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COMMENT

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Comparing smoking-related disease rates from e-cigarette use with those from tobacco cigarette use: a reanalysis of a recently-published study

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Abstract

Background A recent meta-analysis by Glantz et al. combined odds ratios (ORs) relating e-cigarette use (vaping) to cardiovascular disease, stroke, chronic obstructive pulmonary disease (COPD) and other endpoints. They assessed all included studies as having a low risk of bias, and concluded that vaping and smoking have a "comparable" disease odds, with dual use associated with more risk than smoking.

Aim To examine the accuracy of these conclusions, giving particular attention to myocardial infarction (MI), stroke and COPD.

Methods We determined (1) whether the pooled random-effect estimates were correctly calculated from the ORs included, (2) whether the detailed outcomes were correctly described and appropriate and whether additional OR estimates could have been included from the studies considered, (3) whether the data were correctly extracted from the source papers, (4) whether some studies should definitely or possibly have been excluded, (5) what the pooled OR estimates were for MI, stroke and COPD after excluding definitely invalid results and restricting attention to data based on appropriate disease definitions, (6) how estimates of the excess risk (ER = OR − 1) for vaping compare to those we estimate for quitting, (7) whether various sources of bias were adequately accounted for, and (8) whether conclusions were confirmed in studies where reverse causation was not an issue, i.e. where disease onset could not have preceded uptake of vaping.

Results We found no major issues regarding pooled estimation, description of diagnoses and extraction of data from the source papers, but some studies should have been excluded, and one further result was available for MI. Using data appropriately extracted for valid diagnoses, we derived pooled OR estimates for vaping vs. smoking of 0.48 (95%CI: 0.35–0.67) for MI, 0.65 (0.49–0.86) for stroke and 0.46 (0.35–0.60) for COPD. These showed a significantly reduced risk for vaping, similar to or lower than expected for quitting smoking for 5 to 10 years, highly relevant given the short period of vaping following earlier smoking for most study participants. For dual use vs. smoking, pooled OR estimates were 1.41 (1.18–1.68) for MI, 1.39 (1.06–1.82) for stroke and 1.32 (1.17–1.50) for COPD. The studies considered were predominantly cross-sectional so could not account for reverse causation, or for those who smoked and became dual users possibly having smoked more cigarettes or smoked for a longer period than those not doing so. Only three

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publications accounted for reverse causation, each using the same data source, and each found a significant effect of smoking, but not vaping, on the diseases considered.

Conclusion The claim in the original meta-analysis that the studies had a low risk of bias is demonstrably incorrect, and even the biased data suggests that switching to e-cigarettes may reduce disease risk similarly to quitting. Biases may also explain the somewhat higher risk observed in those who smoked and vaped than in those smoking exclusively. Very limited unbiased data found no significant effect of vaping on the diseases considered. Though more good studies are urgently needed, the conclusions of Glantz et al. are not supported by the currently available evidence.

Keywords E-cigarettes, Cigarettes, Smoking, Dual use, Meta-analysis, Myocardial infarction, Stroke, COPD, Bias

Background

Tobacco harm reduction has generated intense debate among the scientific community, some suggesting that there are expected public health benefits from adopting such a strategy in smoking control, and others concerned about issues such as the renormalization of smoking, the perpetuation of nicotine dependence, possible unknown future risks and the adoption of nicotine use by youth. E-cigarettes have been at the center of this debate since the time they first became available [1], with contrasting views still presented today, after years of availability in the market [2–10].

One of the major determinants of the public health impact of vaping (use of e-cigarettes) is their effect on the risk of smoking related-disease, both in terms of their relative risk compared to tobacco cigarettes but also in the context of their absolute risk [10]. Understandably, the best quality evidence is expected to come from long-term epidemiological studies, with detailed examination of the smoking status of participants and any changes in it over time, as well as of the temporal association between smoking, smoking cessation, vaping initiation and disease development. While such long-term evidence does exist for another harm reduction product, snus [11–13], the time e-cigarettes have been available is still not long enough to provide much data. Thus, any current analysis of the risk of vaping compared to smoking is based on short-term observational, often cross-sectional, studies of smoking-related disease rates, an approach that is susceptible to bias and limits the interpretation of association as causation.

