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COMMENTARY

Drug and Alcohol Review APSAD WILEY

A critical analysis of 'Electronic cigarettes and health outcomes: Systematic review of global evidence'

1 | INTRODUCTION

The Australian Department of Health recently funded a review of vaping by Banks and colleagues that aimed to examine the 'contemporary evidence on the health outcomes of nicotine and non-nicotine e-cigarette use' and integrate this with 'systematic reviews on smoking uptake and cessation' to guide the formulation of evidence-based policy and practice [1].

In our view, the review failed to achieve its aims because it did not compare the relative risk of the harms of vaping to conventional cigarettes; it did not consider the net public health impact of vaping; it ignored evidence that vaping is effective in smoking cessation; and it confused causation and correlation in interpreting the association between youth vaping and cigarette smoking.

Banks et al. also used evidential double standards: they were prepared to accept a causal interpretation for the gateway hypothesis based on an association in observational studies but rejected similar evidence from observational studies of cessation. More importantly, they adopted a sceptical attitude towards the findings of randomised controlled trials showing that vaping is effective in assisting smoking cessation.

In this analysis, we summarise evidence that is inconsistent with the main findings of the review.

2 | VAPING AND SMOKING CESSATION

The Banks review concludes that 'There is limited evidence that, in the clinical context, freebase nicotine e-cigarettes may be more efficacious for smoking cessation than existing NRT [nicotine replacement therapy]' [1].

The most recent Cochrane review of randomised controlled trials (RCT) of electronic cigarettes versus nicotine replacement therapy (NRT) concluded that 'There is moderate-certainty evidence that electronic cigarettes with nicotine increase quit rates compared to NRT (RR 1.53)' [2]. Other meta-analyses report that electronic cigarettes are superior to placebo and NRT but the authors differ in their confidence in the results [3–5].

Modern vaping devices may be even more effective than the cigalikes used in earlier trials [6]. A recent RCT in smokers unable to quit using conventional methods found that vaping was six times more effective than NRT at 6 months (relative risk 6.4, $p = 0.01$, 95% confidence interval 1.5–27.3) [7].

A recent network meta-analysis of 171 RCTs of all smoking cessation medications concluded that vaping was the most effective monotherapy, followed by varenicline and NRT [8]. The width of the confidence interval indicates the need for larger trials.

In assessing the effectiveness of vaping, the review also disregarded supportive evidence from observational studies, population studies and declines in national smoking rates. 'Triangulation' of all data provides a more accurate picture than relying on RCTs alone and increases confidence that vaping is an effective quitting aid [9].

Observational cohort studies have had mixed results, but two reviews of higher-quality studies found that vaping nicotine was significantly associated with an increased chance of an individual quitting smoking [10, 11].

Surveys in Australia, the United States and the UK have found that smokers who used a vaping device were significantly more likely to quit than those who did not vape [12–14]. Daily vaping delivers more effective nicotine replacement and is associated with higher quit rates than less frequent use. Those who vape daily are two to eight times more likely to quit smoking than smokers who do not vape [14–16]. Accelerated declines in adult smoking rates have been seen in the UK and United States where vaping rates are much higher than in Australia.

3 | VAPING AS A GATEWAY TO SMOKING

The Banks review claims that 'there is strong evidence that e-cigarettes increase combustible smoking uptake in

