



Physical and mental health outcomes associated with adolescent E-cigarette use

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ABSTRACT

Introduction: Use of electronic cigarettes (e-cigarette) and other electronic nicotine delivery systems (ENDS) among adolescents has increased dramatically, creating a need for research to examine the consequences of e-cigarette use on adolescent health. Given the emergent state of the research literature, this integrative review sought to summarize what is currently known about the physical and mental health outcomes associated with e-cigarette use in an adolescent population, and to identify directions for future research.

Method: The methodology for this integrative review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. A methodical search was conducted in February 2020 in PubMed, CINAHL, and Web of Science databases. To be eligible for inclusion, studies had to address e-cigarette use, have samples that were between 13 and 24 years of age, be published in a peer-reviewed journal, and examine health outcomes associated with e-cigarette use. After the screening process, 18 studies were included.

Results: Physical health outcomes associated with e-cigarette use included oral health and respiratory problems as well as nicotine dependence. Mental health outcomes included depression and suicidal ideation. In studies that compared e-cigarette use to conventional cigarette use and non-use, e-cigarettes tended to be associated with more problems than non-use, but fewer problems than conventional cigarette use. Dual use, that is, use of both conventional cigarettes and e-cigarettes, was associated with the greatest harm.

Conclusion: Although somewhat less harmful than conventional cigarettes, e-cigarette use is related to a variety of negative physical and mental health outcomes among adolescent users.

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Introduction

Adolescents' use of electronic cigarettes (e-cigarettes) has increased rapidly and dramatically in recent years, making e-cigarettes the most commonly used tobacco products among U.S. adolescents and young adults (Gentzke et al., 2020). Electronic cigarettes are a type of electronic nicotine delivery system (ENDS) that resemble traditional cigarettes, through which liquid nicotine is vaporized and inhaled. According to Monitoring the Future (MTF) data from 2020, the rate of e-cigarette use among adolescents more than doubled from 2017 to 2019, resulting in the largest two-year increase observed by MTF, which stalled in 2020 (Miech et al., 2020). The prevalence rates for 2020 were 19.6% among high school students and 4.7% among middle school students; 40% of high school users were frequent or daily users (Miech et al., 2020). As e-cigarette use increases, many questions about the progression of use, long-term health consequences, and

impact on adolescent developmental outcomes remain unanswered. The potential for long-term harm, coupled with its perceived attractiveness makes adolescent e-cigarette use a critical public health problem that requires urgent attention (Centers for Disease Control and Prevention [CDC], 2020a).

"E-cigarettes" refer to devices that resemble traditional cigarettes and are marketed under various names, such as "e-cigs," "e-hookahs," "mods," "vape pens," "vapes," and "tank systems." The term e-cigarette is often interchangeably used with the term, "ENDS." E-cigarettes deliver nicotine and other types of addictive chemicals that have flavors added to make them more attractive to users (Audrain-McGovern et al., 2019). They can also be used to deliver substances other than nicotine, such as marijuana. New devices are being continuously developed. For example, recently, JUUL, a type of e-cigarette, has become increasingly prevalent among youth, accounting for 76% of the dollar share of e-cigarettes in 2018 (Fadus et al., 2019). This device delivers nicotine at a concentration of 5%, has the appearance of a USB drive, and can fit in the palm of the user's hand, making it attractive and easy to conceal. In spite of the fact that it is illegal to sell e-cigarettes to anyone under the age of 21 years (US Food and Drug Administration, 2021), adolescents are able to access e-cigarettes

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through purchasing them online or from others (Pepper et al., 2018). Due to the lack of consistency and regulation in the manufacture of e-cigarette devices and solutions, the concentration of nicotine and other chemicals varies greatly across devices (Cobb & Abrams, 2014). This lack of consistency and regulation could place adolescents at heightened risk of addiction or other harm resulting from exposure to toxins that may be present in the vaping solution (Cobb & Abrams, 2014).

E-cigarettes were originally marketed as a smoking reduction/cessation alternative for adult cigarette smokers. Although e-cigarette use may reduce harm among adult smokers, research indicates that it could place adolescents at greater risk for adverse outcomes, including other substance use and nicotine dependence (Park et al., 2020; Ren & Lotfipour, 2019; Westling et al., 2017). Compounding this risk is the perception among adolescents that e-cigarette use is relatively harmless, which increases likelihood of use (Park et al., 2019). Even though e-cigarettes may be less harmful than conventional cigarettes, they contain deleterious substances (Goniewicz et al., 2014; Kosmider et al., 2014). Nicotine, which most e-cigarettes contain, is a highly addictive chemical that has detrimental effect on brain cells and blood vessels, and causes cardiovascular disease and brain diseases (Cross et al., 2017). Some cancer-causing toxins, such as formaldehyde and acetaldehyde, have been found in e-cigarette flavoring and vapor (Kosmider et al., 2014; Lavacchi et al., 2020). E-cigarettes also affect lung function and the respiratory system by causing a pulmonary inflammatory response (Davidson et al., 2019; Glynos et al., 2018). In particular, when flavoring substances were added to propylene glycol, vegetable glycerol, and nicotine, which are common chemicals in e-cigarettes, this effect was exacerbated. This may pose a risk to adolescents who are attracted to using flavored e-cigarettes (Soneji et al., 2019). Diacetyl is another toxic substance that have been reported to cause severe lung problems, such as acute bronchiolitis obliterans caused by e-cigarette flavorings (Barrington-Trimis et al., 2014). In addition, vitamin E acetate or tetrahydrocannabinol (THC) contained in e-cigarette vapor are among the major substances linked with e-cigarette or vaping product use-associated lung injury (EVALI), outbreak, which is one of the most commonly reported clinical cases (CDC, 2020b).

E-cigarette use also exerts a potential impact on mental health outcomes among adults. As with other substances, associations between e-cigarette use and mental health symptoms were reported (Grant et al., 2019; Marsden et al., 2019; Pham et al., 2020). For example, among university students, e-cigarette users were more likely to have mental health issues, such as higher impulsivity (Grant et al., 2019). Another study found that e-cigarette use was associated with depressive symptoms and suicide attempts, and this association was stronger than among non-cigarette smokers (Pham et al., 2020). Although there has been some research to document the harmful effects of e-cigarettes among adults, there is scant research examining the mental health risks associated with e-cigarette use in adolescent populations.

Purpose of this review

Adolescence is a particularly sensitive time in human development characterized by tremendous biological and social change. Involvement in risky behavior, including experimentation with substances is common (Steinberg, 2014). Developmental changes in the brain increase adolescents' sensitivity to rewards, so the positive effects of substances like nicotine are especially reinforcing, particularly when peers are approving of use (Steinberg, 2014). Introduction of substances during this period can adversely affect brain development, increasing risk of addiction (Vogel et al., 2019) and other substance use (Ren & Lotfipour, 2019). Once initiated, e-cigarette use tends to progress over the course of adolescence along with other substance use and carries over into emerging adulthood (Dunbar et al., 2017; Park et al., 2020). Thus, the health consequences of e-cigarette use might be more serious and far reaching for adolescents compared with adult-initiated users (Buchmann et al., 2013; Ren & Lotfipour, 2019).

Given this rapid increase in e-cigarette use among adolescents, who are at a developmentally sensitive stage in their lives, a great deal of concern has been expressed about the present and future public health implications. Much of the extant research on adolescent e-cigarette use has focused on e-cigarettes as a risk factor for traditional cigarette use or other types of substance use (e.g., Fulton et al., 2018; Park et al., 2020; Soneji et al., 2017). Research on physical and mental health outcomes associated with e-cigarette use in an adolescent population is beginning to emerge, providing some evidence of serious health consequences with mental and physical outcomes, including potential influences on the risk of addiction to nicotine and respiratory complaints such as asthma (Clapp & Jaspers, 2017). The purpose of this integrative review is to organize and summarize what is presently known about the health consequences associated with e-cigarette use among adolescents and to identify the gaps in that research. Integrative reviews are particularly useful in the early stages of understanding a phenomenon because they use a broad and diverse sampling approach to synthesize extant research (Toronto, 2020). This information can then be used to draw conclusions and guide future areas of research. This review was guided by the following questions: (1) What physical health concerns have been associated with e-cigarette use among adolescents? (2) What mental health concerns have been associated with e-cigarette use among adolescents? (3) What are the gaps in the literature related to understanding the health consequences associated with e-cigarette use among adolescents?

Method

Search overview

The methodology for this integrative review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA; Moher et al., 2009) guidelines. Integrative reviews are the broadest type of research review and can be used to evaluate and summarize research evidence from a variety of sources (Whittemore & Knaf, 2005). Given our objectives of summarizing existing research evidence identifying associations between e-cigarette use and health outcomes among adolescents, we restricted the review to quantitative studies conducted with adolescent samples. In keeping with the PRISMA guidelines, the authors developed a protocol to define objectives, methods, and inclusion/exclusion criteria prior to study selection and data extraction.

Data sources

A methodical search was conducted in February 2020 in PubMed, CINAHL, and Web of Science databases using keywords and medical subject headings (MeSH) listed in Table 1.

