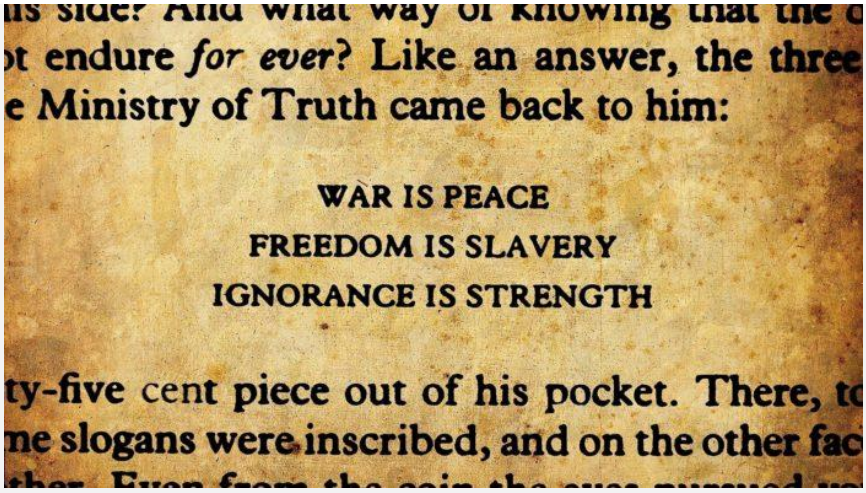
Vaping risk compared to smoking: challenging a false and dangerous claim by Professor Stanton Glantz

14 August 2019



…and VAPING IS SMOKING

In this blog (online), I examine an extraordinary claim by Professor Stanton Glantz of the University of California at San Francisco. Professor Glantz claims that the US public is right to believe that vaping is as harmful as smoking and that science is now catching up with public opinion. It is a long blog and for navigation, there is a table of contents.

A paper on risk perceptions has disturbing results 2

Professor Stanton Glantz provides a commentary 3

A review of Professor Glantz's commentary 3

Claim 1: the public perception is correct, and science is catching up 4

Claim 2: 'optimists' ignore toxins and ultrafine particles 4

Claim 3: only one-third of Americans think e-cigarettes are less harmful than cigarettes 6

Claim 4: National Academies report understates the risk of vaping 7

Claim 5: long-term health effects of vaping are unknown 9

Claim 6: vaping causes heart attacks and strokes 11

Claim 7: vaping is a cause of respiratory disease 14

Claim 8: some vaping risks approach those of cigarettes 17

Claim 9: vaping is implicated in cancer 18

Claim 10: dual-use undermines the value of vaping 19

Claim 11: e-cigarettes are ineffective for real-world smoking cessation 23

Claim 12: the explosion of youth use outweighs any benefits to adults 26

Claim 13: the people are right and science is catching up 30

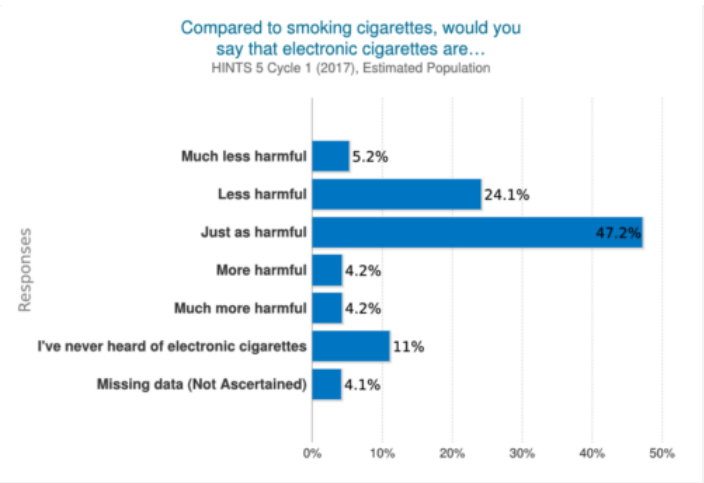
This claim is profoundly and dangerously false, and it demands a challenge. Professor Glantz makes his claim in a commentary in response to a substantive paper on perceptions of the relative risk of smoking and vaping. Both articles appeared in the American Medical Association's *JAMA Network Open*. This blog is a 13,000-word review looking in detail at Professor Glantz's 700-word commentary and its supporting citations, examining thirteen claims that form the basis of the overall claim. I am hoping the critique provided here will be a useful primer to some of the arguments in this controversial field.

A paper on risk perceptions has disturbing results

The story starts with a report in JAMA Open that confirms what we already knew: (1) that a majority of the American public believes that e-cigarettes are as harmful or more harmful than cigarettes and; (2) only a small proportion believe, correctly, that they are *much less harmful* than cigarettes. Not only that, the accuracy of public perception is deteriorating and the misunderstandings are becoming more pronounced over time. This deterioration is happening despite hundreds of millions of dollars in research grants and despite FDA recognition of a 'continuum of risk' in nicotine delivery products.

> *Our analysis revealed a consistent pattern and a change in perceived relative harm of e-cigarettes among US adults in both surveys, which showed that a large proportion of US adults perceived e-cigarettes as equally or more harmful than cigarettes, and this proportion has increased substantially from 2012 to 2017.*
>
> *Huang J, Feng B, Weaver SR, Pechacek TF, Slovic P, Eriksen MP. Changing Perceptions of Harm of e-Cigarette vs Cigarette Use Among Adults in 2 US National Surveys From 2012 to 2017. JAMA Netw Open. American Medical Association; 2019 Mar 29;2(3):e191047. [link]*

The HINTS survey 2017 showed 55.6% thought that e-cigarettes were as harmful (47.2%), more harmful (4.2%) or much more harmful (4.2%).



Most Americans think e-vaping is worse than smoking

This is *terrible*. One of the most important reasons for switching from smoking to vaping is the (correct) perception that it will reduce the risk of serious disease and other harms. If people don't believe that, why should they switch? Why not remain a smoker? Or stick with 'dual-use'? FDA analysts have presented evidence of this relationship between perception and behaviour for vaping – see *Persoskie & O'Brien, 2019*. Beliefs affect behaviour and behaviour affects wellbeing, life and death.

The authors of the substantive paper raise precisely this concern.

> *Given the demonstration by previous studies that perception of risk plays a critical role in decisions to use tobacco, our results imply that at least some smokers may have been deterred from using or switching to e-cigarettes due to the growing perception that e-cigarettes are equally harmful or more harmful than cigarettes. Our results underscore the urgent need for accurate communication of the scientific evidence on the health risks of e-cigarettes and the importance of clearly differentiating the absolute harm from the relative harm of e-cigarettes.*

So, who can be found to comment on this appalling state of affairs?

Professor Stanton Glantz provides a commentary

Inexplicably, JAMA turns to Professor Stanton Glantz, an outspoken tobacco control academic and activist based in the University of California at San Francisco. Professor Glantz is a relentless opponent of vaping and tobacco harm reduction and has been tireless in his efforts to argue that vaping products are dangerous, and possibly *as dangerous* as cigarettes. In response to the substantive article, JAMA offered Professor Glantz space for a 700-word commentary, *The Evidence of Electronic Cigarette Risks Is Catching Up With Public Perception*. In this, he argues that the public is right to have these (wrong) views and 'new science' will confirm this.

> "the declining public perception that e-cigarettes are less harmful than cigarettes is a good thing that may turn out to be where the scientific consensus lands"

A review of Professor Glantz's commentary

Professor Glantz's commentary tries to support this overarching claim by making a series of assertions to which he attaches footnotes as if the underlying citation supports the point he is making. It is instructive to go through Professor Glantz's entire comment and examine the embedded claims and see what we can learn about his argument and what the evidence says. It requires the hapless but critical reader to do three things:

1. Check if the cited study actually says what the commentary says it does;
2. Check if the conclusions of the cited study are a fair representation of the underlying research or are a misrepresentation;
3. Sometimes, as with modelling or meta-analysis, the critical reader also has to examine other studies that underpin the cited study.

This makes dismantling such claims extremely time-consuming and, as a result, quite rare. But we shall have a go at breaking the commentary into a series of claims, which form the structure for this blog. Text and citations from Professor Glantz's commentary are drawn out in quote boxes and coloured navy blue. Each claim is followed by a series of responses examining the claim and its supporting citations.

Claim 1: the public perception is correct, and science is catching up

> ***The Evidence of Electronic Cigarette Risks Is Catching Up With Public Perception***

Response: this is the title claim, and it is wholly untrue. First, let me give some credit: this phrasing is a clever and eye-catching counter-intuitive peg for his argument that vaping is as harmful as smoking. As a communications device, it works well. This is the only positive thing I will say about this commentary.

In reality, public perception is wildly off-target, and these *misperceptions are getting worse over time.* A substantial and increasing proportion believe that e-cigarettes are as harmful or more harmful than cigarettes, but only a tiny minority agrees that the products are much less harmful.

The evidence of profound harm from cigarette smoking is deep and broad and has developed since the 1950s. There is extensive epidemiology with major multi-decade cohort studies, studies in animals, systems toxicology, insights into biological mechanisms – see the 2014 US Surgeon General Report: The Health Consequences of Smoking: 50 Years of Progress. There is simply no equivalent for e-cigarettes. There are a few studies observing that vaping has *effects* on the body or on cells exposed *in vitro*, often with unrealistic exposures operating conditions, but nothing that suggests these effects amount to a substantial risk to health, let alone a risk equivalent to cigarette smoking. On the other hand, there are many credible studies suggesting vaping risks, if any, are much lower than for smoking. I will provide more detail as we go through the commentary.

