as	
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safer alternatives to conventional cigarettes. Reported e-cigarette use among conventional cigarette users range from 15.9% in the United States (Schoenborn and Gindi 2015) to 21.9% in the United Kingdom (Brown et al. 2014).

The deleterious effects of tobacco smoking are numerous and well established. Included among these are conditions affecting oral health, which the World Health Organization describes as any condition, disease or disorder impacting oral, dental, and/or craniofacial tissues (Petersen 2003). Oral health sequelae related to tobacco smoking include oral cancer (Gandini et al. 2008) and periodontal disease (Bergström 2006) leading to tooth loss (Dietrich et al. 2015). E-cigarettes are aggressively marketed as a healthier, cost-effective, and more socially acceptable alternative to conventional cigarettes (Rom et al. 2015), but the impact of these products on oral health is still unknown. In fact, toxicology studies have identified components in e-cigarette products that are concerning. These include nicotine, diacetyl, ultrafine particulate matter, volatile organic compounds like benzene, and heavy metals like nickel, tin, and lead (U.S. Department of Health and Human Services 2016). This study, therefore, aims to systematically review the available research evidence on the oral health impact of e-cigarette use.

Materials and methods

This systematic review was conducted according to PRISMA guidelines (Moher et al. 2009). Studies were evaluated using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool in terms of the evidence provided for oral health outcomes (Thomas et al. 2004). The EPHPP was designed to evaluate quantitative study designs. It is deemed appropriate for systematic reviews (Deeks et al. 2003) with proven content and construct validity (Thomas et al. 2004; Jackson and Waters 2005). The EPHPP has six subscales, including participant selection bias, study design, confounding, blinding, data collection methods, and participant withdrawals and drop-outs. The subscales pertaining to study design, confounding, and blinding are appropriate evaluation metrics for intervention studies but not for nonintervention studies. Therefore, a modified version of the assessment tool excluding these subscales was used for nonintervention studies.

Data collection

Two researchers independently performed a comprehensive search for research literature from three databases: PubMed, Web of Science, and Embase. The following terms were used to search PubMed and Web of Science databases for articles written in English: e-cig*/"electronic cigarette"/ecig AND oral/periodon*/gingivitis/caries/cavities/throat/mouth. Emtree (list of subject headings unique to Embase database) preferred terms were used to search Embase as follows: electronic cigarette/vaping AND mouth disease/mouth/gingivitis/periodontal disease/sore throat/tooth disease. Date ranges were

applied to each database search to include articles up to and including December 2019.

Study selection

After removal of duplicates, the title, abstract, and in some cases, the full manuscript of the 265 resulting articles were reviewed to ensure that the study partly or exclusively concerned oral health effects related to use of e-cigarettes or direct contact with e-cigarette liquid or devices. Oral health was defined as any condition impacting the exterior or interior aspect of the mouth, up to and including the throat.

Both researchers independently analyzed the search results to find potentially eligible studies. Because research on the impact of e-cigarettes on oral health is just beginning to emerge, this review included all designs, including case reports. Studies pertaining to the secondhand exposure of e-cigarettes and studies focused exclusively on dual use (e-cigarettes and combustible cigarettes), however, were excluded. No limitations were placed on type of study participant, e-cigarette device, or e-liquid/flavor used. Recommendations, expert statements, reviews, technical reports, and other non-original papers were excluded; however, reference lists from these documents were closely examined for further articles that fit the inclusion criteria. With the addition of 13 articles identified from the review of reference lists, a total of 99 articles were fully reviewed and included in this systematic review (Figure 1).

Data extraction

Both researchers reviewed the full text of each eligible study: study location, aim/objective, study design, oral health outcome of interest, and conflict of interest (Table 1).

Results

Of the 99 articles, there were eight randomized control (or crossover) trials, 11 quasi-experimental studies, 46 correlational or descriptive studies, 15 case reports, and 19 *in vitro* studies. Publication dates of the reviewed studies were from 2010 to 2019, and the majority of studies with human participants were conducted in Europe or North America. The outcomes were grouped by symptom similarity and/or focus. Categories included: mouth effects, throat effects, periodontal effects, dental effects, cytotoxic/genotoxic/oncologic effects, oral microbiome effects, and traumatic/accidental injury. While several of the studies in this review did not identify or describe the contents of the e-liquid being vaped by cases/participants (Table 1), the underlying assumption in these studies, based on introduction or discussion sections of the articles, is that the e-liquids contained nicotine.

Mouth effects

Thirty-five of the reviewed articles reported symptoms of e-cigarette use pertaining to the lips, tongue, hard palate,

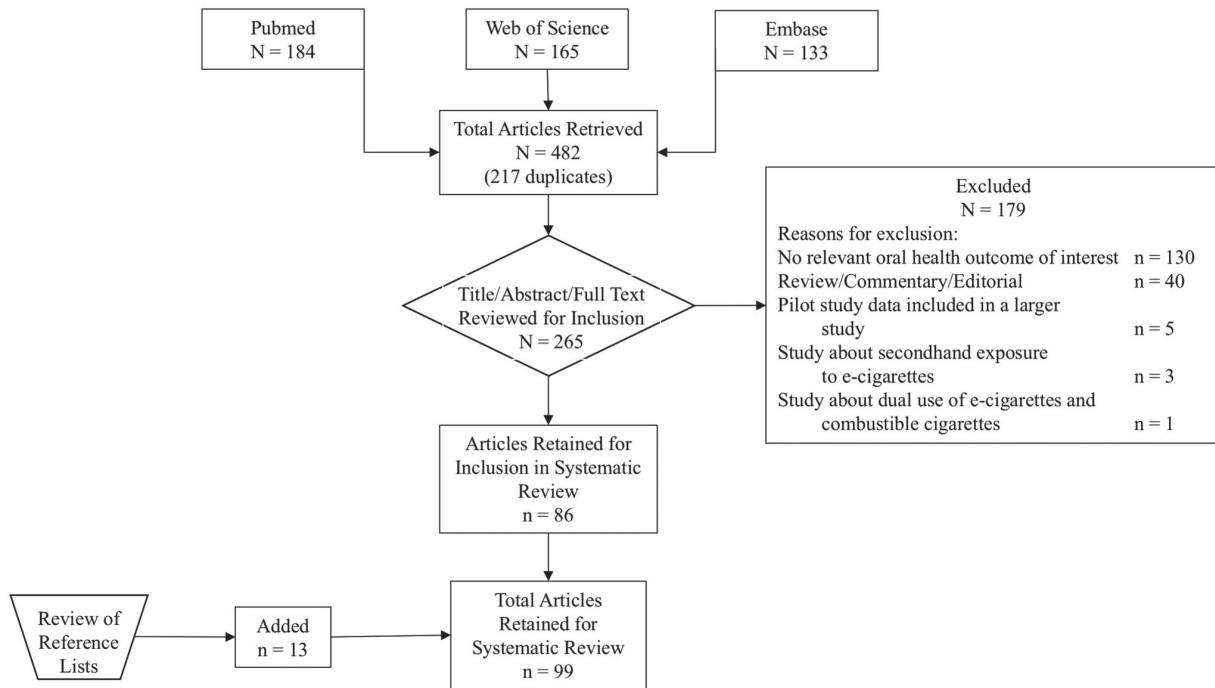


Figure 1. Strategy used to select articles used in analysis.

and/or soft tissue (Table 2). In addition to mouth effects for firsthand e-cigarette users, mouth effects for secondhand exposure were only considered if they involved direct contact with a device or with the e-liquid. The majority of these studies were weak in terms of the quality of evidence provided with regard to oral symptoms since the effects were, by and large, self-reported, descriptive, and without consideration of other confounders. Commonly reported mouth symptoms related to e-cigarette use or direct e-liquid exposure included dryness (Etter 2010; Hua et al. 2013; Adriaens et al. 2014; Farsalinos et al. 2014; Polosa et al. 2014; McRobbie et al. 2015; Baweja et al. 2016; Cravo et al. 2016; Gomes et al. 2016; Li et al. 2016; Rahman et al. 2016; Stein et al. 2016; Holliday et al. 2019; King et al., 2019; Lewek et al., 2019), burning (Nides et al. 2014; Li et al. 2016), irritation (Bullen et al. 2010; Caponnetto, Campagna et al. 2013b; Dawkins et al. 2013; Hua et al. 2013; Adriaens et al. 2014; Dawkins and Corcoran 2014; Nides et al. 2014; Polosa et al. 2014; Hajek et al. 2015; Oncken et al. 2015; Hughes and Hendrickson 2019; Hajek et al., 2019; King et al., 2019), bad taste (Etter 2010; Adriaens et al. 2014), bad breath (Baweja et al. 2016), pain/discomfort (Cravo et al. 2016; Cho 2017; Holliday et al. 2019).

Researchers for six of the studies noted that oral symptomatology was decreased in e-cigarette users compared to conventional smokers. Adriaens et al. (2014) found that e-cigarette users had significantly less adverse complaints and more positive symptoms compared to conventional cigarette users. Bullen et al. (2010) compared e-cigarette users to nicotine inhalator users and found the e-cigarette users were less likely to report mouth irritation. Caponnetto, Campagna et al. (2013b) found that former smokers who used e-cigarettes, regardless of nicotine concentration, experienced a decrease in mouth irritation. Other researchers

reported improved taste and mouth odor for conventional smokers who switched to e-cigarettes (Etter 2010; Farsalinos et al. 2013; Hua et al. 2013; Van Staden et al. 2013).

While oral symptomatology was decreased in e-cigarette users compared to conventional smokers, other researchers found that e-cigarette use was associated with greater oral symptomatology compared to nonusers/nonsmokers. Cho (2017) found that e-cigarette users were more likely to have oral discomfort compared to never-users. Hajek et al. (2019) reported that mouth irritation was more frequently reported by e-cigarette users compared to people using nicotine replacement therapy.

Other mouth symptoms reported by e-cigarette users included various oral mucosal lesions, black tongue, and burns (Hua et al. 2013; Farsalinos et al. 2014; Bartram et al. 2016; Cravo et al. 2016; Yao et al. 2017; Cant et al. 2017). In particular, nicotine stomatitis and hairy tongue were significantly more prevalent in e-cigarette users compared to former smokers (Bardellini et al. 2018) and significantly more exclusive e-cigarette users (former smokers) complained of mouth or tongue sores/inflammation compared to dual users (Farsalinos et al. 2014). Holliday et al. (2019) found that mouth ulceration was only reported in the intervention (e-cigarette using) group.

Asgarian et al. (2018) sought to model the deposition of individual e-cigarette constituents by studying droplet dynamics. They found that only a very small fraction (4%) of commonly found e-cigarette aerosol constituents (nicotine, propylene glycol, and glycerin) were deposited in the oral cavity (mouth and throat), while the remainder traveled beyond the mouth and throat and were likely deposited in the airways. The effect of these oral depositions, however, was not clear.

Table 1. Description of included publications (n = 99 articles).

Author	Location of Participant(s)	Aim/Objective	Study design	Nicotine containing e-cigs	Outcome of interest	Conflict of interest ^a
1. Adriaens et al. 2014	Belgium	Investigated the efficacy of second-generation e-cigarettes on acute craving reduction, smoking reduction, and experienced benefits and complaints	Randomized control trial (RCT) • E-cigarette groups x 2 • Control group (Conventional cigarette users)	Yes	• Mouth effects • Throat effects	No
2. Al-Aali et al. 2018	Pakistan	Compared clinical and radiographic peri-implant parameters and levels of tumor necrosis factor alpha and interleukin-1b levels among individuals using e-cigarettes and never smokers	Comparative descriptive • E-cigarette users • Never smokers	Not stated	• Periodontal effects	No
3. Alanazi et al. 2019	Canada	Examined impact of e-cigarettes on expression of virulent <i>C. albicans</i> genes and effect of e-cigarette vapor-exposed <i>C. albicans</i> on gingival epithelial cell morphology, growth, and LDH activity	<i>In vitro</i>	Yes	• Oral microbiome effects	No
4. AlHarthi et al. 2019	Saudi Arabia	Assessed impact of conventional smoking and vaping on periodontal tissues following ultrasonic scaling	Comparative descriptive • E-cigarette users • Conventional smokers • Waterpipe smokers • Non-smokers	Not stated	• Periodontal effects	No
5. AlQahtani et al. 2018	Saudi Arabia	Compared clinical and radiographic peri-implant parameters and proinflammatory cytokine profile in peri-implant sulcular fluid among conventional smokers, waterpipe smokers, vapers, and non-smokers	Comparative descriptive • E-cigarette users • Conventional smokers • Waterpipe smokers • Non-smokers	Not stated	• Periodontal effects	No
6. AlQahtani et al. 2019	Saudi Arabia	Compared cotinine levels in the peri-implant sulcular fluid among conventional smokers, waterpipe users, e-cigarette users, and nonsmokers.	Comparative descriptive • E-cigarette users • Conventional smokers • Waterpipe smokers • Nonsmokers	Not stated	• Periodontal effects	No
7. Andresen et al. 2018	USA	Reported a case of an e-cigarette striking the posterior pharynx during a fall	Case report	Not stated	• Traumatic/Accidental injury	No
8. ArRejaie et al. 2019	Saudi Arabia	Compared clinical and radiographic peri-implant parameters and levels of matrix MMP-9 and IL-1β levels among conventional smokers, e-cigarette users, and non-smokers	Comparative descriptive • E-cigarette users • Conventional smokers • Non-smokers	Not stated	• Periodontal effects	No
9. Asgharian et al. 2018	USA	Developed a deposition model for EC aerosol in the oral cavity based on realistic vaping scenarios	Descriptive	Yes	• Mouth effects	No
10. Atuegwu et al. 2019	USA	Determined association between electronic nicotine product use and periodontal disease	Comparative descriptive • Never vapers • Long-term regular vapers • Occasional vapers	Yes	• Periodontal effects	No
11. Bardellini et al. 2018	Italy	Evaluated the prevalence and characteristics of oral mucosal lesions in former smokers compared to e-cigarette consumers	Comparative descriptive • Former smoker • E-cigarette consumer	Not stated	• Mouth effects • Cytotoxic, and genotoxic, and oncogenic effects • Oral microbiome effects	No
12. Bartram et al. 2016	United Kingdom	Presented a case of lichen planus after e-cigarette usage	Case report	Not stated	• Mouth effects	No

(continued)

Table 1. Continued.