Search strategy

The objectives of the review were to synthesize the literature that examined physical and mental health-related outcomes associated with e-cigarette use in adolescent samples. In addition, we sought to

Table 1
Keywords and medical subject headings (MeSH):

Category 1 (consequences)	Category 2 (e-cigarette)	Category 3 (population)
<ul style="list-style-type: none"> • Physical health • Mental health • Addiction • Substance • Health-related • Health outcomes • Health consequences • Health problems 	<ul style="list-style-type: none"> • Electronic cigarette • Electronic vaporizer • Electronic nicotine • Electronic nicotine delivery systems (ENDS) • Vaping • Electronic cigarette use • E-cigarettes • E-cigarette use 	<ul style="list-style-type: none"> • Adolescent • Young adult

identify and summarize gaps in the existing literature related to understanding the impact of e-cigarette use on adolescent physical and mental health. The Medical Subject Heading (MeSH) key words used in the search were organized around three concepts: health outcomes, e-cigarette use, and target population. The term “health outcomes” refers to studies that examined a physical (e.g., respiratory symptoms) or mental health (e.g., depression) problem, condition, or symptoms that were associated with e-cigarette use. Sample key words included “physical health,” “mental health,” “health consequences,” and “health outcomes.” To identify studies that addressed e-cigarette use, we searched on “electronic cigarettes,” “e-cigarettes,” and related terms including “ENDS,” and “vaping.” Our target population was adolescents ages 13–24 years of age, thus we searched for “adolescent” and “young adult.” The full list of key words organized by these categories are presented in Table 1. A step-wise method to search the databases was used by exploring and combining three concepts from the MeSH key words, as represented by three categories in Table 1, with assistance of a Health Science Librarian who had expertise in systematic and integrative review searching. An example of full Web of Science search strategy is provided in Table 2. This search strategy was adapted to the syntax and consistently applied to the rest of the database.

Inclusion and exclusion criteria

Quantitative and mixed-method research papers were searched and selected using specific inclusion and exclusion criteria (see Table 3). We excluded qualitative studies due to our focus on reviewing empirical studies that examined health outcomes in a measurable or observable way. In order to keep the scope of the review as broad as possible, the reviewers did not restrict study inclusion to a particular health outcome, geographic location, gender, or target population with the exception of excluding participants under age 13 or above age 24. This age range was selected given our interest in adolescents. We opted to include samples up through 24 years of age in light of evidence that brain development continues into the 20’s, as well as cultural shifts that have extended adolescence into the early 20’s (Steinberg, 2014). Studies were restricted to those performed within the past ten years (2010–2020), that included empirical data and at least one condition in which e-cigarette use was examined independent of conventional cigarettes and marijuana (i.e., permitted an examination of the unique effects of e-cigarettes). Studies that focused on attitudes or beliefs about e-cigarette use without measurement of a health outcome were excluded, as were studies that included other substance use as the only outcome. Intervention studies, reviews, and animal models were also excluded. A full list of inclusion and exclusion criteria are presented in Table 3.

Data extraction, analysis, and synthesis

The search identified 2255 studies; after 538 duplicates were removed, 1717 studies were screened for inclusion (Figure 1). All titles

Table 2
Syntax of web of science search.

Number	Query	Results
1	ALL FIELDS: (physical health) OR ALL FIELDS: (mental health) OR ALL FIELDS: (addiction) OR ALL FIELDS: (substance) OR ALL FIELDS: (health-related) OR ALL FIELDS: (health outcomes) OR ALL FIELDS: (health consequences) OR ALL FIELDS: (health problems)	2,636,590
2	ALL FIELDS: (electronic cigarette) OR ALL FIELDS: (electronic vaporizer) OR ALL FIELDS: (electronic nicotine) OR ALL FIELDS: (electronic nicotine delivery systems) OR ALL FIELDS: (vaping) OR ALL FIELDS: (electronic cigarette use) OR ALL FIELDS: (e-cigarettes) OR ALL FIELDS: (e-cigarettes use)	7267
3	ALL FIELDS: (adolescent) OR ALL FIELDS: (young adult)	698,620
4	#3 AND #2 AND #1	706

Table 3
Inclusion and exclusion criteria:

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • age 13–24 years • electronic cigarettes or ENDS • peer-reviewed journal • published between 2010 and 2020 • focused on health outcome associated with e-cigarette or ENDS use 	<ul style="list-style-type: none"> • age < 13 • age > 24 • published prior to 2010 • studies focused on perceptions of e-cigarettes or ENDS rather than actual outcomes • studies focused on only substance use associated with e-cigarette or ENDS use without reporting physical or mental health outcomes • studies in which e-cigarette use was not examined independent of combustible cigarette use or other vaporized substances • feasibility-focused paper • review article • intervention study • conference abstract • dissertation study • animal model

and abstracts were imported into Covidence, a program that assists with management of systematic and integrative reviews. All four authors participated in the review process. Each title and abstract were independently reviewed by two of the four reviewers to determine if the article met the eligibility criteria presented in Table 3. From the pool of 1717 articles, 165 were retained for full text review. The full texts for these articles were imported into Covidence and each article was subjected to an in-depth review by two of the authors to confirm that the inclusion criteria had been met (i.e., addressed a physical or mental health outcome associated with e-cigarette use in an adolescent sample). In cases where there was ambiguity about whether the inclusion criteria had been met, the two senior authors (authors 1 and 4) reviewed the measures and outcomes and determined whether the study should be included. For example, there were some studies that considered “vaping” and did not clearly differentiate between use of nicotine or other substances (e.g., THC, non-nicotine flavored cartridges). These studies were excluded. Another example would be studies that included outcomes based on self-report. If the self-reported outcome referred to a specific, measurable condition, symptom, or problem (e.g., shortness of breath, cough), they were retained; outcomes that focused on subjective perceptions of harm without reference to specific conditions, problems or symptoms were excluded. The full text review resulted in a final sample of 18 studies. For each of these studies we extracted the study purpose, design (i.e., cross-sectional, longitudinal), sample size and characteristics (e.g., age, geographic location), measurement of e-cigarette and health outcomes, key findings, and the study limitations and summarized them in a matrix. Extracted data is summarized in Table 4.

Quality appraisal

Study quality was evaluated by the Agency for Healthcare Research and Quality (AHRQ) quality evaluation guideline for observational studies (West et al., 2002). Six domains were evaluated, including (a) the study question, (b) the study population, (c) outcome measures, (d) statistical analysis, (e) results, and (f) discussion. (a) The study question domain is evaluated according to whether the purpose of the study is clearly written and appropriate. (b) The Study population domain is evaluated according to whether that population is clearly described, with inclusion and exclusion criteria and the sampling procedures, described in detail. (c) The outcome measure domain was evaluated according to whether the primary and secondary outcomes were clearly defined, outcomes were assessed with valid and reliable measures. (d) The statistical analysis domain was evaluated

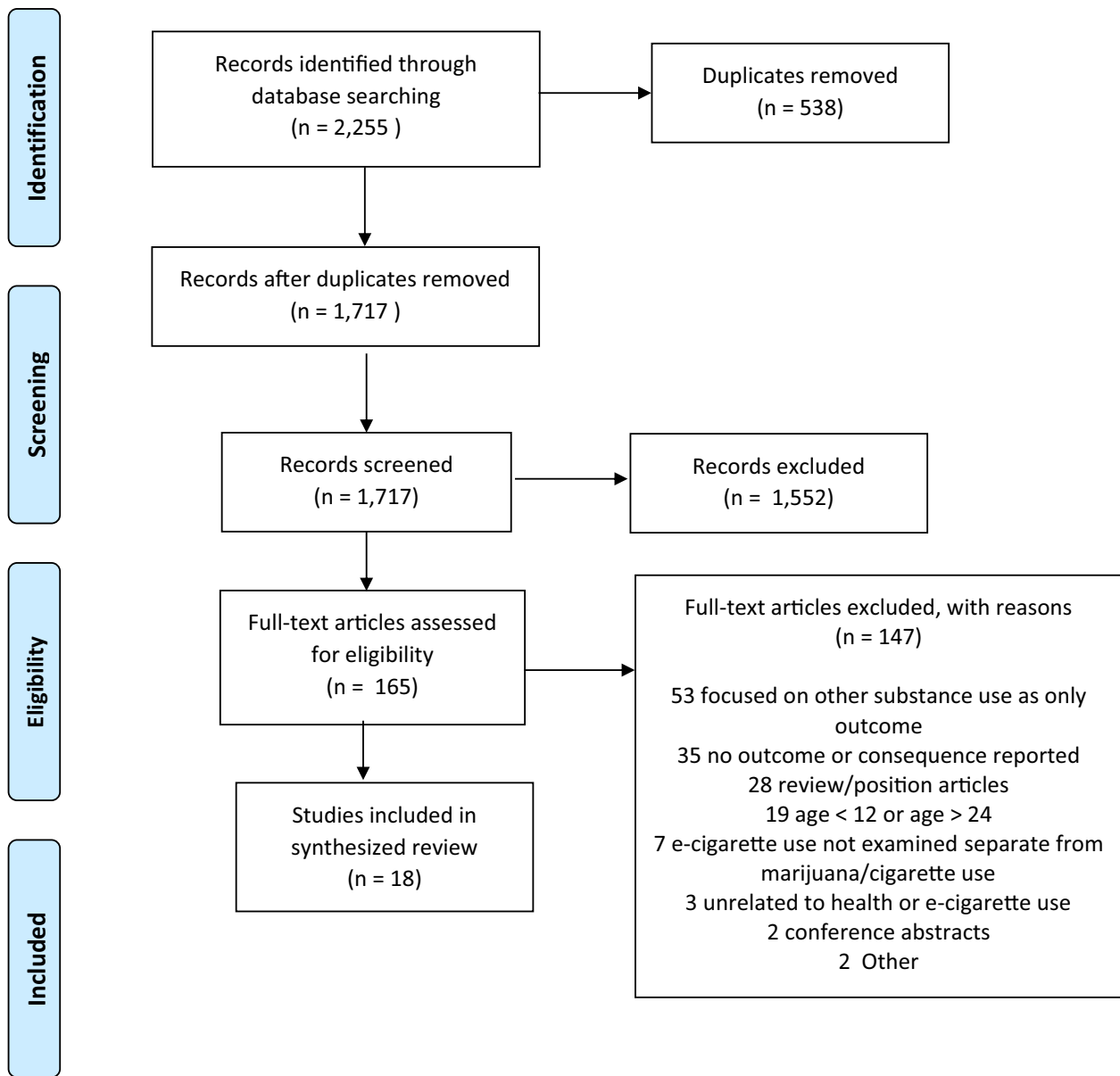


Fig. 1. PRISMA flow diagram.

according to whether appropriate statistical tests were used for research questions, confounding variables and multiple comparisons were considered. (e) The results domain was assessed according to whether the results were supported by the study method and analysis. (f) Discussion domain was assessed by whether the conclusions were supported by results with the consideration of potential bias or limitations. Each domain was evaluated by the two authors to ascertain whether each domain was completely addressed, partially addressed, or not addressed.