Claim 2: 'optimists' ignore toxins and ultrafine particles

> The advent of electronic cigarettes (e-cigarettes), devices that deliver a nicotine aerosol to the lungs by heating a nicotine-containing liquid rather than burning tobacco, has triggered an intense debate over their value for reducing the harm tobacco products cause. The optimists see e-cigarettes delivering nicotine without all the combustion byproducts of conventional cigarettes,[1] whereas others point out that e-cigarettes still deliver an aerosol of ultrafine particles and other toxicants that carry substantial health risks.[2]
>
> *1. Abrams DB, Glasser AM, Pearson JL, Villanti AC, Collins LK, Niaura RS. Harm minimization and tobacco control: reframing societal views of nicotine use to rapidly save lives. Annu Rev Public Health. 2018;39(1):193-213. [link]*
>
> *2. Glantz SA, Bareham DW. E-cigarettes: use, effects on smoking, risks, and policy implications. Annu Rev Public Health. 2018;39:215-235. [link]*

Response: the harm reduction concept recognises toxic exposure and residual risk (the clue is in the name: harm *reduction*). The *Abrams et al.* review is not an 'optimistic' perspective in any way – it is realistic and grounded in science and experience. Professor Glantz cites his own review to imply that he is the one counting toxic risks where others are ignoring it. In fact, *Abrams et al.,* like all who back the concept of tobacco harm reduction, recognise that there are residual risks and toxic exposures – hence the phrase 'harm *reduction*'. *Abrams et al.* is an exemplary and balanced account of the science. It does not pretend there are no toxic exposures: the authors stress that the key issue is the risk of vaping *relative* to the risk of smoking.

Most reviews of toxicological, clinical, and epidemiological evidence indicate that the chemicals found in e-cigarettes, when used as intended, are far fewer and well below levels seen in cigarette smoke

Response: e-cigarette aerosol does not mainly consist of 'ultrafine' particles. Professor Glantz refers to the e-cigarette aerosol as consisting of 'ultrafine particles', both in the context of this commentary and many other situations (Google search). Ultrafine particles are defined as having a diameter of less 0.1 µm or 100 nm. The aerosol particle size distribution for e-cigarette vapour was studied in *Ingbrethsen et al., 2012* and shown to be typically in the range 250-450 nm – not ultrafine particles. *Sundhal et al., 2017*found "Mass Median Aerodynamic Diameters (MMAD) for the investigated electronic cigarettes were in the range 0.5–0.9 µm [500-900 nm]" and *Sosnowski & Kramek-Romanowska, 2016* found "average mass median diameter of droplets emitted from ECs was 410 nm".

Ingbrethsen et al. did discuss the detection of 'ultrafine' particles in e-cigarette aerosol but concluded these were just liquid droplets on their way to complete evaporation.

> *In contrast, average particle diameters determined for e-cigarettes by the electrical mobility method are in the 50 nm range and total particulate masses calculated based on the suggested diameters are orders of magnitude smaller than those determined gravimetrically. This latter discrepancy, and the very small particle diameters observed, are believed to result from almost complete e-cigarette aerosol particle evaporation at the dilution levels and conditions of the electrical mobility analysis.*

The language of 'particles' is quite misleading when used outside the specialised context of aerosol science. In everyday language, the word 'particle' implies a solid or perhaps a highly viscous liquid – something that would be trapped in the lung. The word 'ultrafine' also conveys something dangerous – the prefix 'ultra' meaning extreme or beyond normal. Use of the phrase 'ultrafine particles' to describe vapour aerosol is incorrect and more likely to cause unwarranted alarm than to explain.

Response: the chemistry and physics of aerosol particles determine their toxicity. Professor Glantz raises the question of 'ultrafine particles'. The size of aerosol particles affects where they are absorbed in the respiratory tract and lungs. But it is what they are made of – how toxic and how sticky – that determines any damage they cause.

Professor Glantz draws attention to his views on particulates or "ultrafine particles" – a long-standing theme in his arguments against vaping. Yes, there is a science of particulate exposure, and it is possible to show quite adverse effects. However, this science rests primarily on the study of particulate *products of combustion* such as diesel exhaust or cigarette smoke, particles of road surfaces, particulates from cooking, and so on. The size of particles is only one consideration: *it really does matter what the particles are made of and how toxic this is*. With vaping the 'particles' are in fact droplets of liquid aerosol with relatively simple chemistry (because there is no combustion) that is similar to the chemistry of the e-liquid. The much higher temperatures and energy of combustion processes create thousands of new and toxic chemicals in tobacco smoke or diesel engines.

There is nothing to suggest that the 'ultrafine particles' in vape aerosol (tiny droplets of liquid) are remotely similar to the solid or viscous (sticky) particulates from products of combustion. I tracked the 'science-by-analogy' in this post: Scientific sleight of hand: constructing concern about 'particulates' from e-cigarettes

Claim 3: only one-third of Americans think e-cigarettes are less harmful than cigarettes

> A key to realizing the optimists' vision for e-cigarettes is smokers switching completely from cigarettes to e-cigarettes. Because perceived risks play an important role in selecting tobacco products, Huang and colleagues[3] examined how perceptions of the risk of e-cigarettes compared with cigarettes have changed from 2012 to 2017 using 2 national surveys, the Tobacco Products and Risk Perceptions Surveys they conducted and the Health Information National Trends Surveys (HINTS). They found that the fraction of respondents who believed that e-cigarettes were less harmful than cigarettes decreased from approximately 45% in 2012 to approximately 35% in 2017, whereas the fraction who thought they were about the same increased to approximately 45%. (These estimates combine the 2 surveys. The estimates of "about the same" in 2012 were very different in the 2 surveys, so are not listed here; the other results were more similar.) The fractions who thought e-cigarettes were more dangerous than cigarettes increased but remained low, at less than 10%.
>
> *3. Huang J, Feng B, Weaver SR, Pechacek TF, Slovic P, Eriksen MP. Changing perceptions of harm of e-cigarette vs cigarette use among adults in 2 US national surveys from 2012 to 2017. JAMA Netw Open. 2019;2(3):e191047 [link]*

Response: the results are shocking, not a cause for celebration. The main problem with this claim is that it is true. Professor Glantz summarises the results shown in the substantive paper. The current perceptions all incline nicotine users to choose more harmful products and to be excessively concerned about vaping and other smoke-free products. The proportion believing e-cigarettes were *more harmful* than cigarettes was indeed less than 10%. It was 9.9% – and that is shockingly high. There is little comfort in the one-third who believe vaping is less harmful than smoking – 'less harmful' can mean 2%, 20%, 70% or 98% less harmful. The right answer is 'much less harmful'.

Interested readers can directly consult US surveys of risk perception. For example, the National Cancer Institute, Health Information National Trends Survey (HINTS) with data for 2017 or 2018*:

- E-cigarettes compared to cigarettes [link]. Only 2.6% correctly think e-cigarettes are much less harmful than smoking (2018). Yet 'much less harmful' is the most realistic statement of current expert consensus.
- E-cigarettes harm to health [link]. 45.4% think e-cigarettes are 'very harmful' to health. So far, there is no evidence of material harm to health, but it is plausible that some harm will emerge.
- Smokeless tobacco compared to cigarettes [link]. 71% do not think smokeless is less harmful than smoking and 13% don't know (it is likely to be less than 1% of the risk of smoking)
- Nicotine as a cause of cancer [link]. 51% agree or strongly agree that nicotine is the main cause of cancer. Nicotine is not a cause of cancer – products of combustion cause cancer.

[*Note: reported relative risk perception vary between 2017 and 2018 because in the latter survey 'don't know' was a permitted response. Excluding 'don't knows' shows continued deterioration in perceptions from 2017 to 18.]

Claim 4: National Academies report understates the risk of vaping

> Huang and colleagues[3] express concern that as fewer people view e-cigarettes as less harmful than cigarettes, fewer will be interested in switching from combustible cigarettes to e-cigarettes. Based on the evidence available in 2017, the National Academies of Sciences, Engineering, and Medicine [NASEM] concluded that "e-cigarettes pose less risk to an individual than combustible tobacco cigarettes."[4(p11)]
>
> The [NASEM] report emphasized that at the time, no studies on the long-term health effects of e-cigarettes had been performed, which they recognized as a limitation. However, the data are catching up with public perception.
>
> *4. National Academies of Sciences, Engineering, and Medicine. Public Health Consequences of e-Cigarettes. Washington, DC: National Academies Press; 2018.[link]*

Response: NASEM correctly bases its view on the much lower vape aerosol toxicity and toxic exposures than arise through smoking. NASEM came to a conclusion at radical variance to Professor Glantz. It is astonishing that he can argue that a few papers and conference abstracts invalidate the work of this panel. NASEM is right: and it is no accident that the risks are *much* lower. It is the products of combustion that do the real damage with smoking, and vaping products do not involve combustion. The difference between combustion and non-combustion means that vaping is a very different kind of exposure to smoking. NASEM explains:

> *Laboratory tests of e-cigarette ingredients, in vitro toxicological tests, and short-term human studies suggest that e-cigarettes are likely to be far less harmful than combustible tobacco cigarettes.*

Consequently, NASEM concluded:

