# Symposium 4 – Health effects of vaping – a comprehensive systematic review


## Ann McNeill, Professor of Tobacco Addiction (Chair)


International scientific conference on e-cigarettes, Paris December 2022

# Government-commissioned evidence updates

**2015**
E-cigarettes: an evidence review

**2018**
Evidence review of EC & HTP

Focus on cessation and health risks

**2019**
Vaping in England

Focus on SE indicators

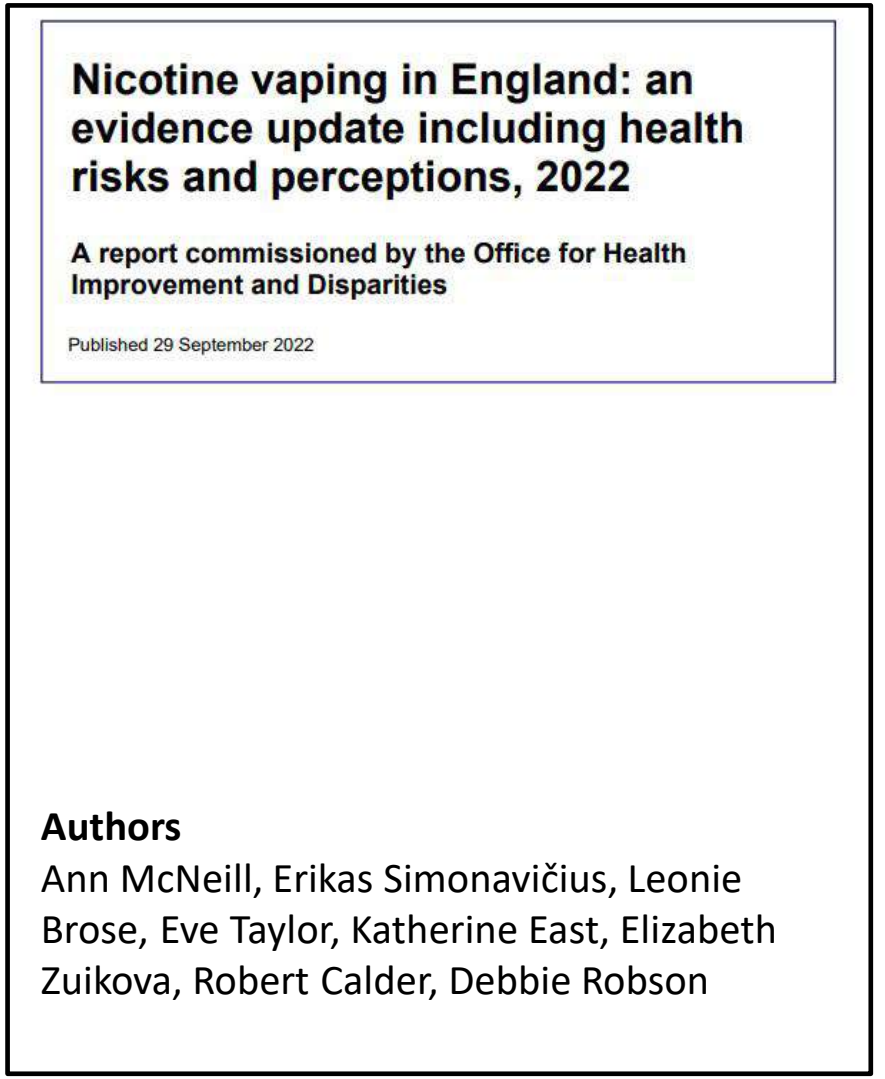
**2020**
Vaping in England

Focus on mental health & pregnancy

**2021**
Vaping in England

Focus on smoking cessation

**2022**



**Nicotine vaping in England: an evidence update including health risks and perceptions, 2022**

**A report commissioned by the Office for Health Improvement and Disparities**

Published 29 September 2022

**Authors**
Ann McNeill, Erikas Simonavičius, Leonie Brose, Eve Taylor, Katherine East, Elizabeth Zuikova, Robert Calder, Debbie Robson

# 2022 evidence update

## Full report

www.gov.uk/government/publications/nicotine-vaping-in-england-2022-evidence-update

## Collaborators

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Sofia Hemrage, King's
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Action on Smoking & Health (ASH), UK
University College London Tobacco & Alcohol Research Group, UK
ITC Project, University of Waterloo, Canada

## We would also like to thank our independent reviewers

# Chapters

1. Introduction
2. Methods
3. Vaping among young people
4. Vaping among adults
5. Nicotine
6. Flavours in vaping products
7. Biomarkers of exposure to nicotine and potential toxicants
8. Biomarkers of potential harm cutting across several diseases
9. Cancers
10. Respiratory diseases
11. Cardiovascular diseases
12. Other health outcomes
13. Poisonings, fires & explosions
14. Heated tobacco products
15. Harm perceptions & communications
16. Conclusions

1400 pages

# Funding & Competing Interests


- This work was funded by Public Health England, now Office for Health Improvement and Disparities, part of the Government's Department of Health & Social Care
- The authors have no links with any tobacco or vaping product manufacturers or distributors


- See our full statements:

www.gov.uk/government/publications/nicotine-vaping-in-england-2022-evidence-update

@KingsNRG

# Order of Play

**Methods & health risks of nicotine & flavourings**

- Dr Debbie Robson, Senior Lecturer in Tobacco Harm Reduction

**Biomarkers of exposure**

- Eve Taylor, Research Assistant & PhD Student

**Cancer, respiratory & cardiovascular disease**

- Dr Leonie Brose, Reader in Addictions Education & Nicotine Research

**Overview of methodological limitations when assessing vaping effects on health biomarkers**

- Dr Erikas Simonavičius Research Associate

**Q&A**

# Methods
# Nicotine & Flavours

Presenter: Debbie Robson

Senior Lecturer in Tobacco Harm Reduction

# Chapters

1. Introduction
2. **Methods**
3. Vaping among young people
4. Vaping among adults
5. **Nicotine**
6. **Flavours in vaping products**
7. Biomarkers of exposure to nicotine and potential toxicants
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# Methods

