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A Systematic Review and Meta-Analysis of the Association Between E-Cigarette Use and Cigarette Abstinence or Changes in Continued Cigarette Smoking Among Individuals Who Smoke Cigarettes

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ABSTRACT (340 words)

Aims: With recent marked increase in e-cigarette use, potential associations between e-cigarette use and combustible cigarette smoking are an important public health issue. Following AMSTAR 2 and PRISMA guidelines, this evidence synthesis identified and characterized associations between e-cigarette use and abstinence from/quitting smoking cigarettes and changes in cigarette smoking quantity/frequency.

Methods: The protocol was registered on November 06, 2018 (PROSPERO 2018 CRD42018115674). Three databases (MEDLINE, EMBASE, and PsycINFO) and gray literature were queried from January 01, 2007 to August 20, 2022. Search terms using medical subject headings (MeSH) and general terms were applied to identify studies related to the associations between e-cigarette use among combustible cigarette users and cessation from cigarette smoking. There was restriction to age or study design applied to the population of interest including individuals who use e-cigarettes (intervention) and individuals who do not use e-cigarettes (control). *A priori* abstinence outcome measures included: abstinence from/quitting smoking cigarettes, duration of abstinence from cigarette smoking, number of 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. Results were screened using the PICOS review method.

Results: Two meta-analyses comparing e-cigarettes and nicotine replacement therapy (NRT) were non-significant. Findings from three additional meta-analyses comparing nicotine-containing e-cigarettes with behavioral support found significant associations between e-cigarettes and cigarette smoking abstinence at the longest follow-up duration (RR=2.73, 95% CI: 1.15-6.50), 6-month (RR=2.70, 95% CI: 1.39-5.23), and 3-month (RR=3.49, 95% CI: 1.71-7.12) follow-up. Further meta-analyses examining the change in cigarette smoking quantity/frequency was significantly associated with e-cigarette use and a reduction in the number of cigarettes smoked per day (CPD) at the longest follow-up (MD=4.27, 95% CI: 3.02-5.53), and at the 6-month (MD=4.70, 95% CI: 3.34-6.07), 3-month (MD=4.14, 95% CI: 1.11-7.17), 2-month (MD=4.62, 95% CI: 0.01-9.22), and 1-month (MD=5.44, 95% CI: 0.74-10.14) follow-up.

Conclusions: Evidence suggests that the use of nicotine-containing e-cigarettes supports cigarette smoking cessation and reduction among individuals who smoke cigarettes regularly. Further studies are required to see if these patterns hold past the 1-year time point.

KEY WORDS: e-cigarettes; abstinence; cigarette smoking cessation; systematic review; meta-analysis; PRISMA; AMSTAR

INTRODUCTION

Given that most of the 7,000 or so chemicals in cigarette smoke are not contained within inhaled e-cigarette vapor, it is generally accepted that electronic cigarettes (e-cigarettes) present a considerably lower public health risk than combustible cigarettes, [1, 2]. The prevalence of electronic e-cigarette use has increased substantially during the past decade as cigarette smoking prevalence has continued to decline [3-6].

The impact of e-cigarettes on individual health and, in turn the broader public's health, has become a point of controversy in recent years. While generally considered to be associated with a reduction in harm relative to cigarettes, there is an opposing view that e-cigarette use may be associated with cigarette smoking initiation [7-9]. In order to determine the associated benefits and risks, an assessment of causality is central to understanding the public health effect of e-cigarettes. Central to such an assessment is determining whether the risks associated with e-cigarettes are offset by the benefits to the public health, which in turn will play a pivotal role in developing regulatory strategies [2].

To date, systematic reviews examining the relationship between e-cigarette use among individuals who smoke cigarettes and changes in continued cigarette smoking have predominantly focused on the relationship between e-cigarettes and cigarette smoking abstinence [10-14]. Unlike previous systematic— and an order to capture the full trajectory of behaviors that may ultimately lead to cigarette smoking abstinence—the current systematic review evaluated various cigarette smoking behaviors and their potential association with e-cigarette use, and how such behaviors may relate to cessation. Specifically, multiple facets of cessation were considered in the wider systematic review., to include: abstinence from/quitting smoking cigarettes; change in cigarette smoking quantity/frequency; quit attempts made to abstain from cigarettes smoking; and relapse to cigarette smoking. Such a novel expansion of outcomes measures related to cessation allowed for a broader search strategy with the potential to

capture more relevant studies on each individual outcome measure. Lastly, while RCT data were prioritized, both adjusted and unadjusted non-RCT studies were also synthesized where available. This not only allowed for a broader reach of the evidence base, but also acknowledges the importance of real-world evidence in the investigation of tobacco product use behaviors.

The level of methodological rigor applied in the current systematic review provides an approach not previously applied most reviews on the Key Question, while also synthesizing a wider evidence base. Additionally, the current systematic review serves as a timely update to previous reviews, given the rapid emergence of evidence examining the global impact of e-cigarette use.

METHODS

Overview

This specific review was focused on identifying and assessing the potential relationships between e-cigarette use among current and former combustible individuals who smoke cigarettes and the outcomes of *abstinence from/quitting smoking cigarettes, duration of abstinence from cigarette smoking,* and *changes in cigarette smoking quantity/frequency*. The methodology and results are extracted from a broader systematic review assessing the Key Question, "Are there any potential associations between e-cigarette use and changes in continued cigarette smoking." The review protocol for the full systematic review was registered with PROSPERO (The International Prospective Register of Systematic Reviews) on November 06, 2018 (PROSPERO 2018 CRD42018115674; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=115674).

AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews [AMSTAR] 2) [15]) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA]) [16]) standards were adhered to in this systematic review; an overall rating of "high" was assessed using the AMSTAR 2 tool.

Terminology

Refer to **Supplemental Section 1** for a glossary of relevant terminology used in this review.

Literature Search Methods

An information specialist conducted a systematic search of MEDLINE, EMBASE, and PsycINFO; search terms were developed using medical subject headings (MeSH) and general terms related to the associations between e-cigarette use among combustible cigarette users and cessation from cigarette smoking. The initial database search, conducted on October 15, 2018, spanned from January 1, 2007 to October 15, 2018. An updated search, conducted on October 17, 2019, spanned from January 1, 2018 to October 17, 2019; a second literature search update, conducted on January 5, 2021, spanned from January 1, 2019 to January 5, 2021; and a third literature review search update, conducted on August 20, 2022, spanned from 6 January 2021 and 31 December 2022. Search dates were restricted to 2007 onwards, as this was when e-cigarettes were introduced to the mass market in the US [1, 2]. The complete search strategy is provided in **Supplemental Section 2**.

The PICOS (Population or participants and conditions of interest, Interventions or exposures, Comparisons or control groups, Outcomes of interest, and Study designs) review method was applied to screen the search results (see **Supplemental Section 3)**. There was no age restriction applied to the population of interest including individuals who use e-cigarettes (intervention) and individuals who do not use e-cigarettes (control). *A priori* abstinence outcome measures included: abstinence from/quitting smoking cigarettes, duration of abstinence from cigarette smoking, number of 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. Study design was not restricted, as initial scoping searches indicated that relevant RCTs were sparse; however, results from RCTs were considered the highest level of evidence. The search strategy considered: published peer-reviewed literature; theses and dissertations; government and industry documents; clinical trial registries

(clinicaltrials.gov); gray literature according to a search of Google Scholar; and reference lists of included studies. Subject matter experts in the field were consulted. All studies were restricted to only English-language studies due to translation resource constraints.

Although the measure of regular e-cigarette use would be expected to provide the strongest evidence, this review was designed to capture the evidence more broadly and minimize the risk of potentially losing data if the level of e-cigarette use was restricted.

Evidence Synthesis

DistillerSR (Evidence Partners, Ottawa, Canada) was the platform used for all data extraction and management (refer to **Supplemental Sections 3 through 6** for full details on search results)**.** Articles were first screened at the title/abstract level. Then, full-text articles were obtained for studies not excluded based on the title/abstract alone. Two reviewers independently screened the full text based on the inclusion/exclusion criteria and any discrepancies between the two were resolved in a joint decision between reviewers. If any disagreements remained unresolved between the two reviewers, they were adjudicated by a third clinical reviewer, and reasons for excluding articles were documented.

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

Estimates of the difference between individuals who use e-cigarettes and those who do not are presented with the best measure of precision (e.g., 95% confidence intervals [CIs]) or statistical significance reported in the included studies. The words “significant” and “significantly” are specified herein to indicate statistical significance (e.g., alpha level of 0.05, CI excludes 1 for ratios, CI excludes 0 for mean differences).

Assessment of Confounding

Framed within the Socio-Ecological Model created by McLeroy et al. [17], this review considered the interrelationships between individuals and their social (micro-), physical (meso-), and policy (macro-) environments (further detail reported in **Supplemental Section 7**).

The following steps were taken to consider confounding factors, in accordance with Cochrane guidelines for systematic reviews [18]: 1) 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; and 2) During the systematic review process, the variables that individual study authors considered were recorded for additional *post hoc* consideration.

Potential confounders were identified and categorized as micro-, meso-, or macro-level variables, according to the socio-ecological model and the available empirical evidence [17]. The minimum key confounders identified were: race/ethnicity, age, and gender based on the magnitude and strength of their association with cigarette smoking behaviors [19-21]. For this review, observational studies were considered to adequately control for confounding bias if 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); and, if appropriately randomized, RCTs were considered to adequately control for these key demographics. Studies that also adjusted for meso- (e.g., living with a smoker) or macro-level factors (e.g., cigarette taxes) were flagged for possible inclusion in sensitivity analyses.

Sensitivity Analyses

If data permitted, sensitivity analyses were planned for an executed according to 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, when appropriate according to reported data, stratification by age group, and a sensitivity analysis by age, was executed.

Consideration of Industry Funding Bias

The potential impact of funding bias on reporting and conclusions has been a topic addressed in the evidence base [22-24]. As reported in the conflict-of-interest disclosure for this review, and with the growth in of peer-reviewed systematic reviews and meta-analytic publications, this particular topic may have a heightened importance as a methodological concern. To specifically address any potential concerns of funding bias in this reported evidence synthesis, this review was executed with complete transparency and rigor according to the highest standards of systematic review methodology including: *a* priori protocol registration (PROSPERO 2018 CRD42018108540; http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018108540); strict adherence to the PICOS throughout the execution of this review, a transparent and replicable search strategy executed by an information specialist with corresponding literature research results (**Supplemental Section 4: Literature Search Output, Studies Reviewed at the Full-Text Level**); full reporting of excluded studies including reason for exclusion (**Supplemental Section 5: List of Excluded Studies**); full reporting details on quantitative methods; and the expected details, per AMSTAR-2 and PRISMA guidelines, to disseminate a fully transparent and replicable evidence synthesis. Overall, the methodological rigor of this review with fully transparent and replicable reporting can also serve as a measure to minimize publication bias with systematic reviews.

Outcomes and Related Psychometrics

Considering all the outcome measures are not likely to be equally valid and reliable, this review also examined the evidence based according to the following Contextual Question (CQ), “Have measures used to examine associations between e-cigarette use among individuals who smoke cigarettes 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 [25] (further detail is reported in **Supplemental Section 8**).

Study Quality Assessment

Study quality was independently appraised by two research associates, using the Downs and Black checklist [26]. Individual studies ratings were graded "excellent," "good," "fair," or "poor" according to Downs and Black criteria (details are provided in **Supplemental Section 9**).

Strength of Evidence Evaluation

Strength of evidence (SOE) was separately assessed for RCTs, studies that adequately 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 (full SOE grading is reported in **Supplemental Section 10**).

Meta-Analysis

All meta-analyses were executed using results from RCTs, as these studies were considered the highest level of evidence. All statistical analyses and forest plots were performed and developed with Review Manager version 5.4 [27]. For meta-analyses of abstinence from/quitting smoking, a random effects inverse variance method for dichotomous data was used to calculate the pooled risk ratio (RR). For meta-analyses of change in cigarette smoking quantity/frequency, a random effects inverse variance method for continuous data was used to calculate the pooled mean differences (MD). The I^2 statistics were likewise computed to check for heterogeneity among the included studies of a given meta-analysis. A p-value less than 0.10 was considered statistically significant to accommodate for the inherent low power of statistical tests for heterogeneity. I^2 expresses the percent of variability in point estimates due to heterogeneity scored as "low" (I^2=25%), "moderate" (I^2=50%), and "high" (I^2=75% or

