

Association between e-cigarette use and asthma: A systematic review and meta-analysis

Benjamin R Chand, Hassan Hosseinzadeh

University of Wollongong, School of Health and Society, Wollongong, 2522 Australia

bchand@uow.edu.au

Abstract

Objective

Increasing e-cigarette use combined with emerging evidence of their respiratory effects raises concerns about their potential impact on asthma prevalence. This review evaluates the most recent available evidence on the association of e-cigarette use and asthma world-wide.

Methods

A literature search was performed in Pub Med, Scopus, CINAHL, Cochrane Library, Web of Science and ProQuest in March 2021. This study was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) registered with PROSPERO (registration number: CRD42020211812)

Study Selections

Cross-sectional and cohort studies assessing the association between e-cigarette use and Asthma were eligible for inclusion. Studies examining exacerbations in asthma symptoms and severity were excluded. The quality of the included studies was assessed using the Appraisal tool for Cross-Sectional Studies (AXIS).

Results

Thirteen cross-sectional studies with the sample size of 1,039,203 met the eligibility criteria. Odds ratios were pooled using a random effects model. Pooled analysis found a significant association between current e-cigarette use and asthma (pOR = 1.36, 95% CI 1.21-1.52) and ever e-cigarette use and asthma (pOR = 1.24 95% CI 1.13-1.36).

Conclusion

Our review found that e-cigarette use and ever e-cigarette use are correlated with asthma. However, heterogeneity and inconsistencies between covariates limited the interpretation of the results. This warrants further studies to investigate any potential causal association between e-cigarette use and asthma. No funding was received for this systematic review.

Keywords: Electronic cigarette, e-cigarette, Electronic nicotine delivery systems, ENDS, vaping, Asthma, cardiopulmonary.

Introduction

Originally developed as a less harmful substitute for smoking and a smoking cessation aid, e-cigarettes are increasingly being used by non-smokers and youth at low risk of initiating cigarette smoking (1, 2). Although e-cigarette use is thought to be safer than smoking, claims of the relative safety of e-cigarettes are contested (3). As global tobacco use declines, the use of e-cigarettes has increased rapidly (4). The prevalence of current e-cigarette use varies from country to country ranging from 1.1% to 5.5% of adults and 1% to 35% of adolescents (4). Increasing e-cigarette use and emerging evidence of the respiratory effects of e-cigarette use raises concerns about their potential impact on the incidence of respiratory conditions (1).

E-cigarettes heat a liquid, consisting of vegetable glycerin, propylene glycol, flavoring agents and often, but not always, nicotine (5). The vapor produced by e-cigarettes exposes users to ultrafine particles and substances which are toxic to the lung (5, 6). Several flavoring agents used in e-cigarettes are known airway irritants and asthma sensitizers including substances reported to cause occupational asthma (7). E-cigarette use has been associated with increased risk of respiratory symptoms including dyspnoea, decreased lung function and airway inflammation (5, 8-11). Several observational studies have reported an association between e-cigarette use, asthma exacerbations and asthma diagnosis (12-15). Studies have also found an association between e-cigarette use and the development of chronic obstructive pulmonary disease (COPD) and chronic bronchitis (5, 8)

Asthma is a heterogeneous disease with genetic and environmental etiological pathways affecting over 339 million people worldwide (16, 17). Despite a relatively low mortality rate, more than 400,000 deaths are attributed to Asthma annually (17, 18). People living with Asthma experience poorer quality of life and higher rates of depression, anxiety, obesity and hypertension compared to the general population (19, 20). E-cigarettes are a relatively new device therefore the long-term effects of their use on the development of asthma are not well understood. This review aims to fill this gap by evaluating the findings of the most recent studies exploring the association between e-cigarette use and asthma worldwide.

Methods

Data sources and search strategy

A literature search was performed in Pub Med, Scopus, CINAHL, Cochrane Library, Web of Science and ProQuest. The search was conducted in October 2020 and re-run prior to final analysis in March 2021. The search terms included “asthma” combined with the following commonly used synonyms for e-cigarettes; “e-cigarette”, “electronic cigarette”, “vapor cigarette”, “vapour cigarette”, “vape”, “vaping”, “electronic nicotine delivery”, “electronic nicotine device”, “electronically heated cigarette”, “e-liquid”, “juul”, “personal vaporizer”, “personal vapouriser”. The fields were adapted to the search features of each database using identical search terms. The search was limited to papers published in English between 2007, the earliest known e-cigarette literature, and March 2021. Reference lists of included studies were screened to identify additional eligible studies. The search strategy employed for Pubmed has been included in Appendix A. This systematic review is registered with PROSPERO (registration number: CRD42020211812) and reported in accordance with the PRISMA guidelines. The protocol for this review can be accessed at https://www.crd.york.ac.uk/prospere/display_record.php?RecordID=211812.

Selection criteria

Cross-sectional and cohort studies that assessed the association between e-cigarette use and Asthma diagnosis in any location were eligible for inclusion. Experimental studies, case series, case reports, reviews and other non-original papers were excluded. Studies measuring current e-cigarette use, ever e-cigarette use and dual current use of e-cigarettes and cigarettes with current or incident asthma diagnosis were included. Studies assessing exacerbations in asthma symptoms or severity were not included. Articles identified in the initial search were extracted and managed using citation management software Endnote (21). Titles and abstracts were first reviewed by a single investigator to exclude irrelevant articles. Both authors independently reviewed full-text articles for eligibility. Consensus on the inclusion of studies was reached through discussion based on the aims and inclusion criteria of the review. The PRISMA flow chart for the selection of studies is presented in Fig. 1. There are only two eligible longitudinal studies (44, 43). However, we excluded them to have a consistent study type in meta-analysis using cross-sectional studies. Further, combining the results of longitudinal cross-sectional studies were not possible. We used the eligible longitudinal studies in the discussion section to support our findings.

Data extraction

Data extracted for each study included study design, population age group, sample size, geographic location of study sample, definition(s) of e-cigarettes use, definition of asthma diagnosis, adjusted odds ratios (aORs) and covariates accounted for in adjusted models. Data was extracted from full-text articles by the first author (BC) and verified independently by the second reviewer (HH). Data were extracted from each study into a table developed based on the eligibility criteria and piloted with several included studies to assess suitability. The most common measure of association used in the included studies was a prevalence odds ratio (OR). Data pertaining to the association between current, ever and dual use of e-cigarettes and cigarettes with asthma were extracted.

