A Systematic Review and Meta-analysis of the Association between E-cigarette Use among Cigarette Smokers and Quit Attempts Made to Abstain from Cigarette Smoking

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Objective: Following AMSTAR 2 and PRISMA guidelines, in this synthesis of evidence we sought to identify and characterize any associations between e-cigarette use among cigarette smokers and cigarette smoking quit attempts. **Methods:** We queried 3 databases from January 1, 2007 to January 5, 2021. Search results were screened using the PICOS review method. Included studies examined e-cigarette use and cigarette smoking quit attempts across e-cigarette use statuses. Risk of bias was assessed according to the Agency for Healthcare Research and Quality Evidence-Based Practice Center approach. Finally, 4 random-effects models compared e-cigarette users and non-e-cigarette-users in terms of past year and prospective (6 to 12 months) cigarette smoking quit attempts. **Results:** We qualitatively synthesized 17 adjusted studies for this review. Two meta-analyses showed past year quit attempts were significantly associated with current e-cigarette users and 2 prospective data analyses found no significant association. **Conclusions:** The results of the meta-analyses emphasize temporality in the association between e-cigarette use and cigarette smoking quit attempts. Numerous methodological limitations, including inadequate definitions of e-cigarette use and non-adjustment for confounding variables, limit the confidence in conclusions that can be drawn on the causal association between e-cigarette use and cigarettes smoking quit attempts.

Key words: e-cigarettes; health behavior; quantitative methods; smoking cessation; tobacco control

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The prevalence of electronic cigarette (e-cigarette) use has increased substantially during the past decade as cigarette smoking prevalence has continued to decline.[1-4] Consequently, the potential association between e-cigarette use and cigarette smoking has become an important and controversial issue.[5-7] Understanding the public health effect of e-cigarettes requires an objective examination of the relationship between e-cigarette use and the use of combustible cigarettes, in addition to considering the inherent risks to health presented by e-cigarettes themselves.[8] Among the public health concerns associated with the use of e-cigarettes is that youth will transition from e-cigarettes to cigarette smoking and that existing cigarette smokers who adopt the use of e-cigarettes will be diverted from quitting cigarette smoking.[8] In both instances, an assessment of

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causality is central to understanding the public health effect of e-cigarettes. Moreover, determining whether the risks associated with e-cigarettes are offset by the benefits to public health is key to developing future regulatory strategies.[8] However, it is generally believed that e-cigarettes present fewer health risks than combustible cigarettes, given that the inhaled e-cigarette vapor does not contain most of the approximately 7000 chemicals present in cigarette smoke.[8,9]

The Current Evidence Base

The current systematic review and meta-analysis evaluated potential associations between e-cigarette use among current and former combustible cigarette smokers and quit attempts made to abstain from cigarette smoking, by applying a level of methodological rigor not observed in previous reviews. Outcome measures were defined *a priori* based on a general understanding of the available published literature on e-cigarette use and cigarette smoking. Although several systematic reviews have examined the relationship between e-cigarette use among cigarette smokers and changes in continued cigarette smoking, few have made mention of quit attempts,[10] and none have explored quit attempts as an explicit outcome measure. As such, the current systematic review provides a unique focus on the key measure of smoking quit attempts, a significant segment of the smoking cessation trajectory, and serves as a timely update to previous reviews given the rapid rate of emerging evidence on e-cigarette use.

METHODS

Overview

The methods and results reported are from a larger systematic review addressing the key research question: *Are there any potential associations between e-cigarette use among cigarette smokers and changes in continued cigarette smoking?* The focus of the current review was to identify and characterize any potential associations between e-cigarette use among current and former combustible cigarette smokers and quit attempts made to abstain from cigarette smoking. Age at quit attempt from cigarette smoking also was predefined as an outcome of interest because of the potential influence of age on successful cessation.[11,12]

The review protocol was registered with PROSPERO (The International Prospective Register of Systematic Reviews) on November 6, 2018 (PROSPERO 2018 CRD42018115674). The record is available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=115674. This review strictly followed standards of systematic review methodology ("high" overall rating by A MeaSurement Tool to Assess systematic Reviews [AMSTAR] 2)[13] and reporting (Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA]).[14]

Terminology

Descriptions of terminology used in this review are provided in SUPPLEMENTAL SECTION 1: Glossary of Key Terminology.

Literature Search Methods

A comprehensive search of MEDLINE, EMBASE, and PsycINFO was performed by an information specialist, applying search terms developed using medical subject headings (MeSH) and text words related to the associations between e-cigarette use among combustible cigarette users and cessation of cigarette smoking. An initial database search conducted on October 15, 2018, included articles published from January 1, 2007, to October 15, 2018. This was updated with a search conducted on October 17, 2019, that included articles published from January 1, 2018, to October 17, 2019; an additional literature search update was conducted on January 5, 2021, that included articles published from January 1, 2019, to January 5, 2021. Because searches are best conducted from the first of the year, an overlap in the 2 search timeframes was unavoidable. There were no geographical restrictions in the search strategy. However, the search strategy timeframe was restricted to 2007 onward, as this was when e-cigarettes were introduced to the mass market in the United States (US),[8,9] to standardize the varying availability of e-cigarettes globally. The complete search strategy is provided in SUPPLEMENTAL

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SECTION 2: Literature Search Strategy.

Search results were screened using the PICOS (Population or participants and conditions of interest, Interventions or exposures, Comparisons or control groups, Outcomes of interest, and Study designs) review method (SUPPLEMENTAL SECTION 3: Inclusion/Exclusion Criteria). The population of interest was not restricted by age. The interventions and controls were e-cigarette users and non-users, respectively. Outcome measures identified *a priori* included abstinence/quitting from smoking cigarettes, duration of abstinence from cigarette smoking, quit attempts made to abstain from cigarette smoking, age at quit attempt/quitting from cigarette smoking, change in cigarette smoking quantity/frequency, and relapse to smoking cigarettes. Scoping searches indicated limited available evidence from randomized controlled trials (RCTs); therefore, the review was not limited by study design, although results from RCTs, where available, were considered the highest level of evidence. The search strategy included published peer-reviewed literature, theses and dissertations, government and industry documents, clinical trial registries (clinicaltrials.gov), a gray literature search of Google Scholar, and the checking of reference lists of included studies. Additionally, we consulted content experts in the field. Due to resource constraints, we included only English-language studies. Although the evaluation of regular e-cigarette use would have provided the strongest evidence, this review was designed to be broader, given the potential loss of data if the definition was restricted.

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Evidence Synthesis

Data were extracted and managed through DistillerSR (Evidence Partners, Ottawa, ON, Canada). Articles were initially screened at the title/abstract level; full-text articles were obtained for studies not excluded based on the title/abstract alone. Two reviewers independently screened the articles based on the inclusion/exclusion criteria. Any discrepancies between the 2 were resolved in a joint decision between reviewers. Any unresolved disagreements were adjudicated by a third clinical reviewer, and reasons for excluding articles were documented.

Data were independently extracted by one research associate and checked by a second research associate. Discrepancies were resolved through discussion and included a third team member when necessary. Data extraction forms were created in DistillerSR.