Author	Location of Participant(s)	Aim/Objective	Study design	Nicotine containing e-cigs	Outcome of interest	Conflict of interest ^a
13. Baweja et al. 2016	USA	Described perceptions that e-cigarette users have about e-cigarettes and factors they believe are important from a public health prospective	Descriptive	Not stated	<ul style="list-style-type: none"> • Mouth effects • Throat effects 	Yes
14. BinShabaib et al. 2019	Saudi Arabia	Compared clinical periodontal status and gingival crevicular fluid cytokine profile among cigarette-smokers, e-cigarette users and never-smokers	Comparative descriptive <ul style="list-style-type: none"> • Conventional smokers • E-cigarette users • Non-users 	Yes	<ul style="list-style-type: none"> • Periodontal effects 	No
15. Brooks et al. 2017	USA	Presented a case of extensive intraoral injuries after e-cigarette usage	Case report	Yes	<ul style="list-style-type: none"> • Traumatic/Accidental injury 	No
16. Brownson et al. 2016	USA	Presented various injuries related to e-cigarette explosion	Case report	Not stated	<ul style="list-style-type: none"> • Traumatic/Accidental injury 	No
17. Bullen et al. 2010	New Zealand, Auckland	Measured the short-term effects of an electronic nicotine delivery device on desire to smoke, withdrawal symptoms, acceptability, pharmacokinetic properties and adverse effects	Randomized repeated measures cross-over trial <ul style="list-style-type: none"> • E-cigarette 16 mg nicotine • E-cigarette 0 mg nicotine • Nicotine inhalator • Conventional cigarettes 	Yes	<ul style="list-style-type: none"> • Mouth effects • Throat effects 	Yes
18. Bustamante et al. 2018	USA	Analyzed N'-Nitrosomonicotine in the saliva of e-cigarette users	Comparative descriptive <ul style="list-style-type: none"> • Conventional smokers • E-cigarette users • Non-users 	Yes	<ul style="list-style-type: none"> • Cytotoxic, genotoxic, and oncogenic effects 	No
19. Cant et al. 2017	United Kingdom	Presented a case of palatal necrotic ulcer after e-cigarette use	Case report	Yes	<ul style="list-style-type: none"> • Mouth effects 	No
20. Caponnetto, Auditore et al. 2013	Italy	Monitored possible modifications in the smoking habits of conventional smokers with schizophrenia experimenting with a popular brand of e-cigarette	Quasi-experimental	Yes	<ul style="list-style-type: none"> • Throat effects 	Yes
21. Caponnetto, Campagna et al. 2013	Italy	Investigated the efficacy and safety of an electronic cigarette	RCT <ul style="list-style-type: none"> • 7.2 mg nicotine for 12 weeks • 7.2 mg nicotine for 6 weeks, followed by 5.4 mg nicotine • No nicotine for 12 weeks. 	Yes	<ul style="list-style-type: none"> • Mouth effects • Throat effects 	Yes
22. Cason et al. 2016	USA	Presented a case of e-cigarette explosion injury to the user	Case report	Not stated	<ul style="list-style-type: none"> • Traumatic/Accidental injury 	No
23. Chi et al. 2018	USA	Presented a case of e-cigarette explosion causing orofacial trauma	Case report	Not stated	<ul style="list-style-type: none"> • Traumatic/Accidental injury 	No
24. Cho, 2017	South Korea	Assessed the relationship between e-cigarette use and oral health	Comparative descriptive <ul style="list-style-type: none"> • Daily e-cigarette users • Past month e-cigarette users • Former e-cigarette users • Never e-cigarette users 	Yes	<ul style="list-style-type: none"> • Mouth effects • Periodontal effects • Dental effects 	Not stated
25. Cichońska et al. 2019	Poland	Estimated changes in selected physicochemical properties of saliva e-cigarette users	Comparative descriptive <ul style="list-style-type: none"> • E-cigarette users • Conventional smokers • Non-users 	Yes	<ul style="list-style-type: none"> • Oral microbiome effects 	No
26. Cravo et al. 2016	UK	Evaluated the safety profile of an e-cigarette product in smokers of conventional cigarettes switching to use the e-cigarette for 12 weeks	RCT <ul style="list-style-type: none"> • E-cigarette user • Conventional cigarette user 	Yes	<ul style="list-style-type: none"> • Mouth effects • Throat effects • Dental effects • Oral Microbiome effects 	Yes

(continued)

Table 1. Continued.

Author	Location of Participant(s)	Aim/Objective	Study design	Nicotine containing e-cigs	Outcome of interest	Conflict of interest ^a
27. Cuadra et al. 2019	NA	Tested impact of flavorless e-cigarette aerosol on oral commensal streptococci	<i>In vitro</i>	Yes	<ul style="list-style-type: none"> • Oral microbiome effects 	No
28. Dawkins and Corcoran 2014	UK	Explored the effect of using an 18-mg/ml nicotine e-cigarette on blood nicotine, tobacco withdrawal symptoms, and urge to smoke	Descriptive correlational	Yes	<ul style="list-style-type: none"> • Mouth effects • Throat effects 	Yes
29. Dawkins et al. 2013	Europe	Characterized e-cigarette use, users, and effects; in a sample of one particular brand of e-cigarette users	Comparative descriptive <ul style="list-style-type: none"> • Ex-smokers (i.e. former smokers now exclusive e-cigarette users) • Dual users 	Not exclusively	<ul style="list-style-type: none"> • Mouth effects • Throat effects 	Yes
30. Diamantopoulou et al. 2019	Greece	Examined characteristics and patterns of e-cigarette use and smoking of vape shop customers in Greece	Descriptive	Range of nicotine concentrations	<ul style="list-style-type: none"> • Throat effects 	None in past 36 months
31. D'Ruiz et al. 2015	USA	Compared the nicotine pharmacokinetics, impacts on smoking urge and tolerability of various formulations of one brand of e-cigarette with that of a conventional cigarette	Randomized crossover trial <ul style="list-style-type: none"> • Five formulations of e-cigarette (varied flavor, nicotine concentration, glycerin concentration, and propylene glycol concentration) • Conventional tobacco cigarette 	Yes	<ul style="list-style-type: none"> • Throat effects 	Yes
32. Duggar et al. 2018	NA	Tested hypothesis that exposure to e-cigarette vapor would adversely affect the growth of cells that reside in the oral cavity.	<i>In vitro</i>	Range of nicotine concentrations	<ul style="list-style-type: none"> • Cytotoxic, genotoxic, and oncogenic effects 	Not stated
33. Etter, 2010	France, Canada, Belgium, and Switzerland	Assessed usage patterns of e-cigarettes, reasons for use, and users' opinions of these products.	Descriptive	Yes	<ul style="list-style-type: none"> • Mouth effects • Throat effects 	No
34. Farsalinos et al. 2013	Greece	Examined profile and e-cigarette use patterns in a specific group of ex-smokers who have switched completely to e-cigarette use without using any other aid.	Quasi-experimental	Yes	<ul style="list-style-type: none"> • Mouth effects • Throat effects • Periodontal effects 	No
35. Farsalinos et al. 2014	Europe, USA, Asia, Australia, Africa	Assessed characteristics and experiences of e-cigarette users and examine differences between those who partially and completely substituted smoking with e-cigarette use	Comparative descriptive <ul style="list-style-type: none"> • Former smokers • Current smokers 	Yes	<ul style="list-style-type: none"> • Mouth effects • Throat effects • Periodontal effects 	No
36. Flieger et al. 2019	Not stated	Estimated salivary thiocyanate levels in conventional smokers compared to e-cigarette users and nonsmokers	Comparative descriptive <ul style="list-style-type: none"> • Conventional smokers • E-cigarette users • Non-smokers 	Not stated	<ul style="list-style-type: none"> • Cytotoxic, genotoxic, and oncogenic effects 	No
37. Franco et al. 2016	Italy	Assessed the safety of e-cigarettes and establish its role in primary prevention of oral cavity cancer	Comparative descriptive <ul style="list-style-type: none"> • Conventional smokers • E-cigarette users • Non-smokers 	Yes	<ul style="list-style-type: none"> • Cytotoxic, genotoxic, and oncogenic effects 	No
38. Frossard et al. 2015	USA	Presented a case of acute uvulitis secondary to e-cigarette use	Case report	Not stated	<ul style="list-style-type: none"> • Throat effects 	No
39. Ganapathy et al. 2017	NA	Determined the genotoxicity and the mechanisms induced by e-cigarette aerosol extracts on human oral and lung epithelial cells	<i>In vitro</i>	Range of nicotine concentrations	<ul style="list-style-type: none"> • Cytotoxic, genotoxic, and oncogenic effects 	No
40. Gomes et al. 2016	UK	Sought community pharmacists' perception on use, safety and possible effectiveness of e-cigarettes as quit smoking tools, and their future regulation	Descriptive	Yes	<ul style="list-style-type: none"> • Mouth effects • Throat effects 	No
41. Hajek et al. 2015	UK	Described a pilot expanding an existing smoking cessation service to include free e-cigarettes with refills for 4-weeks	Quasi-experimental	Yes	<ul style="list-style-type: none"> • Mouth effects • Throat effects 	Yes
42. Hajek et al. 2019	UK	Described a pilot expanding an existing smoking cessation service to include free e-cigarettes with refills for 4-weeks	RCT	Yes	<ul style="list-style-type: none"> • Mouth effects • Throat effects 	Yes

(continued)

Table 1. Continued.

Author	Location of Participant(s)	Aim/Objective	Study design	Nicotine containing e-cigs	Outcome of interest	Conflict of interest ^a
43. Harrison and Hicklin 2016	USA	Evaluated 1-year efficacy of refillable e-cigarettes compared to nicotine replacement combined with in-person behavioral support for smoking cessation	<ul style="list-style-type: none"> Nicotine replacement group E-cigarette group Case report	Yes	<ul style="list-style-type: none"> Trauma/Accidental injury 	No
44. Hirschi et al. 2017	NA	Presented a case of e-cigarette injury resulting in intraoral burns, luxation injuries, and alveolar fractures	<i>In vitro</i>	Range of nicotine concentrations	<ul style="list-style-type: none"> Cytotoxic, genotoxic, and oncogenic effects 	Not stated
45. Holliday et al. 2019	UK	Determined the effects of e-liquid on RAGE expression and levels of several pro-inflammatory cytokines	RCT	Range of nicotine concentrations	<ul style="list-style-type: none"> Mouth effects Periodontal effects Dental effects Mouth effects Throat effects 	No
46. Hua et al. 2013	International	Assess the feasibility of delivering and evaluating a vaping intervention for smoking cessation within the dental setting	Descriptive	Not stated	<ul style="list-style-type: none"> Dental effects Throat effects 	No
47. Hughes Hendrickson 2018	USA	Documented the positive and negative short-term health effects produced by e-cigarette use through an analysis of original posts from three online e-cigarettes forums	Descriptive	Range of nicotine concentrations	<ul style="list-style-type: none"> Mouth effects Throat effects 	No
48. Huilgol et al. 2018	USA	Described the cases involving e-cigarettes called into a poison center	Descriptive	Range of nicotine concentrations	<ul style="list-style-type: none"> Mouth effects Throat effects 	No
49. Iskandar et al. 2019	USA	Measured associations between daily as well as intermittent e-cigarette use and poor oral health among adults in the USA	Comparative descriptive	Not stated	<ul style="list-style-type: none"> Periodontal effects Dental effects 	Yes
50. Iskandar et al. 2019	NA	Compared impact of exposure to e-cigarette aerosols with that of conventional smoke on buccal epithelial and small airway epithelial cell cultures	<ul style="list-style-type: none"> Good oral health Poor oral health <i>In vitro</i>	Yes	<ul style="list-style-type: none"> Cytotoxic, genotoxic, and oncogenic effects 	Yes
51. Ismail et al. 2019	Malaysia	Investigate effects of e-cigarette use on oral health in 6-month period	Longitudinal descriptive	Not stated	<ul style="list-style-type: none"> Periodontal effects Dental effects Throat effects 	Not stated
52. Jankowski et al. 2017	Poland	Compared health effects of conventional smokers and e-cigarette users, with special emphasis on their influence on respiratory system	Comparative descriptive	Not stated	<ul style="list-style-type: none"> Periodontal effects Dental effects Throat effects 	Not stated
53. Javed et al. 2017	Saudi Arabia	Assessed periodontal parameters and self-perceived oral symptoms among users of e-cigarettes, conventional cigarettes, and non-users of either product	<ul style="list-style-type: none"> E-cigarette users Conventional smokers Comparative descriptive E-cigarette users E-cigarette users Conventional smokers Non-users 	Not stated	<ul style="list-style-type: none"> Periodontal effects 	No
54. Jeong et al. 2019	South Korea	Examined association of conventional smoking and e-cigarette use with periodontal disease	<ul style="list-style-type: none"> Comparative descriptive E-cigarette users Conventional smokers Former smokers Non-users <i>In vitro</i> using e-liquid with varying nicotine strengths	Not stated	<ul style="list-style-type: none"> Periodontal effects 	Not stated
55. Ji et al. 2016	NA	Characterized e-cigarette aerosols and assess their biological hazard on oral epithelial cells	<ul style="list-style-type: none"> Comparative descriptive E-cigarette users Conventional smokers Former smokers Non-users <i>In vitro</i> using e-liquid with varying nicotine strengths	Yes	<ul style="list-style-type: none"> Cytotoxic, genotoxic, and oncogenic effects 	No
56. Ji et al. 2019	NA	Understood if e-cigarette aerosol exposure impacts the gene pathways of normal human oral keratinocytes	<i>In vitro</i>	Yes	<ul style="list-style-type: none"> Cytotoxic, genotoxic, and oncogenic effects 	No
57. Kim et al. 2018	NA	Investigated changes in cariogenic potential when tooth surfaces are exposed to e-cigarette aerosols with sweet flavors	<i>In vitro</i>	Yes	<ul style="list-style-type: none"> Cytotoxic, genotoxic, and oncogenic effects Dental effects Oral microbiome effects 	No
58. King et al. 2019	USA	Examined prevalence of self-reported adverse symptoms attributed to e-cigarette use	Descriptive	Not stated	<ul style="list-style-type: none"> Mouth effects Throat effects Oral microbiome effects 	No
59. Kumar et al. 2019	Not stated	Presentation of two studies investigating: <ul style="list-style-type: none"> impact of e-cigarettes on oral microbiome in subjects with periodontitis (Study #1) 	<ul style="list-style-type: none"> Study #1: Comparative descriptive E-cigarette users Conventional smokers 	Study #1: Not stated Study #2: Yes	<ul style="list-style-type: none"> Mouth effects Throat effects Oral microbiome effects 	No

(continued)

Table 1. Continued.