Results

The structured database search is depicted in a PRISMA diagram (see Figure 1).

Characteristics of included studies

A total of 18 studies met eligibility criteria and were included in this review. Of these, 14 were conducted in the United States, four were

done in South Korea, and one study was conducted in Canada. Most of the studies were cross-sectional (15/18) and used high school and middle school samples (15/18). Three of the studies used college samples (Bandiera et al., 2016; Bandiera et al., 2017; King et al., 2018). The review revealed that health outcomes associated with e-cigarette use, specifically, use of e-cigarettes, could be classified into physical health and mental health problems.

Physical health problems associated with E-cigarettes use

E-cigarettes users inhale an aerosol by heating a liquid solution containing nicotine and flavoring chemicals through the mouth into the lungs (CDC, 2020b). The chemicals and oxidant metals present in aerosol from e-cigarette use have the potential to cause damage to tissues in the mouth, lungs and heart (Barrington-Trimis et al., 2014; National Academies of Sciences, Engineering and Medicine, 2018). Consistent with this, the physical health outcomes addressed by studies in this review included oral health, respiratory disease symptoms (Akinkugbe, 2019; Chen et al., 2017; Cho, 2017; Cho & Paik, 2016; McConnell et al.,

Table 4
Summary matrix of the included articles (*n* = 18).

First author, year	Study purpose	Design	Sample size (characteristics; location)	E-cig related measurements	Health outcome measurements	Main findings related to e-cig use and health outcomes	Limitations
Ainkugbe, 2019	Investigate associations between self-reported use of cigarettes and e-cig on the oral health status of US adolescents	Cross-sectional (secondary data analysis from the 2013–2014 wave of the Population Assessment of Tobacco and Health [PATH] study)	N = 13,650 (12–17 yo, 48.7% female; US)	Ever use: ever tried vaping e-cig Current use: past 30-day use of e-cigs; Composite variable: current use of both cigarettes and e-cig, e-cig only, cig only, never-use	Self-reported provider diagnosis with dental problems (past yr)	<ul style="list-style-type: none"> Reported past 30 days reported use of both conventional cigarettes and e-cig, and ever use of both were 1.39% and 7.08%, respectively. Compared to never-users, those who had used e-cig in the past 30 days had higher odds of having dental problems, although modest and statistically non-significant. Current use of both conventional cigarettes and e-cigs in the past 30 days was associated with a significant increased prevalence odd of past-year provider diagnosis with dental problems. 	Self-report; cross-sectional; limited heterogeneity
Bandiera et al., 2016	Examine the associations between four alternative tobacco and nicotine products (i.e., cigars, smokeless tobacco, hookah, e-cig) and depressive symptoms in college students	Cross-sectional (secondary data analysis from the 2014–2015 wave 1) of the Marketing and Promotions across Colleges in Texas Project [Project M-PACT])	N = 5438 (college students, 18–29 yo [mean age 20.5 years], 63.8% female; US)	Current use: past 30-day use of cigarettes, smokeless/snus tobacco, large cigars/cigarillos/little cigar, hookah, and/ e-cig	Center for Epidemiologic Studies Depression Scale – short form (CES-D 10, past week)	<ul style="list-style-type: none"> Among cigars, smokeless tobacco, hookah, and e-cig, only e-cigs use was positively associated with depressive symptoms, after controlling socio-demographic characteristics and current use of the other alternative tobacco and nicotine products. 	Self-report; cross-sectional
Bandiera et al., 2017	Examine the longitudinal associations between e-cig use and elevated depressive symptoms in college students	Longitudinal (secondary data analysis from the 2014–2015 [wave 1–3] of the Marketing and Promotions across Colleges in Texas Project [Project M-PACT])	N = 5445 (college students, 18–29 yo [mean age 20.5 years], 63.8% female; US)	Current use: past 30-day use of cigarettes, smokeless/snus tobacco, large cigars/cigarillos/little cigar, hookah, and/ e-cig	Center for Epidemiologic Studies Depression Scale – short form (CES-D 10, past week)	<ul style="list-style-type: none"> Elevated level of depressive symptoms predicted subsequent e-cig use 6 months later, after controlling for socio-demographic characteristics and current use of the other alternative tobacco and nicotine products. 	Self-report; limited generalizability
Case et al., 2018	Examine the prevalence and association between symptoms of e-cig dependence, e-cig usage group, and e-cig cessation-related items among adolescents	Cross-sectional (secondary data analysis from the 2016 [wave 4] of the Texas Adolescent Tobacco and Marketing Surveillance System [TATAMS])	N = 132 (7th, 9th, and 11th grade students; US)	Current use: past 30-day use of cigarettes, smokeless/oral tobacco, large cigars/cigarillos/little cigar, hookah, and/ e-cig Use category: exclusive e-cig use; dual-users (both e-cig and combustible tobacco products)	Symptoms of e-cig dependence: adapted from the Hooked on Nicotine Checklist (5-items), Fagerstrom Tolerance Questionnaire (1-item) E-cig cessation: adapted from the Population Assessment of Tobacco and Health (PATH) survey (1-item, past yr)	<ul style="list-style-type: none"> Among 132 adolescents that reported current e-cig use, 68.9% were exclusive e-cig users and 31.1% were dual users. Strong urge to use an e-cig (13.5%), and 'really need an e-cig' (12.3%) were most frequently reported symptoms of e-cig dependence. Dual users reported higher prevalence of e-cig dependence compared to exclusive e-cig users (<i>p</i> < 0.001). Exclusive e-cig users reported significantly higher proportion of wanting to quit e-cig as compared to dual users (<i>p</i> = 0.04). 	Self-report; small sample size; cross-sectional; limited generalizability
Chadi et al., 2019	Examine the associations between e-cig and marijuana use and depressive symptoms and suicidality among high school students	Cross-sectional (secondary data analysis from the 2015 and 2017 of the Youth Risk Behavior Survey [YRBS])	N = 26,821 (9–12th grade students, 51.3% female; US)	Current use: past 30-day use of e-cig or marijuana Use category: e-cig only use, never-use, marijuana-only use, dual use	Depressive symptom: feeling of sadness or hopeless (1-item, past yr) Suicidal ideation: seriously considering attempting suicide (1-item, past yr)	<ul style="list-style-type: none"> Across waves, those reporting e-cig-only use, marijuana only use, and dual use had higher odds of reporting depressive symptoms and suicidal ideation when adjusting for demographic factors. 	Self-report; cross-sectional; limited generalizability

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Table 4 (continued)

First author, year	Study purpose	Design	Sample size (characteristics; location)	E-cig related measurements	Health outcome measurements	Main findings related to e-cig use and health outcomes	Limitations
Chen et al., 2017	Evaluate the difference in adolescents' initial reactions to cigarette and e-cig use, and the association between these symptoms and current use	Cross-sectional	N = 41 (13–17 yo; US)	Current use: past 30-day use of e-cig or cigarette	Symptoms experienced during first time cigarette/e-cigarette use: open-ended survey (telephone interview); symptoms (negative vs. positive symptoms)	<ul style="list-style-type: none"> The negative symptoms that adolescents reported about their first experiences with cigarettes and e-cig included feeling dizzy, sick, bad taste in their mouth, difficulty breathing and headache. Compared to conventional cigarettes, e-cig users reported fewer negative symptoms such as felt bad, coughing, chest pain, and irritated eyes, bad taste upset stomach dizzy, or lightheaded ($p < 0.05$). Among those who had tried e-cig ($n = 29$), symptoms (neither positive nor negative) experienced at first e-cig use were not associated with current e-cig use. Overall, approximately 1.9% reported that they had been diagnosed with asthma in the past yr. Prevalence rates of those diagnosed with asthma in the past yr in current e-cig users, former e-cig users, and never e-cig users were 3.9%, 2.2%, and 1.7%, respectively. Compared to never e-cig users, current EC users increased the odds of asthma diagnosis, when unadjusted. Current e-cig use increased the odds of school absences due to asthma symptoms among never and current cigarette users. 	Self-report; small sample size; cross-sectional; limited generalizability
Cho & Paik, 2016	Investigate the association between e-cig use and asthma among high school adolescents	Cross-sectional (secondary data analysis from the 2014 of the 11th Korean Youth Risk Behavior Web-based Survey [KYRBWS])	N = 35,904 (10th–12th high school students, 50.1% female; South Korea)	Ever use: ever tried e-cig or cigarette (yes/no) Current use: past 30-day use of e-cig or cigarette (+number of days smoked)	Self-reported provider diagnoses of asthma (past yr)	<ul style="list-style-type: none"> Overall, approximately 1.9% reported that they had been diagnosed with asthma in the past yr. Prevalence rates of those diagnosed with asthma in the past yr in current e-cig users, former e-cig users, and never e-cig users were 3.9%, 2.2%, and 1.7%, respectively. Compared to never e-cig users, current EC users increased the odds of asthma diagnosis, when unadjusted. Current e-cig use increased the odds of school absences due to asthma symptoms among never and current cigarette users. 	Self-report; cross-sectional; case-crossover
Cho, 2017	Examine the relationship between e-cig use and oral symptoms among middle and high school students	Cross-sectional (secondary data analysis from the 2016 of the 12th Korean Youth Risk Behavior Web-based Survey [KYRBWS])	N = 65,528 (9th–12th high school students, 48.4% female; South Korea)	Ever use: ever tried e-cig (yes/no) Current use: past 30-day use of e-cig Other: reasons for using e-cig; purchase source of e-cig liquids	Self-reported symptoms related to oral health (i.e., gingival pain, bleeding, tongue and/or inside cheek pain; past yr)	<ul style="list-style-type: none"> Overall, approximately 18.5% reported having experienced gingival pain and/or bleeding, and 11.0% reported 'tongue and/or inside--cheek pain' in the past yr. Comparing to the "never e-cig user", the odds ratio of having 'cracked or broken tooth' increases among e-cig users. Comparing to the "never e-cig user", the odds ratio of having 'gingival pain and/or bleeding' increases among e-cigarette users. Comparing to the "never e-cig user", the odds ratio of having 'tongue and/or inside-cheek pain' increases among e-cig users. Among all, 3.2% used cigarette only; 15.8 electronic vapor products only; 7.5% dual use; while 73.5% did not use cigarettes or electronic vapor products. 	Self-report; cross-sectional
Demissie et al., 2017	Examine the association between electronic vapor products and a broad range of health risk behaviors among high school students, and compare the frequency of electronic vapor products	Cross-sectional (secondary data analysis from the 2015 of the Youth Risk Behavior Survey [YRBS])	N = 15,624 (9th to 12th grad high school students; US)	Current use: past 30-day use of cigarette and electronic vapor products (i.e., e-cig, e-cigars, e-pipes, vape pens, vaping pens, e-hookahs, hookah pens)	Health-risk behaviors: unintentional injuries and violence, substance use behaviors, sexual risk behaviors, dietary behaviors and physical activity	<ul style="list-style-type: none"> Among all, 3.2% used cigarette only; 15.8 electronic vapor products only; 7.5% dual use; while 73.5% did not use cigarettes or electronic vapor products. 	Self-report; cross-sectional