A total of 4486 articles were retrieved from the specified databases, and 2 additional articles were identified through other sources. Of the 4488 potentially relevant articles, 3161 were excluded at the title/abstract level, resulting in 1327 articles eligible for review at full-text level (SUPPLEMENTAL SECTION 4: Literature Search Output, Studies Reviewed at the Full-Text Level). Subsequently, a further 1154 articles were excluded for not meeting the inclusion criteria (SUPPLEMENTAL SECTION 5: List of Excluded Studies), resulting in 173 studies eligible for inclusion in the larger systematic review (SUPPLEMENTAL SECTION 6: List of Included Studies). The weighted overall kappa for inter-rater reliability at Level 2 screening was 0.86. All selection steps are presented as a PRISMA flowchart (Figure 1).

Estimates of the difference between e-cigarette and non-e-cigarette users are presented with the best measure of precision (ie, 95% confidence intervals [CIs]) or statistical significance (ie, p-value) reported in the included studies. The words "significant" and "significantly" are used herein to indicate statistical significance (ie, $p<.05$ and/or CI excludes 1.0).

Sensitivity Analyses

Data permitting, sensitivity analyses were conducted, to include stratification of results (or removal of data inputs) from studies that did not adjust for meso- and macro-level variables in addition to age, race/ethnicity, and gender; studies that did not define e-cigarette use or regular cigarette smoking, and with a questionable definition of e-cigarette use and/or regular cigarette smoking. Additionally, data permitting, stratification by age group, and a sensitivity analysis around age, was conducted.

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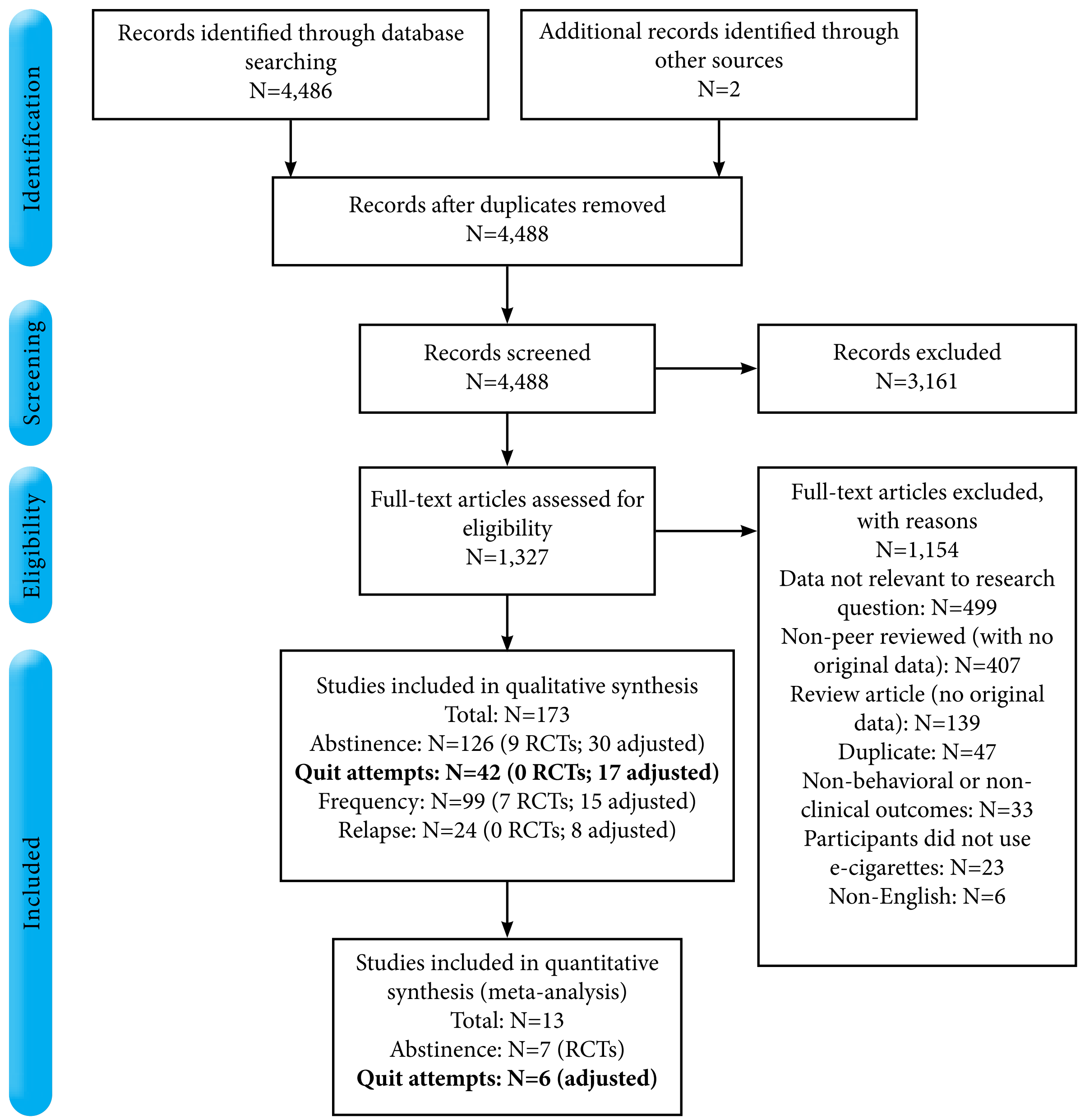
Figure 1
PRISMA Flowchart When Examining the Potential Association between E-cigarette Use among Cigarette Smokers and Quit Attempts Made to Abstain from Cigarette Smoking



Assessment of Confounding

This review applied the Socio-ecological Model created by McLeroy et al.[15] to guide consideration of the interrelationships between individuals and their social (micro-), physical (meso-), and policy (macro-) environments. Further detail is provided in SUPPLEMENTAL SECTION 7: Conceptual Framework.

To evaluate confounding, the following steps were taken in accordance with Cochrane guidelines for systematic reviews:[16]

- During protocol writing, a list of potential confounding factors was identified *a priori* based on evidence and expert opinion from members of the research team and external advisors.

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- During the systematic review process, the variables that individual study authors considered were recorded for additional *post hoc* consideration.

Based on the available empirical evidence and expertise of the review team, potential confounders were identified and categorized as micro-, meso-, or macro-level variables, according to the Socio-ecological Model.[15] Key confounders were identified as race/ethnicity, age, and gender based on the magnitude and strength of their association with cigarette smoking behaviors.[17-19] An observational study in this review was considered to control adequately for confounding bias if it adjusted for age, gender, and race/ethnicity (if the study did not adjust for race/ethnicity, it was considered acceptable if the study was conducted in a non-diverse racial/ethnic geographic region); if appropriately randomized, RCTs were considered to control adequately for these key demographics. Studies that also adjusted for meso- (eg, living with a smoker) or macro-level factors (eg, cigarette taxes) were flagged for possible inclusion in sensitivity analyses.

Outcomes and Related Psychometrics

Recognizing that not all the outcome measures are likely to be equally valid and reliable, this review examined the following contextual question (CQ): *Have measures used to examine associations between e-cigarette use among cigarette smokers and changes in continued cigarette smoking been psychometrically assessed as reliable and valid?* The specific criteria were applied to assess reliability and validity across the outcome measures.[20] Further detail on the CQ assessment can be found SUPPLEMENTAL SECTION 8: Contextual Questions.

