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REVIEW ARTICLE

Association Between E-Cigarettes and Asthma in Adolescents: A Systematic Review and Meta-Analysis

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Introduction: Numerous studies have revealed the relationship between E-cigarettes and asthma but have shown inconsistent results. This study systematically evaluated the potential association between E-cigarette use and asthma in adolescents.

Methods: PubMed, Embase (Ovid), Cochrane Library, and the China Biological Medicine Database were searched for relevant articles published between database inception and February 28, 2021. The quality of included studies was evaluated using the Agency for Healthcare Research and Quality assessment, and a quantitative meta-analysis was conducted to pool outcomes of ORs with 95% CIs.

Results: A total of 10 cross-sectional studies incorporating a total of 483,948 participants were included. All the study participants were middle- and high-school students with a mean age of 15−16 years. The median prevalence of ever E-cigarette use was 11.2% (range=2.2%, 45%), and that of current use was 7.5% (range=2.7%, 25%). Overall, E-cigarette use was associated with significantly higher odds of having asthma (pooled OR=1.31, 95% CI=1.22, 1.42) than nonuse, and both current use (OR=1.36, 95% CI=1.26, 1.48) and ever use (OR=1.20, 95% CI=1.12, 1.28) showed similar associations.

Discussion: This study shows that both current and ever E-cigarette use have significant associations with asthma in adolescents. This knowledge might provide potential evidence for developing primary prevention strategies and serve as a reference for public health policy.

INTRODUCTION

E-cigarettes are alternative, nonconventional tobacco products, which primarily use a rechargeable battery to heat disposable E-liquid cartridges, generating an inhalable aerosol consisting of nicotine, flavors, propylene glycol, and vegetable glycerin.[1] As an alternative product with a fashionable appearance, E-cigarettes are an attractive option for current smokers, former smokers, and young people who have never smoked. These E-cigarettes were initially designed and produced by a Chinese pharmacist in 2000 and, after further improvements, were exported throughout the world, gaining significant popularity since 2006.[2] Today, the global E-cigarette market has reached a multibillion-dollar value.[3] In South Korea, it has been introduced as a healthy alternative to

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conventional cigarettes and publicized as an effective device for smoking cessation.[4] However, no preclinical toxicology testing or long-term safety trials were conducted before E-cigarette marketing. In 2019, an outbreak of lung injury associated with E-cigarettes occurred in America, where >2,600 cases were reported, mainly involving young students.[5] Thus, the potential adverse health effects of exposure to E-cigarettes need to be investigated further, especially in adolescents.

Asthma is a chronic inflammatory airway disease characterized by variable airflow limitations secondary to airway narrowing and wall thickening, leading to shortness of breath, chest tightness, and cough.[6] It has been reported to be predominantly caused by a combination of genetic and environmental factors. Diverse environmental factors, including smoking, outdoor air pollution, or dust mites, could trigger an asthma attack.[7] As an incurable disease, any effective measure might also involve minimal exposure to the various trigger factors present in the environment for patients with asthma. However, owing to low awareness of avoiding exposure to different environmental irritants, children have been found to exhibit a higher prevalence of asthma than adults.[8] At present, it is established that smoking tobacco can induce significant airway inflammation and further trigger asthma attacks.[9,10] By contrast, the role of E-cigarettes in asthma attacks remains unclear. In recent years, with the rising public health concern about the widespread use of E-cigarettes among children globally,[11,12] many studies have been conducted to investigate the possible association between E-cigarettes and asthma. In this study, a meta-analysis was performed to examine the association between E-cigarettes and asthma among adolescents, thus providing a theoretical basis for further research.

METHODS

This study was conducted according to the PRISMA checklist.[13] The protocol for this study has been registered in the International Prospective Register of Systematic Reviews (CRD42021239273).

Search Strategy and Selection Criteria

A total of 3 English databases (PubMed, Embase [Ovid], and Cochrane Library) and 1 Chinese database (China Biological Medicine Database) were searched for relevant articles from inception through August 30, 2020. To maximize search feasibility, the reference lists of selected studies were scrutinized manually. An updated search was carried out on February 28, 2021 to ensure that all recent studies were included. The database search was conducted by YZ, and construction of the retrieval strategy was based on the Patient/Population, Intervention, Comparison, Outcome, Study framework. The search strategy for PubMed is presented in Appendix Table 1 (available online).