Author	Location of Participant(s)	Aim/Objective	Study design	Nicotine containing e-cigs	Outcome of interest	Conflict of interest ^a
59. Kumetz et al. 2016	USA	<ul style="list-style-type: none"> effects of sole and dual use of e-cigarettes on the oral metagenome of periodontally healthy young adults (Study #2) 	<ul style="list-style-type: none"> Non-users Study #2: Comparative descriptive E-cigarette users Conventional smokers Non-users Former smokers Dual users 	Not stated	<ul style="list-style-type: none"> Trauma/Accidental injury 	No
60. Lewek et al. 2019	Social media	Presented two cases with severe injuries secondary to e-cigarette use, one of which was to the oral area	Descriptive	Both with and without nicotine	<ul style="list-style-type: none"> Mouth effects Throat effects 	No
61. Li et al. 2016	Not stated	Identified factors that influence decision to use e-cigarettes and their adverse effects	Descriptive correlational	Range of nicotine concentrations	<ul style="list-style-type: none"> Mouth effects Throat effects 	Yes
62. McRobbie et al. 2015	UK	Mined potential relationships between symptoms and e-cigarette liquid components using data collected from Reddit	Quasi-experimental	Yes	<ul style="list-style-type: none"> Mouth effects Throat effects Throat effects 	Yes
63. Miller and Hajek 2017	UK	Investigated exposure to carbon monoxide, nicotine and acrolein before and after 4 weeks of e-cigarette use	Case report	Range of nicotine concentrations	<ul style="list-style-type: none"> Throat effects 	No
64. Mokeem, Abduljabbar et al. 2018	Saudi Arabia	Presented a case with positive effect of e-cigarette usage	Case report	Range of nicotine concentrations	<ul style="list-style-type: none"> Oral microbiome effects 	No
65. Mokeem Alasqah et al. 2018	Saudi Arabia	Compared oral Candida carriage among users of cigarettes, water pipes, e-cigarettes, and never-smokers	Comparative Descriptive	Range of nicotine concentrations	<ul style="list-style-type: none"> Periodontal effects 	No
66. Moore et al. 2016	UK	Compared the clinical and radiographic periodontal parameters and whole salivary cotinine, interleukin (IL)-1 β and IL-6 levels among cigarette-smokers, water-pipe users, e-cigarette users and never-smokers	<ul style="list-style-type: none"> Conventional smokers Water pipe users E- cigarette users Never-smokers 	Range of nicotine concentrations	<ul style="list-style-type: none"> Oral microbiome effects 	No
67. Nelson et al. 2019	NA	Presented a case of injury associated with e-cigarette explosion	Case report	Not stated	<ul style="list-style-type: none"> Trauma/Accidental injury 	No
68. Nguyen et al. 2017	Not stated	Compared impact of e-cigarette aerosol versus conventional smoke on planktonic growth of oral commensal streptococci	<i>In vitro</i>	Both with and without nicotine	<ul style="list-style-type: none"> Oral microbiome effects 	No
69. Nides et al. 2014	USA	Presented two cases of oral carcinoma associated with chronic use of E-cigarettes	Case report	Not stated	<ul style="list-style-type: none"> Cytotoxic, genotoxic, and oncogenic effects Mouth effects Throat effects 	Yes
70. Noril and Plate 2017	USA	Evaluated nicotine delivery from an electronic nicotine delivery system and its short-term potential for smoking reduction or cessation	Quasi-experimental	Yes	<ul style="list-style-type: none"> Mouth effects Throat effects 	Yes
71. Oncken et al. 2015	USA	Presented a case of oral injury and fracture of C1 and C2 vertebrae after e-cigarette explosion	Case report	Not stated	<ul style="list-style-type: none"> Trauma/Accidental injury 	No
72. Pintado-Palomino et al. 2019	USA	Examined overall changes in serum nicotine and cotinine concentrations when using a popular e-cigarette and 18 mg/mL nicotine e-juice, and explore effects of sex and flavorings on these concentrations	Randomized crossover trial	Yes	<ul style="list-style-type: none"> Mouth effects Throat effects 	Yes
73. Polosa et al. 2014	Italy	Evaluated whether e-cigarette aerosol could alter the color of dental enamel	<ul style="list-style-type: none"> E-juice flavored with tobacco and menthol E-juice flavored with tobacco 	Range of nicotine concentrations	<ul style="list-style-type: none"> Dental effects 	No
		Evaluated smoking reduction/abstinence in smokers not intending to quit using an e-cigarette	<i>In vitro</i>	Yes	<ul style="list-style-type: none"> Mouth effects Throat effects 	Yes
		Longitudinal descriptive	<ul style="list-style-type: none"> Participants followed for 24 months after a 24-week intervention phase 			

(continued)

Table 1. Continued.

Author	Location of Participant(s)	Aim/Objective	Study design	Nicotine containing e-cigs	Outcome of interest	Conflict of interest ^a
74. Pratt et al. 2016	USA	Evaluated behavioral appeal and addiction liability of e-cigarettes in patients with psychiatric disorders	Quasi-experimental	Yes	• Throat effects	No
75. Rahman et al. 2016	Malaysia	Assessed smoking cessation rate, adverse effects, withdrawal symptoms, and smoking-related diseases in Malaysian vapers	Comparative Descriptive • Exclusive vapers • Dual user (e-cigarettes + tobacco cigarettes)	Range of nicotine concentrations	• Mouth effects • Throat effects	No
76. Reuther et al. 2016	UK	Analyzed the effect of e-cigarettes on the flow of buccal mucosal blood, before and immediately after vaping	Quasi-experimental	Range of nicotine concentrations	• Mouth effects	No
77. Richmond et al. 2018	Canada	Explored the spectrum of injury related to e-cigarette exposure among Canadian children and adolescents	Descriptive	Range of nicotine concentrations	• Throat effects	No
78. Roger et al. 2016	USA	Presented a case of oral and abdominal burns, oral lacerations, tooth fracture, and tooth avulsion from an explosion of an e-cigarette	Case report	Not stated	• Trauma/Accidental injury	Not stated
79. Rosbrook and Green 2016	USA	Measured the perception of menthol in an e-cigarette and assess its analgesic effect on the sensory irritation produced by inhaled nicotine	Quasi-experimental	Range of nicotine concentrations	• Mouth effects • Throat effects	No
80. Rouabhia et al. 2017	Canada	Investigated the effect of e-cigarette vapor on primary gingival epithelial cell adhesion, cell morphology, cell apoptosis/necrosis, and caspase-3 expression	<i>In vitro</i>	Yes	• Cytotoxic, genotoxic, and oncogenic effects	No
81. Rudy and Durmowicz 2017	USA	Identified number and nature of electronic nicotine delivery system -associated overheating, fire or explosion events in the USA	Descriptive	Not stated	• Trauma/Accidental injury	No
82. Sancilio et al. 2016	NA	Investigated the effects of e-cigarette liquids on human gingival fibroblasts and compare the effects of nicotine-containing fluid to the fluid itself	<i>In vitro</i>	Range of nicotine concentrations	• Cytotoxic, genotoxic, and oncogenic effects	No
83. Sancilio et al. 2017	NA	Investigated the effects of e-cigarette liquids (with and without nicotine) on human gingival fibroblasts	<i>In vitro</i>	Range of nicotine concentrations	• Cytotoxic, genotoxic, and oncogenic effects	No
84. Sinharoy et al. 2018	Participants accessed via online survey	Identified patterns of e-cigarette flavor use and adverse side effects	Descriptive correlational	Not stated	• Mouth effects • Throat effects	Not stated
85. Stein et al. 2016	USA	Pilot trialed the use of e-cigarettes as a smoking cessation aid among methadone-maintained smokers	Quasi-experimental	Yes	• Mouth effects • Throat effects	No
86. Stewart et al. 2018	USA	Determined if e-cigarettes or tobacco smoking alter the oral and gut microbiota in comparison to non-smoking controls	Comparative descriptive • E-cigarette users • Tobacco smokers • Controls <i>In vitro</i>	Range of nicotine concentrations	• Throat effects • Oral microbiome effects	No
87. Sun et al. 2019	NA	Examined effect of e-cigarette aerosol on human oral cell metabolism of benzo(a)pyrene	<i>In vitro</i>	Yes	• Cytotoxic, genotoxic, and oncogenic effects	No
88. Sundar et al. 2016	NA	Determined the mechanism of gingival epithelial inflammation and pro-senescence by e-cigarette aerosols with flavorings in human oral epithelial cells and periodontal ligament fibroblasts	<i>In vitro</i>	Range of nicotine concentrations	• Cytotoxic, genotoxic, and oncogenic effects	No
89. Tatullo et al. 2016	Italy	Verified the clinical variations of periodontal health induced by e-cigarette use in former conventional smokers, and investigate awareness of changes in general health status	Comparative descriptive • < 10 years of prior conventional smoking • > 10 years of prior conventional smoking Comparative descriptive • E-cigarette users • Conventional smokers • Non-smokers	Range of nicotine concentrations	• Periodontal effects	Not stated
90. Tommasi et al. 2019	USA	Determined effects of vaping versus conventional smoking on gene regulation by interrogating the oral transcriptome	Comparative descriptive • E-cigarette users • Conventional smokers • Non-smokers	Yes	• Cytotoxic, genotoxic, and oncogenic effects	No

(continued)

Table 1. Continued.

Author	Location of Participant(s)	Aim/Objective	Study design	Nicotine containing e-cigs	Outcome of interest	Conflict of interest ^a
91. Vakali et al. 2014	Not stated	Assessed the effect of a single e-cigarette, use on clinical symptoms, vital signs and airway inflammatory markers after inhaling either 0 mg or 11 mg of nicotine	Comparative Descriptive <ul style="list-style-type: none"> • Never and healthy smokers given single e-cig containing nicotine • Never and healthy smokers given e-cig with no nicotine 	Range of nicotine concentrations	<ul style="list-style-type: none"> • Throat effects 	Not stated
92. Van Staden et al. 2013	South Africa	Determined whether smoking an e-cigarette containing nicotine in a vegetable-based glycerin substance, would reduce carboxyhemoglobin (COHb) levels in regular cigarette smoker	Quasi-experimental	Yes	<ul style="list-style-type: none"> • Mouth effects • Throat effects 	No
93. Vora and Chaffee 2019	USA	Evaluated self-reported gingival disease among cigarette smokers and users of other types of tobacco products	Comparative descriptive <ul style="list-style-type: none"> • Pipe users • E-cigarette users • Multiple product users • Recent quitters 	Not stated	<ul style="list-style-type: none"> • Periodontal effects 	No
94. Wadia et al. 2016	UK	Compared the gingival health of a group of established smokers before and after substituting vaping for smoking tobacco	Longitudinal descriptive	Yes	<ul style="list-style-type: none"> • Periodontal effects 	Not stated
95. Walele et al. 2018	UK	Evaluated the long-term effects of e-cigarette products	Quasi-experimental	Yes	<ul style="list-style-type: none"> • Throat effects • Dental effects • Cytotoxic, genotoxic, and oncogenic effects 	Yes
96. Welz et al. 2016	NA	Investigated the biomolecular effects of e-liquids on human pharyngeal tissue cultures to evaluate whether e-liquids and their components present a risk factor for head and neck squamous cell carcinoma.	<i>In vitro</i>	Range of nicotine concentrations	<ul style="list-style-type: none"> • Cytotoxic, genotoxic, and oncogenic effects 	Not stated
97. Willershausen et al. 2014	NA	Assessed the influence of the different e-smoking liquids on the viability and proliferation of human periodontal ligament fibroblasts	<i>In vitro</i>	Range of nicotine concentrations	<ul style="list-style-type: none"> • Cytotoxic, genotoxic, and oncogenic effects 	No
98. Yao et al. 2017	USA	Examined the relationship between spending on e- cigarettes and disease symptoms compared with the relationship between 30-day e-cigarette use and disease symptoms	Descriptive correlational	Not stated	<ul style="list-style-type: none"> • Mouth effects • Periodontal effects • Dental effects 	No
99. Yu et al. 2016	NA	Evaluated the cytotoxicity and genotoxicity of short- and long-term e-cigarette vapor exposure on a panel of normal epithelial and head and neck squamous cell carcinoma (HNSCC) cell lines	<i>In vitro</i>	Range of nicotine concentrations	<ul style="list-style-type: none"> • Cytotoxic, genotoxic, and oncogenic effects 	No

^aPer reported conflict of interest statement.

Table 2. Publications Describing Mouth Effects ($n = 35$).

Study	Study Design	Participants ^a	Sample Size	Effects/Symptoms	Measure/Tool ^b	Quality of Evidence ^c
1. Adriaens et al. 2014	RCT	Smokers not intending to quit randomized to: • E-cigarette Type 1 brand ($n = 16$) • E-cigarette Type 2 brand ($n = 16$) • Conventional cigarette control ($n = 16$)	$N = 48$	<ul style="list-style-type: none"> Both e-cigarette groups had a lower total complaint score compared to control group (complaints inclusive of bad taste, dry mouth, irritation) ($F [1,37] = 7.30, p < 0.05$) Both e-cigarette groups had higher total benefits score compared to control (inclusive of improved taste and fresher breath) 	Online diary	Weak
2. Asgharian et al. 2018	Descriptive	NA	NA	4% deposition of nicotine, propylene glycol, and glycerin in oral cavity. The rest of the constituents travelled beyond into airways.	Mathematical modeling for aerosol mixture transport based on e-cigarette vapor inhalation topology	NA
3. Bardellini et al. 2018	Comparative descriptive	<ul style="list-style-type: none"> Former conventional cigarette smokers ($n = 45$) Current e-cigarette smokers ($n = 45$) 	$N = 90$	E-cigarette smokers had significantly higher frequency of nicotine stomatitis and hairy tongue	Clinical exam	Weak
4. Bartram et al. 2016	Case report	NA	$N = 1$	Development of oral cavity lichenoid lesions with use of e-cigarette liquid high in propylene glycol	Clinical exam	Weak
5. Baweja et al. 2016	Descriptive	E-cigarette users	$N = 200$	Most common negative effect included dry mouth, chapped lips and bad breath	Online survey	Weak
6. Bullen et al. 2010	Randomized cross-over trial	Smokers not intending to quit randomized to: • E-cigarette with 16 mg nicotine • Placebo e-cigarette • Nicorette nicotine inhalator • Conventional cigarette control	$N = 40$	Mouth irritation less commonly reported with placebo and 16 mg nicotine e-cigarette compared to inhalator	Self-report	Moderate
7. Cant et al. 2017	Case report	NA	$N = 1$	Necrotic ulcer on hard palate following use of e-cigarette	Clinical exam	Weak
8. Caponnetto, Campagna et al. 2013	RCT	Smokers desiring to quit randomized to: • E-cigarette group with 7.2 mg nicotine cartridges for 12 weeks ($n = 100$) • E-cigarette group 7.2 mg nicotine cartridges for 6 weeks followed by 5.4 mg nicotine cartridges for 6 weeks ($n = 100$) • Control: no-nicotine cartridges for 12 weeks ($n = 100$)	$N = 300$	Frequency for complaints of mouth irritation significantly decreased from baseline for all three groups.	Study diary	Weak
9. Cho, 2017	Comparative descriptive	Grouped according to e-cigarette use • Never user ($n = 56,017$) • Former user ($n = 5,499$) • Past month user ($n = 2,109$) • Daily user ($n = 1,903$)	$N = 65,528$	Odds of tongue and/or inside-cheek pain' among daily users over 50% higher ($p = 0.028$) compared to never users	Online survey	Moderate
10. Cravo et al. 2016	RCT	Current smokers randomized to: • E-cigarette group ($n = 306$) • Conventional cigarette group ($n = 102$)	$N = 419$	Oral symptoms reported in the e-cigarette group included: mouth ulceration (3.9%), dry mouth (2.6%), and oral pain (1%)	Diary cards	Weak
11. Dawkins and Corcoran 2014	Descriptive correlational	E-cigarette users	$N = 14$	Mouth irritation (mean score of 16.54, SEM = 4.75)	200 mm Visual analog scale	Weak
12. Dawkins et al. 2013		E-cigarette users	$N = 1,347$		Online survey	Weak

(continued)

Table 2. Continued.