Study Quality Assessment

Study quality was independently appraised by 2 research associates, using the Downs and Black checklist. Individual studies were graded either "excellent," "good," "fair," or "poor." Further information is provided in SUPPLEMENTAL SECTION 9: Study Quality Assessment. Publication bias, best assessed using funnel plots, requires 10 or more RCTs included in a meta-analysis. An assessment of publication bias would have been performed had these criteria been met.

Strength of Evidence Evaluation

Strength of evidence (SOE) was separately assessed for RCTs, studies that controlled for age, gender, and race/ethnicity, and studies that did not control for key confounders. The overall SOE was graded as "high," "moderate," "low," or "insufficient" using the Agency for Healthcare Research and Quality (AHRQ) Evidence Based Practice (EPC) grading system. Further information is provided in SUPPLEMENTAL SECTION 10: Strength of Evidence.

Meta-analysis

The generic inverse variance method was used, as described by DerSimonian et al.[21]. This method combines adjusted odds ratios (AORs), resulting in pooled odds ratios (ORs) and 95% confidence intervals (CIs) with 2-sided p-values. Variations among pooled studies were assessed using Tau^2 and heterogeneity was quantified using Cochran's Q test and the inconsistency index I^2. Study authors were contacted to obtain missing data. All data were analyzed through Review Manager version 5.3,[22] in Macintosh operating system X version 10.14.6.

RESULTS

Overview

Of the 173 studies identified in the systematic review, 42 studies reported outcomes related to quit attempts made to abstain from cigarette smoking and were subsequently eligible for both the qualitative and quantitative syntheses of evidence; no studies were identified that evaluated age at quit attempt from cigarette smoking. For each study, information regarding the study characteristics (SUPPLEMENTAL SECTION 11: Study and Sample Characteristics), demographic and baseline characteristics (SUPPLEMENTAL SECTION 12: Demographics and Baseline Characteristics), and study outcomes (SUPPLEMENTAL SECTION 13: Evidence Tables) were extracted.

The highest number of studies (16 studies) were published in 2018, followed by 7 studies in both 2015 and 2019, 6 studies in 2017, 2 studies in both 2014 and 2016, and one study in both 2013 and 2020. The majority of studies (30 studies) were cross-sectional, whereas 12 studies were longitudinal in design; no RCTs were identified. About half of the included studies were from

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registered surveys. Half of all included studies (21 studies) were conducted in the US. The majority of studies (24 of 42 studies) identified their study populations as "adults" (≥ 18 years old). Five studies applied definitions of youth participants (< 18 years old), 2 studies applied definitions of "young adults" (18 to 23 years old or undergraduate students 18 years or older), and one study applied a definition of "older adults" (≥ 25 years old) to their study populations. Five studies broadly identified their study populations in terms that could potentially include "adult," "young adult," and "youth" participants. Three studies did not define their study populations by age, but instead sampled smokers from addiction treatment centers, smokers in the refugee population, or smokers with mental health conditions. Two studies did not report the age of their study populations.

Overall, 17 of the 42 included studies adjusted for gender, age, and race/ethnicity between groups (ie, adjusted for key demographic characteristics) and were subsequently included in the qualitative review of the evidence. In addition to the demographic characteristics specified, most studies included further adjustments with varying combinations of other micro-, meso-, and macro-covariates (eg, the presence of a tobacco user at home, highest parental education, and exposure to tobacco advertisements). Of the 17 studies that adjusted for gender, age, and race/ethnicity, 6 met the criteria for inclusion in the quantitative synthesis of evidence.

The reliability and validity of the relevant outcome measures, quit attempts made to abstain from cigarette smoking and age at quit attempt from cigarette smoking, were evaluated (as contextual questions, with comprehensive but not systematic reviews of the literature) to provide fuller context for the interpretation of the synthesis of evidence. These were single-item measures related to changes in cigarette smoking. Empirical data regarding the reliability and/or validity of quit attempts made to abstain from cigarette smoking were identified, and therefore, qualified as "acceptable." Empirical data regarding the reliability and/or validity of age at quit attempt from cigarette smoking were lacking, and therefore, qualified as "inconclusive." Further details, including a CQ evidence table of reliability and validity data identified for quit attempts made to abstain from cigarette smoking, can be found in SUPPLEMENTAL SECTION 8: Contextual Questions.

Two investigators appraised the included studies for quality according to the Downs and Black checklist.[23] Altogether, 23 studies (54.8%) were rated "good" quality, 15 (35.7%) were rated "fair," 4 studies (9.5%) were rated "poor" quality, and no studies were rated "excellent" quality (SUPPLEMENTAL SECTION 9: Study Quality Assessment).

The overall SOE among the adjusted data regarding the association between e-cigarette use and quit attempts made to abstain from cigarette smoking was graded "moderate." The SOE domain score table and the SOE and CQ ratings summary table for both the adjusted and unadjusted data are presented in SUPPLEMENTAL SECTION 10: Strength of Evidence.

Definitions of E-cigarette Use by Outcome Measure

Among the 42 included studies that examined quit attempts made to abstain from cigarette smoking, 7 studies evaluated the association between regular e-cigarette use and quit attempts from cigarette smoking, of which 4 reported demographically adjusted results. Two unadjusted studies evaluated cigarette smoking quit attempts among daily e-cigarettes users;[24,25] 2 studies (both adjusted) evaluated cigarette smoking quit attempts among weekly e-cigarette users;[26,27] one adjusted study evaluated cigarette smoking quit attempts among participants reporting use on 25 or more days in the past 30 days;[28] and one adjusted study evaluated cigarette smoking quit attempts in participants reporting e-cigarette use in 20 or more days in the past 30 days.[29] Another unadjusted study did not explicitly quantify their definition of regular e-cigarette use; however, because it delineated respondents according to their past 30-day use, grouping "sometimes," "rarely," and "never" users versus "regular" users together, this was deemed to be a sufficiently regular measure of e-cigarette use.[30]

In terms of non-regular definitions of e-cigarette use among studies examining quit attempts made to abstain from cigarette smoking, current e-cigarette use was the most commonly applied definition in 20 studies (9 adjusted), followed by 13 studies that used ever e-cigarette use (8 adjusted), and 4 studies that used non-current ever e-cigarette use (2 adjusted). In addition, 5 unadjusted studies evaluated participants who reported using e-cigarettes in past cigarette smoking quit attempts.

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Qualitative Synthesis of Best Available Evidence

Only those studies that were not included in the quantitative synthesis were included in the qualitative synthesis. Results in the qualitative analysis were stratified by regular versus non-regular e-cigarette use. Although RCTs were considered the highest level of evidence, we could identify no relevant RCTs. Consequently, the qualitative synthesis was restricted to studies that controlled for 3 key demographic variables (age, gender, and race/ethnicity). Tables providing both adjusted and unadjusted data for quit attempts made to abstain from cigarette smoking are provided in SUPPLEMENTAL SECTION 13: Evidence Tables.

Quit Attempts Made to Abstain from Cigarette Smoking (Regular E-cigarette Use)

We identified 4 adjusted studies that investigated the association of regular e-cigarette use and quit attempts made to abstain from cigarette smoking among regular e-cigarette users. Table 1 reports the summary characteristics of these 4 studies.

