Actual human disease data contradicts the low assumed e-cigarette risk FDA uses to justify an exception for "reduced risk" cigarettes in its product standard prohibiting menthol

Docket No. FDA-2021-N-1349
for "Tobacco Product Standard for Menthol in Cigarettes"

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We generally support FDA's proposed product standard prohibiting menthol as a characterizing flavor in cigarettes, because, as FDA states in the preamble and supports with good science, prohibiting menthol in cigarettes "will reduce initiation rates of smoking cigarettes, particularly for youth and young adults, and thereby decrease the likelihood that nonusers of cigarettes who experiment with these tobacco products would progress to regular cigarette smoking. Additionally, the proposed tobacco product standard is anticipated to improve the health of current smokers of menthol cigarettes by decreasing cigarette consumption and increasing the likelihood of cessation among this population."[1] However, FDA proposes including a provision allowing applicants to seek an exemption from the product standard for certain products, including low nicotine cigarettes and heated tobacco products, and specifically requests public comment on this proposed provision.

FDA's rationale for this exemption is based on the assumption that some tobacco products, notably e-cigarettes, are "reduced risk" products. However, the FDA's low assumed risks for e-cigarettes grossly underestimate the harmful health effects of e-cigarette use and dual use. Epidemiological studies on actual disease patterns show that e-cigarettes are not significantly less risky than cigarettes in terms of cardiovascular and oral disease and, while less risky than cigarettes for lung diseases, e-cigarettes are still several times more dangerous than FDA assumes. Dual use (using e-cigarettes while continuing to smoke cigarettes at the same time) is significantly riskier than smoking for all these outcomes. ***Because it dramatically underestimates the risks, FDA's justification for the exception falls apart. FDA should not include this provision allowing exemptions from the product standard for purported "reduced risk" products in its proposed product standard.***

[1] US Food and Drug Administration, Tobacco Product Standard for Menthol in Cigarettes, May 4, 2022, Proposed Rule, 87 FR 26454 at 26458.

Specifically, in support of its proposal to allow exemptions for certain products from the menthol standard, FDA relies on an analysis of the effects of having e-cigarettes (which would not be affected by the menthol rule because they are not considered "cigarettes" under the law) based on a model published by Levy et al.[2] Following Levy et al, FDA ***assumes*** that e-cigarettes are 15% as toxic as cigarettes and that dual use (using e-cigarettes while continuing to smoke cigarettes) has similar risks to smoking. ***No specific evidence is cited to support these assumptions.***

FDA's marketing granted orders for several e-cigarettes[3] assume that e-cigarettes are substantially less risky than cigarettes based on the fact that some biomarkers of exposure are lower in e-cigarettes than cigarettes.[4] A comprehensive 2021 review and modeling analysis of the biomarker data estimated that e-cigarettes are likely one-third as dangerous as cigarettes.[5] The difficulties with relying on biomarkers is that the number of biomarkers studied and included in these analyses is small in comparison to the large number of toxins in cigarettes and e-cigarettes[6] and the dose-response relationship between exposure and risk may not be linear. For example, smoking even one cigarette a day generates about 53% of the risk of coronary heart disease for men and 38% for women as smoking a pack (20 cigarettes) a day and 64% for men and 36% for women for stroke.[7]

The 2018 National Academies of Science, Engineering and Medicine report, *Public Health Consequences of E-Cigarettes* concluded that "whether e-cigarettes have an overall positive or negative impact on public health is currently unknown … More and better research on e-cigarettes' short- and long-term effects on health and on their relationship to conventional smoking is needed to answer that question with clarity."[8] As of July 2022, however, there has

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[2] Levy, D.T., R. Meza, Z. Yuan, et al. "Public Health Impact of a US Ban on Menthol in Cigarettes and Cigars: A Simulation Study." Tobacco Control, 2021. Available at https://doi.org/10.1136/tobaccocontrol-2021-056604.

[3] US Food and Drug Administration, Premarket Tobacco Product Marketing Granted Orders. Available: https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-granted-orders

[4] Anic GM, Rostron BL, Hammad HT, van Bemmel DM, Del Valle-Pinero AY, Christensen CH, Erives G, Faulcon LM, Blount BC, Wang Y, Wang L, Bhandari D, Calafat AM, Kimmel HL, Everard CD, Compton WM, Edwards KC, Goniewicz ML, Wei B, Hyland A, Hatsukami DK, Hecht SS, Niaura RS, Borek N, Ambrose BK, Chang CM. Changes in Biomarkers of Tobacco Exposure among Cigarette Smokers Transitioning to ENDS Use: The Population Assessment of Tobacco and Health Study, 2013-2015. Int J Environ Res Public Health. 2022 Jan 27;19(3):1462. doi: 10.3390/ijerph19031462. PMID: 35162490; PMCID: PMC8835100.

[5] Wilson N, Summers JA, Ait Ouakrim D, Hoek J, Edwards R, Blakely T. Improving on estimates of the potential relative harm to health from using modern ENDS (vaping) compared to tobacco smoking. BMC Public Health. 2021 Nov 8;21(1):2038. doi: 10.1186/s12889-021-12103-x. PMID: 34749706; PMCID: PMC8577029.

[6] Tehrani MW, Newmeyer MN, Rule AM, Prasse C. Characterizing the Chemical Landscape in Commercial E-Cigarette Liquids and Aerosols by Liquid Chromatography-High-Resolution Mass Spectrometry. Chem Res Toxicol. 2021 Oct 18;34(10):2216-2226. doi: 10.1021/acs.chemrestox.1c00253. Epub 2021 Oct 5. PMID: 34610237

[7] Hackshaw A, Morris JK, Boniface S, Tang JL, Milenković D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. BMJ. 2018 Jan 24;360:j5855. doi: 10.1136/bmj.j5855. Erratum in: BMJ. 2018 Apr 11;361:k1611. Erratum in: BMJ. 2018 Nov 28;363:k5035. PMID: 29367388; PMCID: PMC5781309.

[8] National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems; Kathleen Stratton, Leslie Y. Kwan, and David L. Eaton, Editors. Public Health Consequences of E-Cigarettes. Washington, DC: National Academies Press, 2018. https://nap.nationalacademies.org/catalog/24952/public-health-consequences-of-e-cigarettes

been substantial progress in filling the knowledge gap that the National Academies identified. There are now at least 61 epidemiological studies that contain data that allow comparisons of e-cigarettes and cigarettes or dual use vs. cigarettes.

In addition to studies that have directly estimated these risks to people who use e-cigarettes available in the market, there are other studies that separately estimate the risks of e-cigarette use and cigarette use compared to non-use of tobacco products as well as the risks of dual use of e-cigarettes and cigarettes, generally compared to non-use of tobacco products. These studies make it possible to conduct meta-analyses to estimate the risks of e-cigarettes compared to cigarette use and dual use compared to cigarette smoking in the general population for cardiovascular disease, asthma, chronic obstructive lung disease (COPD) and related respiratory conditions, and oral disease. In addition, single studies on the association between e-cigarette use and several other disease outcomes were identified.

This public comment presents preliminary results of a meta-analysis of 61 papers (Table S1) assessing 66 outcomes.

The population-level risks of actual disease associated with e-cigarette use for cardiovascular diseases and oral disease for e-cigarettes are not significantly different from cigarettes. The risk of lung disease (asthma and chronic obstructive pulmonary disease [COPD] and related respiratory conditions) is lower, but still much higher than the FDA assumes. There are also single studies of several other outcomes showing similar effects. In all cases, dual use is more dangerous than cigarettes alone.

For these reasons, the FDA's logic for the exemption melts away. FDA should update its analysis of e-cigarettes and other reduced risk products to focus on actual disease outcomes rather than extrapolating from biomarkers. The exemption to the menthol rule should be removed.

FINDINGS

The Appendix presents the details of study identification and the statistical aspects of the analysis.

A total of 61 studies reporting 66 outcomes were included in the meta-analysis (Table S2): cardiovascular disease (11), asthma (26), COPD/respiratory risks (13), oral disease (9) and other outcomes (7; bone fracture, cancer, COVID, depression, general health status, metabolic syndrome, obesity).

Most of the 61 studies were based on large ongoing US nationally representative surveys (PATH: 20 [33%], BFRSS: 13 [21%], NHANES: 4 (7%), NHIS: 3 [5%], YRBSS: 2 [3%]). The rest were from US state surveys (2 [3%]), national surveys outside the US (Korea: 8 [13%]; Other 4 [7%]) or data collected by the study's authors (5 [8%]).

Table 1 and Figure 1 show the results comparing e-cigarette use with cigarette use. ***The adjusted odds of cardiovascular disease (coronary heart disease, erective dysfunction,***

hypertension, myocardial infarction, and stroke) (OR=0.86; 95% CI 0.64-1.15; p=0.319) and oral disease (0.90; 0.73-1.10; p=0.294) and were not significantly different from 1.00. E-cigarette users were less likely to report having asthma (0.81; 0.70-0.94, p=.006) and COPD/composite respiratory endpoints than cigarette smokers (0.59; 0.43-0.81, p<.001). Among the other outcomes, COVID and general health risks for e-cigarettes and cigarettes were comparable, although there was only one study with each outcome. Cancer risk was higher among e-cigarette users than smokers, although the specific cancers were different.[33] Because the other outcomes were only assessed in one study each, these results were not pooled and should be interpreted cautiously.

Table 2. Odds of disease (95% CI)

	Cardiovascular	Asthma	COPD/respiratory	Oral disease
Versus cigarettes				
E-cigarettes vs cigarettes	0.86 (0.64-1.15) p=0.319	0.81 (0.70-0.94) p=.006	0.59 (0.43-0.81) p<.001	0.90 (0.73-1.10) p=.294
Dual use vs. cigarettes	1.37 (1.20-1.58) p<.001	1.24 (1.13-1.35) p<.001	1.45 (1.26-1.65) p<.001	1.56 (1.16-2.08) p=.003
Versus no use of either product				
E-cigarette	1.36 (1.10-1.69) p=0.004	1.31 (1.22-1.40) p<.001	1.57 (1.40-1.75) p<.001	1.57 (1.22-2.02) p<.001
Cigarette	1.74 (1.42-2.13) p<.001	1.64 (1.41-1.92) p<.001	2.77 (2.02-3.81) p<.001	2.02 (1.80-2.26) p<.001
Dual use	2.02 (1.54-2.64) p<.001	2.09 (1.54-2.83) p<.001	5.02 (3.73-6.76) p<.001	2.04 (1.40-2.97) p<.001

Table 1 and Figure 2 shows significantly higher risks associated with dual use compared to using cigarettes alone for all outcomes: ***cardiovascular disease (1.37; 1.20-1.58, p<.001), asthma (1.24; 1.13-1.35, p<.001), COPD/respiratory (1.45; 1.26-1.65, p<.001) and oral disease (2.04; 1.40-2.97, p<.001).*** Odds of some other outcomes (cancer, general health metabolic syndrome, obesity) but not others (bone fracture, COVID) were significantly elevated compared to cigarettes. As noted above, these results were not pooled and need to be interpreted cautiously because there is only one study of each outcome.

Table 2 and Figures S1, S2 and S2 present the meta-analyses for e-cigarette, cigarette and dual use vs. no product use; all show significantly elevated odds of disease compared to non-users.