The inclusion criteria were as follows: (1) studies that investigated the association between E-cigarette use and asthma (i.e., cross-sectional or longitudinal studies), (2) participants aged ≤18 years, (3) reasonable measures of asthma, (4) appropriate method used to measure participants' use of E-cigarettes, and (5) clear statistical indicators that reflected the strength of associations (i.e., OR). The exclusion criteria were as follows: (1) articles for which the data could not be obtained, (2) participants used E-cigarettes in combination with marijuana, and (3) studies that were not in English or Chinese and for those where full text was not available.

Study Selection and Data Extraction

After the studies were retrieved from the databases, duplicates were removed using Endnote (version X8). Then, the rest of the articles were screened further through 2 independent steps of selection by 2 independent reviewers (XCL and YZ), which included scanning the titles and abstracts, and full-text retrieval to determine whether a study was eligible for inclusion.

After screening the relevant studies, the data and basic information were extracted from the eligible articles by XCL and YZ independently. A prespecified Excel form was used during the process of data extraction. Any discrepancies in the data extraction were settled through consensus with a third reviewer (LZ). The extracted information was as follows: (1) study characteristics (i.e., first author, publication year, country, study design, sample size), (2) participant characteristics (i.e., mean age, sex distribution), (3) definitions of E-cigarette use and asthma, (4) factors adjusted by statistical models, and (5) statistical measures of ORs with 95% CIs. However, if several ORs were reported for the same indicator, only the results with the most adjusted confounding factors were extracted.

Assessment of Risk of Bias

The quality of each included study was further appraised by 2 independent researchers (XCL and FC) using the Agency for Healthcare Research and Quality (AHRQ) assessment for cross-sectional studies,[14] and adjudication with input from a third reviewer (LZ) was used to resolve any potential discrepancies. The AHRQ assessment consisted of 11 items based on 3-dimensional selection, comparability, and outcomes. The scores of 8−11 were considered low risk, 4−7 were considered moderate risk, and 0−3 were considered high risk of bias.

Statistical Analysis

A meta-analysis was conducted for the ORs with associated 95% CIs. Statistical heterogeneity was examined using chi-square tests and quantified using I^2 statistics,[15] with an I^2 value threshold of 25% considered low, 50% considered moderate, and ≥75% considered substantial heterogeneity. However, if moderate or substantial heterogeneity was identified, random-effect models were used to pool outcomes. Otherwise, a fixed-effect model was used.[16] Potential publication bias was gauged graphically through funnel plots and statistically through Egger linear regression tests. If the previous test was statistically significant, the trim-and-fill method was employed thereafter.[17] To explore potential sources of heterogeneity and thereby obtain additional information wherever possible, subgroup analysis was performed on the basis of the types of E-cigarette use (exclusive E-cigarette use versus E-

cigarette use), different regions where studies were conducted (North American versus Asian), sample size (≥50,000 vs <50,000), and participant populations (only high-school students versus middle and high-school students). All analyses were conducted in RevMan, version 5.4, and Stata SE, version 15.0, with a 2-sided $p<0.05$ considered statistically significant.

RESULTS

A PRISMA flow diagram summarizing the process of selecting the relevant studies is depicted in Figure 1. After the removal of duplicates, 3,992 relevant articles were reviewed, and 90 articles were considered potentially eligible after screening the titles and abstracts. After full-text review, 10 cross-sectional studies[18–27] fulfilled the inclusion criteria and were subjected to final analysis.

The characteristics of the 10 included studies with a total of 483,948 participants are described in Table 1.[18–27] All the participants were middle- or high-school students. However, 1 of the included studies[21] did not provide mean participant age, and another study[27] applied an age range rather than the mean age; the mean participant age in the remaining studies was 15–16 years. Of all the included eligible studies, 5 studies[19,21,22,26,27] were conducted in the U.S., 4 studies[18,20,23,25] were conducted in South Korea, and 1 study[20] was conducted in Canada.

Use of E-cigarettes was assessed by a self-administrated questionnaire in all included studies. The association between E-cigarette use and asthma was investigated on the basis of ever use versus never use in 2 studies,[24,25] current use versus never use in 3 studies,[21–23] and current use and ever use versus never use in 5 studies.[18–20,26,27] Asthma was identified on the basis of the participant's self-reported diagnosis that was confirmed by a doctor within the past year. Among the included studies, the prevalence of ever E-cigarette use ranged from 2.2% to 45%, with a median of 11.2%, whereas the prevalence of current E-cigarette use ranged from 2.7% to 25%, with a median of 7.5%.

The detailed quality assessment of all included studies is shown in Appendix Figure 1 (available online). The overall quality of the studies was found to be above average, with a mean AHRQ score of 6.6 and a range of 5–7.