Table 1
Summary Characteristics of Adjusted Studies for Quit Attempts Made to Abstain from Cigarette Smoking among Regular E-cigarette Users

Citations	Study design	Definition of e-cig user	Definition of non-e-cig user	Definition of study outcome
(Chiang et al 2019)[26]	Prospective cohort	Current smokers (at least one puff in the past 2 weeks) who answered "yes" to "Have you used an e-cigarette, even once, in the past 7 days?"	Current smokers (at least one puff in the past 2 weeks) who answered "no" to "Have you used an e-cigarette, even once, in the past 7 days?"	Reported quitting for more than 1 day between baseline and 1-month follow-up
(Levy et al 2018)[29]	Cross-sectional-analytic	Regular users: ever users who answered, "Every day" to the question, "On how many of the past 30 days did you use e-cigs?" (Stratified by number of days out of the past 30 where e-cig was used: 1-4 days, 5-9 days, 10-14 days, 15-19 days, 20-24 days, 25-30 days, or non-concurrent days)	Current and former smokers who answered "no" to question, "Have you ever used e-cigs even one time?"	Participants having smoked more than 12 days in the past 30 days and answering "yes" when asked if they "stopped smoking for 1 day or longer because of trying to quit smoking during the past 12 months"
(Sweet et al 2019)[27]	Prospective cohort	Self-reported dual users of daily cigarettes with lifetime use of at least 100 cigarettes and every day or some days per week use of e-cig;	Self-reported daily exclusive cigarette smokers with lifetime use of at least 100 cigarettes	A quit attempt was defined as 24 or more hours of not using any tobacco in an attempt to quit all tobacco products
(Weaver et al 2018)[28]	Prospective cohort	Daily e-cig users: Baseline smokers who used e-cigs daily or used it ≥25 days during the past 30 days at baseline and/or during the 12-month follow-up period	Baseline smokers who reported no baseline current use of e-cigs ("not at all") and no use of e-cig during the 12-month follow-up period	Smokers self-reporting an attempt to quit smoking during 12-month follow-up

Note:
e-cig=electronic cigarette; smokers=cigarette smokers; smoking=cigarette smoking

In a secondary analysis of an RCT of pregnant current smokers (defined as at least one puff in the past 2 weeks) at least 14 years old, Chiang et al.[26] assessed quit attempts in current e-cigarette users (defined as current smokers who answered "yes" to the question *Have you used an e-cigarette, even once, in the past 7 days?*) and non-e-cigarette users (defined as current smokers who answered "no" to the question *Have you used an e-cigarette, even once, in the past 7 days?*). A quit attempt was defined as reporting quitting for more than one day between baseline and one-month follow-up. There was no evidence of an association between e-cigarette use and quit attempts (AOR=1.20, 95% CI: 0.56-2.55, p=.64). The majority (80.56%) of e-cigarette users reported the reason for using e-cigarettes being to help them quit smoking.

Levy et al.[29] conducted a cross-sectional analytic study of adult smokers (18 years old and older) and found that regular e-cigarette users (reporting use on

20 or more days in the past 30 days) were significantly more likely to have made a quit attempt in the past year, compared with e-cigarette never-users (AOR=4.90, 95% CI: 4.09-5.85; p<.001). The authors also reported the odds of having made a past year quit attempt among non-regular e-cigarette user groups ("ever," "current," and at least 5 days in the past 30), all of which also showed a significant and positive association; however, the reported odds were progressively higher as regularity of e-cigarette use increased. Moreover, in a model that applied a continuous variable for specific number of days of e-cigarette use in the last 30 days, the authors reported significantly higher odds of having made a past year quit attempt associated with days of e-cigarette use compared with e-cigarette never use (AOR=1.25, 95% CI: 1.05-1.49, p<.05).[29]

Sweet et al.[27] reported on a prospective cohort study that calculated the adjusted odds of adult e-cigarette users (self-reported dual users of daily cigarettes with lifetime use of at least 100 cigarettes and every day or some days per week use of e-cigarettes) enumerating quit attempts (defined as 24 or more hours of not using any tobacco in an attempt to quit all tobacco products). The authors stated that "[d]ual users were no more likely than cigarette smokers to make one or more attempt to quit using all tobacco products at any time interval (data not shown)."

Finally, Weaver et al.[28] reported findings from a prospective cohort study of adult smokers and calculated the adjusted odds of any quit attempts during the 12-month follow-up period between regular e-cigarette users (use during ≥ 25 of the past 30 days at either baseline or follow-up) and non-e-cigarette users (no current use at baseline and at follow-up and no use in between baseline and follow-up). The authors found that, among baseline smokers, regular e-cigarette users were not significantly different in their likelihood to report past 12-month quit attempts than non-e-cigarette users (AOR=0.93, 95% CI: 0.32-2.65). By comparison, current, non-regular e-cigarettes users (< 25 days in the past 30 at either baseline or follow-up) were significantly more likely to report past 12-month quit attempts compared to non-e-cigarette users. When limiting the sample to baseline daily smokers, the authors found no significant difference in odds of past 12-month quit attempts between regular e-cigarette and non-e-cigarette users (AOR=1.77, 95% CI: 0.48-6.50); however, current, non-regular e-cigarette users were found to be significantly more likely to report past 12-month quit attempts than non-e-cigarette users.

Quit Attempts Made to Abstain from Cigarette Smoking (Non-regular E-cigarette Use)

We identified 15 adjusted studies that investigated the association of non-regular e-cigarette use and quit attempts made to abstain from cigarette smoking. Table 2 reports the summary characteristics of these 15 studies.

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Table 2
Summary Characteristics of Adjusted Studies for Quit Attempts Made to Abstain from Cigarette Smoking among Non-regular E-cigarette Users

Citations	Study design	Definition of e-cig user	Definition of non-e-cig user	Definition of study outcome
(Al-Delaimy et al 2015)[31]	Prospective cohort	Smokers (≥ 100 cigarettes/lifetime and smoked on at least some days at the time of the survey) who chose answer "You have used e-cigs" to question, "What describes you best regarding your use of e-cigarettes?"	Smokers (≥ 100 cigarettes/lifetime and smoked on at least some days at the time of the survey) who chose answer, "You will never use e-cigarettes" to question, "What describes you best regarding your use of e-cigarettes?"	Self-reported quit attempts by response at follow-up to the question, "During the past 12 months, have you quit smoking intentionally for one day or longer?"
(Chen et al 2018)[32]	Cross-sectional analytic	Smokers (used cigarettes in the past 30 days) who answered "yes" to the question "During the past 30 days, have you used an e-cig?"	Smokers (used cigarettes in the past 30 days) who answered "no" to the question "During the past 30 days, have you used an e-cig?"	Self-reported quit attempt