# Systematic literature review: Health risks of vaping

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Print | PDF

**A systematic review of the health risks and health effects of vaping**

*Debbie Robson, Leonie Brose, Robert Calder, Eve Taylor, Linda Bauld, Ann McNeill*

**Citation**

Debbie Robson, Leonie Brose, Robert Calder, Eve Taylor, Linda Bauld, Ann McNeill. A systematic review of the health risks and health effects of vaping. PROSPERO 2020 CRD42020215915 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020215915

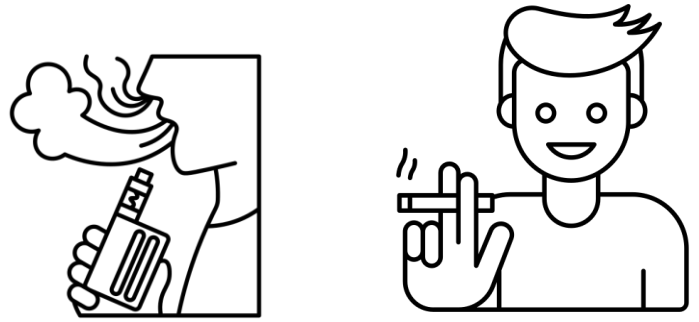
We assessed

1.What effect does vaping (active and second-hand) have on the risk of getting cancers, respiratory disease and cardiovascular disease?

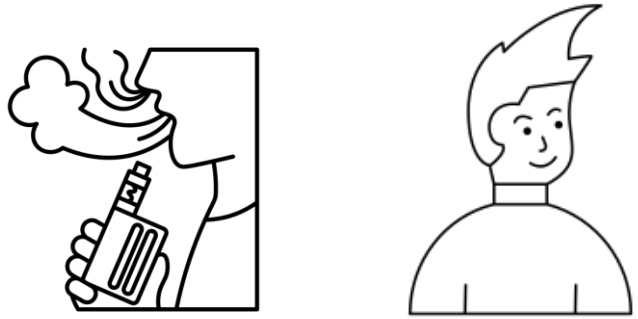
2. Among people with existing health conditions (as above), what are the effects of vaping on disease outcomes?

# Compared

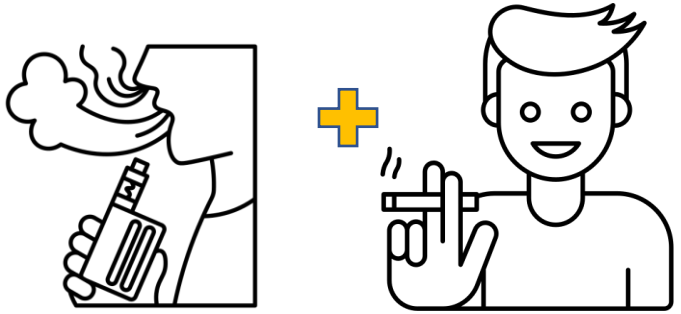
People who vaped with people who smoked



People who vaped with people who did not smoke or vape



Dual use poorly defined – we reported this but focused on exclusive use in the narrative and meta analyses



Searched & reviewed literature published from **Aug 2017 to July 2021**

Start date follows on from NASEM and PHE 2018 reports end dates

Records identified
**(n = 10,305)**

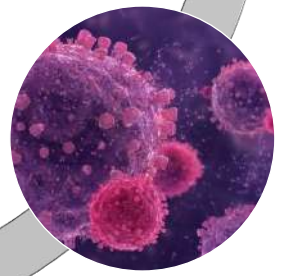
Records screened
**(n = 8,092)**

Full-text articles assessed
**(n = 772)**

413 studies

Humans
(n=275)

Animals
(n=81)



Cells
(n=58)

## Biomarker of exposure (BoE)

- A measure of how much of a substance (toxicant), or its metabolite is in the body (in urine, saliva, blood or hair)

## We defined length of exposures as

**Acute** single use to 7 days

**Short to medium** 8 days to 12 months

**Long term** more than 12 months

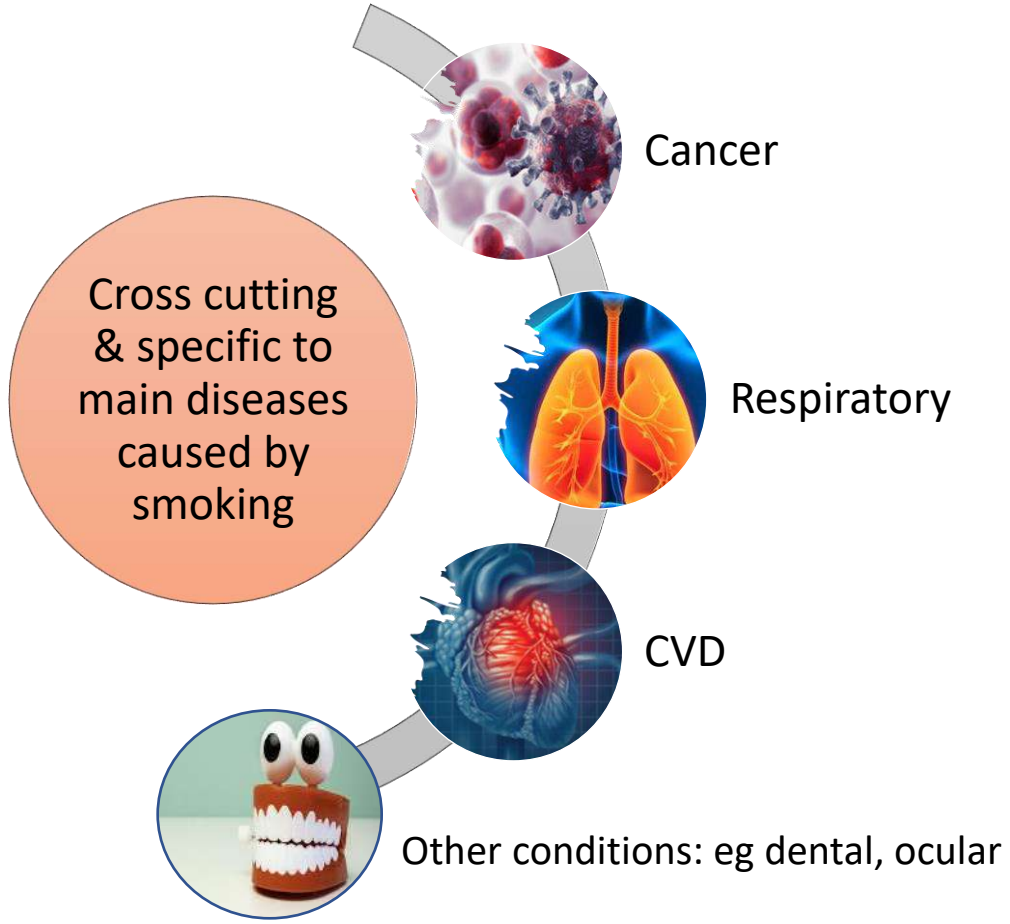
## WHO biomarkers of priority toxicants (and metabolites) for tobacco