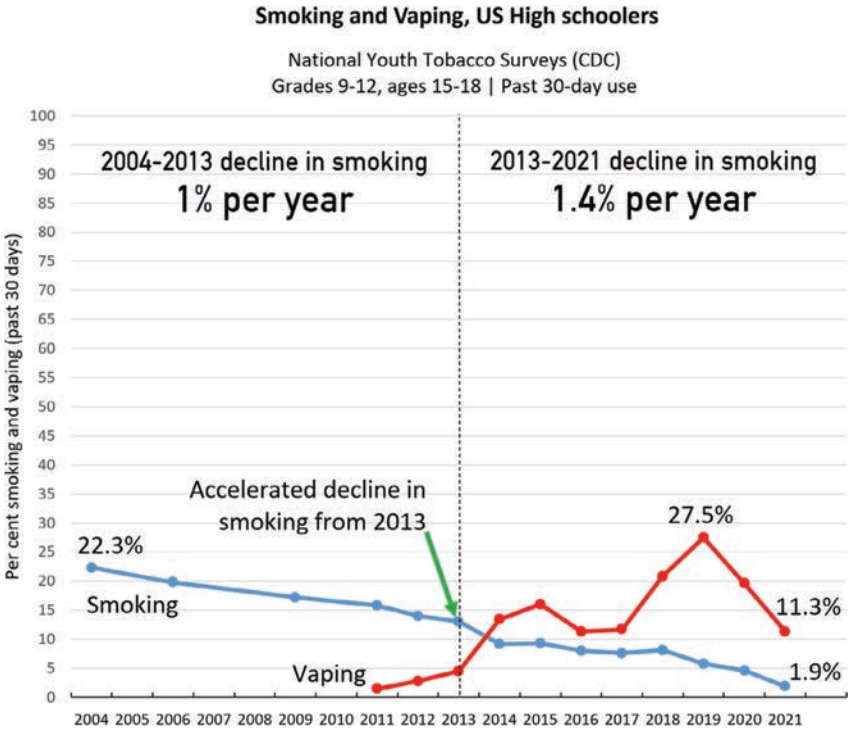

FIGURE 1 Accelerated decline in youth smoking in the United States as vaping rates increased [24]

non-smokers, particularly youth'. However, in making this claim they confuse evidence of association for causation.

There is an association between vaping and smoking, but the most likely explanation is a common liability for risk taking, that is, that young people who experiment with vaping are more prone to take risks for personal, environmental or genetic reasons [17]. More rigorous prospective studies that adjust for a wide range of common risk factors for smoking and vaping (confounders) have found that the association between vaping and smoking largely disappears, as predicted by the common-liability model [18].

Evidence from population studies also suggests that vaping more likely diverts young people from smoking than encourages them to smoke [19–22]. Indeed, declines in youth and young adult smoking rates in the United States accelerated from around the time vaping became popular [23]. This population finding is the opposite of that predicted by the gateway hypothesis (Figure 1).

Most young people who vape have first smoked cigarettes [25]. Most vaping by never-smokers is experimental and transient, and regular vaping is rare [25, 26].

Regular vaping is rare in adult never-smokers. In Australia in 2019, less than 1 in a 100 adult never-smokers vaped once or more in the previous 12 months [27].

4 | COMPARATIVE HARMS OF VAPING AND SMOKING

The Banks review does not address the critical issue of relative risk. A meaningful assessment of the risk from vaping nicotine should compare it to the enormously greater risk of continuing to smoke tobacco.

The vast majority of frequent vapers are current or former smokers who have been unable to quit smoking using other methods.

Harm reduction from vaping is based on the substantially reduced exposure to toxins and carcinogens in vapour compared to smoke [28, 29] and is confirmed by a considerable reduction in biomarkers of harm in the blood, urine and saliva of smokers who switch to vaping [30, 31].

Smoke contains over 7000 toxic chemicals and solid particulate matter. Vaping liquid aerosols generally have fewer than 100 detectable chemicals, most in far lower concentrations [29].

Some additional chemicals not found in smoke are present in vapour but these do not appear to pose a significand hazard when inhaled [32]. The effect of inhaled food flavourings is largely unknown and could have potential risk. No harms from flavourings have been demonstrated so far but ongoing monitoring is needed [33].

Most of the cardiovascular effects of vaping are consistent with the known effects of nicotine [34]. These include transiently raised pulse and blood pressure, cardiac contractility and arrhythmogenesis. Nicotine may pose some risk in people with pre-existing cardiovascular disease [34]. Cardiotoxic constituents of smoke are either absent from vapour or are present in much lower levels [34].

Human studies on cardiovascular outcomes are limited. However, two studies showed a significant and sustained reduction in blood pressure in smokers who switched to vaping [35, 36]. Another study demonstrated substantial improvements in vascular function in smokers who switched to vaping after 4 weeks [37].