Methodological quality appraisal

The Appraisal tool for Cross-Sectional Studies (AXIS) was used to assess the quality of each study (22). The AXIS tool includes items to assess the appropriateness of the study design, selection of participants, response rates, the validity of exposure/outcome measures and potential for bias. The AXIS tool does not utilize a numerical scale to assess study quality, however, a score of one was allocated for a positive response to each question in the AXIS checklist to assist in the overall assessment of each study. Each study was given an overall assessment of “poor”, “fair” or “good”. The first reviewer (BC) extracted relevant data to assess the quality of each study, completed the AXIS checklist for each study and made an overall assessment of the quality of each study. The second author (HH) reviewed the AXIS criteria and quality assessment of each study. Disagreements on the quality of each study were resolved through discussion. The quality assessments of the selected studies are presented in Table 2.

Statistical analysis

Statistical analysis was performed using Review Manager version 5.4.1 (23). The chi-square and the Higgins I^2 test were used to test between study heterogeneity (24). A pooled odds ratio with 95% confidence intervals (CI) was calculated using the inverse variance method, which gives greater weight to larger sample sizes, with a random effects model (24). A causal diagram (Fig. 3) was developed to identify potential confounders in the hypothesized relationship between e-cigarette use and asthma. The variables adjusted for in each study were identified as shown in Appendix D. Adjusted ORs were used in the meta-analysis where available, otherwise unadjusted ORs were used. Subgroup analysis was undertaken to examine the differences in effect between adolescent and adult participants and US and non-US studies. Heterogeneity between subgroups was assessed using the Chi-Square test for heterogeneity and I^2 test measuring the variability in effect estimates due to subgroup differences as opposed to sampling error (24, 25). There was insufficient data to perform

further subgroup analysis and meta-regression. Sensitivity analysis was performed restricting analysis to “good” quality studies and using a fixed effects model (24). Publication bias was assessed by visually inspecting funnel plots (24). Forest plots were used to display the results of individual studies and pooled odds ratios.

Results

Literature search & study selection

As presented in Fig. 1, the literature search identified 2,335 records after screening titles and abstracts, and removing duplicates 62 full-text articles were assessed for eligibility. Thirteen cross-sectional studies met the eligibility criteria. The most common reasons for exclusion were “inappropriate outcome measure” and “data presented in another study”. The included studies comprised of a total sample size of 1,039,203 participants with sample sizes of individual studies ranging from 1,345 to 402,822 participants. Eight studies used data from nationally representative surveys (13, 26-32). Studies were published between 2016 and 2020 with data collection occurring between 2012 and 2018. Ten studies were assessed to be of “good” quality and four were assessed to be of “fair” quality. The characteristics of included studies are presented in Table 1.

Current e-cigarette use and asthma

Thirteen cross-sectional studies assessing the association between current e-cigarette use and asthma, were included in the meta-analysis (13, 26-37). Ten studies examined adolescent participants (13, 28-30, 32, 34-38) and three included adult participants (26, 27, 31). Seven studies examined participants from the US (26, 27, 31, 32, 34, 35, 37), four from South Korea (13, 28-30), one from Canada (36) and one from Kuwait (38). Current e-cigarette use was defined as any e-cigarette use in the past 30 days. The unexposed participants were never e-cigarette or cigarette users or never e-cigarette users with multi-variate model adjusting for cigarette use. Asthma was defined as self-reported Asthma diagnosis. Out of thirteen cross-sectional studies, ten reported a positive association between current e-cigarette use and current asthma diagnosis (13, 26-28, 30, 32, 34-37).

Data from the cross-sectional studies were pooled using a random effects model (Fig. 2). The pooled odds ratio for current e-cigarette use and asthma was 1.36 (95% CI 1.21-1.52). The Chi-square test for heterogeneity was significant ($p < .001$). The I^2 index indicated a substantial heterogeneity (73%) between studies (24). There was no significant difference between adolescent and adult subgroups ($p = .59$). Subgroup analysis showed no significant difference in effect ($p = .32$) between US and non-US studies). Sensitivity analysis showed that restricting analysis to studies that only included never cigarette users ($n = 4$) in the analysis resulted in a higher pooled OR (pOR = 1.62, 95% CI 1.13-2.31). Pooling studies assessed to be of “good” quality ($n = 10$) resulted in a lower, but still significant pooled OR (pOR = 1.24, 95% CI 1.11-1.40). Pooling using a fixed effects model resulted in a lower pooled odds ratio (pOR = 1.19, 95% CI 1.14-1.25, $I^2 = 73\%$). None of the included studies adjusted their findings for potential confounders identified in Appendix D. Visual inspection of the funnel plot showed some asymmetry indicating potential publication bias (see Appendix C).

Ever e-cigarette use and asthma

Seven cross-sectional studies (162,182 participants in total) examined the association between ever use of e-cigarettes and asthma (28, 29, 31-33, 37, 39). Six studies examined adolescent participants (28, 29, 32, 34, 37, 38) and one examined adult participants (31). Four studies examined participants from the US (31, 32, 34, 37), two from South Korea (28, 29) and one from Kuwait (38). Ever e-cigarette use was defined as ever use of an e-cigarette but not in the past 30-days. The unexposed participants were never e-cigarette or cigarette users or never e-cigarette users with multi-variate model adjusting for cigarette use. Asthma was defined as self-reported Asthma diagnosis. Four of

these studies reported a positive association between ever use of e-cigarettes and asthma (29, 32, 34, 37). The results of the remaining three studies were not significant (28, 31, 33).

The data from studies examining the association between ever use of e-cigarettes and asthma were pooled using a random effects model (Fig. 3). The pooled odds ratio for ever e-cigarette use and asthma was 1.24 (95% CI 1.13-1.36). The Chi-square test for heterogeneity was not significant ($p=.38$). The I^2 index was also indicated low levels of heterogeneity (6%) between studies. Subgroup analysis indicated no significant difference between US and non-US studies ($p=.29$). There were insufficient studies in the adult subgroup to make a comparison with adolescent participants. Sensitivity analysis resulted in similar pooled ORs and similar levels of heterogeneity using a fixed effects model in comparison with a random effect model. Including only “good” quality studies also produced a similar pooled OR with lower levels of heterogeneity. There were insufficient studies to draw any conclusions from visual inspection of the funnel plot.

Dual current e-cigarette and cigarette use, and asthma

Dual current use of e-cigarettes and cigarettes was assessed in six studies representing a total of 146,241 participants (27-29, 31-33). Five studies examined adolescent participants (27-29, 32, 38) and one study examined adult participants (31). Three studies included participants from the US (27, 31, 32), two from South Korea (28, 29) and one from Kuwait (38). Dual current e-cigarette use was defined as use of an e-cigarette and cigarette in the past 30-days. The unexposed participants were never e-cigarette or cigarette users or never e-cigarette users with multi-variate model adjusting for cigarette use. Asthma was defined as self-reported Asthma diagnosis. A positive association between dual current use of e-cigarettes and cigarettes was reported in four of these studies reporting OR's ranging from 1.62 (95% CI 1.32-1.99) to 20.92 (95% CI 7.79-56.20) (27, 31-33). The data from studies examining the association between dual current use of e-cigarettes and cigarettes with asthma were not pooled due to high levels of heterogeneity between studies ($I^2=93\%$).