| Nicotine | Carbon Monoxide | Tobacco-specific nitrosamines | Volatile organic compounds | Metals | Other potential toxicants (eg PAHs) |
|---|---|---|---|---|---|
| e.g. Cotinine<br>TNEQ<br>3HC | COHb | e.g. NNK (NNAL);<br>Anabasine (NAB);<br>Anatabine (NAT);<br>Nornicotine (NNN) | e.g. Acetaldehyde (acetate); Acrolein (3-HPMA, CEMA);<br>Benzene(S-PMA, Mu) | Arsenic<br>Cadmium<br>Lead<br>Mercury | e.g.<br>Benzo[a]pyrene (Total-3-OHB[a]P)<br>Pyrene (1-HOP) |

# Biomarker of potential harm (effect)

Objective* medical sign used to measure the effect of a substance on the body, or the presence or progress of disease

- Simple to measure e.g. blood pressure, white blood cell count, lung function
- Complex to measure e.g. changes in the way genes are expressed




*We did not include self reported symptoms

# Assessment of study quality and bias

| Study type | Tool |
|---|---|
| RCT | Cochrane Risk of Bias toll (V2) |
| Non randomised | Risk of Bias in Non-randomized Studies of Interventions tool |
| Cohort /Repeated cross sectional | Adapted Newcastle Ottawa Scale |
| Cross sectional | BIOCROSS |

# Steps for selecting which studies (in humans) to meta-analyse

### COMPARISON GROUPS

Included studies that had at least 2 out of 3 following comparison groups: vapers, smokers, non-users

### CLEAR DEFINITIONS OF BASELINE & FOLLOW UP GROUPS

Included studies that clearly defined smoking/vaping frequency. Excluded studies that only defined vaping less than weekly

### ADHERENCE TO STUDY GROUPS

Included studies that ensured participants allocated to vaping groups were not smoking (preferably bioverified)

### DATA REPORTED IN GEOMETRIC/ ARITMETRIC MEANS

Able to be log transformed

### DATA SOURCE

Where multiple published studies used the same data set the study with the largest sample size was selected for data extraction

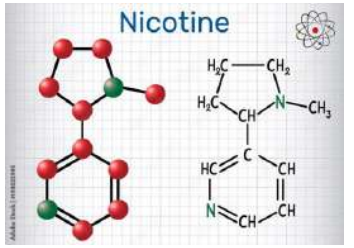
**55 meta analyses**

**Total number of studies =231**

**31 of those studies were included across meta-analyses**

# Nicotine

# **Nicotine exposure** to vaping products compared with smoking & across different types of vaping products



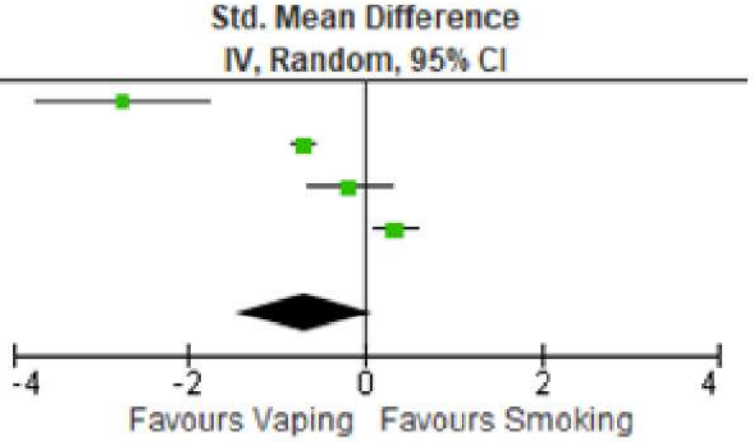

## Pharmacokinetic studies (n=20)

- Sample sizes ranged from 5-71
- Most studies compared nicotine delivery after acute standardised vaping sessions (eg 10 puffs, one taken every 30 seconds)
- Under controlled conditions, vaping products, regardless of their device type or e-liquid nicotine concentration, expose users to significantly **lower peak** (Cmax) and **total** (AUC) **nicotine levels** than smoking a cigarette
- **Increased exposure** to nicotine with……
  - using e-liquids with higher nicotine concentration
  - using e-liquids based on nicotine salts rather than freebase nicotine
  - using tank or modular type vaping devices vs cartridges or disposables