and cigarette use among exclusive and dual users

Use category:
non-use, cigarette smoking only, electronic vapor, product use only; and dual use (cigarettes and electronic vapor products)

- Cigarette-only, electronic vapor products only, and dual users were significantly more likely than non-users to engage in a physical fight and attempt suicide; more likely than non-users to currently drink alcohol, use marijuana, ever use synthetic marijuana, ever use other illicit drugs, and report ever non-medical use of prescription drugs; more likely than non-users to have ≥4 lifetime partners and be currently sexually active; and more likely than non-users to drink soda ≥3 times/day.
- Electronic vapor products only users were significantly less likely to not engage in daily physical activity compared with non-users.
- Both electronic vapor products only and dual users were significantly more likely than non-users to text or e-mail while driving.
- Dual users were significantly more likely than non-users to carry a weapon; more likely than nonusers not to use a condom at last sexual intercourse; and less likely to eat vegetables <3 times per day compared with non-users.
- E-cig only users had significantly higher rates of heavy drinking, alcohol, marijuana and other drug use compared with non-users, however reported significantly lower rates when compared with dual users.
- E-cig only users tended to have shorter sleep duration on weekends compared with non-users, and lower anxiety and depressive symptoms when compared with dual users and cigarette-only users. However, there was no difference on overall physical health, physical activity, sedentary behavior or diet.
- There were no significant associations observed between frequency of e-cig use and overall physical health, depression or anxiety symptoms, physical activity, sedentary behavior, weekday sleep duration or sleep quality.
- The odds for suicidal ideation, plans, attempts and medically serious were higher among e-cig users compared to non-users.

Dunbar et al., 2017

Examine the health profiles of youth that report e-cig use compare to those of youth who use cigarettes only, use both cigarettes and e-cigs (dual users), or use neither type of product

Cross-sectional (secondary data analysis from of the wave 7, Project CHOICE)

N = 2488 (mean age 17 yo, high school students, 54% female; US)

Frequency of e-cig use: times used or tried e-cig (past yr)
Use category: non-use, cigarette smoking only, e-cig use only; and dual use (cigarettes and e-cig)

Self-reported physical and mental health status; health protective behaviors (i.e., physical activity, healthy diet, sleep duration); health risk behaviors (i.e., substance use, sedentary behavior)

Self-report; cross-sectional

Kim & Kim, 2019

Examine the association between e-cig use patterns and suicidal ideation, plans, attempts, and medically serious attempts among adolescents

Cross-sectional (secondary data analysis from the 2016 of the 12th Korean Youth Risk Behavior Web-based Survey [KYRBWS])

N = 5405 (mean age 15.9 yo, 7th to 12th grade students, 18.9% female; South Korea)

Frequency of current e-cig use: number of days used or tried e-cig in the past 30-days

Self-reported suicidal ideation, plans, attempts and medically serious attempts (past yr)

Self-report; cross-sectional

(continued on next page)

Table 4 (continued)

First author, year	Study purpose	Design	Sample size (characteristics; location)	E-cig related measurements	Health outcome measurements	Main findings related to e-cig use and health outcomes	Limitations
King et al., 2018	Examine the association between tobacco products (i.e., e-cig, waterpipe, cigar, cigarette, smokeless tobacco) and mental health status among college students	Cross-sectional	N = 2370 (mean age 21.1 yo, college students, 64.1% female; US)	Current use: past 30-day use of tobacco products (i.e., cig, waterpipe, cigar, cigarette, smokeless tobacco)	Self-reported provider diagnoses of mental health (past 6 mo.); Perceived Stress Scale-10 (PSS-10, past mo.); Center for Epidemiologic Studies Depression Scale–short form (CES-D 11, past week)	Higher stress and depression were associated with increased odds of e-cig use after adjusting for age, sex, race and ethnicity, mother's education, and past 30-day cigarette use.	Self-reported; cross-sectional; limited generalizability
Lechner et al., 2017	Examine the bi-directional relationship between depressive symptoms and onset and sustained use of e-cig over past yr in adolescents those who have never used cigarettes or e-cig at baseline	Longitudinal	N = 2460 (baseline mean age 14.1 yo, 53.4% female; US)	Ever and past 6-mo. e-cig use; Frequency of current e-cig and cigarette use (number of days)	Center for Epidemiologic Studies Depression Scale (CES-D 20-item, past week)	Baseline depressive symptoms were associated with onset of e-cigarette use. Sustained use of e-cig over the 12-month observation (vs. non-use) was associated with a greater rate of increase in depressive symptoms over time. Among those who sustained use of e-cig, higher frequency of use was associated with higher depressive symptoms at the 12-mo. follow-up.	Self-report
Lee & Lee, 2019	Examine the relationship between depression and suicidality with tobacco user categories	Cross-sectional (secondary data analysis from the 2017 of the 13th Korean Youth Risk Behavior Web-based Survey [KYRBWS])	N = 62,276 (13–18 yo, middle and high school students; South Korea)	Ever use category: non-use, cigarette only, e-cig only; and dual use; Current use: past 30-day use of e-cig and cigarettes	Depressive symptom: feeling too sad or desperate to have a daily life (1-item, past yr); Suicidality: suicidal ideation, plans, attempts (past yr)	E-cig-only users had higher levels of depression and suicidality than non-users for both ever use and current use. Dual users (cigarette and e-cig) had a higher prevalence of depression and suicidality; and among female adolescents, conventional--cigarette-only users, e-cig-only users, and dual users had a higher prevalence of depression and suicidality than male adolescents.	Self-report; cross-sectional
Leventhal et al., 2016	Characterize the mental health of adolescent conventional and e-cig use	Cross-sectional	N = 3310 (mean age 14.0 yo, 9th grade students; US)	Ever use: ever used or tried e-cig, cigarettes or other substances; Ever use category: non-use, cigarette only, e-cig only; and dual use	Revised children's Anxiety and Depression Scale (RCADS); Mood disorder questionnaire (MDQ); distress Tolerance Scale (DTS, 14-items); childhood Anxiety Sensitivity Index (CASI, 18-items); Snaith-Hamilton Pleasure Scale (SHAPS, 14-item); Temperament and Character Inventory–Impulsivity (TCI-I, 5-item) Scale; Impulsive Behavior Scale- Positive and Negative Urgency Subscales (JPPS-P); The Early Adolescent Temperament Questionnaire – Revised Inhibitory Control Scale (EATQ-R, 5-item); Drug Abuse Screening Test-Adolescent Version (DAST, 10-item); Cannabis Abuse Screening Test (CAST, 6-item); Rutgers Alcohol Problem Index (RAPI, 23-item)	E-cig only users had higher elevations of mental health outcomes (i.e., mania anhedonia, major depression, panic disorder, anxiety, obsessive compulsive disorder, anxiety sensitivity, distress tolerance, negative urgency, positive urgency, impulsivity, inhibitory control) than non-users, but the following problems were found in lower levels when compared to cigarette-only or dual users.	Self-report; cross-sectional
McConnell et al., 2017	To examine the associations of e-cigarette use and chronic bronchitis symptoms and wheeze in adolescent population.	Cross-sectional. Secondary data analysis of 2014 data collected from Southern California	N = 2086 (11th and 12th grade students, mean age = 17.3, SD =	Items modified from National Youth Tobacco Survey, Users: Never used, past users (used but not in past 30 days), Current	Chronic bronchitic symptoms: cough 3 months in a row, congestion/phlegm not accompanied by cold, bronchitis in past 12 months.	Past and current e-cig use were associated with higher odds of bronchitis (OR = 1.71, 95% CI [1.20, 2.43]; OR = 1.41, 95% CI [0.92, 2.17])	Cross-sectional. E-cig use only assessed at one time point.

