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The future of vaping and e-cigarettes



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Disclosures

Financial: In the past 5 years, I have received:

- honoraria for speaking at smoking cessation meetings and attending advisory board meetings that have been organised by Pfizer and Johnson & Johnson
- grants from the National Institute of Health Research (UK) and National Health and Medical Research Council (Australia) to undertake research on vaping for smoking cessation.

Non-financial: I believe that vaping can, overall, make a positive contribution to public health.

I have **no links** with the manufacturers of tobacco or vaping products.

Smoking tobacco

- Health risks are almost completely from tobacco smoke (as opposed to nicotine)
- Smokers should be encouraged to stop smoking completely
 - Cardiovascular risks associated with smoking just 1-2 cigarettes per day
- Ongoing nicotine use is a harm reduction approach



What are e-cigarettes?

- Battery operated products that heat and aerosolise a liquid that usually contains:
 - Propylene glycol
 - Vegetable glycerin
 - Flavouring
 - Nicotine
- Technology is continuing to evolve



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Lancet Editorial “E-cigarettes: time to realign our approach?”

A multistate, US outbreak of lung injury associated with e-cigarette use has affected at least 1080 people and caused 18 deaths as of Oct 1, according to the US Centers for Disease Control and Prevention (CDC). This number looks set to grow as more cases are discovered and reported. 80% of the patients affected are younger than 35 years, and all report using e-cigarettes, many with tetrahydrocannabinol. The specific exposure is unknown,

Manufacturers of e-cigarettes, and some public health advocates, have supported their use as a smoking cessation tool and a safer alternative to cigarettes. However, the evidence for both of these claims is weak. No e-cigarettes have been tested or launched as smoking cessation products; all are sold directly to the consumer as tobacco, not medicinal, products. Three randomised trials of third-generation products show low rates of abstinence at 6 months. Data also suggest that smokers switch to e-cigarettes, then remain dependent long term. The very

- ➡ US outbreak of lung injury associated with e-cigarette use
- ➡ 80% of patients affected are <35 years
- ➡ Most were vaping THC, but specific exposure is unknown
- ➡ Weak evidence for claims that e-cigarettes
 - a) Can help people stop smoking
 - b) Are safer than smoking

Lancet Editorial “E-cigarettes: time to realign our approach?”

Claims that e-cigarettes are useful harm-reduction tools are further undermined by their high uptake among young people. Cigarette smoking among US adolescents had declined substantially in the past 20 years, but there has been a huge rise in adolescents using e-cigarettes, with rates of use at around 25% among 18-year-olds and 20% among 16-year-olds. The availability of flavoured e-liquids is cited by nearly a third of users as a major reason to start vaping, especially among younger adults.

As concerns mount about the safety of e-cigarettes, several countries and national bodies have tightened regulations. India plans to ban e-cigarettes. Several US states have moved to ban flavoured e-cigarettes. The European Respiratory Society has aligned its recommendations on e-cigarettes with those on cigarettes, both encapsulated in one word: don't. They also announced that the same membership restrictions will apply for those with conflicts of interest related to e-cigarettes as for cigarettes. Public Health England, however, continues to endorse e-cigarettes as safer than cigarettes.

- ➡ Any benefit of vaping as a harm reduction tool are undermined by high uptake among young people
- ➡ Flavours are cited as a reason to start vaping
- ➡ India banning e-cigarettes
- ➡ Some US states banning flavours
- ➡ Public Health England continues to endorse e-cigarettes as safer than cigarettes

Lancet Editorial “E-cigarettes: time to realign our approach?”

Surely it is time to align the public health approach to e-cigarettes with that of cigarettes. ■ *The Lancet*



Let's start with the situation in the USA

Acute lung illness



Centers for Disease Control and Prevention
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Updated October 11, 2019 at 1:00 PM ET

Smoking & Tobacco Use

[Home](#) > [Basic Information](#) > [Electronic Cigarettes](#)



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Office on Smoking and +

Outbreak of Lung Disease Associated with E-Cigarette Use, or Vaping

- 1299 cases of lung injury
- 26 deaths
- Most patients report using THC containing products

*For context...in the USA approximately **1,300 people die every day** as a consequence from smoking; 130 deaths per day are associated with opioid overdose*

What we know

- As of October 8, 2019, 1,299* lung injury cases associated with the use of e-cigarette, or vaping, products have been reported to CDC from 49 states, the District of Columbia, and 1 U.S. territory.
- Twenty-six deaths have been confirmed in 21 states.
- All patients have reported a history of using e-cigarette, or vaping, products.
- Most patients report a history of using tetrahydrocannabinol (THC)-containing products. The latest national and state findings suggest products containing THC, particularly those obtained off the street or from other informal sources (e.g. friends, family members, illicit dealers), are linked to most of the cases and play a major role in the outbreak.
- Therefore, CDC recommends that you should not use e-cigarette, or vaping, products that contain THC.

Lung disease associated with the use of electronic cigarettes

Histopathology

“Although it is difficult to discount the potential role of lipid, we believe that the histologic changes instead suggest that vaping-associated lung injury represents a form of airway-centered chemical pneumonitis from one or more inhaled toxic substances rather than exogenous lipid pneumonia as such, but the agents responsible remain unknown”

Butt et al NEJM, October 2, 2019

- Respiratory symptoms:
 - Tachypnoea
 - Hypoxia
- Other symptoms included:
 - Fever
 - Tachycardia
- Blood tests showed
 - Serum leucocytosis (predominantly increased neutrophils)
 - Increased markers of inflammation
- CT scans revealed diffuse infiltrates and ground-glass opacity

Recommendations for the Public



FDA and CDC recommend...

- Do not use vaping products that contain THC.
- Do not use vaping products—particularly those containing THC—obtained off the street or from other illicit or social sources.
- Do not modify or add any substances, such as THC or other oils, to vaping products, including those purchased through retail establishments.

What's the evidence for using e-cigarettes for smoking cessation?

Vaping can help some smokers quit

Study	Nicotine vape	Placebo vape	RR (95% CI)
Bullen 2013	7% (21/289)	4% (3/73)	1.77 (0.54–5.77)
Caponnetto 2013	11% (22/200)	4% (4/100)	2.75 (0.97–7.76)
Total	9% (43/489)	4% (7/173)	2.29 (1.05–4.96)

Study	Nicotine vape	NRT	RR (95% CI)
Bullen 2013	7% (21/289)	6% (17/295)	1.26 (0.68–2.34)

TEC study (2019): 1-year sustained quit rates

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy

Peter Hajek, Ph.D., Anna Phillips-Waller, B.Sc., Dunja Przulj, Ph.D.,
Francesca Pesola, Ph.D., Katie Myers Smith, D.Psych., Natalie Bisal, M.Sc.,
Jinshuo Li, M.Phil., Steve Parrott, M.Sc., Peter Sasieni, Ph.D.,
Lynne Dawkins, Ph.D., Louise Ross, Maciej Goniewicz, Ph.D., Pharm.D.,
Qi Wu, M.Sc., and Hayden J. McRobbie, Ph.D.