# Meta analysis of cross sectional studies urinary cotinine

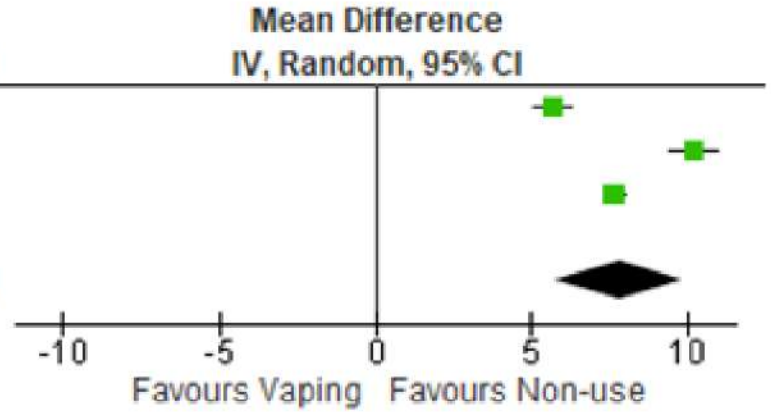
| | Vaping | | | Smoking | | | | Std. Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI |
| Boykan 2019 | 4.258343 | 1.405137 | 51 | 8.002025 | 0.16965914 | 6 | 19.3% | -2.75 [-3.75, -1.76] |
| Goniewicz 2018 | 4.822698 | 4.736778 | 247 | 7.512563 | 3.73303 | 2411 | 28.0% | -0.70 [-0.83, -0.57] |
| Keith 2020 | 6.34536 | 0.9018608 | 17 | 6.491234 | 0.80398875 | 237 | 25.3% | -0.18 [-0.67, 0.31] |
| Smith 2020 | 7.663877 | 1.281619 | 124 | 7.226936 | 1.279666 | 127 | 27.4% | 0.34 [0.09, 0.59] |
| **Total (95% CI)** | | | **439** | | | **2781** | **100.0%** | **-0.68 [-1.45, 0.10]** |

Heterogeneity: Tau² = 0.56; Chi² = 73.78, df = 3 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.72 (P = 0.09)




| | Vaping | | | Non-use | | | | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI |
| Goniewicz 2018 | 4.822698 | 4.736778 | 247 | -0.8675 | 3.199546 | 1655 | 33.3% | 5.69 [5.08, 6.30] |
| Keith 2020 | 6.34536 | 0.9018608 | 17 | -3.88544 | 3.111577 | 87 | 32.7% | 10.23 [9.45, 11.01] |
| Smith 2020 | 7.663877 | 1.281619 | 124 | 0 | 1.403928 | 110 | 34.0% | 7.66 [7.32, 8.01] |
| **Total (95% CI)** | | | **388** | | | **1852** | **100.0%** | **7.85 [5.78, 9.91]** |

Heterogeneity: Tau² = 3.23; Chi² = 81.19, df = 2 (P < 0.00001); I² = 98%
Test for overall effect: Z = 7.45 (P < 0.00001)



# **Nicotine exposure** to vaping products compared with smoking & across different types of vaping products


Biomarker of exposure to nicotine & metabolites (n=60)

- Acute vaping vs smoking (single use – 7 days) = lower exposure to nicotine
- Short-to -longer-term vaping vs smoking (>7 days) = similar levels of exposure
- Higher exposure associated with tank and modular vaping devices
- Compensatory puffing behaviour to achieve preferred nicotine levels when using lower nicotine strength liquids

# Flavours

# Flavours

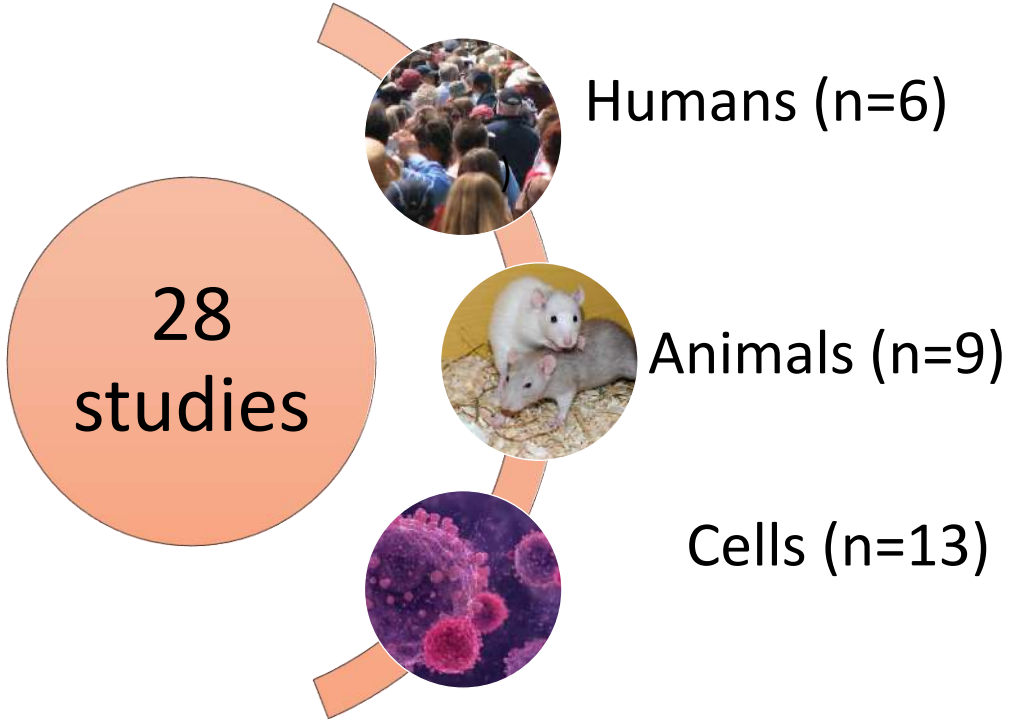

Most common flavours in England:

**Adults:** Fruit, menthol, tobacco

**Youth**: Fruit, menthol, candy/ dessert

Non-tobacco flavours appeal to smokers to start and stay vaping – and stop smoking

## Health effects



# Flavours


## Humans

- Sample sizes ranged from 18-212
- Limited evidence on health effects
- Levels of TSNAs and VOCs were significantly reduced in smokers and dual users who switched to vaping products with different flavours

## Cell and animal studies

- Relative to tobacco smoke, flavours had significantly less effect on cells (e.g. tissue viability, inflammation, oxidative stress)
- Absolute harm (from 3 cell & 1 animal study) – cinnamaldehyde flavouring had an effect on cardiac electrophysiological outcomes, temporarily impaired airway cilia motility, caused dose-dependent reduction in mitochondrial function and glycolysis.
- Findings re exposure to PG/VG showed little effect
- Recommended further research (cinnamaldehyde) and standardized assessment