Discussion

The findings of this review suggest an overall positive association between current and ever e-cigarette use and self-reported asthma diagnosis. Among the thirteen studies included in the quantitative syntheses, the majority found an association between current and ever e-cigarettes use and asthma. In a pooled analysis there was a significant association between current e-cigarette use and asthma (pOR = 1.36, 95% CI 1.21-1.52) and ever e-cigarette use and asthma (pOR = 1.24 95% CI 1.13-1.36).

This review builds upon existing evidence of the potential links between inhalation of the constituents of e-cigarette vapor and asthma(40). Current research suggests that e-cigarettes expose users to toxic substances, airway irritants and asthma sensitizers which may be harmful to the respiratory system (7, 12, 41). In a longitudinal analysis of nationally representative study of US adults, Xie et al. (42) reported an increased risk of developing asthma following current e-cigarette use (IRR 1.32, 95% CI 1.01-1.72) and ever e-cigarette use (IRR 1.24, 95% CI 1.01-1.53). Using the same data, Bhatta & Glantz (43) reported similar results. Despite evidence that switching to e-cigarettes can reduce respiratory symptoms, many users continue to use both cigarettes and e-cigarettes, which is more strongly associated with asthma than either product alone (4, 44). E-cigarette users may also be at greater risk of taking up cigarette smoking, threatening to undermine efforts to address the global tobacco epidemic (45, 46). Public health initiatives should be implemented to reduce e-cigarette use.

Limitations

There are several limitations to this systematic review. The review is susceptible to publication bias as it only included published studies. Visual inspection of the funnel plot indicates that publication bias is likely. Further, EMBASE was not available to the researchers to expand search pool. Although the review included a small number of studies it represents a large number of participants ($n = 1,039,203$). The review is unable to establish a causal relationship due to the cross-sectional design of the majority of the studies. Reverse causality, where participants with Asthma choose to use e-cigarettes at a higher rate than participants without asthma, cannot be ruled out. All studies included in the review are subject to recall bias as they relied on self-reported e-cigarette exposure and asthma. Self-reported measures of e-cigarette use were consistent between studies, however, exposure to e-cigarette vapor varies depending on the type of e-cigarette, the settings, e-liquid used and frequency of use (7). None of the studies accounted for this variation. At present, there is no standardized measure of e-cigarette dose (47). Statistical analysis showed substantial between study heterogeneity, however, the small number of studies in the review limited sub-group analysis and sensitivity analysis. The unknown source of heterogeneity means the results should be interpreted with caution. Residual confounding cannot be ruled out due to inconsistency in covariates adjusted for in each study and potentially unmeasured covariates. Future epidemiological research should further investigate potential confounders. There were only two eligible longitudinal studies however we excluded them because combining their results with cross sectional studies was not possible.

Conclusion

The findings of this systematic review suggest that there is a link between current and ever use of e-cigarettes, with an asthma diagnosis. However, the selected studies were cross-sectional and heterogeneous. Further studies are warranted to explore any potential causal association between e-cigarette use and asthma.

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Declaration of interest statement

The authors report no conflicts of interest.

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Author contributions

Both authors conceptualized and designed the study. BC performed searches, assessed the eligibility of the retrieved papers in the titles/abstracts and full-text. HH critically assessed the eligible studies and extracted data. BC analyzed and interpreted the data and drafted the manuscript. Both authors critically reviewed the manuscript. HH reviewed and approved the final manuscript.

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Table 1. Characteristics of included studies (n = 13)

Source	Study design	Population	Measure of e-cigarette use	Measure of Asthma	Unexposed	Covariates adjusted	Overall Quality Assessment
Alanazi <i>et al.</i> 2020 (27)	Cross-sectional	Young Adults (18-24), USA (n=26,233)	Self-reported e-cigarette use: • Current (past 30 days) • Ever (former not current)	Self-reported doctor diagnosed Asthma: • Current	never e-cigarette user (multi-variate model adjusts for cigarette smoking status)	Sex, educational attainment, race, COPD, diabetes, chronic kidney disease, arthritis, skin cancer, and other cancers.	Good
Alnajem <i>et al.</i> 2020 (38)	Cross-sectional	High school students (16-19), Kuwait (n = 1,345)	Self-reported e-cigarette use: • Current (past 30 days) • Ever • Never	Self-reported doctor diagnosed Asthma: • Current (within past 12 months and current wheezing and/or treatment in past 12 months)	never smoker/never e-cigarette user	Sex, age, exposure to household secondhand smoke, exposure to household second-hand aerosols from electronic cigarettes, and exposure to second-hand smoke and/or second-hand aerosols from electronic cigarettes in public places.	Good
Cho & Paik 2016 (28)	Cross-sectional	High school students, South Korea (n = 35,904)	Self-reported e-cigarette use: • Current (past 30 days) • Former (ever, not in past 30 days)	Self-reported doctor diagnosed Asthma • Within past 12 months	never e-cigarette user/never cigarette user	Gender, city size, multi-cultural family status, overweight status, second hand smoking at home, atopic dermatitis history, and allergic rhinitis history.	Good
Choi & Bernat 2016 (34)	Cross-sectional	High school students, USA (n = 36,085)	Self-reported e-cigarette use: • Current (past 30 days) • Ever	Self-reported Asthma diagnosis: • Current	never e-cigarette user (multi-variate model adjusts for cigarette use)	Age, gender, race/ethnicity, days smoked cigarettes in past 30 days, asthma status, ever used e-cigarettes, past 30 day use of e-cigarettes.	Fair
Chung <i>et al.</i> 2020 (29)	Cross-sectional	Adolescents 12-18, South Korea (n = 60,040)	Self-reported e-cigarette use: • Current user (more than one day in past 30-days) • Former user (ever but not in past 30-days)	Self-reported Asthma diagnosis: • Within past 12 months • Ever	never e-cigarette user/never cigarette user	Age, sex, body mass index, residential area, regular exercise, sedentary time, exposure to second-hand smoke, socioeconomic status, and the presence of allergic rhinitis.	Good
Fedele <i>et al.</i> 2016 (35)	Cross-sectional	High school students, USA (n = 29,904)	Self-reported e-cigarette use: • Current (past 30 days)	Self-reported doctor diagnosed Asthma • Current	non e-cigarette user/non cigarette user	Age, sex, race/ethnicity, and grade level.	Good
Kim <i>et al.</i> 2017 (13)	Cross-sectional	Adolescents (12-18), South Korea (n = 216,056)	Self-reported e-cigarette use: • Current (past 30 days)	Self-reported doctor diagnosed Asthma: • Within the past 12 months • Ever	never e-cigarette use (multi-variate model adjusts for cigarette use)	Age, physical exercise, sex, obesity, region of residence, economic level, educational level of father, education level of mother, active, passive smoking.	Good