Citations	Study design	Definition of e-cig user	Definition of non-e-cig user	Definition of study outcome
(Comiford et al 2018)[33]	Cross-sectional analytic	Ever e-cig users: Smokers answering "Yes" to question "Have you ever vaped or used an e-cig, even one or 2 times?" Past e-cig users: Smokers answering "Yes" to question "Have you ever vaped or used an e-cig, even one or 2 times?" and reporting no past 30-day use; Current e-cig uses: Smokers answering "Yes" to question "Have you ever vaped or used an e-cig, even one or 2 times?" and reporting e-cig use within the past 30 days;	Smokers answering "No" to question "Have you ever vaped or used an e-cig, even one or 2 times?"	Past-12-month quit attempts were assessed by self-report and were dichotomized as no versus yes
(Johnson et al 2018)[34]	Cross-sectional analytic	Current smokers (≥ 100 cigarettes/ lifetime and answered "every day" or "some days" to the question, "Do you now smoke cigarettes?") and are current e-cig users (Answered "every day" or "some days" to the question "do you now use an e-cig every day, some days, or not at all?");	Current smokers (≥ 100 cigarettes/lifetime and answered "every day" or some days") who answered "not at all" to the question "do you now use an e-cig every day, some days, or not at all?"	Smokers having tried to quit smoking and abstaining for at least 1 day in the past 12 months
(Lee et al 2014)[35]	Cross-sectional analytic	Current users: Current smokers (having smoked in the past 30-days) answering "yes" to the question, "have you ever used e-cig?" and "yes" to the question "have you used e-cig in the past 30 days?" Former users: Current smokers (having smoked in the past 30-days) answering "yes" to the question, "have you ever used e-cig?" and "no" to the question "have you used e-cig in the past 30 days?"	Current smokers (having smoked in the past 30-days) answering "no" to the question, "have you ever used e-cig?"	Current (past 30-day) cigarette smokers answering "Yes/no" to the question "Have you ever attempted to quit smoking in the past 12 months?"
(Levy et al 2018)[29]	Cross-sectional-analytic	Ever users: Current smokers (≥ 100 cigarettes/lifetime, smoking some or every day) or former smokers (≥ 100 cigarettes/lifetime, smoking 12 months ago, but not currently) who answered, "yes" to question, "Have you ever used e-cigs even one time?" Current users: ever users who answered, "Every day" or "some days" to question, "On how many of the past 30 days did you use e-cigs?" (Stratified by number of days out of the past 30 where e-cig was used: 1-4 days, 5-9 days, 10-14 days, 15-19 days, 20-24 days, 25-30 days, or non-concurrent days)	Current and former smokers who answered "no" to question, "Have you ever used e-cigs even one time?"	Participants having smoked more than 12 days in the past 30 days and answering "yes" when asked if they "stopped smoking for 1 day or longer because of trying to quit smoking during the past 12 months"
(Peltier et al 2019)[36]	Cross-sectional analytic	Smokers that answered "Yes" to "Do you currently use e-cigarettes?"	Smokers that answered "No" to "Do you currently use e-cigarettes?"	Current quit attempt: "Currently attempting to quit smoking" (yes/ no); Past quit attempt: "Have you made a previous serious attempt (at least 24 h) in the past?" (yes/ no)
(Popova & Ling 2013)[37]	Cross-sectional analytic	Current smokers (≥ 100 cigarettes/ lifetime and currently smoking) or former smokers (≥ 100 cigarettes/lifetime, having quit ≤ 2 years) with ever use of e-cigs to quit smoking Current smokers (≥ 100 cigarettes/ lifetime and currently smoking) or former smokers (≥ 100 cigarettes/lifetime, having quit ≤ 2 years) with ever use of e-cigs and never tried to quit smoking	NA	"Unsuccessful quitters" currently smoking and had tried to quit smoking within the past 2 years

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Citations	Study design	Definition of e-cig user	Definition of non-e-cig user	Definition of study outcome
(Pulvers et al 2015)[38]	Cross-sectional analytic	Smokers (smoked ≥ 1 cigarette in the past 30 days) reporting current (past 30-day) e-cig use when asked whether they used any in the past 30 days	Smokers (smoked ≥ 1 cigarette in the past 30 days) reporting non-current (at least not in the past 30 days) e-cig use when asked whether they used any in the past 30 days	Self-reporting whether a past 24-hour quit attempt was made in the past 1 year
(Stokes et al 2018)[39]	Cross-sectional analytic	Ever e-cig users: Current smokers ("Every day," "Some days") answering "Yes" to question "Have you ever used an e-cigarette, even one time?" Current e-cig users: Ever e-cig users that answered, "every day" or "some days" to the question "Do you now use e-cigarettes?" Former e-cig users: Ever e-cig users that answered, "not all" to the question, "Do you now use e-cigarettes?"	Current smokers ("Every day," "Some days") answering "No" to the question "Have you ever used an e-cigarette, even one time?"	Smokers self-reporting an attempt to quit smoking within the past year
(Wang et al 2015)[40]	Cross-sectional analytic	Self-reported use of e-cigarettes in the past 30 days	No e-cig use in the past 30 days	Self-reported former smokers attempting to quit
(Wang et al 2017)[41]	Longitudinal panel	Smokers (at least one cigarette in the past 30 days,) reporting at least a single use of e-cigs (even a single puff)	Smokers (at least one cigarette in the past 30 days) reporting never having used e-cigs	Self-reported quit attempt rate, each serious quit attempt is abstaining from smoking for>24 hrs in the past 6 months
(Wang X et al 2018)[42]	Cross-sectional-analytic	Current smokers (> 100 cigarettes total and still smoking), Former smokers (used to smoke but quit) who answered "Often (more than 20 times)," "Occasionally (< 20 times)", "Ever used 1-2 times" to question, "Do you use e-cigarette now?	Current smokers (>100 cigarettes total and still smoking), Former smokers (used to smoke but quit) who answered, "Never used" to question, "Do you use e-cigarette now?", and answered, "patches" or "other methods" to quit smoking	Self-reported smoking abstinence trying behavior
(Weaver et al 2018)[28]	Prospective cohort	Non-daily e-cig users: Baseline smokers who used e-cigs<25 days during the past 30 days at baseline and/or during the 12-month follow-up period	Baseline smokers who reported no baseline current use of e-cigs ("not at all") and no use of e-cig during the 12-month follow-up period	Smokers self-reporting an attempt to quit smoking during 12-month follow-up
(Wu et al 2018)[43]	Prospective cohort	Smokers (≥ 1 cpd for the past 3 months) confirmed with eCO ≥ 4 ppm and who answered yes to ever e-cig use at the 1-week follow-up.	Smokers (≥ 1 cpd for the past 3 months) confirmed with eCO ≥ 4 ppm and who answered no to ever e-cig use at the 1-week follow-up	Self-reported being abstinent for more than 24 hours

Note:
cpd=cigarettes per day; e-cig=electronic cigarette; eCO=exhaled carbon monoxide; hr=hour; NA=not applicable; ppm=parts per million; smoker=cigarette smoker; smoking=cigarette smoking

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Six of these studies met the inclusion criteria of the meta-analysis;[29,31,34,35,38,43] however, the 9 studies excluded from the meta-analysis contained additional information important to the research question and are described below.

Chen et al.[32] analyzed self-reported quit attempt in a cross-sectional analytic study of adolescent smokers 12 to 18 years (who were prompted to quit). The investigators showed that e-cigarette users (past 30 days) had significantly higher odds of making a quit attempt compared with non-e-cigarette users (past 30 days) (AOR=1.21; p<.001).