EC (n=438)	NRT (n=446)	Relative risk (95% CI)
18.1%	9.9%	1.83 (1.30–2.58)

- NRT was provided for 3 months
- EC starter kit provided, then participants sourced their own supply

ASCEND II study (2019): 6-month quit rates

Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: a pragmatic, randomised trial

Natalie Walker, Varsha Parag, Marjolain Verbiest, George Laking, Murray Laugesen, Christopher Bullen

Pragmatic, three-arm, RCT undertaken in New Zealand (2015–2018)

Participants were randomised (1:4:4 ratio) to 14 weeks of:

- 21mg nicotine patches
- 21mg nicotine patches + 18mg nicotine ECs
- 21mg nicotine patches + 0mg nicotine ECs

Minimal behavioural support

Outcome	Patches + 18mg EC (n=500)	Patches + 0mg EC (n=499)	Relative risk (95% CI)
Self-reported	18%	11%	1.68 (1.22-2.30)
CO-verified	7%	4%	1.75 (1.02-2.98)
Outcome	Patches + 18mg EC (n=500)	Patches only (n=125)	Relative risk (95% CI)
Self-reported	18%	8%	2.23 (1.19-4.15)
CO-verified	7%	2%	2.92 (0.91-9.33)

EC vs. brief smoking cessation advice

Holliday et al. *Pilot and Feasibility Studies* (2019) 5:74
https://doi.org/10.1186/s13061-019-0401-4

Pilot and Feasibility Studies

RESEARCH

Open Access

A feasibility study with embedded pilot randomised controlled trial and process evaluation of electronic cigarettes for smoking cessation in patients with periodontitis

Richard Holliday^{1*}, Philip M. Preshaw^{1,2}, Vicky Ryan³, Falko F. Sniehotta³, Suzanne McDonald^{1,4}, Linda Bauld⁵ and Elaine McColl³



- All participants received standard non-surgical periodontal therapies and brief smoking cessation advice
- The **intervention** group additionally received an **e-cigarette starter kit** with brief training

Biochemically verified 6-month continuous abstinence rates: 15% (vaping) vs 5% control

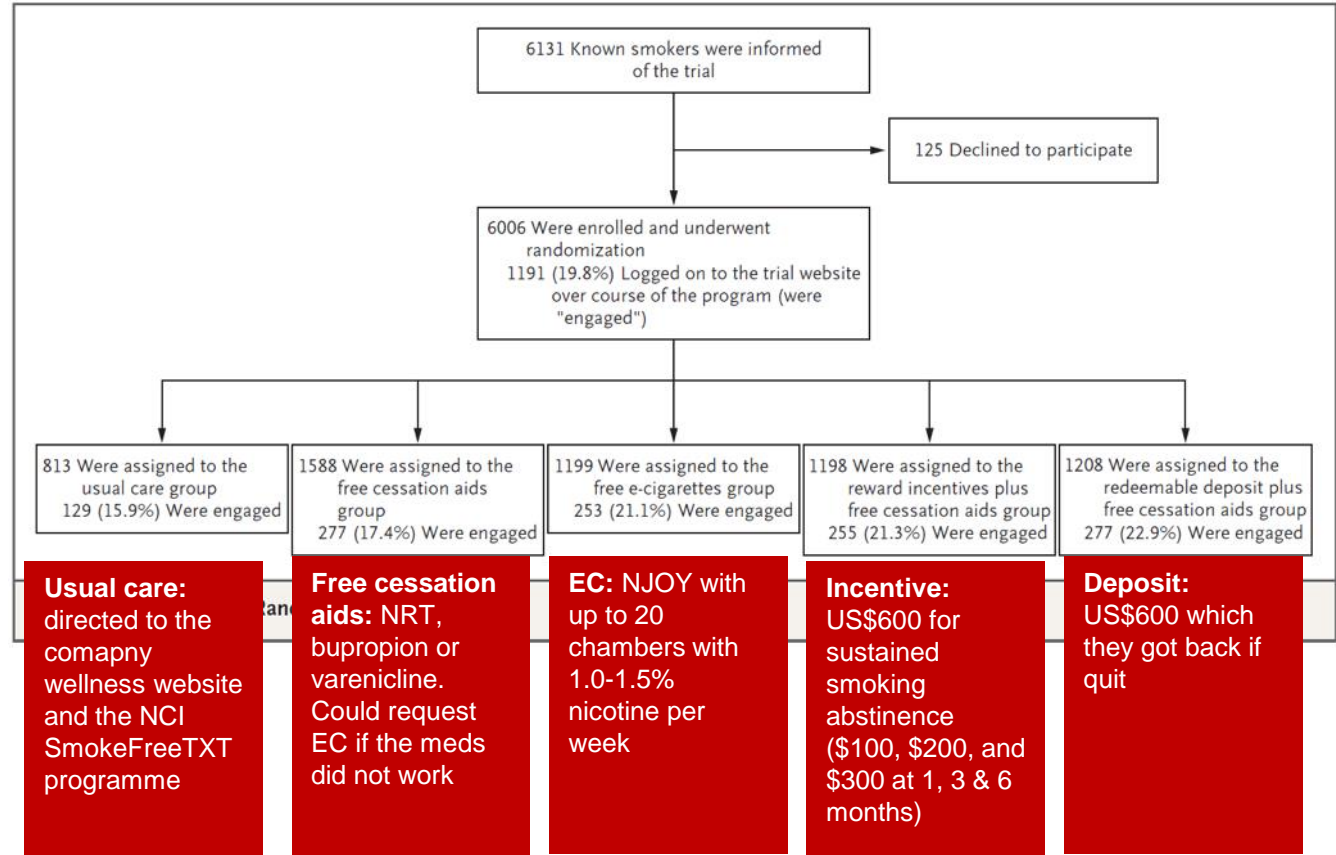
Table 4 Summary of smoking outcome measure data