In a recent publication, Glantz et al. performed a random-effect meta-analysis of data for six disease groupings [14]. Comparing odds ratios (ORs) for vaping and cigarette smoking in their Fig. 1, they reported statistically significant reductions for asthma (OR: 0.84, 95%CI: 0.75–0.95, $n = 29$ studies) and chronic obstructive pulmonary disease (COPD, 0.53, 0.38–0.74, $n = 11$), but not for cardiovascular disease (CVD, 0.81, 0.58–1.14, $n = 9$), stroke (0.73, 0.47–1.13, $n = 5$), metabolic dysfunction (0.99, 0.91–1.09, $n = 6$) and oral disease (0.87, 0.76-1.00, $n = 9$). Comparing ORs for dual use and cigarette smoking in their Fig. 2, statistically significant increases were noted for stroke (1.26, 1.06–1.50, $n = 6$), metabolic dysfunction (1.22, 1.15–1.31, $n = 10$), asthma (1.19, 1.12–1.28, $n = 39$), COPD (1.41, 1.19–1.67, $n = 17$), and oral disease (1.36, 1.12–1.64, $n = 9$), but not for CVD (1.23, 0.99–1.54, $n = 12$). They assessed all the studies included as having "a low risk of bias", noted that results were "generally not sensitive to study characteristics" and also presented (in Figs. 1 and 2) results for some other outcomes which suggest "that e-cigarette use is associated with other diseases".

The purpose of our study was to reanalyze the data presented by Glantz et al. [14], focusing on three of the most studied smoking-related diseases, COPD, stroke and myocardial infarction (MI) as we wished to also investigate ratios of the excess risk (ER = OR – 1), and compare these with estimates derived for these diseases from recent literature of the decline following quitting or switching to a reduced risk product [15].

Methods

Our analyses attempted to answer eight questions or sets of questions. These are listed below in order, together with the methods used to answer them.

(Q1) Given the ORs for CVD, stroke and COPD presented in Figs. 1 and 2 of Glantz et al. [14], *were the pooled random-effect estimates correctly calculated?*

Standard meta-analysis calculations [16] were used to check the correctness of the meta-analyses reported based on the ORs included.

(Q2) For the ORs for CVD, stroke and COPD included in Figs. 1 and 2 of the original meta-analysis, were the detailed outcomes correctly described, which corresponded to a standard definition of CVD, stroke, COPD and also of MI, and which studies listed did provide results for MI, stroke or COPD though not presented in these tables?

All the source papers used in the sections on CVD, stroke and COPD were obtained and used to check the diagnoses shown there. Studies were rejected which provided data only for detailed outcomes not corresponding to the standard ICD definitions of CVD, stroke or MI.

These detailed outcomes included "erectile dysfunction" and "heart failure" (listed under cardiovascular disease in Figs. 1 and 2 of Glantz et al. [14]), and also "respiratory symptoms" (listed under COPD in the same Figures). Studies were also rejected where the definition of COPD included asthma, not considered as being part of COPD. Studies with detailed outcomes given as "CHD" or "Composite (CHD, MI, stroke, CVD)" under cardiovascular disease in these figures were checked to see if they did provide separate data for MI or stroke.

(Q3) For those studies which provided OR estimates for the standard definitions of MI, stroke and COPD did the estimates in the source papers correspond to those given in Figs. 1 and 2?

The same source papers were also used to check whether the data cited there were consistent with the data cited in the source.

(Q4) Should some study results have definitely been excluded from consideration by Glantz et al. [14] *as the data used was clearly invalid, or possibly excluded for other reasons?*

For those papers accepted as having a disease diagnosis corresponding to MI, stroke or COPD, the source papers were examined to check whether the OR presented in the source paper was evidently far too narrow for the number of cases observed, and should not have been included in the meta-analyses.

When examining the data extracted from the source papers, we also identified those where the estimation of the OR comparing those who smoked cigarettes and vaped with those who only smoked cigarettes was not based on an analysis restricted to those who smoked cigarettes, but involved the possibly dubious assumption that the effects of vaping and of cigarette smoking were multiplicative, suggesting that such results might possibly have been excluded.

(Q5) What were the OR estimates based on data using the standard disease definitions and after any exclusions of studies with inappropriate disease diagnosis or clearly invalid data?

For each of the three diseases of interest we carried out our own random-effect meta-analyses of all the ORs which provided appropriate data on the comparative ORs (vaping vs. cigarettes; dual use vs. cigarettes), and compared them to those estimated from Figs. 1 and 2 for studies which provided data with the stated detailed outcome.

(Q6) How did the excess risks (ER = RR – 1) for vaping compare to those that can be estimated for quitting smoking?

While Glantz et al. [14] had concentrated on estimating relative ORs for vaping vs. cigarettes, we opted to additionally estimate relative ERs for this comparison. The rationale behind this is that it is the ER, not the OR, which should represent the effect of exposure [17]. Thus if the true OR for cigarette use (relative to non-use) for a disease is, say 3, so the ER is 2, and ecigarettes have, say, 10% of the effect of cigarettes, one might expect their ER to be 0.2 and their OR to be 1.2. The ratio of the ORs (1.2/3 = 0.4) might wrongly suggest to the uninitiated that vaping has 40% of the effect of cigarette smoking when the ratio of the ERs, 0.1, gives the correct picture. Thus, relative ERs were also calculated for MI, stroke and COPD from each study with relevant data.