Comiford et al.[33] reported on a cross-sectional analytic study that assessed past-12-month quit attempts in American Indian Cherokee adults (18 years of age or older). The sample included adults who were ever e-cig users (answering "Yes" to question *Have you ever vaped or used an e-cig, even one or 2 times?*), former e-cig users (answering "Yes" to question *Have you ever vaped or used an e-cig, even one or 2 times?* and reporting no past 30-day use), current e-cig users (answering "Yes" to question *Have you ever vaped or used an e-cig, even one or 2 times?* and reporting e-cig use within

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the past 30 days), and non-e-cig users (smokers answering "No" to question *Have you ever vaped or used an e-cig, even one or 2 times?*). For the probability of quit attempts of ever e-cig users versus non-e-cig users, authors stated "[e]-cigarette use was significantly associated (p=.04) with having made a quit attempt in the past 12 months" (AOR not provided). Additionally, the adjusted odds ratio of former e-cigarette users reporting one or more past-12-month quit attempts versus non-e-cigarette users was 1.43 (95% CI: 0.89-2.28, p=NR). The adjusted odds ratio of current e-cigarette users (N=60) reporting one or more past-12-month quit attempts versus non-e-cigarette users (N=137) was 2.24 (95% CI: 1.20-4.16, p=NR).

Peltier et al.[36] reported findings from a cross-sectional analytic study that investigated past and current quit attempts in undergraduate college students (≥ 18 years of age) by e-cigarette use. E-cigarette users were defined as smokers that answered "Yes" to *Do you currently use e-cigarettes?* and non-e-cigarette users were defined as smokers that answered "No" to *Do you currently use e-cigarettes?* Hierarchical logistic regression analyses were conducted to examine whether e-cigarette use and smoking expectancies predicted past or current smoking quit attempts. Past or current quit attempt ("yes/no") was the dependent variable in respective analyses, and e-cigarette use and the SCQ scales were predictors. The demographic variables for which the groups differed (gender and race) were entered on the first step, e-cigarette use was entered on the second step, and the 4 SCQ scales were entered on the third step. We found that e-cigarette use was a negative predictor of a past quit attempt (β=-1.086, p=.024), but was not a statistically significant predictor of a current quit attempt.

From their cross-sectional analytic results, Popova et al.[37] concluded that adult smokers "older than 18 years" had a significantly higher odds of ever e-cigarette use in unsuccessful quitters (participants who made a quit attempt in the past but were currently smoking) compared with participants who had never tried to quit (AOR=1.78, 95% CI: 1.25-2.53; p<.05)

Stokes et al.[39] reported on the odds of having made a self-reported attempt to quit smoking within the past year according to a cross-sectional analytic study of adult smokers with a history of CVD. The authors found that both ever e-cigarette use and current e-cigarette use significantly increased the odds of having made a quit attempt compared with not having made a quit attempt (AOR=1.70; 95% CI: 1.25-2.30; p=.001, and AOR=1.97; 95% CI: 1.32-2.95; p=.001, respectively). This study did not report on whether participants intended to quit.

Wang et al.[40] reported on a cross-sectional analytic study of secondary 1 to 6 students (US grade 7 to 12) who were smokers. They found that e-cigarette users (past 30-day) did not have significantly different odds of quit attempts in the past 12 months compared with non-e-cigarette users (no use in past 30 days) (AOR=0.80, 95% CI: 0.56-1.23).

Wang et al.[41] reported findings from a longitudinal panel study of adult smokers at least 25 years old (95% intended to quit) and found that ever e-cigarette users (even a single puff) did not have significantly different odds of quit attempts (24-hour quit in the past 6 months) at 6-months follow up compared with never e-cigarette users (β=1.26; 95% CI: -0.13-2.66).

Wang et al.[42] found significantly higher odds of quit attempts for e-cigarette users (26% often [> 20 times], 36% occasionally [< 20 times], 38% ever [1-2 times]) compared with never e-cigarette users (AOR=1.60; 95% CI: 1.01-2.53; p<.05) according to a cross-sectional analytic study of adolescent smokers 12 to 18 years old This study did not report on whether participants intended to quit.

Weaver et al.[28] reported findings from a prospective cohort study of adult smokers and calculated the adjusted odds of any quit attempts during the 12-month follow-up between current e-cigarette users (use during<25 of the past 30 days at either baseline or follow-up) and non-e-cigarette users (no current use at baseline and at follow-up and no use in between baseline and follow-up). They found that among baseline smokers, current e-cigarette users were significantly more likely to report past 12-month quit attempts than non-e-cigarette users (AOR=2.14, 95% CI: 1.24-3.69). By comparison, as reported earlier, regular e-cigarettes users (≥ 25 days in the past 30 at either baseline or follow-up) were not significantly different than non-e-cigarette users in their likelihood to report past 12-month quit attempts. When limiting the sample to baseline daily smokers, the authors

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found that current e-cigarette users were significantly more likely to report past 12-month quit attempts than non-e-cigarette users (AOR=2.56, 95% CI: 1.37-4.78); no significant difference was found between regular e-cigarette and non-e-cigarette users.

Additionally, one study included in the meta-analysis also stratified results according to regular versus non-regular e-cigarette use. Levy et al.[29] found in a cross-sectional analytic study of adult smokers (18 years old and older) that ever e-cigarette users (AOR=2.31, 95% CI: 2.15-2.48, p<.001), current e-cigarette users (AOR=2.60, 95% CI: 2.32-2.90, p<.001), and e-cigarette users of 5 or more days in the past 30 days (AOR=3.39, 95% CI: 2.97-3.87, p<.001) were all significantly more likely to have made a quit attempt in the past year compared with e-cigarette never users. By comparison, the authors also reported the odds of having made a past year quit attempt among regular e-cigarette users (≥ 20 days in the past 30 days), which also showed a significant and positive association. The reported odds were progressively higher as regularity of e-cigarette use increased.

Quantitative Synthesis of Best Available Evidence

Data synthesis and analysis. Given the lack of RCTs in the evidence base, a meta-analysis of RCTs was not feasible. Consequently, the quantitative synthesis was limited to studies adjusting for key demographic variables (age, gender, and race/ethnicity). Moreover, due to the small number of studies reporting adjusted results related to regular e-cigarette use, and given the comparability issues associated with them, all meta-analyses were performed using results that defined e-cigarette use in non-regular terms (eg, ever or current e-cigarette use). The following data were extracted for each of the studies included in the meta-analysis – AORs, covariates and confounding variables, population data, and research protocol information.

The meta-analysis provided pooled estimates of AORs from studies investigating quit attempts made to abstain from cigarette smoking between current cigarette smokers using e-cigarettes and current cigarette smokers not using e-cigarettes. Complete details on the meta-analysis data sources, study selection, data extractions, and study quality are provided in SUPPLEMENTAL SECTION 14: Meta-Analytic Results.

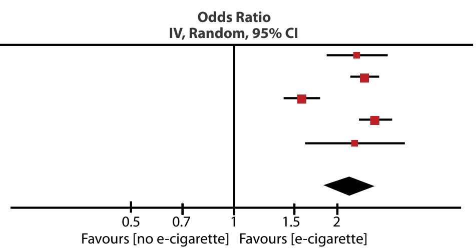
Past Year Quit Attempts Made to Abstain from Cigarette Smoking Among Current E-Cigarette Users

Four studies presented results for current e-cigarette use and past year quit attempts.[29,34,35,38] Among these 4 studies, the study by Johnson et al.[34] had 2 results, one from NHIS and the other from TUS-CPS. Using the 5 AORs from the 4 published studies, the generic inverse variance method was applied to find the log ORs, standard errors, and the corresponding weights. The AORs for past year quit attempts ranged from 1.58 (95% CI: 1.39-1.79) to 2.60 (95% CI: 2.33-2.90) for current e-cigarette users at baseline compared with non-e-cigarette users.[29,35,38] The results of the random-effects model demonstrated that e-cigarette users (ever and past 30-day) had 2 times higher odds of having past year quit attempts compared with non-e-cigarette users (OR=2.20, 95% CI: 1.79-2.69; z=7.59, p<.00001) (Figure 2). The model had high heterogeneity with an I^2 value of 90.0%; Tau^2=0.05; χ^2=39.59%, df=4 (p<.00001).