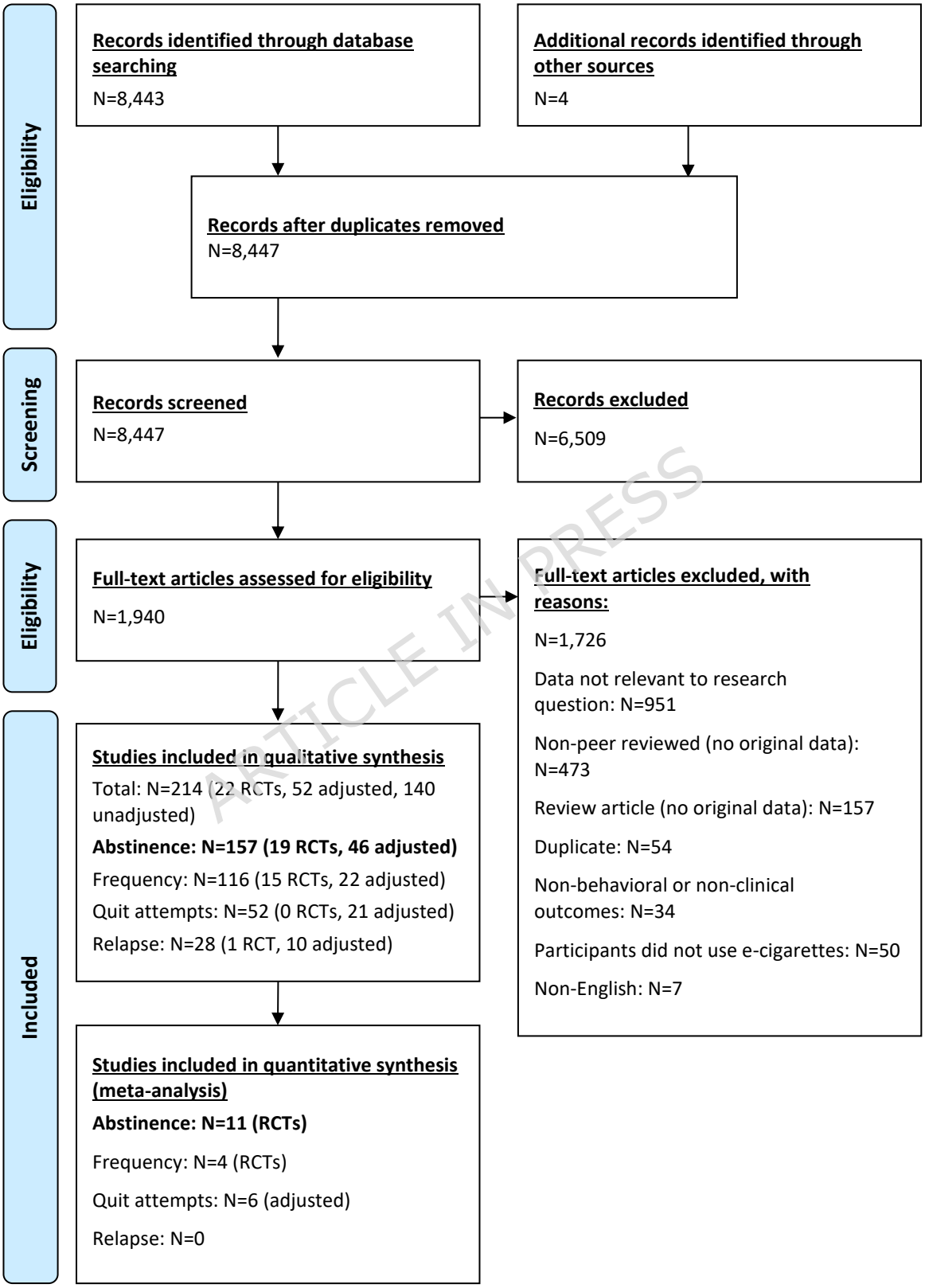
more)[28]. If imputations for missing values were needed, a sensitivity analysis was implemented excluding the studies with imputed values to test the robustness of results. Publication bias, best assessed using funnel plots, requires 10 or more RCTs included in a meta-analysis [29]. An assessment of publication bias would have been performed had this criterion been met.

RESULTS

Overview

A total of 8,443 articles were retrieved from the defined literature search; an additional four articles were identified through the gray literature search (of Google Scholar). Of the 8,447 potentially-relevant articles, 6,509 were excluded at the title/abstract level, resulting in 1,940 articles eligible for review at full-text level (see **Supplemental Section 4**). A further 1,726 articles were excluded for not meeting the inclusion criteria (**Supplemental Section 5**), resulting in 214 studies eligible for inclusion in the wider systematic review (see **Supplemental Section 6**). The weighted overall kappa for inter-rater reliability at Level 2 screening was 0.86. All selection steps are presented as a PRISMA flowchart (see **Figure 1**) and the PRISMA checklist is reported in **Table 4**.

Figure 1: PRISMA Flowchart Examining the Potential Associations Between E-Cigarette Use Among Individuals who smoke cigarettes and Changes in Continued Cigarette Smoking



Twenty of the 214 eligible articles from the wider systematic review, were reported data relating to quit attempts and/or relapse to cigarette smoking and were excluded from this analysis. Of the remaining 194 studies, 22 studies were RCTs, 52 were studies that adjusted for gender, age, and race/ethnicity between groups (i.e., adjusted for key demographic characteristics), and 100 studies reported unadjusted data. The 74 (total) studies, including RCT (22) and adjusted studies (52), are included in the qualitative and/or quantitative synthesis of evidence. For each study, information regarding the study characteristics (**Supplemental Section 11**), demographic and baseline characteristics (**Supplemental Section 12**), and study outcomes (**Supplemental Section 13**) were extracted. Studies that did not report demographically adjusted data are not included in the qualitative and/or quantitative synthesis but information regarding the study characteristics (**Supplemental Section 11**), demographic and baseline characteristics (**Supplemental Section 12**), and study outcomes (**Supplemental Section 13**) were extracted.

Of the 74 included studies, the highest number of studies (18 studies) were published in 2022 [30-46], followed by 14 studies in 2018 [47-60], 10 studies in 2020 [61-70], 10 studies in 2019 [71-80], eight studies in in 2021 [81-88], six studies in 2014 [89-94], three studies in 2017 [95-97], two studies in both 2016 [98, 99] and 2013 [100, 101], and one study in 2015 [102]. Thirty studies were longitudinal (and observational) in design [30, 31, 34-36, 38, 39, 42, 47, 48, 56, 58-62, 65, 67, 69, 71, 77, 80, 81, 84, 85, 87, 92, 96, 97, 102], and 17 studies were cross-sectional [37, 40, 44, 49, 50, 53, 55, 57, 79, 83, 90, 91, 93, 95, 98, 101, 103]. Twenty-two RCTs were identified [32, 33, 41, 43, 45, 46, 51, 52, 54, 64, 66, 68, 70, 74, 76, 78, 82, 86, 89, 99, 100]; an additional four studies were post-hoc analyses of RCTs [36, 72, 88, 94], and one study was a nonrandomized controlled trial [63].

The majority of studies (50 studies) identified their study populations as “adults” [30-36, 38, 40, 43, 45, 47-51, 53, 55-59, 61-66, 70, 74-78, 80-82, 84-87, 89, 90, 92, 94, 95, 100-102]. Among the remaining studies, seven studies identified their population as young adults [39, 42, 79, 83, 88, 96, 97], five studies as “youth and adults” [37, 60, 67, 69, 72], three studies

as "students" [44, 91, 98], two studies as "youth and young adults" [71, 97], and one study as "older adults" [68]. The remaining six studies did not define their study populations by age [41, 46, 52, 54, 99, 103].

Twenty-two identified RCTs were considered the highest level of evidence, and subsequently were included in both the quantitative and qualitative review of the evidence. Nineteen of these RCTs reported outcomes related to abstinence from/quitting cigarette smoking [32, 33, 43, 46, 51, 52, 54, 64, 66, 68, 76, 78, 86, 89, 100], 15 RCTs reported outcomes related to change in cigarette smoking quantity/frequency [33, 43, 45, 54, 64, 66, 68, 70, 76, 78, 82, 86, 89, 99], and one RCT reported outcomes related to duration of abstinence from cigarette smoking [32].

Additionally, 52 studies that adjusted for gender, age, and race/ethnicity between groups (i.e., adjusted for key demographic characteristics) were also included in the qualitative review. In addition to the demographic characteristics specified, most adjusted studies included further adjustments with varying combinations of other micro-, meso-, and macro- covariates (e.g., the presence of an individual(s) using tobacco product(s) at home, highest parental education, and exposure to tobacco advertisements). Of the 52 studies that adjusted for gender, age, and race/ethnicity, 46 studies reported outcomes related to abstinence from/quitting smoking cigarettes [30, 31, 34-37, 39, 40, 42, 44, 47, 48, 50, 53, 55-63, 65, 67, 71-73, 75, 80, 81, 84, 85, 87, 88, 90-97, 101, 102, 104], 22 reported outcomes related to change in cigarette smoking quantity/frequency [34, 35, 48, 49, 58, 59, 61, 63, 69, 72, 77, 79, 80, 83, 84, 88, 94, 97, 98, 102, 105, 106], and two reported outcomes related to duration of abstinence from cigarette smoking [34, 95].

To provide greater context for the interpretation of the evidence, empirical data regarding the reliability and/or validity of the relevant outcome measures—abstinence from/quitting cigarette smoking, duration of abstinence from cigarette smoking, and change in cigarette smoking quantity/frequency—were evaluated (as a CQ, with a comprehensive but not systematic review of the literature). All three

measures qualified as "acceptable", and further details, including a CQ evidence table of all three measures, can be found in **Supplemental Section 8**.

Two investigators appraised the included studies for quality according to the Downs and Black checklist [26]. Five studies (6.8%) were rated "excellent" quality[32, 33, 45, 70, 82], 52 studies (71.2) were rated "good" quality [33-38, 42, 43, 46-51, 54-60, 62, 64-66, 68, 69, 71-74, 76-78, 80, 81, 83, 84, 86, 87, 89, 90, 92-100, 102], 16 studies (21.9%) were rated "fair" quality [30, 31, 39-41, 44, 52, 53, 61, 67, 75, 79, 85, 88, 91, 101], and no studies were rated "poor" quality (see **Supplemental Section 9**).

Definitions of E-cigarette Use by Outcome Measure

Abstinence From/Quitting Cigarette Smoking

Among the 65 included studies that examined cigarette smoking, 32 studies evaluated the association between regular e-cigarette use and abstinence from/quitting cigarette smoking [31-33, 35, 41, 43, 46-48, 51-54, 58, 61, 63, 64, 66, 68, 70, 74-76, 78, 80, 84-86, 89, 94, 100, 107], 27 studies evaluated non-regular e-cigarette use [30, 36, 38-40, 42, 44, 56, 57, 59, 60, 62, 67, 71, 72, 81, 87, 88, 90-93, 95-97, 101, 102], four studies evaluated both regular and non-regular e-cigarette use [50, 55, 65, 73], and one study did not specify e-cigarette use status [37]. Nineteen of the 36 studies evaluating regular e-cigarette use were RCTs in which e-cigarettes were administered to individuals with current established smoking behaviors as part of their interventions [32, 33, 41, 43, 46, 51, 52, 54, 64, 66, 68, 70, 74, 76, 78, 86, 89, 100]. These participants were considered to be individuals who use e-cigarettes regularly in terms of outcomes reported within the defined timeframes of their respective studies. Two additional studies – a secondary analysis of an RCT [94] and a nonrandomized controlled trial[63] – applied the same definition of regular e-cigarette use. In addition, 15 observational studies included definitions of regular e-cigarette use [31, 35, 47, 48, 50, 53, 55, 58, 61, 65, 73, 75, 80, 84, 85]. Definitions of regular e-cigarette use were as follows: daily e-cigarette use in nine studies [35, 50, 58, 61, 65, 73, 75, 84, 85]; non-daily or some-day use in nine studies [35, 50, 58, 61, 65, 73, 75, 84, 85]; and daily or non-daily use presented as a single category in five studies [31, 47, 48, 53, 80].

Among the 31 studies that examined abstinence from/quitting cigarette smoking, using non-regular definitions of e-cigarette use, the most common definitions of non-regular use were ever e-cigarette use [44, 55, 57, 59, 60, 71, 81, 90, 91, 95, 97, 102, 104] and current or past 30-day use [39, 44, 55, 57, 67, 73, 81, 87, 88, 91-93, 96], each applied in 13 studies, use as a cessation aid in two studies [44, 96], and former or noncurrent use in five studies [44, 50, 57, 65, 93]. Three studies [42, 44, 55] stratified past 30-day use by the number of days e-cigarettes were used.

Duration of Abstinence from Cigarette Smoking

One RCT [32] and two observational studies [34, 95] examined duration of abstinence from cigarette smoking. In the RCT, e-cigarettes were assigned to participants to help them quit smoking (considered as regular use) [32]. Of the two observational studies, one study [95] applied a definition of ever e-cigarette use, while the other study included e-cigarette use as a cessation aid [34]; both of these studies were categorized as non-regular use.

Change in Smoking Quantity/Frequency

Among the 37 included studies that examined change in cigarette smoking quantity/frequency, 24 studies evaluated regular e-cigarette use, and 13 studies evaluated non-regular e-cigarette use. Of the 24 studies that evaluated regular e-cigarette use, 15 were RCTs [33, 43, 45, 54, 64, 66, 68, 70, 76, 78, 82, 86, 89, 99], in which e-cigarettes were assigned to individuals with current established smoking behaviors as part of their intervention. These participants were considered regular individuals who use e-cigarettes according to the outcomes reported within the defined timeframes of their respective studies. The same rationale was applied in a secondary analysis of one RCT[94] and one nonrandomized clinical study [63]. In addition, seven observational studies applied definitions of regular e-cigarette use [35, 48, 58, 61, 80, 83, 84]. Five of these studies applied the definitions of daily and nondaily use as separate categories [35, 48, 58, 80, 84], while the remaining two studies applied the definitions of daily or nondaily use as a single category [48, 80].

Among the 13 studies that examined change in cigarette smoking quantity/frequency using non-regular definitions of e-cigarette use, current or past 30-day e-cigarette use was the most common definition applied in five studies [49, 77, 88, 92, 98], followed by ever e-cigarette use in four studies [49, 59, 97, 102]. Other definitions of non-regular e-cigarette use, applied in one study each, were past 7-day use [72], former/noncurrent use [49], use as a cessation aid[108], past 12-month use [79], and past 30-day use stratified by the number of days used [69].

Qualitative Synthesis of Best Available Evidence

Studies that met inclusion criteria for this review but were excluded from the quantitative synthesis were qualitatively synthesized. Results from RCTs and non-RCT adjusted studies were synthesized separately. Results of the qualitative synthesis of both RCTs and non-RCT adjusted studies were stratified by regular versus non-regular e-cigarette use and are presented in **Supplemental Sections 13-18**.