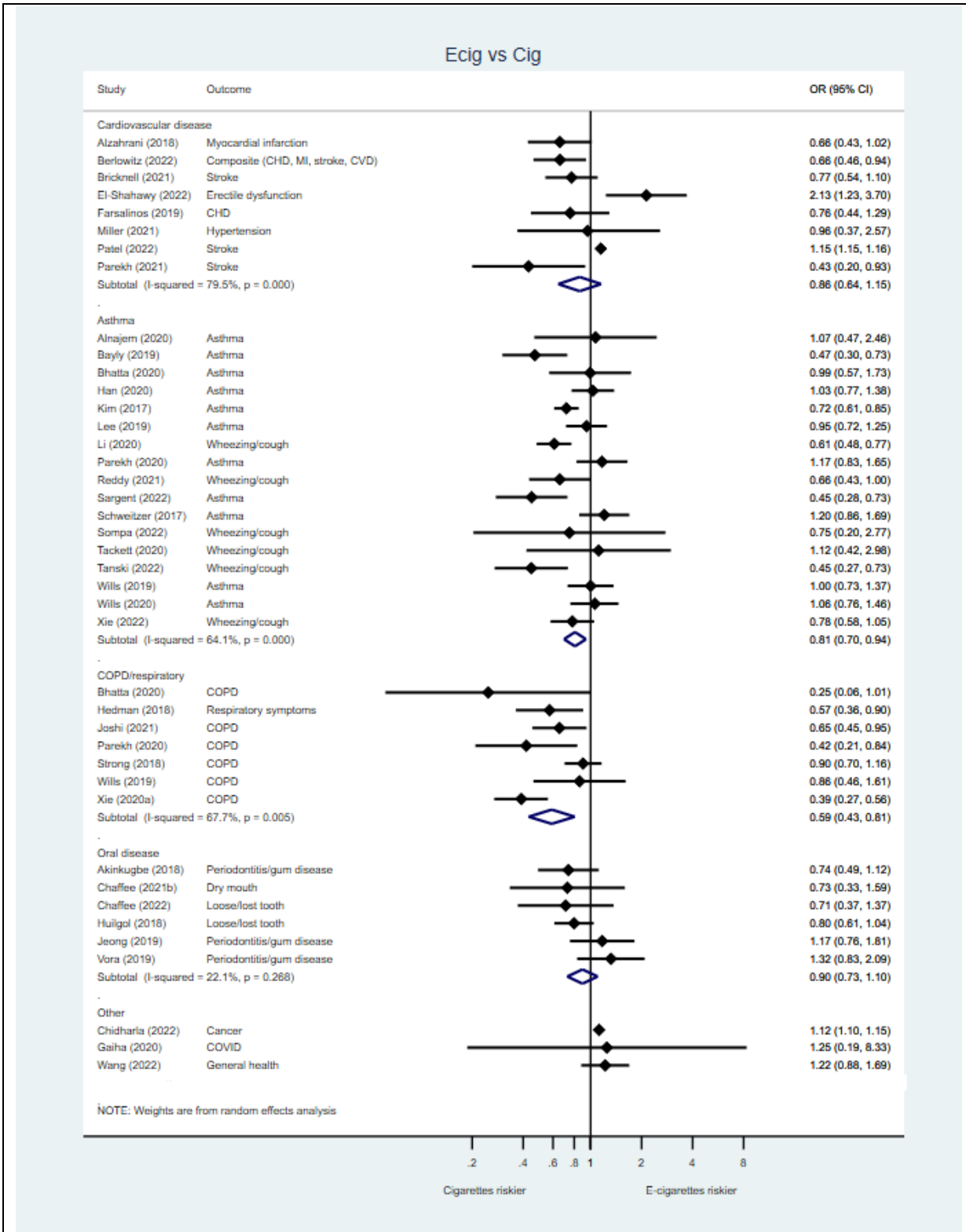

Figure 1. E-cigarette use has similar risks as cigarette smoking for CVD, asthma/bronchitis and dental disease; e-cigarettes have lower risk of COPD and composite respiratory conditions. Diamonds show point estimates and 95% confidence intervals for pooled risks from random effects meta-analysis. Results for "other" studies were not pooled.

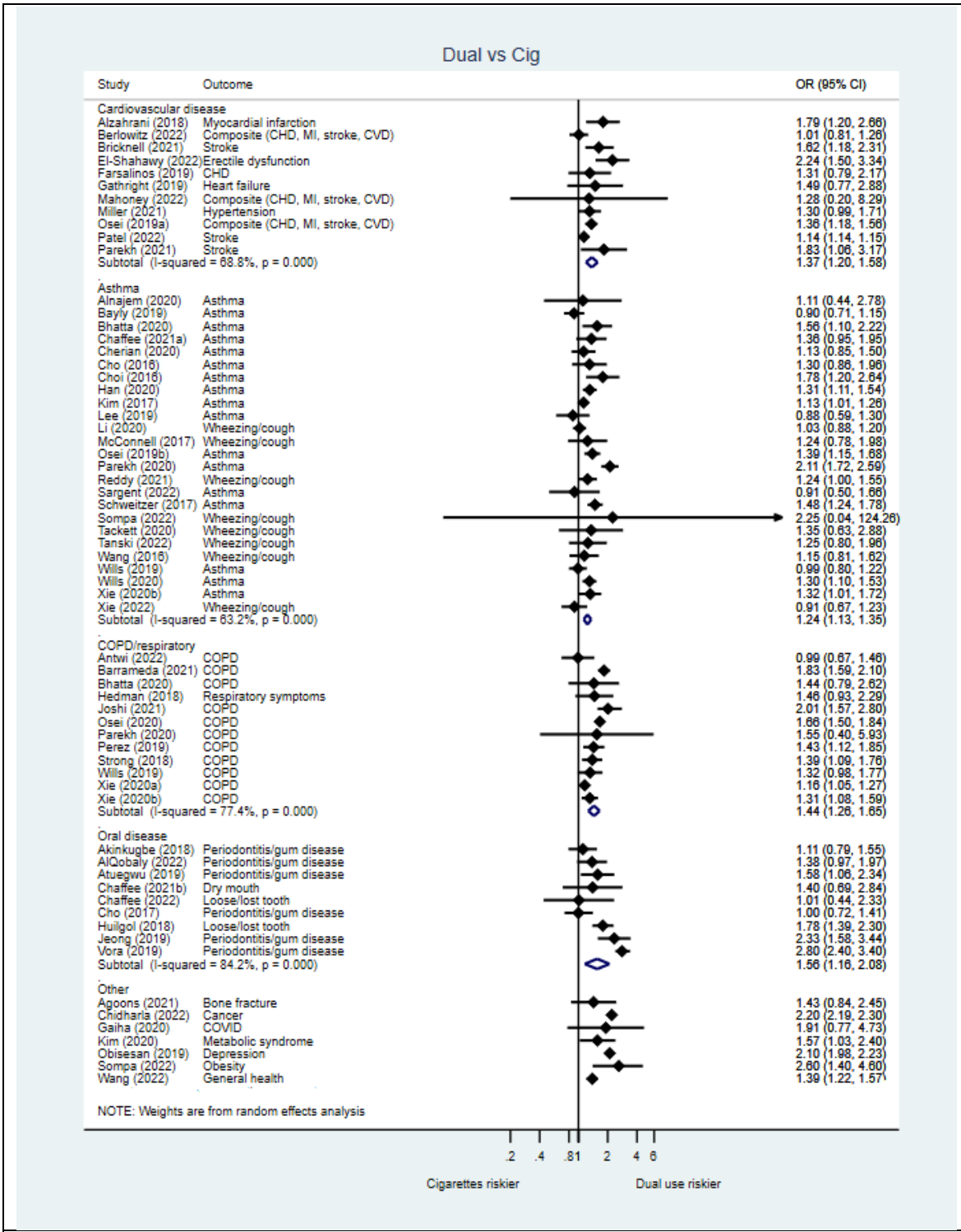

Figure 2. Risk of all outcomes is significantly higher in dual users compared to cigarette smokers. Diamonds show point estimates and 95% confidence intervals for pooled risks from random effects meta-analysis. Results for "other" studies were not pooled.

Discussion

These risks are consistent with biological studies that show a wide range of adverse cardiovascular,[9] pulmonary[10] and oral disease effects.[11] The risks identified in the epidemiological studies are higher than what one would predict from the biomarker studies.[12] This situation may be due to the fact that the biomarker studies focus on a small number of biomarkers which are predominately related to carcinogens in cigarettes. E-cigarettes expose users to thousands of different toxins than cigarettes do.[13] While there is some overlap, e-cigarettes and cigarettes together deliver a wider variety of toxins than either does alone. This fact may explain the higher risks observed among dual users compared to cigarettes.

Sensitivity analysis shows that these findings are independent of the details of study design, including whether the study is longitudinal or cross-sectional, whether the reference condition is never product use or non-current product use, whether studying current or ever use, the statistical model (multivariate or stratified) used in the analysis, whether the sample was adults or youth and whether disease currently present (generally in last 12 months) or ever. The results are also stable over time.

This insensitivity to study design characteristics is evidence against reverse causality. E-cigarette findings are unlikely to be artifacts of former smoking because all the studies either

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[9] Rao P, Han DD, Tan K, Mohammadi L, Derakhshandeh R, Navabzadeh M, Goyal N, Springer ML. Comparable Impairment of Vascular Endothelial Function by a Wide Range of Electronic Nicotine Delivery Devices. Nicotine Tob Res. 2022 Jun 15;24(7):1055-1062. doi: 10.1093/ntr/ntac019. PMID: 35100430; PMCID: PMC9199952.
Keith R, Bhatnagar A. Cardiorespiratory and Immunologic Effects of Electronic Cigarettes. Curr Addict Rep. 2021;8(2):336-346. doi: 10.1007/s40429-021-00359-7. Epub 2021 Mar 5. PMID: 33717828; PMCID: PMC7935224.
Tarran R, Barr RG, Benowitz NL, Bhatnagar A, Chu HW, Dalton P, Doerschuk CM, Drummond MB, Gold DR, Goniewicz ML, Gross ER, Hansel NN, Hopke PK, Kloner RA, Mikheev VB, Neczypor EW, Pinkerton KE, Postow L, Rahman I, Samet JM, Salathe M, Stoney CM, Tsao PS, Widome R, Xia T, Xiao D, Wold LE. E-Cigarettes and Cardiopulmonary Health. Function (Oxf). 2021 Feb 8;2(2):zqab004. doi: 10.1093/function/zqab004. PMID: 33748758; PMCID: PMC7948134.

[10] Gotts JE, Jordt SE, McConnell R, Tarran R. What are the respiratory effects of e-cigarettes? BMJ. 2019 Sep 30;366:l5275. doi: 10.1136/bmj.l5275. Erratum in: BMJ. 2019 Oct 15;367:l5980. PMID: 31570493; PMCID: PMC7850161.
Wills TA, Soneji SS, Choi K, Jaspers I, Tam EK. E-cigarette use and respiratory disorders: an integrative review of converging evidence from epidemiological and laboratory studies. Eur Respir J. 2021 Jan 21;57(1):1901815. doi: 10.1183/13993003.01815-2019. PMID: 33154031; PMCID: PMC7817920.
Tarran R, Barr RG, Benowitz NL, Bhatnagar A, Chu HW, Dalton P, Doerschuk CM, Drummond MB, Gold DR, Goniewicz ML, Gross ER, Hansel NN, Hopke PK, Kloner RA, Mikheev VB, Neczypor EW, Pinkerton KE, Postow L, Rahman I, Samet JM, Salathe M, Stoney CM, Tsao PS, Widome R, Xia T, Xiao D, Wold LE. E-Cigarettes and Cardiopulmonary Health. Function (Oxf). 2021 Feb 8;2(2):zqab004. doi: 10.1093/function/zqab004. PMID: 33748758; PMCID: PMC7948134.

[11] Holliday R, Chaffee BW, Jakubovics NS, Kist R, Preshaw PM. Electronic Cigarettes and Oral Health. J Dent Res. 2021 Aug;100(9):906-913. doi: 10.1177/00220345211002116. Epub 2021 Mar 25. PMID: 33764176; PMCID: PMC8293737.

[12] Wilson N, Summers JA, Ait Ouakrim D, Hoek J, Edwards R, Blakely T. Improving on estimates of the potential relative harm to health from using modern ENDS (vaping) compared to tobacco smoking. BMC Public Health. 2021 Nov 8;21(1):2038. doi: 10.1186/s12889-021-12103-x. PMID: 34749706; PMCID: PMC8577029.

[13] Tehrani MW, Newmeyer MN, Rule AM, Prasse C. Characterizing the Chemical Landscape in Commercial E-Cigarette Liquids and Aerosols by Liquid Chromatography-High-Resolution Mass Spectrometry. Chem Res Toxicol. 2021 Oct 18;34(10):2216-2226. doi: 10.1021/acs.chemrestox.1c00253. Epub 2021 Oct 5. PMID: 34610237

controlled for former smoking in the statistical model or stratified on smoking, with e-cigarette users among never smokers analyzed separately from current and former smokers. The fact that many e-cigarette users are dual users is not a problem because dual use is one of the specific variables in the analysis.

Most epidemiological assessments of e-cigarettes have focused on measuring absolute risk of use vs. non-use, and these assessments are often complicated by the fact that many adult e-cigarette users are former smokers or dual users (i.e., they use e-cigarettes while continuing to smoke). The important question from a policy perspective, however, is how e-cigarette risks compare to cigarette risk (i.e., the potential benefit of "switching completely") and how the risk of dual use compares to just smoking, because dual use is a common behavior among adults who use e-cigarettes[14] and some youth.

In contrast to conclusions drawn based on assessment of some biomarkers of exposure to tobacco products, the available direct epidemiological evidence based on actual use of e-cigarettes in the population suggests that, at least for some outcomes, e-cigarettes are as harmful as cigarettes and dual use is significantly more harmful than smoking. Even for the outcomes that were less risky than smoking disease -- asthma (OR=0.81) and COPD and composite respiratory outcomes (OR=0.59) e-cigarettes had 4-5 times the risk the FDA assumes in the proposed rule prohibiting menthol as a characterizing flavor in cigarettes.[15] The available data is also inconsistent with the FDA's assumption made in its authorizations to sell Vuse Solo e-cigarettes[16] and Logic e-cigarettes and heated tobacco product[17] that dual use is less dangerous or, at most, no more dangerous than smoking, with 1.2 to 1.6 times the odds of disease among dual users compared to smokers. ***These findings suggest a need for a broad reassessment of the value of e-cigarettes as a less risky alternative to cigarettes, particularly given the fact that many adults who use e-cigarettes continue to smoke at the same time (i.e., are dual users).***

Conclusion

FDA's proposed exception for "reduced risk" cigarettes in its proposed product standard prohibiting menthol in cigarettes grossly underestimates the health risks of e-cigarette use and dual use. Analysis of 61 recently published epidemiological studies provides significant evidence

[14] Osibogun O, Bursac Z, Maziak W. Longitudinal transition outcomes among adult dual users of e-cigarettes and cigarettes with the intention to quit in the United States: PATH Study (2013-2018). Prev Med Rep 2022;26:101750 (PMC8897625).