Vaping is also likely to be far less harmful to the lungs than smoking [38]. Human respiratory studies have demonstrated improved pulmonary health in smokers who switch to vaping, including improved respiratory symptoms and lung function [39]; asthma [40]; chronic obstructive pulmonary disease [41]; muco-ciliary clearance [42]; and fewer respiratory infections [43].

In vitro and animal studies have found that harmful cardiovascular and respiratory effects from vapour are generally far less than from tobacco smoke [39, 40, 44, 45].

It is highly implausible that nicotine vaping was a cause of the EVALI outbreak (E-cigarette, or vaping, product use–associated lung injury) in the United States in 2019. This condition was strongly linked to vitamin E acetate added to black-market tetrahydrocannabinol (THC) vaping oils and disappeared after vitamin E acetate was removed from the illicit supply chain [46]. The observation that 14% of EVALI patients denied using THC and had been vaping nicotine does not prove a causal link with nicotine vaping products. Many patients who denied vaping THC were subsequently found to have done so, and no other causal agent has been identified in nicotine e-liquids [47, 48].

Based on the substantial reduction in the number and dose of carcinogens in vapour, the lifetime cancer risk from vaping has been estimated to be less than 0.5% of the risk from smoking [49, 50].

The Cochrane Review did not detect evidence of harm in studies up to 2 years, although the number of studies was small and longer studies are needed [2].

5 | NET PUBLIC HEALTH EFFECTS OF VAPING

The key public health question is whether the net effect of vaping is beneficial or harmful at a population level. The net effect is a function of the harm differential between vaping and smoking, its effectiveness as a cessation aid and uptake by smokers and non-smokers.

Vaping is the most popular quitting aid in Australia [27] and is arguably the most effective monotherapy for quitting [8]. Regular use by adult and youth never-smokers is rare [26, 27]. As a result, vaping has the potential to reduce smoking prevalence more than any other intervention.

Numerous modelling studies (with one exception) [51] have concluded that the overall benefits of vaping are considerably greater than the harms and are likely to improve public health [52–54]. These have evaluated the net effects under a wide range of assumptions about rates of uptake among non-smokers, cessation rates and reduction in harm compared to smoking.

One study estimated that under current patterns of vaping and substitution in the United States, nicotine vaping will translate into 1.8 million premature smoking- and vaping-attributable deaths avoided and 38.9 million life-years gained between 2013 and 2060 [54].

Beard estimated that 50,000 additional smokers stopped smoking in the UK with a vaping product in 2017 who would otherwise have continued smoking [14].

6 | CONCLUSION

Contrary to the conclusions of the Banks review, the evidence suggests that vaping nicotine is an effective smoking cessation aid; that vaping is substantially less harmful than smoking tobacco; that vaping is diverting young people away from smoking; and that vaping by smokers is likely to have a major net public health benefit if widely available to adult Australian smokers.

CONFLICT OF INTEREST

Dr Colin Mendelsohn was a Board Member of the Australian Tobacco Harm Reduction Association (ATHRA), a registered health promotion charity, from October 2017 to January 2020 and Dr Alex Wodak is a Board Member of ATHRA. ATHRA accepted unconditional seed funding from the vape retail industry to get established. Funding ceased in March 2019. Drs Colin Mendelsohn and Alex Wodak were Directors of ATHRA in March 2018 when it received a donation from Knowledge Action Change Communications, a private sector public health agency in the UK. The donation was sourced from a surplus arising from the Global Forum on Nicotine conference in May 2017. Knowledge Action Change Communications is legally separate from Knowledge Action Change (KAC). KAC has received two grants from tobacco companies: (i) In 2012, KAC received a small development research grant from Nicoventures (owned at the time by British American Tobacco) for evaluating the use of a nicotine delivery device in Scottish Prisons. The study was conducted in conjunction

with the Scottish Prison Service. This funding was publicly declared. (ii) In 2018, The Foundation for a Smoke-Free World provided a grant specifically for the preparation of The Global State of Tobacco Harm Reduction report, an international review of tobacco harm reduction and the regulations involved. The Foundation for a Smoke-Free World is funded by an annual grant from Philip Morris International. Under the Foundation's bylaws and pledge agreement, Philip Morris International and the tobacco industry are precluded from having any influence over how the Foundation spends its funds or focuses its activities. Dr Colin Mendelsohn is the author of *Stop Smoking Start Vaping*, published by Aurora Press. He has never received payments from electronic cigarette or tobacco companies. Dr Alex Wodak has never received payments from electronic cigarette or tobacco companies. Professors Wayne Hall and Ron Borland have no interests to declare.