Outcome	Control			Intervention		
	n	Baseline rate	Rate at follow-up (95% CI)	n	Baseline rate	Rate at follow-up (95% CI)
4-week quitter (eCO or SC/SA verified)	40	NA	5% (1 to 17%)	40	NA	28% (16 to 43%)
6-month quitter (RS6)	40	NA	5% (1 to 17%)	40	NA	15% (7 to 29%)
	n	Baseline mean (SD)	Mean change from baseline to 6 months (SD; 95% CI)	n	Baseline mean (SD)	Mean change from baseline to 6 months (SD; 95% CI)
eCO (ppm)	29	17.1 (10.4)	-5.8 (12.3; -10.5 to -1.1)	29	22.0 (12.8)	-12.0 (11.0; -16.2 to -7.9)
FTND	29	4.6 (2.5)	-1.6 (2.1; -2.4 to -0.8)	29	4.6 (1.6)	-1.9 (2.0; -2.7 to -1.2)
MPSS	29	22.8 (7.5)	-2.8 (8.3; -6.0 to 0.3)	29	21.8 (4.9)	-2.8 (8.8; -6.1 to 0.6)
SC (ng/ml)	29	277.2 (131.5)	-37.1 (133.4; -90.0 to 15.7)	29	326.3 (145.5)	-62.2 (132.3; -112.5 to -11.8)
SA (ng/ml)	29	0.8 (0.8)	0.5 (2.3; -0.5 to 1.4)	29	1.2 (1.3)	-0.4 (1.2; -0.9 to 0.0)

In line with recommendations for smoking cessation trials [4], participants with missing smoking outcome data (e.g. those not attending for review) were considered as continuing smokers or to have resumed smoking. Hence, the denominator for the 4-week and 6-month quitter outcome is the baseline number of participants (n = 40). For continuous variables, missing data were not imputed. eCO expired air carbon monoxide, RS6 Russell standard 6-month quitter, FTND Fagerstroms test of nicotine dependence, MPSS Mood and Physical Symptoms Scale, SC salivary cotinine, SA salivary anabasine, NA not applicable

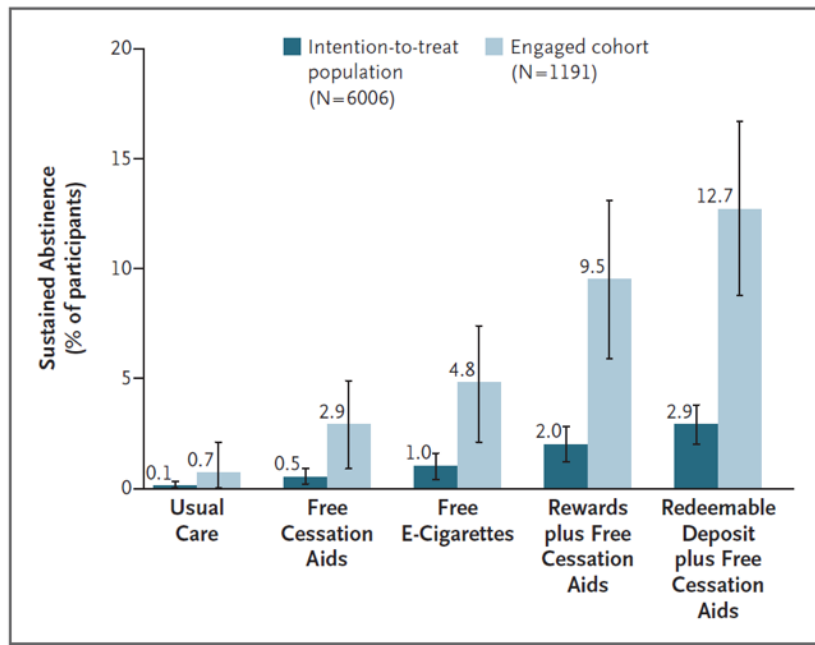
Pragmatic trial

- Trial among employees from 54 US companies using 5 approaches to smoking cessation
- Used 'opt-out' consent



Results

- Biochemically confirmed 6-month quit rate: **1.3%** (N= 80; 95% CI: 1.0 to 1.6)