Also, considering that disease risk decreases gradually after quitting smoking and that most people using e-cigarettes in the studies considered will probably only have used them for little more than 10 years at most, we compared the ratio of observed ERs for vaping vs. cigarette smoking with the ratio of expected ERs for short term quitting vs. continuing smoking, assuming that the decline in risk following quitting follows a negative exponential distribution (as has been shown to be approximately true for various smoking-related diseases [18–21]) and using recent estimates of the disease-specific RRs and half-lives for smoking [15].

(Q7) Were sources of potential bias and non-independence of the OR estimates adequately considered by Glantz et al. [14]*?*

The individual papers providing data with an appropriate diagnosis, and not excluded for other reasons, were examined to determine the extent that they took various potential biases into account. One particular bias considered was reverse causation. Another bias might occur due to failure to adjust for detailed cigarette smoking history. For example, at the time point when those who smoked cigarettes took up vaping additionally, they might have smoked more cigarettes or smoked for a longer duration than did those who did not take up vaping. Another issue studied was whether the analyses reporting ORs for dual use vs. cigarettes only were restricted to those who had smoked cigarettes, or whether they were based on comparisons of those using ecigarettes vs. those who did not using a model which assumed that effects of smoking were multiplicative. We also investigated whether multiple ORs could have derived from the same database, so that they might not have been independent estimates, as required in a properly conducted meta-analysis.

(Q8) Were the conclusions of Glantz et al. [14] *confirmed in studies accounting for reverse causation (where disease onset could not have preceded uptake of vaping)?*

Results were summarised for those selected studies of MI, stroke and COPD that did take account of reverse causation.

Results

(Q1) checking whether the pooled random-effect estimates for CVD, stroke and COPD were correctly calculated.

Assuming initially that the ORs given in Figs. 1 and 2 of the original meta-analysis were correct, we could produce exactly the random-effects pooled OR estimates for CVD and COPD given in those Figures. For stroke, a problem arose due to the inclusion of OR estimates from the Patel study [22] which had identical upper and lower 95%CI. This meant that a random-effect estimate could not be calculated. However using limits of 1.145–1.155 rather than 1.15–1.15 in Fig. 1, and of 1.135–1.145 rather than 1.14–1.14 in Fig. 2, generated pooled estimates of 0.72 (95%CI 0.46–1.13) based on the Fig. 1 data which were very similar to that of 0.73 (0.47–1.13) given in Fig. 1, and of 1.26 (1.06–1.50) for Fig. 2, based on the Fig. 2 data, identical to that given in Fig. 1. While there seems no reason to question the accuracy of the process of carrying out the pooled estimates by Glantz et al. [14], a question is raised about using the Patel et al. study in the meta-analysis since the reported result appears to be seriously inaccurate, as discussed further below.

(Q2) Testing whether the detailed outcomes were correctly described and appropriate and whether some of the studies listed did provide additional useful results.

In Figs. 1 and 2 combined of Glantz et al. [14], there were 12 studies listed under the broad heading CVD, 6 under stroke and 18 under COPD, with 3 studies listed under CVD and stroke [23, 24], one listed under CVD and COPD [25], and one listed under all three diseases [26].

Of the 12 studies listed under CVD, one [27] had a detailed outcome of "erectile dysfunction", which should not have been included, being only a condition possibly linked to CVD, and not CVD itself. There were also five studies, correctly listed under "composite (CHD, MI, stroke, CVD)" [25, 28–31], none of which were found to provide separate results for MI. There was also one listed under "heart failure" [32], which should not be considered under MI. One study was listed under "CHD" [33], but we found that it did provide separate results under MI. This could be added to the other four studies, all of which provide results for MI [23, 24, 26, 34], and are correctly listed as such.

Of the six studies listed under stroke [22–24, 26, 35, 36], all had a detailed outcome of "stroke".

Of the 18 studies listed under COPD, four had a detailed outcome described as "respiratory symptoms" [25, 26, 37, 38], though the source paper for one of these described the results as being for COPD [26]. The remaining 14 studies had a detailed outcome described as "COPD" [39–52], though in three of these results were only given for a definition including asthma [41, 43, 51], which is not considered as being part of COPD.

(Q3) testing whether the data were correctly extracted from the source papers.

Comparison of the OR estimates given in Figs. 1 and 2 of Glantz et al. [14] and in the source papers revealed only minor differences, which are listed below under section (Q5).

