E-Cigarette Use and Adult Cigarette Smoking Cessation: A Meta-Analysis

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See also the "ENDS: Recreational or Prescription Drug?" section, pp. 219–229.

Objectives. To determine the association between e-cigarette use and smoking cessation.

Methods. We searched PubMed, Web of Science Core Collection, and EMBASE and computed the association of e-cigarette use with quitting cigarettes using random effects meta-analyses.

Results. We identified 64 papers (55 observational studies and 9 randomized clinical trials [RCTs]). In observational studies of all adult smokers (odds ratio [OR] = 0.947; 95% confidence interval [CI] = 0.772, 1.160) and smokers motivated to quit smoking (OR = 0.851; 95% CI = 0.684, 1.057), e-cigarette consumer product use was not associated with quitting. Daily e-cigarette use was associated with more quitting (OR = 1.529; 95% CI = 1.158, 2.019) and less-than-daily use was associated with less quitting (OR = 0.514; 95% CI = 0.402, 0.665). The RCTs that compared quitting among smokers who were provided e-cigarettes to smokers with conventional therapy found e-cigarette use was associated with more quitting (relative risk = 1.555; 95% CI = 1.173, 2.061).

Conclusions. As consumer products, in observational studies, e-cigarettes were not associated with increased smoking cessation in the adult population. In RCTs, provision of free e-cigarettes as a therapeutic intervention was associated with increased smoking cessation.

Public Health Implications. E-cigarettes should not be approved as consumer products but may warrant consideration as a prescription therapy. (*Am J Public Health*. 2021;111:230–246. https://doi.org/10.2105/AJPH.2020.305999)

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Electronic cigarettes (e-cigarettes) deliver an aerosol of nicotine by heating a solution typically consisting of nicotine, propylene glycol, glycerin, and flavorings.[1] In the United States, e-cigarettes are mass-marketed consumer products that, according to the 2009 Family Smoking Prevention and Tobacco Control Act (TCA), fall under the jurisdiction of the Food and Drug Administration (FDA) Center for Tobacco Products (CTP). In particular, TCA §910 requires manufacturers to demonstrate to CTP that marketing a new tobacco product (including e-cigarettes) would be "appropriate for the protection of the public health."[2]

E-cigarettes have been promoted for smoking cessation[3,4] even though, as of November 2020, no e-cigarette has been approved as a smoking cessation medication by the FDA Center for Drug Evaluation and Research (CDER).

The standards that CTP and CDER apply to approve e-cigarettes as consumer products or therapeutic devices are fundamentally different. When considering whether e-cigarettes are "appropriate for the protection of public health," CTP must assess population as well as individual impacts for the products as actually used. Observational studies of the effects of e-cigarettes as they are actually used in the general population (which we refer to as "consumer product" use) are relevant to CTP's decision-making. By contrast, when considering whether e-cigarettes warrant approval as a therapy, CDER only considers the efficacy (and risks) of a proposed therapy administered to a specific class of individuals at specified doses under medical supervision. Therefore, randomized clinical trials (RCTs) in which e-cigarettes are provided to selected patient populations as part of a smoking cessation program under medical supervision are relevant to CDER's decision-making.

The question of how e-cigarettes as consumer products have an impact on public health gained urgency when, in 2019, a federal court[5] required e-cigarette companies to submit premarket tobacco product applications to the FDA by September 2020 to continue to

sell e-cigarettes as consumer products. When considering whether allowing the sale of a particular e-cigarette is "appropriate for the protection of the public health,"[2] CTP must consider, among other things, how e-cigarettes as consumer products lead people who smoke to "transition away from combustible tobacco products."[6] The requirement to submit a premarket tobacco product application may also motivate some e-cigarette companies to apply to CDER for approval of their product as a therapeutic smoking cessation device. Therefore, it is important to assess the evidence on the effects of e-cigarettes as consumer products on cigarette smoking cessation as well as, separately, a prescription smoking cessation therapy.

Only 2 previous meta-analyses of the effect of e-cigarette use on smoking cessation included at least 10 studies. One in 2016 included 20 studies (2 RCTs and 18 observational studies) and concluded that the "odds of quitting cigarettes were 28% lower in those who used e-cigarettes compared with those who did not use e-cigarettes (odds ratio [OR] 0.72, 95% CI 0.57-0.91)."[7(p116)] Another meta-analysis in 2017 that included 10 studies (2 RCTs and 8 observational studies) found that "there is very limited evidence regarding the impact of [electronic nicotine delivery systems] . . . on tobacco smoking cessation. . . . Data from [RCTs] are of low certainty and [data from] observational studies of very low certainty."[8(p1)]

Since 2017, the number of studies reporting on the association between e-cigarette use and smoking behavior has continued to accumulate, and they have provided greater understanding of population- and individual-level effects of e-cigarette use on smoking cessation. Increasingly, observational studies are reporting more nuanced findings, with exposure categorized by frequency or intensity of e-cigarette use, or with samples restricted to people motivated to quit cigarette smoking, all of which have been hypothesized to have an impact on the effects of e-cigarette use on smoking cessation. The number and quality of the RCTs evaluating the effects of e-cigarettes on smoking cessation have also increased. The richness of these data prompted this meta-analysis, in which we summarize the state of the current scientific knowledge on the effect of e-cigarette use on cigarette smoking cessation. We conducted 4 analyses, examining (1) the effect of e-cigarette consumer product use among people who smoke, regardless of motivation to quit smoking; (2) the effect of e-cigarette consumer product use among people who smoke who are motivated to quit smoking; (3) the effect of daily and less-than-daily e-cigarette consumer product use among people who smoke; and (4) the effect of being provided with free e-cigarettes as a therapeutic intervention in RCTs compared with conventional therapy.

METHODS

We followed the statements on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Meta-Analysis of Observational Studies in Epidemiology.[9,10] The meta-analysis was registered with PROSPERO on April 9, 2019, (CRD42019128465) and subsequently updated to reflect refinements in the specific questions asked (detailed in the Statistical Analysis section), to clarify what "conventional therapy" among the RCTs meant, and to add another investigator and associated funding. Further updates were made to add use of the Grading of Recommendations Assessment, Development, and Evaluation[11] (GRADE) guidelines for assessing the quality of evidence from RCTs and adjustment of study standard errors and 95% confidence intervals (CIs) for multiple use of some data (usually the reference group). These refinements are detailed in the updated PROSPERO registrations.