[15] U.S. Food and Drug Administration. FDA Proposes Rules Prohibiting Menthol Cigarettes and Flavored Cigars to Prevent Youth Initiation, Significantly Reduce Tobacco-Related Disease and Death. 2022 [updated April 28, 2022; cited 2022 June 26]; Available from: https://www.fda.gov/news-events/press-announcements/fda-proposes-rules-prohibiting-menthol-cigarettes-and-flavored-cigars-prevent-youth-initiation.

[16] Food and Drug Administration. Technical Product Lead (TPL) Review of PMTAs PM0000551, PM0000553, PM0000560 (RJ Reynolds Vapor Co): FDA Center for Tobacco Products 2021 October 12, 2021.https://www.fda.gov/media/153017/download

[17] Food and Drug Administration. Technical Product Lead (TPL) Review of PMTAs PM0000551, PM0000553, PM0000560 (RJ Reynolds Vapor Co): FDA Center for Tobacco Products 2021 October 12, 2021.https://www.fda.gov/media/153017/download
Food and Drug Administration. Technical Product Lead (TPL) Reivew of PMTAs PM0000529-PM0000541 (Logic Technology) 2022 03/23/2022.https://www.fda.gov/media/157144/download

that for several adverse outcomes, e-cigarettes are as harmful as cigarettes and dual use is significantly more harmful than smoking. Therefore, while we generally support FDA's proposed product standard prohibiting menthol as a characterizing flavor in cigarettes, ***we urge FDA to eliminate an exception for so-called "reduced risk" products in the proposed standard.***

APPENDIX: METHODS FOR META-ANALYSIS

Data

Study identification

We started by searching PubMed for studies whose PubMed records were created between January 1, 2005 (before e-cigarettes entered the US market) and June 16, 2022. The search for cardiovascular disease was

> ((e-cigarette* OR ENDS) AND (heart OR cardiac OR cardiovascular OR stroke OR infarct* OR vascular) AND (odds OR "relative risk" OR epidemiolog*)) (("2005/01/01"[Date - Create]: "3000"[Date - Create]))

Similar searches were done for pulmonary and dental disease:

> ((e-cigarette* OR ENDS) AND (lung OR pulmonary OR asthma OR COPD OR bronchitis) and (odds OR "relative risk" OR epidemiolog*)) AND (("2005/01/01"[Date - Create] : "3000"[Date - Create]))[18]

> ((e-cigarette* OR ENDS) AND (dental OR oral OR periodont* OR caries OR cavities OR "oral microbiome" OR tooth OR teeth OR "dry mouth") AND (odds OR "relative risk" OR epidemiolog*)) AND (("2005/01/01"[Date - Create] : "3000"[Date - Create]))

Population-based studies of e-cigarettes that reported the risk of a clinical outcome were included adjusted for possible demographic confounders. The following types of studies were excluded: prevalence and use patterns, cessation studies, biomarkers, studies of EVALI, experimental studies and other studies used to elucidate mechanisms, reviews, meta-analyses and commentaries. The reference lists in reviews and meta-analyses were examined to identify studies that the PubMed searches did not identify. Relevant studies included in publication tracking services on e-cigarettes were also included. Studies identified in one PubMed search that were relevant to a different outcome were included in that outcome.

Several when a study had separate analyses of different outcome categories, we used them in both. In papers that included several measures of the same outcome, we selected the broadest measure.

A total of 61 studies reporting 66 outcomes were included in the analysis (Table S2, full citations in Table S1).

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[18] The pulmonary search was done in two segments, one from April 1, 2020 through June 16, 2022, and another from January 1, 2005 through March 31, 2020 because the initial analysis relied on the papers identified in the review by Wills et al. (Wills TA, Soneji SS, Choi K, Jaspers I, Tam EK. E-cigarette use and respiratory disorders: an integrative review of converging evidence from epidemiological and laboratory studies. Eur Respir J. 2021 Jan 21;57(1):1901815. doi: 10.1183/13993003.01815-2019. PMID: 33154031; PMCID: PMC7817920). For consistency, we later conducted our own search for the period from January 1, 2005 through March 31, 2020.

Definitions of e-cigarette use and smoking and presence of disease

All identified studies used the same definitions for ever- and current- e-cigarette use and smoking. Ever e-cigarette users were defined as respondents who had ever used an e-cigarette, even 1 or 2 puffs or even one time and current e-cigarette users were respondents who used e-cigarettes in the past 30 days. Ever smokers were defined as respondents who had smoked 100 cigarettes in their lifetime and current smokers were respondents who had smoked 100 cigarettes in their lifetime and had smoked in the past 30 days.

Disease diagnoses were self-reported, generally using questions similar to "Has a doctor, nurse, or other health professional told you that you had ___?"

Data extraction

Many studies reported several results (Table S2). The values we used in the quantitative meta-analysis are presented in ***bold italics***.

When a study included multiple measures of similar outcomes, we selected the one with the broadest scope.

When assessed different levels of exposure, we used the highest level of exposure that was reported for both e-cigarettes and cigarettes.

When papers presented models with different numbers of potential confounders, we selected the most highly adjusted model. Several papers included adjustment for other forms of tobacco use and marijuana in their most-adjusted models.

Studies were categorized as multivariate, in which case e-cigarettes and cigarettes were entered into the same logistic regression together, or stratified, in which case different categories of e-cigarette and cigarette use were analyzed separately (e.g., e-cigarette only, cigarette only, dual use). Some papers presented results using both approaches. When that was the case, we selected the ORs with the smallest magnitude.

Some studies reported results based on ever and current use; we used the current use values when both were available. When studies reported days per month used (and not all current use), we used the most frequent use risks.

The comparison groups were sometimes never users and sometimes non-current users. When both were available, we use the comparisons against never users.

Analysis

E-cigarette risk vs cigarette risk

We compared risks associated with e-cigarette use with risks associated with cigarette use by computing

$$OR_{ecig\ vs\ cig} = \frac{OR_{ecig}}{OR_{cig}}$$

To estimate the 95% confidence interval for this odds ratio, first take the logarithm of both sides of this equation:

$$\ln OR_{ecig\ vs\ cig} = lnOR_{ecig} - lnOR_{cig}$$

We can compute the standard errors associated with each of these ORs from the associated 95% confidence intervals:

$$s = \frac{\ln OR_{upper} - lnOR_{lower}}{2 \times 1.960}$$

To get the standard error for $\ln OR_{ecig\ vs\ cig}$ we take advantage of the fact that the formula for the variance of a difference of two independent variables is

$$s_{ecig\ vs\ cig} = \sqrt{s_{ecig}^2 + s_{cig}^2}$$

OR_{ecig} and OR_{cig} are not independent because both use the same group of non-users of either e-cigarettes and cigarettes as the same reference group. When the two variables are correlated,

$$s_{ecig-cig} = \sqrt{s_{ecig}^2 + s_{cig}^2 - 2rs_{ecig}s_{cig}}$$

where r is the correlation of the estimates of the two ORs. That correlation is not reported in the papers, so we conducted a sensitivity analysis assuming the actual standard error of the difference was ¼ of the value computed assuming that the results estimates are independent.

Dual use risk vs cigarette only risk.

Because the risks associated with of e-cigarettes and cigarettes compared to no product use are as independent in the multivariate logistic regressions, the e-cigarette risk is the marginal risk of e-cigarette use over no product use, controlling for cigarette smoking. Therefore, it is also an estimate of the marginal risk of dual use (e-cigarettes plus cigarettes) compared to smoking alone.

Dual use risk is estimated directly in the stratified models. In that case,

$$OR_{dual\ vs\ cig} = \frac{OR_{dual}}{OR_{cig}}$$

is computed as described above. In some cases, studies reported $OR_{dual\ vs\ cig}$ directly, in which case we recorded that value and used that value.

In studies that reported both multivariate and stratified results, we used the results with the smallest OR in the meta-analysis

Statistical models

The odds ratios and estimated 95% confidence intervals were then used in random effects meta-analyses with the Stata 15.1 *metan* command for each outcome separately. We conducted sensitivity analyses to see if details of study design impacted the results using *metareg* of the natural logarithm of the odds ratios against study design characteristics (longitudinal vs. cross-sectional; whether the reference condition was never use or non-current use, whether product use was current or ever, and whether the estimate was based on multivariate or stratified estimates coded as 0/1 dummy variables), controlling for the outcome (4 effects coded dummy variables) and last year of data collection (continuous, centered on 2016.5, its mean). We also tested for an effect of youth samples (minimum age <18 years) and current vs. ever presence of disease on outcomes with *metareg.*

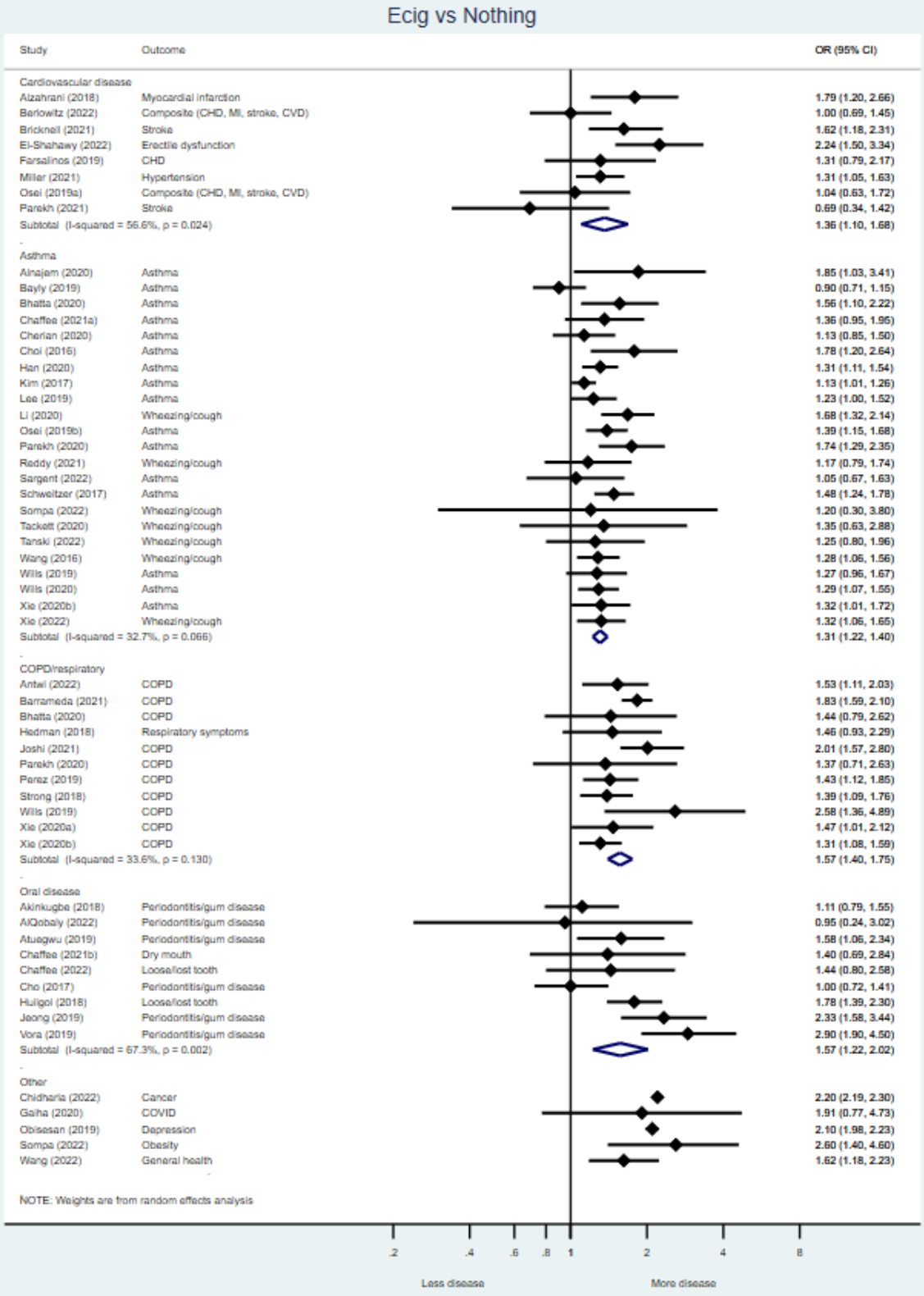

Figure S1. E-cigarettes vs. nothing. Diamonds show point estimates and 95% confidence intervals for pooled risks from random effects meta-analysis. Results for "other" studies were not pooled.

