Review of: "Improving on estimates of the potential relative harm to health from using modern ENDS (vaping) compared to tobacco smoking"

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Findings and conclusions of the paper

Wilson and colleagues seek to provide an 'improved' estimate of the relative risks of smoking and e-cigarette use through biomarkers of toxicant exposure.[1] Based on 17 comparisons of biomarkers in e-cigarette (ENDS) users and cigarette smokers drawing on five studies,[2][3][4][5][6] the authors make a striking claim in their conclusion:

> *This analysis, suggests that the use of modern ENDS devices (vaping)**could be a third as harmful to health as smoking** in a high-income country setting. But this estimate is based on a limited number of biomarker studies and is best be considered a likely upper level of ENDS risk given potential biases in our method (i.e., the biomarkers used being correlated with more unaccounted for toxicants in smoking compared to with using ENDS). (emphasis added)*

It is true that the study does not incorporate biomarkers for hundreds of hazardous or potentially hazardous products of combustion that are found in cigarette smoke but are unlikely to be present in ENDS aerosol because of the absence of combustion. However, this is far from the most serious flaw in the analysis. Below we present four further concerns that we believe render the paper unreliable.

A critique of the methods and findings

The conclusion is not supported by the data or the analysis presented. There are four clear problems beyond the narrow coverage of likely hazardous agents in cigarette smoke.

1. Background exposure is ignored
2. Many "exclusive" ENDS users were in fact smokers
3. Valid adjustment indicates no incremental risk for acrolein
4. Arbitrary inclusion criteria meant important studies were excluded from the analysis

1. Background exposure is ignored

First, the authors ignore background exposures (the ambient exposure experienced by non-users arising from the

environment, food etc.), with the exception of an attempt to correct for acrolein exposures (discussed below). This is a serious error because most of the biomarkers measured are present in nonsmokers at significant levels.[7][8][9][10] Consider this illustration: if smokers have a level of a given chemical of 60 and ENDS users of 20, the authors would assert that exclusive ENDS use poses a third of risks of smoking. However, if non-smokers also have the level of 20 for the given biomarker, ENDS use poses no incremental risk at all.

In fact, in the Jay[6] and Hatsukami[4] studies (comprising 11 of the 17 comparisons), abstinence and NRT arms show near-identical outcomes to those of their ENDS arms, yet this important finding is not reflected in the analysis.

2. Many “exclusive" ENDS users were in fact smokers

Second, many subjects designated as “exclusive ENDS users” were in fact smokers.Table 3 shows high levels of carbon monoxide markers in exclusive ENDS users for three of the five studies, but there are no significant CO emissions from ENDS under normal operating conditions tolerated by users.[11] Son et al. compared CO emissions from e-cigarettes and cigarettes and concluded:[12]

> *All of the tested e-cigarettes under our experimental conditions generated 40 to 3618 times less CO than conventional cigarettes*

That means ENDS CO emissions are respectively 2.5% to 0.03% of the smoking-related exposure. Yet Wilson et al. include comparisons for CO emissions from ENDS at 27.1%, 38.9%, 43.0% and 53.7% of cigarettes in Table 3 and calculate a cardiovascular risk in Table 4 on this basis. It should also be noted that Son et al. recognised the upper end of the range (40 times less CO than cigarettes) was likely caused by the device overheating - something that would produce CO measured in machine tests, but would also make human vaping and therefore human exposure impossible.

Two of these studies explicitly note that some in the exclusive e-cigarette group were smokers. Hatsukami et al.[4] note that only “33% of participants achieved CO-verified 7-day smoking abstinence” in the “exclusive e-cigarette" group. Oliveri et al.[3] state that *“a small proportion of [ENDS users] (17% tank, 25% cartridge) exhibited levels of COHb that exceeded 5% saturation. As [ENDS] are non-combustible products and therefore do not generate carbon monoxide, the observed levels of >5% saturation suggests that a select group of AEVP were not exclusive users and may have been smoking cigarettes.”*

The presence of high carbon monoxide markers should have been used by the authors as a reality check on whether people they classified as exclusive ENDS users were in fact also smoking. Instead, they just took the high exposures and built them into the risk calculation creating a misleading figure for ENDS cardiovascular risk. Once it is clear that study participants designated as exclusive ENDS users have also been smoking, it should be assumed that all their biomarker data are contaminated with smoking exposures and the data are unreliable for comparative purposes. Carbon monoxide exposures should have been used as a reality check on the data, not incorporated into the results.

3. Valid adjustment indicates no incremental risk for acrolein

Third, where correction has been attempted for background exposure, a realistic correction shows *no incremental risk from vaping*. In Table 4 the authors state that they have adjusted for one chemical, acrolein. 3-HPMA is a metabolite of acrolein and one of the biomarkers included in the study. This biomarker is found at a non-trivial level in non-tobacco users, as recorded in Alwis et al. 2015.[7] In Alwis at al, non-smokers had 20.1% of the 3-HPMA level of smokers. Wilson report that in the Jay et al. study, smokers had 1.87 mg and exclusive ENDS users 0.2 mg over 24 hours, suggesting ENDS users had 10.7% of exposure of smokers. However, if 20.1% of the level attributed to smokers (0.37 mg) was deducted from both groups, the exclusive ENDS users would have zero incremental ENDS-associated exposure compared to smokers having 1.5 mg over 24 hours. On this measure, vaping poses 0% of the risk of smoking, not 10.7%. The other studies used to estimate acrolein exposure are compromised through smoking by subjects designated as exclusive ENDS users as described directly above.