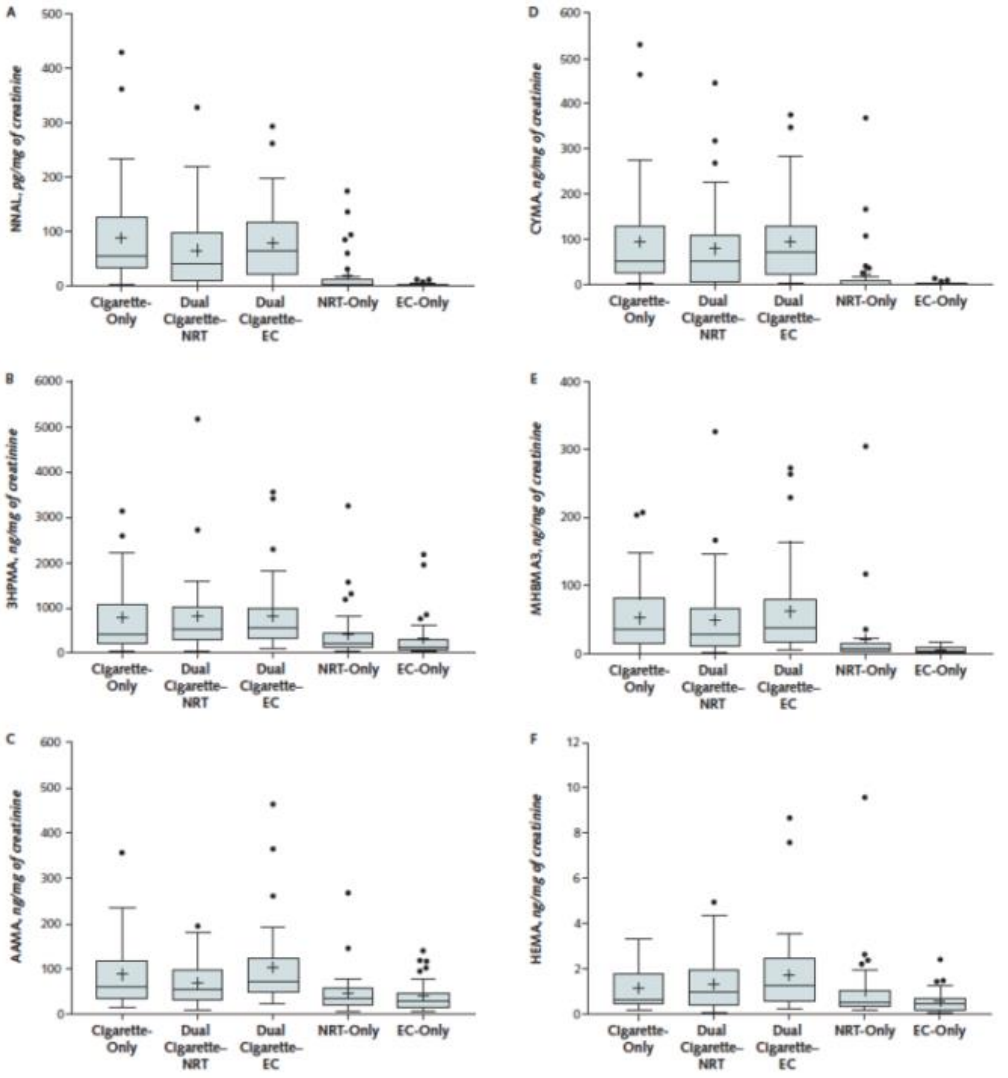
- *While e-cigarettes are not without health risks, they are likely to be far less harmful than combustible tobacco cigarettes.*
- *E-cigarettes contain fewer numbers and lower levels of toxic substances than conventional cigarettes*
- *The long-term health effects of e-cigarettes are not yet clear.*
  NASEM, 2018 [link] Launch presentation summary (slide 44) [link][link]

Response: the data are not "catching up with public perception". Human exposure studies show vapers with much lower toxic exposures than smokers. On human exposures, see for example *Goniewicz et al., 2018*

> *Findings suggest exclusive e-cigarette use results in measurable exposure to tobacco-related constituents; however, compared with cigarette smoking, biomarker concentrations of nicotine and toxicants among e-cigarette–only users were much lower.*

These exposures really are *much lower*. *Shahab et al., 2017*, suggests vaping exposures as low as found with NRT users – see figure 2 from this study reproduced below. Note that some of the exposure could be from background sources, so it is the *differences* that matter in the chart and in all exposure studies. It is biologically implausible that these greatly-reduced exposures would not lead to greatly-reduced health risk.

Figure 2. Urinary metabolite levels for selected toxins and carcinogens, by group.



Data are raw values divided by ratio of observed urinary metabolites to covariate-adjusted creatinine levels. The levels below the limit of detection were imputed by the limit of detection divided by square root of 2. Boxplots show the median with interquartile range (25th percentile, 75th percentile). Error bars show Tukey's whiskers, and cross indicate arithmetic means (geometric means are provided in **Appendix Table 1**). Circles indicate outliers. Significant pairwise comparisons are presented in **Appendix Table 1**. Cigarette = combustible cigarette; EC = e-cigarette; NRT = nicotine replacement therapy. **A.** Tobacco-specific *N*-nitrosamine. NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. **B.** Acrolein. 3HPMA = *N*-acetyl-S-(3-hydroxypropyl)-L-cysteine. **C.** Acrylamide. AAMA = *N*-acetyl-S-(2-carbamoylethyl)-L-cysteine. **D.** Acrylonitrile. CYMA = *N*-acetyl-S-(2-cyanoethyl)-L-cysteine. **E.** 1,3-butadiene. MHBMA3 = *N*-acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine. **F.** Ethylene oxide. HEMA = *N*-acetyl-S-(2-hydroxyethyl)-L-cysteine.

Claim 5: long-term health effects of vaping are unknown

Professor Glantz reaches for one of the most over-used but empty devices relied upon by those opposing smokers switching to non-combustible sources of nicotine including vaping.

> The [NASEM] report emphasized that at the time, no studies on the long-term health effects of e-cigarettes had been performed, which they recognized as a limitation.

Response: we do not know (and cannot know) everything. But we do know a lot and enough to make decisions. There are indeed no long-term studies of the type that would provide conclusive epidemiological data on health effects of multi-decade use. But that is because multiple decades have not yet elapsed since the introduction of e-cigarettes and we cannot travel forward in time to

discover how vaping played out 50 years from now. Furthermore, almost all vapers have also been smokers, so it will *always* be challenging to assess the effects of long-term exclusive vaping. To isolate vaping risks, we would need to follow a sizeable cohort of lifetime exclusive vapers. In my view, the call for 'long term studies' is mainly a device for obfuscating and casting doubt, and it will persist as a device *forever*. There are still activists who deny the role of snus in reducing smoking in Scandinavia, despite more than sufficient long term data to establish this beyond any reasonable doubt. It should not divert attention from *what we do know*, which is a lot – for example, take the *Goniweicz et al.* and *Shahab et al.* exposure studies above. The point is that we can make judgements based *on what is known* (toxicology, exposures, biomarkers of health, acute health effects, experience over 10 years etc.) even if what we do know is incomplete. This approach is better than waiting for what can't be known for decades or possibly forever.

Response: basing vaping policy on supposedly 'precautionary' reactions to unknowns will likely cause harm. Also, the statement "long term health effects are unclear" is simply that. It makes no judgement that the long-term health effects would be significant or even negative. The health impact could equally be negligible or even beneficial (for example, in slowing neurodegenerative diseases). So, before we inject meaning into the "long term is unclear" we should consider *what we do know*. At the heart of the faulty reasoning about long-term uncertainty is the misuse of the *precautionary principle.* The precautionary principle applies to the introduction of a novel risk where none previously existed. That is not the case here. The extraordinary risk of smoking is well known, and the potential for e-cigarettes to decrease that risk is highly plausible based on the 10 years of experience we already have. If material e-cigarette risks do eventually emerge, governments can address them through regulation or consumer information – the risks are not irreversible. I discuss this in greater depth here: Ten perverse intellectual contortions: a guide to the sophistry of anti-vaping activists: part 7. abusing the precautionary principle.

In short, there is an often-unrecognised price to pay for being over-cautious or 'precautionary'. By preventing or obstructing access to much safer alternatives to smoking, so-called precautionary policies can mean more smoking and more harm. In a proper assessment, the policymaker weighs: (1) both the consequences of inaction and action and (2) the consequences of making the right and wrong call on risk. This kind of symmetrical appraisal is rarely done in practice, but objective evaluation would almost certainly show the small and controllable risks and the uncertainties from vaping are worth bearing in return for addressing the obvious and very high consequences of smoking.

Response: if Professor Glantz is successful, we would *never* have the data. Those playing up fears of unknown risks are not tirelessly striving to resolve the uncertainties or conducting the necessary studies. Professor Glantz, for example, backs outright bans on e-cigarettes even in situations where cigarettes continue to be on widespread sale. Take as the recent ban in his institutional home town of San Francisco. As reported by Politico, 9th July 2019:

> *Stanton Glantz, director of UC San Francisco's Center for Tobacco Control Research and Education and a strong anti-tobacco advocate, called the city ban "a totally brilliant way of a local government basically saying to the FDA and to Juul and the other e-cigarette companies that hey, we've got a law here and it should be followed."*

Professor Glantz favours outright bans pending FDA approval of individual vaping products (a process that will become mandatory in 2020) This approval regime is a highly disproportionate, expensive and burdensome process that will remove nearly all vaping products and most companies from the market. I have yet to see a single instance of Professor Glantz supporting the approval of a product or a relative-risk claim through the FDA's regulatory system. For some, regulatory barriers to entry are best if they are insurmountable: *de facto* prohibition.

The primary funder of his Professor Glantz's centre is the FDA most recently through the $20m TCORS grant from FDA awarded in September 2018.

In the next few sections, we shall see why the data are not "catching up with public perceptions".

Claim 6: vaping causes heart attacks and strokes

Professor Glantz now moves on to deal with specific risks, starting with heart attacks and stroke.

> Since the report was completed, evidence has started to emerge that e-cigarette users are at increased risk of myocardial infarction,[5–7] stroke,[6] .
>
> *5. Alzahrani T, Pena I, Temesgen N, Glantz SA. Association between electronic cigarette use and myocardial infarction. Am J Prev Med. 2018;55(4):455-461.[link]*
>
> *6. Ndunda PM, Muutu TM. Electronic cigarette use is associated with a higher risk of stroke. International Stroke Conference 2019 Oral Abstracts. Stroke. 2019;50(suppl 1):abstract 9. [link].*
>
> *7. Bhatta D, Glantz SA. Electronic cigarette use and myocardial infarction among adults in the United States Population Assessment of Tobacco and Health. Paper presented at: Society for Research on Nicotine and Tobacco Annual Meeting; February 20-23, 2019; San Francisco, CA. Abstract P0S4-99. [link].*

Note that Professor Glantz has cited one published paper in which he is the corresponding author and two conference abstracts, one of which is by him. Let's just remark that the evidence base presented here is neither broad nor deep.