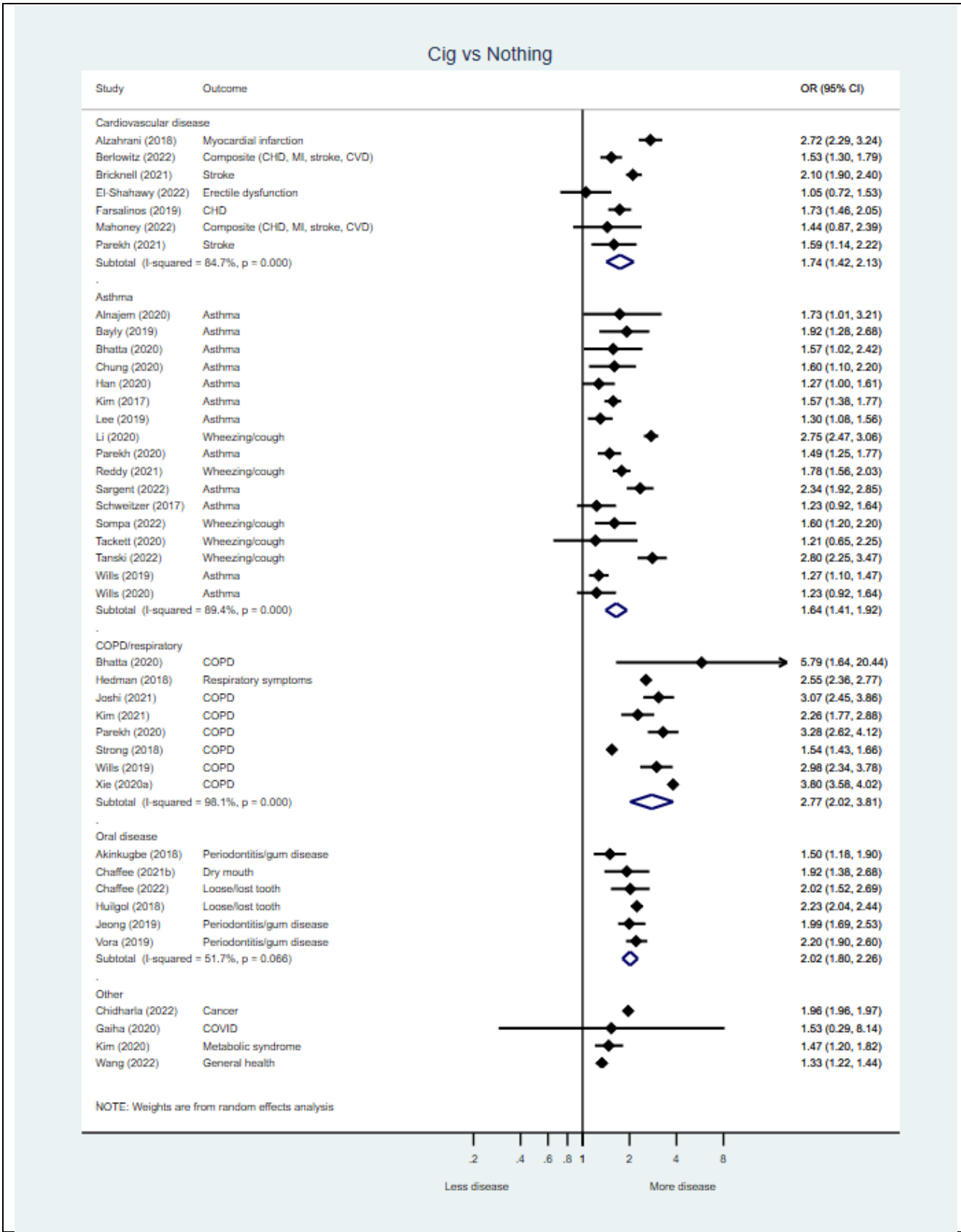

Figure S2. Cigarettes use vs. nothing. Diamonds show point estimates and 95% confidence intervals for pooled risks from random effects meta-analysis. Results for "other" studies were not pooled.

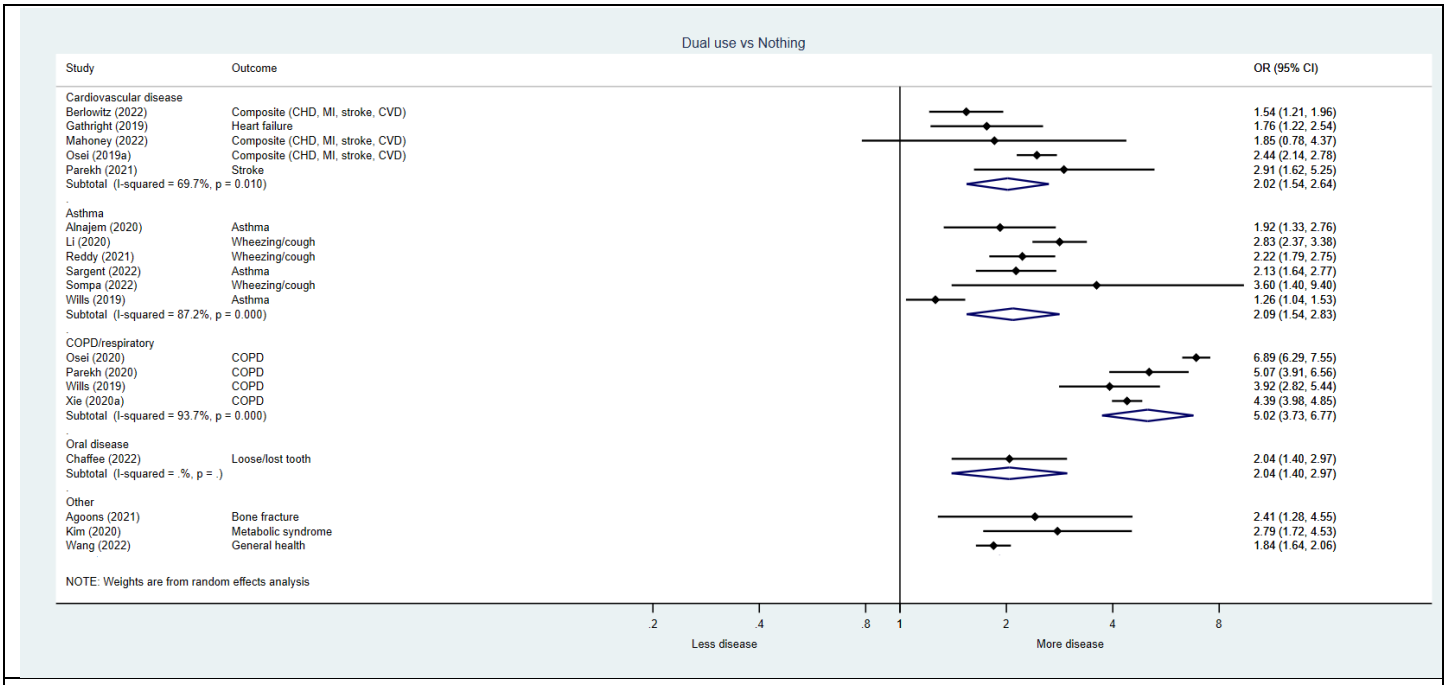

Figure S3. Dual use vs. nothing. Diamonds show point estimates and 95% confidence intervals for pooled risks from random effects meta-analysis. Results for "other" studies were not pooled.

Table S1. Studies included in meta-analysis	
Agoons (2021)	Agoons DD, Agoons BB, Emmanuel KE, Matawalle FA, Cunningham JM. Association between electronic cigarette use and fragility fractures among US adults, American Journal of Medicine Open, Volumes 1–6, 2021, 100002, ISSN 2667-0364, https://doi.org/10.1016/j.ajmo.2021.100002.
Akinkugbe (2019)	Akinkugbe AA. Cigarettes, E-cigarettes, and Adolescents' Oral Health: Findings from the Population Assessment of Tobacco and Health (PATH) Study. JDR Clin Trans Res. 2019 Jul;4(3):276-283. doi: 10.1177/2380084418806870. Epub 2018 Oct 15. PMID: 30931714.
Alnajem (2020)	Alnajem A, Redha A, Alroumi D, Alshammasi A, Ali M, Alhussaini M, Almutairi W, Esmaeil A, Ziyab AH. Use of electronic cigarettes and secondhand exposure to their aerosols are associated with asthma symptoms among adolescents: a cross-sectional study. Respir Res. 2020 Nov 16;21(1):300. doi: 10.1186/s12931-020-01569-9. PMID: 33198741; PMCID: PMC7670675.
AlQobaly (2022)	AlQobaly L, Abed H, Alsahafi Y, Sabbah W, Hakeem FF. Does smoking explain the association between use of e-cigarettes and self-reported periodontal disease? J Dent. 2022 Jul;122:104164. doi: 10.1016/j.jdent.2022.104164. Epub 2022 May 14. PMID: 35580834.
Alzahrani (2018)	Alzahrani T, Pena I, Temesgen N, Glantz SA. Association Between Electronic Cigarette Use and Myocardial Infarction. Am J Prev Med. 2018 Oct;55(4):455-461. doi: 10.1016/j.amepre.2018.05.004. Epub 2018 Aug 22. Erratum in: Am J Prev Med. 2019 Oct;57(4):579-584. PMID: 30166079; PMCID: PMC6208321
Antwi (2022)	Antwi GO, Rhodes DL. Association between E-cigarette use and chronic obstructive pulmonary disease in non-asthmatic adults in the USA. J Public Health (Oxf). 2022 Mar 7;44(1):158-164. doi: 10.1093/pubmed/fdaa229. PMID: 33348361.
Atuegwu (2019)	Atuegwu NC, Perez MF, Oncken C, Thacker S, Mead EL, Mortensen EM. Association between Regular Electronic Nicotine Product Use and Self-reported Periodontal Disease Status: Population Assessment of Tobacco and Health Survey. Int J Environ Res Public Health. 2019 Apr 9;16(7):1263. doi: 10.3390/ijerph16071263. PMID: 30970567; PMCID: PMC6479961.
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Chaffee (2021a)	Chaffee BW, Barrington-Trimis J, Liu F, Wu R, McConnell R, Krishnan-Sarin S, Leventhal AM, Kong G. E-cigarette use and adverse respiratory symptoms among adolescents and Young adults in the United States. Prev Med. 2021 Dec;153:106766. doi: 10.1016/j.ypmed.2021.106766. Epub 2021 Aug 19. PMID: 34418439; PMCID: PMC8595821.
Chaffee (2021b)	Chaffee BW, Halpern-Felsher B, Cheng J. E-cigarette, cannabis and combustible tobacco use: associations with xerostomia among California adolescents. Community Dent Oral Epidemiol. 2021 Dec 20. doi: 10.1111/cdoe.12721. Epub ahead of print. PMID: 34927762.
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Cho (2017)	Cho JH. The association between electronic-cigarette use and self-reported oral symptoms including cracked or broken teeth and tongue and/or inside-cheek pain among adolescents: A cross-sectional study. PLoS One. 2017 Jul 11;12(7):e0180506. doi: 10.1371/journal.pone.0180506. PMID: 28700729; PMCID: PMC5507461
Choi (2016)	Choi K, Bernat D. E-Cigarette Use Among Florida Youth With and Without Asthma. Am J Prev Med. 2016 Oct;51(4):446-53. doi: 10.1016/j.amepre.2016.03.010. Epub 2016 Apr 13. PMID: 27085691; PMCID: PMC5030120.
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Osei (2019a)	Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Uddin SMI, Benjamin EJ, Hall ME, DeFilippis AP, Stokes A, Bhatnagar A, Nasir K, Blaha MJ. Association Between E-Cigarette Use and Cardiovascular Disease Among Never and Current Combustible-Cigarette Smokers. Am J Med. 2019 Aug;132(8):949-954.e2. doi: 10.1016/j.amjmed.2019.02.016. Epub 2019 Mar 8. PMID: 30853474.
Osei (2019b)	Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Uddin SMI, Dardari ZA, DeFilippis AP, Bhatnagar A, Blaha MJ. The association between e-cigarette use and asthma among never combustible cigarette smokers: behavioral risk factor surveillance system (BRFSS) 2016 & 2017. BMC Pulm Med. 2019 Oct 16;19(1):180. doi: 10.1186/s12890-019-0950-3. PMID: 31619218; PMCID: PMC6796489.
Osei (2020)	Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Uddin SMI, Benjamin EJ, Hall ME, DeFilippis AP, Bhatnagar A, Biswal SS, Blaha MJ. Association Between E-Cigarette Use and Chronic Obstructive Pulmonary Disease by Smoking Status: Behavioral Risk Factor Surveillance System 2016 and 2017. Am J Prev Med. 2020 Mar;58(3):336-342. doi: 10.1016/j.amepre.2019.10.014. Epub 2020 Jan 2. PMID: 31902685.
Parekh (2020)	Parekh T, Owens C, Fay K, Phillips J, Kitsantas P. Use of e-Cigarettes and Development of Respiratory Conditions in Women of Childbearing Age. South Med J. 2020 Oct;113(10):488-494. doi: 10.14423/SMJ.0000000000001158. PMID: 33005962.
Parekh (2021)	Parekh T, Pemmasani S, Desai R. Risk of Stroke With E-Cigarette and Combustible Cigarette Use in Young Adults. Am J Prev Med. 2020 Mar;58(3):446-452. doi: 10.1016/j.amepre.2019.10.008. Epub 2020 Jan 7. PMID: 31924460.
Patel (2022)	Patel U, Patel N, Khurana M, Parulekar A, Patel A, Ortiz JF, Patel R, Urhoghide E, Mistry A, Bhriguvanshi A, Abdulqader M, Mehta N, Arumaithurai K, Shah S. Effect Comparison of E-Cigarette and Traditional Smoking and Association with Stroke-A Cross-Sectional Study of NHANES. Neurol Int. 2022 May 27;14(2):441-452. doi: 10.3390/neurolint14020037. PMID: 35736618; PMCID: PMC9227824.
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Xie (2022)	Xie W, Tackett AP, Berlowitz JB, Harlow AF, Kathuria H, Galiatsatos P, Fetterman JL, Cho J, Blaha MJ, Hamburg NM, Robertson RM, DeFilippis AP, Hall ME, Bhatnagar A, Benjamin EJ, Stokes AC. Association of Electronic Cigarette Use with Respiratory Symptom Development among U.S. Young Adults. Am J Respir Crit Care Med. 2022 Jun 1;205(11):1320-1329. doi: 10.1164/rccm.202107-1718OC. PMID: 35089853.