Study	Study Design	Participants ^a	Sample Size	Effects/Symptoms	Measure/Tool ^b	Quality of Evidence ^c
13. Etter, 2010	Comparative descriptive	<ul style="list-style-type: none"> Ex-smokers (i.e. exclusive e-cigarette users) ($n = 1,123$) Dual users ($n = 218$) Never-smokers (6) E-cigarette users (63% were former conventional smokers) 	$N = 81$	0.5% of entire sample of participants reported mouth irritation	Online survey	Weak
14. Farsalinos et al. 2013	Descriptive	Exclusive e-cigarette users (former conventional smokers)	$N = 111$	<ul style="list-style-type: none"> Dry mouth ($n = 16$) Bad taste ($n = 4$) Improved taste ($n = 11$) Improved mouth odor ($n = 10$) Improved gustatory senses (81.9%) 	Face to face interview	Weak
15. Farsalinos et al. 2014	Comparative descriptive	<ul style="list-style-type: none"> Former smokers ($n = 15,671$) Current smokers ($n = 3,682$) 	$N = 19,353$	<ul style="list-style-type: none"> Sore or dry mouth (38.9%) – no difference between groups Mouth or tongue sores/inflammation higher among former smokers ($p < .005$) Black tongue (0.7%) – no difference between groups 	Online questionnaire	Weak
16. Gomes et al. 2016	Descriptive	Community pharmacies	$N = 154$	Dry mouth reported to pharmacists ($n = 7$)	Paper questionnaire	Weak
17. Hajek et al. 2015	Quasi-experimental	Smokers seeking to quit	$N = 100$	One report of mouth irritation	Client feedback	Weak
18. Hajek et al. 2019	RCT	<ul style="list-style-type: none"> Smokers seeking to quit Nicotine replacement group ($n = 447$) E-cigarette group ($n = 439$) 	$N = 886$	<ul style="list-style-type: none"> Mouth irritation reported more frequently in e-cigarette group vs. nicotine replacement group Percent of participants reporting mouth irritation did not differ between groups Both groups reported similar dryness at baseline and improvements after 6 months Mouth ulceration and soreness were only reported in the intervention group 	Self-report	Weak
19. Holliday et al. 2019	RCT	<ul style="list-style-type: none"> Current smokers not currently using e-cigarettes Standard smoking cessation advice ($n = 40$) Standard smoking cessation advice + e-cigarette ($n = 40$) 	$N = 80$	<ul style="list-style-type: none"> More negative than positive symptoms reported including: numbness, dryness, inflamed tongue, soreness & irritation, cold sores. Improved mouth odor was the only positive mouth symptom reported Irritation from pediatric exposure by ingestion or contact ($n = 3$) Dryness/irritation from contact or ingestion ($n = 6$) 31% reported dry/irritated mouth Dryness reported by 8.8% of participants Mouth symptoms were mostly negative and described as dryness/burning Posts frequently discussed fruits, cream, and menthol flavors, with nicotine levels of 1–6 mg. 	<ul style="list-style-type: none"> Clinical oral dryness scale Self-report/observation 	Moderate
20. Hua et al. 2013	Descriptive	Posts from three internet e-cigarette forums	$N = 632$	<ul style="list-style-type: none"> More negative than positive symptoms reported including: numbness, dryness, inflamed tongue, soreness & irritation, cold sores. Improved mouth odor was the only positive mouth symptom reported Irritation from pediatric exposure by ingestion or contact ($n = 3$) Dryness/irritation from contact or ingestion ($n = 6$) 31% reported dry/irritated mouth Dryness reported by 8.8% of participants Mouth symptoms were mostly negative and described as dryness/burning Posts frequently discussed fruits, cream, and menthol flavors, with nicotine levels of 1–6 mg. 	Self-report	Weak
21. Hughes and Hendrickson 2018	Descriptive	Poison center cases	$N = 265$	<ul style="list-style-type: none"> Improved mouth odor was the only positive mouth symptom reported Irritation from pediatric exposure by ingestion or contact ($n = 3$) Dryness/irritation from contact or ingestion ($n = 6$) 31% reported dry/irritated mouth Dryness reported by 8.8% of participants Mouth symptoms were mostly negative and described as dryness/burning Posts frequently discussed fruits, cream, and menthol flavors, with nicotine levels of 1–6 mg. 	Self-report	Weak
22. King et al. 2019	Descriptive	E-cigarette users	$N = 1,624$	<ul style="list-style-type: none"> Improved mouth odor was the only positive mouth symptom reported Irritation from pediatric exposure by ingestion or contact ($n = 3$) Dryness/irritation from contact or ingestion ($n = 6$) 31% reported dry/irritated mouth Dryness reported by 8.8% of participants Mouth symptoms were mostly negative and described as dryness/burning Posts frequently discussed fruits, cream, and menthol flavors, with nicotine levels of 1–6 mg. 	Self-report	Weak
23. Lewek et al. 2019	Descriptive	E-cigarette users	$N = 1,142$	<ul style="list-style-type: none"> Improved mouth odor was the only positive mouth symptom reported Irritation from pediatric exposure by ingestion or contact ($n = 3$) Dryness/irritation from contact or ingestion ($n = 6$) 31% reported dry/irritated mouth Dryness reported by 8.8% of participants Mouth symptoms were mostly negative and described as dryness/burning Posts frequently discussed fruits, cream, and menthol flavors, with nicotine levels of 1–6 mg. 	Self-report	Weak
24. Li et al. 2016	Descriptive correlational	Reddit posts	$N = 493,994$	<ul style="list-style-type: none"> Improved mouth odor was the only positive mouth symptom reported Irritation from pediatric exposure by ingestion or contact ($n = 3$) Dryness/irritation from contact or ingestion ($n = 6$) 31% reported dry/irritated mouth Dryness reported by 8.8% of participants Mouth symptoms were mostly negative and described as dryness/burning Posts frequently discussed fruits, cream, and menthol flavors, with nicotine levels of 1–6 mg. 	Self-report	Weak
25. McRobbie et al. 2015	Quasi-experimental	Smokers seeking to quit	$N = 40$	Dry mouth ($n = 2$)	Self-report	Weak
26. Nides et al. 2014	Quasi-experimental	Smokers not interested in quitting	$N = 25$	Mouth irritation ($n = 7$) and burning of lips ($n = 1$)	Self-report	Weak

(continued)

Table 2. Continued.

Study	Study Design	Participants ^a	Sample Size	Effects/Symptoms	Measure/Tool ^b	Quality of Evidence ^c
27. Oncken et al. 2015	Randomized crossover trial	Non-treatment seeking smokers randomized to: • E-cigarette with tobacco and menthol flavors • E-cigarette with tobacco flavor only Smokers not interested in quitting	N = 27	Mouth irritation (n = 4)	Self-report	Weak
28. Polosa et al. 2014	Longitudinal descriptive	• E-cigarette with tobacco flavor only Smokers not interested in quitting	N = 40	Dry mouth/mouth irritation	Self-report	Weak
29. Rahman et al. 2016	Comparative descriptive	• E-cigarette only users (n = 70) • Dual users (E-cigarette + conventional cigarettes) (n = 148)	N = 220	More than 60% of participants in both groups reported dry mouth	Study questionnaire	Strong
30. Reuther et al. 2016	Quasi-experimental	Non-smokers: • Plain e-liquid (n = 5) • E-liquid with nicotine (n = 5) Adult smokers	N = 10	Nicotine containing e-cigarettes caused more capillary perfusion in the buccal mucosa	Laser doppler to measure blood flow	Weak
31. Rosbrook and Green 2016	Quasi-experimental		N = 32	Mouth irritation/harshness increased with menthol concentration, but not nicotine concentration	Self-report	Weak
32. Sinharoy et al. 2018	Descriptive correlational	Long-term e-cigarette users	N = 552	Cinnamon flavor associated with mouth irritation	Self-report	Weak
33. Stein et al. 2016	Quasi-experimental	Smokers in methadone maintenance treatment desiring to quit	N = 12	Dry mouth (n = 4)	Modified Minnesota Behavior Rating Scale Questionnaire	Weak
34. Van Staden et al. 2013	Quasi-experimental	Smokers	N = 15	Improved taste 2 weeks post switching from conventional cigarettes to e-cigarettes		Weak
35. Yao et al. 2017	Descriptive correlational	Current conventional and e-cigarette adult users in US	N = 533	Reporting of mouth sores/ulcers related to increased e-cigarette expenditures (AOR = 1.36 [1.08, 1.72])	Tobacco and Attitudes Beliefs Survey	Weak

^aWhen applicable.^bMeasure/Tool used for the oral health symptom.^cNote. The level of evidence was evaluated for mouth effects.

A few researchers honed in on individual ingredients of e-cigarettes and mouth effects. Researchers testing the effect of nicotine in e-cigarettes on buccal mucosa perfusion noted that nicotine containing e-cigarettes increased blood flow to the oral mucosa in the short term (Reuther et al. 2016). Rosbrook and Green (2016) tested both nicotine and menthol, another ingredient commonly found in e-cigarettes, and found that the frequency of mouth irritation increased with menthol concentration, but not nicotine concentration. Sinharoy et al. (2018) found that in long-term e-cigarette users, there was an association between cinnamon flavor and mouth irritation.

Throat effects

Throat symptoms were frequently reported (Table 3). Similar to studies that reported mouth symptoms, the majority of studies were weak in terms of the evidence provided regarding throat symptoms. That is, the throat effects were, by and large, self-reported, descriptive, and without consideration of other confounders. Common mild and temporary complaints from inhalation or accidental ingestion of e-cigarette fluid included throat dryness (Adriaens et al. 2014; Farsalinos et al. 2014; Nides et al. 2014; McRobbie et al. 2015; Cravo et al. 2016; Li et al. 2016; Pratt et al. 2016; King et al. 2019), irritation (Bullen et al. 2010; Caponnetto, Auditore et al. 2013a; Caponnetto, Campagna et al. 2013b; Dawkins et al. 2013; Hua et al. 2013; Adriaens et al. 2014; Dawkins and Corcoran 2014; Nides et al. 2014; Polosa et al. 2014; D’Ruiz et al. 2015; Hajek et al. 2015; Oncken et al. 2015; Baweja et al. 2016; Hughes and Hendrickson 2019; Richmond et al. 2018; Diamantopoulou et al. 2019; Hajek et al. 2019; King et al. 2019; Sinharoy et al. 2018), soreness (Etter 2010; Farsalinos et al. 2013; Hua et al. 2013; Farsalinos et al. 2014; Cravo et al. 2016; Gomes et al. 2016; Li et al. 2016; Pratt et al. 2016; Rahman et al. 2016; Stein et al. 2016; Jankowski et al. 2017; Walele et al. 2018; Sinharoy et al. 2018), and cough (Caponnetto, Campagna et al. 2013b; Farsalinos et al. 2013, 2014; Hajek et al. 2015; Cravo et al. 2016; Gomes et al. 2016).

Similar to mouth effects, researchers from nine studies found that these complaints were mitigated in e-cigarette users compared to conventional cigarette smokers or dual users, with some e-cigarette users stating benefits of less coughing (Etter 2010; Caponnetto, Campagna et al. 2013b; Dawkins et al. 2013; Adriaens et al. 2014; Farsalinos et al. 2014), sore throat (Etter 2010; Farsalinos et al. 2013; Hua et al. 2013; Adriaens et al. 2014), irritation (Hua et al. 2013; Adriaens et al. 2014), and phlegm (Van Staden et al. 2013), regardless of nicotine content in e-cigarette fluid (Caponnetto, Campagna et al. 2013b). Throat irritation also was less commonly reported in e-cigarette users compared to the nicotine inhalator (Bullen et al. 2010) (an FDA approved and prescription based nicotine replacement therapy which delivers aerosolized, non-heated nicotine). Researchers in only one study noted differences in throat effects between e-cigarette users and users of nicotine replacement therapy. Hajek et al. (2019) reported that throat irritation was more frequently reported by e-cigarette users

compared to people using various nicotine replacement therapies.

Researchers in four studies investigated flavors/constituents of e-liquid. Participants using nicotine containing e-cigarettes were more likely to report sore throat and cough compared to users of nicotine-free e-cigarettes (Vakali et al. 2014). The symptom of throat irritation or harshness appeared to be mediated by menthol, with a stronger symptomatology at low nicotine concentrations, and weaker symptomatology at higher nicotine concentrations, suggesting that menthol may mask or reduce the perception of airway irritation and harshness caused by high levels of nicotine (Rosbrook and Green 2016). Some e-cigarette users described negative throat symptoms as being associated with particular e-liquid flavors like citrus, sour, cola, custard, or cinnamon (Li et al. 2016; Sinharoy et al. 2018).

Tonsillitis, tonsilloliths, uvulitis, para-tracheal edema and laryngitis were also reported by e-cigarette users (Hua et al. 2013; Frossard et al. 2015; Cravo et al. 2016). Contrary to these findings, in one case report of a nonsmoker turned e-cigarette user, the e-cigarette user experienced complete resolution of her tonsillitis and marked improvement in her tonsilloliths once she began using e-cigarettes (Miler and Hajek 2017). Other throat effects reported by e-cigarette users included throat throbbing, itchiness, numbness, persistent clearing of the throat, choking sensation, lump in throat sensation, difficulty swallowing, tenderness, hoarseness, and a burnt feeling (Hua et al. 2013; Li et al. 2016; Lewek et al. 2019).

Periodontal effects

Researchers examined periodontal effects in 20 studies (Table 4). The quality of evidence in this category ranged from weak to moderate. Researchers in a group of independent studies identified associations between e-cigarette use and periodontal disease. Al-Aali et al. (2018) found that e-cigarette users had increased levels of plaque, deeper probing depths, more bone loss, higher concentrations of localized inflammatory markers, and a high volume of sulcular fluid. Ismail et al. (2019) followed a cohort of e-cigarette users over 6 months and found significantly deteriorating periodontal health. In another study, researchers found that e-cigarette users were more than twice as likely to have periodontal disease compared to nonusers (Jeong et al. 2019). Similarly, Atuegwu et al. (2019) found that long-term e-cigarette users were more likely to have any kind of periodontal disease, or bone loss compared to occasional e-cigarette users. Other researchers found that e-cigarette users were almost three times more likely to report gingival disease compared to nonsmokers/nonusers (Vora and Chaffee 2019).

Some researchers, however, have noted that symptoms of periodontal disease are less likely in e-cigarette users compared to conventional smokers. Researchers from two independent studies found that clinical periodontal status and pro-inflammatory markers of e-cigarette users were similar to that of nonusers, with levels that were significantly less than that of conventional smokers (Javed et al. 2017; BinShabaib

Table 3. Publications describing throat effects ($n = 37$).