(Q4) Checking whether some study results cited by Glantz et al. [14] should have been excluded, or possibly excluded.

Examination of the papers apparently providing results for a valid definition of MI, stroke or COPD revealed that one study did not actually provide useful results. This was the study by Patel et al. [22] where the source paper presented adjusted ORs of 1.15 (95%CI: 1.15–1.16) for the e-cigarette vs. cigarette comparison, and of 1.14 (95%CI: 1.14–1.15) for the dual use vs. cigarettes comparison, where the 95%CI were slightly different from those with identical lower and upper limits reported in Figs. 1 and 2 of the original meta-analysis. It is clear that the 95%CI are far too narrow for both comparisons. From the unadjusted data in the source paper, the ratio of the upper to the lower confidence limit could readily be estimated as 1.63 for the first comparison, and as 1.17 for the second, far higher than the 1.01 for both comparisons based on the ORs given by Patel et al. Since adjustment can only increase the width of the CI, it is clear that the results given in the source paper are invalid. It is also clear that a valid adjusted estimate could not be calculated from the results in the paper, and as adjustment was required (given *inter alia* the age difference between the groups) one must therefore reject this paper from any valid meta-analysis.

We also noted that there were a number of studies where the estimation of the OR comparing those who smoked cigarettes and vaped with those who only smoked cigarettes was not based on an analysis restricted to those who smoked cigarettes, but involved the assumption that the effects of vaping and of cigarette smoking were multiplicative [26, 33–35, 42, 48, 50]. We include such results in our analyses, but we also show the effect of excluding them from the pooled estimates that we derive.

After choosing studies which provided results for a valid diagnosis, and also excluding the Patel et al. study considered in the paragraphs above, attention was limited to five studies for MI [23, 24, 26, 33, 34], five for stroke [23, 24, 26, 35, 36] and 11 for COPD [39, 40, 42, 44–50, 52].

(Q5) carrying out meta-analyses for the standard disease definitions based on the appropriate OR data.

Table 1 summarizes vaping vs. cigarettes results for the selected studies, and shows differences between the ORs extracted from the sources and those given in Fig. 1 of Glantz et al. [14].

Three points are evident from this table. First, there are a number of minor differences within studies between the

Table 1 Comparative ORs for vaping vs. cigarette smoking

Study	Disease	Estimate from source	Estimate in Fig. 1 of Glantz et al. [14]
Alzahrani [34]	MI	0.66 (0.43–1.02)	Same
Falk [23]		0.35 (0.19–0.63)	0.35 (0.19–0.62)
Farsalinos [33]		0.43 (0.25–0.75)	Only gave CHD estimate
Goldberg Scott [26]		Not available[1]	No
Hirschtick [24]		0.31 (0.06–1.60)	0.30 (0.04–2.22)
Pooled		0.48 (0.35–0.67)	Same[2]
Bricknell [35]	Stroke	0.77 (0.54–1.10)	Same
Falk [23]		0.50 (0.27–0.92)	0.50 (0.33–0.77)
Goldberg Scott [26]		Not available[1]	No
Hirschtick [24]		0.77 (0.23–2.61)	0.77 (0.25–2.38)
Parekh [36]		0.43 (0.20–0.95)	0.43 (0.18–1.04)
Pooled		0.65 (0.49–0.86)	0.62 (0.48–0.82)
Antwi [39]	COPD	0.32 (0.23–0.45)	0.32 (0.22–0.47)
Barrameda [40]		0.76 (0.31–1.89)	No
Cook [42]		0.67 (0.42–1.09)	0.67 (0.39–1.17)
Kim [44]		Not available[3]	No
Osei [45]		Not available[1]	No
Parekh [46]		0.42 (0.21–0.84)	0.42 (0.17–1.01)
Paulin [47]		0.71 (0.26–1.91)	0.71 (0.23–2.23)
Perez [48]		Not available[1]	No
Wills [49]		0.87 (0.44–1.71)	0.86 (0.46–1.61)
Wills [50]		0.31 (0.26–0.38)	Same
Xie [52]		0.39 (0.27–0.56)	0.39 (0.25–0.62)
Pooled		0.46 (0.35–0.60)	0.46 (0.35–0.62)[4]

[1] Paper gave no ORs for those who smoked cigarettes

[2] Including the estimate we extracted from Farsalinos [33]

[3] Paper did not separate out those who only vaped

[4] Including the estimate we derived from Barrameda [40]

Table 2 Comparative ORs for those who smoked cigarettes and vaped with those who only smoked cigarettes