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Cardiovascular Disease								
Alzahrani (2018)	n=69,046 US adults NHIS 2014 and 2016	Myocardial infarction	***Daily e-cigarette use vs. never ENDS use =1.79 (1.20, 2.66)*** Some day vs. never =1.16 (0.83, 1.62) Former vs. never=1.06 (0.86, 1.30)	***Daily smokers vs. never smokers = 2.72 (2.29, 3.24)*** current vs. never= 2.64 (2.24, 3.12) Some day smokers vs. Never smokers= 2.36 (1.80, 3.09) Former smokers vs. Never smokers =1.70 (1.51, 1.91)			demographic (sex, age, BMI, race/ethnicity) and clinical covariates (hypertension, diabetes mellitus, high cholesterol)	Table 2
Berlowitz (2022)	**Longitudinal** n=24,027 US adults without CVD history PATH 2013-2019	Incident CVD	***sole ENDS vs. nonusers = 1.00 (0.69, 1.45)***	***sole cig vs. nonusers = 1.53 (1.30, 1.79)***	***DU vs. non use=1.54 (1.21, 1.96)*** ***DU vs. sole cig=1.01 (0.81, 1.26)***	***sole ENDS vs. sole Cig = 0.66 (0.46, 0.94)***	cigarette pack years and its square, time-varying current use of combustible (cigars, cigarillos, pipes, or hookah) and noncombustible (snus or other smokeless tobacco) tobacco use age, sex, race and ethnicity, education, BMI, high blood pressure,high cholesterol, diabetes, close relative with MI or heart surgery, marijuana use	Table (no number)
Bricknell (2021)	n=465,594 US adults BRFSS 2016	Stroke	***Every day vs never=1.62 (1.18-2.31)*** Some days vs never = 1.28 (1.02-1.61) Former vs never = 1.09 (0.98-1.23)	***Every day vs never = 2.1 (1.9-2.4)*** Some day vs never = 1.8 (1.6-2.1) Former vs never = 1.3 (1.2-1.4)			smokeless tobacco use sex, age, race, body mass index, coronary artery disease, chronic kidney disease, diabetes mellitus	Tables 2-3

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
El-Shahawy (2022)	n=13,711 US males (20+ yro) PATH 2016-2018 age-restrcted CVD-free sample (i.e., aged <65 years with no reported CVD; n=11,207).	Erectile dysfunction	***Daily vs. never = 2.24 (1.50- 3.34)*** Some day vs. never=1.43 (0.88-2.31) Former vs never: 1.12 (0.87-1.45)	***Current vs. never=1.05 (0.72-1.53)*** Former vs. never= 0.84 (0.60- 1.19)	***DU vs. never users of both ENDS and cig= 1.68 (1.05, 2.69)*** among people without CVD diagnosis	Current ENDS users who were former smokers vs. Never users of both=1.85 (1.06, 3.24) among people without CVD diagnosis	other tobacco product use age, sexual orientation, race/ethnicity, educational attainment, annual household income, U.S. region, BMI, physical activity frequency, diabetes, hypertension, high cholesterol, and mental health status	Tables 2-4
Farsalinos (2019)	n=59,770 US adults NHIS 2016-2017	Coronary Heart Disease (CHD)	For CHD: ***Daily use vs. never = 1.31 (0.79 - 2.17)*** Some days vs. never = 1.13 (0.70 - 1.83) Former vs. never= 1.03 (0.83-1.28) For MI: ***Daily use vs. never =1.35 (0.80-2.27)*** Some days vs. never = 1.22 (0.78 - 1.91) Former vs. never=0.96 (0.77 - 1.20)	For CHD: **Daily use vs. never =1.73 (1.46 - 2.05)** Some days vs. never = 1.75 (1.32 - 2.32) Former<=6 years vs. never= 1.96 (1.58 - 2.44) Former > 6 year vs. never = 1.43 (1.28 - 1.60) For MI: ***Daily use vs. never =3.13 (2.63 - 3.73)*** some days vs. never = 2.47 (1.79 - 3.40) Former<=6 years vs. never= 2.82 (2.22 - 3.57) Former > 6 year vs. never = 1.51 (1.32 - 1.74)			demographics (age, gender, race/ethnicity, other established risk factors for CVD (hypertension, hypercholesterolemia, and diabetes) and body-mass index (BMI)	Tables 2-3

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Gathright (2019)	n= 32,320 adults PATH 2013-2014	Heart failure	***Current (y vs. n)= 1.49 (0.77-2.88)***	***current (y vs. n) = 0.92 (0.75 – 1.14)***	***Current (y vs. n)= 1.76 (1.22 – 2.54)***		age, sex, race, and income	text
Mahoney (2022)	**Longitudinal** n=7,820 adults (40+ yro) without CVD history PATH 2013-2019	CVD incidence (in last 12 months)	NA (due to very small sample size)		***DU vs. never users= 1.85 (0.78-4.37)***	***sole combustible tob vs. never users=1.44 (0.87-2.39)*** tob quitters vs. never users= 1.18 (0.33-4.26)	sex, age, cigarette pack-years, ever report of high blood pressure or cholesterol, diabetes, BMI≥ 35, and family history of premature heart disease	Table 2 Table 1: average number of cigarette pack-years among continuing exclusive combustible-tobacco users was 25.1 years, compared to 16.1 years among those transitioning to exclusive ENDS use, 28.0 years among those transitioning to dual use, and 11.2 years among those who quit using tobacco

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Miller (2021)	n=19,147 US young and middle-aged adults (18-55 years old) PATH 2015-2016	Hypertension (last 12 mo)	***Current ecig vs not current: 1.31 (1.05-1.63)***	***Current cig vs not current: 1.27 (1.10-1.47)*** **Versus never smokers** Former smoker 1.28 (1.05-1.57) Exclusive smoker 1.36 (1.15-1.62) **Versus former smoker** Exclusive smoker: 1.06 (0.87-1.30)	***Dual use vs never smoker 1.77 (1.32-2.39)*** ***DU vs. sole cig= 1.30 (0.99, 1.71)***	**Versus never smokers** ***Exclusive vaper (never smoker) : 1.32 (0.50-3.53)*** Exclusive vaper (former smoker): 1.42 (0.98-2.06) **Versus former smokers** Exclusinve vaper (never smoker): 1.03 (0.38-2.83) Exclusive vaper (former smoker): 1.11 (0.74-1.66) **Versus exclusive smokers** ***Exclusive vaper (never smoker): 0.96 (0.37-2.57)*** Exclusive vaper (former smoker): 1.30 (0.99-1.71)	age, sex, race-ethnicity, education, annual household income, insurance status, marital status, leisure-time physical activity, body mass index (BMI), heavy alcohol use, hypercholesterolemia, and diabetes mellitus	Table 2 and Figure 2

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Osei (2019a)	n=449,092 US adults BRFSS 2016-2017,	composite of coronary heart disease, myocardial infarction, or stroke	Among never smokers: ***current vs. never = 1.04 (0.63-1.72)*** Daily vs. never= 1.35 (0.74-2.46***)*** occasional use vs. never = 0.95 (0.50-1.82) Among current smokers: ***current vs. never= 1.36 (1.18-1.56)*** Daily vs. never=1.59 (1.20-2.08) Occasional use vs. never = 1.30 (1.12-1.52)		***DU vs. current smoker with never use of ENDS=1.36 (1.18-1.56)*** ***DU vs. never use of both = 2.44 (2.14 - 2.78)*** DU with daily use of ENDS vs. current smokers with never use of ENDS= 1.59 (1.20 - 2.08)		age, sex, race, educational status, income, physical activity, body mass index, diabetes, and heavy alcohol drinking	Table 2 and text
Patel (2022)	n=79,825 US adults with smoking history NHANES 2015-2018	Stroke	***Current e-cig vs cig: 1.15 (1.15-1.16)*** Current ecig vs non-current ecig: 1.60 (1.60-1.61)		***Dual vs cig: 1.14 (1.14-1.15)***		age, gender, income, and comorbidities diabetes, cholesterol, hypertension, depression, cancer), substance abuse (marijuana, cocaine/heroin/methamphetamine, illegal injectable drug), alcohol use, and preventive aspirin use.	Table 3
Parekh (2021)	n=161,529 US adults aged 18-44 BRFSS 2016-2017	Stroke	Stratified ***current sole ecig use vs never use both: 0.69 (0.34–1.42)***	Stratified ***Current sole cig vs never use both: 1.59 (1.14-2.22)***	Stratified ***Dual use vs never use both: 2.91 (1.62-5.25)*** ***Dual use vs smokers: 1.83 (1.06-3.17)***	Stratified ***Sole ecig users vs never use both: 0.69 (0.34-1.42)*** ***Sole e-cig users vs sole cig users: 0.43 (0.20-0.93)***	age, sex, race, ethnicity, education, income, marital status, health insurance, census region, BMI, physical activity, binge drinking, diabetes, and hypertension, cholesterol (only available in BRFSS 2017)	Text and Figure 1
Asthma								

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Alnajem (2020)	n=1,565 adolescents (aged 16-19 years) a school-based cross-sectional study in Kuwait	Current asthma	***Current ecig vs never ecig & never smoker: 1.85 (1.03–3.41)***	***Current smoker vs never ecig & never smoker: 1.73 (1.01–3.21)***	***Current dual use vs never ecig never smoker: 1.92 (1.33–2.76)***		exposure to household secondhand smoke, exposure to household secondhand aerosols from electronic cigarettes, and exposure to secondhand smoke and/or secondhand aerosols from electronic cigarettes in public places sex, age	Table 2
Bayly (2019)	n=11,830 US youth (11-17 years old with asthma) The 2016 Florida Youth Tobacco survey	Past year asthma attack	risk for asthma attack: ***current vs. never= 0.90 (0.71-1.15)*** former vs. never=1.01 (0.81-1.25) secondhand ENDS aerosol exposure (y/n)= 1.27 (1.11-1.47)	Risk for asthma attack: ***current vs. never=1.92 (1.28-2.68)*** former vs. never=1.23 (0.99-1.52) secondhand exposure=1.19 (1.05-1.35)			Cigar, hookah, second smoke, secondhand aerosol age, sex, race/ethnicity, metropolitan status, housing type	Table 2
Bhatta (2020)	**Longitudinal** 23 760 (18–65 years) PATH Waves 1-3 2013-2016	incident asthma	***current vs. never = 1.56 (1.10-2.22)*** former vs. never = 1.23 (0.90-1.69)	***current vs. never =1.57 (1.02-2.42)*** former vs. never =0.87(0.53-1.42)			age, sex, race/ethnicity, poverty level, BMI, high blood pressure, high cholesterol, diabetes	Appendix Table 6

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Chaffee (2021a)	n=10,483 (13-21 years old) Pooled data from 4 ongoing studies 2018-2020	Adverse respiratory symptoms: bronchitis, asthma , and shortness of breath	**Risk for Asthma** ***6-30 days vs. never= 1.36 (0.95-1.95)*** 1-5 days vs. never = 1.27 (0.91-1.77) ever vs. never = 0.99 (0.85-1.15) **Risk for Bronchitis** 6-30 days vs. never= 1.56 (1.37-1.77) 1-5 days vs. never = 1.11 (0.94-1.31) ever vs. never = 1.07 (0.93–1.22) **Risk for Shortness of Breath:** 6-30 days vs. never = 1.68 (1.35-2.08) 1-5 days vs. never = 1.27 (0,95-1.17) ever vs. never = 1.08 (0.93-1.26)				past 30-day combustible tobacco use gender, race/ethnicity, school lunch program participation (adolescent studies only), personal income (young adult studies only), age, past 30-day cannabis use	Figure 1
Cherian (2020)	n=9750 adolescents (aged 12-17) PATH W3 2015-2016	diagnosis of asthma Wheezing/whistling in chest past 12 months	**Asthma diagnosis** ***ENDS in last year vs no, controlling for combustible tobacco use in last year: 1.13 (0.85-1.50)*** ENDS in last year vs no, controlling for combustible tobacco use in last year: 1.37 (1.11-1.71)				tobacco used by other household members, rules about combustible tobacco product use inside home, lifetime number of cigarettes used, and lifetime number of cigars used age, sex, race/ethnicity, parent education	Table 2