Figure 2
Forrest Plot, Past Year Quit Attempts Made to Abstain from Cigarette Smoking among Current E-cigarette Users

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Johnson et al., 2018 (NHIS)	0.8286	0.1044	19.1%	2.29 [1.87,2.81]
Johnson et al., 2018 (TUS everday smokers)	0.8838	0.0502	22.5%	2.42 [2.19, 2.67]
Lee et al., 2014	0.4574	0.0637	21.8%	1.58 [1.39, 1.79]
Levy et al., 2018	0.9555	0.0557	22.2%	2.60 [2.33, 2.9]
Pulvers et al., 2015	0.8154	0.1726	14.3%	2.26 [1.61 ,3.17]
Total (95%CI)			**100.0%**	**2.20 [1.79, 2.69]**

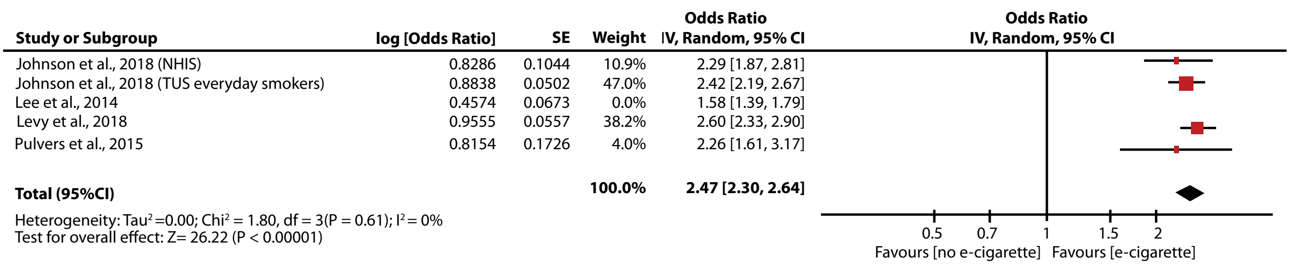
Heterogeneity: Tau^2 = 0.05; Chi^2 = 39.59, df = 4 (P < 0.00001); I^2 = 90%
Test for overall effect: Z = 7.59 (P < 0.00001)



 DOI: doi.org/10.5993/AJHB.46.4.2

While examining the high heterogeneity, we observed that the study by Lee et al.[35] contributed the greatest amount of between-study variance, and therefore, was excluded. The impact of removing the study (as represented by the 0% weighting) and reanalyzing the results are presented in Figure 3.

Figure 3
Forrest Plot, Current E-cigarette Use with Past Year Quit Attempts Made to Abstain from Cigarette Smoking (Excluding Lee at al 2014)

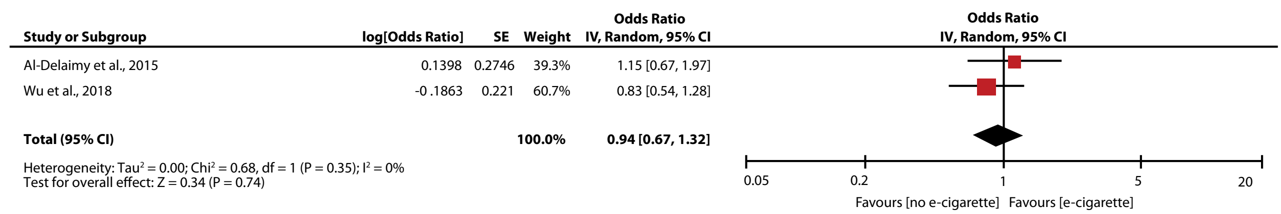


When the study by Lee et al.[35] was excluded from the model, the odds of past year quit attempts increased slightly for current e-cigarette users compared with non-e-cigarettes users (OR=2.47, 95% CI: 2.30-2.64, p<.00001). Furthermore, when the study by Lee et al.[35] was removed, the overall heterogeneity dropped to an I^2 of 0.0%.

Baseline e-cigarette users with quit attempts made to abstain from cigarette smoking at follow-up. In addition to studies evaluating current e-cigarette use and past year quit attempts, 2 studies were identified that prospectively evaluated quit attempts in baseline e-cigarette users, presenting the odds of quit attempt at follow up (6-12 months) among baseline e-cigarette users compared with non-e-cigarette users.[31,43] From the published AORs, the generic inverse variance method was applied to find the log ORs, standard errors, and the corresponding weights.

The studies had varying AORs, with reported AORs of 0.83 (95% CI: 0.54-1.28)[43] and 1.15 (95% CI: 0.67-1.97).[31] The results of the random-effects model reveal no significant difference in the odds of quit attempts at 6- to 12-month follow-up for baseline e-cigarette group (ever users) compared with non-e-cigarette users, with an OR of 0.94 (95% CI: 0.67-1.32; z=0.34, p=.74) (Figure 4) (model had low heterogeneity with an I^2 value of 0%; Tau^2=0.00; and χ^2=10.86, df=1 (p=.35)).

Figure 4
Forrest Plot, Ever E-cigarette Use with Past Year Quit Attempt



Results of Sub-group Analysis

Due to differences in the results between the 2 quit attempt groups, a sub-group analysis was conducted to determine the degree of variation between the 2 groups (Figure 5). Testing for subgroup differences, a high degree of heterogeneity was identified according to the I^2 value of 94.3%; χ^2=17.66 df=1 (p<.0001), thereby substantiating that the differences between time of e-cigarette use and when quit attempts are measured can affect the data.

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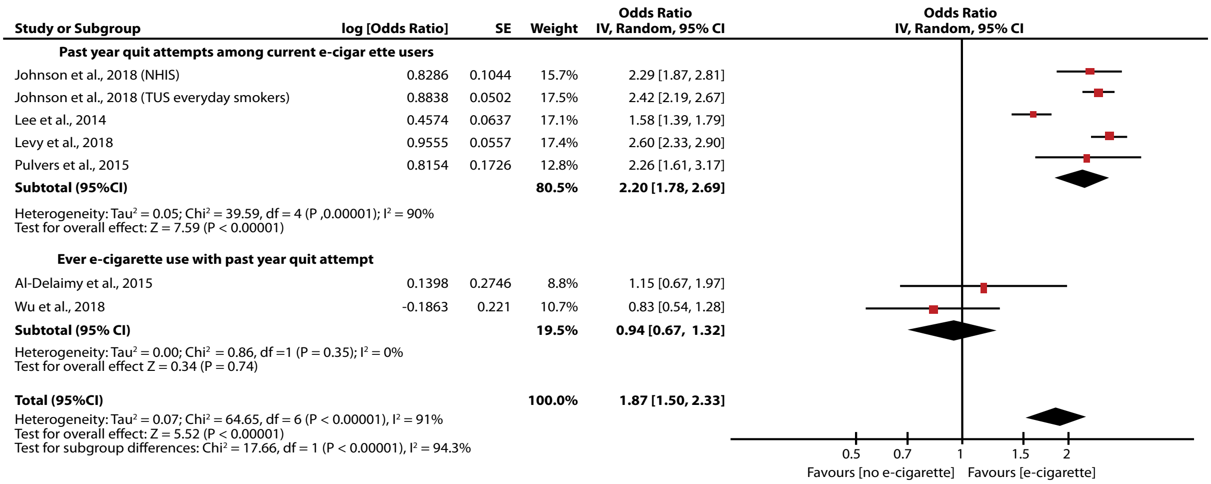
Figure 5
Forrest Plot of Sub-group Analysis between 2 Quit Attempt Groups



DISCUSSION

Our literature review identified a number of "good" quality studies (according to the Downs and Black quality metrics[23]) that evaluated the association between e-cigarette use among cigarette smokers and quit attempts made to abstain from cigarette smoking. No RCTs were identified, which would have provided the highest level of evidence. However, 17 of the included studies controlled for age, gender, and race/ethnicity, ie, reporting adjusted results at a higher level of evidence than the unadjusted results. Both the qualitative and quantitative reviews focused on these adjusted studies in the synthesis of results.