Kim <i>et al.</i> 2020 (30)	Cross-sectional	Adolescents (12-18), South Korea (n = 195,847)	Self-reported e-cigarette use: • Current (past 30 days) • Ever	Self-reported doctor diagnosed Asthma: • Ever	never e-cigarette user (multi-variate model adjusts for cigarette use)	Age, sex, grade, socioeconomic status, academic achievement, drinking, smoking, and mental health variables.	Good
Larsen <i>et al.</i> 2016 (36)	Cross-sectional	High school students (12-19), Canada (n = 6,159)	Self-reported e-cigarette use: • Past 12 months	Self-reported doctor diagnosed Asthma • Ever	non e-cigarette user/non cigarette user	Grade, sex, socioeconomic status.	Fair
Osei <i>et al.</i> 2019 (26)	Cross-sectional	Adults (18+), USA (n = 402,822)	Self-reported e-cigarette use (among never cigarette smokers): • Current (daily and occasional) • Daily (every day) • Occasional (some days)	Self-reported doctor diagnosed Asthma • Current	never e-cigarette user/never cigarette user	Age, sex, race, income/federal poverty line, level of education and body mass index.	Good
Schweitzer <i>et al.</i> 2017 (37)	Cross-sectional	High school students, USA (n = 6,089)	Self-reported e-cigarette use: • e-cig user current (past 30 days, 7 response options from 0 days to all 30 days) • e-cig user (ever)	Self-reported doctor diagnosis Asthma: • Current • Previous	never e-cigarette user (multi-variate model adjusts for cigarette use)	Gender, age, race, education intentions, body mass index, cigarette use, marijuana use.	Good
Wang <i>et al.</i> 2019 (31)	Cross-sectional	Adult immigrants (18+), USA (n = 7,954)	Self-reported e-cigarette use: • Current (every day or some days) • Ever	Self-reported diagnosed Asthma • Ever	never e-cigarette user/never cigarette user	Age, sex, race/ethnicity, educational attainment, marital status, poverty status and history of combustible cigarette smoking.	Fair
Wills <i>et al.</i> 2020 (32)	Cross-sectional	Adolescents (12-18), USA (n = 14,765)	Self-reported e-cigarette use: • Current (past 30 days) • Ever	Self-reported doctor diagnosed Asthma • Ever	never e-cigarette user/never cigarette user	Age, gender, race/ethnicity, overweight status, obesity status, e-cigarette use, cigarette smoking, and marijuana use (ever or any past-30-day use).	Good

Table 2: Quality assessment using the Appraisal tool for Cross-Sectional Studies (AXIS)

	AXIS Checklist Question																				Overall Quality Assessm ent (Good, Fair, Poor)
Author (Year)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Alanazi <i>et al.</i> 2020 (27)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Good
Alnajem <i>et al.</i> 2020 (38)	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	Good
Cho & Paik 2016 (28)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Good
Choi & Bernat 2016 (34)	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Fair
Chung <i>et al.</i> 2020 (29)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	N	Y	N	Y	Good
Fedele <i>et al.</i> 2016 (35)	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	Good
Kim <i>et al.</i> 2017 (13)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Good
Kim <i>et al.</i> 2020 (30)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Good
Larsen <i>et al.</i> 2016 (36)	Y	Y	N	Y	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Fair
Osei <i>et al.</i> 2019 (26)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Fair
Schweitzer <i>et al.</i> 2017 (37)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Good
Wang <i>et al.</i> 2019 (31)	Y	Y	N	Y	Y	Y	N	Y	N	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	Fair
Wills <i>et al.</i> 2020 (32)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Good

1. Were the aims/objectives of the study clear?; 2. Was the study design appropriate for the stated aim(s)?; 3. Was the sample size justified?; 4. Was the target/reference population clearly defined? (Is it clear who the research was about?); 5. Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?; 6. Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?; 7. Were measures undertaken to address and categorize non-responders?; 8. Were the risk factor and outcome variables measured appropriate to the aims of the study?; 9. Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously?; 10. Is it clear what was used to determined statistical significance and/or precision estimates? (e.g. p-values, confidence intervals); 11. Were the methods (including statistical methods) sufficiently described to enable them to be repeated?; 12. Were the basic data adequately described?; 13. Does the response rate raise concerns about non-response bias?; 14. If appropriate, was information about non-responders described?; 15. Were the results internally consistent?; 16. Were the results presented for all the analyses described in the methods?; 17. Were the authors' discussions and conclusions justified by the results?; 18. Were the limitations of the study discussed?; 19. Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?; 20. Was ethical approval or consent of participants attained?