Data Sources and Searches

An academic librarian developed the search strategy and searched PubMed, Web of Science Core Collection, and EMBASE databases on January 14, 2020. Search terms included "vaping," "electronic cigarette," "stop," "quit," "smoking cessation," and "abstain" (search strategy in the Appendix, available as a supplement to the online version of this article at http://www.ajph.org). Search results were not limited by language, publication dates, or for being an abstract only.

Eligibility Criteria

We considered studies eligible if (1) the target population was adults aged 18 years or older; (2) the exposure was e-cigarette use, however this was defined by study authors (definitions included ever use, current use, and daily use, among others); and (3) the outcome was smoking cessation, however this was defined by study authors (definitions included point prevalence of abstinence, continuous abstinence, self-reported abstinence, and biochemically verified abstinence, among others). Both observational studies and RCTs were eligible. For RCTs, we limited the definition of e-cigarette use to nicotine e-cigarettes; we excluded studies that compared nicotine e-cigarettes with nonnicotine e-cigarettes.

Study Selection and Data Extraction

We conducted study selection and data extraction by using the Covidence Web-based software platform (Veritas Health Innovation, Melbourne, Australia). The second author screened abstracts for inclusion into the full-text review. The first 2 authors performed full-text review of 36 randomly chosen studies and established a concordance rate of 81% ($\kappa = 0.57$; $P < .001$). The third investigator resolved uncertainty on the discordant studies. The remaining full-text review and data extraction was split evenly between the first 2 authors. The third author reviewed and confirmed every study that was excluded. Although we did not exclude abstracts from our search, all studies that met criteria for inclusion in this meta-analysis were full peer-reviewed journal publications.

Data extraction was completed by the first 2 authors, including study design (longitudinal observational study, cross-sectional observational study, or RCT), study population, period of time over which data were collected, whether sampling was restricted by motivation to quit smoking, definition of smoking cessation, the definition or definitions of e-cigarette use, whether e-cigarette exposure was categorized by frequency of use, how the unexposed group was defined, which variables were adjusted for, and reported OR for the association between e-cigarette use and smoking cessation. A study was considered examining motivation to quit smoking if evidence of this motivation was part of inclusion or exclusion criteria for the study or for the analysis. For example, a study that excluded potential participants because they had not made at least 1 quit attempt during the year before enrollment was considered to have restricted their sampling to participants motivated to quit smoking. Studies that categorized e-cigarette use by frequency of use almost universally used 2 (daily vs less-than-daily e-cigarette use) or 3 (daily vs less-than-daily vs experimental or prior e-cigarette use) levels.

When unadjusted and adjusted ORs were presented, we used the adjusted ORs. When an aggregate OR was presented in addition to ORs categorized by frequency of e-cigarette use, we used both aggregate and frequency-specific ORs in separate analyses; when only frequency-specific ORs were presented in the absence of an aggregate OR, we extracted and used the frequency-specific ORs. When an aggregate OR was presented in addition to ORs stratified by a variable other than frequency of use, we only used the aggregate OR. When only stratified ORs were presented in the absence of an aggregate OR, we used the stratified ORs. When no OR was presented but could be calculated from the absolute numbers presented in the study, we calculated the OR.

For 4 observational studies, measures of association other than ORs were presented.[12–15] For these 4 studies, we contacted the study authors for further information. For one study, the authors provided an OR, which we included in the meta-analysis.[12] For 2 other studies, the authors did not provide an OR, but the journal article reported a prevalence ratio or risk ratio, which we included in the meta-analysis.[13,14] For the fourth study, the authors did not provide an OR and the journal article reported a prevalence difference, so we excluded this study.[15]

For RCTs, we extracted relative risk (RR) and absolute risk differences as the measures of association. For one RCT with multiple comparison groups,[16] we used the comparison with free cessation aid; the groups provided with financial incentives in addition to free cessation aids were not considered a meaningful comparison with the exposure group, which was provided with free e-cigarettes.

Three RCTs included study arms in which participants were provided with nonnicotine e-cigarettes as a control condition.[17–19] Participants randomized to these study arms were excluded from analysis because the goal of the analysis was to compare smoking cessation in people who smoke who used e-cigarettes with those who do not, not to assess the importance of the nicotine in the e-cigarettes.

We assessed risk of bias by using a modification of the ACROBAT-NRSI tool[20] for observational studies and the Cochrane Risk of Bias Tool[21] for RCTs by the first author in consultation with the third author (details in Appendix).

We applied the GRADE[11] approach to assess the quality of evidence for the RCTs. We did not use the GRADE approach to assess the observational studies because GRADE is designed to assess the quality of evidence for therapeutic interventions, not behavioral effects associated with consumer products.

Statistical Analysis

The observational studies and RCTs addressed fundamentally different questions (the behavioral effects of e-cigarettes as consumer products vs e-cigarettes as a smoking cessation therapy), and there was substantial heterogeneity in study design among the observational studies of e-cigarettes as consumer products, including differences in sampling methodologies (with or without restriction on motivation to

quit smoking) and approach to analyses (whether e-cigarette use was or was not categorized by frequency of use). Given this variability, combining all studies in a single meta-analysis would result in a measure of association that would be difficult to interpret. In addition, many of the studies reported several different ORs, such as ORs for different exposure groups (daily e-cigarette use vs less-than-daily e-cigarette use) or different cigarette smoking characteristics (daily smoking vs less-than-daily smoking). To use as much of the available information as possible and to enhance interpretability, we posed 4 separate questions:

1. What is the effect of e-cigarette consumer product use on smoking cessation among all people who smoke, regardless of their intention to quit? For this analysis, we included observational studies for which inclusion and exclusion criteria were not predicated on motivation to quit smoking.
2. What is the effect of e-cigarette consumer product use on smoking cessation among people who smoke who express some motivation to quit smoking? For this analysis, we included observational studies that restricted participant eligibility to those who expressed some motivation to quit smoking.
3. Among people who smoke, what is the effect of intense e-cigarette consumer product use, defined as use of e-cigarettes at least daily, on smoking cessation, and is the effect different from that of less-than-daily use of e-cigarettes? For this analysis, we included observational studies that categorized exposure by frequency of e-cigarette use or restricted participant eligibility to those who met a specified threshold for frequency of use.
4. What is the effect of the provision of free e-cigarettes as a smoking cessation therapeutic intervention? For this analysis, we included only RCTs.

Different ORs from the same study were sometimes used to answer different questions. There were 2 situations in which we used multiple estimates from a single study.