As depicted in Figure 2, the meta-analysis clearly showed that E-cigarette use was associated with significantly higher odds of having asthma than nonuse (pooled OR=1.31, 95% CI=1.22, 1.42). Both current

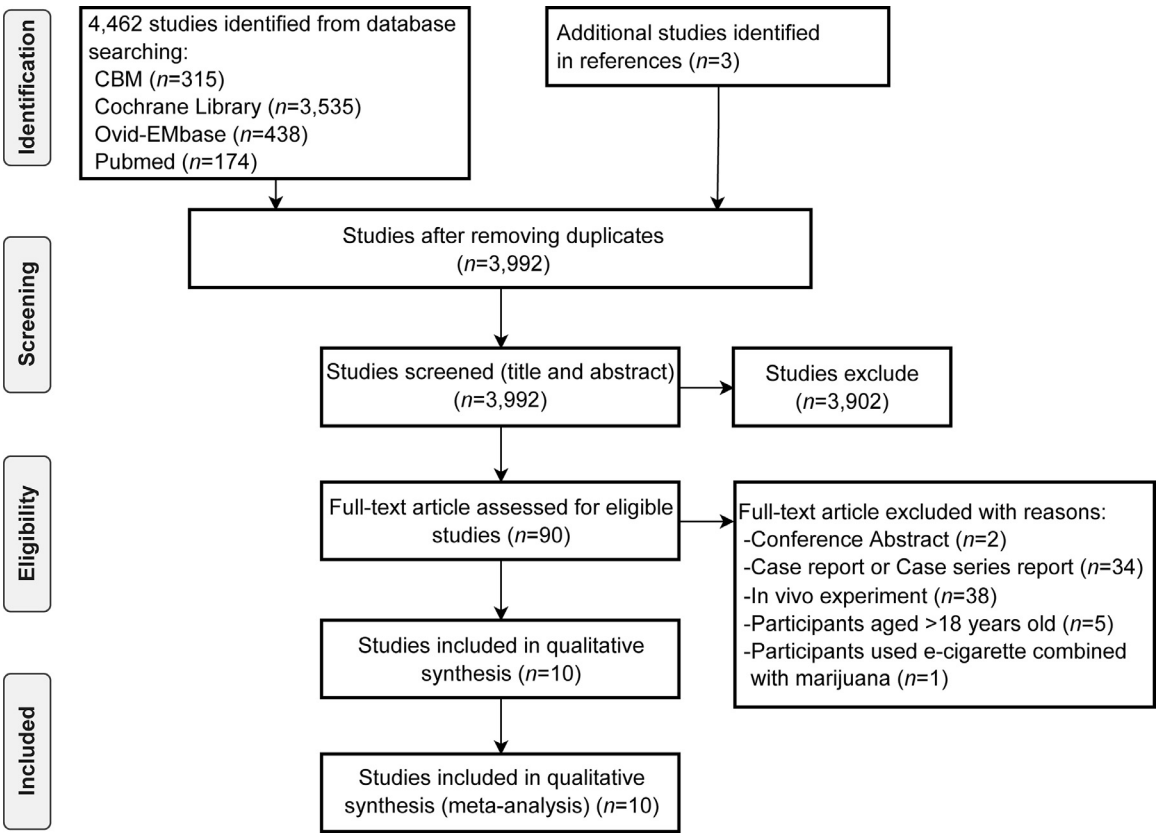

Figure 1. Flowchart of study selection.
CBM, China Biological Medicine Database.