# Biomarkers of exposure to nicotine and potential toxicants

Eve Taylor

PhD student and Research Assistant

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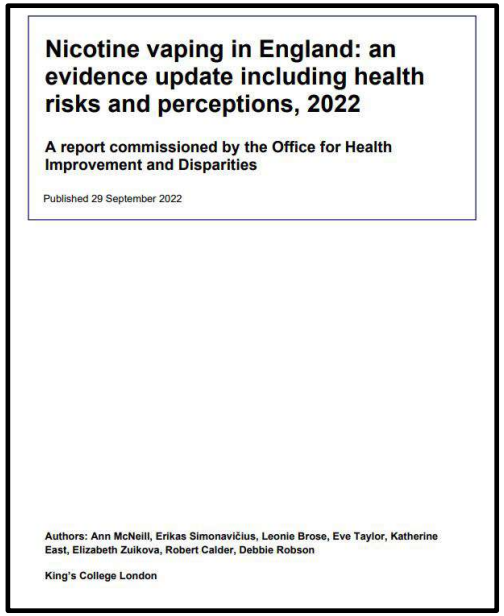
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King's College London

# Biomarker of Exposure Investigated

**Nicotine**

Cotinine

TNE

3HC

**TSNAs**

NNK(NNAL)

NNN

NAB

NAT

**VOCs**

Acrylamide

Acrolein

Acrylonitrile

Benzene

1,3-Butadiene

Butyraldehyde

**VOCs**

Crotonaldehyde

Formaldehyde

Isoprene

Toulene

Formaldehyde

Isoprene

**PAHs**

Pyrene

Benzo[a]pyrene

**Carbon monoxide**

Carboxyhaemoglobin

**Aromatic Amines**

1-Aminonaphthalene

2-Aminonaphthalene

3-Aminobiphenyl

4-Aminobiphenyl

**Metals**

Arsenic

Cadmium

Lead

Mercury

**Other**

O-Toluidine

Thiocyanate

O-Cresol

# Biomarker of Exposure Study Characteristics

| TSNAs: | VOCs: | PAHs: | CO: | Metals: |
|---|---|---|---|---|
| **28 total** | **24 total** | **8 total** | **33 total** | **10 total** |
| 6 RCTs, 2 cross-overs, 4 other longitudinal study designs, 16 cross-sectional | 4 RCTs, 1 cross-over, 6 other longitudinal study designs, 13 cross-sectional studies | 2 RCTs, 1 cross-over, 1 other longitudinal study design, 4 cross-sectionals | 7 RCTs, 7 cross-overs, 14 other longitudinal study design, 5 cross-sectional | 10 cross-sectional |

| Metabolites (toxicants) | Vaping vs Smoking (relative risk) | Vaping vs Non-use (absolute risk) |
|---|---|---|
| ↓ significantly lower, ↑ significantly higher, = no significant difference, – not enough data to meta-analyse | | |
| **Tobacco-specific nitrosamines** | | |
| NNAL (NNK) | ↓ | ↑ |
| NNN | ↓ | – |
| NAB | ↓ | ↑ |
| NAT | ↓ | ↑ |
| **Volatile organic compounds** | | |
| AAMA (Acrylamide) | = | = |
| GAMA (Acrylamide) | ↓ | = |
| CEMA (Acrolein) | = | = |
| 3-HPMA (Acrolein) | ↓ | = |
| CNEMA (Acrylonitrile) | ↓ | ↑ |
| S-PMA (Benzene) | = | = |
| MU (Benzene) | = | – |
| MHBMA (1,3-Butadiene) | ↓ | = |
| DHBMA (1,3-Butadiene) | = | = |
| HMPMA (Crotonaldehyde) | ↓ | = |
| S-BMA (Toluene) | = | = |
| **Carbon monoxide** | ↓ | – |

Due to study heterogeneity, few studies were included

# Biomarker of Exposure Investigated

**Nicotine**

Cotinine

TNE

3HC

**TSNAs**

NNK(NNAL)