Figure 1. PRISMA flow diagram

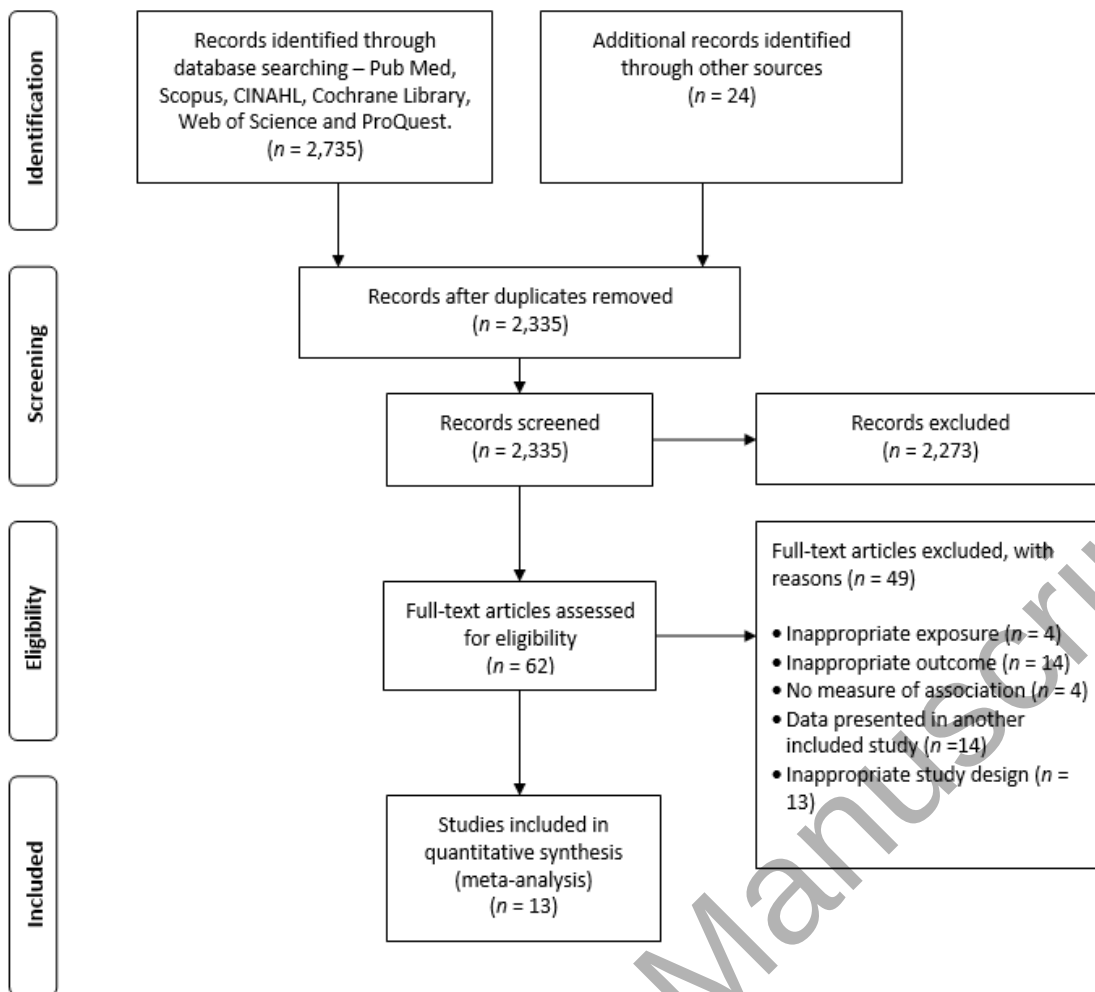
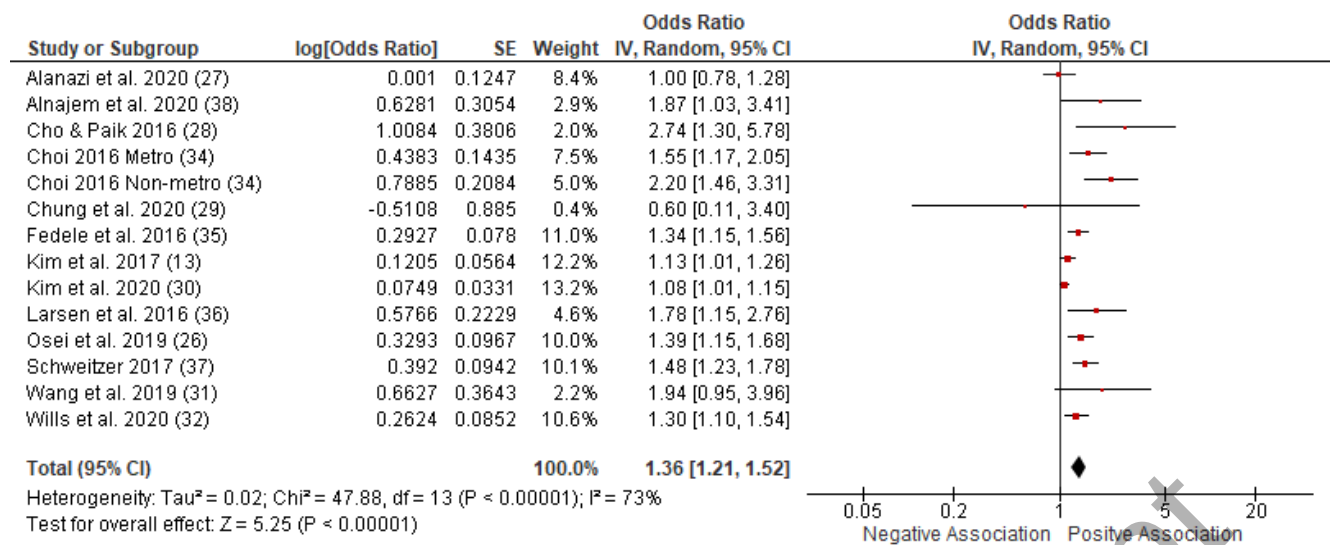
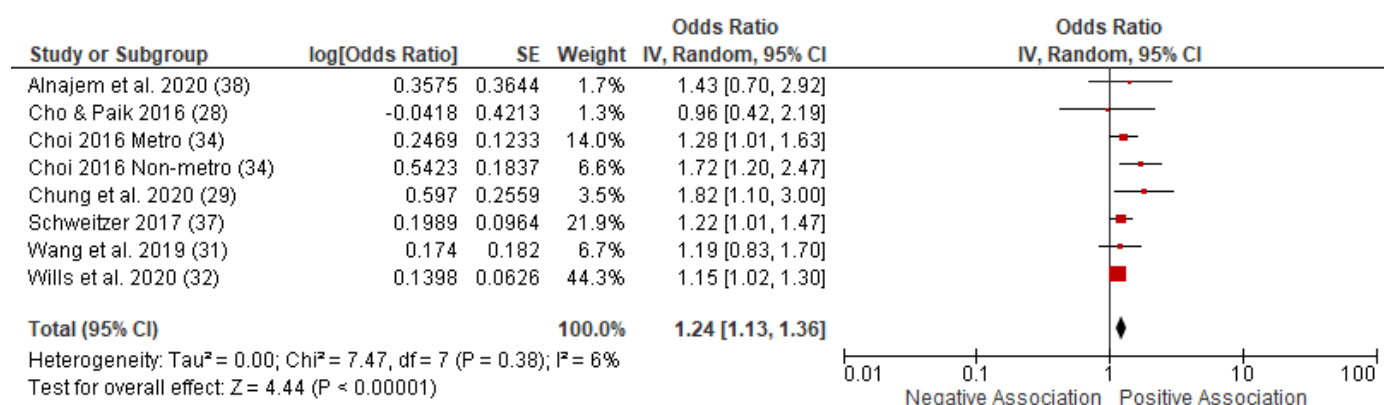


Figure 2. Forest plot for current e-cigarette use and asthma



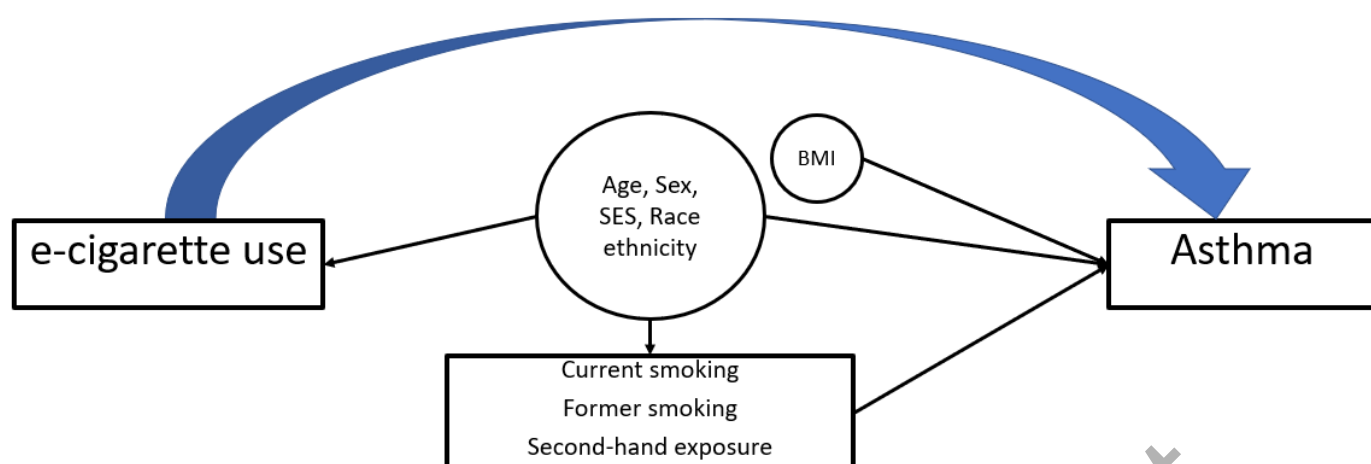
Current e-cigarette use = past 30 days; Asthma = self-reported current asthma diagnosis.