<p>Children's Health Study.</p>	<p>0.6, 49.6% female, US)</p>	<p>users (used in past 30 days). Freq of use 1–2 times or 3+ times in past 30 days.</p>	<p>Wheeze in past 12 months.</p>	<p>respectively); however, after controlling for demographics, secondhand smoke in home, and lifetime cigarette use only past-e-cigarette use remained predictive of symptoms. Effects also remained for e-cig users who never used cigarettes (OR = 1.70, 95% CI [1.11, 2.59]). Bronchitic symptoms increased with number of days used e-cigs but were attenuated after adjusting for demographics, second hand smoke exposure and lifetime number of cigarettes used. Wheeze was not associated with current or past e-cigarette use after adjusting for second hand smoke exposure and lifetime number of cigarettes smoked.</p> <ul style="list-style-type: none"> Stronger nicotine dependency was associated with being in a higher grade, vaping at an earlier age, vaping more frequently, and using higher nicotine concentrations ($p < 0.01$). E-cig nicotine dependency was significantly associated with using nicotine e-liquid, nicotine free, and past month cigarette smoking ($p < 0.001$), but not with sex or race. 80.3% of the sample continued to use e-cigarettes at 12 mo., with significantly greater e-cigarette use frequency, dependence, and nicotine exposure. Both e-cig dependence and cotinine levels significantly increased over time. The percentage of daily e-cig users doubled from 14.5% at baseline to 29.8% at 12-mo follow-up. The pattern of e-cig use observed over time indicate substantial persistence and the use of greater amounts of nicotine over time (i.e., tolerance). At baseline 13.3% met criteria for moderate to heavy dependence, this increased to 23.3% at 12-month assessment.
<p>Morean et al., 2018</p>	<p>N = 520 (mean age 16.2 yo, 9th- 12th grade high school students, 50.5% female; US)</p>	<p>Current use: past 30-days use of e-cig with nicotine; Frequency of use: cigarette use (number of days) Other: age at vaping onset</p>	<p>E-cig nicotine dependence (PROMIS-E, 4-item)</p>	<p>Self-report; cross-sectional</p>
<p>Vogel et al., 2019</p>	<p>N = 173 (13–18 yo, 23.9% female; US)</p>	<p>Frequency of e-cig use in a typical month; Current use: past 30-day use of cigarettes; Others: product preference (i.e., brands), e-cig flavors, reasons for continued e-cig use (open-ended response)</p>	<p>E-cig dependence (Penn State Electronic Cigarette Dependence Index [ECDI], 10-item); Biomarkers of nicotine and tobacco exposure: levels of salivary cotinine measured using liquid chromatography-tandem mass spectrometry</p>	<p>Limited generalizability: majority-male; small sample size</p>

Abbreviations. e-cig = electronic cigarettes; mo. = month; US=United States; yo = years old; yr = years.

2017), as well as nicotine dependence symptoms (Case et al., 2018; Morean et al., 2018; Vogel et al., 2019).

Oral health

The vapor inhaled from e-cigarette devices first passes through the mouth, creating the potential for harm to the tissues of the mouth, making oral health an important focus for e-cigarette research. The relationship between e-cigarettes use and oral health consequences among adolescents was examined in two large sample epidemiological studies (Akinkugbe, 2019; Cho, 2017). The Twelfth Korean Youth Risk Behavior Web-based Survey (KYRBWS) was given to 65,528 7th to 12th school grade students in Korea in 2016 to assess the association between e-cigarettes use and oral symptoms (Cho, 2017). The KYRBWS study found that e-cigarette use significantly increased odds of 'gingival pain and/or bleeding', 'tongue and/or inside-cheek pain', and 'cracked or broken teeth'. Even after adjusting for conventional cigarette smoking, daily e-cigarette users were more likely to report 'tongue and/or inside-cheek pain' and 'cracked or broken teeth' than adolescents who used conventional cigarettes but never used e-cigarettes (Cho, 2017). The authors discussed ways that nicotine and other chemicals contained in e-cigarette vapor may cause inflammation and other reactions that lead to the development of caries and other dental problems.

The Population Assessment of Tobacco and Health (PATH) study was conducted among 13,650 adolescents (ages 12–17 years) in United States to evaluate the negative effects of e-cigarette use on oral health (Akinkugbe, 2019). Unlike the study by Cho (2017), results of Akinkugbe's (2019) study indicated that e-cigarette use alone was not significantly more likely to be associated with self-reported diagnosed dental problems (e.g., cavities, gum disease, or dental stains); dual users of conventional cigarettes and e-cigarettes had the highest odds of being diagnosed with dental problems (1.72, 95% CI [1.24, 2.38]) compared to non-users (Akinkugbe, 2019).

Both of these studies employed large, cross-sectional, and representative samples of adolescents of approximately the same age. The contradictory findings of these two studies are likely due to differences in how oral health problems were assessed. One study asked parents or emancipated minors to report on the occurrence of cavities, gum disease and dental stains as diagnosed by a dental professional (Akinkugbe, 2019), whereas in another study, adolescents self-reported on their experiences with 'gingival pain and/or bleeding', 'tongue and/or inside-cheek pain', and 'cracked or broken teeth' (Cho, 2017). These results indicate that while e-cigarette use alone does not appear to have an effect on diagnosed dental problems that is different from conventional cigarette use, e-cigarettes are uniquely associated with oral pain and cracked or broken teeth. This suggests that the act of vaping or the content of the vaporized product may pose a threat of damaging the tissues in the mouth. Additional research using comparable measures of oral health problems, as well as longitudinal studies to document the long-term influence of e-cigarette use and different types of e-cigarette devices on oral health are needed.

Respiratory problems

The adverse effects of e-cigarette use related to respiratory disease symptoms among adolescents were reported in the three studies (Chen et al., 2017; Cho & Paik, 2016; McConnell et al., 2017). Cho and Paik (2016) conducted a study with 35,904 high school students in South Korea. They found that compared to those who never used e-cigarettes, current e-cigarette users were 2.36 times more likely to be diagnosed with asthma in the past 12 months (95% CI: 1.89, 2.94). In order to control for the effect of conventional cigarette smoking on adolescent e-cigarette users' asthma diagnosis, subjects were stratified into three groups based on whether or not they never, currently, or previously used conventional cigarettes. The study showed that adolescent e-cigarette users who never used conventional cigarettes were more likely to be diagnosed with asthma than those who concurrently used conventional cigarettes when adjusted for overweight status, second

hand smoking at home, atopic dermatitis history, and allergic rhinitis history (2.74 vs. 1.30). The authors posited that the glass fibers found in the cartridges and the metals contained in the aerosols may cause bronchial inflammation that contribute to asthma (Cho & Paik, 2016). However, it is unclear as to why asthma risk would appear to be lower among those e-cigarette users who also smoke conventional cigarettes compared with those who use e-cigarettes alone. One possibility is that dual users use e-cigarettes less often than exclusive e-cigarette users, potentially reducing their exposure to the harmful elements contained in the vapor.

Using an American sample, Chen et al. (2017) further examined the respiratory symptoms associated with e-cigarette and conventional cigarette use among 41 13–17-year-old adolescents who used e-cigarettes, conventional cigarettes, or both (dual users). The study found that adolescents who used e-cigarettes and conventional cigarettes reported coughing and chest tightness, and difficult breathing; however, these symptoms were experienced by a greater percentage of conventional cigarette users compared with e-cigarette users (59% vs. 17%, respectively) (Chen et al., 2017).

One study examined the associations between e-cigarette use and chronic bronchitis symptoms and wheezing among a sample of US high school students (McConnell et al., 2017). Based on self-reported lifetime and past 30-day e-cigarette use, adolescents were classified as never, past, or current users and then compared on the outcome measures. The e-cigarette users who did not use e-cigarettes in the last 30 days were classified as "past users," and those who used e-cigarettes in the last 30 days were classified as "current users." Compared with never users, current and past e-cigarette users had higher odds of reporting bronchitic symptoms, and the number of symptoms increased as a frequency of e-cigarette use increased. However, after controlling for sociodemographics, conventional cigarette use, and exposure to second-hand smoke, the effects were attenuated and only past e-cigarette use remained significantly related to bronchitic symptoms. When the analyses were re-run only among those who never smoked conventional cigarettes, the bronchitic symptoms of past e-cigarette users remained significantly elevated (1.70, 95% CI 1.11, 2.59), but not for the current e-cigarette user (1.41, 95% CI 0.92, 2.17). E-cigarette use was not related to wheezing after adjusting for cigarette use.

In summary, adolescents who used e-cigarettes in the past 30 days were likely to have the symptoms of respiratory disease and bronchitis, including coughing, tightness in the chest, difficulty breathing, and wheezing (Chen et al., 2017; McConnell et al., 2017). Adolescent e-cigarette users also had a higher likelihood of being diagnosed with asthma, particularly among those who have never used conventional cigarettes (Cho & Paik, 2016). There were only three studies exploring these relationships; all studies were cross-sectional, and more studies need to be conducted, particularly with longitudinal data analyses. In addition, there were inconsistent findings related to cigarette smoking; one study reported that symptoms of respiratory disease were less common among e-cigarette users than conventional cigarette users (Chen et al., 2017), and another study reported that only past e-cigarette use was associated with bronchitic symptoms after controlling for conventional cigarette use (McConnell et al., 2017). Thus, future studies need to investigate the mechanisms of respiratory symptoms that e-cigarette users experience, particularly considering the effects of conventional cigarette use.

Nicotine dependence

Nicotine is an addictive substance, increasing risk for dependence, especially among adolescents whose brains are still developing (Goriounova & Mansvelde, 2012). Because e-cigarettes often contain nicotine, there is the concern that use of e-cigarettes can contribute to nicotine dependence. Research on nicotine dependence among adolescent e-cigarette users has been limited due to the lack of instruments validated for use in an adolescent population (Case et al., 2018). The three studies included in this review used or adapted existing

instruments that had been designed to assess nicotine dependence among adolescent conventional cigarette users (Case et al., 2018) or adult e-cigarette users (Morean et al., 2018; Vogel et al., 2019).

Case et al. (2018) used a modified version of the Hooked on Nicotine Checklist (HONC; DiFranza et al., 2007) to examine prevalence of dependence symptoms among a sample ($N = 132$) of 7, 9, and 11th grade students who reported using e-cigarettes in the past 30 days. Of these students, 69% were exclusive e-cigarette users and 31% were dual users (i.e., used both e-cigarettes and conventional cigarettes). The associations between type of e-cigarette use (exclusive vs dual user) and dependence symptoms and attitudes towards cessation were also examined. Results indicated that there were significant differences in the proportion of dependence symptoms with dual users reporting a higher prevalence of dependence than exclusive e-cigarette users. A significantly higher proportion of exclusive e-cigarette users reported wanting to quit e-cigarettes as compared to dual users (53.3% vs 24.2%, $p = 0.04$). Odds of wanting to quit and attempting to quit were lower among those with higher dependence symptoms (AOR = 0.61, 95% CI = 0.41, 0.92; AOR = 0.52, 95% CI = 0.30, 0.92, respectively). These findings suggest that dual users likely use nicotine more frequently compared to e-cigarette only users and are more likely to become addicted.