The first situation was when a study reported different estimates of effect that could be used to answer different questions. An example of this is a study by Subialka Nowariak et al.[22] In this study, the authors presented an OR for the effect of e-cigarette use as a binary variable on smoking cessation for all participants in the study (0.63; 95% CI = 0.48, 0.82). They also presented ORs for the effect of e-cigarette use on smoking cessation categorized by frequency of e-cigarette use compared with no e-cigarette use. For daily use, the OR was 1.16; for intermediate use, the OR was 0.50; and for infrequent use compared with no use, the OR was 0.35. In this case, we used the aggregate OR when answering question 2 and we used frequency-specific ORs when answering question 3. There were 7 studies that reported multiple ORs that were used to answer different questions.

The second situation in which we used multiple estimates was when a study only reported multiple estimates of effect without reporting aggregate estimates of effect. An example of this is Biener and Hargraves.[23] In this study, the authors presented an OR for smoking cessation comparing daily e-cigarette users to never e-cigarette users and an OR comparing less-than-daily e-cigarette users to never e-cigarette users. No aggregate OR was presented. In this case, we included both ORs for our analysis in question 1. There were 11 studies for which multiple ORs were included for this reason.

Among the studies that contributed multiple ORs to the meta-analyses, different exposure groups were compared with the same reference group except for 1 study (in which the same e-cigarette users were compared with 2 different control groups, no cessation aid, or nicotine replacement therapy[24]). Reusing some data to compute several ORs resulted in a correlation between the estimated intervention effects. We adjusted for these correlated comparisons by adjusting the reported standard errors and 95% CIs using Bonferroni corrections. Because Bonferroni can be overly conservative, we also did a sensitivity analysis in which we used the reported standard errors and 95% CIs without Bonferroni corrections.

We performed random effects meta-analysis with Stata version 15.0 (StataCorp LP, College Station, TX) *metan* command. We assessed statistical heterogeneity by using the I^2 statistic. Using the *metareg* command, we tested the effect of study characteristics (study type [cross-sectional vs longitudinal], whether controlled for nicotine dependence, quit definition [7 vs ≥ 30 days], and e-cigarette use [ever vs current]), and when the studies were conducted on our findings for the observational studies used to answer questions 1 through 3. (For question 4, there were only 9 RCTs, which was not enough studies to do such analysis.) Except for when the study was conducted, the study characteristics were coded as dummy variables (0 or 1), so the coefficient and *P* value associated with each variable assessed the impact of that characteristic on the reported ORs across observational studies. Using the

metabias command, we conducted Egger's test for the presence of publication bias. The Stata *do* file used to conduct the analysis, including applying the Bonferroni corrections to the standard errors and 95% CIs, is in the Appendix. All the data for the analysis appears in Table A (available as a supplement to the online version of this article at http://www.ajph.org).

RESULTS

The systematic search of articles before January 15, 2020, identified 6575 records, of which 64 studies were included in this systematic review and meta-analysis (Figure A and Table A, available as supplements to the online version of this article at http://www.ajph.org). Fifty-five of these were observational studies,[12–14,22–72] and 9 were RCTs.[16–19,73–77] We extracted 95 ORs.

We grouped the studies according to which of the 4 questions they could help answer (Table B, available as a supplement to the online version of this article at http://www.ajph.org). A given study could be included in the analysis for 1 or more questions.

Study Characteristics

Of the 55 observational studies, 41 were cohort studies and 14 were cross-sectional studies. Most (36) of the observational studies were from the United States. The others were from Great Britain (5), France (3), Italy (3), Canada, the European Union, Germany, Greece, Hong Kong, Japan, or Switzerland (1 each); 1 observational study included participants from the United States, Great Britain, Canada, and Australia (Table 1 and Table A). Two of the studies had high risk for selection bias, 3 for bias in exposure measurement, 12 for bias in outcome measurement, 5 for bias from confounding, and 6 for bias from missing data (Table 1 and Table C, available as a supplement to the online version of this article at http://www.ajph.org). None had unknown risk of selection bias, 27 had unknown risk of exposure measurement, 37 had unknown risk of outcome measurement, 14 had unknown risk of confounding, and 24 had unknown risk of missing data.

Of the 9 RCTs, 3 were from the United States, 2 from Great Britain, 2 from New Zealand, and 1 each from Italy and Korea (Table A). One had high risk for performance bias, 3 had high risk for attrition bias, and 1 had high risk of reporting bias (Table 1 and Table D, available as a supplement to the online version of this article at http://www.ajph.org). In 7 of the 9 RCTs,[16,17,19,73,74,76,77] the comparison group was directly provided with nicotine replacement therapy or with the means to obtain such aid freely; in the other 2 RCTs, participants randomized to the comparison group were provided only with smoking cessation counseling.[18,75]

When we applied the GRADE approach to assess the quality of evidence in the RTCs, we judged there to be no serious limitations with regard to risk of bias, inconsistency, imprecision, or publication bias (Table 2). However, there was substantial concern for indirectness of evidence that derives from the limited number of e-cigarette products that have been studied in RCTs compared with the very large number of e-cigarette products available for sale to the public. Seven e-cigarette products were tested in the 9 RCTs (Elusion, One Kit, Vuse, Vype, eGO-C, and eVOD were used in 1 clinical trial each; NJOY was used in 2; the product was not named in 1 clinical trial). Whether the results from these clinical trials can be universally applied to the thousands of e-cigarette products available in the global market is unknown. It is possible that differences in e-cigarette product, nicotine concentration of e-liquid, nicotine formulation (salt vs free-base), flavoring agents, distribution strategy (free e-liquid refills vs limited e-liquid refills; e-liquids with a consistent nicotine concentration vs e-liquids with a declining nicotine concentration), and cointerventions would reduce the external validity of these studies as applied outside of the clinical trial setting. As such, the overall quality of evidence from the RCTs was judged to be moderate.

Answers to the 4 Questions

1. Among all people who smoke, e-cigarette consumer product use was not significantly associated with smoking cessation. To evaluate the effect of e-cigarette consumer product use on smoking cessation among all adults who smoke, we used observational studies that did not restrict sampling by motivation to quit smoking. The total sample for this analysis comprised 44 ORs from 35 studies.[13,14,23,25,26,28,31,33,34,36,40,42,43,45,47,-50,52,54,56,58,59,62,64,67,70,72,79] In this population, the point estimate for the effect of e-cigarettes on smoking cessation was close to the null, with a 95% CI that spanned the possibility of a small negative to a small positive effect on smoking cessation (OR = 0.947; 95% CI = 0.772, 1.160; $P = .293$; Figure 1 and Table 3). There was no significant difference between longitudinal and cross-sectional studies ($P = .09$).