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Cho (2016)	n= 35904 (10th–12th graders) The 2014 Korean Youth Risk Behavior Survey	Past year Dx with asthma	***current vs. never = 2.77 (1.31-5.85)*** former vs. never = 0.96 (0.42-2.19)	***current vs. never = 1.47 (1.05-2.06)*** former vs. never = 0.99 (0.75-1.31)	***DU vs. sole smokers = 1.30 (0.86-1.96)***		second hand smoke exposure Age (high school grade), Gender, city size, student's economic status, residential type, multi-cultural family status, academic performance, overweight status, stress, atopic dermatitis history, allergic rhinitis history, asthma history, attempt to quit smoking,	Table 5-6
Choi (2016)	n=36,085 (9th–12th graders) The 2012 Florida Youth Tobacco Survey	asthma attack in past 12 mo	**Risk for asthma attack:** ***current (y/n)= 1.78 (1.20, 2.64)***				positive social norm toward smoking, exposure to secondhand smoke age, sex, race/ethnicity, metropolitan status, housing type	Figure 1
Chung (2020)	n=60,040 Korean students (aged 13-18) Korea Youth Risk Behavior Survey (June 2018)	Asthma (past 12 months) Allergic rhinitis	**Asthma** na **Allergic Rhinitis** Current ecig never cig vs nothing: 1.0 (0.4-2.2)	**Asthma** ***Current cig vs never cig never ecig: 1.6 (1.1-2.2)*** **Allergic rhinitis** Current cig vs never cig never ecig: 1.3 (1.1-1.6)	**Asthma** ***Current dual vs never ecig never cig: 1.2 (0.80-2.0)*** **Allergic rhitinis** Current dual use vs never cig never ecig: 1.6 (1.2-2.2)		exposure to secondhand smoke age, sex, body mass index, residential area, regular exercise, sedentary time, socioeconomic status	Table 4 (asthma) and Table 3 (allergic rhinitis) Model 2 results Data for never HTP users

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Han (2020)	n=21,532 respondents (9th -12th grade) YRBSS 2015 & 2017	Asthma (lifetime)	**In model including ecigs, cigs, marijuana** ***≥10 days/mo cigs vs none:1.31 (1.11-1.54)*** <10 days/mo vs none: 1.13 (0.97-1.31) **In model just including ecigs** ≥10 days/mo cigs vs none:1.25 (1.09-1.45) <10 days/mo vs none: 1..25 (1.09-1.45)	**In model including ecigs, cigs, marijuana** ***≥10 days/mo cigs vs none:1.27 (1.00-1.61)*** <10 days/mo vs none: 1.03 (0.85-1.25) **In model just including cigs** ≥10 days/mo cigs vs none:1.65 (1.31-2.08) <10 days/mo vs none: 1..24 (1.05-1.47)			age, sex, race/ethnicity, overweight or obesity, and at least 1 dental office visit in the previous year	Table 1 (Model 4)
Kim (2017)	n=216,056 (12-18 yrs old in Korea) The 2011-2013 Korea Youth Risk Behavior Web-based Survey	Past year Dx with asthma	***current (yes vs. no)= 1.13 (1.01-1.26)***	***>= 20 days/month = 1.57 (1.38–1.77)*** 6–19 day/month = 1.32 (1.08–1.61) 1–5 days/month = 1.39 (1.20–1.62)			age, physical exercise, sex, obesity, region of residence, economic level, educational level of father, education level of mother	Table 3 (Model 3)
Lee (2019)	n=58,336 (12-18 yro Korean) The 2018 Korean Youth Risk Behavior Survey	Past year Dx with asthma	Multivariate: ***ever vs. never = 1.23 (1.00–1.52)***	Multivariate: ***ever vs. never = 1.32 (1.12–1.55)***	Stratified: ***DU vs. never tobacco use = 1.14 (0.84–1.54***) (DU + HTP) vs. never tob use = 1.59 (1.17–2.15)	Stratified: ***Sole ENDS vs. never tob use= 1.42 (0.86–2.34)*** ***sole cigarettes vs. never tobacco use = 1.30 (1.08–1.56)***	age, sex, obesity, residential area, family economic status, and physical activity	Tables 3-4

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Li (2020)	n=28,171 adults PATH Wave 2 October 2014 to October 2015	Wheezing or whistling in chest in past 12 months	***current vapers vs non-users: 1.68 (1.32 –2.14)*** ***Current vapers vs. current smokers: 0.61 (0.48 – 0.77)*** Current vapers who were ex-Smokers vs. Ex-smokers: 1.54 (1.20, 1.98)	***current smokers vs non-users: 2.75 (2.47-3.06)*** current smokers vs never smokers: 3.33 (2.87, 3.85) Ex-smokers vs. Never-Smokers: 1.43 (1.26, 1.63)	***dual users vs non-users: 2.83 (2.37-3.38)*** ***dual users vs current smokers: 1.03 (0.88 – 1.20)***	***Current vapers who never smoked vs. Never-Smokers: 1.49 (0.84 - 2.67)***	second-hand smoke exposure, duration of e-cigarettes use age, sex, race/ethnicity, income level, BMI categories, self-reported asthma, self-perception of physical health, self-perception of mental health	Table 2 and Table 3
McConnell (2017)	n=2,086 (high schoolers) The 2014 Southern California Children's Health Study	wheeze past 12 months	***Risk for wheeze: current vs. never= 1.24 (0.78, 1.98***) Risk for bronchitis: current vs. never= 1.41 (0.92, 2.17) former vs. never = 1.71 (1.20, 2.43) 1-2 days vs. never = 1.37 (0.79, 2.37) >= 3 days vs. never= 1.64 (0.88, 3.05)			wheeze: ***among never smokers:*** ***current vs. never ENDS=1.52 (0.89, 2.61)*** Bronchitits: among never smokers: current vs. never ENDS=1.52 (0.89, 2.61) former vs. never ENDS= 1.70 (1.11, 2.59)	sex, ethnicity, parental education, community, secondhand smoke, and lifetime number of cigarettes smoked	Wheeze: Figure 4 and text Bronchitis: Figure 1-3 Table E1
Osei (2019b)	n=402,822 never adult smokers (⩾18 years) BRFSS 2016 & 2017	Ever Dx with asthma and still have asthma (past 12 mo)	***current vs. never = 1.39 (1.15, 1.68) among never-smokers***				Age, sex, race, income, level of education and body mass index	text

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Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Parekh (2020)	n=131,965 childbearing age women (18–44 years old) **BRFSS 2016–2017**	asthma (current)	***Current e-cigarette users with history of combustible cigarette smoking vs never users of anything: 1.33 (0.95–1.86)*** ***Current e-cigarette users without history of combustible cigarette smoking vs never users of anything = 1.74 (1.29–2.35)***	***Current combustible cigarette smokers without history of e-cigarette use vs never users of anything: 1.49 (1.25–1.77)***	***Current dual users (e-cigarette + combustible cigarette) vs never users of anything: 2.11 (1.72–2.59)***	***Current e-cigarette users without history of combustible cigarette smoking vs never users of anything: 1.74 (1.29–2.35)*** Former e-cigarette users without history of combustible cigarette smoking vs never users of anything: 1.14 (0.98–1.32)	age, race/ethnicity, marital status, education household income, health insurance, BMI, binge drinking	Table 4
Reddy (2021)	**Longitudinal** n= 20,882 participants without past 12-month respiratory symptoms at W3 (⩾12 yro) PATH W3-W4	incident respiratory symptoms (wheezing or whistling in the chest, or a nocturnal dry cough not associated with a cold or chest infection in the past 12 months)	Daily vs. someday= 0.88 (0.52–1.50) ***sole ENDS vs. noncurrent use= 1.17 (0.79-1.74)***	***sole smokers vs. noncurrent use=1.78 (1.56-2.03)*** Daily vs. someday=1.81 (1.46–2.26)	***DU vs. none current use= 2..22 (1.79-2.75)*** ***DU vs. sole cig= 1.24 (1.00-1.55).*** DU vs. sole ENDS= 1.90 (1.23-2.93)	***sole ENDS vs. noncurrent use= 1.17 (0.79-1.74)***	In the main analysis: age, sex, race/ethnicity In the sensitivity analysis: history of asthma, COPD, chronic bronchitis, or emphysema	Table 2

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Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Sargent (2022)	n=16,295 US adults without COPD PATH W2-W3 2014-2016;	Composite score based on seven wheezing/cough questions from the International Study of Allergies and Asthma in Childhood (ISAAC)	**Cross-sectional association (Tab 2):** ***Sole ENDS vs. never=1.05 (0.67,1.63);*** ORs were attenuated by adjustment for cigarette pack-years from unadjusted OR=1.53 (0.98,2.40) to adjusted OR=1.05 (0.67,1.63); There was also an increase in respiratory symptoms with higher intensity of e-cigarette use, but the trend did not reach statistical significance (p = 0.12) Longitudinal association (Tab 3): Sole ENDS vs. never= 1.58 (0.84, 2.96)	**Cross-sectional association (Tab 2):** ***Sole cig vs. never=2.34 (1.92-2.85)*** There was a significant linear increase in % with functionally-important respiratory symptoms (at a cutoff of ≥3) with higher intensity of smoking. Each additional 5 pack-years: aOR= 1.13 (1.09-1.16) Longitudinal association (Tab 3): Sole cig vs. never= 2.80 (2.08, 3.76)	**Cross-sectional association (Tab 2):** ***DU vs. never= 2.13 (1.64, 2.77)*** post hoc testing indicated that risk ratios for dual use of cigarettes+e-cigarettes were never different compared to exclusive cigarette use Longitudinal association (Tab 3): Dual use vs. never= 2.64 (1.88, 3.70)	***Sole cig vs. never=2.34 (1.92-2.85)***	Adults reported their lifetime and past 30 day use of cigarettes, cigars (traditional cigars, cigarillos, and filtered cigars), pipe tobacco, hookah, snus pouches, other smokeless tobacco, secondhand smoke, pack years of smoking history age, sex, race/ethnicity, education, income, urbanicity, BMI (overweight), asthma, congestive heart failure, heart attack, diabetes, cancer, use of antihypertensives known to cause coughing or wheezing (beta blockers, angiotensin receptor blockers, and ace inhibitors), marijuana use	Table 2

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Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Schweitzer (2017)	n=6,089 (9th–12th graders) The 2015 Hawaii Youth Risk Behavior Survey	Ever Dx with asthma; still have asthma	Risk for current asthma (vs. never have asthma) ***current (y/n) =1.48 (1.24, 1.78)*** ever (y/n)= 1.22 (1.01, 1.47)	Risk for current asthma (vs. never have asthma) ***current (y/n) =1.23 (0.92, 1.64)*** ever (y/n)= 1.25 (1.05, 1.54)			Age, sex. race/ethnicity, overwight, marijuana	Table 3
Sompa (2022)	n=2,270 Swedish young adults (aged 22-25) The the Swedish population-based prospective birth cohort BAMSE in 2018-2020	Breathing difficulties or wheeze in the past 12-month	***Sole e-cig current use vs. non-current users of ecig-cig-snus= 1.2 (0.3-3.8)***	***Current sole smoking vs. non-current users of ecig-cig-snus= 1.6 (1.2-2.2)***	***Dual use ecigs+cigs vs. non-current users of ecig-cig-snus: 3.6 (1.4-9.4)***		snus use, waterpipe use, second-hand tobacco exposure, any tobacco use at 12, and any tobacco use at 16 gender, educational level, occupational status	Table 4
Tackett (2020)	**Longitudinal** n=7,049 youth without asthma (aged 12-17) PATH Waves 3-4	past 12-month wheezing	Ecig use within past __ vs no ecig use in the past year or never use: ***Past 30 d 1.35 (0.63-2.88)*** Past 7 d 0.74 (0.28-1.97) Pat year 1.37 (0.91-2.05)	***Combustible tobacco use in past 30 days vs not: 1.21 (0.65-2.25***) combustible tob included cigarettes, traditional cigars, cigarillos, filtered cigars, pipes, hookahs, bidis, and kreteks			traditional cigars, cigarillos, filtered cigars, pipes, hookahs, bidis, and kreteks, secondhand smoke Age, sex, race/ethnicity, household income	Table 2

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Tanski (2022)	n=21,054 youth/young adults aged 12-24) PATH Wave 4 (2016-2017)	Presence of functionally important respiratory symptoms was defined by questions regarding wheezing and nighttime cough at a cutoff score (>=3) associated with poorer functional health status.	***Current noncombstible use only vs never use of anything: 0.87 (0.67-1.13)*** ***Daily use vs. never use=1.25 (0.80, 1.96)***	***Current combustible use only vs never use of anything: 1.52 (1.29-1.80)*** ***Daily use vs. never use=2.80 (2.25, 3.47)***			age, sex, race/ethnicity, asthma diagnosis (based on self-report of "have you been told by a doctor, nurse or other health professional that you have asthma") and obesity (based on body mass index [BMI]), SHS, marijuana use	Table 2 Model 1 Tab 2 Model 2
Wang (2016)	n= 45,128 Chinese adolescents in Hong Kong	Cough or phlegm for 3 consecutive months in past year	**Multivariate** ***current (y/n) = 1.28 (1.06-1.56)*** **Stratified** among ever smoker: 1.39 (1.14-1.70) among former smoker: 1.40 (1.02-1.91) among experimental smoker: 1.09 (0.66-1.80)		**Stratified** ***DU vs. sole smoker = 1.15 (0.81-1.62)***	**Stratified** ***sole ENDS vs. never tob user = 2.06 (1.24-3.42)***	secondhand smoke exposure age, perceived family affluence	Table (no number) aOR for ENDS reported by smoking status
Wills (2019)	n=8,087 adults (18–79 yro) The 2016 Hawaii BRFSS	asthma (current)	***current (y/n)= 1.27 (0.96 – 1.67) among total sample*** current (y/n)=1.33 (1.00-1.77) among nonsmokers current (y/n)= 0.92 (0.73 – 1.15) among smokers	***current (y/n) = 1.27 (1.10– 1.47) among overall sample*** ***current cig vs. current ENDS=1.00 (0.74, 1.35)***	***DU vs. neither = 1.26 (1.04– 1.53)*** ***DU vs. sole cig = 0.99 (0.80– 1.22)*** DU vs. sole ENDs =1.00 (0.73– 1.35)		Secondhand smoke age, gender, educational level, ethnicity, BMI, financial stress	Table 2