Morean et al. (2018) sought to validate a measure of nicotine dependence (PROMIS-E) among adolescent e-cigarette users as well as to identify characteristics of adolescent vapers that are associated with dependency. They also examined the relationship between nicotine concentration and nicotine dependency among a sample of high school students ($N = 520$; 50.5% female, 85% White) who had vaped in the past month. The 4-item PROMISE-E comprised a single factor with good fit and $\alpha = 0.91$. Among e-cigarette users, dependence was associated with being in a higher grade, vaping more frequently and using higher nicotine concentrations. Similar to Case et al. (2018), nicotine dependence was also associated with past month cigarette smoking. There were no racial or sex differences in reported dependence symptoms. The PROMISE-E does not have cut off for clinical diagnosis; however, 55.6% endorsed at least some nicotine dependence symptoms. Limitations of the study included use of self-reported e-cigarette use, lack of biochemical confirmation of e-cigarette use, and lack of information on nicotine concentration.

In one of the only longitudinal studies to examine the consequences of adolescent e-cigarette use prospectively, Vogel et al. (2019) studied the stability of e-cigarette use and dependency. Vogel and colleagues surveyed a community sample of 13–18-year-old adolescents ($N = 173$; 54.9% White, 10% Asian; 75% male), three times over a 12-month period (baseline, six- and 12-months). In addition to collecting self-report measures of frequency of e-cigarette use, type of device used and dependency symptoms, saliva samples were collected at each time point to assess cotinine levels as a biomarker of nicotine use. Results indicated that 80% of those who used e-cigarettes at baseline were still using them 12 months later. The percentage of adolescents in the sample who used e-cigarettes doubled from baseline to 12-month assessment (14.5% at baseline, 29.8% at 12-month follow up), indicating that use increases with age. Among those who used e-cigarettes at baseline, the frequency of e-cigarette use, dependency symptoms, and cotinine levels all increased significantly.

To summarize, both cross-sectional and longitudinal studies reported that adolescent e-cigarette use is associated with symptoms of nicotine dependence, although e-cigarette users less frequently use nicotine and are less likely to become addicted compared to dual users (Case et al., 2018; Morean et al., 2018). Half of adolescent e-cigarette users reported symptoms of nicotine dependence (Morean et al., 2018). Findings from the longitudinal study indicate that adolescent e-cigarette usage tends to become more frequent over time (Vogel et al., 2019). In keeping with this, findings from cross-sectional research shows that older adolescents tend to have higher nicotine dependence symptoms (Morean et al., 2018). Whether this increase in use and

dependence symptoms is due to developmental factors or whether it reflects increasing dependence over time is unknown; more prospective and developmental research is needed. Overall, the results indicate a need for early intervention to reduce the likelihood of escalating use and dependence among adolescents.

Mental health problems associated with E-cigarette use

Depression

Depression and depressive symptoms emerged as one of the most common health concerns among adolescent e-cigarette users. Eight studies have explored the relationship between e-cigarette use and depression among adolescents (Bandiera et al., 2016; Bandiera et al., 2017; Chadi et al., 2019; Dunbar et al., 2017; King et al., 2018; Lechner et al., 2017; Lee & Lee, 2019; Leventhal et al., 2016). For high school students, this association was significant in cross-sectional studies (Chadi et al., 2019; Lechner et al., 2017; Lee & Lee, 2019; Leventhal et al., 2016). Current and lifetime e-cigarette users have a greater likelihood of experiencing depressive symptoms compared with nonusers (Chadi et al., 2019; Dunbar et al., 2017; Leventhal et al., 2016), although no significant association between frequency of e-cigarette use and depressive symptoms has been found (Dunbar et al., 2017). The depressive symptoms were less serious among e-cigarette only users than among conventional cigarette only and dual users (Leventhal et al., 2016; Dunbar et al., 2017). An international study reported a similar trend. Regarding middle and high school students in South Korea (Lee & Lee, 2019), depressive symptoms were more common among current and lifetime e-cigarette users (current users: 37.4%) than nonusers (24.0%), which was similar to cigarette-only users (37.0%), and less prevalent compared with dual users (47.0%). Female adolescent e-cigarette users have a higher prevalence of depression than male adolescent users (Lee & Lee, 2019). Only one longitudinal study has explored this relationship among high school students. High school students who used e-cigarettes for over 1 year were more likely to have increased depressive symptoms (Lechner et al., 2017); there was a similar trend among cigarette smokers. A bidirectional association was observed between e-cigarette use and depressive symptoms in adolescents because those with a higher level of depressive symptoms were likely to use e-cigarettes at 6- and 12-month follow-up.

This trend was similar among college students in cross-sectional studies (Bandiera et al., 2016; Bandiera et al., 2017; King et al., 2018). Two cross-sectional studies showed that e-cigarette use over the course of 30 days was associated with depression. Interestingly, Bandiera et al. (2016) showed there were higher odds of having depressive symptoms while using e-cigarettes, but there was no association between depression and users of other alternative tobacco products, such as cigars, smokeless tobacco, and hookah. In King et al.'s (2018) study, current e-cigarette users were likely to have a higher level of depressive symptoms than nonusers (OR = 1.04). This trend was similar to cigarette users but nonsignificant among water pipe, cigar, and smokeless tobacco product users. However, in a longitudinal study among college students (Bandiera et al., 2017), e-cigarette use did not predict high levels of depressive symptoms at 6-month and 1-year follow-ups; even though the opposite paths were significant, a high level of depressive symptoms predicted e-cigarette use 6 months later.

In sum, adolescent e-cigarette use was associated with depression and depressive symptoms. Current and lifetime e-cigarette use was associated with depression, and depressive symptoms were less serious among e-cigarette users than conventional cigarettes or dual users (Bandiera et al., 2016; Bandiera et al., 2017; Chadi et al., 2019; Dunbar et al., 2017; King et al., 2018; Lechner et al., 2017; Lee & Lee, 2019; Leventhal et al., 2016). Only two longitudinal studies explored these relationships, and there were inconsistent findings (Bandiera et al., 2016; Lechner et al., 2017). One longitudinal study reported that high school students after using e-cigarettes over 1 year were more likely to have increased depressive symptoms (Lechner et al., 2017). However, another

longitudinal study (Bandiera et al., 2016) showed that e-cigarette use did not predict depressive symptoms among college students, although both studies confirmed that depression was associated with subsequent e-cigarette use. Thus, more longitudinal studies need to explore the timing and directionality of the associations between e-cigarette use and depression.

Suicidality

Three cross-sectional studies examined the association between e-cigarette use and suicidality (Chadi et al., 2019; Kim & Kim, 2019; Lee & Lee, 2019), and overall, the findings suggest that past use of e-cigarette was associated with suicidality. E-cigarette only use was associated with higher odds of reporting seriously considering attempting suicide in the past year when compared to no-use among the nationally representative sample of US high school students (Chadi et al., 2019). This result was also similar among the nationally representative samples of Korean middle and high school students (Kim & Kim, 2019; Lee & Lee, 2019). Current e-cigarette use (i.e., in the past 30 days) was associated with suicidal ideation, plans, attempts and medically serious attempts that required hospital admission in the past year when compared to no-use (Kim & Kim, 2019; Lee & Lee, 2019). Rates of suicidal ideation were highest among dual users (Lee & Lee, 2019). Lifetime e-cigarette only users were three times more likely to have engaged in suicide planning, and five times more likely to have made a suicide attempt than non-users, while current e-cigarette only users were six times more likely to have made a suicide attempt than non-users (Lee & Lee, 2019). When difference in sex was observed, the increased risk of suicide attempt was higher among female than male adolescents who were both cigarette and e-cigarette users (Lee & Lee, 2019).

All three cross sectional studies, including studies with nationally representative samples, reported that e-cigarette uses have an increased likelihood of suicidal ideation or suicidal attempts, compared to non-users (Chadi et al., 2019; Kim & Kim, 2019; Lee & Lee, 2019). The rates of suicidal ideation were less common for e-cigarette only users than for dual users (Lee & Lee, 2019). This relationship has not yet been reported by longitudinal studies, thus, the temporal relationship cannot be confirmed.

Anxiety and other psychiatric symptoms

Anxiety symptoms have been associated with cigarette smoking (e.g. Ulrich et al., 2004); however, it has been studied less extensively among adolescent e-cigarette users. Two studies examined the association between e-cigarette use and anxiety and other psychiatric diagnoses in adolescent samples. Both of these studies were conducted with a large sample of adolescents from high schools in Los Angeles, CA (47% Hispanic, 46% male), although different age groups were studied. Among a sample of 9th graders ($N = 3310$, $M_{age} = 14.08$, $SD = 0.42$), Leventhal et al. (2016) compared non-users, e-cigarette only users, conventional cigarette only users, and dual users (i.e., uses both e-cigarettes and conventional cigarettes) on levels of clinical symptoms of generalized anxiety and related psychiatric symptoms including panic, social phobia, and obsessive compulsion. Leventhal and colleagues found that e-cigarette only users did not differ from non-users in terms of generalized anxiety, obsessive compulsive disorder or social phobia. Both of these groups reported fewer general anxiety and obsessive-compulsive symptoms than cigarette only users and dual users. E-cigarette only users had higher levels of panic symptoms compared to non-users, but lower levels of panic compared with conventional cigarette users and dual users. In terms of social phobia symptoms, conventional cigarette only users reported higher levels than the other three groups. Similarly, among a sample of 10th–12th graders ($N = 2488$, $M_{age} = 17$, $SD = 0.69$), Dunbar et al., (2017) found that there were no differences in the anxiety symptoms of non-users compared with those who used only e-cigarettes. Use of e-cigarettes alone was associated with fewer anxiety symptoms than use of cigarettes and dual users had the highest rates of anxiety. Dual

users also used cigarettes and e-cigarettes more frequently than those who used e-cigarette or conventional cigarettes only, suggesting that there is something particularly risky about dual use.