Response: all three citations refer to an association, but they have been included here as if they show causation. These types of studies cannot be used to establish that vaping caused the observed heart attacks and strokes. For example, *Alzahrani et al.* [ref 5] state in their limitations section:

> *The NHIS is a cross-sectional study, so it only permits identifying associations rather than causal relationships.*

The language used in Professor Glantz's commentary may be technically hedged and ambiguous: "*e-cigarette users are at increased risk of myocardial infarction, stroke*". However, this statement is included in a commentary designed to support Professor Glantz's claim that the public is right to see vaping as being as harmful as smoking – it is, therefore, a causal claim in the context in which it is presented.

Response: much of the recorded heart attack and stroke events happened before the user started vaping. These three papers (5-7) have a common approach – they look at the history of myocardial

infarction (commonly known as a 'heart attack') or stroke in vapers and non-vapers and compare. They count the heart attacks and strokes *irrespective of when they happened*. These temporal issues mean there is a huge volume of noise and bias in the data from heart attacks or strokes that occurred *before* the person started vaping. These events could not have been caused by vaping.

Given that nearly all vapers are former or current smokers, it is far more likely that differences in smoking history between vapers and non-vapers explain the differences in heart-attack and stroke outcomes. In other words, does being a vaper today signify that you were more likely to be a heavy smoker for longer in the past? Might many of these individuals have taken up vaping precisely *because* they had suffered heart attacks due to smoking? If so, how does the researcher eliminate that confounding effect to reveal only the underlying signal of excess risk arising from vaping? This challenge is not faced in any of the three papers cited.

Response: did the heart attack cause the vaping? Finally, there is also the question of reverse causation. This arises when people are using e-cigarettes *because* they have had a heart attack or stroke and are trying to give up or cut down smoking the best and quickest way they can. A letter to the editor, *Farsalinos & Niaura, 2019*, responding to reference [5] made fun of Professor Glantz's method by running the numbers on whether taking cholesterol-lowering drugs would also appear to increase risks of heart disease and heart attacks (MI):

> *To more clearly demonstrate the perils of such an approach, we performed logistic regression analyses of the 2016 and 2017 (pooled) NHIS to examine if ever taking prescribed medicine to lower cholesterol is associated with MI and coronary heart disease (CHD).*

And so it did:

> *Ever taking prescribed medicine to lower cholesterol was independently associated with increased odds of having had an MI (OR=2.15, 95% CI=1.65, 2.80, p<0.001) and having CHD (OR=2.05, 95% CI=1.65, 2.55, p<0.001)*

Leading Professor Glantz's critics to conclude:

> *Obviously, it would be inappropriate to conclude that ever taking prescribed medicine to lower cholesterol, adjusted for having hypercholesterolemia as well as other risk factors, is associated with increased risk of MI and CHD. Our findings show the well-established limitations of cross-sectional studies, which cannot justify any claims about causal inference, as mentioned in the conclusion by Alzahrani and colleagues. Therefore, the conclusion of their study is incorrect and should be revised.*

Response: Reference 7 has since become a published paper and subject to severe criticism – it should never have been published. The paper is:

> *Bhatta DN, Glantz SA. Electronic Cigarette Use and Myocardial Infarction Among Adults in the US Population Assessment of Tobacco and Health. J Am Heart Assoc. 2019 Jun 18;8(12):e012317. [link]*

Naturally, the paper provides far more information about the study than the abstract cited in the commentary. Once readers could see the data and method in more detail the study attracted extremely strong criticism (see below). It illustrates the danger of citing conference abstracts because sceptical readers are unable to access the information that allows a proper appraisal of the study.

Response: again a cross-sectional study has been used improperly to make a causal claim. The whole purpose of Professor Glantz's commentary is to argue that it is for the public to believe vaping is as harmful as smoking. The inclusion of this study (in the form of the abstract that came before the paper) is to support this causal claim. However, the limitations section of *Bhatta & Glantz* again highlights the inappropriate use of this data to support the assertion that vaping *caused* the observed heart attacks.

> *While PATH is a longitudinal study, there were only 8 people who used e-cigarettes and had first myocardial infarctions during this follow-up, so there was not enough power to detect an effect. Confirming this problem, every-day and former-conventional cigarette smoking were not significant either. While longitudinal studies are more desirable than cross-sectional studies, the reality is that it will be years before enough myocardial infarctions have occurred to do a meaningful analysis.*

So the answer was to present a meaningless analysis? Professor Glantz has ignored his own acknowledgement of limitations and presented cross-sectional data to support his broad causal claim that vaping is as harmful as smoking, in this case, that it causes heart attacks. If it isn't a causal claim, what is it doing in this commentary?

If that was the only problem with this study, it would be merely misguided. But it gets worse.

Response: many of the heart-attacks in Bhatta & Glantz happened *before* the user started vaping. The failings that were clear when it was an abstract have survived untouched by peer review or the journal's editorial quality control in the paper. In a data-grounded and excoriating critique, Brad Rodu and Nantaporn Plurphanswat fatally challenge the underlying premise of the study in a letter to the journal. This is how their letter was reported in USA Today:

> *The study, co-authored by Dharma Bhatta, claimed adult vaping was "associated with" a doubled risk of heart attack, but Glantz went farther in a blog post, saying the study represented "more evidence that e-cigs cause heart attacks."*
>
> *However, when Rodu obtained the federal data, he found the majority of the 38 patients in the study who had heart attacks had them before they started vaping — by an average of 10 years earlier. In his letter to the editors, Rodu called Glantz's findings "false and invalid."*
>
> *"Their analysis was an indefensible breach of any reasonable standard for research on association or causation," wrote Rodu and Nantaporn Plurphanswat, a research economist at University of Louisville's James Graham Brown Cancer Center. "We urge you to take appropriate action on this article, including retraction."*

Response: the data were available to do this job properly but the authors chose not to use it. Rodu and Plurphanswat followed up a week later with a further letterhighlighting flaws in the secondary analysis related to the timing of heart attacks and uptake of vaping. Importantly, this survey *did* have the timing information *Bhatta, Glantz et al.* could have used to perform the obvious proper analysis. They chose not to do so, in favour of publishing a falsehood. The Journal of the American Heart Association should urgently consider the case for retraction of this paper – the argument is overwhelming, and the journal should scrub this paper from the academic record.

Claim 7: vaping is a cause of respiratory disease

Professor Glantz moves on to claim that the evidence is now showing material risks to respiratory health from e-cigarette use.

> ...and chronic obstructive pulmonary disease and other respiratory diseases,[8–10]controlling for smoking and other demographic and risk factors.
>
> *8. Perez M, Atuegwu N, Mead E, Oncken C, Mortensen E. E-cigarette use is associated with emphysema, chronic bronchitis and COPD (A6245). American Thoracic Society Session D22: Cutting Edge Research in Smoking Cessation and E-cigarettes. [link].*
>
> *9. Wills TA, Pagano I, Williams RJ, Tam EK. E-cigarette use and respiratory disorder in an adult sample. Drug Alcohol Depend. 2019;194:363-370. [link]*
>
> *10. Bhatta D, Glantz SA. Electronic cigarette use is associated with respiratory disease among adults in the United States Population Assessment of Tobacco and Health: a longitudinal analysis. Paper presented at: Society for Research on Nicotine and Tobacco Annual Meeting; February 22-23, 2019; San Francisco, CA. Abstract P0S2-146. [link].*

Response: the more relevant evidence shows vaping *improves* COPD outcomes. The source quoted by Professor Glantz is another conference abstract, *Perez et al*. (reference 8). The authors sink Professor Glantz's story by acknowledging the limitations with this rather important caveat:

> *Due to the fact that the data is cross-sectional, it is unknown whether E-cigs could contribute to COPD development, or if people who have COPD are more likely to use E-cigs (possibly as a harm reduction method). Prospective data are needed to better determine the nature of this association.*

But wait… are there other studies that do address this issue with prospective data (i.e. by following a cohort of patients)? Yes, there are! See, for example, *Polosa et al. 2018*, which presents findings from a long-term prospective assessment of respiratory outcomes in a cohort of COPD patients who reduced or quit smoking with e-cigarettes.

> *The present study suggests that EC [electronic cigarettes] use may ameliorate objective and subjective COPD outcomes and that the benefits gained may persist long-term. EC use may reverse some of the harm resulting from tobacco smoking in COPD patients.*

Response: smokers may have started using e-cigarettes in response to asthma or pulmonary disorder. The second source, *Wills et al.* (reference 9) discusses possible limitations in their paper but dismiss the most likely causes.

> *Because the items did not determine exactly when symptoms of asthma or pulmonary disorder originated, there are two possible interpretations of the data. One possible interpretation is that participants began using e-cigarettes when they developed asthma or pulmonary disorder; but it is difficult to think of a reason for why people would do this because e-cigarette vapor has lung irritant properties (e.g., Anderson et al., 2016; Larcombe et al., 2017; Reidel et al., 2018; Wu et al., 2014).*

It is, in fact, not difficult to think of a reason. How about this? The irritants detected in the four cited mouse and *in vitro* studies are just not that irritating to actual human smokers, yet the relief from switching from smoking to vaping is palpable. That would be borne out by the literature on human subjects using vaping to relieve smoking-related respiratory disease – for example, *Mojaria et al., 2017. E-cigarettes in patients with COPD: current perspectives*. The authors are bluntly assuming this can't happen, even though this is documented quite extensively.

Response: the authors consider and dismiss another possible (and very likely) explanation.