Study	Disease	Estimate from source	Estimate in Fig. 2 of Glantz et al. [14]
Alzahrani [34]	MI	1.79 (1.20–2.66)	1.79 (1.20–2.67)
Falk [23]		1.35 (1.08–1.70)	1.35 (1.08–1.69)
Farsalinos [33]		1.35 (0.80–2.27)	Only gave CHD estimate
Goldberg Scott [26]		1.30 (0.66–2.55)	1.30 (0.66–2.56)
Hirschtick [24]		0.92 (0.30–2.82)	0.93 (0.28–3.07)
Pooled A		1.41 (1.18–1.68)	1.41 (1.18–1.68)
Pooled B		1.33 (1.06–1.66)	1.33 (1.07–1.66)
Bricknell [35]	Stroke	1.62 (1.18–2.31)	1.62 (1.16–2.27)
Falk [23]		1.13 (0.90–1.43)	1.14 (0.90–1.43)
Goldberg Scott [26]		1.65 (0.94–2.89)	Same
Hirschtick [24]		0.50 (0.14–1.79)	0.50 (0.15–1.67)
Parekh [36]		1.83 (1.06–3.17)	1.83 (0.98–3.42)
Pooled A		1.39 (1.06–1.82)	1.37 (1.05–1.81)
Pooled B		1.22 (0.76–1.94)	1.19 (0.74–1.91)
Antwi [39]	COPD	0.99 (0.67–1.46)	0.99 (0.63–1.55)
Barrameda [40]		1.47 (1.13–1.92)	1.83 (1.59–2.10)
Cook [42]		1.10 (0.78–1.56)	1.10 (0.74–1.64)
Kim [44]		1.25 (0.69–2.27)	Same
Osei [45]		1.66 (1.50–1.84)	1.66 (1.46–1.89)
Parekh [46]		1.55 (1.10–2.18)	1.55 (1.00-2.40)
Paulin [47]		1.04 (0.77–1.40)	1.04 (0.74–1.46)
Perez [48]		1.43 (1.12–1.85)	1.43 (1.07–1.91)
Wills [49]		1.32 (0.98–1.77)	Same
Wills [50]		1.44 (1.21–1.71)	Same
Xie [52]		1.16 (1.05–1.27)	1.16 (1.03–1.31)
Pooled A		1.32 (1.17–1.50)	1.37 (1.19–1.57)
Pooled B		1.31 (1.11–1.54)	1.29 (1.07–1.54)

Note that Pooled A estimates include all the ORs given, while Pooled B estimates (indicated by the study name being shown in bold) are restricted to those ORs calculated from analyses restricted to those who smoked, as shown in Table 4. For the Barrameda study, only our estimate was from analyses restricted to those who smoked

ORs we extracted, and those given in Glantz et al. [14], the reason for this not being evident to us. Second, there were three studies of COPD, and one of MI and stroke, where it was not possible to derive an estimate of the comparative ORs for reasons explained in the footnotes to Table 1. Third, there was a highly significant lower OR for vaping than for cigarette smoking for all three disease endpoints, the ORs being 0.48 (95%CI: 0.35–0.67) for MI, 0.65 (95%CI: 0.49–0.86) for stroke and 0.46 (95%CI: 0.35–0.60) for COPD based on the data extracted from the source papers. These ORs were little affected by using the data given in Fig. 1 of Glantz et al. [14].

Table 2 summarizes the results for the comparison of dual use vs. cigarette smoking for the selected studies, and also shows any differences between the ORs we extracted from the source papers and those given in Fig. 2 of Glantz et al. [14].

As is the case for Table 1, there were a number of differences within studies between the ORs we derived from the source papers, and those given in Glantz et al. [14], which were mainly minor. Based on the data we extracted, there was a similar and significantly increased OR for dual use compared to cigarette smoking for all three disease endpoints. The ORs were 1.41 (95%CI: 1.18–1.68) for MI, 1.39 (1.06–1.82) for stroke and 1.32 (1.17–1.50) for COPD. Restricting attention to ORs calculated from analyses restricted to those who smoked cigarettes, the ORs reduced somewhat, but remained significant except for stroke. Pooled estimates derived from the estimates of Glantz et al. [14] were quite similar to ours.

(Q6) comparing excess risks for vaping with those we estimated for quitting smoking.