Among the 24 ORs of all people who smoke in which a range of study characteristics were reported, these characteristics (cross-sectional vs longitudinal study design, whether e-cigarette

TABLE 1— Summary Table of Study Characteristics: E-Cigarette Use and Adult Cigarette Smoking Cessation: A Meta-Analysis

Study Characteristic	Observational Studies, No. (%)	Randomized Clinical Trials, No. (%)
Total no.	55 (100)	9 (100)
Study type		
Cohort	41 (75)	
Cross-sectional	14 (25)	
Population		
United States and Canada	38 (69)	3 (33)
United Kingdom	6 (11)	2 (22)
Europe	10 (19)	1 (11)
Australia and New Zealand	1 (2)	2 (22)
Asia	2 (4)	1 (11)
Sample restriction by motivation to quit smoking		
Restricted	20 (36)	
No restriction	35 (64)	
Specification of exposure intensity		
At least daily	15 (27)	
Less than daily	10 (18)	
No specification	40 (73)	
Comparator group		
For observational studies, never use	15 (27)	
For observational studies, any other definition	40 (73)	
For randomized clinical trials, direct provision of pharmacologic cessation aid or of means to obtain such aid freely		7 (78)
For randomized clinical trials, no provision of pharmacologic cessation aid		2 (22)
Smoking outcome ascertainment		
Biochemical verification	3 (5)	9 (100)
Self-report only	52 (95)	0 (0)
Adjustment for nicotine dependence		
Yes	38 (69)	
No	17 (31)	
Risk of bias assessment		
Selection		
Low risk	53 (96)	9 (100)
High risk	2 (4)	0 (0)
Unknown risk	0 (0)	0 (0)
Exposure measurement		
Low risk	15 (27)	
High risk	3 (5)	
Unknown risk	27 (49)	
Outcome measure (observational)		
Low risk	6 (11)	
High risk	12 (22)	
Unknown risk	37 (67)	

Continued

TABLE 1— Continued

Study Characteristic	Observational Studies, No. (%)	Randomized Clinical Trials, No. (%)
Confounding		
Low risk	36 (71)	
High risk	5 (9)	
Unknown risk	14 (25)	
Missing data		
Low risk	23 (42)	
High risk	6 (11)	
Unknown risk	24 (44)	
Performance		
Low risk		8 (89)
High risk		1 (11)
Unknown risk		0 (0)
Detection		
Low risk		9 (100)
High risk		0 (0)
Unknown risk		0 (0)
Attrition		
Low risk		6 (67)
High risk		3 (33)
Unknown risk		0 (0)
Reporting		
Low risk		8 (89)
High risk		1 (11)
Unknown risk		0 (0)

exposure was defined as either current use or ever use, the duration of abstinence that defined smoking cessation [7 days vs ≥ 30 days], whether nicotine dependence was adjusted for in the analysis, when the data were collected or the risk of bias in individual studies) did not significantly affect the OR estimate (Table E, available as a supplement to the online version of this article at http://www.ajph.org).

2. Among people who smoke who express some motivation to quit smoking, e-cigarette consumer product use was not significantly associated with smoking cessation. To evaluate the effect of e-cigarette consumer product use on smoking cessation among people who smoke who were motivated to quit smoking, analysis was limited to observational studies that restricted participant eligibility to those who expressed some motivation to quit smoking. The total sample for this analysis comprised 24 ORs from 20 studies.[12,22,24,27,29,30,35,41,44,46,51,53,57,60,61,65,66,68,69,71] In this population, the point estimate for the effect of e-cigarettes on smoking cessation was below the null, but the 95% CI did not exclude the possibility of a very small positive effect on smoking cessation (OR = 0.851; 95% CI = 0.684, 1.057; $P = .143$; Figure 2 and Table 3). In addition, there was a significant reduction in quitting among the longitudinal studies (OR = 0.751; 95% CI = 0.591, 0.954). There was no significant difference between longitudinal and cross-sectional studies ($P = .11$). Studies that defined quitting using 7-day point prevalence shows significantly less quitting than studies using 30-day or longer point prevalence; other study characteristics did not significantly affect the estimated OR (Table F, available as a supplement to the online version of this article at http://www.ajph.org).

3. Among people who smoke, daily e-cigarette consumer product use was associated with significantly increased

TABLE 2— GRADE Evidence for E-Cigarettes as a Smoking Cessation Therapy Compared With Conventional Therapy

Criteria	Quality Assessment	Comments
No. studies and design	9 RCTs	
Limitations	No serious limitations	All studies included for analysis were randomized. Because comparator groups were provided with treatments other than e-cigarettes, blinding was not generally possible. However, all studies incorporated biochemical verification as part of outcome assessment, mitigating risk of bias posed by lack of blinding. Rates of loss to follow-up were generally consistent across all studies.
Inconsistency	No serious inconsistency	Point estimates ranged from 0.70 to 3.35. CIs for the point estimates had substantial overlap, and the summary estimate of effect was within the bounds of all CIs with the exception of 1. The I^2 was 26%, indicating low variation attributable to among-study differences.
Indirectness	Serious indirectness problem because of varying products being assessed	A major challenge to extrapolating from RCTs of e-cigarettes to e-cigarettes in general relates to the diversity and heterogeneity of products that aerosolize nicotine-containing solutions. There were 7 different products tested across the 9 RCTs (Elusion, One Kit, Vuse, Vype, eGO-C, and eVOD were used in 1 clinical trial each; NJOY was used in 2; the product was not named in 1 clinical trial). Whether the results from these clinical trials can be applied to other e-cigarette products available in the global market is unknown.
Imprecision	No serious imprecision	Multiple adequately powered studies were included in this meta-analysis, indicating that the threshold for optimum information size was exceeded and that the precision of the summary estimate and confidence intervals was adequate.[78]
Publication bias	Undetected	Although we did not search a registry for unpublished clinical trials, visual inspection of a funnel plot and associated statistical test based on the 9 published RCTs does not suggest the presence of publication bias.
Summary of findings		
No. of patients		
Conventional therapy	2726	
Free e-cigarettes	2708	
Relative risk (95% CI)	1.555 (1.173, 2.061)	
Absolute cessation rate		
Conventional therapy (95% CI)	0.086 (0.043, 0.129)	
Cessation difference (95% CI)	0.040 (0.008, 0.073)	
Quality	Moderate	

Note. CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; RCT = randomized clinical trial.