Abstinence from/quitting smoking Cigarettes Among Regular Individuals Who Use E-Cigarettes

This systematic review identified 19 RCTs and 17 non-RCT adjusted studies that investigated the association of regular e-cigarette use and abstinence from/quitting smoking cigarettes. Eleven of 19 RCTs met the inclusion criteria of the meta-analysis and are not described in the qualitative analysis below [32, 33, 51, 54, 64, 66, 68, 78, 86, 89, 100]. The remaining eight RCTs and 17 non-RCT adjusted studies are included in the qualitative synthesis; summary characteristics of the RCT studies are provided in

Table 1 and results are discussed below. Summary characteristics and results of non-RCT adjusted studies are presented in **Supplemental Section 14**.

RCTs

Hajek at al. (2022) conducted an RCT comparing the efficacy of e-cigarettes to that of nicotine patches as smoking cessation aids in pregnant individuals who smoke cigarettes [33]. The primary outcome was exhaled carbon monoxide (eCO)-validated cessation at the end of pregnancy. Smoking cessation was defined as per the Russell Standard, with up to five lapses being allowed with no smoking at all during the previous week at the time of follow-up, in the intention-to-treat (ITT) analysis, validated prolonged quit rates at the end of pregnancy were not significantly different between the e-cigarette group (6.8%) and the nicotine patch group (4.4%, RR=1.55, 95% CI: 0.95-2.53). This may be due in part to the low return of saliva samples (6.8% in the e-cigarette arm and 4.4% in the nicotine patch arm). Additionally, some participants in the nicotine patch group also used e-cigarettes during the study. In a pre-specified sensitivity analysis excluding abstinent participants who used non-allocated products, abstinence rate was significantly higher in the e-cigarette group (6.8%) compared with the nicotine patch group (3.6%; RR = 1.93, 95% CI: 1.14-3.26)[33].

Tattan-Birch et al. (2022) investigated whether the use of e-cigarettes together with varenicline was associated with higher abstinence rates compared with varenicline alone among adult individuals who smoke cigarettes in a behavioral support program for smoking cessation [46]. In this two-group, parallel arm, pragmatic RCT, participants were randomized 1:1 to a varenicline-only group or a varenicline + e-cigarette group. Results demonstrated that the 9- to 12-week abstinence rate verified with eCO <10 parts per million (ppm; primary outcome) was numerically higher in the e-cigarette + varenicline group (47.9%) than in the varenicline-only group (31.8%), although the difference was not statistically significant (RR=1.51, 95% CI: 0.91-2.64). Analysis of 2- to 4-week abstinence rates (secondary outcome)

also showed that the rate of abstinence was numerically higher among individuals who use e-cigarette + varenicline (68.8%) compared to individuals who use varenicline-only (50.0%; RR=1.37, 95% CI: 0.98-2.01), although the difference was not statistically significant. However, in a sensitivity analysis that adjusted for nonadherence (i.e., being assigned to try e-cigarettes but not using e-cigarettes), and contamination (i.e., being assigned to the control group but using e-cigarettes), 9- to 12-week abstinence was significantly higher in the e-cigarette + varenicline group compared with varenicline only group (RR 2.66, 95% CI 1.17-6.05). Notably, 26 of the 48 participants randomized to the e-cigarette + varenicline group and 16 of 44 participants randomized to the varenicline-only group completed the 12-week follow-up [46].

Pratt et al. (2022) conducted an RCT to evaluate the impact of e-cigarettes on smoking cessation in participants with serious mental illness [43]. Participants were randomly assigned to receive disposable e-cigarettes for 8 weeks, or to the control group. At baseline, mean number of cigarettes smoked per day (CPD), verified with eCO of less than 6 ppm, was not significantly different between the e-cigarette (18.1 CPD, 95% CI 16.4-19.8) and control (19.2 CPD; 95% CI 17.5-20.9) groups (p=0.3636). However, between Weeks 2 and 8, 18.6% to 22.1% of participants in the e-cigarette group and no participants in the control group (0%) reported smoking zero CPD. This difference remained substantial at Week 13 (14.7% vs. 0.9%), but narrowed at Week 26 (10.7% vs. 5.7%) [43].

In a pragmatic RCT, Morphett et al. (2022) investigated whether the addition of e-cigarettes to standard smoking cessation treatment could improve quit rates in populations with heavy smoking prevalence (people living with human immunodeficiency virus [HIV], hepatitis C virus [HCV] and/or opiate dependence) [41]. Participants from these populations were randomized to receive either e-cigarettes and nicotine patches, or combination nicotine replacement therapy (NRT; in this case nicotine patches plus nicotine gum or lozenge) and referral to a smoking cessation support line. Both groups received a

referral to a smoking cessation support line. At 6 month follow-up, the quit rate (not a puff in last 3 months) was 19.9% among those in the e-cigarette and nicotine patches group and 5.2% in the NRT arm [41].

In a pragmatic, three-arm parallel RCT by Walker et al. (2020), e-cigarette naïve individuals who smoke cigarettes who were eager to quit were randomized to receive either nicotine e-cigarettes in combination with nicotine patches, non-nicotine e-cigarettes in combination with nicotine patches, or nicotine patches alone [70]. At 6 months, the prevalence of eCO-verified continuous smoking abstinence – the primary outcome – was significantly higher in the nicotine e-cigarette plus nicotine patch group (7%) than in the nicotine patch alone group (2%; RR=1.75, 95% CI 1.02-2.98, p=0.038; RD=2.99, 95% CI 0.17-5.81). Prevalence of eCO-verified abstinence at 1- and 3-month follow-up (both p<0.001), and of self-reported abstinence at 1 (p<0.001), 3 (p<0.001), and 6 months (p=0.007), as well as rate of 7-day point-prevalence abstinence (PPA) at 1- (p=0.001), 3- (p=0.001), and 6 months (p=0.005) were also significantly higher in the nicotine e-cigarette plus nicotine patch group compared with the nicotine patch alone group. Six-month eCO-verified continuous abstinence was not significantly different among participants in the non-nicotine e-cigarettes plus nicotine patch group, compared with those who received nicotine patches alone (4.0% vs. 2.0%, RR=1.69, 95% CI 0.50-5.53, p=0.39; RD=1.61, 95% CI -1.58-4.80) [70].

Holliday et al. (2019) conducted a pilot RCT to evaluate the feasibility of offering smoking cessation treatment through a dental care setting. Individuals who smoke cigarettes who were not using e-cigarettes were randomized to receive smoking cessation intervention alone or smoking cessation intervention and an e-cigarette starter kit [74]. At 4 weeks, the prevalence of eCO-verified abstinence was 28% (95% CI: 16% to 43%) in the e-cigarette group, and 5% (95% CI: 1% to 17%) in the group of individuals not using e-cigarettes. At 6 months, the prevalence of abstinence was 15% (95% CI: 7% to 29%) in the e-cigarette group and 5% (95% CI: 1% to 17%) in the group of individuals not using e-

cigarettes. However, the study authors also reported contamination in the control group – that is – five of 40 participants in the control group were using e-cigarettes at the 4 month follow-up, and three participants were using them at 6 months. Additionally, one participant (3%) in the e-cigarette group was not using them at the 4-month follow-up, and eight participants (20%) were not using them at 6 months [74].

In an RCT by Ioakeimidis et al. (2018), individuals who smoke cigarettes daily (10 or more CPD) with a history of acute coronary syndrome and expressing a motivation to quit cigarettes were randomized to receive either a 12 mg/mL e-cigarette or a smoking cessation aid (varenicline) [52]. At the 24-week follow-up, significantly fewer individuals who use e-cigarettes were abstinent compared to individuals who use varenicline (32.5% versus 47.3%, respectively; percent difference=14.8%, 95% CI: 3.9% to 25.8%, $p<0.05$).

In an RCT by Lee et al. (2018), preoperative elective surgery patients who currently smoked cigarettes (two or more CPD, and having smoked one or more cigarettes in 7 days prior to baseline) were screened using electronic chart review, and subsequently randomized to receive either an e-cigarette or an NRT (i.e., nicotine patch) [54]. At various time points, cigarette smoking cessation for at least 48 hours was assessed. On the day of surgery, there was no significant difference in cigarette smoking cessation between the two groups, neither in terms of self-reported cessation (RR=0.67, 95% CI: 0.18-2.42, p=0.66) nor biochemically-verified cessation (RR=0.75, 95% CI: 0.15-3.79, p=1.0). Similarly, rates of cigarette smoking cessation were not significantly different between the two groups: at 30-day follow-up self-reported cessation (RR=0.83, 95% CI: 0.25-2.80, p=1.0); at 8 weeks, for both self-reported (RR=2.5, 95% CI: 0.34-18.6, p=0.63) and biochemically-verified (RR=undefined, p=0.53; RR undefined due to individuals who had not reported cessation in the NRT group, RD=15%, 95% CI: -6.5%-30.6%) cessation; and at 6 months for self-reported cessation (RR=2.5, 95% CI: 0.34-18.6, p=0.63).

Abstinence from/quitting smoking Cigarettes Among Individuals Who Use E-Cigarettes Non-Regularly

This systematic review identified 33 non-RCT adjusted studies that investigated the association of e-cigarette use and abstinence from/quitting cigarette smoking among individuals who use e-cigarettes non-regularly. No RCT studies met inclusion criteria for this outcome, however, summary characteristics and results of the non-RCT adjusted studies are provided in **Supplemental Section 15**.

Duration of Abstinence from Cigarette Smoking Among Individuals Who Use E-Cigarettes Regularly

One RCT study was identified that evaluated duration of abstinence from cigarette smoking among individuals who regularly use e-cigarettes [32]. Summary characteristics of the RCT study are provided in **Table 2** and results are discussed below.

Foulds et al. (2022) conducted a four-arm RCT among adult individuals who smoke cigarettes and were interested in reducing cigarette smoking but not planning to quit. Participants were randomized to receive e-cigarettes that contained either no nicotine (i.e., 0 mg/mL nicotine), 8 mg/mL nicotine or 36 mg/mL nicotine, or a cigarette substitute – a cigarette-shaped plastic tube with no electronic vapor or aerosol. The mean duration of abstinence – defined as the number of days without smoking at Week 24 – was significantly higher among participants in the 36 mg/mL nicotine e-cigarette group (15.6 ±36.4 days) compared with those in the cigarette substitute group (5.3±18.5 days; $p<0.02$). The mean duration of abstinence among those in the 0 mg/mL nicotine e-cigarette group was 4.7±17.0 days, and 7.4±23.1 days among those in the 8 mg/mL nicotine e-cigarette group (p-values and cigarette substitute group not reported).

Duration of Abstinence from Cigarette Smoking Among Individuals Who Use E-Cigarettes Non-Regularly

Two studies were identified that investigated the association of non-regular e-cigarette use and duration of abstinence from cigarette smoking. No RCT studies met inclusion criteria for this outcome. However,

summary characteristics and results of the non-RCT adjusted studies are provided in **Supplemental Section 16.**

Change in Cigarette Smoking Quantity/Frequency Among Individuals Who Use E-Cigarettes Regularly

Fifteen RCTs and nine non-RCT adjusted studies were identified that investigated the association of regular e-cigarette use and change in cigarette smoking quantity/frequency. Three RCTs were included in the quantitative analysis and are not described in the qualitative analysis below. Summary characteristics of the 12 RCTs are presented in **Table 3** and the results are discussed below. Summary characteristics and results of the non-RCT adjusted studies are provided in **Supplemental Section 17**.Error! Reference source not found.

RCTs

Hajek at al. (2022) conducted an RCT comparing the efficacy of e-cigarettes to that of NRT, specifically nicotine patches, as smoking cessation aids in pregnant individuals who smoke cigarettes [33]. Among women who did not abstain from cigarette smoking, the rate of self-reported smoking reduction at the end of pregnancy – defined as a reduction of at least 50% compared to baseline – was significantly higher among women randomized to the e-cigarette arm (42.4%) than in women randomized to the NRT arm (33.8%; RR=1.25, 95% CI: 1.06-1.48; p=0.007). Similar results were observed in a sensitivity analysis in which participants using non-allocated products were excluded: self-reported cigarette smoking reduction was significantly higher among individuals who use e-cigarettes (41.7%) compared with individuals who use NRT (27.8%; RR=1.50, 95% CI: 1.25-1.81; p<0.001) [33].

Pratt et al. (2022) evaluated the impact of e-cigarettes on daily use of cigarettes among participants with serious mental illness [43]. Participants were randomly assigned to receive disposable e-cigarettes for 8 weeks, or not to receive e-cigarettes. At baseline, the mean number of CPD was not different between participants randomized to the e-cigarette group (18.1 CPD, 95% CI: 16.4-19.8) and those randomized to

the e-cigarette non-user group (19.2 CPD, 95% CI: 17.5-20.9). By Week 2, mean CPD was substantially reduced in the e-cigarette group (7.5 CPD, 95% CI: 5.9-9.2) and unchanged in the e-cigarette non-user group (18.1 CPD, 95% CI: 16.4-19.8). The CPD continued to be significantly lower in the e-cigarette group until the final follow-up at Week 26 (individuals who use e-cigarettes: 14.4 CPD, 95% CI: 12.3-16.5; individuals who do not use e-cigarettes: 18.7 CPD, 95% CI: 16.7-20.7, p=0.0275). Likewise, the proportion of participants who reported smoking one to five CPD was significantly higher in the e-cigarette group compared with the group of individuals not using e-cigarettes at Week 2 (32.8% vs. 2.6%; p<0.01), Week 4 (38.1% vs. 2.7%; p<0.01), Week 6 (28.3% vs. 6.3%; p<0.01), and Week 8 (27.4% vs. 6.4%; p<0.01). The difference was still significant at Week 13 (11.0% vs. 3.7%; p<0.01), but not at Week 26 (2.7% vs. 5.7%; p=NS) [43].