Study	Study design	Participants*	Sample size	Effects/symptoms	Measure/tool†	Quality of evidence‡
1. Adriaens et al. (2014)	RCT	Smokers not intending to quit randomized to: • E-cigarette Type 1 brand ($n = 16$) • E-cigarette Type 2 brand ($n = 16$) • Conventional cigarette control ($n = 16$) E-cigarette users Smokers not intending to quit randomized to: • E-cigarette with 16 mg nicotine • Placebo e-cigarette • Nicorette nicotine inhalator • Conventional cigarette control Smokers (not intending to quit) with schizophrenia	$N = 48$	Both e-cigarette groups had a lower overall complaint score than control group (inclusive of dry and irritated throat)	Online diary	Weak
2. Baweja et al. (2016)	Descriptive	Smokers desiring to quit randomized to: • E-cigarette group with 7.2 mg nicotine cartridges for 12 weeks ($n = 100$) • E-cigarette group 7.2 mg nicotine cartridges for 6 weeks followed by 5.4 mg nicotine cartridges for 6 weeks ($n = 100$) • Control: no-nicotine cartridges for 12 weeks ($n = 100$)	$N = 200$ $N = 40$	Throat irritation ($n = 8$) Throat irritation less commonly reported with placebo and 16 mg nicotine e-cigarette compared to inhalator	Online survey Self-report	Weak Moderate
3. Bullen et al. (2010)	Randomized cross-over trial	Smokers desiring to quit randomized to: • E-cigarette group with 7.2 mg nicotine cartridges for 12 weeks ($n = 100$) • E-cigarette group 7.2 mg nicotine cartridges for 6 weeks followed by 5.4 mg nicotine cartridges for 6 weeks ($n = 100$) • Control: no-nicotine cartridges for 12 weeks ($n = 100$)	$N = 14$	Throat irritation (14.4%)	Study diary	Weak
4. Caponnetto, Auditore et al. (2013a)	Quasi-experimental	Smokers desiring to quit randomized to: • E-cigarette group with 7.2 mg nicotine cartridges for 12 weeks ($n = 100$) • E-cigarette group 7.2 mg nicotine cartridges for 6 weeks followed by 5.4 mg nicotine cartridges for 6 weeks ($n = 100$) • Control: no-nicotine cartridges for 12 weeks ($n = 100$)	$N = 300$	Frequency for complaints of throat irritation and cough significantly decreased ($p < 0.001$) from baseline for all three groups.	Study diary	Weak
5. Caponnetto, Campagna et al. (2013b)	RCT	Current smokers randomized to: • E-cigarette group ($n = 306$) • Conventional cigarette group ($n = 102$)	$N = 419$	Throat symptoms reported in the e-cigarette group included: sore throat (27.8%), cough (17.0%), dry throat (2.9%), tonsillitis (1.3%) • Throat symptoms reported in the conventional cigarette group included sore throat (8.8%), cough (7.8%), and tonsillitis (1%)	Diary cards	Weak
6. Cravo et al. (2016)	RCT	Current smokers randomized to: • E-cigarette group ($n = 306$) • Conventional cigarette group ($n = 102$)	$N = 14$ $N = 1347$	Throat irritation (mean score of 27.25, SEM = 7.53) • 0.5% of both groups reported throat irritation • More ex-smokers reported improved cough ($p < 0.001$)	200 mm Visual analog scale Online survey	Weak Weak
7. Dawkins and Corcoran (2014)	Descriptive correlational	E-cigarette users	$N = 14$	16.8% of participants reported throat irritation after e-cigarette initiation	Self-report	Weak
8. Dawkins et al. (2013)	Comparative descriptive	E-cigarette users • Ex-smokers (i.e. exclusive e-cigarette users) ($n = 1123$) • Dual users ($n = 218$) • Never-smokers (6)	$N = 314$ $N = 38$	Throat irritation (8 reports by 5 subjects)	Self-report Self-report	Weak Weak
9. Diamantopoulou et al. (2019)	Descriptive	E-cigarette users recruited from vape shops	$N = 81$	• Sore throat ($n = 16$) • Less cough and fewer sore throats ($n = 23$) • Sore throat (27%) • Cough (13.5%) • Improved morning cough (58.6%) • Overall: Sore or dry throat (38.9%) and cough (12.8%) • Cough reported more frequently in current smoker group ($p < 0.001$)	Online survey	Weak
10. D'Ruiz et al. (2015)	Randomized cross-over trial	Conventional smokers	$N = 111$	Uvulitis and edema of para-tracheal musculature	Face to face interview	Weak
11. Etter (2010)	Descriptive	Exclusive e-cigarette users (former conventional smokers)	$N = 19,441$	Sore throat ($n = 3$) and cough ($n = 10$) reported to pharmacists	Online questionnaire	Weak
12. Farsalinos et al. (2013)	Descriptive	E-cigarette users • Former smokers ($n = 15,671$) • Current smokers ($n = 3682$)	$N = 1$		Clinical exam	Weak
13. Farsalinos et al. (2014)	Comparative descriptive	Community pharmacies	$N = 154$		Paper questionnaire	Weak
14. Frossard et al. (2015)	Case report	NA				
15. Gomes et al. (2016)	Descriptive	Community pharmacies				

(continued)

Table 3. Continued.

Study	Study design	Participants*	Sample size	Effects/symptoms	Measure/tool [†]	Quality of evidence [‡]
16. Hajek et al. (2015)	Quasi-experimental RCT	Smokers seeking to quit	N = 100	Some reports of throat irritation and minor coughing	Client feedback	Weak
17. Hajek et al. (2019)	RCT	Smokers seeking to quit • Nicotine replacement group (n = 447) • E-cigarette group (n = 439)	N = 886	<ul style="list-style-type: none"> Throat irritation reported more frequently in e-cigarette group Percent of participants reporting throat irritation did not differ between groups More negative than positive symptoms including: soreness, irritation, tenderness, throbbing, numbness, swelling, persistent clearing of throat, choking sensation, laryngitis, tonsillitis, tonsil stones, difficulty swallowing, hoarseness. Improved soreness, irritation and itchiness were also reported 	Self-report	Weak
18. Hua et al. (2013)	Descriptive	Posts from three internet e-cigarette forums	N = 632	<ul style="list-style-type: none"> Throat irritation (n = 4) 	Self-report	Weak
19. Hughes and Hendrickson (2019)	Descriptive	Poison center cases	N = 265	Throat irritation (n = 4)	Self-report	Weak
20. Jankowski et al. (2017)	Comparative descriptive	University students	N = 1906 (3.2% E-cigarette users)	38.2% e-cigarette users reported sore throat as immediate short-term side-effect	Self-report	Weak
21. King et al. (2019)	Descriptive	E-cigarette users	N = 1624	31% reported dry/irritated throat	Self-report	Weak
22. Lewek et al. (2019)	Descriptive	E-cigarette users	N = 1142	Throat itchiness reported by 4.5% of participants	Self-report	Weak
23. Li et al. (2016)	Descriptive correlational	Reddit posts	N = 493,994	<ul style="list-style-type: none"> "Throat feeling symptoms" were largely negative and described as dry, harsh, sore, and burnt. Some posts associated these negative symptoms with citrus, sour, cola, or custard flavors. 	Self-report	Weak
24. McRobbie et al. (2015)	Quasi-experimental	Smokers seeking to quit	N = 40	Dry throat (n = 2)	Self-report	Weak
25. Miller and Hajek (2017)	Case report	NA	N = 1	Nonsmoker with frequent tonsillitis and tonsilloiths who experience complete resolution of tonsillitis and marked improvement of tonsilloiths after several months of vaping	Self-report	Weak
26. Nides et al. (2014)	Quasi-experimental	Smokers not interested in quitting	N = 25	Throat irritation (n = 7) and dry throat (n = 1)	Self-report	Weak
27. Oncken et al. (2015)	Randomized crossover trial	Non-treatment seeking smokers randomized to: • E-cigarette with tobacco and menthol flavors • E-cigarette with tobacco flavor only Smokers not interested in quitting	N = 27	Throat irritation (n = 4)	Self-report	Weak
28. Polosa et al. (2014)	Longitudinal descriptive	Chronic smokers with serious mental illness	N = 40	Throat irritation	Self-report	Weak
29. Pratt et al. (2016)	Quasi-experimental	E-cigarette only users (n = 70)	N = 21	58% reported side effects including dry/sore throat	Researcher interview	Weak
30. Rahman et al. (2016)	Comparative descriptive	Dual users (E-cigarette + conventional cigarettes) (n = 148) Pediatricians	N = 220	Sore throat experienced by both groups	Study questionnaire	Strong
31. Richmond et al. (2018)	Descriptive	Pediatricians	N = 520	Pediatricians report throat irritation symptoms in children/teens who vape or ingest e-liquid	Survey	Weak
32. Rosbrook and Green (2016)	Quasi-experimental	Adult smokers	N = 32	Throat irritation/harshness increased with menthol concentration at low nicotine	Self-report	Weak

(continued)

Table 3. Continued.

Study	Study design	Participants*	Sample size	Effects/symptoms	Measure/tool [†]	Quality of evidence [‡]
33. Sinharoy et al. (2018)	Descriptive correlational	Long-term e-cigarette users	N= 552	concentrations, but had an ameliorating effect at high concentrations <ul style="list-style-type: none"> • Cinnamon flavor associated with throat irritation • Prevalence of sore throat significantly lower among long-term vapers (surveyed 3–5 years after baseline) 	Self-report	Weak
34. Stein et al. (2016)	Quasi-experimental	Smokers in methadone maintenance treatment desiring to quit	N= 12	Sore throat (n= 2)	Modified Minnesota Behavior Rating Scale Questionnaire	Weak
35. Vakali et al. (2014)	Comparative descriptive	Smokers and nonsmokers divided into two groups <ul style="list-style-type: none"> • E-cigarettes with 11 mg nicotine (n= 12/29) • E-cigarettes with 0 mg nicotine (n= 14/9) 	N= 64	Sore throat and cough more frequently reported for users of e-cigarettes containing 11 mg nicotine	Questionnaire	Weak
36. Van Staden et al. (2013)	Quasi-experimental	Conventional smokers	N= 15	Less phlegm (n= 10)	Questionnaire	Weak
37. Walele et al. (2018)	Quasi-experimental	Conventional smokers	N= 209	Sore throat (19.6%)	Medical Dictionary for Regulatory Activities and Investigator assessment	Weak

*When applicable.

[†]Measure/tool used for the oral health symptom.[‡]Note. The quality of evidence was evaluated for mouth effects.

et al. 2019). Researchers followed a group of conventional smokers and e-cigarette users longitudinally for 6 months after providing full mouth ultrasonic scaling (ALHarthi et al. 2019) and found deteriorating periodontal parameters over time in the conventional smokers, but not in e-cigarette users or nonusers. Mokeem et al. (2018) also found similarities between e-cigarette users and nonusers, in terms of probing depth, clinical attachment level, and marginal bone loss; however, they found that the plaque levels of e-cigarette users were lower than conventional smokers and higher than never-smokers. Descriptive findings from a pilot RCT testing the feasibility of a vaping intervention for smokers undergoing periodontal treatment were that improvements in mean pocket probing depths were similar between the group receiving standard smoking cessation advice and the one receiving a vaping intervention (Holiday et al. 2019).

Gingival bleeding is a symptom of periodontal disease and most of the studies in this category indicated that e-cigarette use was associated with decreased gingival bleeding on probing compared to nonuse (Farsalinos et al. 2014; Javed et al. 2017; Al-Aali et al. 2018; Mokeem et al. 2018). This suggests that e-cigarette use, like conventional smoking, may have a suppressive effect on gingival bleeding (Dietrich et al. 2004). The suppressive effect of e-cigarette use on gingival bleeding, however, may not be as strong as that of conventional cigarettes. Gingival pain/swelling, for example, was more frequently self-reported among conventional smokers than e-cigarette users or nonusers (Javed et al. 2017). Consistent with this, conventional smokers who switched to e-cigarette use (Wadia et al. 2016) or conventional smokers who exhibited increased purchasing of e-cigarettes experienced increased gingival bleeding (Wadia et al. 2016; Yao et al. 2017) and volume of gingival crevicular fluid (Wadia et al. 2016). Longitudinally, this effect may be attenuated. Tatullo et al. (2016) found that gingival bleeding on probing decreased over a 4-month period in e-cigarette users who were former smokers, even if they had been smoking for more than 10 years. They found that plaque levels also declined over time in former smokers who switched to e-cigarette use.

The effect of e-cigarettes on the success of implants was also investigated by various researchers. Peri-implant parameters (probing depth ≥ 4 mm, radiographic bone loss, proinflammatory cytokines, plaque index, peri-implant sulcular fluid) were significantly higher in e-cigarette users, conventional smokers, and water-pipe users compared to non-smokers/users (AlQahtani et al. 2018, 2019; ArRejaie et al. 2019). Researchers in two of these studies, however, noted that e-cigarette users demonstrated diminished periodontal symptoms compared to conventional smokers. AlQahtani et al. (2018) found significantly lower probing depths and bone loss measurements compared to conventional cigarette and waterpipe smokers. ArRejaie et al. (2019) also showed that plaque index scores and marginal bone loss were lower in e-cigarette users compared to conventional smokers.

Finally, Huilgol et al. (2019) suggested that daily e-cigarette use was associated with poorer oral health. They operationalized poor oral health by the number of permanent teeth removed. Tooth loss is a complex measure of oral

health since it can be caused by multiple determinants. However, considering that two of primary contributors of tooth loss are periodontal disease and dental caries (Haworth et al. 2018), the results of this study were considered to be relevant to both the periodontal and dental effects categories.

Dental effects

Nine studies included dental effects. The quality of evidence in this category was primarily weak, with two moderate quality study and two *in vitro* studies. Particular dental symptoms that were covered included: cracked or broken teeth (Cho 2017), toothache (Cravo et al. 2016; Yao et al. 2017; Walele et al. 2018), change in tooth coloration (Pintado-Palomino et al. 2019), caries (Ismail et al. 2019), tooth abscess (Walele et al. 2018), tooth sensitivity (Yao et al. 2017), and tooth loss/extraction (Huilgol et al. 2019; Walele et al. 2018). Cho (2017) found that the odds of reporting a “cracked or broken tooth” increased for e-cigarette users versus never users (daily users aOR = 1.65 [95% CI: 1.19–2.27]; past month users aOR = 1.26 [95% CI: 1.06–1.51]; former users aOR = 1.16 [95% CI: 1.04–1.30]). Toothache was reported as an adverse event among 6.9% of e-cigarette users compared to 3.9% of conventional cigarette users (Cravo et al. 2016), in 8.1% of conventional smokers who switched to e-cigarette use (Walele et al. 2018), and in 16.7% of conventional smokers who were “ever users” of e-cigarettes (Yao et al. 2017). Tooth abscess was reported as an adverse effect by 2.4% of conventional smokers who switched to e-cigarette use (Walele et al. 2018). Tooth sensitivity was reported by 29.1% of conventional smokers who were “ever users” of e-cigarettes (Yao et al. 2017). Many similar symptoms, i.e. toothache, dentine hypersensitivity, tooth loss, abscesses, and fractured/carious fillings were reported by smokers with periodontitis regardless of whether they were receiving standard smoking cessation advice or a vaping intervention (Holliday et al. 2019).

Ismail et al. (2019) found that a measure of dental caries significantly worsened over a 6-month period in a cohort of e-cigarette users ($p=0.002$). Dental caries are a major determinant of tooth loss, which was the measure that Huilgol et al. (2019) used to assess poor oral health. Poor oral health was found to be associated with daily e-cigarette use (aOR = 1.78, 95% CI: 1.39–2.30, $p<0.001$). Tooth extraction was reported as an adverse effect of e-cigarette use among 2.9% of conventional smokers who switched to e-cigarette use (Walele et al. 2018). Kim et al. (2018) suggested that a combination of viscosity of e-liquids and sweet flavors may increase the cariogenic potential of e-cigarettes. Exposure to flavored e-cigarette aerosols may potentiate cariogenic bacteria (see *Oral Microbiome Effects*) and was also associated with a 27% decrease in enamel hardness compared to unflavored control aerosols. Kim et al. (2018) identified calcium, iron and copper in e-cigarette aerosols, all metals which play a role in the mineralization/demineralization process of enamel. Flavors may also play a role in the discoloration of enamel. Researchers of an *in vitro* study (Pintado-Palomino

et al. 2019) assessed the impact of different e-liquid flavors (neutral, menthol, and tobacco) and nicotine concentrations on enamel color and found alterations in luminosity, particularly when enamel was exposed to e-liquids containing menthol and tobacco flavors.