smoking cessation, while less-than-daily e-cigarette use was associated with significantly less smoking cessation. To evaluate the effect of different intensities of e-cigarette consumer product use on smoking cessation, analysis was limited to studies that reported ORs stratified by frequency of e-cigarette use or that restricted participant eligibility to those who met a specified threshold for frequency of use—for example, at least 50 puffs per week for at least the past 6 months.[55] The total sample for this analysis comprised 31 ORs from 15 studies.[13,14,22,23,28,32,38,39,45,49,52,55,56,64,67] Compared with no e-cigarette use, daily e-cigarette use was associated with significantly higher odds of smoking cessation (OR = 1.529; 95% CI = 1.158, 2.019; $P = .005$; Figure 3 and Table 3). Compared with no e-cigarette use, less-than-daily e-cigarette use was associated with significantly lower odds of smoking cessation (OR = 0.508;

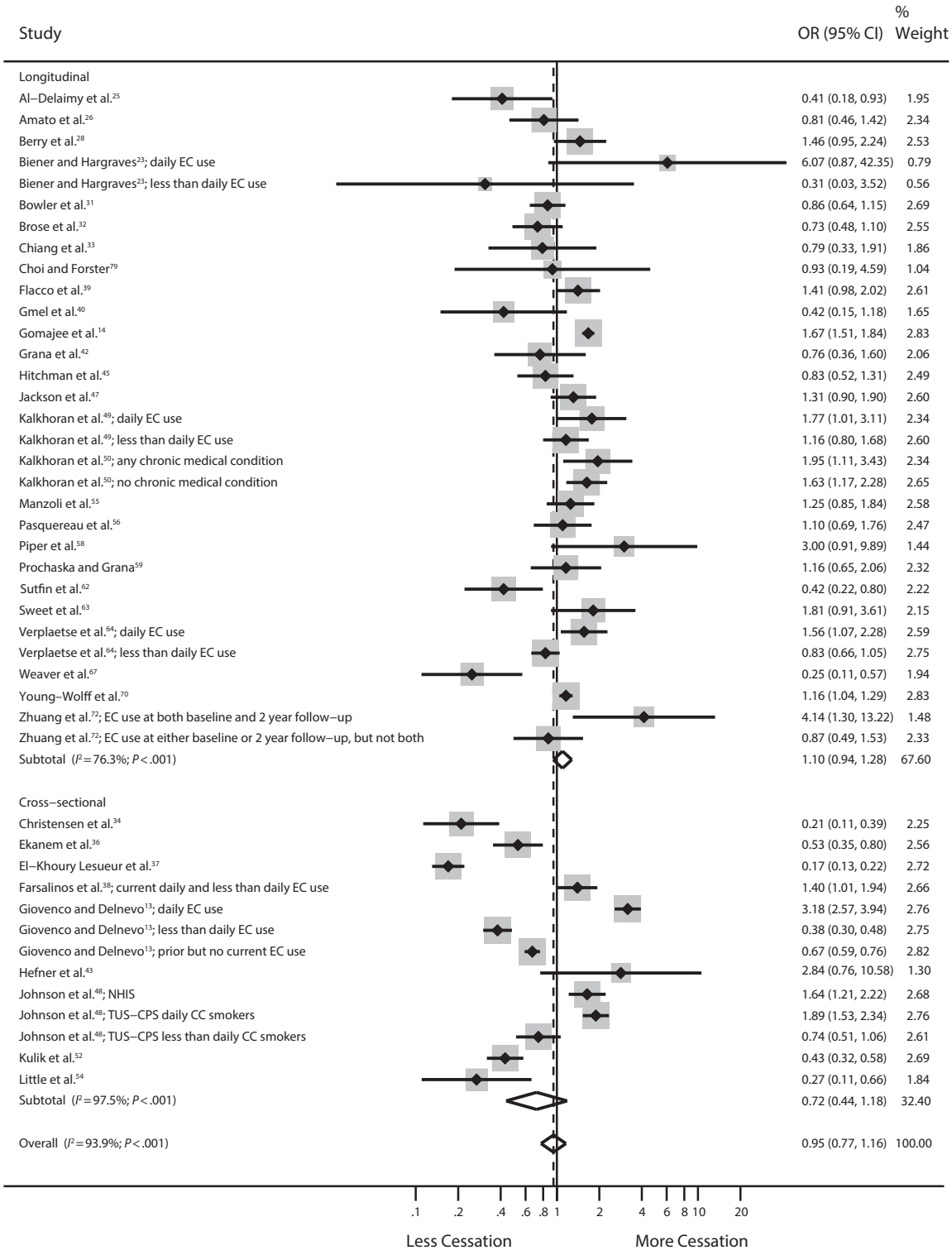

FIGURE 1— Association of E-Cigarette Consumer Product Use With Smoking Cessation Among All People Who Smoke Based on Studies as of January 20, 2020

Note. CC = combustible cigarette; CI = confidence interval; EC = e-cigarette; NHIS = National Health Interview Survey; OR = odds ratio; TUS-CPS = Tobacco Use Supplement to the Current Population Survey. Weights are from random effects analysis.

TABLE 3— Results of Meta-analyses of the Association Between E-Cigarette Use and Smoking Cessation

	OR or RR (95% CI)	No. of Estimates	Heterogeneity, I^2 % (*P*)	Publication Bias, Egger's *P*	Comparison of 2 Groups, *P*[a]
Observational studies of e-cigarettes as a consumer product, OR					
Smokers, regardless of motivation to quit					
All	0.947 (0.772, 1.160)	44	93.9 (<.001)	0.29	.09
Longitudinal	1.110 (0.944, 1.276)	31	76.3 (<.001)	0.06	
Cross-sectional	0.719 (0.437, 1.183)	13	97.5 (<.001)	0.75	
Smokers who are motivated to quit					
All	0.851 (0.684, 1.057)	24	90.4 (<.001)	0.07	.11
Longitudinal	0.751 (0.591, 0.954)	16	83.6 (<.001)	0.28	
Cross-sectional	1.089 (0.740, 1.603)	8	93.6 (<.001)	0.62	
E-cigarette intensity					
All	0.890 (0.675, 1.173)	31	94.3 (<.001)	0.29	<.001
Daily	1.529 (1.158, 2.019)	16	86.5 (<.001)	0.51	
Less than daily	0.514 (0.402, 0.656)	15	79.9 (<.001)	0.28	
Randomized clinical trials of e-cigarettes as smoking cessation therapy, RR					
All	1.555 (1.173, 2.061)	9	26.8 (.21)	0.98	

Note. CI = confidence interval; OR = odds ratio; RR = relative risk.

[a] *P* computed using METAREG.

95% CI = 0.400, 0.645; *P* < .001). The effect of daily e-cigarette use was significantly different from the effect of less-than-daily e-cigarette use (*P* < .001). Study characteristics did not significantly affect the estimated OR (Table G, available as a supplement to the online version of this article at http://www.ajph.org).