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REFERENCES

1. Banks E, Yazidjoglou A, Brown S, Nguyen M, Beckwith F, Daluwatta A, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. Canberra: National Centre for Epidemiology and Population Health; 2022. Available from: https://openresearch-repository.anu.edu.au/bitstream/1885/262914/1/Electronic%20cigarettes%20health%20outcomes%20review_2022_WCAG.pdf.
2. Hartmann-Boyce J, McRobbie H, Butler AR, Lindson N, Bullen C, Begh R, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 2021;9:CD010216.
3. The Joanna Briggs Institute. E-cigarettes for smoking cessation guideline update: technical report of evidence review and summary of findings. Adelaide, South Australia: The Joanna Briggs Institute; 2019. Available from: https://www.racgp.org.au/getmedia/2e90f512-a8a8-4c89-b226-56ada993c7f1/ECigarettes-for-Smoking-Cessation-Technical-Report.pdf.aspx
4. Chan GCK, Stjepanović D, Lim C, Sun T, Shanmuga Anandan A, Connor JP, et al. A systematic review of randomized controlled trials and network meta-analysis of e-cigarettes for smoking cessation. Addict Behav. 2021;119:106912.
5. Grabovac I, Oberndorfer M, Fischer J, Wiesinger W, Haider S, Dorner TE. Effectiveness of electronic cigarettes in smoking cessation: a systematic review and meta-analysis. Nicotine Tob Res. 2021;23:625–34.
6. Hitchman SC, Brose LS, Brown J, Robson D, McNeill A. Associations between e-cigarette type, frequency of use, and quitting smoking: findings from a longitudinal online panel survey in Great Britain. Nicotine Tob Res. 2015;17:1187–94.
7. Myers Smith K, Phillips-Waller A, Pesola F, McRobbie H, Przulj D, Orzol M, et al. E-cigarettes versus nicotine replacement treatment as harm reduction interventions for smokers who find quitting difficult: randomized controlled trial. Addiction. 2022;117:224–33.
8. Thomas KH, Dalili MN, López-López JA, Keeney E, Phillippo D, Munafò MR, et al. Smoking cessation medicines and e-cigarettes: a systematic review, network meta-analysis and cost-effectiveness analysis. Health Technol Assess. 2021;25:1–224.
9. Munafò MR, Davey SG. Robust research needs many lines of evidence. Nature. 2018;553:399–401.
10. Villanti AC, Feirman SP, Niaura RS, Pearson JL, Glasser AM, Collins LK, et al. How do we determine the impact of e-cigarettes on cigarette smoking cessation or reduction? Review and recommendations for answering the research question with scientific rigor. Addiction. 2017;113:391–404.
11. Glasser AM, Collins L, Pearson JL, Abudayyeh H, Niaura RS, Abrams DB, et al. Overview of electronic nicotine delivery systems: a systematic review. Am J Prev Med. 2017;52:e33–66.
12. Chambers MS. Effect of vaping on past-year smoking cessation success of Australians in 2019-evidence from a national survey. Addiction. 2022;117:2306–15.
13. Zhu SH, Zhuang YL, Wong S, Cummins SE, Tedeschi GJ. E-cigarette use and associated changes in population smoking cessation: Evidence from US current population surveys. BMJ. 2017;358:j3262.
14. Beard E, West R, Michie S, Brown J. Association of prevalence of electronic cigarette use with smoking cessation and cigarette consumption in England: a time-series analysis between 2006 and 2017. Addiction. 2020;115:961–74.
15. Sun T, Lim CCW, Rutherford BN, Johnson B, Leung J, Gartner C, et al. Is smoking reduction and cessation associated with increased e-cigarette use? Findings from a nationally representative sample of adult smokers in Australia. Addict Behav. 2022;127:107217.
16. Berry KM, Reynolds LM, Collins JM, Siegel MB, Fetterman JL, Hamburg NM, et al. E-cigarette initiation and associated changes in smoking cessation and reduction: the population assessment of tobacco and health study, 2013-2015. Tob Control. 2018;28:42–9.
17. Vanyukov MM, Tarter RE, Kirillova GP, Kirisci L, Reynolds MD, Kreek MJ, et al. Common liability to addiction and "gateway