Cytotoxic, genotoxic, and oncogenic effects

Twenty studies testing various brands, flavors, and nicotine concentrations of e-cigarette fluids investigated the cytotoxic, genotoxic, or oncogenic effect of e-cigarette vapors on oral cells/tissue. The quality of the evidence of human studies included in this section was all weak (Table 5). Ten studies describe the cytotoxic effect of e-cigarettes along with underlying mechanisms. Reductions in cell proliferation (Willershausen et al. 2014; Duggar et al. 2018), ATP detection (Willershausen et al. 2014), and cell viability (Welz et al. 2016; Yu et al. 2016) were demonstrated with e-liquid or vapor exposure. Exposure of e-cigarette vapor also resulted in L-lactate dehydrogenase (LDH) activity (Rouabhia et al. 2017), apoptosis (Yu et al. 2016; Rouabhia et al. 2017), and necrosis (Yu et al. 2016). Similarly, cytotoxic effects of nicotine containing e-cigarette fluid on human gingival fibroblast cells were confirmed with increased LDH levels, development of cytoplasmic vacuoles, decreased collagen I production, and augmented LC3 II expression (Sancilio et al. 2017). There were conflicting findings regarding the effect of e-cigarette vapor on cell morphology with one study reporting alterations (Rouabhia et al. 2017) and another reporting no effect (Iskandar et al. 2019).

Researchers from several studies examined mechanisms underlying the cytotoxicity of e-cigarette exposure on oral tissue cells. E-cigarette aerosols were noted to cause cytotoxicity to human oral keratinocytes via an oxidative stress response, as indicated by a significant dose-dependent decrease of intracellular glutathione levels (Ji et al. 2016). Another proposed mechanism may be the upregulation of the unfolded protein response (UPR) pathway, which may lead to apoptosis and cytotoxicity (Ji et al. 2019). Increased cellular activity leading to apoptosis included increased reactive oxygen species (ROS) production and BAX (a strong proapoptotic protein) expression (Sancilio et al. 2016). Exposure to e-cigarette aerosols with flavorings has also been associated with increases in protein carbonylation, a hallmark of oxidative cell damage, in periodontal ligament fibroblasts and human gingival epithelium progenitors (Sundar et al. 2016).

Researchers in two independent studies investigated the presence of harmful downstream metabolites known to be associated with conventional smoking among e-cigarette users. The presence of *N*'-nitrosonornicotine (NNN), a known oral carcinogen was detected in the saliva of 16 out of 20 exclusive e-cigarette users (Bustamante et al. 2018) suggesting the possibility that e-cigarette use may be linked with the endogenous formation of this tobacco-specific *N*-nitrosamine. Another known carcinogen, thiocyanate, was identified in the saliva of e-cigarette users at similar levels to that of conventional smokers (Flieger et al. 2019).

Researchers in six *in vitro* studies demonstrated the genotoxic effects of e-cigarette vapor exposure. Two different brands of e-cigarette aerosol extracts, independent of nicotine concentration, induced DNA damage in a dose-dependent manner, with chronic exposure resulting in highly mutagenic oxidative DNA damage (Ganapathy et al. 2017) and Yu et al. (2016) found increased DNA strand breaks with exposure to e-cigarette vapor exposed cells. Mechanistically, while exposure to e-cigarette extracts increased ROS, total antioxidant capacity (TAC) decreased, as did the expression of 8-oxoguanine DNA glycosylase (OGG1), an enzyme critical for the removal of oxidative DNA damage (Ganapathy et al. 2017). Similar increases in DNA damage were found with e-cigarette aerosol exposure in periodontal ligament fibroblasts, human gingival epithelium progenitors, and a human epigingival tissue model (Sundar et al. 2016). E-cigarette vapor exposure also induced the metabolism of benzo(a)pyrene, a known tobacco carcinogen, to several genotoxic metabolites suggesting that dual users who are exposed to benzo(a)pyrene may be at even greater risk for cancer (Sun et al. 2019). Two studies that examined markers of genotoxicity in human subjects provide ambivalent results. Whereas Tommasi et al. (2019) identified the deregulation of critically important genes in the oral transcriptome associated with cancer related pathways and functions, Franco et al. (2016) performed a cytologic examination of oral mucosal scrapings from three groups (conventional smokers, e-cigarette users, and nonsmokers) and found that oral cavity cells of e-cigarette users had a prevalence of micronuclei similar to those of healthy controls, and significantly lower than that of conventional smokers.

Researchers conducting five independent studies with human subjects used flavored e-liquids to investigate cytotoxic and genotoxic effects. Ji et al. (2016) and Sundar et al. (2016) used both tobacco and menthol flavors, however, their findings spoke to cytotoxic effects of the overall e-liquids and were not designed to parse out the effects of individual components of the liquids. Duggar et al. (2018) demonstrated that grape flavor liquid, regardless of nicotine content adversely effected cell growth. Welz et al. (2016) demonstrated that fruit flavored e-liquids were associated with DNA fragmentation, whereas the tobacco flavored product was not. Willershausen et al.'s (2014) results of reduced cell proliferation and detection of ATP were a result of exposure to menthol flavored liquid.

Exposure to e-cigarette aerosols with flavorings was associated with increases in pro-inflammatory cytokines and inflammation in periodontal ligament fibroblasts, human gingival epithelium progenitors, and a human epigingival tissue model (Sundar et al. 2016). Further evidence of the inflammatory effect of e-cigarette liquid was its influence on inducing receptor for advanced glycation end-products (RAGE) signaling with the transcription of various pro-inflammatory cytokines (Hirschi et al. 2017). RAGE is a multiligand pattern recognition receptor implicated in chronic inflammation (Rouhiainen et al. 2013). Exposure to e-cigarette aerosols may induce an inflammatory response that is different from that induced by cigarette smoke. Researchers identified that e-cigarette aerosols induced the secretion of $IL-1\alpha$ suggesting the

Table 4. Publications Describing Periodontal Effects ($n = 20$).

Study	Study Design	Participants	Sample Size	Effects/Symptoms	Measurement/Tool ^a / Assay	Quality of Evidence ^b
1. Al-Aali et al. 2018	Comparative descriptive	<ul style="list-style-type: none"> E-cigarette users ($n = 47$) Never smokers ($n = 45$) 	$N = 92$	<ul style="list-style-type: none"> Plaque index, probing depth, peri-implant bone loss and proinflammatory cytokines higher in e-cigarette users Less bleeding on probing in e-cigarette users 3 and 6 months post scaling follow up: Conventional smokers had higher plaque index and probing depth than e-cigarette users ($p < .05$) No significant difference in plaque index or probing depth at either time point between e-cigarette users and non-users 	<ul style="list-style-type: none"> Clinical and radiographic examination Self – reported Questionnaire Clinical Periodontal examination 	Moderate
2. AlHarthi et al. 2019	Comparative descriptive	<ul style="list-style-type: none"> Conventional smokers ($n = 30$) E-cigarette users ($n = 28$) Non-users ($n = 31$) 	$N = 89$	<ul style="list-style-type: none"> Peri-implant plaque index ($p < .05$), Probing depth ($p < .05$), bone loss ($p < .01$) and proinflammatory cytokines were higher in waterpipe, conventional cigarette and e-cigarette users compared to non-smokers. Probing depth and bone loss lower in e-cigarette users compared to other smokers. 	<ul style="list-style-type: none"> Questionnaire Clinical and radiographic examination 	Moderate
3. AlQahtani et al. 2018	Comparative descriptive	<ul style="list-style-type: none"> Waterpipe smokers (40) E-cigarette users (40) Conventional smokers (40) Non-smokers (40) 	$N = 160$	<ul style="list-style-type: none"> Plaque index and probing depth were higher in all smokers compared to non-smokers ($p < .05$) 	<ul style="list-style-type: none"> Clinical examination Questionnaire 	Weak
4. Alqahtani et al. 2019	Comparative descriptive	<ul style="list-style-type: none"> Waterpipe smokers (33) E-cigarette users (34) Conventional smokers (35) Non-smokers (35) 	$N = 102$	<ul style="list-style-type: none"> Peri-implant plaque index, probing depth, bone loss and cytokines were higher in conventional smokers compared to other groups ($p < .001$) Bleeding on probing highest in non-smokers compared other groups ($p < .001$) 	<ul style="list-style-type: none"> Clinical and radiographic examination 	Moderate
5. ArRejaie et al. 2019	Comparative descriptive	<ul style="list-style-type: none"> E-cigarette users (31) Conventional Smokers (32) Non-smokers (32) 	$N = 95$	<ul style="list-style-type: none"> Compared to never vapers, long-term vapers had increased odds of having: Gum disease (OR = 1.76, CI 1.12-2.76) Bone loss around teeth (OR = 1.67, CI 1.06-2.63) 	<ul style="list-style-type: none"> Population based survey (Population Assessment of Tobacco and Health Adult Survey) 	Moderate*
6. Atuegwu et al. 2019	Correlational	<ul style="list-style-type: none"> Never vapers ($n = 9,632$) Long-term regular vapers ($n = 329$) Occasional vapers ($n = 8,298$) 	$N = 18,289$	<ul style="list-style-type: none"> Higher levels of gingival crevicular fluid in conventional smokers compared to e-cigarette users or non-smokers ($p < .05$) Higher levels of pro-inflammatory cytokines in conventional smokers compared to e-cigarette users and non-smokers ($p < .05$) No differences gingival crevicular fluid or pro-inflammatory cytokines between in e-cigarette and non-smoker groups 	<ul style="list-style-type: none"> Clinical and radiographic examination 	Weak
7. BinShabaib et al. 2019	Comparative descriptive	<ul style="list-style-type: none"> Conventional cigarette smokers ($n = 46$) E-cigarette users ($n = 44$) Non-Smokers ($n = 45$) 	$N = 135$	<ul style="list-style-type: none"> No association with gingival pain/bleeding controlling for various confounders 	<ul style="list-style-type: none"> Web-based survey 	Moderate
8. Cho, 2017	Comparative descriptive	<ul style="list-style-type: none"> Korean high school students Never user ($n = 56,017$) Former user ($n = 5,499$) Past month user ($n = 2,109$) Daily user ($n = 1,903$) 	$N = 65,528$	<ul style="list-style-type: none"> Gingival bleeding ($< 5\%$) 	<ul style="list-style-type: none"> Face to face interview 	Weak
9. Farsalinos et al. 2013	Quasi-experimental	<ul style="list-style-type: none"> Exclusive e-cigarette users (former conventional smokers) 	$N = 111$	<ul style="list-style-type: none"> Gingivitis/gum bleeding higher among former smokers (14.4%) compared to current smokers (7.4%) ($p < .001$) 	<ul style="list-style-type: none"> Online questionnaire 	Weak
10. Farsalinos et al. 2014	Comparative descriptive	<ul style="list-style-type: none"> E-cigarette users Former smokers ($n = 15,671$) Current smokers ($n = 3,682$) 	$N = 19,441$			

(continued)

Table 4. Continued.

Study	Study Design	Participants	Sample Size	Effects/Symptoms	Measurement/Tool/ ^a Assay	Quality of Evidence ^b
11. Holliday et al. 2019	RCT	Current smokers not currently using e-cigarettes • Standard smoking cessation advice ($n = 40$) • Standard smoking cessation advice + e-cigarette ($n = 40$) • Good oral health ($n = 221, 336$) • Poor oral health ($n = 234, 977$) • E-cigarette users at baseline and at 6 months • E-cigarette users ($n = 31$) • Conventional smokers ($n = 33$) • Non-users ($n = 30$)	$N = 80$	• Baseline mean pocket probing depths and six-month improvements similar between both groups	Clinical exam	Moderate
12. Huilgol et al. 2018	Comparative descriptive	• E-cigarette users ($n = 456, 343$) • Good oral health ($n = 221, 336$) • Poor oral health ($n = 234, 977$)	$N = 456, 343$	Daily e-cigarette use associated with higher odds of poor oral health (aOR = 1.78, 95% CI: 1.39-2.30, $p < 0.001$)	Phone survey	Weak
13. Ismail et al. 2019	Longitudinal descriptive	• E-cigarette users at baseline and at 6 months • E-cigarette users ($n = 31$) • Conventional smokers ($n = 33$) • Non-users ($n = 30$)	$N = 45$	Measures of periodontal health declined at 6 months ($p < .05$)	Clinical exam	Weak
14. Javed et al. 2017	Comparative descriptive	• E-cigarette users ($n = 31$) • Conventional smokers ($n = 33$) • Non-users ($n = 30$)	$N = 94$	• Plaque index and probing depth higher in conventional smokers than e-cigarette users or non-users ($p < 0.01$) • BOP higher in non-users compared to the other two groups ($p < 0.01$) • Gingival pain and swelling more frequently self-reported among conventional smokers than e-cigarette users or non-users ($p < 0.01$) • Gingival bleeding more frequently self-reported in non-users compared to conventional smokers • Periodontal disease more likely for: • E-cigarette users compared to non-users (OR = 2.34, CI: 1.52-3.59) • Conventional smokers compared to non-users (OR = 2.17, CI: 1.76-2.68)	• Questionnaire • Clinical periodontal examination • Radiographs	Weak
15. Jeong et al. 2019	Comparative descriptive	• E-cigarette users ($n = 222$) • Conventional smokers ($n = 2,320$) • Former smokers ($n = 2,667$) • Non-users ($n = 8,342$) • Conventional smokers ($n = 39$) • Water pipe users ($n = 40$) • E-cigarette users ($n = 37$) • Never-smokers ($n = 38$)	$N = 13,551$	Percentage of sites with plaque higher for conventional smokers and water pipe users compared to e-cigarette users and never-smokers ($p < .05$). However, percentage of sites with plaque higher for e-cigarette users compared to never-users ($p < .05$) • Sites with bleeding on probing higher for never-smokers compared to the other three groups ($p < .05$) • Probing depth, clinical attachment level, and marginal bone loss higher among conventional and water pipe users compared to e-cigarette and never-smokers ($p < .05$)	Population based survey	Moderate
16. Mokeem, Alasqah et al. 2018	Comparative Descriptive	• E-cigarette users ($n = 222$) • Conventional smokers ($n = 2,320$) • Former smokers ($n = 2,667$) • Non-users ($n = 8,342$) • Conventional smokers ($n = 39$) • Water pipe users ($n = 40$) • E-cigarette users ($n = 37$) • Never-smokers ($n = 38$)	$N = 129$	Percentage of sites with plaque higher for conventional smokers and water pipe users compared to e-cigarette users and never-smokers ($p < .05$). However, percentage of sites with plaque higher for e-cigarette users compared to never-users ($p < .05$) • Sites with bleeding on probing higher for never-smokers compared to the other three groups ($p < .05$) • Probing depth, clinical attachment level, and marginal bone loss higher among conventional and water pipe users compared to e-cigarette and never-smokers ($p < .05$)	Clinical and radiographic examination	Weak
17. Tatullo et al. 2016	Comparative descriptive	E-cigarette users with: • < 10 years of prior conventional smoking ($n = 60$) • > 10 years of prior conventional smoking ($n = 50$) • Never users (28.1% conventional cigarettes (13.1%) • E-cigarette (0.3%) • Cigar (1.1%) • Pipe (0.1%) • Hookah (0.5%)	$N = 110$	Improvement in plaque index levels over time for both groups • Decreased bleeding on probing over time for both groups	Clinical examination	Weak
18. Vora and Chaffee 2019	Comparative descriptive	• E-cigarette users (28.1% conventional cigarettes (13.1%) • E-cigarette (0.3%) • Cigar (1.1%) • Pipe (0.1%) • Hookah (0.5%)	$N = 32,320$	Compared to never users the highest odds for gingival diagnosis were: • E-cigarette users (OR = 2.9, CI: 1.9 - 4.5) • Multiple tobacco product users (OR = 2.8; CI: 2.4 - 3.4), • Pipe users (OR = 2.7, CI: 1.3 - 5.3)	Population based survey	Strong

(continued)

Table 4. Continued.