4. Provision of free e-cigarettes was associated with significantly increased smoking cessation in randomized clinical trials of e-cigarettes as smoking cessation therapy. Nine RCTs[16–19,73–77] were included for analysis. In 7 of the 9 RCTs, the control group was provided free cessation aids[16,17,19,73,74,76,77]; 2 RCTs provided the control group with smoking cessation counseling only.[18,75] In RCTs, provision of free e-cigarettes was associated with higher smoking cessation compared with conventional therapies (RR = 1.555; 95% CI = 1.173, 2.061; *P* = .002; Figure 4 and Tables 2 and 3). The absolute cessation rate for the conventional therapy was 0.086 (95% CI = 0.043, 0.129); e-cigarette use increased the absolute cessation rate by 0.040 (95% CI = 0.008, 0.073; *P* = .014; Figure 4 and Table 2).

There was no evidence of significant publication bias based on the available published studies used to answer any of the 4 questions (Table 3). There was significant study heterogeneity among the published studies used to answer questions 1 through 3, but not the RCTs used to answer question 4 (Table 3).

The sensitivity analysis in which we did not adjust for multiple comparisons in several of the studies produced similar results to the main analysis (Tables H–K, available as supplements to the online version of this article at http://www.ajph.org).

DISCUSSION

E-cigarette companies[3] and e-cigarette advocates[4] have promoted e-cigarettes as effective cigarette smoking cessation tools. In this meta-analysis, we found that, in observational studies of adults who smoke cigarettes, e-cigarette consumer product use was not significantly associated with cigarette smoking cessation. In observational studies of adults who smoke cigarettes and express some motivation to quit smoking, e-cigarette consumer product use was not significantly associated with cigarette smoking cessation. Among observational studies that categorized e-cigarette consumer product use by frequency of use, daily use of

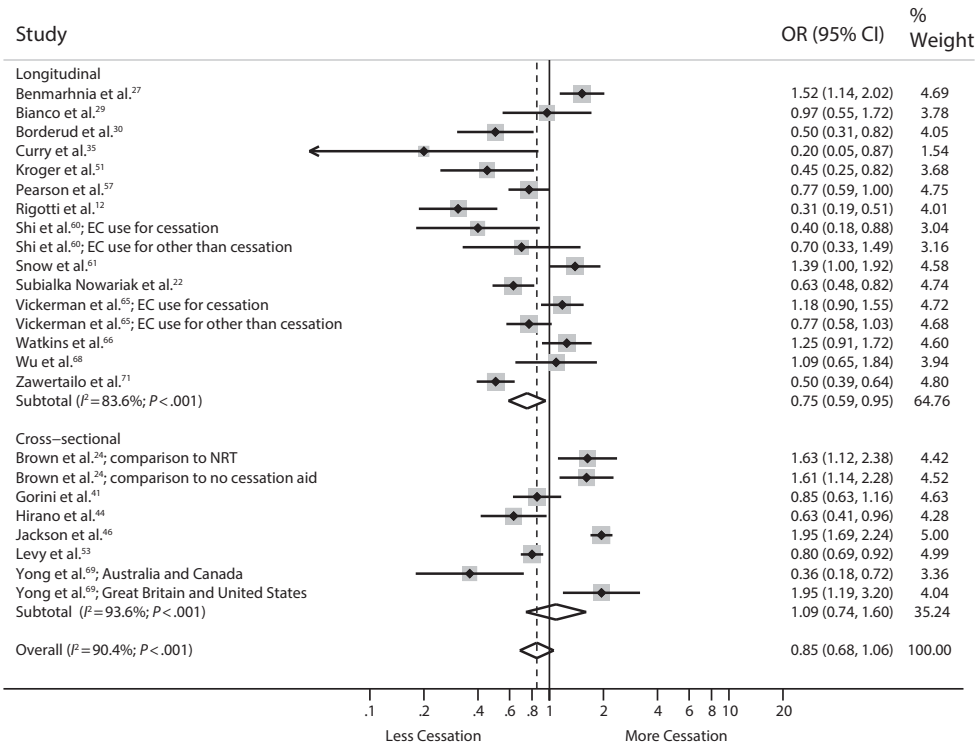

FIGURE 2— Association of E-Cigarette Consumer Product Use With Smoking Cessation Among People Who Express Some Motivation to Quit Smoking Based on Studies as of January 20, 2020

Note. CI = confidence interval; EC = e-cigarette; NRT = nicotine replacement therapy; OR = odds ratio. Weights are from random effects analysis.

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e-cigarettes was associated with increased smoking cessation, while less-than-daily e-cigarette use was associated with decreased smoking cessation. In the United States, most e-cigarette users use e-cigarettes less than daily (United States: 66% in 2011–2012,[23] 79% in 2013–2014,[64] and 66% in 2014–2015[13]). In the European Union the percentage of less-than-daily smokers was 48% in 2014.[52] In contrast to the results from observational studies of e-cigarettes as consumer products, provision of free e-cigarettes as a smoking cessation therapy in the context of RCTs was significantly associated with increased smoking cessation.

Study Heterogeneity

As with many meta-analyses, there was substantial heterogeneity (Table 3) among the observational studies of e-cigarettes as consumer products, which were designed to answer different questions and which adjusted for different covariates and potential confounders. While most of the observational studies were conducted in the United States, about one third of studies were from outside of the United States (Table A), which may also have contributed to the heterogeneity because of the availability of different e-cigarette products and differences in regulatory environments. We partially addressed this problem by subdividing the observational studies according to major differences in the definition of the target population and of the exposure. In addition, a sensitivity analysis did not find any statistically significant effects that resulted from differences in key characteristics of observational study design, when the studies were conducted, or assessment of bias in individual studies (Table E).

Substantial heterogeneity is a major challenge to interpreting results, but reflects the nature of e-cigarettes as a broad class of diverse consumer products currently available for sale and consumption across global markets. E-cigarette devices differ in their design and their component materials. They differ in nicotine formulation, nicotine concentration, flavoring agents, and other additives. E-cigarette products differ in branding, marketing, and appeal to population subsegments. Local regulation of e-cigarettes varies across national and subnational jurisdictions, affecting patterns and topologies of use.