King et al. (2018) examined the odds of reporting cigarette and e-cigarette use among a sample of college students ($N = 3146$, 64% female, 17% non-White) reporting a mental health diagnosis (i.e., composite of depression, anxiety, or ADHD). Reporting a mental health diagnosis was associated with increased odds of past 30-day conventional cigarette use. E-cigarette use was marginally associated with increased odds of a mental health diagnosis.

Unlike conventional cigarette use, e-cigarette use alone does not appear to be related to anxiety or anxiety-related clinical disorders (i.e., panic, social phobia, obsessive compulsive). However, dual e-cigarette and conventional cigarette use appears to be linked to more anxiety-related psychiatric symptoms. However, only two cross sectional studies explored the associations between e-cigarette use and other psychiatric symptoms (King et al., 2018; Leventhal et al., 2016) in teenagers and college students; More studies are needed to explore these relationships.

Quality appraisal

Table 5 summarizes the methodological study evaluation. Overall, the included studies were of high quality. Studies did not have methodological issues in the domains of study question, study analysis, results, and discussion with complete details. However, although most studies addressed study population and outcome measures completely, a few studies that recruited participants from a large study need to describe the sampling methods in more detail (Dunbar et al., 2017; Morean et al., 2018). The most important methodological issue identified was related to outcome measures. Although most studies used standard measures, about half of the studies did not provide information on reliability and validity of those measures (Chadi et al., 2019; Cho & Paik, 2016; Demissie et al., 2017; Kim & Kim, 2019; McConnell et al., 2017; Morean et al., 2018; Vogel et al., 2019). Regarding e-cigarette use-related measures, some studies used measures adapted from the instruments assessing other types of tobacco products. Given that e-cigarette use is a relatively newly developed product, it will be important to develop and test the validity of the measures. All studies included used surveys, and a number of studies were based on nationally representative samples (Akinkugbe, 2019; Chadi et al., 2019; Cho, 2017; Cho & Paik, 2016; Demissie et al., 2017; Kim & Kim, 2019; Lee & Lee, 2019). Most studies were cross-sectional, and only a few studies used a longitudinal study design (Bandiera et al., 2016; Lechner et al., 2017; Vogel et al., 2019).

Discussion

As e-cigarette use continues to rise among adolescents, it is critical that we understand the implications of use for adolescent health. In this integrative review, we examined the health outcomes associated with adolescent e-cigarette use. Our search strategy resulted in retaining 18 empirical studies that covered a variety of physical and mental health problems. Results of this review indicate that e-cigarette use is associated with adverse physical and mental health outcomes among adolescents including dental problems, asthma, bronchitic symptoms, nicotine dependence, depression, and suicidality. The wide range of negative outcomes underscores the urgent need for more focused research in each of these areas to understand the health consequences of adolescent e-cigarette use.

Physical health

The potential harm associated with e-cigarette devices came to the forefront during a national outbreak of 'e-cigarette, or vaping, product use-associated lung injury' (EVALI) which was reported in February

Table 5
Assessment of study quality.

Study authors, year	Domains					
	Study Question ^a	Study Population ^b	Outcome Measure ^c	Statistical Analysis ^d	Results ^e	Discussion ^f
Akinkugbe, 2018	●	●	●	●	●	●
Bandiera et al., 2016	●	●	●	●	●	●
Bandiera et al., 2017	●	●	●	●	●	●
Case et al., 2018	●	●	●	●	●	●
Chadi et al., 2019	●	●	◐	●	●	●
Chen et al., 2017	●	●	●	●	●	●
Cho & Paik, 2016	●	●	◐	●	●	●
Cho, 2017	●	●	◐	●	●	●
Demissie et al., 2017	●	●	◐	●	●	●
Dunbar et al., 2017	●	◐	●	●	●	●
Kim & Kim, 2019	●	●	◐	●	●	●
King et al., 2018	●	●	●	●	●	●
Lechner et al., 2017	●	●	●	●	●	●
Lee & Lee, 2019	●	●	●	●	●	●
Leventhal et al., 2016	●	●	●	●	●	●
McConnell et al., 2017	●	●	◐	●	●	●
Morean et al., 2018	●	◐	◐	●	●	●
Vogel et al., 2019	●	●	●	●	●	●

Note. ● = domain completely addressed; ◐ = domain partially addressed; ◑ = domain not addressed.

^a Study question: Was the purpose of the study clear and appropriate?

^b Study population: Was the study population adequately described? Were the detailed description of sampling procedures reported?

^c Outcome measure: Were primary and secondary outcomes clearly defined? Were outcomes assessed on objective findings? Was the method of assessment standard valid and reliable?

^d Statistical analysis: Were statistical tests appropriate? Was there an assessment of confounding? Were multiple comparisons taken into consideration?

^e Results: Were the results supported by the study method and analysis?

^f Discussion: Were conclusions supported by results with the consideration of potential biases of the studies?

2020, resulting in a total of 2807 hospitalized EVALI cases or deaths in United States (Gentzke et al., 2020; Griffiths et al., 2020; U.S. Food and Drug Administration, 2021). Many of those who experienced EVALI were young; the youngest being 13 years of age and with an overall median age of 24 (Krishnasamy et al., 2020). Several of the EVALI incidents were linked to vaping liquids that contained tetrahydrocannabinol (THC); however, 57% of EVALI patients also reported using nicotine products (Krishnasamy et al., 2020). One recent systematic review evaluated acute lung injury of vaping among 216 adult patients whose median age was between 19 and 35 and reported cough, dyspnea, and constitutional symptoms attributed to vaping (Jonas & Raj, 2020). Similar to Jonas and Raj (2020)'s findings in young adult populations, we also identified negative respiratory symptoms (i.e., cough, difficult breathing, chest tightness) associated with e-cigarettes use among adolescents (Chen et al., 2017; Cho & Paik, 2016; McConnell et al., 2017). Although the exact mechanism behind the EVALI is unknown (Crotty Alexander et al., 2020), the negative respiratory symptoms observed in adolescent samples might be early indicators of EVALI. More research is needed to determine whether adolescent e-cigarette users who exhibit negative respiratory symptoms are at high risk to develop EVALI or other respiratory problems over time.

Findings from this review also revealed oral health problems among adolescent e-cigarette users, including cracked teeth and mouth/cheek pain (Cho, 2017), although there was no evidence that e-cigarette use alone contributed to diagnosed dental problems cavities or gum disease (Akinkugbe, 2019). It is believed that nicotine and other chemicals in e-cigarette vapor can cause inflammation in the dental pulp, weakening teeth and making them susceptible to caries and cracking (Cho, 2017). Such oral damage may lead to more serious dental problems over time that may be observable in older samples. Indeed, studies of adult e-cigarette users have shown that e-cigarette use is prospectively linked to periodontal disease and bone loss (Atuegwu et al., 2019; Rouabhia, 2020), although case control and observational evidence on adults suggest that while e-cigarette use presents a greater susceptibility to undesirable changes in oral biological tissues (e.g., oral mucosal lesions, pain and swelling of the gums etc.), it is less harmful than conventional cigarettes (Ralho et al., 2019). Nonetheless, evidence from the current review suggests that dental providers should be screening their

adolescent patients for nicotine use, especially when mouth pain is reported or cracked teeth are detected. This may provide an opportunity for early intervention.

One of the biggest concerns associated with adolescent e-cigarette use is the risk of nicotine dependence. Due to sensitivities in the developing brain, adolescents are especially vulnerable to developing dependence following nicotine exposure (see Kong & Krishnan-Sarin, 2017; Ren & Lotfipour, 2019). All three of the studies in this review that examined dependence symptoms associated with adolescent e-cigarette use found evidence of dependence symptoms. Frequency of use and dependency symptoms appear to increase with age, although it is unclear whether this is due to developmental factors (e.g., older adolescents have greater access), whether it reflects an increase in dependency-related use, or a combination of both. More frequent usage increases exposure to nicotine, thereby increasing risk for dependency (Morean et al., 2018; Vogel et al., 2019). Frequent and increasing usage also increases exposure to other harmful chemicals found in e-cigarette vapor which may also elevate risk for other health effects (e.g., respiratory, oral problems) associated with e-cigarette use (Jones & Salzman, 2020). Whereas adult cigarette smokers may use e-cigarettes to reduce and manage their nicotine dependence, adolescents who are first introduced to nicotine through e-cigarettes may become dependent and graduate to using of conventional cigarettes either alone or in conjunction with e-cigarette use (i.e., dual use) (Morean et al., 2018). A meta-analysis examining longitudinal studies that include participants of ages between 14 and 30 years-old at baseline demonstrated that e-cigarette use was linked with an increased risk for initiating and continuing cigarette smoking (Soneji et al., 2017). This suggests that not only is e-cigarette use a risk factor for future cigarette use among young people, but that users may transition to other forms of tobacco use in order to satiate their nicotine cravings (Soneji et al., 2017). Ultimately, more prospective developmental research is needed to understand the mechanisms and pathways through which e-cigarette use and dependence unfolds among adolescents.