Table 3 shows, for the studies of MI, stroke and COPD that we have considered, the observed ratio of ERs for vaping vs. cigarette smoking and the expected value of the ratio of ERs for those who quit smoking (5 years or

Table 3 Comparing excess risk ratios for vaping compared to cigarette smoking with those for quitting compared to continuing smoking

		ER Ratio	Expected ER ratio if	
Study	**Disease**	**e-cigs/cigs**	**quit 5 years**	**quit 10 years**
Alzahrani [34]	MI	0.459	0.521	0.272
Falk [23]		−0.009		
Farsalinos [33]		0.164		
Hirschtick [24]		−0.394		
Bricknell [35]	Stroke	0.564	0.484	0.235
Falk [23]		0.052		
Hirschtick [24]		0.587		
Parekh [36]		−0.525		
Antwi [39]	COPD	0.141	0.771	0.594
Barrameda [40]		0.713		
Cook [42]		0.159		
Parekh [46]		0.162		
Paulin [47]		0.391		
Wills [49]		0.798		
Wills [50]		0.122		
Xie [52]		0.168		

Note: Assuming half-lives of 5.32 years for MI, 4.78 years for stroke and 13.32 years for COPD [15]. Half-lives for stroke and COPD are age-independent, but for MI are not, the value selected for MI being for age 50–59. Expected ER ratios are 0.629 (quit 5 years) and 0.396 (quit 10 years) using the half-life of 7.48 for age 60–69

10 years) vs. continued smoking based on recently published estimates of the half-life (the time in years taken for those who have quit to halve their excess risk of disease) [15]. Of the 16 results considered, it is notable that for 11 the observed ER for vaping vs. cigarette smoking was less than would be expected comparing 10 year quitting with continuing smoking. For 13 of them, it was less than expected comparing 5 year quitting with continuing smoking, with the other 4 having quite similar ER ratios.

(Q7) considerations of various sources of bias and of non-independence.

Table 4 gives some characteristics of the 18 studies considered in Tables 1, 2 and 3, all except one [44] conducted in the USA. It shows the data source from which each study came, nine studies coming from BRFSS (Behavioral Risk Factor Surveillance Survey), four from PATH (Population Assessment of Tobacco and Health), three from NHIS (National Health Interview Survey) and one each from the Kaiser Permanente study and the Korean NHANES (National Health and Nutrition Survey). It shows whether "reverse causation" was accounted for, "No" in the final column indicating that the possibility that disease onset occurred before the switch to vaping was not ruled out. It also shows the diseases studied, whether the ratios were reported by Glantz et al. [14] in their Figs. 1 and 2, and whether the estimates of the comparative risk of those who smoked and vaped and those only smoking were based on analyses restricted to those who smoked.

The fact that the 18 papers were based on only five source databases implies that the individual study estimates are not independent, as is the usual requirement for meta-analyses. It is also notable that much of the data

Table 4 Some features of the studies considered in Tables 1–3

	Data	**Reverse causation**		**Ratio reported by Glantz et al. [14]**		**Ratio restricted**
Study	**Source**	**allowed for**	**Diseases studied**	**vaping**	**both products**	**to those who smoked**
Alzahrani [34]	NHIS	No	MI	✓	✓	No
Antwi [39]	BRFSS	No	COPD	✓	✓	Yes
Barrameda [40]	BRFSS	No	COPD	X	✓	Yes/No[1]
Bricknell [35]	BRFSS	No	Stroke	✓	✓	No
Cook [42]	PATH	Yes	COPD	✓	✓	No
Falk [23]	NHIS	No	MI, stroke	✓	✓	Yes
Farsalinos [33]	NHIS	No	MI	✓[2]	✓	No
Goldberg Scott [26]	KAISER	No	MI, stroke	X	✓	No
Hirschtick [24]	PATH	Yes	MI, stroke	✓	✓	Yes
Kim [44]	KOREA NHANES	No	COPD	X	✓	Yes
Osei [45]	BRFSS	No	COPD	X	✓	Yes
Parekh [36]	BRFSS	No	Stroke	✓	✓	Yes
Parekh [46]	BRFSS	No	COPD	✓	✓	Yes
Paulin [47]	PATH	Yes	COPD	✓	✓	Yes
Perez [48]	PATH	No	COPD	X	✓	No
Wills [49]	BRFSS	No	COPD	✓	✓	Yes
Wills [50]	BRFSS	No	COPD	✓	✓	No
Xie [52]	BRFSS	No	COPD	✓	✓	Yes

[1] Only for the estimates by us

[2] Only for CHD

came from cross-sectional surveys, such as NHIS and BRFSS, where the sequencing of disease initiation and the uptake of vaping was not recorded. Only four of the studies presented some results of prospective analyses of incidence of disease following vaping uptake [24, 26, 42, 47]. Additionally only 11 of the 18 studies comparing risk in those using both products and those only smoking actually presented comparative OR estimates based on analyses restricted to those who smoked cigarettes, as would seem appropriate. Finally, of the studies presenting the comparative ORs for dual use the great majority did not adjust for cigarette consumption at all, while those that did so used measures based on pack-years [24, 42, 47, 52], when daily consumption and duration of exposure may have different effects. None of the studies appeared to have compared cigarette consumption in those using both products and those who continued to smoke cigarettes before and after the switch to e-cigarettes, or to take this into account in analysis. Thus, the interpretation of the approximately 30–40% higher risk of MI, stroke and COPD in those using both products with those exclusively smoking shown in Table 3 is far from straightforward.