hypothesis": theoretical, empirical and evolutionary perspective. Drug Alcohol Depend. 2012;123(Suppl 1):S3–17.
18. Sun R, Mendez D, Warner KE. Is adolescent e-cigarette use associated with subsequent smoking? A new look. Nicotine Tob Res. 2022;24:710–8.
19. Walker N, Parag V, Wong SF, Youdan B, Broughton B, Bullen C, et al. Use of e-cigarettes and smoked tobacco in youth aged 14-15 years in New Zealand: findings from repeated cross-sectional studies (2014-19). Lancet Public Health. 2020;5:e204–e12.
20. Sokol NA, Feldman JM. High school seniors who used e-cigarettes may have otherwise been cigarette smokers: evidence from monitoring the future (United States, 2009-2018). Nicotine Tob Res. 2021;23:1958–61.
21. Selya AS, Foxon F. Trends in electronic cigarette use and conventional smoking: quantifying a possible 'diversion' effect among US adolescents. Addiction. 2021;116:1848–58.
22. Foxon F, Selya AS. Electronic cigarettes, nicotine use trends and use initiation ages among US adolescents from 1999 to 2018. Addiction. 2020;115:2369–78.
23. 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. 2019;28:629–35.
24. Centers for Disease Control and Prevention. Smoking & Tobacco Use; Historical NYTS Data and Documentation, 1999–2021. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/tobacco/data_statistics/surveys/nyts/data/index.html.
25. Guerin N, White V. ASSAD 2017 statistics & trends: Australian secondary Students' use of tobacco. Alcohol, over-the-counter drugs, and illicit substances. Victoria: Cancer Council Victoria; 2018. Available from: https://www.health.gov.au/resources/publications/secondary-school-students-use-of-tobacco-alcohol-and-other-drugs-in-2017
26. Action for Smokefree 2025 (ASH). ASH Year 10 Snapshot Survey 2021. Topline—Youth Smoking and Vaping 2022. Available from: http://ash.org.nz.
27. Australian Institute of Health and Welfare. National Drug Strategy Household Survey 2019. Drug Statistics series no. 32. PHE 270. Canberra: Canberra AIHW; 2020. Available from: https://www.aihw.gov.au/reports/illicit-use-of-drugs/national-drug-strategy-household-survey-2019/contents/summary
28. Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tob Control. 2014;23:133–9.
29. Margham J, McAdam K, Forster M, Liu C, Wright C, Mariner D, et al. Chemical composition of aerosol from an e-cigarette: a quantitative comparison with cigarette smoke. Chem Res Toxicol. 2016;29:1662–78.
30. Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Alwis KU, et al. Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: a cross-sectional study. Ann Intern Med. 2017;166:390–400.
31. Goniewicz ML, Smith DM, Edwards KC, Blount BC, Caldwell KL, Feng J, et al. Comparison of nicotine and toxicant exposure in users of electronic cigarettes and combustible cigarettes. JAMA Netw Open. 2018;1:e185937.
32. Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT). Statement on the potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes). London; 2020. Available from: https://cot.food.gov.uk/sites/default/files/2020-09/COT%20E%28N%29NDS%20statement%202020-04.pdf
33. McNeill A, Brose LS, Calder R, Bauld L, Robson D. Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England. London: Public Health England; 2018. Available from: https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review
34. Benowitz NL, Fraiman JB. Cardiovascular effects of electronic cigarettes. Nat Rev Cardiol. 2017;14:447–56.
35. Farsalinos K, Cibella F, Caponnetto P, Campagna D, Morjaria JB, Battaglia E, et al. Effect of continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to electronic cigarettes. Intern Emerg Med. 2016;11:85–94.
36. Polosa R, Morjaria JB, Caponnetto P, Battaglia E, Russo C, Ciampi C, et al. Blood pressure control in smokers with arterial hypertension who switched to electronic cigarettes. Int J Environ Res Public Health. 2016;13:1123.
37. George J, Hussain M, Vadiveloo T, Ireland S, Hopkinson P, Struthers AD, et al. Cardiovascular effects of switching from tobacco cigarettes to electronic cigarettes. J Am Coll Cardiol. 2019;74:3112–20.
38. Polosa R, O'Leary R, Tashkin D, Emma R, Caruso M. The effect of e-cigarette aerosol emissions on respiratory health: a narrative review. Expert Rev Respir Med. 2019;13:899–915.
39. Cibella F, Campagna D, Caponnetto P, Amaradio MD, Caruso M, Russo C, et al. Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. Clin Sci (Lond). 2016;130:1929–37.
40. Polosa R, Morjaria JB, Caponnetto P, Caruso M, Campagna D, Amaradio MD, et al. Persisting long term benefits of smoking abstinence and reduction in asthmatic smokers who have switched to electronic cigarettes. Discov Med. 2016;21:99–108.
41. Polosa R, Morjaria JB, Prosperini U, Busà B, Pennisi A, Malerba M, et al. COPD smokers who switched to e-cigarettes: health outcomes at 5-year follow up. Ther Adv Chronic Dis. 2020;11:1–15.
42. Polosa R, Emma R, Cibella F, Caruso M, Conte G, Benfatto F, et al. Impact of exclusive e-cigarettes and heated tobacco products use on muco-ciliary clearance. Ther Adv Chronic Dis. 2021;12:1–9.
43. Miler J, Mayer B, Hajek P. Changes in the frequency of airway infections in smokers who switched to vaping: results of an online survey. J Addict Res Ther. 2016;7:290.
44. Caruso M, Emma R, Distefano A, Rust S, Poulas K, Zadjali F, et al. Electronic nicotine delivery systems exhibit reduced bronchial epithelial cells toxicity compared to cigarette: the replica project. Sci Rep. 2021;11:24182.
45. Iskandar AR, Zanetti F, Kondylis A, Martin F, Leroy P, Majeed S, et al. A lower impact of an acute exposure to electronic cigarette aerosols than to cigarette smoke in human organotypic buccal and small airway cultures was demonstrated using systems toxicology assessment. Intern Emerg Med. 2019;14:863–83.