Wills et al. decide that another obvious explanation for their findings can be ruled out:

> *As a variant explanation, it could be posited that persons who used e-cigarettes did so to reduce or quit smoking when they developed a respiratory disorder. However, this interpretation would be inconsistent with the data, which showed that the significant associations of e-cigarettes with respiratory disorder occurred primarily among nonsmokers, not among smokers.*

This finding should draw immediate suspicion – why would you expect an association in non-smokers but not smokers? The most likely reason why they would be non-smokers is that they had quit smoking. This would arise either because they had COPD and wanted to reduce the symptoms (or fire risk if using oxygen) and improve their prognosis, or because they had been heavy smokers. Strangely, the supplementary material shows only 45 non-smoker vapers – given the population prevalence of COPD is about 6% this seems a very small sample from which to draw statistical inferences.

The paper is so poorly written, it is hard to tell what the authors have done. So let me hand over to Professor Mike Siegel to give a rather more frank assessment of this paper.

Response: "ridiculous", says Professor Siegel. Mike Siegel, Professor of Community Health Sciences at Boston University, provides a searing critique of this study: Researchers Tell Public that Vaping Causes COPD as Scientific Rigor in Tobacco Control Drops to an All-Time Low (9 February 2019).

> *There is absolutely no way one can conclude, or even speculate, based on the results of this cross-sectional study, that vaping is a cause of chronic obstructive lung disease. Remember,*

we are talking here about emphysema and chronic bronchitis (that's what is meant by COPD).

To see how ridiculous such a conclusion, or even such speculation is, one needs only to look at the sample size of never smokers in the 2016 Hawaii BRFSS who were current e-cigarette users and reported having COPD. It's 13 (based on the CDC's BRFSS online analysis tool). According to the article itself, the total sample of never smokers who were current vapers was only 45. A simple bivariate online analysis of the relationship between ever use of e-cigarettes and ever diagnosis of COPD among the never smokers in the 2016 Hawaii BRFSS reveals no significant association.

If you do the same analysis using the entire 2016 BRFSS (including all states), the proportion of never smokers who report having been diagnosed with COPD is actually higher among non-vapers (2.9%) than ever vapers (2.4%).

Response: it is implausible that e-cigarettes would cause COPD in just a few years. The arguments above are not the most lethal blow to this reasoning: it is something much more obvious. In smokers, it takes several decades of heavy smoking for COPD to develop. By what plausible mechanism could vaping, which has a far lower toxic burden than smoking, somehow create COPD in the few years in which it has been in existence? Over to Mike Siegel again:

There is simply no way that you can develop COPD from vaping for five years. Even among heavy chain smokers, it takes several decades before they develop COPD. I'm not aware of more than a handful of smokers who were diagnosed with COPD (caused by smoking) before they reached the age of 40. Population-level data show that the observed increase in COPD incidence among smokers does not begin until about age 45.

Response: prior smoking was more likely to be the cause of the observed respiratory conditions. Professor Glantz deploys Bhatta & Glantz (reference 10) in another act of self-citation and again a conference abstract. Here is what this study says:

Among people who did not report respiratory disease at Wave 1, the longitudinal analysis reveals statistically significant associations between former e-cigarette use (adjusted odds ratio, 1.24, 95% CI: 1.03, 1.51) and current e-cigarette use (1.23, 95% CI: 1.00, 1.52) at Wave 1 and having incident respiratory disease at Waves 2 or 3, controlling for cigarette smoking, demographic, and clinical variables. Current cigarette smoking (2.68, 95% CI: 2.10, 3.42) was also significantly associated with having respiratory disease at Waves 2 or 3.

The fundamental issue here is confounding by smoking, given that most e-cigarette users are or were recent smokers. They show a substantial risk for smokers (OR=2.68) and only just statistical significance for former and current e-cigarette use. Given the data cover three waves each about a year apart, the data is capturing the onset of disease with increasing age and continuing lung decline in lung function. The question for Professor Glantz is what exactly do you mean by 'controlling for cigarette smoking'? Separating the effect of vaping from prior or current smoking over this timescale would require, at least, very high fidelity information on smoking behaviour and history and is probably impossible. See discussion below.

Response: 'controlling for smoking' is a gross approximation and it is impossible to control completely. Professor Glantz argues that the results in the citations he presents were 'controlled for smoking'. But what does that even mean?

Smoking is the likely cause of the observed results and smoking is tightly bound to vaping through users' history of nicotine use. That means it would require highly sophisticated (by which I mean implausible or impossible) 'deconfounding' to eliminate the effect of smoking and to isolate an independent impact of vaping. To do that would require a detailed smoking history, for example. Carl V Phillips describes this problem in a review of an earlier poster version of one of Professor Glantz' papers that claims to control for smoking:

> *This research approach is fatally flawed because of unrecorded details of someone's smoking history. [Professor] Glantz has absurdly insisted that the study controlled for smoking by including variables for current and former smoking. But smoking is not a dichotomous (or trichotomous) exposure. Smokers who smoke more, or used to smoke more, have higher risk of disease. Former smokers who quit recently are at much higher risk than those who quit long ago. Former smokers who vape will have quit smoking relatively recently and are more likely to have been hardcore smokers (less intense smokers who could take-it-or-leave-it are more likely to just stop, not switch to vaping). Current smokers who vape are probably more intense smokers who are motivated to search for a useful aid to quitting or are more interested in a substitute for when they cannot smoke.*

Imagine what you would want to know if you were an investigator designing a survey to figure out if vaping causes heart attacks, stroke or COPD. Your first problem is how to exclude somehow the residual risks arising from being a former smoker or current smoker. However, these risks are likely to be larger and may overwhelm any signal suggesting a vaping risk. That residual risk itself is difficult to characterise (e.g. age of initiation, years of smoking, years since quit, smoking intensity in cigarettes per day etc.). It should, therefore, be evident that just knowing the smoking status (never, former, some days, daily) is entirely inadequate.

Response: respiratory disease has a gradual onset and continuing deterioration, so linking vaping behaviour to respiratory disease onset is difficult. There is never an abrupt *onset* of the most serious respiratory diseases like COPD. The only fixed point might be a *diagnosis* by a physician. But that is not the same as the *onset* of the disease, which has no fixed point and will have been in progression long before the diagnosis. So to claim that vaping is causing the *onset* of respiratory disease, an investigator would need to take account of the gradual onset of symptoms, the lag between symptoms and diagnosis, and the fact that deterioration continues as part of ageing, even if the smoking stops. How would that be done?

Claim 8: some vaping risks approach those of cigarettes

Next is an interim declaration that is critical to Professor Glantz's central claim –that the public is right to believe that vaping is as harmful cigarette smoking.

> Some of these risks approach those of smoking cigarettes.

Response: this assertion has no basis in the evidence presented in the commentary, in the wider evidence base or in common sense. No. Sorry. The citations so far don't even show *any* meaningful risk, let alone a risk comparable to smoking. Even in Professor Glantz's claims, there is nothing to quantify and compare the magnitude of the risk with the risks of smoking. Yet this is the entire premise of the commentary. This comment, which is made without support or context, will encourage false and misleading activist claims. Readers are likely to believe that – if published in the JAMA network – it must have at least some loose attachment to reality. It does not.

Claim 9: vaping is implicated in cancer

> There is also emerging evidence that e-cigarettes deregulate biologically significant genes associated with cancer.[11]
>
> *11. Tommasi S, Caliri AW, Caceres A, et al. Deregulation of biologically significant genes and associated molecular pathways in the oral epithelium of electronic cigarette users. Int J Mol Sci. 2019;20(3):738. [link]*

Response: gene deregulation does not establish a material cancer risk. This statement about gene deregulation is technically correct, but it is a *long way* from reliably establishing a cancer risk. I consulted two experts; both highlighted the possible role of smoking in the e-cigarette group; both noted that the effects were lower in the e-cigarette group; both pointed out that the clinical significance was unknown.

> *1. I think the authors provide sufficient proof that vapers were exclusive vapers (based on plasma COHb and exhaled CO) but there is no information on how many of them were former smokers. In fact, the inclusion criterion for vapers was not to have smoked in the past 6 months, so it is possible that they were smoking before that (and there is no way to verify if they had stopped smoking 6 months or 1 week before the study). Besides that, they identified substantially lower effects of e-cigs but also some effects that are different (qualitative difference) compared to smoking. The clinical context of those findings is unknown.*
>
> *2. The data supports the classification within the limitations of the available tests. It has to be noted that e-cig users have slightly elevated COHb, which may point to a partial dual-use given that the COHb washout period is very short (less than 24 hrs). This part, which is crucial, was performed and reported using standard tools, i.e. cotinine and COHb. In summary, the paper provides some data of questionable accuracy compared with previous studies [Boyle et al. 2010] for cigarette smoke exposure of the oral mucosa. The data supports a clear distinction between smoke and vapor exposed samples. It is not good enough to draw a conclusion regarding the dysregulation of disease-associated pathways and disease risk in e-vapor exposed samples.*

Response: more direct evidence suggests vaping has less than 1% of the cancer risk of smoking. On the subject of cancer risks, we should consult a different source using a different approach:

> *Most e-cigarette analyses indicate cancer potencies <1% that of tobacco smoke and <10% that of a heat-not-burn prototype, although a minority of analyses indicate higher potencies.*

Stephens WE. Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. Tob Control. 2018 Jan 4;27(1):10–7. [link]

The authors in this study looked at exposures to a subset of 14 of the main carcinogens found in tobacco smoke and, to some extent, in aerosol emissions from e-cigarettes, heated tobacco products and a medical nicotine inhaler. They estimated the cancer potencies based on these carcinogens and computed the lifetime risk of cancer arising from regular exposure.

Table 1 in this study provides the main summary findings. The estimated mean excess lifetime cancer risks are simplified and summarised below:

	Cigarette smoke	Heated tobacco emission	E-cigarette vapour	Nicotine inhaler
Lifetime excess cancer risk	2.4%	0.057%	0.0095%	0.00089%
Risk relative to smoke	100%	2.4%	0.4%	0.04%

The lifetime risk for cigarette smoke is likely to be higher in reality because there are many more significant carcinogen exposures and extra risk may arise from interactions within the smoke chemistry.

For context, the U.S. National Cancer Institute says that 38.4% of Americans will be diagnosed with cancer at some point in their lifetime (based on 2013-15 data).