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Wills (2020)	n=14,765 (9th–12th graders) The 2017 Youth Risk Behavior Survey	Ever DX with asthma	***current ENDS (y/n, Tab 3)= 1.30 (1.10, 1.53)*** ***sole ENDS vs. neither (Tab 4)=1.29 (1.07, 1.55***) ever (y/n)=1.16 (1.01, 1.33)	***current Cig (y/n)= 1.24 (1.03, 1.51)*** ***Sole cig vs. neither=1.23 (0.92, 1.64)*** ever (y/n)= 1.01 (0.81, 1.25)	***Current vs. neither= 1.62 (1.32, 1.99)*** ever vs. neither = 1.13 (0.97, 1.31) ***DU vs. sole Cig=1.32 (0.95, 1.84)***	***sole ENDS. vs. sole Cig=1.06 (0.76, 1.46)***	demographics (age, gender, race/ethnicity), overweight status, obesity status, marijuana use (ever or any past-30-day use).	Tables 3-4 and text
Xie (2020b)	**Longitudinal** n=21,618 adults (18+ yro) without prevalent respiratory conditions PATH W1-W4 2013-2018	Incident asthma	***current vs. never: IRR= 1.32 (1.01-1.72) for asthma*** ever vs. never=1.24 (1.01-1.53) former vs. never= 1.19 (0.95-1.50)				other combustible products (ie, pipe, cigar, cigarillo, or hookah) age, sex, and race/ethnicity, educational attainment, US census region, ever use of illicit substances (ie, heroin, inhalants, or hallucinogens), BMI, and hypertension, cholesterol, heart failure, stroke, diabetes	Table 2 (Model d; fully adjusted model)
Xie (2022)	**Lonigitudinal** n= 6,378 young adults (18-24 yro) without prevalent respiratory disease PATH W2-W5 2014-2019	Incident respiratory symptoms including: 1) wheezing or whistling in the chest; 2) chest sounded wheezy during or after exercise; and 3) dry cough at night not associated with a cold or chest infection.	Among the total sample: ***current vs. never=1.32 (1.06–1.65)*** former vs. never=1.20 (1.04–1.39) Among never smokers: ***current vs. never= 1.86 (1.35–2.58)*** former vs. never= 1.22 (1.00–1.49)	***sole cig vs. none=2.07 (1.75–2.46)***	***DU vs. none current use of both= 1.88 (1.41–2.51)*** ***DU vs. sole cig= 0.91 (0.67 –1.23)***	***sole ENDS vs. none= 1.62 (1.23–2.12)*** ***sole cig vs. none=2.07 (1.75–2.46)*** ***sole ENDS vs. sole cig= 0.78 (0.58–1.05)***	current use of other tobacco product (cigar, cigarillo, filtered cigar, pipe, hookah, smokeless, or snus exposure, secondhand smoke age, sex, race, BMI, marijuana use, other recreational drug use,	Tabless 2-3 Figure 2A
COPD or composite respiratory symptoms								

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Antwi (2022)	2018 BRFSS excluding people with a history of asthma. N=177,209	COPD	**Multivariate Model** ecig use controlling for cig use vs no use of either: ***Daily user 1.53 (1.11–2.03)*** Some days 1.43 (1.13–1.80) Former user 1.46 (1.28–1.67)	**Multivariate model** ***Current smokers vs never controlling for ecig use: 4.75 (4.11-5.49)***	**Stratified** ***Daily ecig vs none among current smokers: 0.99 (0.67–1.46)*** Some day ecig vs none among current smokers: 0.99 (0.67–1.46)	**Stratified** Among never smokers: ***Daily ecig use vs never: 3.17 (1.04–9.63)*** Some days vs never 1.61 (0.87–3.09) Former vs never: 1.55 (1.01–2.38)	age, gender, race/ethnicity, marital status, educational level, past month leisure time physical activity and BMI.	Tables 2 and 3
Barrameda (2021)	2016 BRFSS age 18+ n=459,098	COPD, emphysema, or chronic bronchitis	**Single multvariate model including ecigs and cigs** ***Every day vs never: 1.83 (1.59-2.10)*** Some-day vs never: 2.33 (2.07-2.62) Former vs never: 1.92 (1.82-2.03) **Among former smokers** Every day vs never: 1.46 (1.23-1.88) Some-day vs never: 2.05 (1.42-2.94) Former vs never: 2.05 (1.78-2.37)	**Single multvariate model including ecigs and cigs** ***Every day vs never: 5.71 (5.39-6.05)*** Former vs never: 3.87 (3.65-4.10)	**Among current smokers** ***Every day ecig vs never: 1.47 (1.13-1.92)*** Some-day vs never: 1.82 (1.56-2.14) Former vs never: 1.65 (1.48-1.84)	**Among never smokers** ***Every day vs never: 4.36 (1.76-10.77)*** Some-day vs never: 1.27 (0.77-2.08) Former vs never: 1.58 (1.24-2.02)	tobacco chewing age, sex, race/ethnicity, annual household income, health insurance, personal physician, health status, body mass index, education, marital status, exercise, alcohol use, metropolitan status	Tables 2 and 3
Bhatta (2020)	**Longitudinal** n=23,760 (18–65 years) PATH Waves 1-3 2013-2016	incident COPD	***current vs, never = 1.44 (.79- 2.62)*** former vs. never = 1.82 (1.23- 2.69)	***current vs. never=5.79 (1.64-20.44)*** former vs. never=1.47 (0.42-5.20)			age, sex, race/ethnicity, poverty level, BMI, high blood pressure, high cholesterol, diabetes	Appendix Table 6

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Hedman (2018)	Obstructive Lung Disease in Northern Sweden study and West Sweden Asthma Study n= 6519 and 23,753 (20–75 years) Two Sweden surveys, 2016	long-standing cough, sputum production, chronic productive cough, wheeze (past 12 mo)	***sole ENDS vs. none=1.46 (0.93-2.29)*** ENS with former smoking vs. none= 1.47 (0.91-2.37)	***sole smokers vs. none= 2.55 (2.36-2.77)*** Former smoker without ENDS vs.non= 1.27 (1.19-1.36)	***DU vs. none= 4.03 (3.23-5.02)***		sex, age group, survey, educational level	Table 3 and Supplement doc
Joshi (2021)	Canadian Longitudinal Study on Aging (CLSA) participants 45–85 years at the time of recruitment (2012–2015); spirometry measures were available for 20,347 participants (cross sectional analysis)	Obstructive lung function impairment (current measure)	**Model 1** ***E-cigarette ever use vs e-cigarette never use (controlling for smoking): 2.10 (1.57-2.80)***	**Model 3** ***15+ pack years cig and no e-cig vs none: 3.07 (2.45-3.86)*** 15+ pack years and ever ecig vs none: 7.43 (5.30-10.38)	**Model 1** ***E-cigarette ever use vs e-cigarette never use (controlling for smoking): 2.10 (1.57-2.80)***		Age, sex, ethnic background, education status, total annual household income, urban/rural area of residence, number of individuals living in household, number of chronic conditions	Table 2

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Kim (2021)	2013–2018 Korea National Health and Nutrition Examination Survey; of them, 12,919 participants aged ≥ 40 who underwent spirometry, n=12,919	COPD by pulmonary function test (current measure)		***Current smokers vs never smokers: 2.26 (1.77–2.88)*** Former smokers vs never smokers: 1.67 (1.31–2.12)	***Dual users vs never smokers: 2.83 (1.64–4.86)***		age, sex, residence, educational level, household income, BMI, high-risk drinking	Table 3
Osei (2020)	705,159 (⩾18 years) the 2016-2017 Behavioral Risk Factor Surveillance System	ever Dx with bronchitis, emphysema or COPD	***current vs. never= 1.75 (1.25-2.45) for the total sample*** ***Among never smokers: current vs. never=1.75 (1.25-2.45)*** daily vs. never=2.64 (1.43-4.89) occasionally vs. never=1.51 (1.03-2.23) Among former smokers: current vs. never= 2.13 (1.82-2.50) daily vs. never=2.05 (1.72, 2.44) occasionally vs. never= 2.30 (1.71, 3.08)		***DU vs. never tob=6.89 (6.29-7.55)*** ***DU vs. sole cig= 1.66 (1.50-1.84)*** DU with daily vaping vs. sole cig= 1.64 (1.34-2.00) DU with occasional vaping vs. sole cig = 1.67 (1.50-1.86)		age, sex, race, federal poverty line-adjusted income level, educational status	Table 2 and main text

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Parekh (2020)	BRFSS 2016–2017 131,965 women of childbearing age (18–44 years old). n=131,965	COPD	Current e-cigarette users with history of combustible cigarette smoking vs never users of anything: 2.65 (1.53–4.58) Former e-cigarette users without history of combustible cigarette smoking vs never users of anything: 1.67 (1.21–2.30)		***Current dual users (e-cigarette + combustible cigarette) vs never users of anything: 5.07 (3.91–6.56***)	***Current e-cigarette users without history of combustible cigarette smoking vs never users of anything: 1.37 (0.71–2.63)*** ***Current combustible cigarette smokers without history of e-cigarette use vs never users of anything: 3.28 (2.62–4.12)***	age, race/ethnicity, marital status, education household income, health insurance, BMI, binge drinking	Table 4
Perez (2019)	3,642 (18–64 years) PATH Wave 1 2013-2014	ever Dx with bronchitis, emphysema or COPD	***current (y/n)= 1.43 (1.12–1.85) in the propensity-matched sample*** current (y/n)=1.47 (1.21–1.79) for total sample Daily vs. never=1.59 (1.06–2.37), someday vs. never=1.97 (1.55–2.49) Former vs. never= 1.73 (1.46–2.06)			***current ecig (y/n) =2.94 (1.73–4.99) for nonsmokers***	childhood and current home SHS exposure, ever use of cigars, little cigars, pipe, hookah, oral tobacco Age, sex, race/ethnicity, poverty level, census region, education, BMI, asthma, high blood pressure, high cholesterol, congestive heart failure, stroke, heart attack, and diabetes, history of exposure to heroin, marijuana use (as blunts with cigars)	Main text section 3.2
Strong (2018)	PATH Wave 1 2013-2014 n=32,320 (⩾18 years)	ever Dx with COPD, chronic bronchitis, asthma or emphysema	***Sole ENDS vs. non-current users= 1.39 (1.09–1.76)***	***Cig only vs. non-current users= 1.54 (1.43–1.66)***	***DU vs. non-current users= 2.07 (1.71–2.51)***		cigar, hookah, smokeless age, sex, race/ethnicity, marijuana	Main text section 3.5

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Wills (2019)	8,087 (18–79 yro) The 2016 Hawaii BRFSS	Ever Dx with COPD	risk for COPD: ***ever (y/n) = 2.58 (1.36 – 4.89) for the total sample*** ever (y/n)=1.29 (0.94 −1.77) for smokers	***ever (y/n)= 2.98 (2.34 −3.78)***	***DU vs. neither = 3.92 (2.82– 5.44)*** ***DU vs. Cig= 1.32 (0.98 – 1.77)*** DU vs. ENDS= 1.52 (0.81 – 2.87)	***ever (y/n)=2.58 (2.34 –3.78) rs*** ***ever ecig vs ever cig: 0.86 (0.46-1.61)*** [ever Cig vs. ever ENDS = 1.16 (0.62 – 2.17)]	Secondhand smoke age, gender, educational level, ethnicity, BMI, financial stress	Table 3
Xie (2020a)	2016 and 2017 BRFSS age 18+ n=887,182	COPD	***Current ecig vs never among never smokers: 1.47 (1.01-2.12)*** ***Current ecig vs cig among never smokers: 0.39 (0.27-0.56)*** Current ecig vs never among ex-smokers: 3.24 (2.78-3.78) Curren ecig vs cig among ex-smokers: 0.85 (0.73-0.99)	***Current smokers vs never users: 3.80 (3.58-4.02)***	***Dual users vs never smokers: 4.39 (3.98-4.85)*** ***Dual users vs current smokers: 1.16 (1.05-1.27)***		age, sex, race/ethnicity, marital status, employment status, education level, income level, body mass index, and general health	Table 1