The RCT by Myers Smith et al. (2022) compared the efficacy of e-cigarettes to NRT in reducing cigarette smoking. Participants were randomized to receive either e-cigarettes or NRT of their choice [107]. The rate of achieving the primary outcome of eCO-validated at least 50% reduction in cigarette smoking was significantly higher in the e-cigarette arm than in the NRT arm (e-cig non-user group) at Week 4 (42.7% in the e-cigarette arm, 23.9% in the NRT arm; RR=1.8, 95% CI: 1.1-3.0; p=0.03) and at 6 months, (26.5% in the e-cigarette arm, 6.0% in the NRT arm, RR=4.4, 95% CI: 1.6-12.4; p=0.005). Similar results were reported for self-reported at least 50% reduction in cigarette smoking: the rate of self-reported at least 50% reduction in cigarette smoking was significantly higher in the e-cigarette group than in the NRT group at Week 4 (70.6% vs. 52.2%, RR=1.4, 95% CI: 1.0-1.8; p=0.03) and at 6 months (66.2% vs. 37.3%, RR=1.8, 95% CI: 1.3-2.5; p=0.002). When any reduction in cigarette smoking was considered, not specifically at least 50%, self-reported reduction at 6 months was 58.2% in the e-cigarette group versus 33.9% in the NRT group (RR=1.7, 95% CI: 1.1-2.6, p=0.009), although eCO-validated readings showed that fewer participants reduced their cigarette smoking (9.1% for individuals who use e-cigarettes and 3.1% for individuals who do not use NRTs; RR=3.0, 95% CI: 0.6-14.6, p=0.18). Among participants who

had not quit cigarette smoking during the trial, the mean change in cigarette consumption from baseline to 6 months for was significantly greater in the e-cigarette group (-12.8±8.9 CPD) than in the NRT group (-8.1±8.1 CPD, p=0.01) [107].

Russell et al. (2021) conducted an RCT to assess the effectiveness of e-cigarettes and NRT for reducing and replacing conventional cigarettes [86]. Established daily cigarette smokers (18 years and older) were randomized to receive a 3-month supply of over-the-counter NRTs, an e-cigarette system containing nicotine salt e-liquid (NSP), or an e-cigarette system containing freebase nicotine e-liquid (FBNP). Among participants who were not abstinent at 6 months, total past 30-day cigarette consumption was significantly lower at 6 months than at study enrolment in all three groups (p value not reported). Magnitude of reduction was comparable across groups: participants in the NRT group smoked 174.1±19.1 fewer cigarettes per person per month (pp/pm), those in the e-cigarette/NSP group smoked 156.3±19.9 fewer cigarettes pp/pm, and those in the e-cigarette/FBNPs group smoked 140.3±19.4 fewer cigarettes pp/pm.

In an RCT of adult individuals who smoke cigarettes who were interested in reducing cigarette smoking but not planning to quit, Cobb et al. (2021) compared changes in the number of CPD between participants randomized into one of four groups: non-nicotine e-cigarettes (i.e., 0 mg/mL nicotine), e-cigarettes containing 8 mg/mL nicotine, e-cigarettes containing 36 mg/mL nicotine, or cigarette substitute control for 24 weeks[82]. Within all groups, the estimated mean CPD significantly decreased over time compared with baseline ($p<0.0001$). In the unadjusted model of the ITT population, there were no significant differences at baseline in the estimated mean CPD between groups. However, the estimated mean CPD was significantly lower in all e-cigarette groups compared with the control group at all follow-up times starting at Week 1 through Week 24. After adjusting for demographic characteristics, including age, sex, race and ethnicity, and site, as well as other baseline measures, the estimated number of CPD was again significantly lower in all e-cigarette groups compared with the cigarette

substitute control group at all follow-up times, with the exception of the 8 mg/mL nicotine e-cigarette group at 12 weeks, which was not significantly different from the control group ($p<0.0083$) [82].

In a pragmatic, three-arm, parallel RCT by Walker et al. (2020), e-cigarette naïve individuals who smoke cigarettes who were eager to quit were randomized to receive either nicotine e-cigarettes in combination with NRT (i.e., nicotine patches), non-nicotine e-cigarettes in combination with NRT, or NRT only [70]. While the primary outcome was cigarette smoking abstinence, among participants who were still smoking at 6 months, the change in CPD from baseline was not different between the nicotine e-cigarette plus NRT group compared with NRT only group at any time point (i.e., 1, 3, or 6 months). However, the proportion of participants who reduced the number of CPD by at least 50% was significantly higher in the nicotine e-cigarette plus NRT group than in the NRT only group at 1 month (59% vs. 35%, RR=1.68, 95% CI: 1.31-2.16; $p< 0.0001$), 3 months (54% vs. 31%, RR=1.74, 95% CI: 1.32-2.28; $p< 0.0001$), and 6 months (44% vs. 26%, RR=1.70, 95% CI: 1.24-2.23, $p=0.0002$). In the non-nicotine and NRT group, the proportion of those who reduced smoking by at least 50% was 55% at 1 month, 46% at 3 months, and 38% at 6 months.

In an RCT by Hatsukami et al. (2020), adults who currently smoke cigarettes (smoking at least five CPD for the past year with a breath CO of at least 10 ppm or NicAlert test of level six, if CO was less than 10 ppm) in stable physical and mental health were randomized into four groups: administered e-cigarettes and told to use it, as well as smoke cigarettes *ad libitum* throughout the course of the trial (ad libitum e-cigarette group); administered e-cigarettes to use *ad libitum* and instructed to stop smoking cigarettes during the course of the trial (intent-to-quit e-cigarette group); administered NRT and instructed to stop smoking cigarettes during the course of the trial (intent-to-quit NRT group); and not administered any treatment (control group) [66]. Self-reported CPD was assessed at 1, 2, 4, 6, and 8 weeks follow-up. Participants in the *ad libitum* e-cigarette, intent-to-quit e-cigarette, and NRT groups all significantly reduced their CPD from baseline at each of the five time points (all $p<0.001$). In the control group, CPD

significantly reduced from baseline at Weeks 1 and 2 ($p<0.05$), but not significantly at the subsequent follow-up points. Median reduction in CPD was significantly different across all four groups, both at Week 4 ($p<0.001$) and at Week 8 ($p>0.001$) follow-up. At both time points, the intent-to-quit e-cigarette group reported the highest median CPD reduction (-12.3 [-31.0, 0.7] CPD; -12.2 [-31.0, 2.8] CPD), followed by the NRT group (-9.4 [-44.1, -1.8] CPD; -9.6 [-40.7, -0.9] CPD), *ad libitum* e-cigarette group (-2.3 [-25.4, 5.9] CPD; -2.7 [-25.4, 3.5] CPD), and the control group (0.0 [-12.1, 3.8] CPD; -0.7 [-12.0, 3.6] CPD). Moreover, median CPD reduction was significantly higher in the *ad libitum* e-cigarette group compared to the control group at both time points (both $p<0.001$); no significant differences in median CPD reduction were reported between the intent-to-quit e-cigarette group and the NRT group at either time point.

Pravettoni et al. (2016) reported a significant reduction in CPD among individuals who use e-cigarettes compared to individuals who do not use e-cigarettes at 1-month follow up (7.94±7.20 CPD versus 10.692±6.935 CPD ; $p<0.024$); baseline CPD was only reported for the overall sample (19.77±8.47 CPD) [99]. Moreover, it is unclear from this study (published as a conference abstract) whether the e-cigarette group combines both nicotine and non-nicotine e-cigarettes or includes only the nicotine e-cigarette group.

Lucchiari et al. (2020) [68] reported 6-month follow-up data from the same study as Pravettoni et al. (2016) [99]. Among all participants, baseline CPD was 19.17±6.14 CPD in the nicotine e-cigarette arm, 19.70±8.25 CPD in the non-nicotine e-cigarette arm, and 19.27±8.93 CPD in the control arm[68]. At 6 months, among participants who reported a reduction in cigarette smoking of at least 20%, those in the nicotine e-cigarette arm smoked 11.007±6.51 CPD, those in the non-nicotine arm smoked 14.026±7.92 CPD, and those in the control arm smoked 13.454±6.49 CPD. In an analysis of covariance (ANCOVA) using baseline CPD as a covariate, participants in the nicotine e-cigarette group smoked significantly fewer CPD than those in other groups ($F(2, 118) = 4.005$, $p<0.020$).

In an RCT by Lee et al. (2019), male adult individuals who smoke cigarettes (having smoked for at least 3 years and smoking 10 CPD over the past year) who were motivated to stop smoking entirely or to reduce their cigarette consumption were randomized to receive either e-cigarettes or NRT (nicotine gum) [76]. At the 12-week follow-up, the proportion of participants who successfully reduced their daily cigarette consumption was not significantly different between the e-cigarette and NRT groups (21.3% versus 20.0%, respectively; p=0.840); however, at the 24-week follow-up, the proportion of participants who successfully reduced their daily cigarette consumption was significantly higher in the e-cigarette group compared to the NRT group (41.3% versus 25.3%, respectively; p=0.038). Mean reduction in CPD was not significantly different between the e-cigarette and NRT groups at either the 12-week (11.06±7.03 CPD versus 12.6±5.65 CPD, respectively; p=0.509) or the 24-week follow-up (6.65±2.87 CPD versus 6.60±3.75 CPD, respectively; p=0.974).

In an RCT by Lee et al. (2018), preoperative elective surgery patients who currently smoke cigarettes (two or more CPD, and having smoked one or more cigarettes in 7 days prior to baseline) were screened using electronic chart review, and subsequently randomized to receive either an e-cigarette or an NRT (nicotine patch) [54]. In terms of reductions in CPD by 50% or greater, there were no significant differences between the two groups at all time points: day of surgery (RR=0.93, 95% CI: 0.55-1.56, p=1.0); 30-day follow-up (RR=0.90, 95% CI: 0.41-1.98, p=1.0); 8-week post-randomization (RR=1.75, 95% CI: 0.78-3.94, p=0.14); and 6-month follow-up (RR=0.62, 95% CI: 0.31-1.24, p=0.43). Similarly, mean CPD reduction was not significantly different between the two groups at: day of surgery (MD=10%, 95% CI: 42% to -22%, p=0.52); 30-day follow-up (MD=-18%, 95% CI: 22% to -61%, p=0.39); 8-week post-randomization (MD=17%, 95% CI: 45% to -12%, p=0.23); and 6-month follow-up (MD=-23%, 95% CI: 8% to -55%, p=0.14).

One RCT reported data from the ongoing lung cancer screening trial (COSMOS II) [99]. This study was part of three studies from the same ongoing trial, each reporting cigarette smoking reduction data from

different follow-up points among adult individuals who smoke cigarettes (55 years or older) who reported having smoked 10 or more CPD for at least the past 10 years. Participants were randomly allocated to either: a nicotine e-cigarette plus support trial arm and administered an e-cigarette kit with twelve 10-mL liquid cartridges (8 mg/mL nicotine concentration); a non-nicotine e-cigarette plus support trial arm and administered an e-cigarette kit with twelve 10-mL liquid cartridges (0 mg/mL nicotine concentration); and, a support only trial arm.

In an RCT by Adriaens et al. (2014), adult individuals who smoke cigarettes (at least 10 CPD for at least the past 3 years) unwilling to quit smoking (but willing to try a less unhealthy alternative) and with no prior use of e-cigarettes were randomized to be administered an e-cigarette or to not be administered an e-cigarette [89]. Although there were two intervention arms evaluating two different models of e-cigarettes, only the data combining the two arms into a single intervention group were considered for the purposes of this review. At the Week 7/8 follow-up period, 22% of the e-cigarette group reduced their daily cigarette consumption by at least 50%, and 13% of the e-cigarette group reduced their daily cigarette consumption by at least 80%; no participants in the non-e-cigarette group reduced their daily cigarette consumption by 50 or 80%. Among the individuals who use e-cigarettes, mean CPD decreased by 77% from baseline to Week 7/8 follow up (20.38±8.01 CPD versus 4.7±6.5 CPD, respectively).

Change in Cigarette Smoking Quantity/Frequency (Non-Regular E-Cigarette Use)

Thirteen non-RCT adjusted studies were identified that investigated the association of non-regular e-cigarette use and change in cigarette smoking quantity/frequency. Three of these studies were secondary analyses of RCTs [56, 72, 88], seven were longitudinal studies [59, 67, 69, 77, 92, 97, 102], and three were cross-sectional studies [49, 79, 98]. No RCT studies met inclusion criteria for this outcome. However, summary characteristics and the results of the 13 non-RCT studies are provided in **Supplemental Section 18**.

Quantitative Synthesis of Best Available Evidence

Data Synthesis and Analysis

All meta-analyses were performed using results from RCTs, as these studies were considered the highest level of evidence. Complete details on the meta-analysis data sources, study selection, data extractions, and study quality are provided in **Supplemental Section 19** (all relevant code is publicly available at https://zenodo.org/doi/10.5281/zenodo.11287077).

Abstinence from/quitting smoking Cigarettes

Six-Month Continuous Abstinence, Non-nicotine E-cigarette Versus NRT

Two studies compared cigarette smoking abstinence at 6-month follow-up between e-cigarette use and NRT use. The study by Lee et al. (2019) [76] used nicotine gum for their NRT group, while the study by Bullen et al. (2013) [100] used nicotine patches. Lee et al. (2019) [76] evaluated "0.01 mg/mL" nicotine e-cigarettes, which were considered to be non-nicotine e-cigarettes, while Bullen et al. (2013) [100] reported the use of non-nicotine e-cigarettes as their intervention (**Figure 2**).