Based partly on such data, some UK authorities claim vaping is at least 95% less risky than smoking and suggest this estimate is conservative.

Claim 10: dual-use undermines the value of vaping

> Equally important, the risks of e-cigarette use are in addition to any risks of cigarette smoking, which means that dual users (people who continue to smoke cigarettes while using e-cigarettes) have higher risks of heart and lung disease than people who just smoke. This finding is particularly important because, contrary to the hopes of the e-cigarette optimists, about two-thirds of adult e-cigarette users are dual users (ie, continue to smoke).

Response: there is less dual-use than asserted, and it may be beneficial. The claim that two-thirds of adult vapers are dual users is unreferenced and wrong. In a recent analysis of US PATH data, (*Coleman et al. 2019*) FDA analysts showed that dual-use was 59% (in 2016, vapers were 40.5% daily smokers, 18.4% non-daily smokers). So some of the non-daily smokers may have become non-daily smokers because of vaping – so this may be a benefit. It is a common mantra to argue that dual-use has no benefits. The evidence is mixed and changing over time as improved devices are better able

to substitute for smoking. *Brandon et al. 2019* showed that dual users were cutting down smoking substantially:

> *They reported smoking a median of 16-20 cigarettes per day (CPD) for a mean of 13 years before vaping, which was initiated a median of 13-24 months earlier. Smoking declined to 6-10 CPD currently, with 79% reporting decreased and 3% reporting increased smoking. 69% reported daily vaping, with 57% reporting vaping "continuously" or at least 30 times/day.*

For some smoking risks – cancer and COPD – the risk is pretty well linearly proportional to exposure, so cutting down does help.

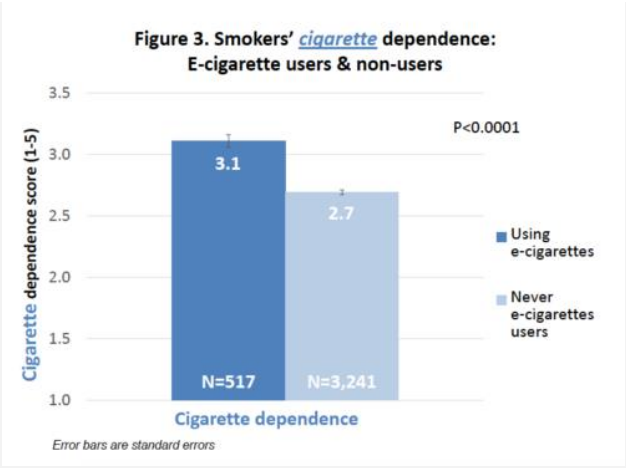
In the UK, the proportion of dual users in the vaping population is falling over time – probably as the products improve and users understand them better.

Response: the risks of smoking and vaping are not additive. The idea that the risks are *additive* has no established basis. Professor Glantz provides no conclusive evidence to support this claim – see a discussion by Carl Phillips here: *Dual-use and the arithmetic of combining relative risks*. In fact, my opening expectation is that users tend to 'titrate' their nicotine intake (control it to achieve their desired exposure). Their nicotine-seeking behaviour would adjust to provide about the same amount of nicotine, whether they were exclusive smokers or dual-users. That expectation may be challenged by contrary evidence, of course, but it is a reasonable starting point.

There is, however, evidence that dual users have *higher exposure* to nicotine than exclusive smokers. In both *Shahab et al. 2017* and *Goniewicz et al. 2018*, the subjects classed as dual users had about 50% higher nicotine exposure. With the higher total nicotine exposure, you would also expect higher exposure to toxins. How much higher would depend on how much of their nicotine they were taking from cigarettes (high toxin to nicotine ratio) and how much from vaping (low toxin to nicotine ratio). However, there are basically two explanations for the observed higher nicotine exposure:

1. **The exposures are additive**. The switch from exclusive smoker to dual-user changes the pattern of nicotine intake in a way that increases total nicotine exposure. That might happen either because nicotine titration no longer works or because the user was previously constrained and could not achieve their desired nicotine dose. In this case, the risk would *increase* to the extent that the source of additional nicotine drew in additional toxins.
2. **Selection bias – more dependent smokers are likely to vape.** The use of an e-cigarette as a dual user is a marker for more dependent smokers. Less dependent smokers would find it easier to become exclusive vapers. In this case, the risk would *decrease* as more of the user's desired nicotine demand would be met from a much cleaner source.

To my knowledge, we do not conclusively know which of these dominates. However, there is some preliminary evidence that smokers that are e-cigarette users are more dependent on smoking *Shiffman et al., 2019* – an SRNT conference poster.



Smokers who vape are more dependent on cigarettes – findings from PATH

This would tend to support the second explanation. So it is premature to declare that the dual-use is an additional risk. It is conceptually a possibility. [Please comment or let me know if you know of studies that follow users through transitions from exclusive smoking to dual use].

However, such complications did not deter Professor Glantz. Following the publication of the *Goniewicz et al.* study, Professor Glantz informed potential switchers that they would be "*better off just smoking*".

The problem is that this amounts to advice never to try switching to e-cigarettes and to smoke instead – and this tweet is unqualified and without reference to dual-use. The first problem is that the Goniewicz study cannot tell us if the exposures increased due to becoming a dual user or the dual users were more dependent to start with (as discussed above). But even if Professor Glantz was right (*and it's a big if*) and the increased exposure was caused by switching from smoking to dual-use, potential switchers do not know *in advance* if they will switch completely or if they will enter a period of dual-use prior to switching completely, and if so, for how long. As we shall see below, dual-use should be seen as an encouraging first step on the path to complete switching – but a smoker cannot reach the destination if they do not take the first step.

Response: dual-use is an *optimistic* signal of intent. *Simonavicius et al. 2017* showed that "*Current dual users were more motivated to stop smoking than past users*". Dual-use may be seen, therefore, as an encouraging first step on a pathway to smoking abstinence that will play out over time.

Dual-use is not one thing – what matters is how much smoking there is, and whether uptake of vaping reduces smoking. Going from one pack per day to one cigarette per week is still 'dual-use' on some measures, but is obviously not the equivalent risk. Lighter use might be part of a transition to smoking cessation.

Response: a period of dual-use may improve smoking cessation outcomes. There is some evidence that an initial period of 'dual-use' of NRT along with smoking before quitting improves the chance of subsequent smoking cessation – see Cochrane review.

> *There is moderate-certainty evidence that using NRT prior to quitting may improve quit rates versus using it from quit date only; however, further research is needed to ensure the robustness of this finding.*

For the same reasons, we might expect less abrupt transitions via dual-use to work with vaping too. So for some users, dual-use might well be a rational and optimum pathway to smoking cessation.

Response: almost every pathway to smoking cessation involves continued smoking. There is a further point on 'dual-use'. Unless a smoking cessation method is 100% immediately successful, then there will *always* be smoking on the pathway from the decision to quit smoking to becoming a permanent ex-smoker. Typically, this might happen through serial quitting and relapse. In this way, 'dual-use' is a feature of *every* pathway from smoker to ex-smoker, whatever the method: cold turkey, NRT, prescription meds, behavioural therapy etc. These methods have relatively low success rates (5-20%), and many people struggle to quit at will.

Response: misinformation about risk is a cause of dual-use. But the most important thing to understand here is that the extent of dual-use is an outcome of behavioural influences – including perceptions of relative risk. A recent analysis of PATH data found that, unsurprisingly, risk perceptions predicted whether a user was an exclusive vaper or dual user.

> *U.S. adult dual users of e-cigarettes and cigarettes who perceive e-cigarettes as less harmful than cigarettes appear to be more likely to switch to exclusive e-cigarette use, more likely to remain dual users, and less likely to switch to exclusive cigarette use one year later than dual users with other perceptions of e-cigarette harm.*

So here's the funny thing*… those spreading of fear and confusion about e-cigarettes are themselves a *cause* of dual-use. False risk perceptions mean that dual-use is higher than it would otherwise be and are responsible for any harms that arise from that.

* not funny

Claim 11: e-cigarettes are ineffective for real-world smoking cessation

> In addition, although 1 randomized clinical trial[12] has shown that e-cigarettes improve cessation when used as part of a clinically supervised smoking cessation program that includes intensive counseling, as used in the population as a whole as a mass-marketed consumer product, e-cigarettes are associated with reduced odds of cessation.[13]
>
> *12. Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. N Engl J Med. 2019;380(7):629-637. [link]*
>
> *13. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. Lancet Respir Med. 2016;4(2):116-128. [link]*

Response: it is wrong to ignore the valuable insights from an RCT, and there are reasons why vaping may do better in real-life conditions. Professor Glantz acknowledges a randomised controlled trial that shows vaping is effective. However, he argues that real-life experience is what matters and his own 'meta-analysis' of observational studies (discussed and debunked below) is more relevant. I share some of Professor Glantz scepticism about RCTs for assessing the impact of vaping. RCTs are a kind of artificial test in which researchers try to isolate the impact of the technology by holding everything else constant. In this case, the vaping technology does very well: about twice as effective as NRT. This finding is important and a valuable part of the full picture. It is likely to be because vaping does more than 'replace nicotine'. *Notley et al., 2018* found that:

> *E-cigarettes meet the needs of some ex-smokers by substituting physical, psychological, social, cultural and identity-related aspects of tobacco addiction*

There are other reasons to think that vaping would have a good real-world impact too:

- Vaping is designed to be appealing and pleasurable for adults, and so we might expect uptake and continuation of use to be better in the population than NRT. In an RCT the products are usually allocated to equal-sized arms and not based on which they choose.
- Vaping is more customisable and personalisable than other smoking cessation treatments, allowing users to explore and find what works for them – not just in terms of replacing nicotine
- Vaping is underpinned by an extensive support 'ecosystem' of vape shops, social media, vape-meets and fellow vapers. It is embedded in a highly positive culture driven by the joy and self-esteem of many people who have finally quit smoking. This ecosystem provides a kind of behavioural support, often highly expert and also very practical, but just not in a medicalised setting, which may be off-putting for many.
- Vaping operates in a different paradigm to the "illness > treatment > cure" paradigm of established medicalised approaches to smoking cessation. Vaping is better understood in a consumer paradigm "smoking > better product > more welfare".