NNN

NAB

NAT

**VOCs**

Acrylamide

Acrolein

Acrylonitrile

Benzene

1,3-Butadiene

Butyraldehyde

**VOCs**

Crotonaldehyde

Formaldehyde

Isoprene

Toulene

Formaldehyde

Isoprene

**PAHs**

Pyrene

Benzo[a]pyrene

**Carbon monoxide**

Carboxyhaemoglobin

**Aromatic Amines**

1-Aminonaphthalene

2-Aminonaphthalene

3-Aminobiphenyl

4-Aminobiphenyl

**Metals**

Arsenic

Cadmium

Lead

Mercury

**Other**

O-Toluidine

Thiocyanate

O-Cresol

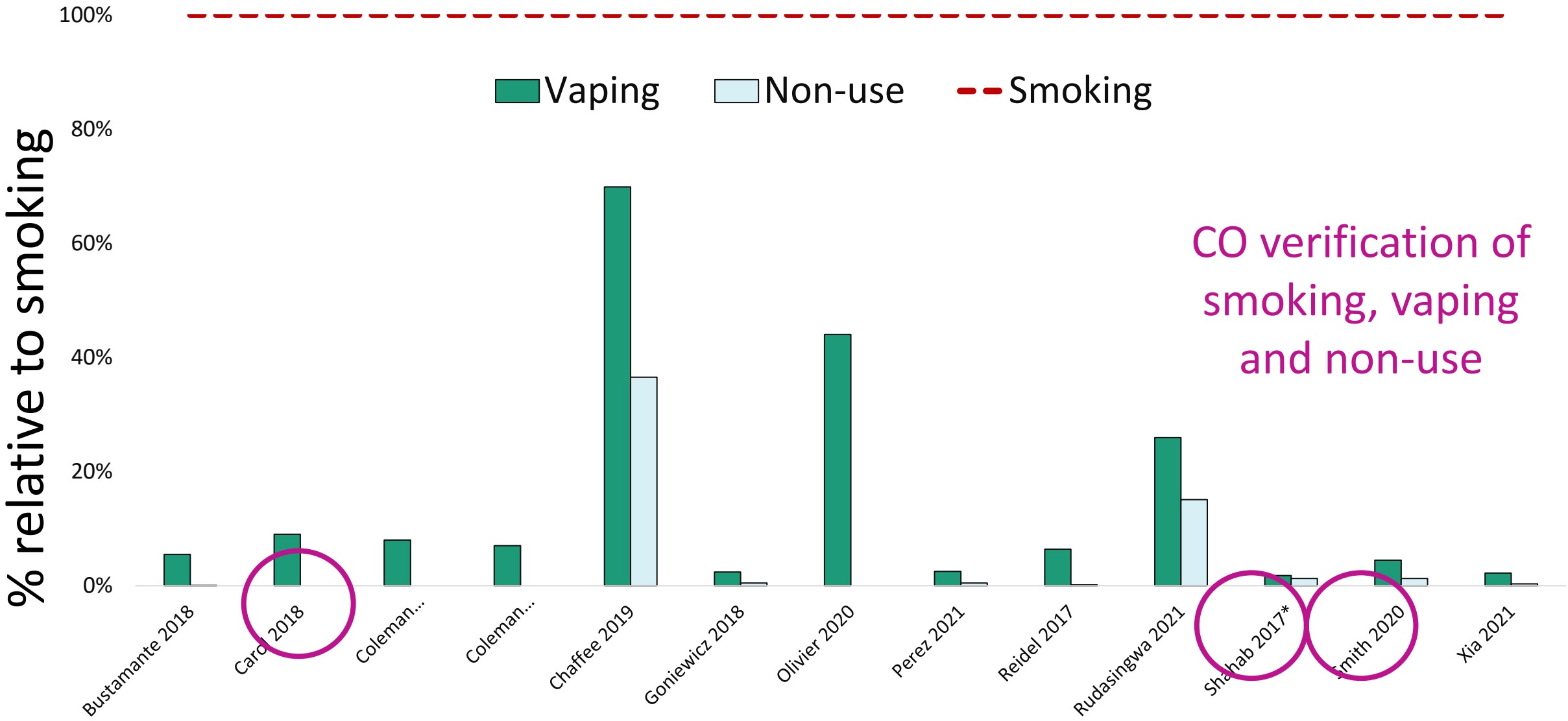
NNK(NNAL)

Health effects: Carcinogenic.

Known exposures: cured and smoked tobacco.

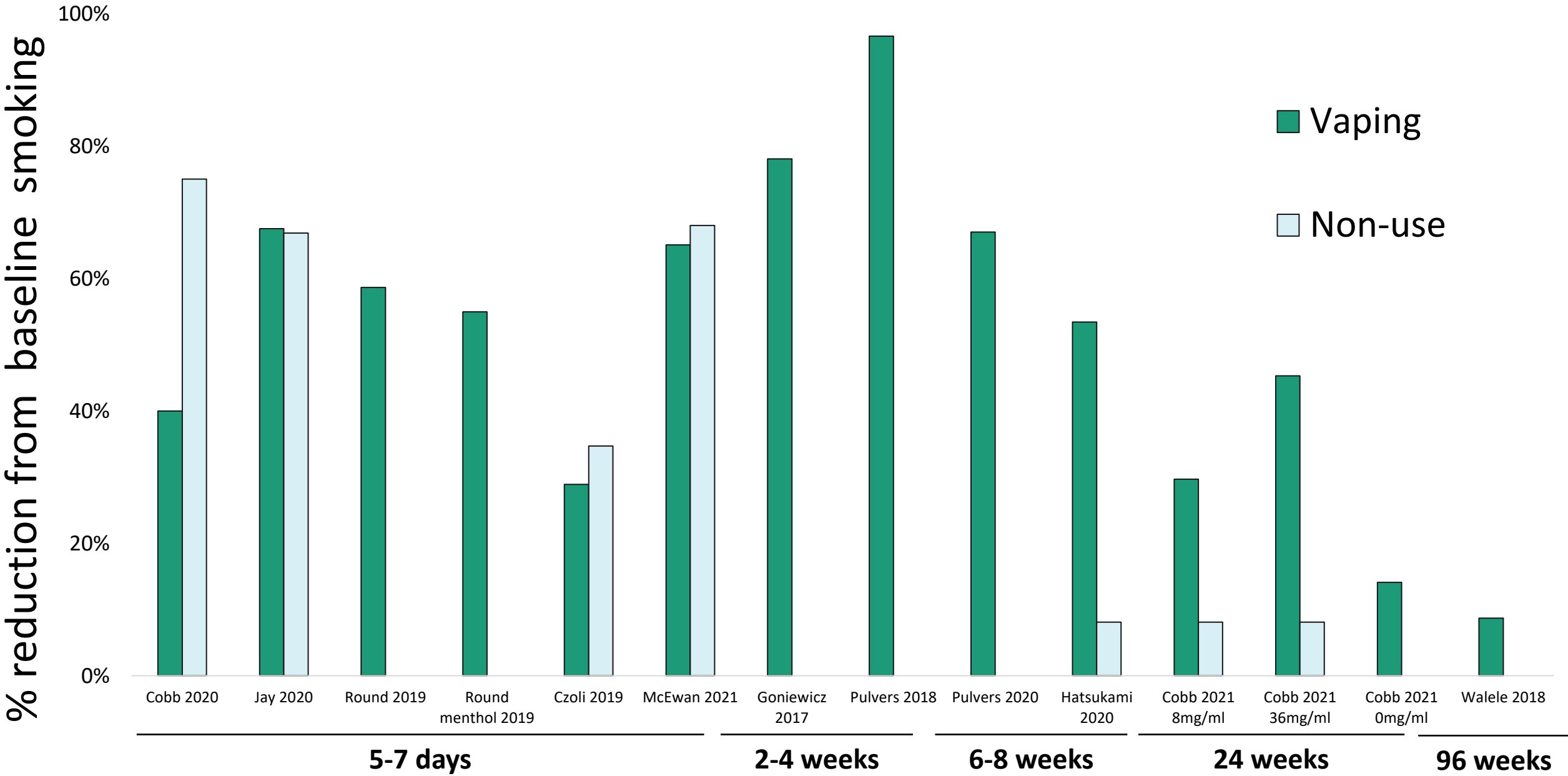
Half-life: 10-45 days.