46. Centers for Disease Control and Prevention. Outbreak of lung injury associated with E-cigarette use, or vaping 2020. Atlanta, GA: 2020. Available from: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html.
47. Ghinai I, Navon L, Gunn JKL, Duca LM, Brister S, Love S, et al. Characteristics of persons who report using only nicotine-containing products among interviewed patients with E-cigarette, or vaping, product use-associated lung injury - Illinois, August-December 2019. MMWR Morb Mortal Wkly Rep. 2020;69:84–9.
48. Blount BC, Karwowski MP, Morel-Espinosa M, Rees J, Sosnoff C, Cowan E, et al. Evaluation of bronchoalveolar lavage fluid from patients in an outbreak of e-cigarette, or vaping, product use-associated lung injury - 10 states, August-October 2019. MMWR Morb Mortal Wkly Rep. 2019;68:1040–1.
49. Stephens WE. Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. Tob Control. 2018;27:10–7.
50. Scungio M, Stabile L, Buonanno G. Measurements of electronic cigarette-generated particles for the evaluation of lung cancer risk of active and passive users. J Aerosol Sci. 2018;115:1–11.
51. 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:e0193328.
52. Summers JA, Ait Ouakrim D, Wilson N, Blakely T. Updated health and cost impacts of electronic nicotine delivery systems, using recent estimates of relative harm for vaping compared to smoking. Nicotine Tob Res. 2022;24:408–12.
53. Mendez D, Warner KE. A magic bullet? The potential impact of e-cigarettes on the toll of cigarette smoking. Nicotine Tob Res. 2021;23:654–61.
54. Levy DT, Tam J, Sanchez-Romero LM, Li Y, Yuan Z, Jeon J, et al. Public health implications of vaping in the USA: the smoking and vaping simulation model. Popul Health Metr. 2021;19:19.

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