Response: the claim that vaping reduces population quitting is false and has been convincingly refuted. Professor Glantz highlights his own meta-analysis [13] with Sara Kalkhoran to make this point. They concluded that:

> *As currently being used, e-cigarettes are associated with significantly less quitting among smokers.*

Now, this review has been subject to quite a monstering from its critics. For example, see comments at Science Media Centre:

> *Publication of this study represents a major failure of the peer review system in this journal.* (Professor Robert West, Editor of the journal *Addiction*).

The fundamental problem with the study is that this meta-analysis combines very different studies, including some that no-one would expect to show smoking cessation effects. For example, Peter Hajek comments:

> *The studies that are presented as showing that vaping does not help people quit only recruited people who were currently smoking and asked them if they used e-cigarettes in the past. This means that people who used e-cigarettes and stopped smoking were excluded. The same approach would show that proven stop-smoking medications do not help or even undermine quitting.*

Response – the meta-analysis aggregates completely inappropriate studies. There are many other problems with the meta-analysis, which I detail in more depth here: Who will be duped by error-strewn 'meta-analysis' of e-cigarette studies? But David Abrams and Ray Niaura sum it up in a comment:

> *While the majority of the studies we reviewed are marred by poor measurement of exposures and unmeasured confounders, many of them have been included in a meta-analysis that claims to show that smokers who use e-cigarettes are less likely to quit smoking compared to those who do not. This meta-analysis simply lumps together the errors of inference from these correlations. As described in detail above, quantitatively synthesizing heterogeneous studies is scientifically inappropriate and the findings of such meta-analyses are therefore invalid.*

To illustrate this, we can take one example of a study included in this meta-analysis. We will use:

> Al-Delaimy WK, Myers MG, Leas EC, *et al.* E-cigarette use in the past and quitting behavior in the future: a population-based study. *Am J Public Health* 2015;**105**:1213–9. [link]

This is cited at ref 36 and included in the Kalkoran and Glantz 'meta-analysis'.

In this study, the authors divided a sample of smokers at baseline into those who had ever used e-cigarettes (even just one) and those who said they never would use e-cigarettes. They then measured smoking behaviour 12 months later and drew conclusions about the impact of e-cigarettes on quitting behaviour. But past use and future intent to use e-cigarettes are not reliable

proxies for trying to quit with and without e-cigarettes. They did not check whether e-cigarettes had been used during the 12 months. They did not establish whether the smokers were trying to quit.

However, despite these multiple shortcomings, the *Al-Delaimy et al.* study was included in the Kalkhoran & Glantz meta-analysis. It was entered with an odds ratio of for smoking cessation of 0.4, meaning that it added to the case that e-cigarette use reduces the likelihood of quitting smoking.

For an academic treatment of the failings of the Kalkhoran & Glantz meta-analysis, please consult *Villanti et al. 2018*. Referring to this study as reference [17], *Villanti et al.* say:

> *The other two published meta-analyses included heterogeneous studies from RCTs, longitudinal and cross-sectional designs in their pooled analyses [17,23]. There are three key issues related to combining results from non-randomized studies with respect to adjustment for confounding. First, effect estimates and standard errors from non-randomized studies do not correct for imbalance in the exposed and unexposed groups (as in randomized studies). Secondly, nonrandomized studies on the same topics are likely to control for different confounders in their analyses; this creates further heterogeneity in the included studies. Thirdly, adjustment for confounding in individual studies—and in pooled analyses—may yield a more precise estimate, but does not reduce bias. The Cochrane Handbook warns: 'meta-analyses of studies that are at risk of bias may be seriously misleading. If bias is present in each (or some) of the individual studies, meta-analysis will simply compound the errors, and produce a 'wrong' result that may be interpreted as having more credibility'*

Response: other studies show increased cessation rates. There were, of course, many other studies that showed a promising association between vaping and smoking cessation. Take *Zhu et al., 2017*:

> *The substantial increase in e-cigarette use among US adult smokers was associated with a statistically significant increase in the smoking cessation rate at the population level. These findings need to be weighed carefully in regulatory policy-making regarding e-cigarettes and in planning tobacco control interventions.*

Note that this is what a rational observer would expect. E-cigarettes are a rival product category to cigarettes. Vaping has various attributes that are superior to smoking, including less of the death and disease, stigma, cost, and mess. It also has some positive things that smoking doesn't have: like flavour choice, tech features, and personalisation. We should expect vaping to take sales and customers away from the established incumbent cigarette trade. We should recognise that claiming that vaping increases smoking is an extraordinary and counter-intuitive claim that should, in the absence of compelling evidence, be met with deep scepticism.

Response: the impact of e-cigarettes is not fixed in time. Vaping technology is constantly advancing and any individual study applies only to the technology with which it was conducted or the era in which it was done. Most of the studies cited in the Kalkhoran & Glantz meta-analysis were done in 2010-13, with the latest in 2015 – see Table 1. A meta-analysis that covers studies that were mainly done in the infancy of the technology has little of value to say about the impact of the technologies as they are today, for example including the highly successful Juul pod products. This

isn't the main problem with this meta-analysis but it illustrates a casual and uncritical approach to citation. It will be interesting to see when tobacco control academics stop referring to this analysis.

Response: the lead author of Kalkhoran and Glantz has since developed the opposite analysis. Let me reserve the last point of the critique of *Kalhoran & Glantz* for Dr Sara Kalkhoran. Dr Kalkhoran was Professor Glantz's former collaborator and has since liberated herself from the University of California at San Francisco. She has moved to Harvard Medical School and has recently published a relevant study, *which completely contradicts the analysis earlier work*

> *In this longitudinal cohort study of U.S. adult cigarette smokers, daily but not non-daily e-cigarette use was associated with higher odds of prolonged cigarette smoking abstinence over two years, compared to no e-cigarette use. Daily use of e-cigarettes may help some smokers to stop smoking combustible cigarettes.*
>
> *Kalkhoran S, Chang Y, Rigotti NA. Electronic Cigarette Use and Cigarette Abstinence Over Two Years among U.S. Smokers in the Population Assessment of Tobacco and Health Study. Nicotine Tob Res. 2019 Jul 11; [link]*

Kalkhoran, Chang & Rigotti, 2019 draw similar observations to *Villanti et al., 2017* about *Kalkhoran & Glantz, 2016*, which is reference [26] in their paper:

> *In contrast to our findings, several prior observational studies examining the relationship between e-cigarette use and cigarette abstinence found that e-cigarette use was associated with a lower likelihood of successful cessation. [26] This is likely due to heterogeneity in the way that these prior studies defined current e-cigarette use. Our findings suggest that combining daily and non-daily e-cigarette users is likely to underestimate the association between e-cigarette use, and subsequent cigarette abstinence and may miss differences in smoking abstinence among subgroups of e-cigarette users. Observational studies should account for the frequency of e-cigarette use when evaluating the association between e-cigarette use and cigarette smoking abstinence.*

Again, it is important to qualify the findings in Kalkhoran, Chang & Rigotti – they are showing an association, and there are several ways to explain it. People motivated to quit might be drawn to trying e-cigarettes. However, it does not lend support to the idea that e-cigarettes are reducing quit rates.

I should say I respect Dr Kalkhoran for her honesty and rigour and nothing I have written here is a criticism of her.

Claim 12: the explosion of youth use outweighs any benefits to adults

> Increased perceived risks of e-cigarettes is also an important element for curbing their use by youth. Youth who believe that e-cigarettes are not harmful or are less harmful than cigarettes are more likely to use e-cigarettes than youth with more negative views of e-cigarettes.[14] In terms of overall public health effects, this explosion of youth use swamps any potential harm reduction that may accompany adults switching from cigarettes to e-cigarettes.[15]

14. Gorukanti A, Delucchi K, Ling P, Fisher-Travis R, Halpern-Felsher B. Adolescents' attitudes towards e-cigarette ingredients, safety, addictive properties, social norms, and regulation. Prev Med. 2017;94:65-71. [link]

15. Soneji SS, Sung HY, Primack BA, Pierce JP, Sargent JD. Quantifying population-level health benefits and harms of e-cigarette use in the United States. PLoS One. 2018;13(3):e0193328. [link]

Response – this is a blunt disclosure of a propaganda motive. Reference 14, *Gorukanti et al.* neatly betrays an activist agenda by rather blatantly making a case for a propaganda approach to risk communications:

> *Increased perceived risks of e-cigarettes is also an important element for curbing their use by youth. Youth who believe that e-cigarettes are not harmful or are less harmful than cigarettes are more likely to use e-cigarettes than youth with more negative views of e-cigarettes.*
>
> *This study indicates that adolescents are aware of some of the risks of e-cigarettes, although many harbor misperceptions and hold more favorable attitudes towards e-cigarettes than cigarettes. Of concern is the relationship between favorable e-cigarette attitudes and use. Findings suggest the need to provide adolescents with correct information about e-cigarette ingredients, risks, and the insufficient evidence of their role in cigarette cessation.*

This is an extraordinary attitude when you think about it. They are starting from the premise it is wrong for adolescents to have a more favourable view of e-cigarettes than cigarettes – even though on any rational basis a favourable view is exactly what you would expect. This is because the authors think teens should not use e-cigarettes and this matters more than addressing them truthfully. In the face of the inconvenient truth about relative risk, the authors argue for convincing adolescents that e-cigarettes are no better than smoking. This is the mindset of the omniscient public health authority figure – but what if they are wrong? What is the effect of their approach is to deter a teenager who would otherwise be a smoker from being a vaper? What if they persuade adults that their switch from smoking to vaping is doing them no less harm? What if people use this false information in ways not intended by public health authorities? Who would be accountable and how?