The 2 meta-analyses conducted to investigate quit attempts showed contradicting results but provided important insights into the issue of temporality and its importance in determining an association. When examining past year quit attempts among current e-cigarette users, we found a statistically significant increase in quit attempts favoring e-cigarette use. However, when restricting the analysis to prospective data evaluating odds of quit attempts at 6-12 month follow-up, no significant association was found. This highlights the importance of using temporal measurements when determining an association between e-cigarette use and quit attempts.

Of the 17 adjusted studies that investigated the association of e-cigarette use and quit attempts made to abstain from cigarette smoking, only 4 applied definitions of regular e-cigarette use. The study by Levy et al.[29] which was included in the meta-analysis (but for which only non-regular e-cigarette use outcomes were included), additionally stratified results across regular and non-regular user groups. Whereas e-cigarette use was consistently associated with significantly higher odds of having made a past year quit attempt, the odds were progressively higher with increasing frequency and regularity of e-cigarette use. Weaver et al.[28] also stratified their results across regular and non-regular e-cigarette user groups, with mixed findings. Among both baseline and baseline daily smokers, regular e-cigarette use was not significantly associated with past 12-month quit attempts, compared with non-e-cigarette users; however, current e-cigarette use was significantly associated with past 12-month quit attempts among both baseline and baseline daily smokers. Two additional studies evaluated quit attempts among regular e-cigarette users – weekly e-cigarette use applied in both cases – and neither found a significant association between e-cigarettes use and odds of making a quit attempt.[26,27]

Of the studies that reported non-regular measures of e-cigarette use, 7 were cross-sectional analytic studies.[32,33,36,37,39,40,42] Three of these studies showed significantly increased odds of having made a quit attempt for e-cigarette users compared

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with non-e-cigarette users.[32,39,42] The definitions of e-cigarette users were different in the 3 studies: "past-month" in Chen et al;[32] "ever" and "current" in Stokes et al;[39] and "ever" in Wang et al.[42] The fourth study found a significantly higher odds of ever e-cigarette use in unsuccessful quitters. The fifth cross-sectional analytic study did not have significantly different odds of quit attempts in the past 12 months for past 30-day e-cigarette users compared to non-e-cigarette users (not in past 30 days).[40] The last 2 cross-sectional studies reported mixed findings. Comiford et al[33] found e-cigarette use to be significantly associated with having made a past 12-month quit attempt. Specifically, the odds of reporting one or more quit attempts was significantly higher among current e-cigarette users than non-e-cigarette users; however, no such significant association was found among former e-cigarette users. Peltier et al[36] found that e-cigarette use was a negative predictor of a past quit attempt, but was not a significant predictor of a current quit attempt. The final study, a longitudinal panel, also found no significant difference in the odds of quit attempts between e-cigarette and non-e-cigarette users (not in past 30 days).[41]

Our systematic review exhibited 3 major strengths. The first was its comprehensive search procedure that yielded a large number of available studies for review. In addition, our review had a clearly defined PICOS, which assured the identification of the strongest evidence relevant to the research question. Lastly, guidelines for this review ensured that only demographically adjusted studies were included in the qualitative syntheses. Collectively, these considerations allowed us to provide a thorough and methodologically sound synthesis of the literature regarding the overarching key question: *Are there any potential associations between e-cigarette use among cigarette smokers and changes in continued cigarette smoking?*

In spite of these strengths, a number of limitations in the evidence base considerably restrict the interpretation of the findings. First, no RCTs reporting data on quit attempts made to abstain from cigarette smoking, and few studies reported demographically adjusted results – only 17 of the 42 included studies. Such an absence of results from either RCTs or from studies controlling for key demographic variables restricted the evidence pool considerably, thereby limiting the interpretation of findings in the qualitative synthesis. Moreover, the definition of e-cigarette use was not restricted to regular use; doing so would have provided the strongest evidence on potential associations with quit attempts made to abstain from cigarette smoking. Instead, the review was broadened to include any measure of e-cigarette use, with most studies measuring ever or current (past 30-day) use and applying definitions of e-cigarette use that were more consistent with temporary experimentation than regular use. Although results were stratified by regular versus non-regular e-cigarette use, only 4 adjusted studies were found which applied definitions of regular e-cigarette use. Given this small number of studies, it is difficult to draw any conclusions from their findings and indicates a need for future studies to apply definitions of e-cigarette use that identify regular established users. Another drawback to the data was the variation in definitions of outcome measures, with studies often using broad or ambiguous measures. For example, some studies defined quit attempts as periods of cessation of a given minimum duration, eg, 24-hour quit attempts, occurring within a given time frame, eg, the past 12 months.[29,31,34,38] Other studies defined quit attempts in terms of a given minimum duration of cessation, but with no time frame.[43] On the other hand, some studies defined a time frame, but did not define what constituted a quit attempt,[35] while other studies generically define a quit attempt as a self-reported attempt, with no duration or time frame defined.[28] Other limitations include temporality, inadequate follow-up or measurement periods, and the variation in the type of e-cigarettes used, in terms of design, nicotine concentration, flavor, and device generation.

More robust studies are required to determine whether there is an association between e-cigarette use and quit attempts made to abstain from cigarette smoking. Based on findings from this review, the available studies neither sufficiently measure e-cigarette use in a manner consistent with examining causality, nor sufficiently account for known or suspected confounding variables to

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support robust determinations regarding e-cigarette use and cigarette smoking behaviors.

Human Subjects Approval Statement

As a systematic review and meta-analysis of the literature, this research did not require original data collection from human subjects.

Conflict of Interest Disclosure Statement

The authors report no conflicts of interest.

AUTHORS' CONTRIBUTIONS

MMK conceived the study. MMK, IS, RDM, and JC collected and analyzed project data. MMK, IS, RDM, and GMC defined the study design, selection of measures, interpretation of data, and co-wrote the manuscript. All authors have read and approved the final article. The corresponding author attests that the listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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COMPETING INTERESTS

Dr. Kim serves as full-time employee of RAI Services Company, a wholly owned subsidiary of Reynolds American Inc. Dr. Curtin is a retired employee of RAI Services Company.

ETHICS STATEMENT

Ethical approval for this study was not required.

CONSENT FOR PUBLICATION

Not required for this publication as no individual or identifiable information is considered.

AVAILABLITY OF DATA AND MATERIALS

All data and materials considered in this review are publicly available.

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