(Q8) limiting attention to studies which allowed for reverse causation.

As noted in Table 4, only three publications, two on COPD [42, 47] and one on CVD [24] allowed for reverse causation, all of these being based on data from waves 1–5 of the US PATH study. It is notable that each of these publications reported a significant effect of cigarette smoking on the endpoints considered, but none found a significant effect of vaping, whether comparing vaping with non-tobacco use, or comparing those who vaped and smoked with those who only smoked. The fact that the two estimates for COPD were based on the same data is a good example to illustrate that the set of ORs for a give endpoint cited by Glantz et al. [14] were not necessarily independent, contrary to the usual assumptions for a meta-analysis.

Discussion

While we have not attempted to carry out a detailed investigation of all the data and analyses presented by Glantz et al. [14], we have looked quite closely at the evidence relating to MI, stroke and COPD. While we could reproduce exactly the pooled estimates they presented, given the individual study OR (95%CI) estimates, and generally only found minor differences between the individual study estimates that they presented and those that we derived from the source papers, we did find that the set of studies they considered was not completely appropriate. Thus there were some studies that should not have been considered at all, including the self-evidently erroneous estimate for stroke with 95%CI of virtually zero width [22] and the result for erectile dysfunction [27], which is not CVD. Nevertheless it is clear that the overall results suggest that those who exclusively vaped had a somewhat lower risk and those who smoked and vaped had a somewhat higher risk of the diseases we looked at than did those exclusively smoking cigarettes.

In the limitations section of the discussion, Glantz et al. [14] pointed briefly to a number of problems with the data considered. These included the changing nature of e-cigarettes over time, the lack of control for duration and frequency/intensity of vaping and cigarette smoking, the fact that most of the studies were of cross-sectional design, the reliance on self-reported diagnoses, and the fact that "e-cigarettes have been on the market for less than 20 years, which may not be long enough to observe the full manifestation of the disease impact". These issues were also referred to in a number of the publications for MI, stroke and COPD that we have considered, some of which also referred to a number of other problems, including limited control for confounding variables in some studies, and reliance on self-reported e-cigarette use and cigarette smoking. In our view, there are a number of highly relevant features of the data that failed to come across in the review by Glantz et al. [14].

One is that the publications considered were based on very few source surveys, only BRFSS, PATH, NHIS, KAISER and Korean NHANES. Although the analyses may have differed between the publications and did not necessarily use data from the same waves/years it is clear that there must be overlap, with different publications involving the same cases. As such, the individual study estimates were not independent, which the individual data sets combined in meta-analyses should be. What effect this would have is difficult to estimate.

An additional, and very important, problem is that the majority of studies analyzing these datasets were cross-sectional. This means that account was not, or could not, be taken of the fact that some of the cases of disease could have occurred before the start of ecigarette use. In one of the studies examining the association between e-cigarette use and MI it was argued that the possibility that some of the MIs had occurred before initiation of vaping would bias the OR estimates towards the null, meaning that the study results likely underestimated the true risks associated with vaping [34]. However, there is absolutely no logic to this statement, as if a substantial proportion of the disease cases occurred before vaping use was started, and were wrongly attributed to its use, the OR for vaping would be substantially over-estimated. Indeed this argument was not made in other studies which discussed the problem of reverse causation [33, 35, 39]. It is noteworthy that the only publications which took reverse causation into account [24, 42, 47] found no significant effect of vaping, whether comparing vaping with non-tobacco use,

or comparing those who smoked and vaped with those smoking cigarettes only. The fact that all three publications were based on the same data set (waves 1–5 of the US PATH study) and two [42, 47] considered the same disease (COPD) emphasises the limitations described in the previous paragraph, and shows how little good data there actually is on the risks of the major smoking-related diseases associated with vaping.