Response – models produce results that depend on their input assumptions. Reference 15 (*Soneji et al., 2018*) is a case study in modelling being subject to 'garbage-in, garbage-out' problems. Yes, it is true if a modeller builds in highly negative assumptions into a model, then, *hey presto!* it can make a safer product look more dangerous. For example, if you run a model that assumes e-cigarettes reduce smoking cessation among adults and act as a gateway to smoking for adolescents, then it doesn't take much to show: "*e-cigarette use currently represents more population-level harm than benefit*." This is exactly what *Soneji et al* do. It doesn't matter how safe e-cigarettes are – they could be 100% safe – if they trigger more smoking via these mechanisms then the model will show net harm.

So we have to look where the modellers have found their input assumptions. Firstly, the assumption that vaping reduces smoking cessation. Who would have guessed? It is Kalkhoran & Glantz.

> *Table 1 describes the data source of each model parameter. S1 Appendix describes how the difference in transition probabilities of ≥6-month cigarette smoking cessation between current e-cigarette users and non-current e-cigarette users was estimated based on various parameters such as the proportion of current cigarette smokers who used pharmaceutical aids during quit attempt and* ***the pooled odds ratio of quitting smoking among smokers interested in quitting reported by the meta-analysis of Kalkhoran & Glantz*** *(emphasis added).*

Kalkhoran & Glantz is discussed (and dismissed) in the previous section.

Response: modelling should not build in a gateway effect. The next assumption that Soneji et al build in is a gateway effect – teen vaping causes smoking initiation. The authors also assume that e-cigarette uptake by adolescents is a 'gateway' to smoking and therefore that e-cigarette use increases smoking initiation.

> *We assessed three outcomes of interest: […] (2) the additional number of adolescents and young adults who will initiate cigarette smoking through the ever use of e-cigarettes and eventually become daily cigarette smokers at age 35–39, compared to those who never used e-cigarettes […]*

It turns out that the plug-in gateway effect number for the *Soneji et al* modelling comes from a 'systematic review' in which Soneji himself was the lead author (*Soneji et al, 2017*). What these studies tend to do is to find that being a young e-cigarette user is *associated* with being a subsequent smoker. After some statistical wizardry, they determine that the vaping caused the smoking. This association is real – the studies do show this *association*. But there are two rival explanations for the observed associations:

1. **A gateway effect** – that taking up the e-cigarette and starting to vape is the reason why they went onto smoke and they would not have smoked otherwise. *The vaping caused the smoking.*
2. **Common liability** – the common factors about the individual (the home environment and role models, educational performance, delinquency, mental health, community norms etc) that incline a young person to be interested in both smoking and vaping. Both the vaping and the smoking were caused by these factors. *The vaping didn't cause the smoking.*

Statisticians try to isolate the effect of all the common liabilities to leave only the effect of using the e-cigarette. In the effort to isolate the effect of e-cigarettes, these other factors are referred to as 'confounders', and statisticians try to adjust for their effect by 'deconfounding' using the information they have collected about the people in the study. But full deconfounding is impossible in practice. This because no-one knows what all the confounders are and what questions would be necessary to characterise the common liabilities fully – probably hundreds. Possible confounding factors like 'mental illness' or 'delinquent behaviour' are very complicated in themselves and in their interaction with smoking and these can never be thoroughly adjusted for. So the statisticians are always left with 'residual confounding' – common factors that cause vaping and smoking that they have not been able to adjust for. What may look like a gateway effect (the e-cigarette use in

part *caused* the smoking) may just be residual confounding. Adding them together in a 'systematic review and meta-analysis' does not solve this problem. In practice, it is likely combining studies that have very different approaches to measuring smoking and vaping, and very different approaches to addressing confounders. A recent analysis of the 'gateway' literature (*Lee PN et al., 2019*) found that none of the studies purporting to demonstrate a gateway effect were adequately adjusted for confounding factors. The authors concluded:

> *A true gateway effect in youths has not yet been demonstrated. Even if it were, e-cigarette introduction may well have had a beneficial population health impact.*

For more background on the conflicting gateway and common liability theories and the difficulty of establishing gateway effects, please see:

- Vanyukov, et al. Common liability to addiction and "gateway hypothesis" theoretical, empirical and evolutionary perspective. *Drug Alcohol Depend*. 2012. (here).
- Phillips C V. Gateway Effects: Why the Cited Evidence Does Not Support Their Existence for Low-Risk Tobacco Products (and What Evidence Would). *Int J Environ Res Public Health* 2015;12:5439–64. [link]

Response: it is more likely that teenage vaping is forming an *exit* from smoking than increasing it. One study noted that the decline in youth smoking has *accelerated* as youth vaping increased:

> *There was a substantial increase in youth vaping prevalence beginning in about 2014. Time trend analyses showed that the decline in past 30-day smoking prevalence accelerated by two to four times after 2014. Indicators of more established smoking rates, including the proportion of daily smokers among past 30-day smokers, also decreased more rapidly as vaping became more prevalent. The inverse relationship between vaping and smoking was robust across different data sets for both youth and young adults and for current and more established smoking.*
>
> *Levy DT, Warner KE, Cummings KM, Hammond D, Kuo C, Fong GT, et al. Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check. Tob Control. BMJ Publishing Group Ltd; 2018 Nov 20. [link]*

Whilst this analysis cannot *prove* that the vaping caused the accelerated decline in smoking, it does make it difficult to argue that vaping is increasing the number of adolescent smokers and it does make modelling that relies on an assumption of a gateway effect feel unreliable and disconnected from reality.

Response: misleading citations can be combined through modelling to create a misleading big picture. So here we can see how this works: a trail of citations can be carefully laid down to provide input to subsequent analysis that looks internally coherent. However, because of the accumulated misunderstandings or misleading findings, the analysis slips its moorings from reality and becomes externally incoherent – i.e. not reality-based.

Response: other, more reality-based modelling is highly positive. Other modelling are at stark variance with the Soneji model.

Take *Warner & Mendez, 2018* in modelling of a variety of scenarios to assess the impact of vaping products, under a range of assumptions.

> *With base-case assumptions, the population gains almost 3.3 million life-years by 2070. If all people who quit smoking by vaping lose 10% of the benefit of quitting smoking, the net life-year gain falls to 2.4 million. Under worst-case assumptions, in which vaping increases smoking initiation by 6% and cessation by 5%, and vaping-induced quitters lose 10% of the health benefits, the population gains over 580000 life-years.*

Also, consider *Levy et al, 2017* David Levy and colleagues modelled realistic scenarios for the replacement of smoking by vaping. The results suggest very substantial public health benefits are likely in the United States even under a pessimistic scenario.

> *Compared with the status quo, replacement of cigarette by e-cigarette use over a 10-year period yields 6.6 million fewer premature deaths with 86.7 million fewer life years lost in the Optimistic Scenario. Under the Pessimistic Scenario, 1.6 million premature deaths are averted with 20.8 million fewer life years lost.*

To show negative public health effects from vaping requires pessimistic assumptions about vaping reducing smoking cessation, vaping causing a gateway effect and/or vaping being much more harmful than it is. The problem is that such assumptions have no substantiation in fact, and any modelling based on them is an artefact of the assumptions.

Claim 13: the people are right and science is catching up

> From this perspective, the declining public perception that e-cigarettes are less harmful than cigarettes is a good thing that may turn out to be where the scientific consensus lands as the new evidence on the harms of e-cigarettes continues to accumulate.

Concluding response – Professor Glantz's claim is false, dangerous and unethical. It has taken a 13,000-word review just to properly challenge a 700-word commentary, but I believe the analysis above shows the following:

- Professor Glantz's central claim is that: "*the declining public perception that e-cigarettes are less harmful than cigarettes is a good thing that may turn out to be where the scientific consensus lands.*".
- Professor Glantz's central claim in relation to scientific consensus is false, and not even close to true. The scientific consensus is that vaping is much less harmful than smoking, and this is unlikely to change.
- Professor Glantz has presented no evidence that supports his claim and there is a solid body of evidence to refute it. The evidence presented by Professor Glantz has either been

misinterpreted in his analysis or misinterpreted by the original authors of the papers he cites. Professor Glantz has largely ignored the evidence that refutes his claims.

- Professor Glantz's central claim in relation to public perception is therefore also false. It is not *'a good thing'* for the public to have false perceptions of risk. It is a bad and dangerous thing.
- Perceptions of risk influence the behaviour of nicotine users. False perceptions influence behaviour negatively. The false perceptions held by the public are likely to lead to more smoking, more dual-use, less switching and more secondhand smoke exposure. To the extent that these false perceptions perpetuate the smoking epidemic, they will cause harm to health, including serious disease and premature death.
- It is anti-scientific and unethical to promote false public perceptions. This is because *other people* may suffer significant harm by being misled into false perceptions of relative risk. False perceptions, in turn, sustain harmful behaviours and obstruct the pathways to much safer alternatives.
- These risk misperceptions have a major opportunity cost: smoking would decline more rapidly if the public really did understand the relative risks of smoking and vaping. False risk perceptions and flawed analysis of risk and population effects will prolong the epidemic of smoking-related disease and run counter to the objectives of tobacco control.
- Activist opposition to tobacco harm reduction is misplaced and harmful. Harm reduction forms part of the definition of tobacco control in the WHO Framework Convention on Tobacco Control and is compatible and synergistic with other tobacco control measures. It is not an alternative or an industry conspiracy, it is a way of harnessing the benefits of innovation for public health ends.

Article 1 (d) "tobacco control" means a range of supply, demand and harm reduction strategies that aim to improve the health of a population by eliminating or reducing their consumption of tobacco products and exposure to tobacco smoke;

I am not voicing a fringe view of the science and policy issues in this review. There is support for tobacco harm reduction from many senior American and international experts in tobacco control and public health. See this letter to the WHO Director-General from seventy-two specialists in nicotine science, policy and practice, October 2018.

Please add to or debate this analysis in the comments!