Amid these challenging circumstances, the FDA and other regulators must decide whether the sale of

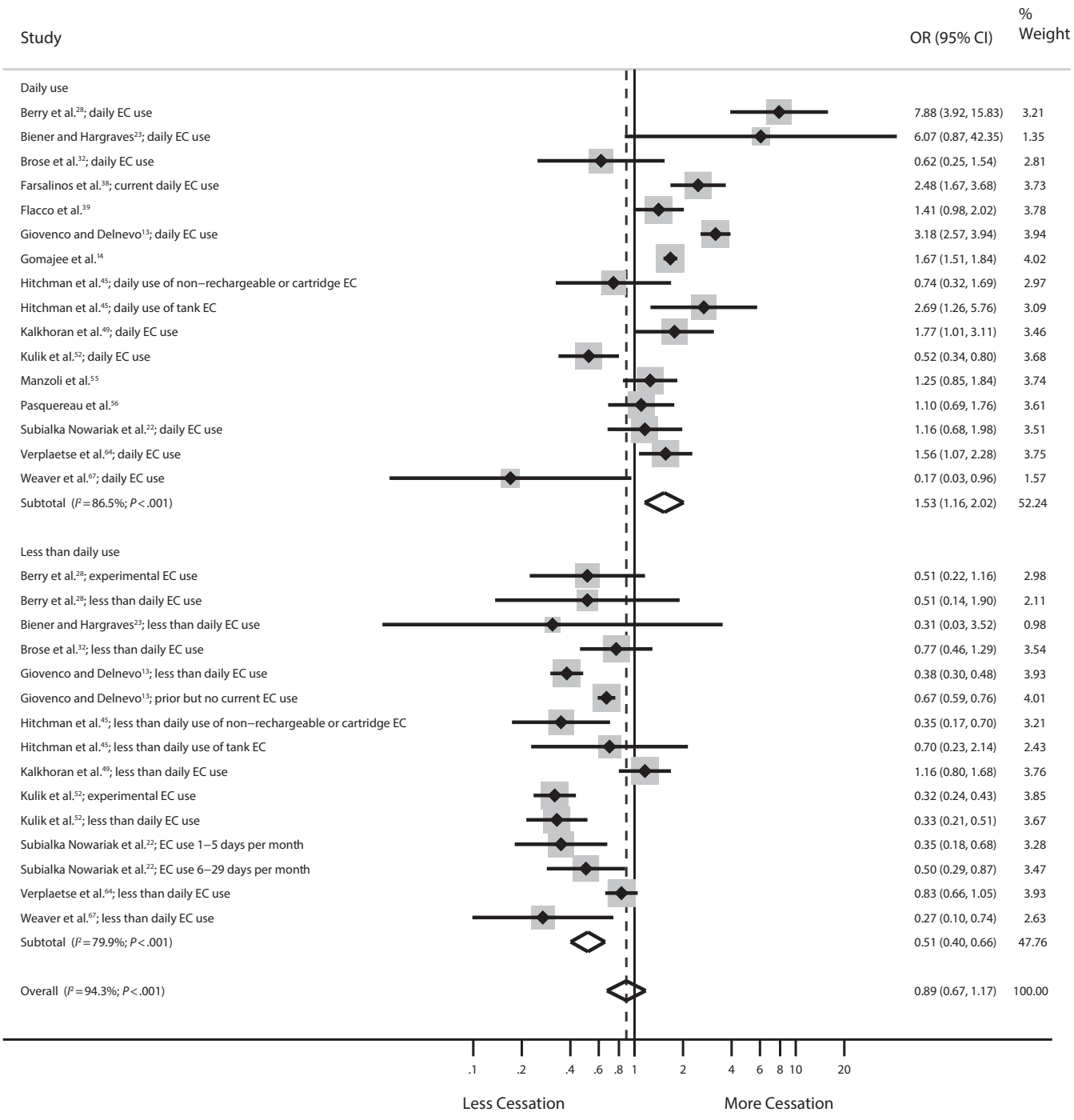

FIGURE 3— Association of Daily and Less-Than-Daily E-Cigarette Consumer Product Use With Smoking Cessation Among People Who Smoke Based on Studies as of January 20, 2020

Note. CI = confidence interval; EC = e-cigarette; OR = odds ratio. Weights are from random effects analysis.

e-cigarettes as consumer tobacco products (as opposed to specific therapeutic interventions administered to specified classes of patients under clinical supervision) would be "appropriate for protection of public health," the standard in the law. Making a quantitative determination about the effects of e-cigarettes as consumer products on smoking behavior is an important element of the regulatory impact analysis that the CTP is required to do. Thus, the heterogeneity observed in the studies reflects variability of use of e-cigarettes as consumer

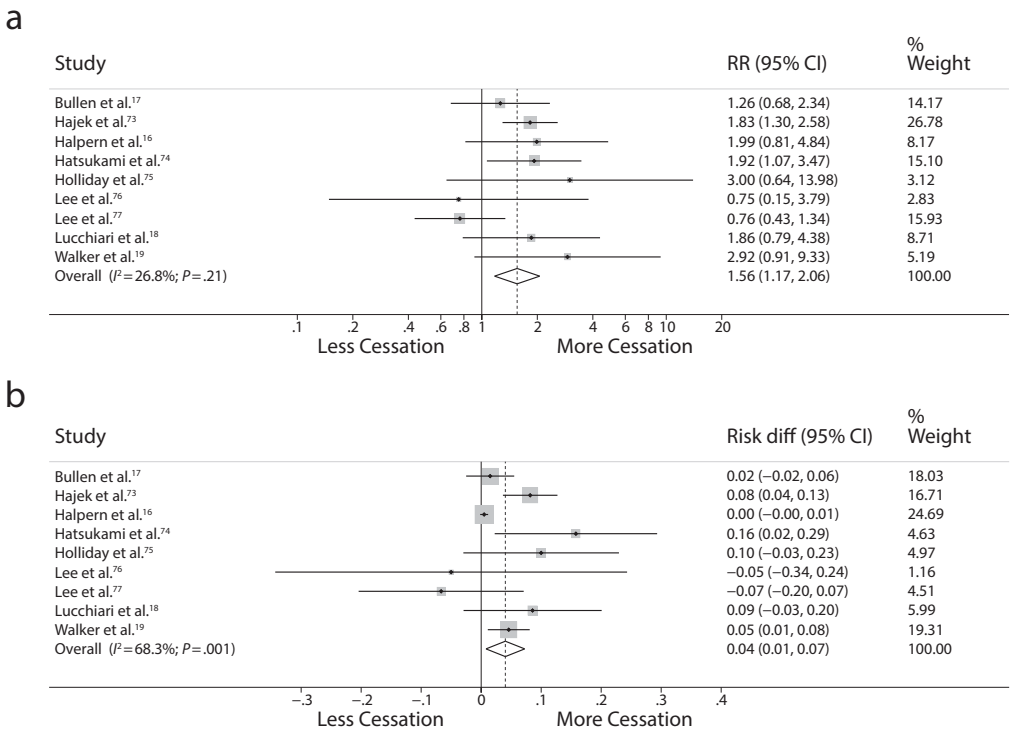

FIGURE 4— Association of Provision of Free E-Cigarettes With Significantly Increased Smoking Cessation in Randomized Clinical Trials of E-Cigarettes as Smoking Cessation Therapy by (a) Relative Risk and (b) Risk Difference Based on Studies as of January 20, 2020

Note. CI = confidence interval; RR = relative risk. Weights are from random effects analysis.

products makes the observational studies more relevant and useful to CTP in developing and implementing regulation of e-cigarettes as consumer products.