Among individuals who smoke cigarettes who were randomized to receive non-nicotine e-cigarettes at baseline compared with individuals who smoke cigarettes randomized to receive NRT, the RRs for continuous abstinence at 6-month follow-up were 0.76 (95% CI: 0.43, 1.34) for Lee et al. (2019) [76] and 0.34 (95% CI: 0.04, 2.55) for Bullen et al. (2013) [100]. Pooled results favored the NRT group compared to non-nicotine e-cigarettes in terms of abstinence, but CIs included no difference (RR=0.72, 95% CI: 0.42-1.24). There was no heterogeneity noted between included studies (I^2=0%).

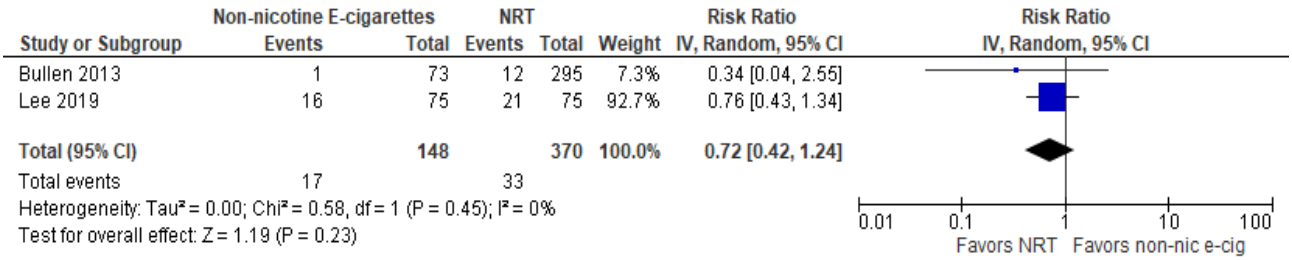


Figure 2: Forest Plot, 6-Month Continuous Abstinence, Non-Nicotine E-Cigarette Versus NRT

Abstinence From/Quitting Cigarette Smoking, Nicotine E-cigarettes Versus NRT

Four studies presented results for the association of nicotine e-cigarette use compared to NRT use—choice of nicotine patch, chewing gum, nasal spray, microtab, inhalator, or mouth spray in Myers Smith et al. (2022) [107], over the counter NRT (type not specified) in Russell et al. (2021) [86], nicotine gum or lozenge in Hatsukami et al. (2020) [66], and nicotine patches in Bullen et al. (2013) [100]—and cigarette smoking abstinence. The study by Russell et al. (2021) [86] included two nicotine e-cigarette liquid groups, freebase nicotine e-liquid and nicotine salt e-liquid. The two nicotine e-cigarette liquid groups were combined as the nicotine e-cigarette group for Russell et al. (2021) [86] in the meta-analysis.

Among individuals who smoke cigarettes randomized to receive nicotine e-cigarettes at baseline compared with individuals who smoke cigarettes randomized to receive NRT, the RRs for cigarette smoking abstinence at follow-up were 6.40 (95% CI: 1.50-27.30) for Myers Smith et al. (2022) [107], 1.29 (95% CI : 0.89-1.86) for Russell et al. (2021) [86], 1.92 (95% CI : 1.07-3.47) for Hatsukami et al. (2020) [66], and 1.02 (95% CI: 0.47-2.23) for Bullen et al. (2013) [100]. Results of the meta-analysis favored the nicotine e-cigarette group versus the NRT group; however, the CIs included no difference (RR=1.59, 95% CI: 0.98-2.57) (**Figure 3)**. The model had moderate heterogeneity with an I^2 value of 51%.

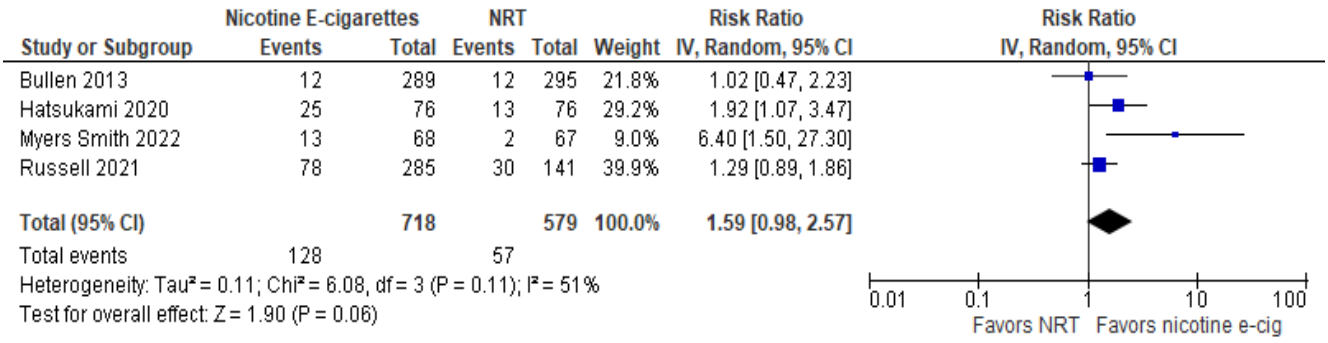


Figure 3: Forest Plot, Abstinence From/Quitting Cigarette Smoking, Nicotine E-Cigarettes Versus NRT

Abstinence From/Quitting Cigarette Smoking Among Individuals Who Use E-Cigarettes, Longest Follow-Up Period

Six studies presented results for the association of e-cigarette use compared to no e-cigarette use, and continuous cigarette smoking abstinence at varying follow-up points [32, 51, 64, 68, 78, 89]. Two studies reported data from the same study and were therefore not pooled in a meta-analysis to avoid double counting of participants [68, 78]. Masiero et al. (2019) [78] reported results from 3-month follow-up for the same study as Lucchiari et al. (2020) [68], who reported results at 6-month. The study by Foulds et al. (2022) [32] included two nicotine e-cigarette groups: one group received e-cigarettes containing 8mg/mL of nicotine and the other group received e-cigarettes containing 36mg/mL of nicotine. The two nicotine e-cigarette groups were combined as the nicotine e-cigarette group for Foulds et al. (2022) [32] in the meta-analysis.

The RRs for cigarette smoking abstinence at the longest follow-up period were: 3.50 (95% CI: 0.81-15.17) at 6-month follow-up for Foulds et al. (2022) [32], 4.73 (95% CI: 0.56-39.88) at 6-month follow up for Eisenberg et al. (2020) [64], 1.86 (95% CI: 0.79-4.38) at 6-month follow-up for Lucchiari et al. (2020) [68], 6.11 (95% CI: 0.33-13.24) at 12-month follow-up for Halpern et al. (2018) [51], and 12.18 (95% CI: 0.76-194.94) at 8-week follow-up for Adriaens et al. (2014) [89] among participants in the e-cigarette group compared to those in the control group . The results of the meta-analysis found a significant association between e-cigarette use and cigarette smoking abstinence (RR=2.73, 95% CI: 1.15-6.50) (**Figure 4**). No heterogeneity was detected (I^2=0%).

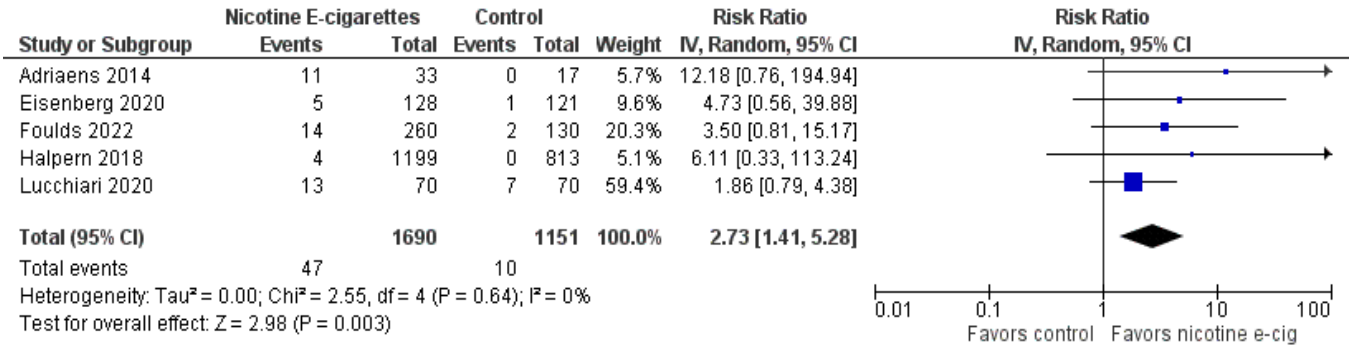


Figure 4: Forest Plot, Abstinence From/Quitting Cigarette Smoking at Longest Follow-Up Period

Abstinence From/Quitting Cigarette Smoking Among Individuals Who Use E-Cigarettes, 6-Month Follow-Up

Four studies reported cigarette smoking abstinence at 6-month follow-up and were pooled in a meta-analysis [32, 51, 64, 68]. The study by Foulds et al. (2022) [32] included two nicotine e-cigarette groups, 8mg/mL and 36mg/mL, which were combined as the nicotine e-cigarette group in the meta-analysis.

Among individuals who smoke cigarettes randomized to receive e-cigarettes at baseline compared with individuals who smoke cigarettes randomized to the control group, the RRs for cigarette smoking abstinence at 6-month follow-up were 3.50 (95% CI 0.81-15.17) for Foulds et al. (2022) [32], 4.73 (95% CI 0.56-39.88) for Eisenberg et al. (2020) [64], 1.86 (95% CI : 0.79-4.38) for Lucchiari et al. (2020) [68], and 8.14 (95% CI: 1.06-62.45) for Halpern et al. (2018) [51]. The results of the meta-analysis showed that individuals who use e-cigarettes had a significantly higher rate of abstinence from smoking at 6 months compared with the control group (RR=2.70, 95% CI: 1.39-5.23) (**Figure 5**). No heterogeneity was detected (I^2=0%).

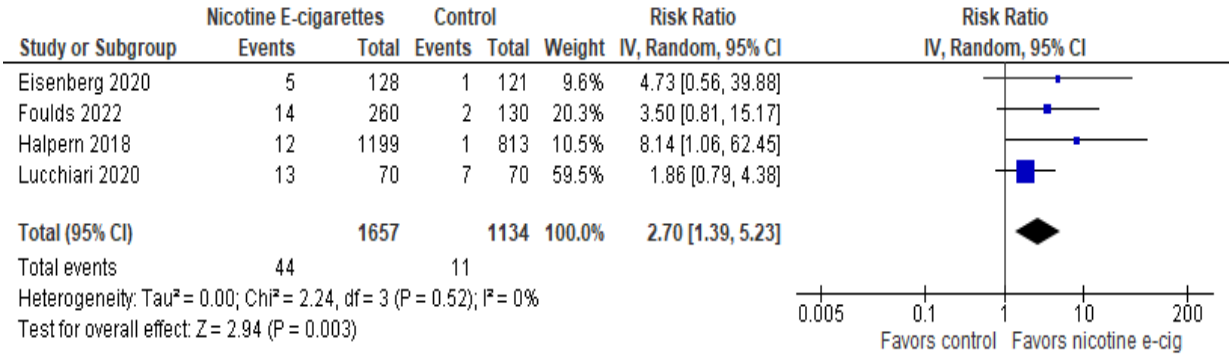


Figure 5: Forest Plot, Abstinence From/Quitting Cigarette Smoking, 6-Month Follow-Up

Abstinence From/Quitting Cigarette Smoking Among Individuals Who Use E-Cigarettes, 3-Month Follow-up Period

Three studies reported cigarette smoking abstinence at 3-month follow-up and were pooled in a meta-analysis [51, 64, 78]. The RRs for cigarette smoking abstinence at 3-month follow-up were 5.67 (95% CI 0.69-46.43) for Eisenberg et al. (2020) [64], 2.50 (95% CI : 1.03-6.07) for Masiero et al. (2019) [78], and 6.78 (95% CI : 1.59-28.93) for Halpern et al. (2018) [51] among individuals who smoke cigarettes randomized to the e-cigarette group at baseline compared with those randomized to the control group. The results of the meta-analysis found a significant association between e-cigarette use and cigarette smoking abstinence (RR=3.49, 95% CI: 1.71-7.12) (**Figure 6**), with no heterogeneity detected (I^2=0%).

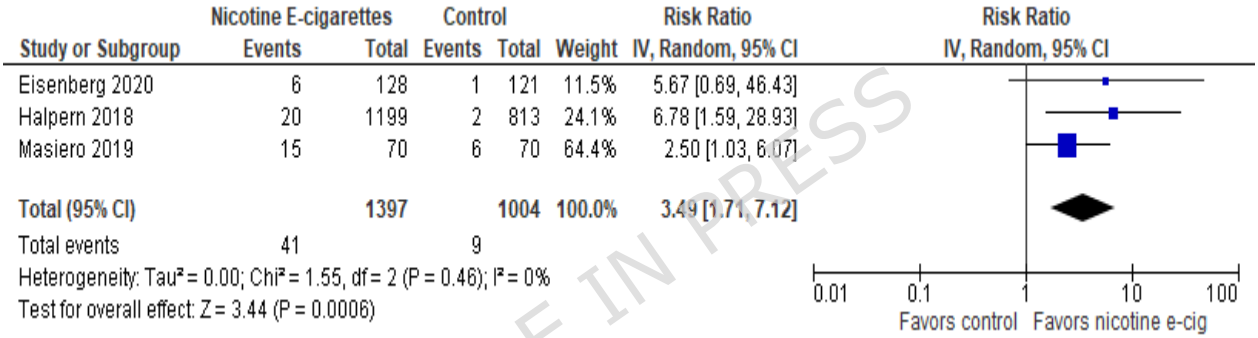


Figure 6: Forest Plot, Abstinence From/Quitting Cigarette Smoking, 3-Month Follow-Up

Change in Cigarette Smoking Quantity/Frequency

Change in Cigarette Smoking Quantity/Frequency Among Individuals Who Use E-Cigarettes at Longest Follow-up

Three studies evaluated a change in cigarette smoking quantity/frequency and were pooled in a meta-analysis [45, 64, 78]. The longest follow-up period was 3 months in the study by Masiero et al. (2019) [78], and 6 months in the studies by Yingst et al. (2022) [45] and Eisenberg et al. (2020) [64]. Among the three studies, the studies by Eisenberg et al. (2020) [64] and Masiero et al. (2019) [78] reported the mean (±SD) change in CPD between baseline and follow-up, while the study by Yingst et al. (2022) [45] reported the mean CPD at baseline and follow-up. For the study of Yingst et al. (2022) [45], the MD for each group was calculated by taking the difference between baseline and follow-up. After computing the MD, an

imputation of the SD for the mean change between baseline and follow-up was required for both nicotine e-cigarette and control groups. Given that the reported values from Eisenberg et al. (2020) [64] did not have the necessary inputs needed to impute the SD for the mean change for the study by Yingst et al. (2022)[45] through a direct approach using methods by Follman et al. (1992) [109] and Abrams et al. (2005) [110], SD was imputed using information available in the study by Masiero et al. (2019) [78]. Correlation factors (corr) obtained from both e-cigarette and control groups, as well as corr proposed by Fu & Holmer [111] were tested. Across the three corr values used, similar results were retrieved (results are available in **Supplemental Section 19**). The corr proposed by Fu and Holmer was used in the main meta-analysis.