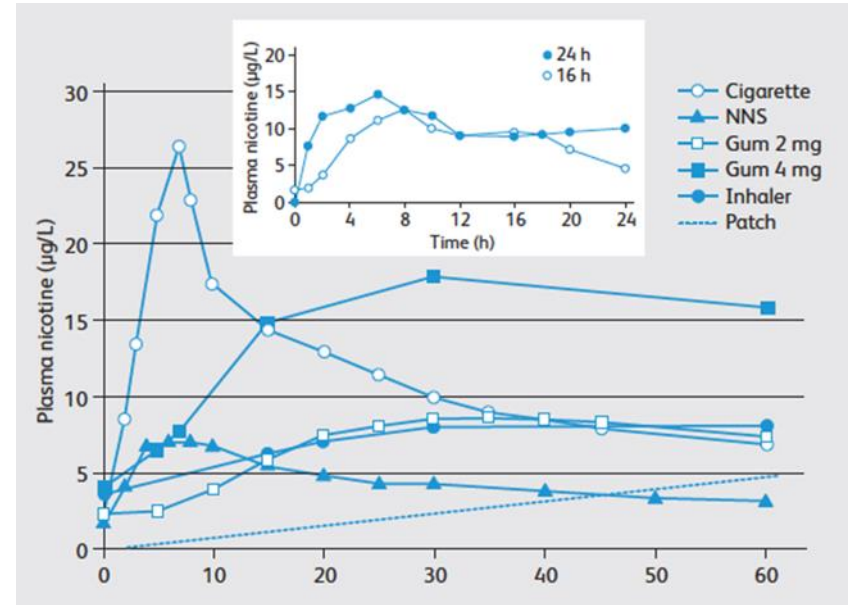


Points to note

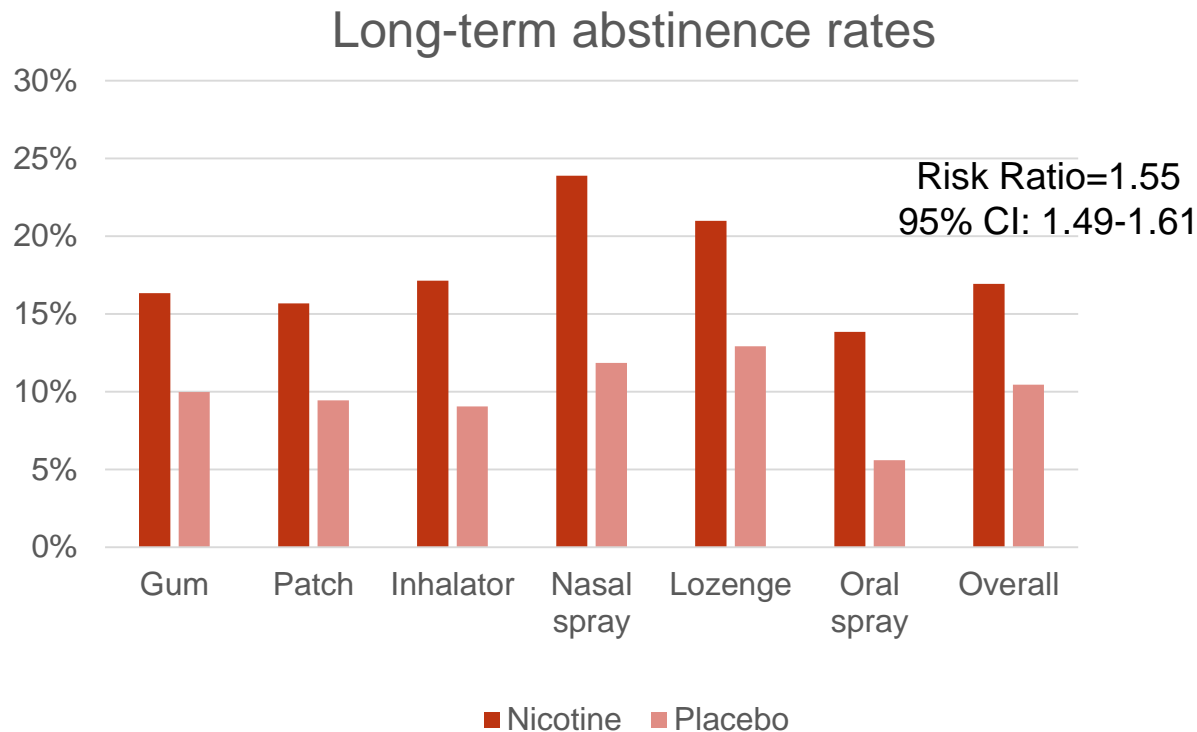
- Of the 1199 smokers who were assigned to receive free e-cigarettes, only 12% actually ordered the product online
- The study did not assess the efficacy of the actual use (as compared with the offer) of these products

Nicotine replacement therapy (NRT)

- Provides a clean source of nicotine
- Reduces tobacco withdrawal symptoms
- No true contraindications
- Good safety record
- Range of products



NRT: Long-term abstinence rates are modest



Some recent 'real world' evidence

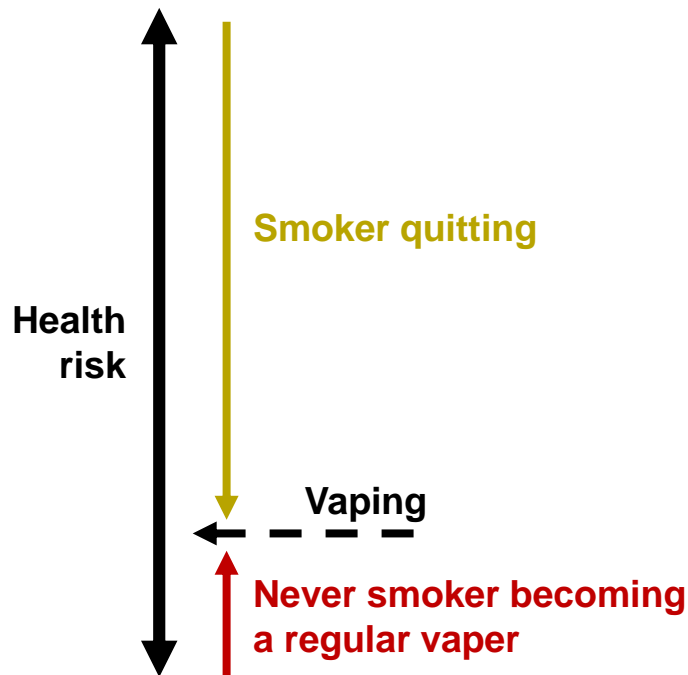
- 18,929 respondents who reported a quit attempt in the last 12 months.
- Asked about use during the most recent quit attempt of:
 - prescription nicotine replacement therapy (NRT)
 - NRT over-the-counter
 - varenicline
 - bupropion
 - e-cigarettes
 - face-to-face behavioural support
 - telephone support
 - written self-help materials
 - websites
 - hypnotherapy
- After adjustment for covariates* and use of other cessation aids users of **e-cigarettes (OR=1.95, 95%CI:1.69–2.24)** and **varenicline (OR=1.82, 95%CI:1.51–2.21)** had higher abstinence rates than those who did not report using them

Are e-cigarettes less harmful than smoking?

Health risk



*“Overall, the evidence reviewed by the committee suggests that e-cigarettes are **not without biological effects in humans**. For instance, use of e-cigarettes results in dependence on the devices, though with apparently less risk and severity than that of combustible tobacco cigarettes. Yet the implications for long-term effects on morbidity and mortality are not yet clear.”*



Substances that are potentially harmful

Aerosol (vapour)¹

- At high temperatures and frequent puffing, PG and VG can form:
 - Acetaldehyde
 - Formaldehyde
 - Acrolein
- Tobacco-specific nitrosamines can be present with tobacco extracts and nicotine
- Oxidising chemicals

Battery and coil¹

- Metals, e.g. nickel, chromium, cadmium, lead, tin, silicates

Liquid¹

- Nicotine
- Flavouring²
 - Benzaldehyde (cherry flavour)
 - Cinnamaldehyde (cinnamon flavours)
 - Diacetyl (butter flavours)

PG, propylene glycol; VG, vegetable glycol.

1. Bals R, *et al. Eur Respir J.* 2019;53:1801151; 2. Allen J, *et al. Environ Health Perspect.* 2016;124:733–9;

What are the potential risks of nicotine use?

Cancer	Cardiovascular disease	Pregnancy	Adolescence
<p>Current evidence does not support the idea that nicotine is a human carcinogen¹</p> <p>National Academy of Sciences concludes: <i>“While there is a biologic rationale for how nicotine could potentially act as a carcinogen in humans, there is no human evidence to support the hypothesis that nicotine is a human carcinogen”</i></p>	<p>Studies in animals, and some epidemiological data in people, suggest that nicotine could contribute to acute events in people with underlying CVD²</p> <p>However... NRT appears to have little, if any, associated increase in CV risk even in those with CVD²</p>	<p>Animal studies show that nicotine exposure in pregnancy is associated with neuro-behavioural problems, impaired lung development and a risk factor for SUDI³</p> <p>However... Human studies of NRT have not demonstrated this risk⁴</p>	<p>Smoking in adolescence has been associated with cognitive and attentional deficits and suggested to impact mental health⁵</p> <p>There is concern that nicotine exposure may predispose adolescents to later smoking and other drug use</p> <p>Adolescents who don't smoke should not vape</p>

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; NRT, nicotine replacement therapy; SUDI, sudden unexpected death in infancy.