Table 1. Basis Characteristics of Included Cross-Sectional Studies

Study	Country	Sample size	Male (%)	Participants	Age (mean ± SD)	Definition of E-cigarette use	Definition of asthma	Effect size	Adjusted factors
Cho et al., 2016[18]	South Korea	35,904	49.87	High-school students	16.4±0.9 years	Definition 2[a]	Self-report	OR	Gender, city size, multicultural family status, overweight status, secondhand smoking at home, atopic dermatitis history, and allergic rhinitis history
Choi et al., 2016[19]	U.S.	36,085	49.2	High-school students	16.08±0.02 years	Definition 2[a]	Self-report	OR	No adjusted factors
Chung et al., 2020[20]	South Korea	60,040	50.74	Middle and high schools	15.2 years	Definition 2[a]	Self-report	OR	Age, sex, BMI, residential area, regular exercise, sedentary time, exposure to secondhand smoke, and SES
Fedele et al., 2016[21]	U.S.	32,414	49.62	High-school students	NR	Definition 3[b]	Self-report	OR	Race, and grade level
Han et al.,2020[22]	U.S.	21,532	51.59	9th through 12th-grade students	16.1±0.02 years	Definition 3[b]	Self-report	OR	Age, sex, race, overweight or obese, and dental office visit in the previous year
Kim et al., 2017[23]	South Korea	216,056	50.71	7th through 13th-grade students	15.0±1.8 years	Definition 3[b]	Self-report	OR	Age, physical exercise, sex, obesity, region of residence, economic level, educational level of father, education level of mother, active, passive smoking
Larsen et al., 2016[24]	Canada	2,840	51.9	High-school students	15.86±1.27 years	Definition 1[c]	Self-report	OR	Grade, sex, and SES
Lee et al., 2019[25]	South Korea	58,336	50.76	Middle and high-school students	15.0±1.8 years	Definition 1[c]	Self-report	OR	Age, sex, obesity, residential area, family economic status, and physical activity
Schweitzer et al., 2017[26]	U.S.	6,089	50	High-school students	15.8±1.2 years	Definition 2[a]	Self-report	OR	Cigarettes smoking, marijuana use, gender, age, race, Filipino/Pacific Islander, education intentions, overweight, school clustering
Wills et al., 2020[27]	U.S.	14,652	49.3	9th through 12th-grade students	14–18 years	Definition 2[a]	Self-report	OR	Gender, overweight, obese, age, race

Note: Self-report: participants self-reported whether they had asthma diagnosed by a doctor within the past year.
[a]Participants who answered *YES* to the question *Have you ever used an E-cigarettes in your life?* were defined as *ever users*, and those who answered *YES* to the question *Have you used E-cigarettes in the past 30 days?* were defined as *Current users*.
[b]If participants answer *YES* for the question *In the last 30 days, have you smoked E-cigarettes?*, they were considered *Current users*, and those who reported not using any substance of interest (cigarette, E-cigarettes, or water pipe) were considered as *Never users*.
[c]Participants were classified as *ever users* if they smoked E-cigarettes in their lives, and those who have never smoked E-cigarettes were considered *never users*.
NR, no report.

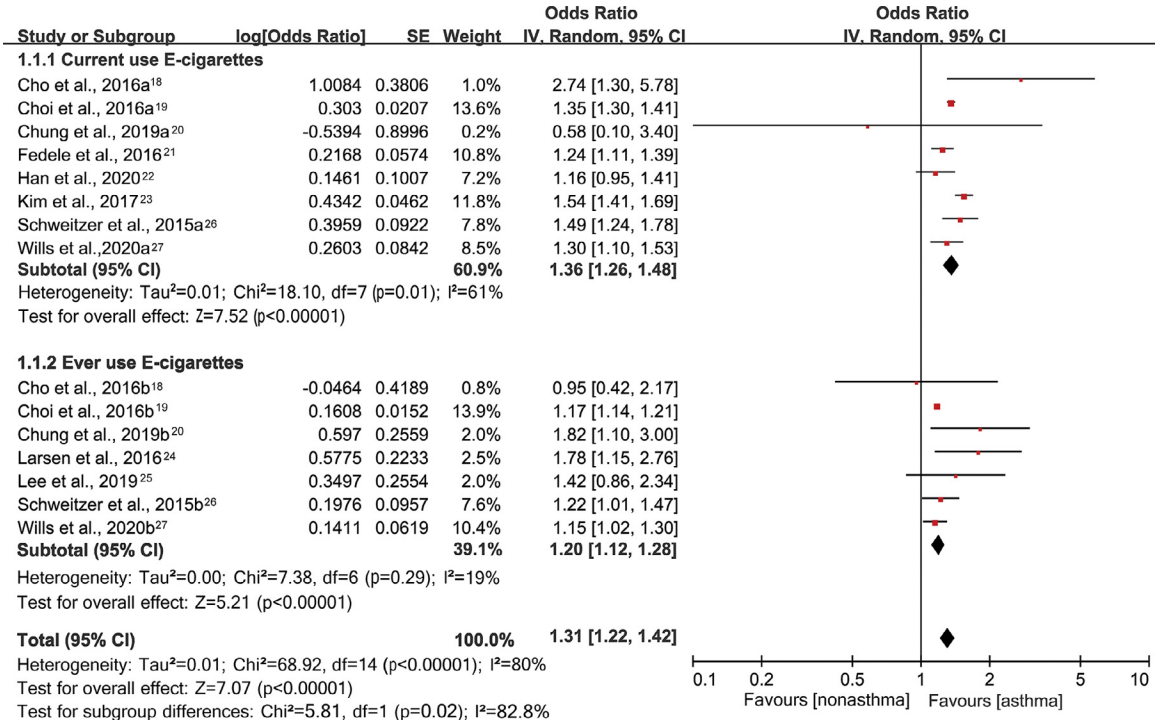

Figure 2. Forest plot of the associations between E-cigarettes use and asthma.
IV, independent variable.