Mental health

There is a well-established relation between conventional cigarette use and mental health symptoms, including depression, anxiety, and

suicidal ideation (e.g., Audrain-McGovern et al., 2012; Windle & Windle, 2001). The results of this review indicate that like conventional cigarettes, e-cigarette use is also linked to depression and suicidality (Chadi et al., 2019; Kim & Kim, 2019; Lechner et al., 2017; Lee & Lee, 2019; Leventhal et al., 2016). This finding is consistent with the associations found between e-cigarette use and depression and suicidality among adults (Pham et al., 2020). Unlike conventional cigarettes, e-cigarette use alone was not associated with anxiety; however, dual use was associated with highest rates of anxiety (Dunbar et al., 2017; Leventhal et al., 2016). The majority of these studies were cross-sectional; thus, the nature and temporal ordering of this relationship could not be established. There were two longitudinal studies that examined whether there was a reciprocal relationship between depression and e-cigarette use. In keeping with the patterns observed in research with combustible cigarettes, Lechner et al. (2017) found a reciprocal relationship between depressive symptoms and e-cigarette use, such that baseline depressive symptoms predicted onset of e-cigarette use among a sample of adolescents and sustained e-cigarette use over a 12-month period was associated with increased depressive symptoms. In contrast, among a sample of college students, Bandiera et al. (2017) found evidence that baseline depressive symptoms predicted e-cigarette use six months later, but e-cigarette use did not predict subsequent depressive symptoms. Taken together, these studies show that depressed adolescents are at greater risk for e-cigarette use, yet there is inconclusive evidence that e-cigarette use exacerbates depressive symptoms.

The mechanisms through which e-cigarette use and depression are linked have yet to be determined. One mechanism through which e-cigarette use may contribute to depressive symptoms is via oxidative stress. Both conventional cigarettes and e-cigarettes have been associated with increased inflammation and oxidative stress (OS) (Tobore, 2019). The developing adolescent brain is particularly sensitive to the damaging effects of OS, and increased levels of OS have been linked to psychiatric disorders including depression and suicidal ideation (Tobore, 2019). Nicotine exposure appears to trigger OS; however, there is conflicting data on whether other factors associated with e-cigarette use, such as flavoring, play a unique role in promoting OS. More research to examine this potential pathway to psychiatric symptoms is needed (Tobore, 2019). Furthermore, additional research is needed to examine whether internalizing or externalizing mental health problems are possible mechanisms through which e-cigarette use and adverse mental health outcomes are related.

Limitations

In this review, we sought to summarize the state of the literature on the outcomes associated with adolescent e-cigarette use. The evidence suggests that e-cigarettes are not benign and are associated with poor health outcomes among adolescents. However, there are several limitations to note. First, the results of our search were limited to studies published in peer reviewed journals. Unpublished gray literature was not included. Although the researchers worked to reduce bias and errors during the screening, coding, and analyzing processes using multiple steps, there is a possibility of errors, such as missing articles during the search process or coding. The relatively nascent body of literature to address outcomes associated with adolescent e-cigarette use resulted in the inclusion of studies that were heterogeneous in terms of the types of health issues addressed, the sample characteristics, and the study design. Thus, it was difficult to arrive at a definite conclusion by comparing all of the studies. Most of the studies are based on self-report, with the exception of Vogel et al. (2019), which also examined cotinine levels. Future studies should confirm the findings using biomarkers. Finally, the majority of the included studies were cross-sectional, pointing to the need for more longitudinal research to determine temporal ordering, causality, and to examine the long-term impacts on adolescent health and well-being.

Directions for future research

The results of this integrative review indicate that e-cigarette use is associated with a variety of negative physical and mental health outcomes among adolescents. Although these studies have identified various physical and mental health problems associated with e-cigarette use among adolescents, mixed findings make it impossible to draw firm conclusions about the association between e-cigarette use and negative health outcomes. For example, there were inconsistent findings with regard to the association between e-cigarette use and oral health problems and whether cigarette use may attenuate respiratory symptoms among e-cigarette users. In addition, the findings about the association between depression and e-cigarette use from two longitudinal studies were contradictory. Inconsistencies in assessment tools may be at least partially responsible for these varied outcomes. Use of validated and standard assessment tools would improve understandings of e-cigarette related outcomes.

Several of the studies that compared e-cigarette use alone to non-use, conventional cigarette use, and dual use found that, in general, e-cigarette use alone appears to be less harmful than conventional cigarette and dual use, but still poses a risk to health outcomes compared to non-use (Case et al., 2018; Dunbar et al., 2017; Lee & Lee, 2019; Leventhal et al., 2016). Dual use may be an indicator of greater dependence and more frequent use, thereby increasing exposure to the harmful agents contained in both conventional cigarettes and e-cigarettes. Dual use may also reflect a more deviance-prone lifestyle that can also have implications for mental and physical well-being. More research is needed to understand who is likely to engage in dual use because these individuals appear to be at greatest risk for poor outcomes. The review also underscores the need for more longitudinal research on the long-term effects of e-cigarette use and to identify mechanisms through which e-cigarette use contributes to these outcomes. Given that e-cigarettes are newly developed and were initially marketed to adult cigarette smokers, the effects of e-cigarette use on adolescents is a relatively new area of research, thus, large gaps exist. Currently, a very limited number of studies have explored the prospective associations between physical and mental health with e-cigarette use among adolescents.

Further research also needs to be conducted among diverse populations of adolescents. Patterns of e-cigarette and e-cigarette use differ by age, gender, sexual identity, and ethnicity (Barrington-Trimis et al., 2019; Caputi, 2018; Krueger et al., 2020). For example, youth who identify as LGBTQ, particularly bisexual females, report higher rates of e-cigarette use compared to their heterosexual peers (Caputi, 2018; Krueger et al., 2020). These different patterns of use are likely associated with different risk factors and health outcomes. However, this review has demonstrated that only a limited number of studies exist and much remains to be learned about the associations between physical and mental health and e-cigarette use are different depending on the adolescent sub-populations.

There are several measurement issues that make it challenging to study e-cigarette use. Importantly, the lack of standard measures validated for use with an adolescent population makes it difficult to compare outcomes across studies (Morean et al., 2018; Vogel et al., 2020). Many of the measures are designed for conventional cigarette use or adult e-cigarette use and need to be modified for adolescents. A few studies have tested and validated modified instruments for use with adolescent e-cigarette users (e.g., Morean et al., 2018; Vogel et al., 2020); such measures should be used more routinely in e-cigarette research. The variety of e-cigarette devices and the lack of regulation over vaping solutions also make it challenging to assess e-cigarette use. Most studies included in this review did not report what types of e-cigarettes were used, the amount of nicotine (if any) that they contained, or what other flavorings or chemicals were present. Flavorings and other chemicals contained in the aerosol may contribute to e-cigarettes adverse impact on health outcomes (Barrington-Trimis et al., 2014).

Future studies should explore and distinguish the impact of different types of e-cigarettes and their contents on health outcomes (The Society for Adolescent Health and Medicine, 2020). Further, most of the research to date has relied on self-report measures and adolescents themselves are not always well-informed about what is in the solution they are vaping (Pepper et al., 2018).

Implications for practice

Healthcare providers in primary care clinics, schools, and community organizations, should consider the findings of this study when educating adolescents on the risks associated with e-cigarette use. Although more research is needed to provide a more accurate picture, several of the studies included in this integrative review indicate that some physical and mental health problems are associated with e-cigarette use in adolescents. Given the findings of this study, healthcare providers should screen for mental and physical outcomes, particularly for depression and suicidality, lung health, and oral health among e-cigarette users. When adolescents present with these health issues, it may be important to screen them for e-cigarette use as well as conventional cigarette smoking as the temporal relationship between these health issues and e-cigarette use has not been confirmed.

The US Food and Drug Administration, along with local schools and agencies should aspire to minimize the potential harmful effect of e-cigarette use on mental and physical health on a policy level. With the current findings of e-cigarettes potential impact on youth health outcomes, restricting youth's e-cigarette access is important. Likewise, regulating e-cigarette marketing messages should be considered as part of proactive effort to prevent adolescents from using e-cigarettes.

There is currently a lack of effective interventions targeting adolescent e-cigarette users (Crotty Alexander et al., 2020; Liu et al., 2020). There are only a few studies that have examined the effectiveness of programs that exist and have shown positive prevention effects, including school-based interventions (Gaiha et al., 2021; Kelder et al., 2020), a media-based prevention program (Huang et al., 2017; Vallon et al., 2017), an online game-based program (Hieftje et al., 2019), and a text-based intervention, (Graham et al., 2020). Research examining the effectiveness of e-cigarette interventions for adolescents should also consider whether the interventions can reduce and physical and mental health issues presented among e-cigarette users.

Adolescents are often unaware of the risks associated with e-cigarettes, and healthcare providers are not very confident about being able to effectively educate adolescents, parents, and public about the harms of e-cigarettes (The Society for Adolescent Health and Medicine, 2020). Given that e-cigarette users are less likely than non-users to believe that e-cigarettes cause health consequences (Rohde et al., 2018; Sharma et al., 2021), there is a need to communicate with youth about the risks associated with e-cigarettes. Until we understand more about the factors that contribute to adolescent e-cigarette use and the mechanisms through which e-cigarette use adversely impacts adolescent health, prevention efforts will be stymied. Effective and timely interventions, focusing on educating the public about the mental and physical health risks associated with adolescent e-cigarette use, need to be developed. Healthcare providers need to receive proper training regarding how to provide e-cigarette prevention and treatment aimed at adolescents. As yet there are no proven interventions or training programs that can be delivered in healthcare settings, including primary care clinics or pediatrics.

Conclusion

Counter to perceptions held by many adolescents (e.g., Park et al., 2019), the findings of this integrative review reveal that e-cigarette use is not harmless. E-cigarette use has been linked to a variety of physical and mental health problems among adolescents, although more research is needed to better document the nature of these harms and the

conditions under which they occur. The review also points to several gaps in the literature on adolescent e-cigarette use. Longitudinal and developmentally-focused research to document the progression of e-cigarette use and the long-term impact on health among adolescents, as well as use of reliable and valid assessment tools are urgently needed.

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CRedit authorship contribution statement

Jennifer A. Livingston: Conceptualization, Formal analysis, Resources, Writing – original draft, Writing – review & editing, Supervision. **Chia-Hui Chen:** Methodology, Project administration, Data curation, Formal analysis, Writing – original draft. **Misol Kwon:** Formal analysis, Writing – original draft. **Eunhee Park:** Conceptualization, Formal analysis, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None.

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