The MD for reduction in CPD among individuals who use e-cigarettes compared with individuals who do not use e-cigarettes was 4.46 (95% CI: 2.78-6.13) at the 6-month follow-up in Yingst et al. (2022), 5.20 (95% CI: 2.83-7.57) at the 6-month follow-up in Eisenberg et al. (2020) [64], and 2.60 (95% CI: -0.12-5.32) at the 3-month follow-up in Masiero et al. (2019) [78]. **Figure 7** presents the pooled result across all three studies showing a significantly higher mean reduction in CPD for the e-cigarette group compared with the control group (MD 4.27, 95% CI: 3.02-5.53). The model had low heterogeneity with an I^2 value of 4%.

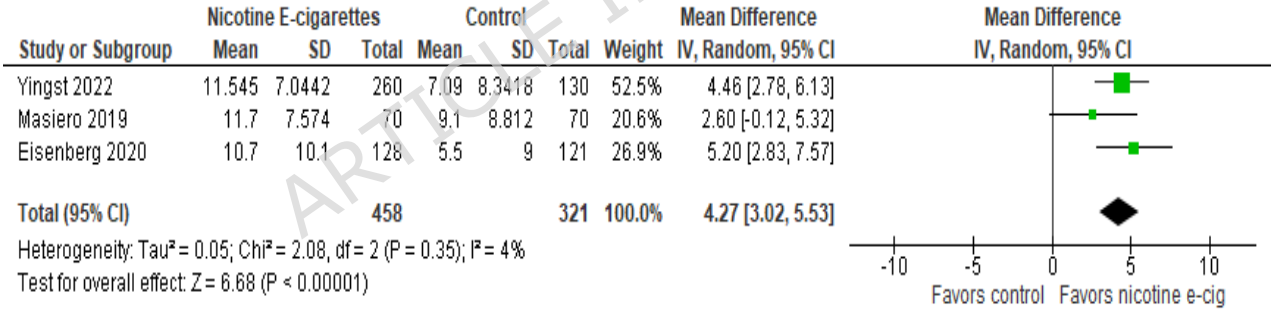


Figure 7: Forest Plot, Reduction in Smoking Quantity/Frequency, Longest Follow-Up

Results were robust in a sensitivity analysis including only studies that reported the mean change in CPD [64, 78] showing a significantly higher reduction in CPD in the e-cigarette compared with control group (MD 3.99 CPD, 95% CI 1.45-6.53) (**Figure 8**). The model had moderate heterogeneity with an I^2 value of 50% after removing the study by Yingst et al. (2022) [45] with imputed SD.

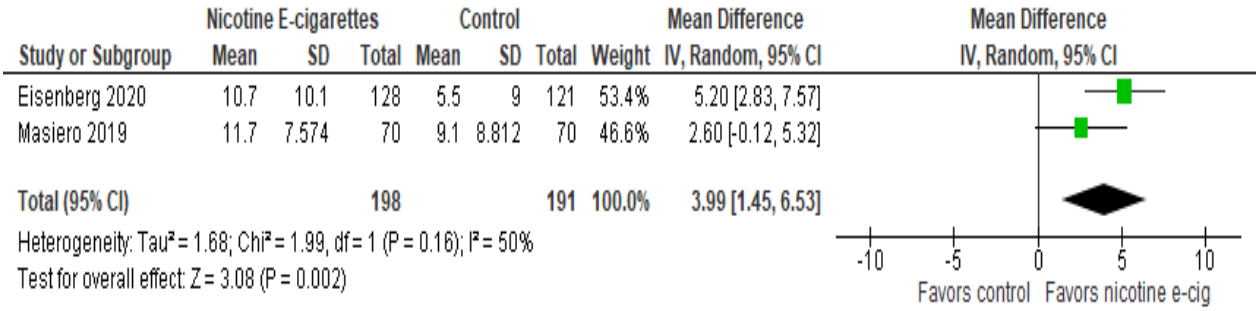


Figure 8: Forest Plot, Reduction in Smoking Quantity/Frequency at Longest Follow-Up, Sensitivity Analysis Including Only Studies Reporting Mean Change in CPD

Change in Cigarette Smoking Quantity/Frequency Among Individuals Who Use E-Cigarettes, 6-Month Follow-Up

Two studies evaluated a change in cigarette smoking quantity/frequency at 6 months and were pooled in a meta-analysis [45, 64]. The study by Eisenberg et al. (2020)[64] reported the mean (±SD) change in CPD between baseline and follow-up, while the study by Yingst et al. (2022) [45] reported the mean CPD at baseline and follow-up. For the study by Yingst et al. (2022) [45], the MD for each group was calculated by taking the difference between baseline and follow-up, while the SD was imputed using methods described above. The MD for reduction in CPD among individuals who use e-cigarettes compared with individuals who do not use e-cigarettes was 4.46 (95% CI: 2.78-6.13) in Yingst et al. (2022) [45], and 5.20 (95% CI: 2.83-7.57) in Eisenberg et al. (2020) [64]. **Figure 9** presents the pooled result across all three studies showing a significantly higher mean reduction in CPD for the e-cigarette group compared with the control group (MD 4.70, 95% CI: 3.34-6.07). No heterogeneity was detected (I^2=0%).

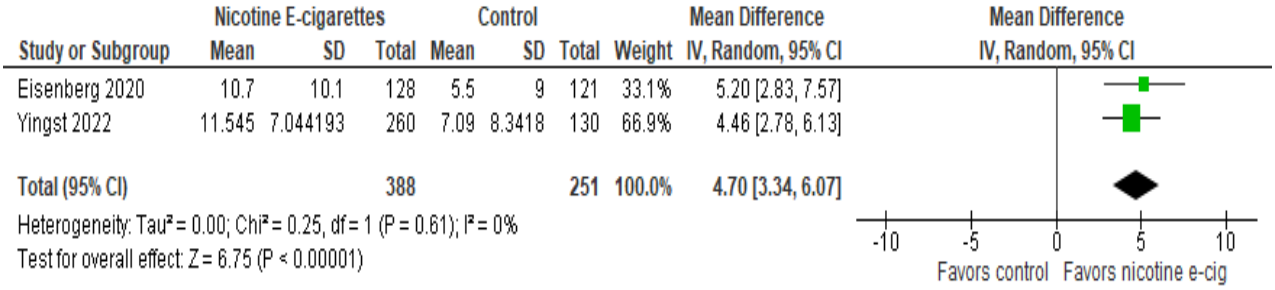


Figure 9: Forest Plot, Reduction in Smoking Quantity/Frequency, 6-Month Follow-Up

Change in Cigarette Smoking Quantity/Frequency Among Individuals Who Use E-Cigarettes, 3-Month Follow-Up

Two studies evaluated a change in cigarette smoking quantity/frequency at 3 months and were pooled in a meta-analysis [64, 78]. The MD for reduction in CPD among individuals who use e-cigarettes compared with individuals who do not use e-cigarettes was 5.60 (95% CI: 3.29-7.91) for the Eisenberg et al. (2020) study and 2.51 (95% CI: -0.22-5.23) for the Masiero et al. (2019) study. The results of the meta-analysis showed that the reduction in CPD was significantly greater among individuals who use e-cigarettes compared with individuals who do not use e-cigarettes (MD=4.14, 95% CI: 1.11-7.17) (**Figure 10**Error! Reference source not found.). The model showed moderate heterogeneity (I^2=65%).

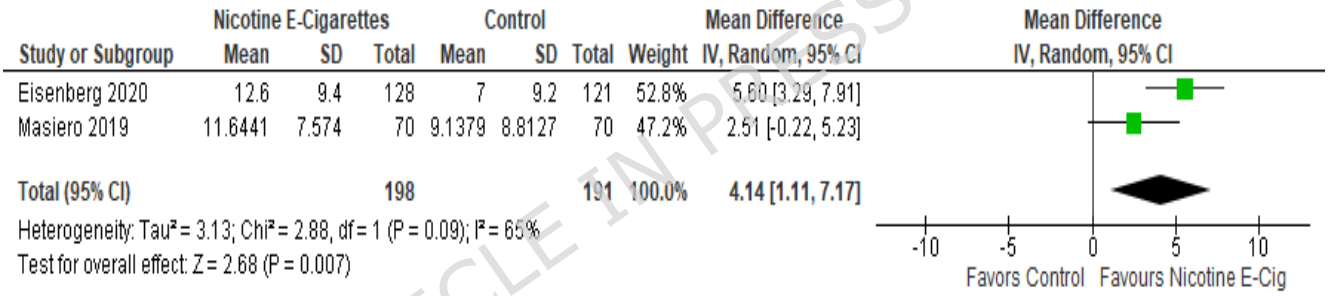


Figure 10: Forest Plot, Reduction in Smoking Quantity/Frequency, 3-Month Follow-Up

Change in Cigarette Smoking Quantity/Frequency Among Individuals Who Use E-Cigarettes, 2-Month Follow-Up

Two studies evaluated a change in cigarette smoking quantity/frequency at 2 months and were pooled in a meta-analysis [64, 78]. The MD for reduction in CPD among individuals who use e-cigarettes compared with individuals who do not use e-cigarettes was 6.90 (95% CI: 4.55-9.25) for the Eisenberg et al. (2020) study and 2.20 (95% CI: -0.62-5.02) for the Masiero et al. (2019) study. The results of the meta-analysis significantly favored e-cigarettes (MD=4.62, 95% CI: 0.01-9.22) (**Figure 11**Error! Reference source not found.). The model showed high heterogeneity (I^2=84%).

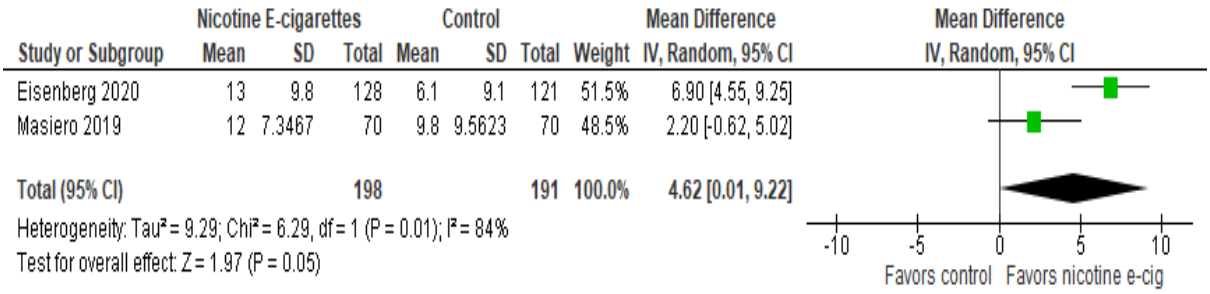


Figure 11: Forest Plot, Reduction in Smoking Quantity/Frequency, 2-Month Follow-Up

Change in Cigarette Smoking Quantity/Frequency Among Individuals Who Use E-Cigarettes, 1-Month Follow-up

Two studies evaluated a change in cigarette smoking quantity/frequency at 1 month and were pooled in a meta-analysis[64, 78]. The mean difference for reduction in CPD among individuals who use e-cigarettes compared with individuals who do not use e-cigarettes was 7.80 (95% CI: 5.46-10.14) in Eisenberg et al. (2020) and 3.00 (95% CI: 0.36-5.64) in Masiero et al. (2019). The results of the meta-analysis significantly favored e-cigarettes (MD=5.44, 95% CI 0.74-10.14) (**Figure 12**). The model showed high heterogeneity (I^2=86%).