use[18–23,26,27] (OR=1.36, 95% CI=1.26, 1.48) and ever use[18–20,24–27] (OR=1.20, 95% CI=1.12, 1.28) showed similar associations.

The results of the subgroup analysis are presented in Table 2. For the types of E-cigarette use, the pooled ORs were 1.22 (95% CI=1.12, 1.33) in exclusive E-cigarette use[18,20,22,25,27] and 1.34 (95% CI=1.22, 1.48) in E-cigarette use[19,21,23,24,26] subgroups. On the basis of the different regions where the included studies were conducted, both North American[19,21,22,24,26,27] and Asian[18,20,23,25] subgroups yielded a significant relationship between E-cigarette use and asthma, with pooled ORs of 1.28 (95% CI=1.19, 1.37) and 1.54 (95% CI=1.42, 1.68), respectively. Similarly, those using E-cigarettes had higher odds of

Table 2. Subgroup Analysis of the Association Between E-Cigarettes Use With Asthma

		Heterogeneity result			Results of meta-analysis	
Subgroup	**Number of studies**	**I^2, %**	***p*-value**	**Model**	**Effect size**	***p*-value**
Types of E-cigarettes use						
Exclusive E-cigarettes use[a]	5	30	0.19	Fixed	1.22 (1.12, 1.33)	<0.001
E-cigarettes use[b]	5	90	<0.001	Random	1.34 (1.22, 1.48)	<0.001
Region						
North America	6	78	<0.001	Random	1.28 (1.19, 1.37)	<0.001
Asia	4	2	0.4	Fixed	1.54 (1.42, 1.68)	<0.001
Sample size						
<50,000	7	75	<0.001	Random	1.28 (1.19, 1.38)	<0.001
≥50,000	3	0	0.67	Fixed	1.54 (1.41, 1.68)	<0.001
Participants						
High-school students only	5	81	<0.001	Random	1.32 (1.21, 1.46)	<0.001
Middle and high school	5	70	0.003	Random	1.32 (1.14, 1.53)	<0.001

[a]Exclusive E-cigarettes use subgroup included those studies that explicitly differentiated between E-cigarettes use and smoking and reported the effect size (ORs) of comparing only E-cigarettes use with nonuse.
[b]E-cigarettes use subgroup included studies that merely reported E-cigarettes use versus nonuse, but whether E-cigarettes use combined with smoking was not to be clearly defined.

having asthma than nonusers in the sample size <50,000[18,19,21,22,24,26,27] and ≥50,000[20,23,25] subgroups, with respective pooled ORs of 1.28 (95% CI=1.19, 1.38) and 1.54 (95% CI=1.41, 1.68). Finally, statistically significant ORs for having asthma and E-cigarette use were also obtained in high-school student participants[18,19,21,24,26] and in middle- and high-school participants,[20,22,23,25,27] with pooled ORs of 1.32 (95% CI=1.21, 1.46) and 1.32 (95% CI=1.14, 1.53), respectively.

Potential publication bias was assessed through Begg's test, which revealed no significant bias (p=0.245). A similar result was obtained after Egger's test (p=0.25), clearly ruling out large publication bias effects in this meta-analysis (Appendix Figure 2, available online).

DISCUSSION

This meta-analysis synthesized the results of 10 cross-sectional studies, which provided integrative evidence about the association between E-cigarette use and asthma in adolescents. The results revealed that E-cigarette use (both current and ever use) was associated with asthma. To rule out possible confounding factors (i.e., smoking), the results from a subgroup analysis of exclusive E-cigarette use were found to be consistent with the main findings. In a similar review, Wills et al.[28] investigated the relationship between E-cigarettes and respiratory disorders, including asthma and chronic obstructive pulmonary disease, and also summarized laboratory studies. However, that review including studies on both adolescents (11 studies) and adults (4 studies) did not report a pooled OR only for adolescents and did not explore the potential source of heterogeneous results by subgroup analyses. In addition, the report by Wills and colleagues[28] did not assess the quality of included studies.