Study	Study Design	Participants	Sample Size	Effects/Symptoms	Measurement/Tool ^a / Assay	Quality of Evidence ^b
19. Wadia et al. 2016	Longitudinal descriptive	Conventional smokers who switch to e-cigarettes	N = 20	<ul style="list-style-type: none"> Bleeding on probing sites and gingival crevicular fluid increased after vaping Minimal change in plaque levels 	Clinical and laboratory examination (for cytokine and GCF fluid detection)	Weak
20. Yao et al. 2017	Descriptive correlational	Current conventional and e-cigarette adult users in US	N = 533	Gingival bleeding related to increased e-cigarette expenditures (AOR = 1.23 [1.02, 1.49])	Tobacco and Attitudes Beliefs Survey	Weak

^aMeasure/Tool used for the periodontal effect.

^bNote. The level of evidence was evaluated for periodontal effects.

triggering of a stress-sensing mechanism (Iskandar et al. 2019).

Researchers in one clinical study examined the oncogenic potential of e-cigarette use. In this case-control study evaluating the prevalence and characteristics of oral mucosal lesions in former smokers compared to e-cigarette users, the prevalence of nicotine stomatitis, a pre-cancerous lesion, was higher in the e-cigarette using group (Bardellini et al. 2018). Case reports of oral carcinomas associated with heavy and long-term e-cigarette use were also found (Nguyen et al. 2017).

Nicotine concentrations of e-liquids tested in *in vitro* studies along with timing of vapor exposure have been listed in Table 5 (when identified in the studies reviewed). Concentrations accurately reflect that of publicly available brands lending validity to the findings that cellular level changes occur with e-liquid exposure. While some *in vitro* studies applied vapor exposures that approximated real-world vaping habits and volumes (Ganapathy et al. 2017), others did not (Hirschi et al. 2017).

Oral microbiome effects

Researchers in ten studies investigated the impact of e-cigarette use on the oral microbiota. The quality of evidence for most of the human studies in this category was weak. Oral candidiasis, primarily caused by *Candida albicans* was significantly more prevalent in e-cigarette users compared to non-smokers/nonvapers and the prevalence of candidiasis did not differ from that of conventional cigarette smokers (Mokeem et al. 2019). Similarly, Bardellini et al. (2018) found that e-cigarette users had a significantly higher frequency of hyperplastic candidiasis compared to former conventional cigarette smokers. Alanazi et al. (2019) demonstrated that exposure to e-cigarette vapor with or without nicotine promoted the growth, chitin content, and hyphal length of *C. albicans*, and increased the expression of virulent *C. albicans* genes like *SAP2*, *SAP3*, and *SAP9*. They also showed that co-culture with e-vapor-exposed *C. albicans* increased gingival epithelial cell differentiation and reduced the growth of this organism. These effects for e-cigarette exposure were significantly greater than that of non-exposed controls, but less than that of cultures exposed to conventional smoke.

Given the prevalence of candidiasis and related symptoms among e-cigarette users, an influence on the oral microbiome would be anticipated. In a diary of adverse symptoms, oral herpes, for example, has been reported by some e-cigarette users (Cravo et al. 2016). Pathogenic *streptococcus* may also be affected by e-cigarette use. An *in vitro* study that analyzed the cariogenic potential for various flavored e-cigarette liquids tested five types of flavors (hexyl acetate-apple/plum, ethyl butyrate-pineapple, sucralose-sugar substitute, triacetin-“velvety” or “smoky” flavor, and ethyl maltol-cotton candy). Four out of five flavors (sucralose, ethyl butyrate, triacetin, hexyl acetate) significantly increased biofilm formation compared to an unflavored e-liquid control, and the viscosity of the e-liquid facilitated the adhesion of cariogenic *S. mutans* to the dental surface (Kim et al. 2018).

Table 5. Publications describing cytotoxic, genotoxic, and oncogenic effects ($n = 20$).

Study	Study design	Participants/cell line	Sample size/E-liquid exposure	Effects/symptoms	Measure/tool/assay	Quality of evidence*
1. Bardellini et al. (2018)	Comparative descriptive	<ul style="list-style-type: none"> Former conventional cigarette smokers ($n = 45$) Current e-cigarette smokers ($n = 45$) 	$N = 90$	E-cigarette smokers had higher frequency of nicotine stomatitis lesions (13.3% versus 2.2%, $p < 0.05$)	Clinical exam	Weak
2. Bustamante et al. (2018)	Comparative descriptive	<ul style="list-style-type: none"> Conventional smokers ($n = 20$) E-cigarette users ($n = 20$) Nonusers ($n = 19$) 	$N = 59$	16/20 e-cigarette users had quantifiable levels of N'-nitrosonornicotine in their saliva	LC-MS/MS	Weak
3. Duggar et al. (2018)	<i>In vitro</i>	Cultured oral keratinocyte model	Grape flavored e-liquid	Adverse effect on cell growth, regardless of the absence or presence of nicotine	Colorimetric assay	NA
4. Flieger et al. (2019)	Comparative descriptive	<ul style="list-style-type: none"> Conventional smokers ($n = 8$) E-cigarette users ($n = 8$) Nonsmokers ($n = 8$) 	$N = 24$	Salivary levels of thiocyanate in e-cigarette users similar to conventional smokers and significantly greater than nonsmokers	HPLC-UV	Weak
5. Franco et al. (2016)	Comparative descriptive	<ul style="list-style-type: none"> E-cigarette users Conventional smokers ($n = 23$) E-cigarette users ($n = 22$) Nonsmokers ($n = 20$) 	$N = 65$	Prevalence of micronuclei decreased in the e-cigarette user group compared to the conventional smokers ($p < 0.005$)	Micronucleus assay test	Weak
6. Ganapathy et al. (2017)	<i>In vitro</i>	<ul style="list-style-type: none"> Human epithelial normal bronchial cells Human premalignant dysplastic oral mucosal keratinocyte cells Human oral squamous cell carcinoma cells 	Two 55mL puffs per minute of: <ul style="list-style-type: none"> NJoy 12 mg/ml nicotine NJoy 18 mg/ml nicotine eGo 0 mg/ml nicotine eGo 12 mg/ml nicotine eGo 18 mg/ml nicotine Exposed to Cutwood brand e-liquid (0, 2%, 4%) for 24 hours	E-cigarette aerosol extracts induced DNA damage in a dose-dependent manner, independent of nicotine concentration	<ul style="list-style-type: none"> DNA damage detection assay (q-PADDA) 8-oxo-dG ELISA assay 	NA
7. Hirschi et al. (2017)	<i>In vitro</i>	<ul style="list-style-type: none"> Gingival epithelium cells Pulmonary epithelium cells Placenta trophoblast cells 	Various concentrations of reference cigarette: Puff duration = 5 secs. Duration of exposure = 28 min	<ul style="list-style-type: none"> RAGE upregulation Increased transcription of IL-1b, IL-6, IL-8 and TNF-a in each cell type 	<ul style="list-style-type: none"> LDH assays Quantitative RT-PCR QPCR 	NA
8. Iskandar et al. (2019)	<i>In vitro</i>	Organotypic human buccal epithelial and small airway epithelial cells	<ul style="list-style-type: none"> Did not affect morphology of buccal cells Induced a different inflammatory response compared to cigarette smoke 	<ul style="list-style-type: none"> Did not affect morphology of buccal cells Induced a different inflammatory response compared to cigarette smoke 	<ul style="list-style-type: none"> Histological assessment Multi-analyte inflammatory mediator assay Transcriptomics 	NA
9. Ji et al. (2016)	<i>In vitro</i>	Normal human oral keratinocytes	<ul style="list-style-type: none"> Three formulations of e-cigarette aerosol (test mix, base, carrier): Puff duration = 2 secs. Duration of exposure = 28 min Tobacco flavor (0 mg/ml nicotine) Tobacco flavor (24 mg/ml nicotine) Menthol flavor (0 mg/ml nicotine) Menthol flavor (24 mg/ml nicotine) 	E-cigarette aerosols induced oxidative stress	ATP Assay	NA
10. Ji et al. (2019)	<i>In vitro</i>	Normal human oral keratinocytes (NHOK)	NHOK culture media treated for 15 min with e-liquid of e-liquid mixture (29.3% propylene glycol, 68.3% vegetable glycerin, and nicotine (2.4 mg/l))	E-cigarette aerosols activate the unfolded protein response pathway	<ul style="list-style-type: none"> DNA microarray qPCR Western blot 	NA
11. Nguyen et al. (2017)	Case report	Two long term daily e-cigarette users	Not stated	Two cases of oral carcinoma	<ul style="list-style-type: none"> Medical diagnosis 	Weak

(continued)

Table 5. Continued.

Study	Study design	Participants/cell line	Sample size/E-liquid exposure	Effects/symptoms	Measure/tool/assay	Quality of evidence*
12. Rouabhia et al. (2017)	<i>In vitro</i>	Human gingival epithelial cells	EMOW brand (12 mg/ml nicotine) – 2 puffs every 60 seconds for 15 minutes for 1–3 days E-liquid from Halo Company (0 and 24 mg/ml nicotine)	E-cigarette vapor: <ul style="list-style-type: none"> Altered morphology of cells Increased LDH activity Increased apoptosis/necrosis Exposure to e-cigarette fluid increased ROS production and Bax expression followed by apoptosis occurrence	<ul style="list-style-type: none"> Microscopy LDH Cytotoxicity Assay FITC Binding assay MTT Assay Flow cytometry Fluorescence optimal microscopy 	NA
13. Sancilio et al. (2016)	<i>In vitro</i>	Human gingival fibroblasts	E-liquid from Halo Company (0 and 24 mg/ml nicotine)	E-cigarette fluids with nicotine exerted cytotoxicity as demonstrated by: <ul style="list-style-type: none"> Increased LDH levels Decreased collagen I production Augmented LC3 II expression 	<ul style="list-style-type: none"> LDH Assay Flow cytometry lysosome compartment analysis ELISA for collagen I Western blot 	NA
14. Sancilio et al. (2017)	<i>In vitro</i>	Human gingival fibroblasts	E-liquid from Halo Company (0 and 24 mg/ml nicotine) Exposure times up to 48 hours	Enhanced metabolism of BaP to genotoxic metabolites	<ul style="list-style-type: none"> HPLC qPCR Western blot 	NA
15. Sun et al. (2019)	<i>In vitro</i>	Human oral keratinocyte	<ul style="list-style-type: none"> BLU Classic tobacco 2.4% nicotine 35 mL puff/minute using a 4 s duration at 30 s intervals BLU® <ul style="list-style-type: none"> Classic tobacco flavor (16 mg nicotine) Magnificent menthol flavor (0 mg or 13–16 mg nicotine) 2 puffs/min for time durations up to 15 min N= 93	<ul style="list-style-type: none"> Increased protein carbonylation and pro-inflammatory responses in HPdLFs and HGEPP Increased inflammation and DNA damage markers in HPdLFs and HGEPP and epiglottal tissue model 	<ul style="list-style-type: none"> Comet assay Protein carbonylation/oxylot ELISA for cytokines Western blotting 	NA
16. Sundar et al. (2016)	<i>In vitro</i>	<ul style="list-style-type: none"> Human periodontal ligament fibroblasts (HPdLFs) Human gingival epithelium progenitors (HGEPP) Human 3D model of epiglottal tissue 	<ul style="list-style-type: none"> E-cigarette users (n= 42) Conventional smokers (n= 24) Nonsmokers/users (n = 27) 	E-cigarette users demonstrated deregulation of genes associated with cancer related pathways and functions	<ul style="list-style-type: none"> RNA Seq analysis Gene ontology and canonical pathway analysis qPCR 	Moderate
17. Tommasi et al. (2019)	Comparative descriptive	<ul style="list-style-type: none"> E-cigarette users (n= 42) Conventional smokers (n= 24) Nonsmokers/users (n = 27) 	<ul style="list-style-type: none"> Happy Liquid brand (each with 12 mg/ml nicotine) Apple flavor Cherry flavor Tobacco flavor Incubated with 250 µl liquid for various lengths of time E-liquids from eSmokersShop <ul style="list-style-type: none"> Hazelnut flavor (20 mg/ml nicotine) Lime flavor (20 mg/ml nicotine) Menthol flavor (22 mg/ml flavor) Incubated for up to 96 hours V2 brand, Red American tobacco flavor (0 and 12 mg/ml nicotine) VaporFI brand, Classic tobacco flavor (0 and 12 mg/ml nicotine) Treated for 1–8 weeks 	<ul style="list-style-type: none"> All liquids caused reduction in cell viability. Fruit flavors showed higher toxicity than tobacco flavor. DNA fragmentation increased in fruit flavors, but not tobacco flavor 	<ul style="list-style-type: none"> Water-soluble tetrazolium-8 assay Alkaline microgel electrophoresis 	NA
18. Welz et al. (2016)	<i>In vitro</i>	Mucosal tissue culture from fresh tissue samples of healthy oropharyngeal mucosa	<ul style="list-style-type: none"> Human periodontal ligament fibroblasts 	Exposure to menthol flavored liquid resulted in: <ul style="list-style-type: none"> Reduced cell proliferation ($p < 0.001$) Reduced detection of ATP ($p < 0.001$) 	<ul style="list-style-type: none"> PrestoBlue Cell Viability Assay ApoGlow Bioassay Microscopy Migration assay 	NA
19. Willershausen et al. (2014)	<i>In vitro</i>	Human periodontal ligament fibroblasts	<ul style="list-style-type: none"> Normal epithelial cells Head and neck squamous cell carcinoma 	Exposure resulted in: <ul style="list-style-type: none"> Reduced cell viability with increased rates of apoptosis and necrosis, regardless of nicotine content. Increased DNA strand breaks. 	<ul style="list-style-type: none"> Annexin V flow cytometric analysis Trypan blue exclusion, and clonogenic assays Neutral comet assay and γ-H2AX immunostaining. 	NA

**In vitro* studies were not evaluated.

Investigators also considered changes in salivary components that affect the oral microbiota. Immunoglobulin A, lactoferrin and lysozymes engage in antimicrobial activity within the oral environment. Cichońska et al. (2019) found levels of these components to be highest among nonusers/smokers, followed by e-cigarette users, and then conventional smokers suggesting that the antibacterial potential of e-cigarette users may be impaired compared to nonusers/smokers.