Figure 3. Forest plot for ever e-cigarette use and asthma



Ever e-cigarette use = any lifetime use; Asthma = self-reported current asthma diagnosis.

Figure 4. Causal diagram of the potential relationship between e-cigarette use and asthma



Appendix A: Pubmed Search Strategy

Database:	PubMed (including Medline)
Date:	8/10/2020
Keywords:	(Asthma) AND ((e-cigarette) OR (electronic cigarette) OR (vapor cigarette) OR (vapour cigarette) OR (vape) OR (vaping) OR (electronic nicotine delivery) OR (electronic nicotine device) OR (electronically heated cigarette) OR (e-liquid) OR (juul) OR (personal vaporizer) OR (personal vapouriser))
Search fields:	Title/Abstract
Language:	English.
Search Period:	2007 – present (October 2020)
Records found:	1574

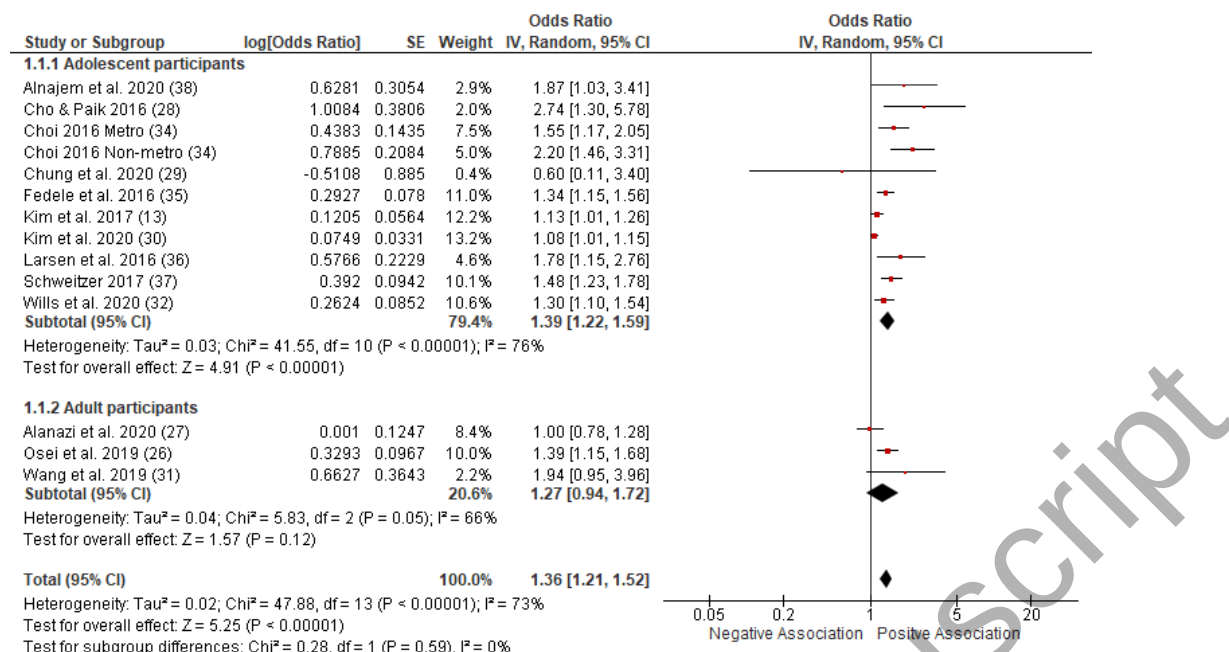
Appendix B: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3/4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5/6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4/5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	p. 20 (Appendix A)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5/6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5/6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6,7
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6,7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6,7
RESULTS			

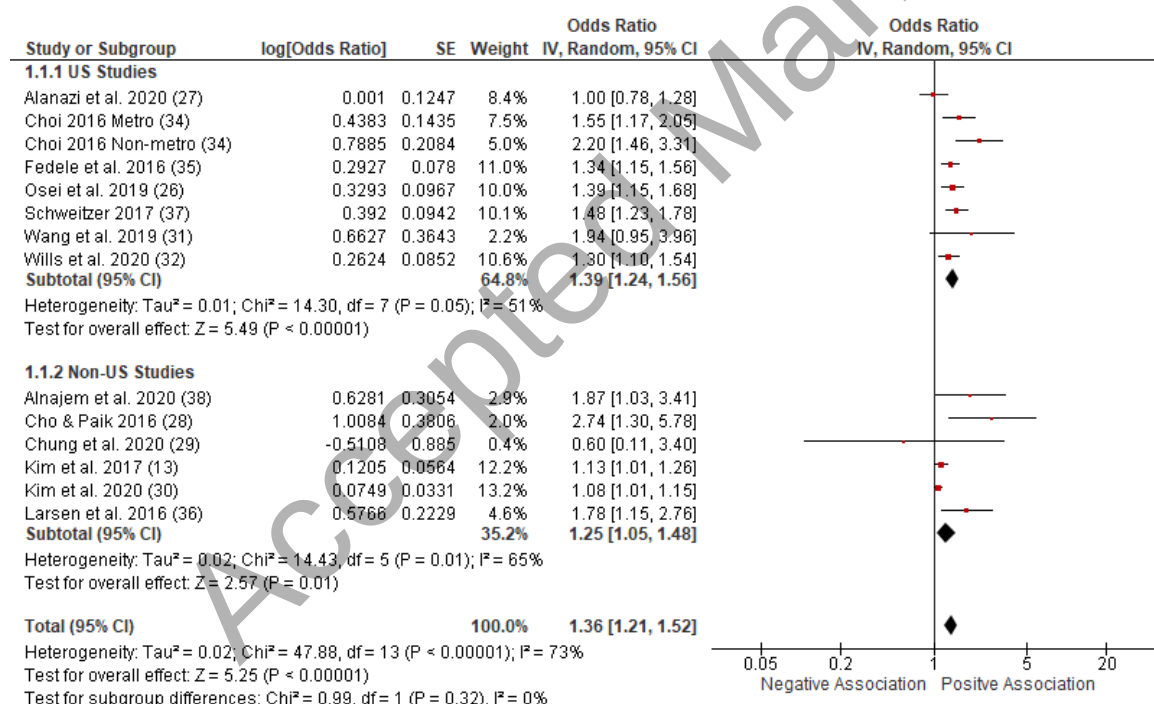
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	p. 37-40 (Table. 1)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Appendix D, E, F. p. 31,36,40.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10/11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11/12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16,17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