4. Arbitrary inclusion criteria meant important studies were excluded

Fourth, the authors impose an arbitrary cut-off date to include only studies that were published and had data collected after 1 January 2017. This excluded 11 studies (references 37-47 in the paper), most of which were informative and explicitly designed to assess biomarkers of exposure. This was ostensibly done only to include the most modern devices, but there is no real reason to exclude high quality older studies based on an arbitrary date. Had that been the reason, the results could have stratified by pre- and post 2017. It is likely that the main difference would arise from improved nicotine delivery, but that could have been addressed by indexing the biomarker exposures to nicotine exposure. The five studies included used different technologies - vape pens, pods, salts, tank systems and several had the problem of ongoing smoking. So device heterogeneity is a challenge with the post January 2017 studies chosen, though the Wilson et al paper has far more serious flaws than this.

Summary of erroneous findings

The table below provides brief comments on the 17 comparisons between cigarettes and e-cigarettes that the authors present. All 17 comparisons are erroneous for one or more of the reasons given below.

Study	Biomarker	Exposure: ENDS/cigarettes	Significant problem
Nga et al. 2020	eCO	38.90%	CO is not emitted from e-cigarettes (NASEM, 2017)[11]
Hatsukami et al. 2020	CEMA	34.00%	Measurements relate to smokers randomized to exclusive ENDS use, but most were noncompliant and still smoked.
Hatsukami et al. 2020	3-HPMA	53.00%	Measurements relate to smokers randomized to exclusive ENDS use, but most were noncompliant and still smoked.
Hatsukami et al. 2020	HMPMA	53.00%	Measurements relate to smokers randomized to exclusive ENDS use, but most were noncompliant and still smoked.
Hatsukami et al. 2020	PheT	79.00%	Measurements relate to smokers randomized to exclusive ENDS use, but most were noncompliant and still smoked.
Hatsukami et al. 2020	eCO	43.00%	Measurements relate to smokers randomized to exclusive ENDS use, but most were noncompliant and still smoked.
Hatsukami et al. 2020	3-HPMA	53.00%	Measurements relate to smokers randomized to exclusive ENDS use, but most were noncompliant and still smoked.
Hatsukami et al. 2020	NNAL	47.00%	Measurements relate to smokers randomized to exclusive ENDS use, but most were noncompliant and still smoked.
Jay et al. 2020	3-HPMA	10.70%	Results are identical to those of the absolute cessation arm in that study.
Jay et al. 2020	3-HPMA	10.70%	Results are identical to those of the absolute cessation arm in that study.
Jay et al. 2020	COHb	27.10%	Results are identical to those of the absolute cessation arm in that study.
Jay et al. 2020	NNN	38.60%	Results are slightly below those of the absolute cessation arm in that study. The authors attribute this to endogenous formation from nicotine/nornicotine, as similar results were reported for NRT which is unlikely pose a measurable cancer risk (NASEM, 2017).
Oliveri et al. 2020	3-HPMA	53.20%	Oliveri et al note that high CO and NNK levels indicate substantial misreporting (unreported smoking)
Oliveri et al. 2020	NNAL	12.40%	Oliveri et al note that high CO and NNK levels indicate substantial misreporting (unreported smoking)
Oliveri et al. 2020	3-HPMA	53.20%	Oliveri et al note that high CO and NNK levels indicate substantial misreporting (unreported smoking)
Oliveri et al. 2020	COHb	53.70%	Oliveri et al note that high CO and NNK levels indicate substantial misreporting (unreported smoking); CO is not emitted by e-cigarettes (NASEM, 2017)[11]
Boykan et al. 2019	NNAL	17.90%	This compares the percentages of subjects above the NNAL cutoff level for non-smokers. However, because NNAL's precursor NNK can indeed be found at low levels in some e-cigarettes but is on average 40 times lower compared to tobacco smoke,[13] relying on a binary measure based on a cutoff level far below the mean exposure level for smokers, would certainly not provide a good measure for quantitative comparison.

Conclusion

The analysis provided by Wilson et al. is flawed, its conclusion is unreliable and retraction should be considered. The results would be misleading if taken seriously by policymakers or incorporated into subsequent analysis as though the paper was a reliable source. For example, the Wilson et al. analysis was reused by some of its authors in a recent public health cost-benefit analysis of ENDS in New Zealand (Summers et al. 2022).[14] The estimates provided in Summers et al are unreliable as a consequence of the underlying assumptions about relative risk from Wilson et al. This paper would be best reformulated as sensitivity testing the credibility of New Zealand policy against extreme assumptions about relative risk. In spite of the exaggerated estimates of relative risk used in its calculation, Summers et al. did conclude that:

> *This study found evidence using updated biomarker studies that ENDS liberalization could result in QALY gains across the New Zealand population lifespan that are also cost-saving to the health system.*

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