When considering the results for those who were vapers and smokers, Glantz et al. [14] did not make the possibility clear that the increased risk seen compared to people who only smoke may have arisen because people who use both products may, prior to taking up vaping, have been smoking more heavily than those who maintained exclusive cigarette smoking [53], creating a bias essentially not studied in the source papers considered. Nor did they make it clear that a substantial number of their comparative OR estimates for those who vaped and smoked were not derived, as they should be, from analyses restricted to the sample that only smoked cigarettes. Additionally, most of the studies examining dual use of e-cigarettes and cigarettes failed to account for the very diverse and heterogeneous nature of the dual use definition. Someone who smokes daily and vapes occasionally, perhaps once per week, and someone who vapes daily and smokes occasionally, perhaps one cigarette per week, are classified into a single group but may have a very different risk for future development of smoking-related disease. Since the classification of dual use includes such highly heterogeneous behaviors, it is unclear how results of studies examining such use can be interpreted unless product consumption patterns are accurately recorded and sub-classifications are made. All the above, together with the limited control for duration and frequency or intensity of e-cigarette and cigarette use, indicate that the assessment of Glantz et al. [14] that all the studies included had a low risk of bias was extremely optimistic, as most ignored the possibility of reverse causation and failed to take into account past history of cigarette smoking.

We also note that Glantz et al. [14] have totally misinterpreted the combined evidence from the comparative risk estimates for vaping vs. cigarette smoking by suggesting that, even for disease conditions where lower comparative ORs were found (asthma, COPD, and oral disease), "*the odds of disease were still substantial.*" Such a statement ignores the fact that most people who exclusively vape were previously smoking, and thus carry a substantial but gradually decreasing disease risk for many years after quitting smoking, even if they quit without using any harm reduction product. Not only did our estimates for MI, stroke and COPD all show a significantly reduced risk for vaping, but the reduction was surprisingly large given the relatively few years that e-cigarettes have been used. The great majority of the studies considered show a reduction in ER for vaping compared to cigarette smoking, that is actually greater than the reduction in the ER that one would expect comparing people who have quit for a relatively short time, without using any alternative nicotine products, to those who continue to smoke. While, we would certainly not argue that switching to e-cigarettes reduces disease risk more than does quitting, and acknowledge that the quality of much of the data is quite poor and there seems to be (contrary to the conclusion of Glantz et al. [14]) a very clear risk of bias, the results summarized seem consistent with vaping being associated with a substantially lower risk than cigarette smoking of the major smoking-related diseases that we have studied.

Clearly though, more and better evidence is needed, both to minimize the effect of the various biases considered, and to extend the list of diseases – to cancer particularly. Additionally, in attempting to assess the relative effects of vaping and cigarette smoking, stronger evidence could be derived by comparing disease incidence in prospective studies of those who at baseline were smoking cigarettes and disease-free who (a) continued smoking, (b) switched to vaping, (c) used both products, or (d) quit tobacco, with account taken of smoking history and confounding variables, and indeed similar studies could be performed for secondary prevention, where the outcome occurs more quickly. However, and somewhat surprisingly, such studies have virtually never been attempted, even for diseases such as CVD where the decline in risk following quitting is quite rapid. In this context, the results from a recent study based on the Korean NHIS which followed smokers who had undergone percutaneous coronary intervention for three years [54] are of interest. Compared with those who continued to smoke cigarettes, the study found that those who switched to e-cigarettes (many of whom were still smoking tobacco cigarettes) had a significantly reduced multivariate-adjusted hazard ratio of a major adverse cardiac event of 0.82 (95%CI 0.69–0.98) which was similar to that of 0.87 (95%CI 0.79–0.96) among those who successfully quit without using any alternative nicotine product.

Conclusions

The analyses by Glantz et al. [14] have numerous weaknesses, as discussed in detail for MI, stroke and COPD, that were largely ignored by the authors. Also, the source studies had various limitations. Notably, most of them were contrary to the assessment of having a low risk of bias of Glantz et al. [14], since they frequently failed to take into account whether the switch to vaping occurred before or after the onset of disease, and failed to take account of duration of smoking and amount smoked before the switch to vaping. While the results suggest a

higher risk of the diseases studied in those vaping and smoking than in those exclusively smoking, the studies considered have not properly adjusted for smoking history before the switch to vaping and for product consumption patterns after initiation of dual use. Glantz et al. [14] obscured the fact that the lower risk observed for vaping than for cigarette smoking, based on the rather weak evidence used, was not only significant, but was actually consistent with the level of reduction expected for those who have quit smoking for a short period without the use of any alternative product. There is certainly a need for more, better designed, prospective studies to be conducted. However, the evidence considered by Glantz et al. [14] certainly does not refute the possibility that vaping provides substantial harm reduction compared to cigarette smoking.

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Lee PN planned the study; Statistical analyses were carried out by Lee PN and checked by Farsalinos K; Lee PN and Farsalinos K were responsible for study interpretation; Lee PN and Farsalinos K drafted and checked the text.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
PN Lee has been a long-term consultant to the tobacco industry. K Farsalinos has no conflict of interest to report.

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