Appendix C: Supplemental analysis for current e-cigarette use and asthma

Subgroup analysis (adolescent and adult participants) for current e-cigarette use and asthma



Subgroup analysis (US and non-US studies) for current e-cigarette use and asthma



Sensitivity analysis summary table for current e-cigarette use and asthma

Subgroup	Pooled OR (95% CI)	Chi ² test for heterogeneity	I ²	Test for overall effect
Fixed effects model	1.17 (95% CI 1.12-1.23)	$p < .001$	74%	$p < .001$
Random effects model	1.34 (95% CI 1.18-1.53)	$p < .001$	74%	$p < .001$

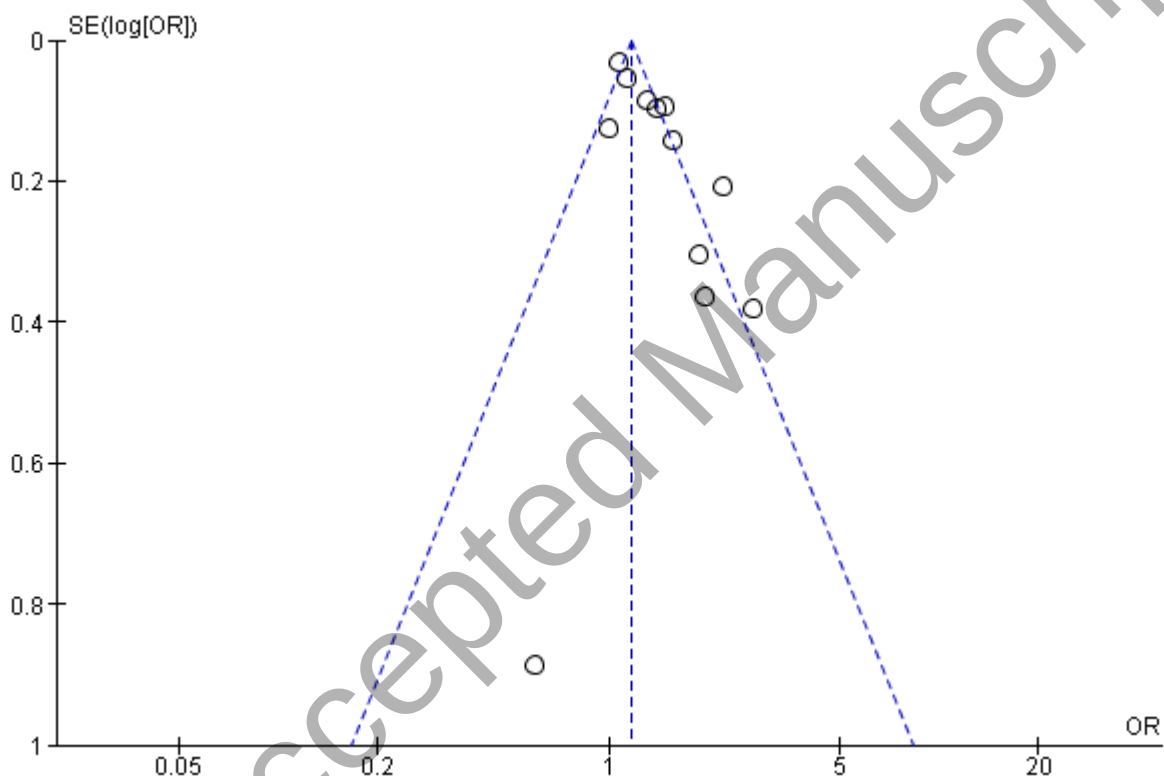
Studies including only never cigarette users	1.62 (95% CI 1.13-2.31)	$p < .20$	36%	$p < .008$
Quality of evidence				
"Good" quality studies only ($n=9$)	1.25 (95% CI 1.11-1.41)	$p < .001$	70%	$p < .001$
"fair" quality studies ($n=2$)	1.75 (95% CI 1.41-2.19)	$p < .001$	0%	$p < .001$

Studies including only never cigarette users ($n=4$) Alnajem *et al.* 2020 (38), Cho & Paik 2016 (28), Chung *et al.* 2020 (29), Osei *et al.* 2019 (26).

"Good" quality studies ($n = 9$) ; Alanazi *et al.* 2020 (27), Alnajem *et al.* 2020 (38), Cho & Paik 2016 (28), Chung *et al.* 2020 (29), Fedele *et al.* 2016 (35), Kim *et al.* 2017 (13), Kim *et al.* 2020 (30), Osei *et al.* 2019 (26), Schweitzer *et al.* 2017 (37), Wills *et al.* 2020 (32).

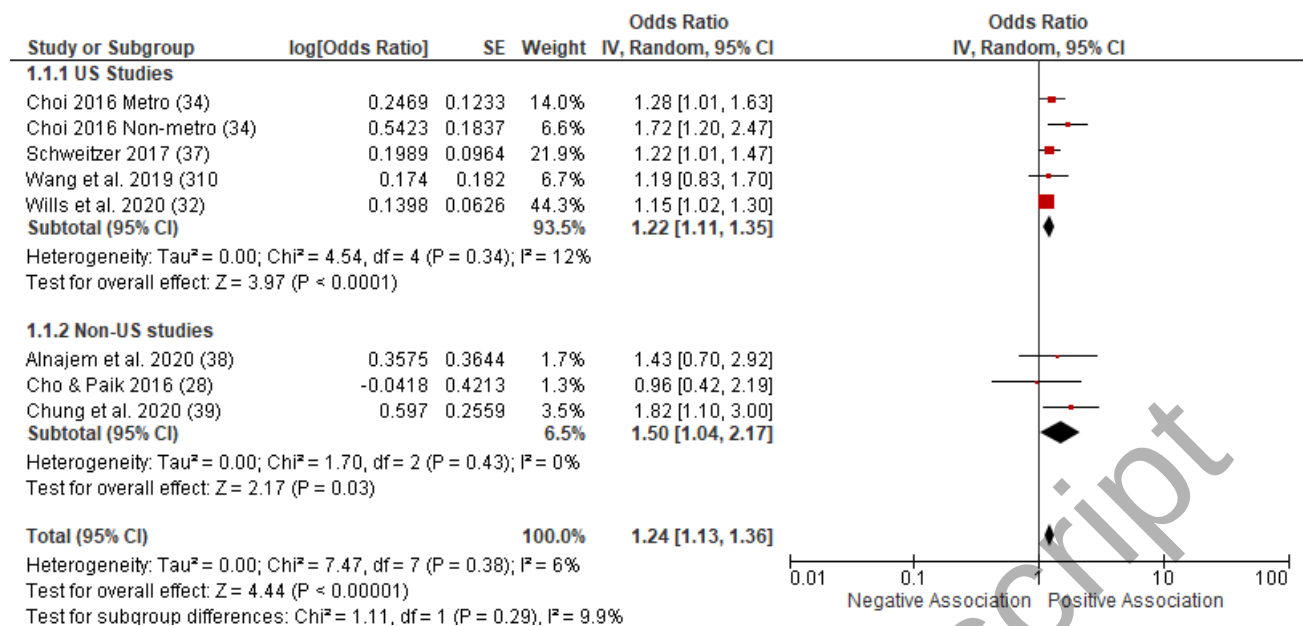
"Fair" quality studies ($n = 2$); Choi & Bernat 2016 (34), Wang *et al.* 2019 (31).