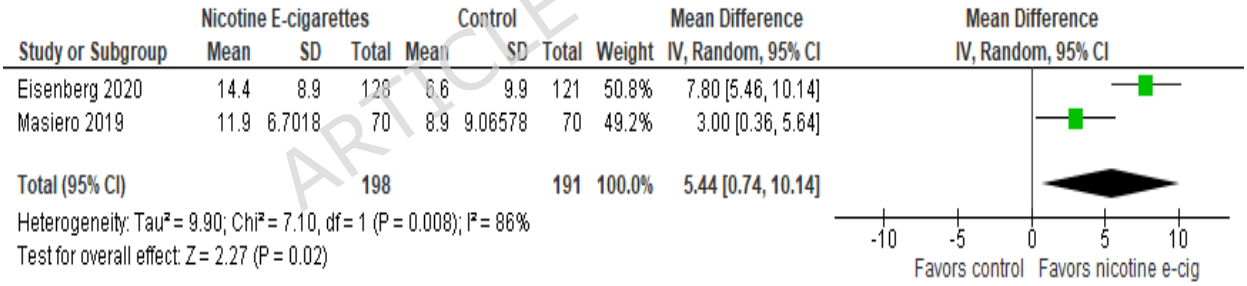


Figure 12: Forest Plot, Reduction in Smoking Quantity/Frequency, 1-Month Follow-Up

Strength of Evidence

The overall SOE among the RCT data regarding the association between e-cigarette use and both abstinence from/quitting cigarette smoking and change in cigarette smoking quantity/frequency were graded "high". Since only one RCT evaluated duration of abstinence from cigarette smoking, an SOE grade could not be attributed to this outcome measure [32]. Among the adjusted data, the SOE regarding the association between e-cigarette use and abstinence from/quitting cigarette smoking, duration of

abstinence from cigarette smoking, and change in cigarette smoking quantity/frequency were graded as "high", "low", and "moderate", respectively. The SOE domain score table and the SOE and CQ ratings summary table for RCT, adjusted, and unadjusted data are presented in **Supplemental Section 10.**

DISCUSSION

This systematic review identified 53 "good" and 5 "excellent" quality studies (according to the Downs and Black quality metrics[26]) reporting on the association between e-cigarette use and individuals who smoke cigarettes but abstain/quit or report changes in cigarette smoking quantity/frequency. Of these, 22 were RCTs, while a further 52 studies presented data controlled for age, gender, and race/ethnicity.

Two meta-analyses were identified that compared e-cigarettes and NRT in terms of cigarette smoking abstinence. One meta-analysis (evaluating non-nicotine e-cigarettes) included two studies with 518 total participants, and the second (evaluating nicotine-containing e-cigarettes) included four studies with 1,297 total participants. Despite the limited number of studies and non-significant findings in both meta-analyses, smoking abstinence following administration of non-nicotine e-cigarettes or NRT directionally favored NRT (RR=0.72, 95% CI: 0.42-1.24), whereas smoking abstinence following administration of nicotine-containing e-cigarettes or NRT directionally favored nicotine-containing e-cigarettes (RR=1.59, 95% CI: 0.98-2.57). These findings are consistent with the living systematic review by Hartmann-Boyce et al. (2022) and the recent systematic review by Grabovac et al. (2021), both of which included a meta-analysis of cigarette smoking abstinence between nicotine-containing and non-nicotine e-cigarettes, finding that nicotine-containing e-cigarettes were significantly associated with cigarette smoking abstinence [14, 112]. In contrast to our review, the systematic review by Hartmann-Boyce et al. (2022) reported a significant association between e-cigarette use and smoking cessation compared with NRT (RR=1.63, 95% CI: 1.30-2.04) [14].

Three meta-analyses, each for different follow-up durations comparing nicotine-containing e-cigarettes to behavioral controls were conducted—follow-up duration (varying across studies according to longest duration reported; five studies), 6-month follow-up (four studies), and 3-month follow-up (three studies). The sample sizes were comparatively larger than those in the meta-analyses comparing nicotine and non-nicotine e-cigarettes versus NRT and included 2,841 total participants (for the analysis of longest follow-up duration), 2,791 participants for the 6-month follow-up analysis, and 2,401 total participants for the 3-month follow-up. The meta-analyses of the longest follow-up duration (RR=2.73, 95% CI: 1.15-6.50), 6-month follow-up (RR=2.70, 95% CI: 1.39-5.23), and 3-month follow-up (3.49, 95% CI: 1.71-7.12) all showed a statistically significant association between nicotine e-cigarettes and cigarette smoking abstinence. These findings are consistent with those from a systematic review and meta-analysis by Hartmann-Boyce et al. (2022), which found that nicotine-containing e-cigarettes were statistically significantly associated with higher rates of cigarette smoking cessation, compared to behavioral support/no support controls (RR=2.66, 95% CI: 1.52-4.65) [14].

These findings from randomized controlled trials are further supported by recent population-level evidence reported by Foxon et al. (2024). In this study Foxon and colleagues analyzed data from the National Health Interview Survey (1990 to 2022) [113]. The results of this analysis observed a significantly lower cigarette smoking prevalence in this current e-cigarette era based on e-cigarette era trends, with discrepancies growing as e-cigarette use prevalence increased, particularly among younger adults aged 18-34 [113]. The observed association between increasing e-cigarette use prevalence and decreasing cigarette smoking prevalence reported by Foxon et al. (2024) further supports a possible population-level displacement of combustible cigarettes by e-cigarettes. This is consistent with potential switching and diversion effects reported across the evidence base.

Of the studies evaluating regular e-cigarette use and abstinence from/quitting cigarette smoking that were *not* included in the meta-analysis, results were mixed. Among the eight RCTs not included in the

meta-analysis, the RCT by Tattan-Birch et al. (2022) compared e-cigarettes and varenicline to varenicline alone and found no significant difference in the rate of smoking abstinence in the main analysis; however, after adjusting for nonadherence and contamination, e-cigarette use was associated with significantly higher rates of abstinence [46]. Walker et al. (2020) reported that e-cigarette use in combination with NRT was associated significantly higher abstinence rates at 1,3, and 6 months than NRT alone [70]. In a feasibility RCT by Holliday et al. (2019), the prevalence of eCO-verified abstinence was numerically higher among individuals who use e-cigarettes compared with those who do not at 4 months [74]. In another RCT, Ioakeimidis et al. (2018) compared e-cigarettes to varenicline and found a significantly lower rate of abstinence associated with e-cigarettes [52].

Of the four RCT studies not included in the meta-analyses due to their inclusion of vulnerable populations, three reported that e-cigarette use was associated with abstinence from cigarette smoking. In an RCT among participants diagnosed with schizophrenia, schizoaffective disorder or bipolar disorder, Pratt et al. (2022) reported a higher proportion of participants smoking zero (0) CPD among those using e-cigarettes compared with those who do not [43]. In an RCT among population with a diagnosis of HIV, HCV, or those receiving opioid substitution therapy, Morphett et al. (2022) reported a higher rate of abstinence among those using e-cigarettes and nicotine patches compared to those using patches only [41]. The RCT by Hajek et al. (2022) compared e-cigarettes to nicotine patches in a sample of pregnant individuals who smoke cigarettes and found that prolonged quitting rates at the end of pregnancy were not significantly different between the two groups in the analysis of the ITT population [33]. However, when participants who used non-allocated products were excluded, abstinence rates were significantly higher in the e-cigarette group than in the nicotine patch group [33]. In contrast, Lee et al. (2018) consistently found no significant association between e-cigarette use and cigarette smoking reductions in a sample of surgery patients before and after their scheduled surgeries. However, given the limited scope of this study, these results may not be generalizable to the greater population [54].

These RCT and population-level findings similarly mirror findings recently reported in an umbrella review by O'Leary et al. (2025) that synthesized evidence across 11 meta-analyses from eight systematic reviews with moderate to high AMSTAR2 ratings encompassing 24 RCTs. Specifically, the Vote Counting of Direction of Effect analytic results found that in 8 of the 11 comparisons, e-cigarettes were more effective than other smoking cessation treatments or no treatment [114]. Among the 11 comparison, 3 showed no statistically difference in effectiveness [114]. Further, the relative risk calculations reported by O'Leary et al. (2025) for all 11 analyses favored e-cigarettes for cessation outcomes [114]. However, notably, none of the reviews synthesized by O'Leary et al (2025) concluded that e-cigarettes were statistically significantly less effective than any treatment or no treatment. This synthesis provides further convergent evidence for the effectiveness of e-cigarettes as a smoking cessation aid .

Meta-analyses investigating the association between nicotine e-cigarettes and changes in cigarette smoking quantity/frequency compared to no e-cigarette intervention at four different follow-up times were possible. Meta-analyses were implemented for the longest follow-up time (3 studies, 779 total participants), follow-up at 6 months (2 studies; 639 total participants), 3 months (2 studies; 389 total participants), 2 months (2 studies; 389 total participants), and 1 month (2 studies; 389 total participants). Despite the limited number of studies included in each analysis, pooled results consistently demonstrated that e-cigarette use was associated with a greater reduction at all follow-up periods.

The current systematic review exhibited three major strengths. The first was its comprehensive search methodology, which yielded a large number of available studies for review. In addition, the current review had a clearly defined PICOS (Population, Intervention, Control groups, Outcomes of interest, and Study designs), which assured the identification of the strongest evidence relevant to the research question. Lastly, the restriction of the meta-analyses to include only RCTS while the qualitative syntheses only include non-RCTs allowed this for a thorough and methodologically sound synthesis of

the literature regarding the research question, “Are there any potential associations between e-cigarette use among individuals who smoke cigarettes and changes in continued cigarette smoking?”

In spite of these strengths, the studies included in the review are subject to several limitations, namely, (1) dissimilarities in baseline definition for “cigarette smoker” between studies, (2) variations in the definition and reason for using e-cigarettes, (3) vast differences in the use topography, extent of use, and types of e-cigarettes, (4) inadequate length of time to observe significant changes in behavior, and (5) differences between studies in the definition of the outcomes.

An important limitation of this review is the inability to systematically distinguish between individuals using e-cigarettes exclusively and individuals who continue to smoke cigarettes while using e-cigarettes across the included studies. This distinction between exclusive and dual use may represent distinct behavioural phenotypes with different dependence profiles, switching trajectories, and cessation outcomes. The heterogeneity in how primary studies defined, measured, and reported dual use versus exclusive e-cigarette use precluded stratified analyses by user type in our meta-analyses. This was not specified *a priori* in our registered protocol, as our research question focused on the association between e-cigarette use and smoking cessation outcomes rather than dependence phenotypes or user trajectories. However, we acknowledge that collapsing these groups may introduce heterogeneity into our effect estimates and potentially obscure differential effects.

The observed associations between e-cigarette use and smoking cessation in our meta-analyses likely represent an aggregate effect across both those who exclusively use e-cigarettes (who may have completely switched) and those who may be in various stages of transitioning away from cigarettes or maintaining concurrent use. Future research should prospectively track and separately analyse outcomes for individuals exclusively using e-cigarettes versus those using e-cigarettes while smoking cigarettes to better understand the specific pathways and effectiveness of e-cigarettes as cessation aids.

Additionally, longitudinal studies that capture transitions between dual use and exclusive e-cigarette use over time would provide valuable insights into switching trajectories and their relationship to sustained smoking abstinence.

Moreover, while this systematic review is considered to be robust, based on its strict adherence to the PICOS, AMSTAR 2, and PRISMA methodological frameworks—which was intended to minimize biases previously seen in other reviews—limitations of this review may include a smaller number of included studies (compared with other published systematic reviews), which may have led to a smaller sample size in the meta-analyses performed. Although this systematic review yielded a relatively high number of studies included in its search compared with other similar systematic reviews, this was significantly reduced at the meta-analysis stage, where included studies were limited to RCTs. Consequently, the small number of included studies for the 11 meta-analyses reported here limited the ability for sub-analyses of the data.

Another potential limitation stems from the exclusion of non-English language publications, which may potentially have omitted relevant results, and introduced bias. However, there is no consensus to-date on the impact of excluding non-English studies in systematic reviews and meta-analyses [115, 116]. Further, there is the potential concern that our search timeframe may not be up-to-date because many review publications related to smoking cessation have been disseminated since 2023 [117-126]. However, among these ten example publications, only 4 surpassed the timeframe of this review [117, 120, 122, 126]. The range of included studies from this example collection of studies included 5 studies [119] to 400 studies [118] (NOTE: This was an umbrella review across numerous health outcomes) with a median number of 54 included studies, compared to the 214 reported on in this review. Finally, in such a rapidly evolving product category, in which the pace of innovation and development has accelerated over the past decade, the effects of specific products (and generations of products) may produce varying degrees of impact on cessation. Moreover, these effects may manifest differently, depending on the definition of smoking

cessation outcomes applied. While this may limit the ability to draw generalizable conclusions, it was necessary to ensure a comprehensive body of results was collected and, as such, was largely unavoidable.

Conclusion

In conclusion, there is strong evidence to suggest that the use of nicotine-containing e-cigarettes may support cigarette smoking cessation among regular, established individuals who smoke cigarettes. Similarly, there is some evidence to suggest that regular e-cigarette use may support reductions in cigarette smoking quantity or frequency. Further RCTs and robust, real-world observational studies are required to solidify the associations between e-cigarette use and increased cigarette smoking cessation, as well as cigarette smoking reduction.

DECLARATIONS

Ethics Statement: Not applicable.

Consent for Publications: Not applicable.

AUTHORS' CONTRIBUTIONS: MMK conceived the study. MMK, IS, RDM, TB, and JC collected and analysed project data. MMK, IS, and RDM 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.

FUNDING: All study activities were executed by providers external to RAI Services Company (Thera-Business), who were financially compensated for services according to contractual terms with RAI Services Company. RAI Services Company is a wholly owned subsidiary of Reynolds American Inc., whose operating companies manufacture and market tobacco products. The conception, analysis, and writing for this manuscript was a collaboration between Thera-Business and RAI Services Company.

COMPETING INTERESTS: Dr. Kim is a former full-time employee of RAI Services Company, a wholly owned subsidiary of Reynolds American Inc.

ETHICS STATEMENT: Review and/or approval by an ethics committee was not needed for this study because all data are publicly available. Informed consent was not required for this study because the data synthesized and reported here are from publicly available references.

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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Generative AI and AI-assisted technologies were not used in any part of this submission.