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Xie (2020b)	**Longitudinal** 21,618 (18+ yro) PATH W1-W4 2013-2018	incident COPD	Any respiratory condition for the total sample: ***current vs. never =1.31 (1.08-1.59)*** ever vs. never= 1.28 (1.10-1.48) former vs. never=1.28 (1.09-1.51) For COPD: current vs. never = 1.57 (1.15-2.13) ever vs. never= 1.62 (1.28-2.04) former vs. never= 1.66 (1.29-2.12)			Any respiratory condition among non smokers: ***current ENDS vs. never = 1.35 (0.87-2.09)*** ever ENDS vs. never= 1.37 (1.05-1.79) former ENDS vs. never= 1.38 (1.03-1.84)	other combustible products (ie, pipe, cigar, cigarillo, or hookah) age, sex, and race/ethnicity, educational attainment, US census region, ever use of illicit substances (ie, heroin, inhalants, or hallucinogens), BMI, and hypertension, cholesterol, heart failure, stroke, diabetes	Table 2 eTable
Oral disease								
Akinkugbe (2018)	13,650 adolescents aged 12 to 17 y in PATH Wave 1 (September 2013 to December 2014)	dental health issues, such as cavities, gum disease or dental stains (ever or in past 12 months)	**Past year dental problems:** ***Current ecig vs never: 1.11 (0.79-1.55)*** Ever ecig vs never: 1.12 (0.90-1.38) **Ever dental problems:** Current ecig vs never: 1.27 (0.95-1.70) Ever ecig vs never: 1.28 (1.07 -1.54)	**Past year dental problems:** ***Current cig vs never: 1.50 (1.18-1.90)*** Ever cig vs never: 1.34 (1.13 -1.58) **Ever dental problems:** Current cig vs never:1.47 (1.17-1.83) Ever cig vs never: 1.29 (1.10 -1.51)	**Past year dental problems:** ***Current dual vs never: 1.72 (1.24 - 2.38)*** Ever dual vs never:1.43 (1.22-1.67) **Ever dental problems:** Current dual vs never: 1.59 (1.20 - 2.09) Ever dual vs never: 1.45 (1.24-1.68)		age, sex, diabetes, race, ethnicity and parental educational level	Tables 4 and 5

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
AlQobaly (2022)	NHANES 2015-6 and 2017-8, n=8129	Periodontal disease Bone loss	**Periodontal disease** **Multivarite** ***Current vs never: 1.38 (0.97-1.97)*** Ever vs never: 1.43 (1.18-1.73) **Bone loss** **Multivariate** Current v never: 1.80 (1.30-2.49) Ever v never: 0.92 (0.65-1.29)	**Periodontal disease** **Multivarite** ***Current vs never: 1.72 (1.47-2.02)*** **Bone loss** **Multivariate** Current v never: 2.75 (2.17-3.40) Ever v never: 0.92 (0.65-1.29)	**Stratified (among smokers)** **Periodontal disease** ***Current ecig (dual) vs never: 1.65 (1.03-2.64)*** **Bone loss** Current ecig (dual) vs never: 0.13 (0.01-1.30) Ever vs never: 2.41 (1.50-3.70)	**Periodontal disease** **Stratified** Nonsmokers: ***Current vs never: 0.95 (0.24-3.02)*** Ever vs never: 0.94 (0.48-1.42) **Bone loss** **Stratified** Nonsmokers: Current vs never: 0.13 (0.01-1.30) Ever vs never: 0.80 (0.27-2.35)	age, gender, education, ethnicity, poverty income ratio, diabetes and dental visit	Tables 2 and 3 (Model 2) and 4 (stratified)

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Atuegwu (2019)	**Longitudinal** PATH from September 2013 to December 2014 (wave 1), October 2014 to October 2015 (wave 2), and October 2015 to October 2016 (wave 3) No history of gum disease at Wave 1 and had teeth cleaned by Wave 3 n=18,259	peridontal disease (past 12 mo)	Ecig use at all three times vs no ecig use controlling for cig and other tobacco use: ***Any periodontal disease (either of previous two): 1.58 (1.06-2.34)*** New gum disease: 1.76 (1.12-2.76) Bone loss around teeth: 1.67 (1.06-2.63)				other tobacco product, secondhand smoke exposure Age, gender, race, education, income, prescription drug abuse, stomach, duodenal or peptic ulcer, marijuana, alcohol, illicit drug use	Table 2

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Chaffee (2021b)	adolescents recruited from public high schools in rural Northern California (2020-21) n=976	Xerostomia (subjective experience of dry mouth) (past 30 days)	**Dry mouth** ***Current e-cig use (6-30 days in past 30) vs nonuse: 1.40 (0.69-2.84)*** Current ecig use (1-5 days in past 30) vs nonuse: 1.22 (0.84-1.78) **Xerostomia** Current e-cig use (6-30 days in past 30) vs nonuse: 0.96 (0.90-1.01) Current ecig use (1-5 days in past 30) vs nonuse: 1.05 (0.99-1.11)	**Dry mouth** ***Current cig use: vs nonuse: 1.92 (1.38-2.68)*** **Xerostomia** Current cig use vs nonuse: 1.13 (0.99-1.29)			gender, race/ethnicity, asthma, physical activity, alcohol, cannabis	Table 4
Chaffee (2022)	PATH Wave 4 (2016-2018) age 18+ n=18,753 in last 12 months. 24,967 for ever loose teeth	incident (past 12 months) Loose teeth	***e-cig only vs never tobacco:*** ***Last 12 months: 1.44 (0.80-2.58)*** Ever: 1.32 (0.93-1.87)	***Cig only vs never tobacco: 2.02 (1.52-2.69)*** Ever: 1.59 (1.31-1.93)	***Dual vs nevet tobacco: 2.04 (1.40-2.97)*** Ever: 1.78 (1.37-2.50)		pack-year smoking history,pack-year smoking history, cigars, smokeless tobacco, hookah, pipe, secondhand smoke age, sex, race/ethnicity, educational attainment, and annual household income, BMI diabetes, alcohol, marijuana	Tables 4 and 5

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Cho (2017)	Twelfth Korean Youth Risk Behavior Web-based Survey (KYRBWS) 2016 n=33,309	gingival pain and/or bleeding, tongue and/or inside-cheek pain, cracked or broken tooth in past 12 months	***gingival pain and/or bleeding Daily ecig vs never:1.00 (0.72-1.41)*** 1-29 days vs never: 0.88 (0.74-1.05) **cracked or broken tooth** daily ecig vs never: 1.65 (1.19-2.27) nondaily vs never: 1.26 (1.06-1.51) **tongue and/or inside-cheek pain**, Daily ecig vs never: 1.54 (1.05-2.26) Nondaily vs never: 1.08 (0.88-1.33)				attempt to quit smoking, and second hand smoking at home age, gender, school grade, economic status, city size, carbonated drink, overweight status, stress, alcohol, vigorous sports activity,	Tables 5, 6 and 7 (Model 3)
Huilgol (2018)	2016 BRFSS n=456 343	Poor oral health defined by having at least one perminant tooth due to non-traumatic cause	***Daily ecig vs nonusers: 1.78 (1.39–2.30)*** Nondaily vs nonuser: 1.78 (1.39–2.30)	***Current smoking (y/n): 2.231 (2.041-2.438)***			smokeless tobacco (e.g. snuff) age, sex, race, education, income, US region, alcohol use, soda intake, dental visit history, physical health status, depression and diabetes mellitus	Table 2
Jeong (2019)	Korean National Health and Nutrition Examination Survey (2013-2015) age 19+ n=13,551	periodontal disease (periodontal pockets) (past 12 mo)	Ecigatette vs no tobacco: [both]***2.33 (1.58-3.44)** [male] 2.34 (1.52–3.59) [female] 2.27 (0.89–5.80)	Cigarette vs no tobacco: [both] ***1.99 (1.69-2.53)** [male] 2.17 (1.76–2.68) [female] 1.73 (1.32–2.27)			age, gender, marital status, education, region, household income level, occupation, alcohol status, number of walking days in a week, self-reported health status, stress level	Table 2

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Vora (2019)	PATH Wave 1 (2013-4) n=32,300	Gum disease diagnosis (N = 32,223) Gum disease treatment (N = 32,187) Pre-cancerous lesion diagnosis (N =32,230)	**Gum disease diagnosis** ***current ecig vs never tobacco: 2.9 (1.9-4.5)*** **Gum disease treatment** current ecig vs never tobacco: 2.3 (1.3-4.1) **Pre-cancerous lesion diagnosis:** current ecig vs never tobacco: 2.4 (0.5-12.4)	**Gum disease diagnosis** ***current cig vs never tobacco: 2.2 (1.9-2.6)*** **Gum disease treatment** current cig vs never tobacco: 1.5 (1.3-1.7) **Pre-cancerous lesion diagnosis:** current cig vs never tobacco: 2.0 (0.9-4.1)	**Gum disease diagnosis** ***current multiple prod vs never tobacco: 2.8 (2.4-3.4)*** **Gum disease treatment** current multiple prod vs never tobacco: 1.6 (1.4-1.9) **Pre-cancerous lesion diagnosis:** current multiple prod vs never tobacco: 3.6 (1.7-7.7)		Age, sex, race/ethnicity, education, income, employment, diabetes, visit to the dentist in past 12 months, medical health coverage	Table 4
Other outcomes								
Agoons (2021)	2017-8 NHANES 5569 participants age 20+	fragility bone fractures	***Current vs never ecig users: 1.43 (0.84-2.45)*** Ever vs never ecig users: 1.46 (1.12-1.89) Former ecig vs never users: 1.46 (1.10-1.94)	***Current smoker vs never smoker never ecig user 1.63 (1.18-2.25)***	***Dual use vs never smoker never ecig user: 2.41 (1.28-4.55)***		age, gender, race, level of education, BMI, physical activity, steroid use, and family history of osteoporosis	Tables 2 and 3, text

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Chidharla (2022)	US NHANES in 2015-2018 n=154,856 participants 18+ years old diagnosed with cancer and complete data on smoking and ecig use	history of cancer	***Ever vs never:2.2 (2.2-2.3)***	***Current vs not current (probably) 1.96 (1.96-1.97)***			Hypertension, diabetes mellitus, hypercholesterolemia, coronary heart disease, stroke, Marijuana or hashish, cocaine/heroin/methampheta mine, illegal drug use, alcohol use disorder, anemia, depression	Table 3
Gaiha (2020)	online national survey of adolescents and young adults (n = 4,351) aged 13-24 years conducted in May 2020	COVID diagnosis	***current ecigs only vs no cigs no ecigs: 1.91 (.77, 4.73)***	***current cigs vs no cigs no ecigs: 1.53 (.29, 8.14)***	***dual use vs never ecigs never cigs: 6.84 (2.40, 19.55)***		Age, sex, race/ethnicity, LQBTQ, mother's education, BMI, state percent positive COVID tests, complying with shelter-in-place	Table 2
Kim (2020)	Korean National Health and Nutrition Examination Survey (2013–2017) n= 7,505 Korean adult males	diagnosis of metabolic syndrome (MetS) (current)			***DU vs. never smokers without past-month use of ENDS= 2.79 (1.72-4.53)*** ***DU vs. cigarette-only smokers = 1.57 (1.03-2.40)***	***sole cig vs. never smokers without past-month use of ENDS = 1.47 (1.20-1.82)***	age, educational level, household income, residence location, occupational status, marital status, perceived high stress, depressive mood, suicidal thoughts, self-rated health status, alcohol consumption, BMI, comorbidities and family history of disease	Table 4

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Obisesan (2019)	2016 and 2017 BRFSS n=892,394	depression	**Diagnosis of depression** ***Current ecig vs never: 2.10 (1.98-2.23)*** Daily vs never: 2.39 (2.19-2.61) Nondaily vs never: 1.96 (1.82-2.10) Subjective poor mental health Current vs never: 1.67 (1.58-1.76) Daily vs never: 1.57 (1.44-1.70) Nondaily vs never: 1.73 (1.61-1.85)		***Current dual user vs never use: 2.11 (1.94-2.30)***	***current e-cig among never smokers 2.16 (1.87-2.49)***	age, sex, race/ethnicity, marital status, education, employment status, alcohol use	Tables 2 and 3
Sompa (2022)	**Longitudinal** Swedish BAMPSE in 2018-2020, age around 24, 2270 respondents	obesity (current)	Current ecig use vs never controlling for smoking: **Body fat (≥33% for women and ≥20% for men): 2.6 (1.4-4.6)** BMI (≥25 kg/m2): 1.8 (1.0-1.32) Waist circumference (≥80 cm for women and ≥93 cm for men): 1.9 (1.0-3.4)				snus use, waterpipe use, second-hand tobacco exposure, any tobacco use at 12, any tobacco use at 16 gender, educational level, occupational status	Table 6

Table S2. Summary of Individual Study Results Used in Meta-analyses (plus some additional results)								
Study	**Population**	**Outcome**	**ENDS risk (95%CI)**	**Cigarettes risk (95%CI)**	**Dual Use risk**	**Sole ENDS or sole Cig**	**Covariates**	**Where to find reported results**
Wang (2022)	109,133 (18+ yro) pooled 2015–2018 NHIS and Medical Expenditure Panel Survey (MEPS) data	ordered logistic regression on health status (1= excellent, 5=poor)			***Current dual use vs never tobacco use: 1.84 (1.64-2.06)*** ***Current dual use vs current smoking: 1.39 (1.22-1.57)***	***exclusive ecig vs. never tob user = 1.62 (1.18, 2.23)*** ***current sole cig vs never tobacco use: 1.33 (1.22-1.44)*** ***exclusive ecig vs smoker: 1.22 (0.88-1.69)***	age, sex, race/ethnicity, education, income level, marital status, region of residence, alcohol consumptiion, BMI, health insurace coverage	Communicatio n with author