Moreover, the findings of this meta-analysis were consistent with those of previous literature reviews[29−31] that summarized the relationship between E-cigarettes and asthma and those of experimental studies[32−34] that explored the biological impact of E-cigarettes. The use of E-cigarettes has increased sharply worldwide in recent years. For example, in the U.S., the prevalence of E-cigarette use was consecutively declining from 2004 but increased significantly during 2013−2014, especially among youth.[35] The regulation of E-cigarettes varies across countries and states, ranging from no regulation to banning them entirely.[12,36] In Japan, E-cigarettes containing nicotine are illegal and banned for use as cigarette alternatives. Some other countries have licensed E-cigarettes as medical devices such as in South Korea and the United Kingdom.[37] However, because of medical drug policies and the companies that manufacture E-cigarettes pushing for laws that support their interests,[38] E-cigarette legislation has been a subject of debate in many countries.[39] Hence, the ambiguity or lack of regulation on E-cigarettes should be settled, with more stringent supervision over E-cigarettes, especially for adolescents.

At present, no available therapeutic regimens can cure asthma; however, associations have been reported between a wide range of environmental factors and asthma such as tobacco smoke, dust mites, and air pollution. These factors are called asthma triggers.[40] On the basis of the findings of this study, E-cigarette appears to serve as a potential trigger for asthma in adolescents. It is not clear why some people develop asthma and others do not, but it is probably due to a combination of environmental and genetic factors. Exposure to various irritants is known to trigger the symptoms of asthma. Thus, the diverse prevalence of asthma among countries or regions may be related to the different distribution of asthma triggers among them, such as different rates of smoking, obesity, or pollution.[41,42]

The study reported by Bhatta et al.[43] revealed that switching from conventional cigarettes to E-cigarettes would lower the risk of developing respiratory disease. This finding is relevant because the controversy continues over whether E-cigarettes should be promoted as a harm-reduction device for smokers. However, the subgroup analysis in this study indicated that exclusive use of E-cigarettes was still significantly associated with asthma in adolescents (pooled OR=1.22, 95% CI=1.12, 1.33). Smoking has been established as a powerful trigger of asthma,[44] which can substantially irritate the lining of the airways, and in some countries, E-cigarettes have been suggested to be used for smoking cessation,[4,45] but their role was reported to be controversial.[46] The results of this study suggest that if E-cigarettes are licensed as medical devices for promoting smoking cessation in adolescents, there should be more research conducted first to investigate their safety.

In this study, except for the studies reported by Chung and colleagues[20] and Cho et al.,[18] all the studies of current use and ever use subgroups were consistent in finding that E-cigarette use was associated with asthma (Figure 2). Indeed, those 2 studies had much wider CIs than those of other studies (Figure 2), which probably caused comparatively significant heterogeneity.[47] Although after carrying out a thorough investigation along with a subgroup analysis, it was found that the results were also consistent with the main finding, indicating that a significantly robust association was identified in this meta-analysis.

Limitations

Some limitations are associated with this review that should be noted. First, because all the studies that were included in the analysis did not directly compare current with ever E-cigarette use or daily with occasional E-cigarette use, the possible association of E-cigarette use with asthma in these patterns was not analyzed. Second, active asthma and nonactive asthma, an important classification, were not reported in the included studies. Therefore, the possible association between E-cigarettes and asthma stratified by active and nonactive asthma status was not included in this study. Third, this meta-analysis incorporated only 1 study[19] that did not present adjusted ORs but only crude ORs; however, when this study was excluded from meta-analysis, the pooled OR and I^2 statistics did not change significantly. Finally, this review only included English and Chinese literature. Consequently, the data published in other languages were missing from this analysis.

CONCLUSIONS

This meta-analysis clearly establishes that both current use and ever use of E-cigarettes have significant associations with asthma in adolescents. This knowledge could provide potential evidence for primary prevention as well as intervention strategies and form the basis of a novel reference for public health policy.

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CREDIT AUTHOR STATEMENT

Xuechao Li: Conceptualization, Literature screening, Data extraction, Formal analysis, Writing - Original Draft, Writing - review & editing. Yi Zhang: Literature screening, Data extraction, Data curation, Writing - Review and Editing. Rongqiang Zhang: Software, Visualization, Interpretation. Fei Chen: Quality assessment of included studies, Interpretation. Lihua Shao: Validation. Li Zhang: Conceptualization, Supervision, Funding acquisition.

SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at https://doi.org/10.1016/j.amepre.2022.01.015.

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