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Table 1: Summary Characteristics of RCTs for Abstinence from/quitting smoking Cigarettes among Regular Individuals Who Use E-Cigarettes (n=8)

Citations	Study design	Definition of e-cig user	Definition of e-cig non-user	Definition of study outcome
RCTs				
[33]	RCT	Pregnant individuals who smoke cigarettes received refillable e-cigs for smoking cessation, and who might also have used NRTs as non-allocated products	Pregnant individuals who smoke cigarettes received NRT for smoking cessation, and who might have also used refillable e-cigs as non-allocated products	Validated prolonged abstinence (primary end-point): Prolonged abstinence from smoking from 2 wks after the target quit date until the end of pregnancy, defines as per Russell Standard (up to 5 lapses allowed with no smoking at all during the previous week at the time of final follow-up). Abstinence was verified using salivary cotinine <10 ng/ml for those reporting using any nicotine product, or by salivary anabasine <1 ng/ml or CO level <8 ppm for those reporting current use of e-cigs or NRT. Self-reported prolonged abstinence: Smoking status/abstinence at the end of pregnancy Self-reported PPA: Self-reported not smoking for ≥7 days at 4 wks and at the end of pregnancy Validated PPA: PPA at the end of pregnancy
[74]	RCT	Use e-cigs: Participants were provided with an approximately 2-week supply of e-liquid with a choice of flavor and nicotine strength, and information on where to buy more. Participants also received smoking cessation advice.	Individuals who do not use e-cigarettes: Participants received smoking cessation advice.	eCO- or salivary cotinine/salivary anabasine-verified abstinence at 4 weeks
[52]	RCT	Individuals who smoke cigarettes (≥10 CPD and expressing motivation to quit) randomized to the e-cig (12 mg/ml nicotine) group	Individuals who smoke cigarettes (≥10 CPD and expressing motivation to quit) randomized to the varenicline group	7-day PPA at 24-week follow-up
[54]	RCT	Treatment arm where individuals who smoke cigarettes (≥2 CPD, smoked ≥1 in last 7 days) provided with e-cigs	Treatment arm where individuals who smoke cigarettes (≥2 CPD, smoked	Smoking cessation for at least 48 hours and confirmed with eCO levels ≤10ppm

Citations	Study design	Definition of e-cig user	Definition of e-cig non-user	Definition of study outcome
			≥1 in last 7 days) provided with NRT (nicotine patch)	
[41]	RCT	E-cig + NRT users: Participants received e-cigs (defined as nicotine vaping products), nicotine patches, and referral to Quitline	Individuals who do not use e-cigarettes (NRT): Participants received combination NRT (patch and choice of gum or lozenge) and referral to Quitline	Not having smoked a puff at 3 months, evaluated at 6 months
[43]	RCT	Individuals who smoke cigarettes (regular smoking for ≥5 yrs, currently smoking on average 10 CPD, eCO ≥10 ppm) with ≥1 quit attempt in the past 5 yrs received a 2-week supply of e-cigs.	Individuals who smoke cigarettes (regular smoking for ≥5 yrs, currently smoking on average 10 CPD, eCO ≥10 ppm) with ≥1 quit attempt in the past 5 yrs were instructed to refrain from using e-cigs.	Self-reported smoking 0 CPD, and/or eCO <6 ppm
[46]	RCT	Individuals who smoke cigarettes were prescribed a 12-week course of varenicline, and were provided with an e-cig starter kit prior to quit date.	Individuals who smoke cigarettes were prescribed a 12-week course of varenicline starting 2 weeks before the target quit date. Participants were not asked to avoid using e-cigs.	9-12-week abstinence (primary outcome): Self-reported not having smoked cigarettes between Weeks 9-12, verified with eCO <10 ppm at Week 12 or later. 2-4-week abstinence: Self-reported not having smoked cigarettes between Weeks 2-4, verified with eCO <10 ppm.
[70]	RCT	Use e-cigs (18 mg/mL + NRT): Participants received 18 mg/mL nicotine e-cigs and nicotine patches Use e-cigs (0 mg/mL + NRT): Participants received 0 mg/mL nicotine e-cigs and nicotine patches	Individuals who do not use e-cigarettes (NRT): Participants received nicotine patches (21 mg)	Continuous smoking abstinence after the agreed quit date (self-reported abstinence since quit date, allowing ≤ 5 CPD in total; eCO ≤ 9 ppm) 7-day PPA (no cigarettes, not a single puff, in the previous 7 days)

Abbreviations: CPD = cigarettes per day; e-cig = electronic cigarette; eCO = exhaled carbon monoxide; NRT = nicotine replacement therapy; PPA = point prevalence of abstinence; ppm = parts per million; RCT = randomized clinical trial; wk/wks = week/weeks; yr/yrs = year/years

Table 2: Summary Characteristics of RCTs for Duration of Abstinence from Cigarette Smoking Among Regular Individuals Who Use E-Cigarettes (n=1)

Citations	Study design	Definition of e-cig user	Definition of e-cig non-user	Definition of study outcome
RCTs				
[32]	RCT	Use e-cigs (0 mg/mL): Individuals who currently smoke cigarettes at baseline who received e-cigs without nicotine to help quit smoking Use e-cigs (8 mg/mL): Individuals who currently smoke cigarettes at baseline who received e-cigs containing 8 mg/mL nicotine to help quit smoking Use e-cigs (36 mg/mL): Individuals who currently smoke cigarettes at baseline who received e-cigs containing 36 mg/mL nicotine to help quit smoking	Individuals who do not use e-cigarettes: Individuals who currently smoke cigarettes at baseline who received cigarette-shaped plastic tube with no electronic or aerosol to help quit smoking	Days without smoking

Abbreviations: E-cig=electronic cigarettes; RCT=randomized controlled trial; mg/mL = milligrams per millilitre

Table 3: Summary Characteristics of RCTs for Change in Cigarette Smoking Quantity/Frequency Among Regular Individuals Who Use E-Cigarettes (n=12)

Citations	Study design	Definition of e-cig user	Definition of e-cig non-user	Definition of study outcome
RCTs				
[89]	RCT	Individuals who smoke cigarettes (≥10 CPD for at least 3 yrs) in the two treatment arms given e-cigs from start of study and allowed to both smoke and use e-cigs; Individuals who smoke cigarettes (≥10 CPD for at least 3 yrs) in control arm given e-cigs after the 3rd session and allowed to only smoke during lab sessions	NR	Self-reported smoking reduction (≥50% or ≥80%)
[82]	RCT	Use e-cigs (0 mg/mL): Individuals who currently smoke cigarettes at baseline who received e-cigs without nicotine to help quit smoking; Use e-cigs (8 mg/mL): Individuals who currently smoke cigarettes at baseline who received e-cigs containing 8mg/mL nicotine to help quit smoking; Use e-cigs (36 mg/mL): Individuals who currently smoke cigarettes at baseline who received e-cigs containing 36 mg/mL nicotine to help quit smoking	Individuals who do not use e-cigarettes: Individuals who currently smoke cigarettes at baseline who received cigarette-shaped plastic tube with no electronic or aerosol to help quit smoking	Self-reported CPD
[33]	RCT	Use e-cigs: Pregnant individuals who smoke cigarettes received refillable e-cigs for smoking cessation, and who might also have used NRTs as non-allocated products	Individuals who do not use e-cigarettes (NRT users): Pregnant individuals who smoke cigarettes received NRT for smoking cessation, and who might have also used refillable e-cigs as non-allocated products	Smoking reduction: Validated >50% reduction in cotinine levels compared to baseline in non-abstainers at end of pregnancy
[66]	RCT	Ad-libitum use e-cigs: Individuals who currently smoke cigarettes (smoking at least 5 CPD for the past year with a breath CO at least 10 ppm or NicAlert test = level 6 if CO less than 10 ppm) who used e-cigs *ad libitum* while smoking	Non-use e-cigs: Individuals who currently smoke cigarettes (smoking at least 5 CPD for the past year with a breath CO at least 10 ppm or NicAlert test = level 6 if CO less than 10 ppm) who did not use e-cigs during the RCT;	Self-reported number of CPD at different time-points of the RCT (Weeks 1, 2, 4, 6, and 8)

Citations	Study design	Definition of e-cig user	Definition of e-cig non-user	Definition of study outcome
		as many or as few cigarettes as they wanted during the RCT; Intent-to-quit use e-cigs: Individuals who currently smoke cigarettes (smoking at least 5 CPD for the past year with a breath CO at least 10 ppm or NicAlert test = level 6 if CO less than 10 ppm) who were instructed to stop smoking cigarettes and only use e-cigs during the RCT	Intent-to-quit NRT users: Individuals who currently smoke cigarettes (smoking at least 5 CPD for the past year with a breath CO at least 10 ppm or NicAlert test = level 6 if CO less than 10 ppm) who were instructed to stop smoking cigs and only use NRT during the RCT	
[54]	RCT	Treatment arm where individuals who smoke cigarettes (≥2 CPD, smoked ≥1 in last 7 days) were provided with e-cigs	Treatment arm where individuals who smoke cigarettes (≥2 CPD, smoked ≥1 in last 7 days) were provided with NRT (nicotine patch)	Reduction of 50% or more CPD compared to baseline, including smoking cessation Self-reported CPD
[76]	RCT	Individuals who smoke cigarettes (10 CPD in past year, individuals who smoked cigarettes for at least 3 yrs, and were motivated to stop smoking entirely or to reduce their cigarette consumption) randomized into an e-cig group	Individuals who smoke cigarettes (10 CPD in past year, individuals who smoked cigarettes for at least 3 yrs, and were motivated to stop smoking entirely or to reduce their cigarette consumption) randomized into an NRT (nicotine gum) group	Self-reported reduction in CPD
[68]	RCT	Nicotine use e-cigs: Participants allocated to the nicotine e-cig plus support trial arm, and administered an e-cig kit with 12 10-mL liquid cartridges (8 mg/mL nicotine concentration) Non-nicotine use e-cigs: Participants allocated to the nicotine-free e-cig plus support trial arm, and received an e-cig kit with 12 10-mL liquid cartridges (0 mg/mL nicotine concentration)	Participants allocated to the support only trial arm	Self-reported CPD at 6-month follow-up among participants who reported a ≥20% change in smoking
[107]	RCT	Individuals who smoke cigarettes with a history of unsuccessful quitting with stop smoking medications randomized to use e-cigs.	Individuals who do not use e-cigarettes (NRT): Individuals who smoke cigarettes with a history of unsuccessful quitting with stop smoking medications randomized to the NRT group. The choice of product included nicotine patch, chewing gum, nasal spray, microtab, inhalator and mouth spray.	Self-reported CPD reduction of ≥50%, confirmed by a ≥50% reduction in eCO levels compared to baseline.

Citations	Study design	Definition of e-cig user	Definition of e-cig non-user	Definition of study outcome
[43]	RCT	Individuals who smoke cigarettes (regular smoking for ≥5 yrs, currently smoking on average 10 CPD, eCO ≥10 ppm) with ≥1 quit attempt in the past 5 yrs received a 2-week supply of e-cigs.	Individuals who smoke cigarettes (regular smoking for ≥5 yrs, currently smoking on average 10 CPD, eCO ≥10 ppm) with ≥1 quit attempt in the past 5 yrs were instructed to refrain from using e-cigs.	Self-reported smoking 0 CPD, and/or eCO <6 ppm
[99]	RCT	Individuals who smoke cigarettes (>10 CPD) enrolled in the experimental group and receiving an e-cig kit;	Individuals who smoke cigarettes (>10 CPD) enrolled in the control group	Self-reported CPD at 1-month follow-up
[86]	RCT	Use e-cigs (nicotine salt e-liquid): Participants received a closed system pod e-vapor product (myblu) containing nicotine salt e-liquid pods. Use e-cigs (freebase nicotine e-liquid): Participants received a closed system pod e-containing freebase nicotine e-liquid pods.	Individuals who do not use e-cigarettes (NRT): Established daily cigarette smokers using NRT.	Self-reported, past 30-day cigarette consumption at 6 months
[70]	RCT	Use e-cigs (18 mg/mL + NRT): Participants received 18 mg/mL nicotine e-cigs and nicotine patches Use e-cigs (0 mg/mL + NRT): Participants received 0 mg/mL nicotine e-cigs and nicotine patches	Individuals who do not use e-cigarettes (NRT): Participants received nicotine patches (21 mg)	Change in CPD

Abbreviations: CPD = cigarettes per day; e-cig = electronic cigarette; eCO = expired carbon monoxide; ENDS = electronic nicotine delivery systems; NRT = nicotine replacement therapy; ppm = parts per million; RCT = randomized controlled trial; wk = week; yr/yrs = year/years

Table 4: PRISMA CHECKLIST 2020

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pg. 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pg. 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg. 3-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg. 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg. 5-6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg. 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Pg. 5 and supp. 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg 6 and suppl. 3-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg. 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg. 7-8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pg. 8-16
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pgs. 9 and 16

Section and Topic	Item #	Checklist item	Location where item is reported
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pg. 9-10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pg. 8-17 and supp. 8-10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pg. 9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pg. 9-10
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pg. 9-10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pg. 7-8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pg. 8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pg. 10
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pg. 9
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pg. 10-17
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Pg. 10 and supp. 4-6
Study characteristics	17	Cite each included study and present its characteristics.	Pg. 12-33, tables 1-3, and supp. 13-18
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 8 and supp. 9

Section and Topic	Item #	Checklist item	Location where item is reported
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pg. 27-35 and supp. 19
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pg. 9 and Supp. 9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pg. 33-42
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pg. 33-42
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pg. 33-42 and Supp. 19
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pg. 9 and Supp. 9
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pg. 42-43 and supp. 10
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg. 43-47
	23b	Discuss any limitations of the evidence included in the review.	Pg. 46
	23c	Discuss any limitations of the review processes used.	Pg. 46
	23d	Discuss implications of the results for practice, policy, and future research.	Pg. 43-46
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pg. 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pg. 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Pg. 4-5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Pg. 1

Section and Topic	Item #	Checklist item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	Pg. 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Pgs. 1 and 33