# NNK(NNAL)-cross sectional




* Shahab 2017 Non-use participants were using NRT

# NNK(NNAL)- longitudinal



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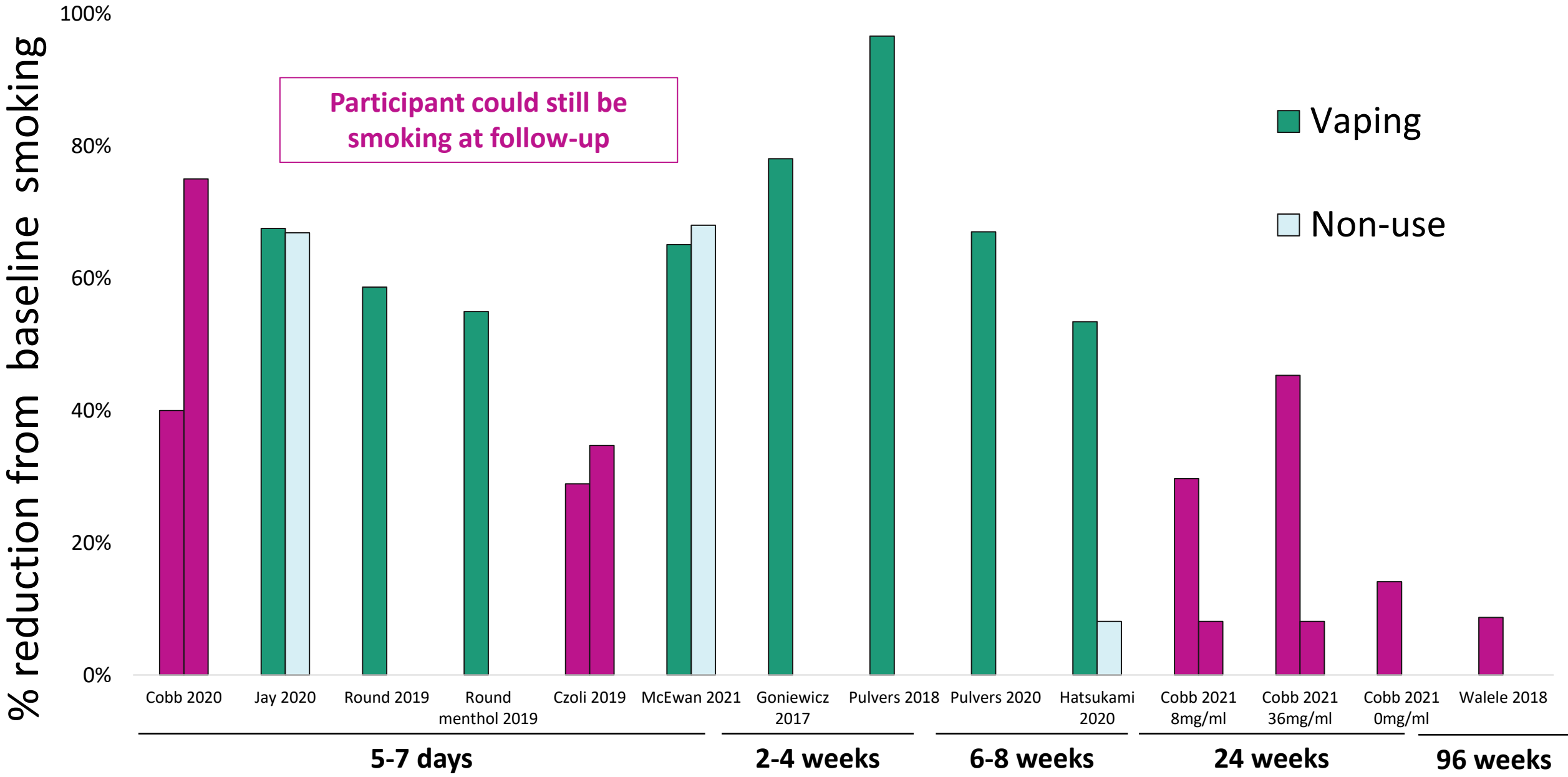
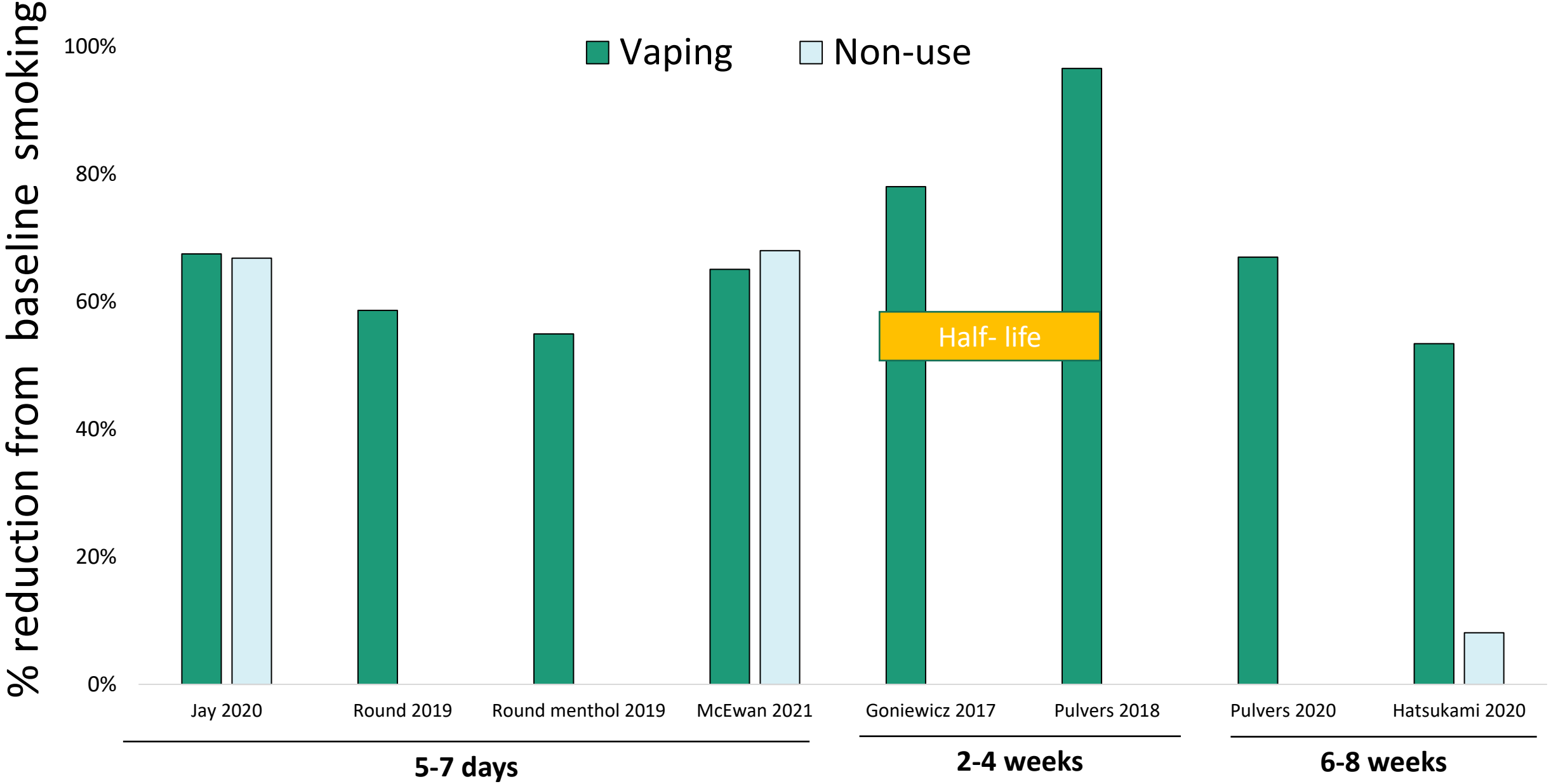