Funnel plot for current e-cigarette use (only) and asthma



Appendix D: Supplemental analysis for ever e-cigarette use and asthma

Subgroup analysis (US and non-US studies) for ever e-cigarette use and asthma



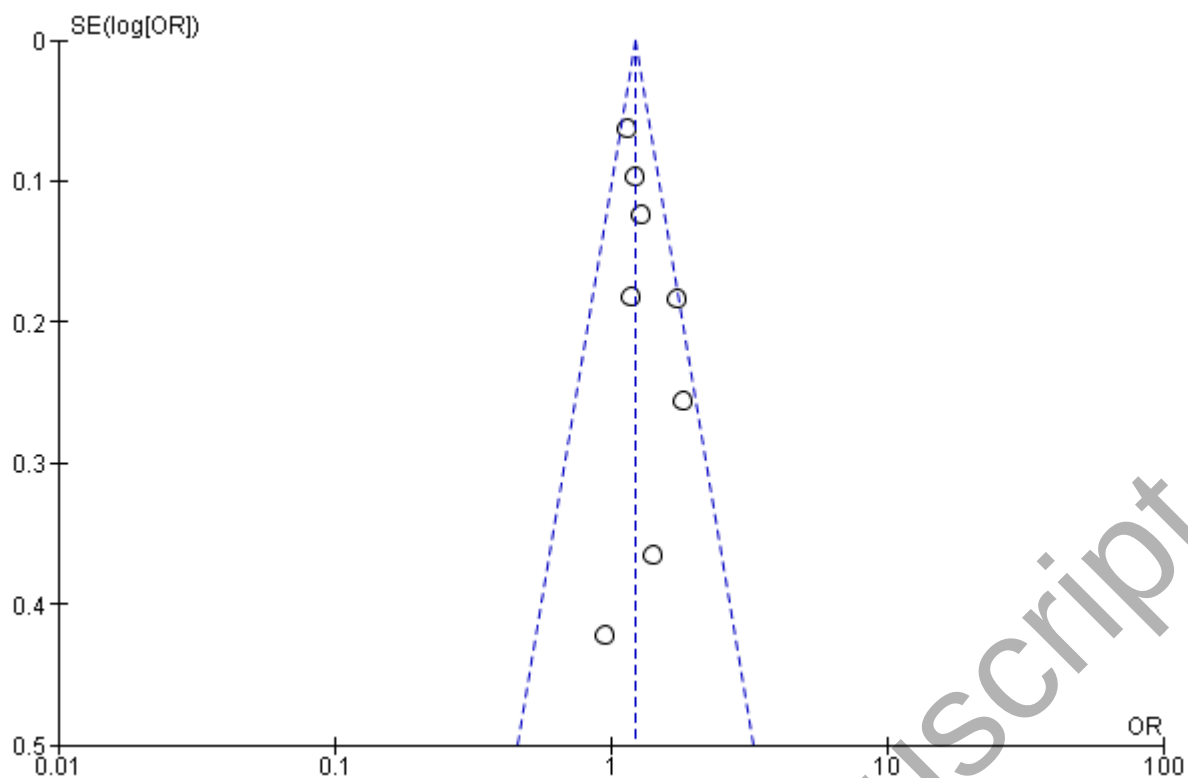
Sensitivity analysis summary table for ever e-cigarette use and asthma

Subgroup	Pooled OR (95% CI)	Chi ² test for heterogeneity	I ²	Test for overall effect
Statistical model				
Fixed effects	1.23 (95% CI 1.13-1.34)	p=.38	6%	p<.001
Random effects	1.24 (95% CI 1.13-1.36)	p=.38	6%	p<.001
Quality of evidence				
"Good" quality studies (n=5)	1.19 (95% CI 1.08-1.32)	p=.46	0%	p<.001
"Fair" quality studies (n=2)	1.35 (95% CI 1.13-1.61)	p=.30	17%	p<.001

"Good" quality studies (n = 5); Alnajem *et al.* 2020 (38), Cho & Paik 2016 (28), Chung *et al.* 2020 (29), Schweitzer *et al.* 2017 (37), Wills *et al.* 2020 (32).

"Fair" quality studies (n = 2); Choi & Bernat 2016 (34), Wang *et al.* 2019 (31).

Funnel plot for ever e-cigarette use and asthma



Appendix E: Causal Diagram – e-cigarette use and Asthma

Appendix E: Table of confounders adjusted in each study.

Source	Age	Sex	SES	Race/Ethnicity	BMI
Alanazi <i>et al.</i> 2020 (27)	N	Y	Y	Y	N
Alnajem <i>et al.</i> 2020 (38)	Y	Y	N	N	N
Cho & Paik 2016 (28)	N	Y	N	Y	Y
Choi & Bernat 2016 (34)	Y	Y	N	Y	N
Chung <i>et al.</i> 2020 (29)	Y	Y	Y	Y	N
Fedele <i>et al.</i> 2016 (35)	Y	Y	N	N	Y
Kim <i>et al.</i> 2017 (13)	Y	Y	Y	N	Y
Kim <i>et al.</i> 2020 (30)	Y	Y	Y	N	N
Larsen <i>et al.</i> 2016 (36)	Y	Y	Y	N	N
Osei <i>et al.</i> 2019 (26)	Y	Y	Y	Y	N
Schweitzer <i>et al.</i> 2017 (37)	Y	Y	N	Y	N
Wang <i>et al.</i> 2019 (31)	Y	Y	Y	Y	N
Wills <i>et al.</i> 2020 (32)	Y	Y	N	Y	Y