Next generation sequencing techniques have been used to study the effect of e-cigarette use on the oral microbiome. Kumar et al. (2019) presented two studies that suggested that the oral microbiome of e-cigarette users may be distinct, with a higher abundance of Proteobacteria as well as the opportunistic pathogens *Rothia* and *Haemophilus*. Additionally, they identified 1353 microbial genes unique to e-cigarette users that encoded for antibiotic resistance, motility chemotaxis, stress response, horizontal gene transfer, cell wall, iron acquisition, and membrane transport. These functions were attributed to several pathogens belonging to genera including *Fusobacteria* and *Prevotella*.

The impact of e-cigarette use on the oral microbiome, however, is equivocal. An *in vitro* study was conducted to evaluate the effect of non-flavored e-cigarette aerosols on commensal and protective oral microbiota from the genus *Streptococcus*: *S. gordonii*, *S. intermedius*, *S. mitis* and *S. oralis*. The bacterial colonies were exposed to conventional smoke and flavorless e-cigarette aerosol with/without nicotine. While the survival and growth of these members of the normal oral flora were severely impacted by conventional cigarette smoke, e-cigarette aerosol with or without nicotine had little to no effect on the viability of these organisms (Cuadra et al. 2019). This study was extended to examine the effect of the same flavorless e-liquid with/without nicotine added directly to culture media on planktonic growth of three species: *S. Gordonii*, *S. Mitis*, and *S. Oralis* (Nelson et al. 2019). Findings confirmed that conventional smoke-treated growth media, but not e-liquid or aerosol, inhibited the growth of oral commensal streptococci. Additionally, researchers used 16S rRNA sequencing to look at the oral microbiome of e-cigarette users and found no effect on microbiome diversity and taxonomic relative abundance (Stewart et al. 2018),

Trauma/accidental injury

In addition to a report identifying e-cigarette overheating, fire, and explosive incidents reported to federal agencies, media outlets, and in the scientific literature before September of 2015 (Rudy and Durmowicz 2017), ten case reports presented oral trauma related to e-cigarette explosions. Details of these injuries can be found in Table 6. Case reports represent the weakest level of evidence. All were published between 2015 and 2018. The majority of the case reports involved an explosion related injury. Out of these, four case reports specifically mention that the e-cigarette devices were powered by a lithium operated battery (Brownson et al. 2016; Harrison and Hicklin 2016; Kumetz et al. 2016; Brooks et al. 2017). The treatment for these traumatic injuries primarily involved wound care, burn care,

dental extractions and other dental treatment. One report identified long-term consequences after an explosive injury which included insomnia, flashbacks, and depression (Kumetz et al. 2016). Explosion injuries primarily resulted in burns and lacerations to the perioral area, and injury to the teeth including fractures, avulsions, or luxation (Cason et al. 2016; Moore et al. 2016; Rogér et al. 2016; Rudy and Durmowicz 2017; Chi et al. 2018). One reported explosion injury resulted in the propulsion of the mouthpiece of the e-cigarette through the pharynx, and into the first cervical vertebra resulting in a spinal fracture (Norii and Plate 2017). Other causes of injury included a fall with the e-cigarette in the mouth (Andresen et al. 2018) and what appeared to be an allergic type reaction that included an onset of symptoms of dyspnea within two days of beginning e-cigarette use (Frossard et al. 2015).

Discussion

Research on the oral health impact of e-cigarette use is only just beginning to emerge. This review describes the current state of the research with implications for future research directions.

The majority of mouth and throat symptoms experienced by e-cigarette users were relatively minor and temporary. Furthermore, the mitigation of mouth and throat symptoms experienced by conventional smokers who switch to e-cigarettes may suggest e-cigarette use as a harm reduction strategy with regard to oral health outcomes. It is important to note, however, that these studies were not designed to test mouth and throat effects of e-cigarette use, were mostly cross-sectional and descriptive, and did not always account for important confounders such as age, general health status, length or duration of previous conventional smoking, or medications, severely hampering the quality of evidence provided. Future clinical, epidemiologic, rigorously designed, and longitudinal research is needed.

Future areas of focus suggested by this review include a closer examination of the association between e-cigarette use and oral lesions, since two studies found that candidiasis was more prevalent in e-cigarette consumers compared to former smokers (Bardellini et al. 2018) or nonsmokers/non-vapers (Mokeem, Abduljabbar, et al. 2018). Testing flavor components of e-cigarette fluids is also warranted given the findings that the frequency of mouth irritation increased with menthol and cinnamon (Rosbrook and Green 2016; Sinharoy et al. 2018) and that negative throat symptoms were associated with particular e-liquid flavors like citrus, sour, cola, or custard (Li et al. 2016).

Periodontal health is an important consideration. Studies have shown associations between periodontal disease and various disease states, including cardiovascular disease, respiratory disease, and adverse pregnancy outcomes (Garcia et al. 2001). Although studies that examined periodontal effects were more rigorously designed for periodontal outcomes, the evidence was not conclusive. Overall, the results appear to be consistent with studies that described mouth and throat effects; namely, there is some evidence that e-

Table 6. Case reports of oral trauma/accidental injury ($n = 10$).

Study	Patient(s) details	Cause	Description/location of injury	Treatment
Andresen et al. (2018)	Male	Fall with e-cigarette in mouth	Diffuse supraglottic edema that was most severe in the epiglottis, arytenoids, aryepiglottic folds	<ul style="list-style-type: none"> Resulted in intubation and eventual tracheostomy which remained in place for 3 months NG tube feeding for 2 weeks and then PEG tube placed At 6 months, patient remained tube feeding dependent
Brooks et al., (2017)	18-year-old male	Explosion	<ul style="list-style-type: none"> Multiple fractures to teeth, avulsion, and luxation Greenstick fracture to premaxilla and comminuted fracture to anterior nasal spine Soft tissue intra oral lacerations Face lacerations 	Extensive extraction of teeth
Brownson et al. (2016)	15 patients over 8 months	Explosions	<p>Injuries included:</p> <ul style="list-style-type: none"> Flame burns Chemical burns Blast injuries resulting in tooth loss and extensive loss of soft-tissue Burns to face, chest and hands Fractured hard palate and nasal septum Dislocation of teeth Fractured finger Corneal abrasion 	<p>Treatment included:</p> <ul style="list-style-type: none"> Operative debridement and closure of tissue defects Wound care and skin grafting
Cason et al. (2016)	23-year-old male	Explosion	<ul style="list-style-type: none"> Burns to face, chest and hands Fractured hard palate and nasal septum Dislocation of teeth Fractured finger Corneal abrasion 	<ul style="list-style-type: none"> Admission to trauma burn ICU Step-down for pain management Repair of hard palate followed by dental implants
Chi et al. (2018)	20-year-old male	Explosion	<ul style="list-style-type: none"> Tooth avulsion Lip burns and lacerations 	<ul style="list-style-type: none"> Treatment for burns and lacerations Tooth extraction Pain medication
Harrison and Hicklin (2016)	28-year-old male	Explosion	<ul style="list-style-type: none"> Teeth fractures Teeth avulsion, fracture, and subluxation 	Dental and implant treatments
Kumetz et al. (2016)	29-year-old male	Explosion	<ul style="list-style-type: none"> Intraoral burns Superficial burns to perioral region Lip lacerations Tooth avulsion Mass of hard and soft palatal tissue 	<ul style="list-style-type: none"> Wound debridement Closure of the lip lacerations Palatal tissue reduction Tooth extraction Dental implant surgery Long-term complication of insomnia, flashbacks to the incident, and depression
Moore et al. (2016)	22-year-old male	Explosion	<ul style="list-style-type: none"> Lower lip laceration Burn over lingual frenulum Tooth fracture and avulsion 	Treated with minimal intervention
Norii and Plate (2017)	27-year-old male	Explosion	<ul style="list-style-type: none"> Mouthpiece of e-cigarette device propelled through the pharynx and into cervical vertebra causing fracture 	Surgical removal of foreign object
Rogér et al. (2016)	18-year-old male	Explosion	<ul style="list-style-type: none"> Oral and abdominal burns Oral lacerations Tooth fracture and avulsion 	<ul style="list-style-type: none"> Extraction Implant and prosthesis

cigarette users are at increased risk for deteriorating periodontal and gingival health compared to nonsmokers/users, but decreased risk compared to conventional smokers. Nicotine has a vasoconstrictive effect on gingival tissue (Al-Bayaty et al. 2013). This would explain why most studies indicated that e-cigarette use was associated with decreased gingival bleeding compared to nonuse, or why conventional smokers who switched to e-cigarette use may experience increased gingival bleeding.

Descriptive findings from this review suggest that e-cigarette use may have dental consequences. In particular, e-liquid flavor constituents may have a role in enamel breakdown as well as potentiating cariogenic bacteria. Furthermore, case reports included in this review describe extensive dental damage as sequelae from explosions occurring with e-cigarette. From 2015 to 2017, there were an estimated 2035 persons with e-cigarette explosions and burn injuries that presented to emergency departments in the United States (Rossheim et al. 2019). The U.S. Food and Drug Administration's (2017) Center for Tobacco Products now regulates all e-cigarette components, including batteries which are often culpable in explosive events. This entity offers an explosion reporting site as well as tips for consumers on how to avoid explosions (U.S. Food and Drug Administration 2017), and recommendations for manufacturers submitting new product applications to provide information regarding battery amperage, voltage, and wattage among other things for the FDA to assess battery risks (U.S. Food and Drug Administration 2017).

Given the implications of microbial ecology on oral health, future research must incorporate investigations of the microbiome. Future research should parse the impact of individual constituents of e-cigarettes on not only individual organisms, but the entire oral ecosystem. Microbiome studies that additionally investigate downstream microbial metabolites and associations with inflammatory markers have the potential to shed light on both oral and extraoral effects of e-cigarette use.

Chemicals and carcinogens in conventional cigarette smoke are known risk factors for various oral diseases including cancer and periodontal disease (Kumar et al. 2016; Vogtman et al. 2017). E-cigarettes are marketed as a safer alternative to conventional smoking. However, components of e-cigarette vapor have known cytotoxic, genotoxic, and carcinogenic properties. E-cigarette vapor contains glycerol, propylene glycol, and nicotine, as well as fine particles of flavors, aroma transporters, trace amounts of carcinogens, and heavy metals (Grana et al. 2014), like nickel and aluminum (U.S. Department of Health and Human Services 2016). Humectants like glycerol and propylene glycol, when oxidized, lead to the formation of aldehydes like formaldehyde, acetaldehyde, and acrolein in e-cigarette vapor (Jensen et al. 2015). These free radical species are well-known as genotoxic agents (Yu et al. 2016) and have been shown to create inflammation leading to tissue damage (Lerner et al. 2015). Propylene glycol, when heated and aerosolized, is converted to propylene oxide, which is considered to be a carcinogen in humans (World Health Organization 2013). Other known carcinogens associated with conventional smoking have also been identified in the saliva of e-cigarette users. These include NNN and thiocyanate (Bustamante et al. 2018; Fliieger et al., 2019).

As with conventional smoking, e-cigarette vapor is delivered directly into the user's mouth, initiating contact with the oral epithelium. The *in vitro* studies in this review demonstrated reduced cell proliferation and viability, altered cell morphology and activity, promotion of apoptosis and necrosis, DNA damage, and increased transcription of pro-inflammatory cytokines suggesting cytotoxic, genotoxic, and inflammatory effects. These studies suggest that e-cigarette vapor is not innocuous at the cellular level. Further research is needed to differentiate the impact of individual components like flavor particles on alterations at the cellular level.

Limitations and recommendations for future research

A major limitation of this review is that the majority of the studies were not primarily designed to evaluate the oral health effects of e-cigarette use. Many of the mouth, throat, and dental effects were measured as ancillary findings, using methods of measurement like self-report surveys or diaries to measure the oral health outcome of interest, without clinical verification. Definitions of e-cigarette smoking varied widely from having used e-cigarettes exclusively for at least 1 year (Javed et al. 2017) to using e-cigarettes in the past month (Cho 2017). Nicotine concentrations when identified in the reviewed studies can be found in corresponding tables. However many studies did not capture nicotine concentrations and/or the frequency/duration of vaping behaviors, further limiting our understanding of the association between exposure dose and response/outcome. Finally, because our literature search was comprehensive, it included studies that were presented as abstracts with limited information making it challenging for us to evaluate the quality of the evidence.

Recommendations for future research include further *in vitro* studies to isolate the effect of e-liquid and aerosol constituents, including flavors. These *in vitro* studies should be followed up with animal models. Clinical studies must include reliable and valid assessment measures/tools to capture exposure dose, evaluate oral health outcomes, rigorously control for confounders related to oral health, and have tightly controlled biomarker validated comparison groups of conventional smokers, e-cigarette users, and nonsmokers. Researchers must also consider that e-liquid may be altered with additional ingredients. This customizable characteristic of e-cigarettes makes it possible for users to inhale drugs other than nicotine (Mulder et al. 2019). Customized e-liquids may be formulated by the e-cigarette user themselves, or purchased commercially. For example, non-nicotine formulations like marijuana-based e-liquids (Peace et al. 2016) are available for purchase. Given the variability of e-cigarette devices and liquids, researchers will need to consider both device, liquid, and alterations to either of the two in order to best understand the impact of e-cigarette use on oral health outcomes.

Conclusion

This review presents a summary of the current landscape of research that exists on e-cigarettes and oral health. Given the low level of evidence in terms of oral health outcomes

among many studies in this review, outcomes are not conclusive, but do suggest that e-cigarette use may mitigate negative mouth, throat, and periodontal symptoms in conventional smokers. Nonsmokers who are considering adopting e-cigarette use as a new behavior, however, should be aware that e-cigarette use may be associated with mouth and throat discomfort, oral mucosal lesions, changes in the oral microbiome, dental, and periodontal damage, and changes at the cellular level of oral tissue, and that constituents of e-liquid/vapor and/or downstream metabolites of these constituents have potentially dangerous genotoxic and carcinogenic properties. Furthermore, e-cigarette users must be made aware of the risks for traumatic injury related to explosions and of toxic cellular effects demonstrated by *in vitro* studies. Further research is needed to understand long-term clinical outcomes of the oral health impact of e-cigarette use, with a particular focus on effects related to age and product flavorings, given the widespread use among adolescents, and the attraction that adolescents have to flavored e-cigarette products.

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Declaration of Interest

The authors declare that there are no conflicts of interest. The employment affiliations of the authors are shown on the cover page. These authors have the sole responsibility for the writing and content of this article. Thoughts and opinions expressed within this work are those of the three authors and do not necessarily reflect those of their employers. The authors involved with this project have received support from numerous other sources for other research projects (detailed below). No funding from these other sources, however, was used in the current review, evaluation, or preparation of this manuscript.

I. Yang and J. Rodriguez have conducted research investigating the oral microbiome of e-cigarette users, and secondhand e-cigarette vapor exposure among children of vapers. Funding for this work was from NIEHS; however, none of it was received for the preparation of this manuscript.

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