1. National Academy of Sciences. Public Health Consequences of E-Cigarettes. 2018; 2. Benowitz NL & Burbank AD. *Trends Cardiovasc Med* 2016;26:515–23; 3. Blood-Siegfried J & Rende EK. *J Midwifery Womens Health* 2010;55:143–52; 4. Coleman T, *et al. Cochrane Database Syst* 26 Rev 2015;(12):CD010078; 5. Goriounova N, *et al. Cold Spring Harb Perspect Med* 2012;2:a012120;

Cell culture and animal studies

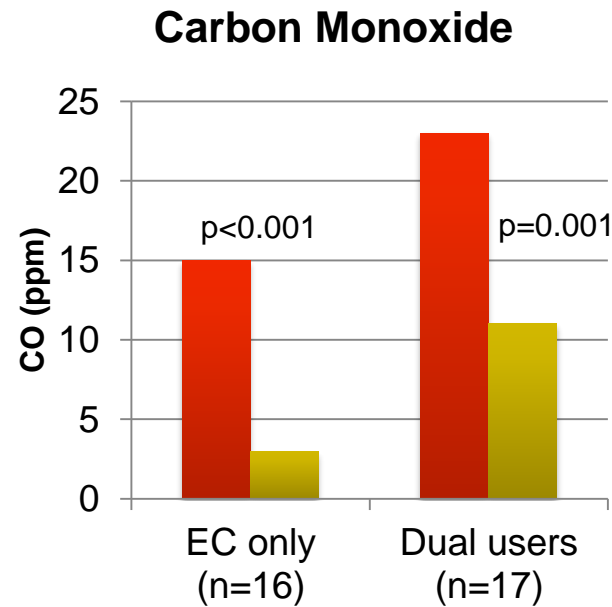
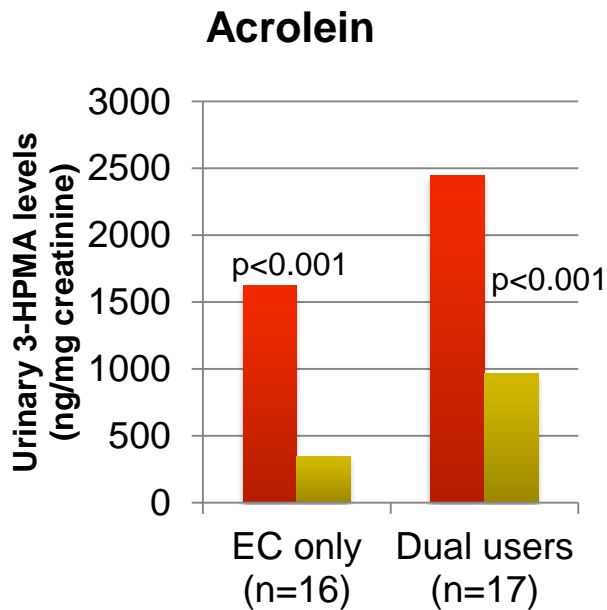
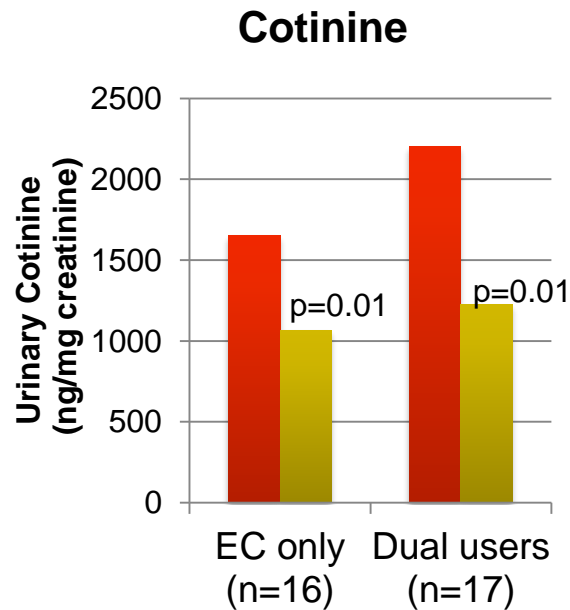
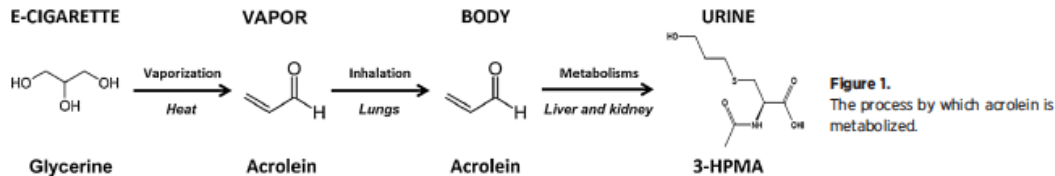
E-liquid/vapour was associated with:¹

- a decrease in cell viability (in some but not all studies)
- changes in oxidative stress
- increased production of inflammatory mediators
- reduction in host defence against infection

“Most of these studies revealed adverse effects of ECIGs, although these were less pronounced than with TCIGs.”¹

“...these in vitro and in vivo exposure studies raise concern regarding the use of ECIGs; conclusive answers will only be obtained with carefully conducted long-term studies in ECIG users.”¹

In humans



■ Baseline ■ 4-weeks

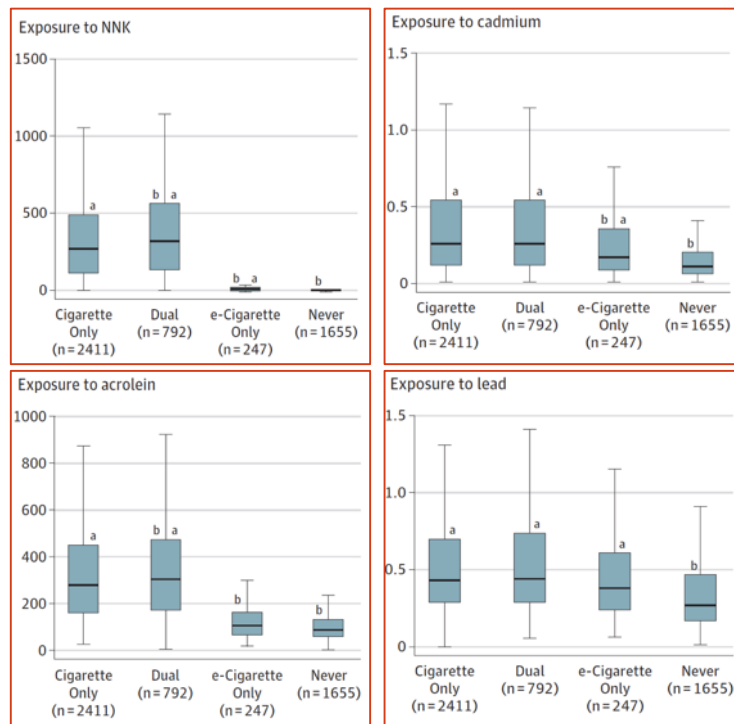
In humans

Measurement of tobacco-related toxicants in urine among:

- current exclusive e-cigarette users (n=247)
- current exclusive cigarette smokers (n=2411)
- users of both products (dual users) (n=792)
- never tobacco users (n=1655)

Compared with exclusive cigarette smokers, exclusive e-cigarette users showed:

- 10% to 98% significantly lower concentrations of biomarkers of exposure, including TSNAs, PAHs, most volatile organic compounds and nicotine
- comparable concentrations of metals and three volatile organic compounds



^aStatistically significant difference from never users;

^bStatistically significant difference cigarette-only users.

NNK, nicotine-derived nitrosamine ketone; PAH, polycyclic aromatic hydrocarbon; TSNA, tobacco-specific nitrosamine.
Goniewicz ML, *et al.* JAMA Netw Open 2018;1:e185937.

Does the presence of these substances translate to harm?

- The harm is largely related to exposure
- There is currently no evidence that vaping is associated with disease,
BUT ECs have not been around for long enough to observe this association¹
- A complicating factor is that most vapers are current or former smokers



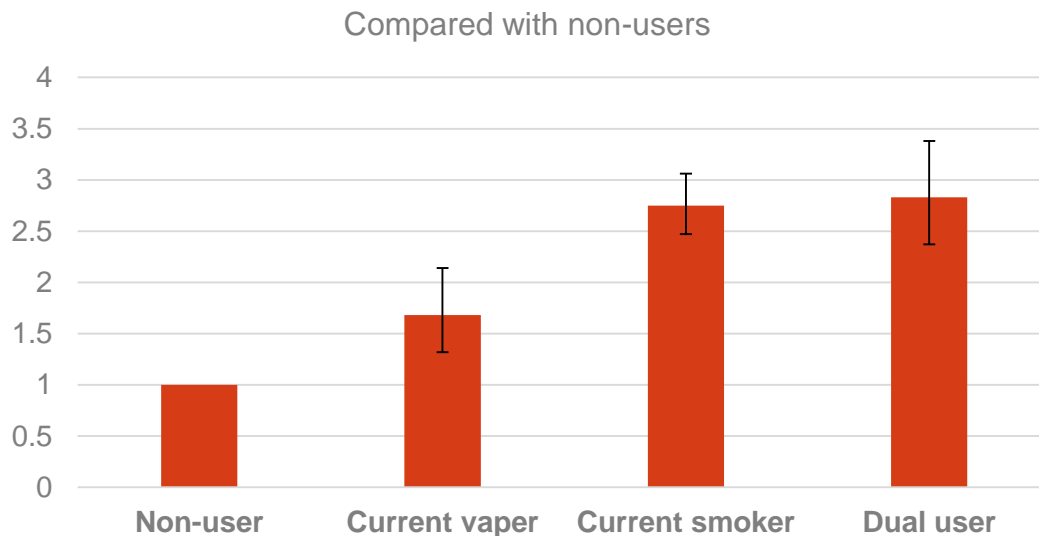
Respiratory symptoms in adults

Cross-sectional survey of
~28,000 adults¹

- 641 current vapers
- 8525 current smokers
- 1106 dual users
- 17,899 non-users

Self-reported wheezing and
other respiratory symptoms

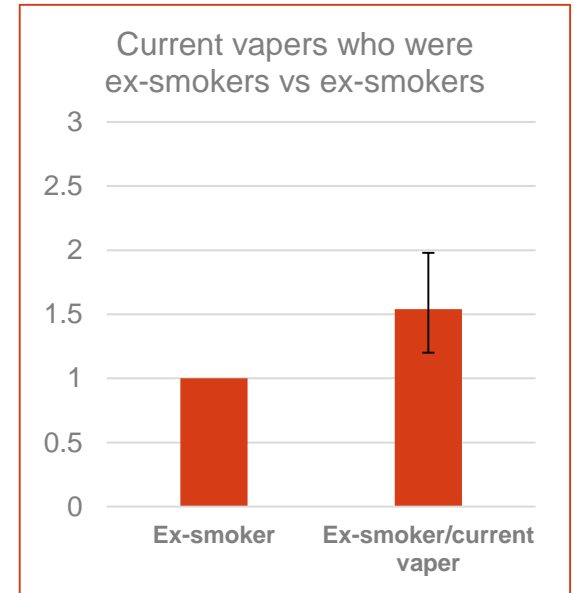
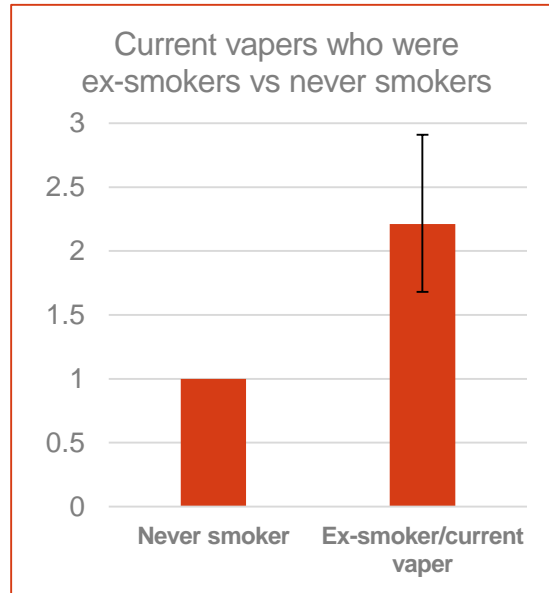
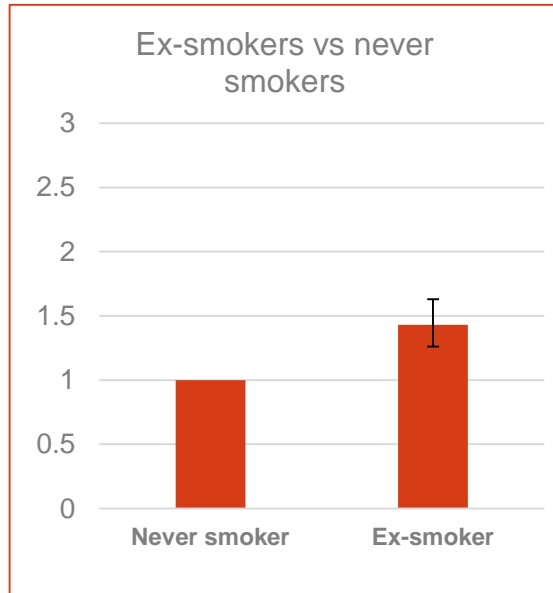
Wheezing or whistling in chest in past 12 months



Bars represent adjusted odds ratios and error lines represent 95% confidence intervals.