The RCTs were conducted in 5 countries (Table A), but did not exhibit significant heterogeneity (Tables 2 and 3), perhaps because of the more tightly controlled environment in terms of participant selection and intervention than exists in real-world observational studies.

Implications for FDA Regulation of E-Cigarettes

The observational studies have substantial implications for FDA regulation of e-cigarettes as tobacco (consumer) products. When determining whether a new tobacco product is appropriate for the protection of the public health, TCA §910(c)(4) requires FDA to consider

> the risks and benefits to the population as a whole including users and nonusers of the tobacco product, and taking into account (A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

Moreover, TCA §911(g)(1) provides that a Modified Risk Tobacco Product order (which would allow a company to sell their e-cigarette with claims that the product is less harmful than other tobacco products on the market or exposes the consumer to reduced exposure to substances found in other tobacco products) can be issued only if FDA determines that the applicant has demonstrated that the product

> as it is actually used by consumers, will (A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

If e-cigarette consumer product use is not associated with more smoking cessation, there is no population-level health benefit for allowing them to be marketed to adults who smoke, regardless of the relative harm of e-cigarettes compared with conventional cigarettes. Moreover, to the

extent that people who smoke simply add e-cigarettes to their cigarette smoking (becoming so-called dual users), their risk of heart disease,[80–83] lung disease,[84,85] and cancer[86] could increase compared with smoking alone.

The other 2 questions CTP is mandated to consider—the direct toxicity of e-cigarettes and the potential that e-cigarette availability increases smoking rates among the youths—are also important and not included in our meta-analysis. The fact that e-cigarettes have attracted millions of youths to nicotine,[87,88] many of whom would have been unlikely to initiate nicotine use with conventional cigarettes,[89–91] further undermines the idea that allowing the marketing of e-cigarettes would be "appropriate for the protection of public health." Evidence of toxicity of e-cigarettes is also growing, including myocardial infarction and other heart disease,[80–83,92] lung disease,[84,85,93,94] and cancer.[86,95,96]

By contrast, the RCTs suggest that specific e-cigarettes may meet the CDER standard as therapeutic interventions to be delivered to specific classes of patients at specified doses under medical supervision. Among the 9 RCTs in this meta-analysis, provision of free e-cigarettes significantly increased smoking cessation compared with conventional therapies, including nicotine replacement therapy. The overall quality of evidence was judged "moderate" (Table 2), however, because whether the results from these clinical trials can be extrapolated to the thousands of products available on the global market is unknown. It is possible that differences in e-cigarette product, nicotine concentration of e-liquid, nicotine formulation (salt vs free-base), flavoring agents, distribution strategy (free e-liquid refills vs limited e-liquid refills; e-liquids with a consistent nicotine concentration vs e-liquids with a declining nicotine concentration), and cointerventions would reduce the external validity of these findings when extrapolated to different e-cigarette products or when extrapolated outside of the clinical trial setting.

Even with these problems, the RCTs suggest that a specific e-cigarette might be able to pass the "efficacy" test for approval as a smoking cessation therapy administered under medical supervision as part of a cessation program. Approval of e-cigarettes as a cessation therapy, however, also requires that they be "safe," meaning that the benefit-to-risk ratio must be favorable. As noted previously, recent evidence links e-cigarette use to heart disease,[80–83,92] lung disease,[84,85,93,94] and cancer[86,95,96]; this evidence raises questions about whether the benefit-to-risk ratio would be favorable enough for approval as a medication. The fact that 80% of people who smoked in the e-cigarette arm of 1 of the RCTs were still using e-cigarettes a year later compared with 9% of nicotine replacement therapy users reinforces this concern.[73] In addition, while outperforming nicotine replacement therapy, the efficacy of e-cigarettes was similar to or below that of FDA-approved therapies including bupropion and varenicline.[97] If approved as a medication, e-cigarettes should be only available under prescription because of their high abuse potential, similar to prescription-only nicotine inhalers that have been approved as cessation medications.[98]

Limitations

Publication bias is always a potential concern. While we did not find evidence of publication bias based on our analysis of the published studies (Table 2), Egger's test suffers from low power when the number of studies is small. In addition, our assessment of publication bias is based on the published studies (i.e., we did not do a search of http://clincaltrials.gov for registered but unpublished RCTs), and there is a chance that other RCTs of e-cigarettes as smoking cessation therapy that yielded null results were never published.[99] Thus, it is possible that we are over-estimating the efficacy of e-cigarettes as therapeutic interventions for smoking cessation.

"Motivation to quit" is defined broadly in this review, following the design of the observational studies. There were studies that restricted sampling to participants who expressed some intent or motivation to quit smoking (as determined by the study investigators), and there were studies that did not restrict sampling to participants who expressed any intent or motivation to quit.

While all RCTs included some form of biochemical verification of smoking status, only 3 of the observational studies did.[12,29,35] (Few population studies ever include biochemical verification.) Self-report is, however, the established standard for population observational studies. The 2020 Surgeon General report *Smoking Cessation: A Report of the Surgeon General* observed that "self-reported data have been found to adequately reflect patterns of cigarette smoking among adults, including whether a respondent who has smoked in the past is currently not smoking, using scientifically validated biomarkers and other approaches."[100(p37)]

There is always the possibility that unspecified confounding variables could be affecting results. The wide range of potential confounders considered in the observational studies reduces the likelihood that this is the case.

CONCLUSIONS

E-cigarette use as a consumer product is not significantly associated with cigarette smoking cessation in the general adult population. E-cigarettes may warrant consideration as a prescription drug to be used as part of a clinically supervised smoking cessation intervention, provided that the associated risks are commensurate with the benefit. AJPH

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CONTRIBUTORS

R. J. Wang and S. Bhadriraju, the co-first authors, collected the data and wrote the first draft. S. A. Glantz reviewed the data collection and resolved differences. R. J. Wang and S. A. Glantz did the statistical analysis and most of the additional analysis required to respond to the reviewers. All authors approved the final draft.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

HUMAN PARTICIPANT PROTECTION

This study did not involve human participants.

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