Respiratory symptoms in adults

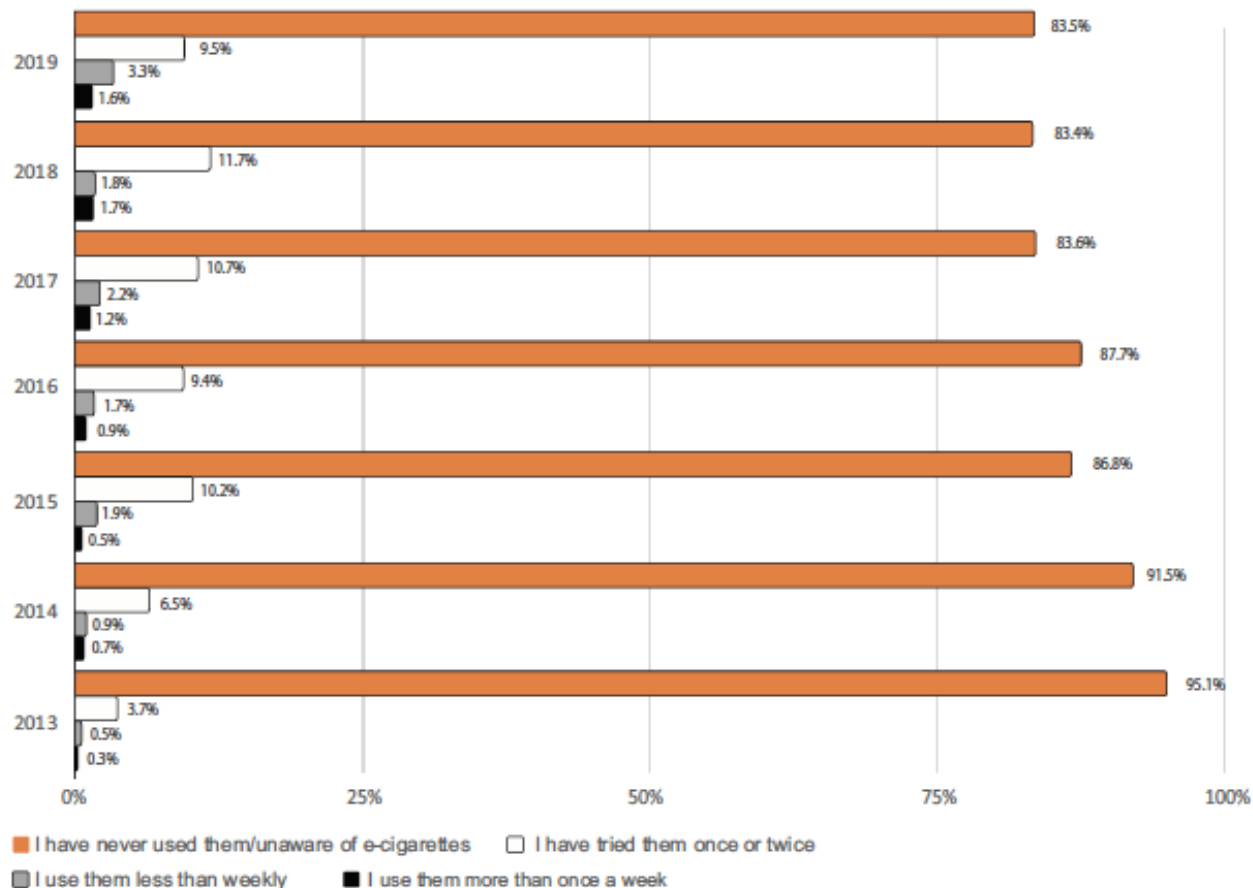
Wheezing or whistling in chest in past 12 months



What about uptake by young people?

Use by youth

Figure 1. Use of e-cigarettes by GB youth (11-18), 2013-2019

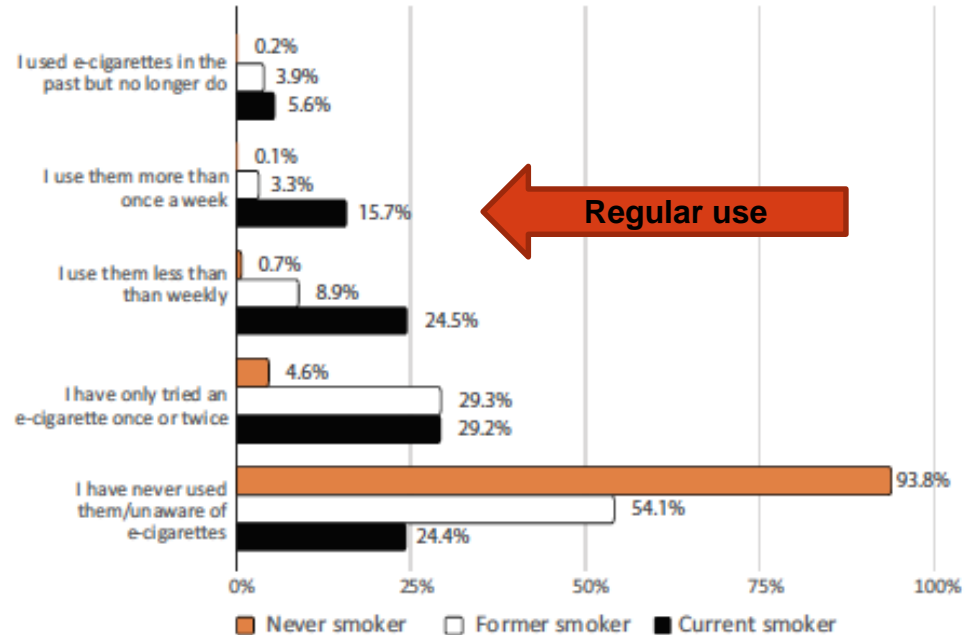


ASH Smokefree GB Youth Survey(s). Unweighted base: All 11-18 year olds (2013 = 2,178, 2014 = 2,068, 2015 = 2,291, 2016 = 2,331, 2017 = 2,623, 2018 = 2,291, 2019 = 2523). Percentages have been rounded to the nearest decimal place.

Vaping in youth by smoking status in Great Britain (GB)

Figure 2. Use of e-cigarettes by tobacco smoking status, GB youth (11-18), 2019

“Young people vape mainly just to give it a try (52.4%) not because they think it looks cool (1.0%).”



ASH Smokefree GB Youth Survey, 2019 (Unweighted bases: Never smokers = 1,895, former smokers = 376, current smokers = 209). Percentages have been rounded to the nearest decimal place.

New Zealand (NZ) – ASH Year 10 survey

2018	n*	% Tried e-cigarettes	% Use e-cigarettes daily	% Use e-cigarettes daily or weekly
All	28,433	29.1	1.8	4.0
- Boys	13,446	33.5	2.3	4.8
- Girls	14,987	25.0	1.3	3.2
By smoking status				
- Never smoking	23,078	21.1	0.4	1.1
- Regular smoking	1,400	94.5	14.4	30.7
- Daily smoking	533	94.6	19.4	34.8

United States (US): National Youth Tobacco Survey (NYTS)

- Nationally representative cross-sectional sample of students from US middle and high schools
- Participants
 - 2017: 10,186
 - 2018: 10,991
- Past-30-day e-cigarette **increased by 78%** between 2017 and 2018
 - 2017: 11.7%
 - 2018: 20.8%

	E-cigarette use			
	Never used any tobacco product		Smoked 100+ cigarettes in lifetime	
	2017	2018	2017	2018
Any use in last 30 days % (N)	2.9% (173)	8.4% (550)	57.2% (174)	71.0% (303)
Used 20+ days	0.2% (8)	1.0% (60)	26.8% (77)	37.2% (163)
Total N	6341	6664	326	433

US: Smoking and vaping time trend

Data show a continuing decline in

(a) current cigarette smoking in high school students

- 1999: 28.5%
- 2018: 8.1%

(b) proportion who have ever tried a combustible product

- 1999: 66.9%
- 2018: 33.4%

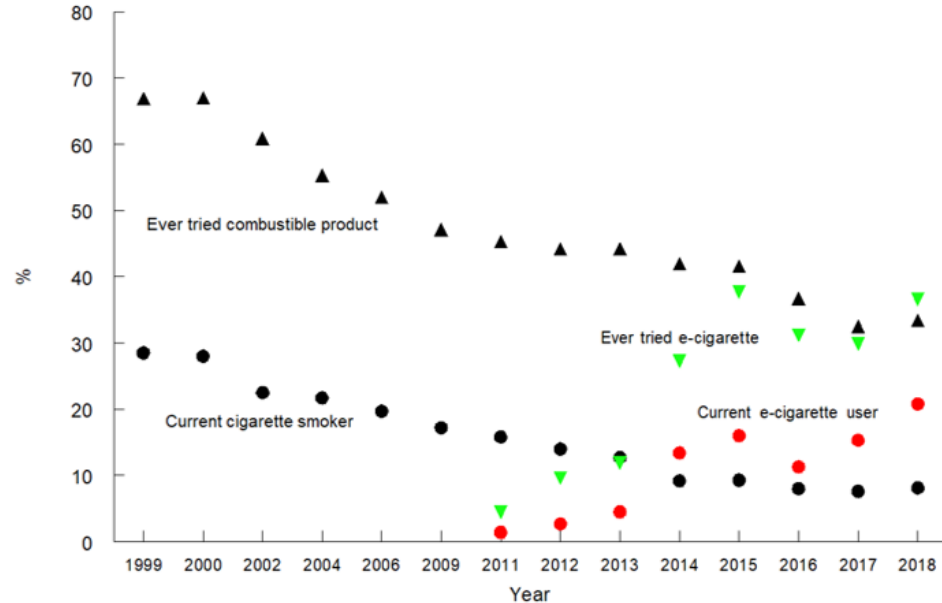


Figure 1

Time trends in use of e-cigarettes (ever-tried & current) and combustible (ever-tried combustible product and current cigarette) NYTS 1999-2018.

E-cigarette use ascertained from 2011 onwards

On flavours...

- The RCT by Hajek et al. 2019 provided one 30-ml bottle of Tobacco Royale flavour e-liquid
- At the end of trial fruit flavour was the most frequently used

Flavours used ** N (%)	1 week (N=155)	4 weeks (N=156)	26 weeks (N=516)	52 weeks (N=511)
Tobacco	15 (10)	44 (28)	163 (32)	127 (25)
Fruit	70 (45)	51 (33)	150 (30)	169 (33)
Menthol/Mint	31 (20)	20 (13)	75 (15)	81 (16)
Tobacco menthol	5 (3.2)	7 (4.5)	13 (2.5)	12 (2.3)
Vanilla	5 (3.2)	1 (0.6)	11 (2.1)	14 (2.7)
Chocolate, dessert, sweet or candy	17 (11)	18 (12)	62 (12)	72 (14)
No flavour	0	0	0	2 (0.4)
Coffee	2 (1.3)	1 (0.6)	6 (1.2)	8 (1.6)
Alcoholic drink	2 (1.3)	2 (1.3)	7 (1.4)	3 (0.6)
Energy drink or soft drink	6 (3.9)	10 (6.4)	17 (3.3)	13 (2.5)
Other	2 (1.3)	2 (1.3)	12 (2.3)	10 (2.0)

* N providing information from which % was calculated

** Some participants used multiple flavours; the N and % are based on the overall number of entries

Conclusions

- There are likely to be some adverse health effects associated with long-term vaping, so concern is warranted
- However, this concern needs to be balanced with the concerns for the health and wellbeing of people who continue to smoke
- Smoking cessation remains the best way to achieve full health benefits
- For smokers, switching to vaping (and stopping smoking completely) is likely to be associated with a reduction in health risks
 - This is supported by the current literature
 - To mitigate concern over unknown health risks associated with long-term vaping, ex-smokers can be advised to stop vaping as soon as they feel able not to relapse to smoking

**THE BEST THING SMOKERS CAN DO TO IMPROVE THEIR
HEALTH IS TO QUIT SMOKING COMPLETELY**

Moving forward

- Appropriate steps can be taken to limit uptake of vaping in young never smokers
- Ensure the public has accurate information regarding vaping
- Encourage ongoing improvement in quality and safety of vaping devices and liquids
- Monitor the emerging literature on health risks of vaping and be prepared to change tack
- Commission monitoring, e.g. tracking a cohort of vapers (non-smokers and ex-smokers) over time
- Establish a system for reporting suspected adverse effects of vaping



Mike Thomson, USA Today

<https://www.usatoday.com/opinion/cartoons/>