# NNK(NNAL)- longitudinal



# Summary: NNK(NNAL)

- NNAL **significantly lower** among people who **vape compared to smoke.**
- NNAL **reduces significantly** after switching to vaping, continues to fall over time.
- NNAL **significantly higher** among people who **vape compared** to people who **neither vape nor smoke.**

# Acrolein

Health effects: Carcinogen and cardiovascular effects.

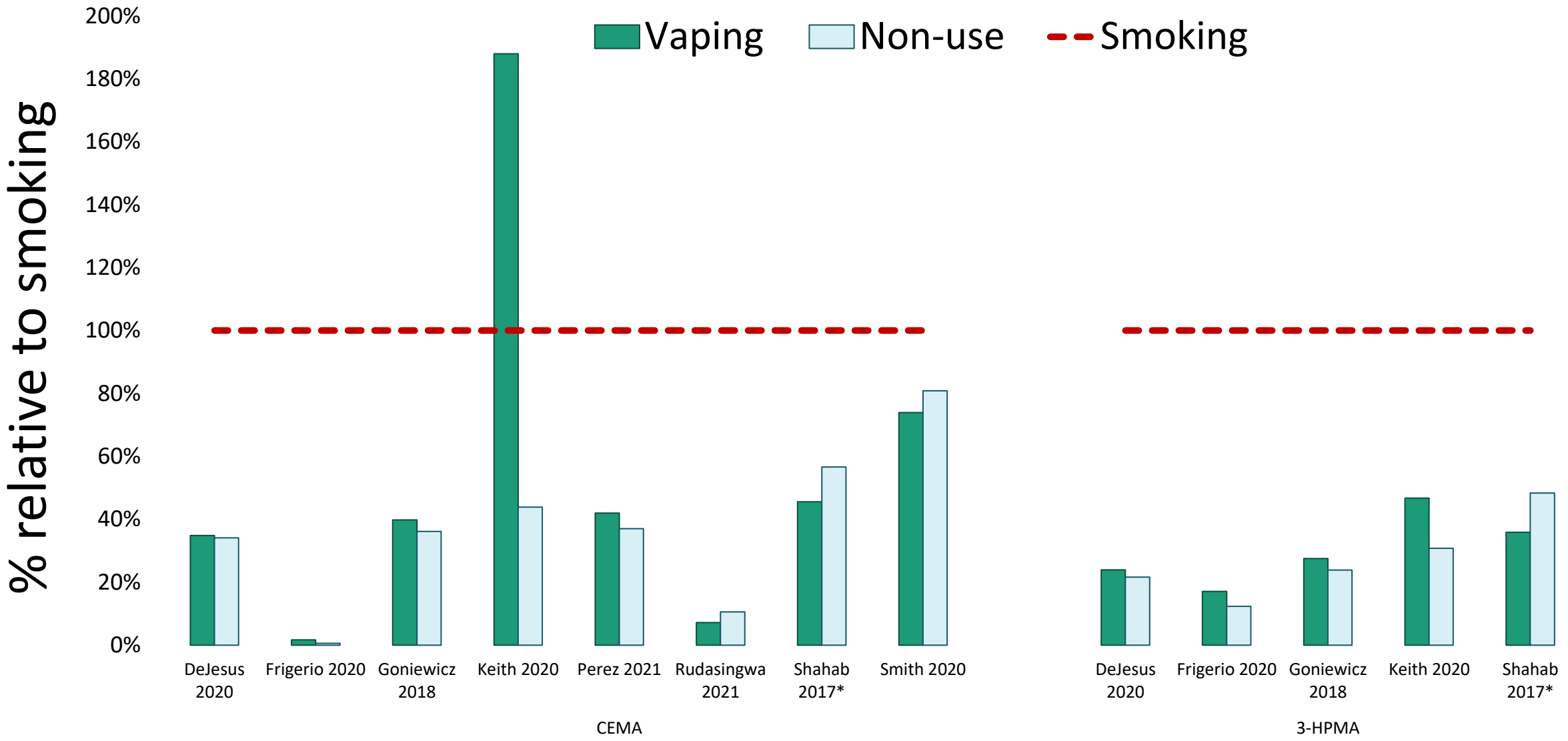
Known exposures: Tobacco smoke, fuel combustion, cooking at high temperatures, air pollution.

Half life:

3-HPMA 9 hours

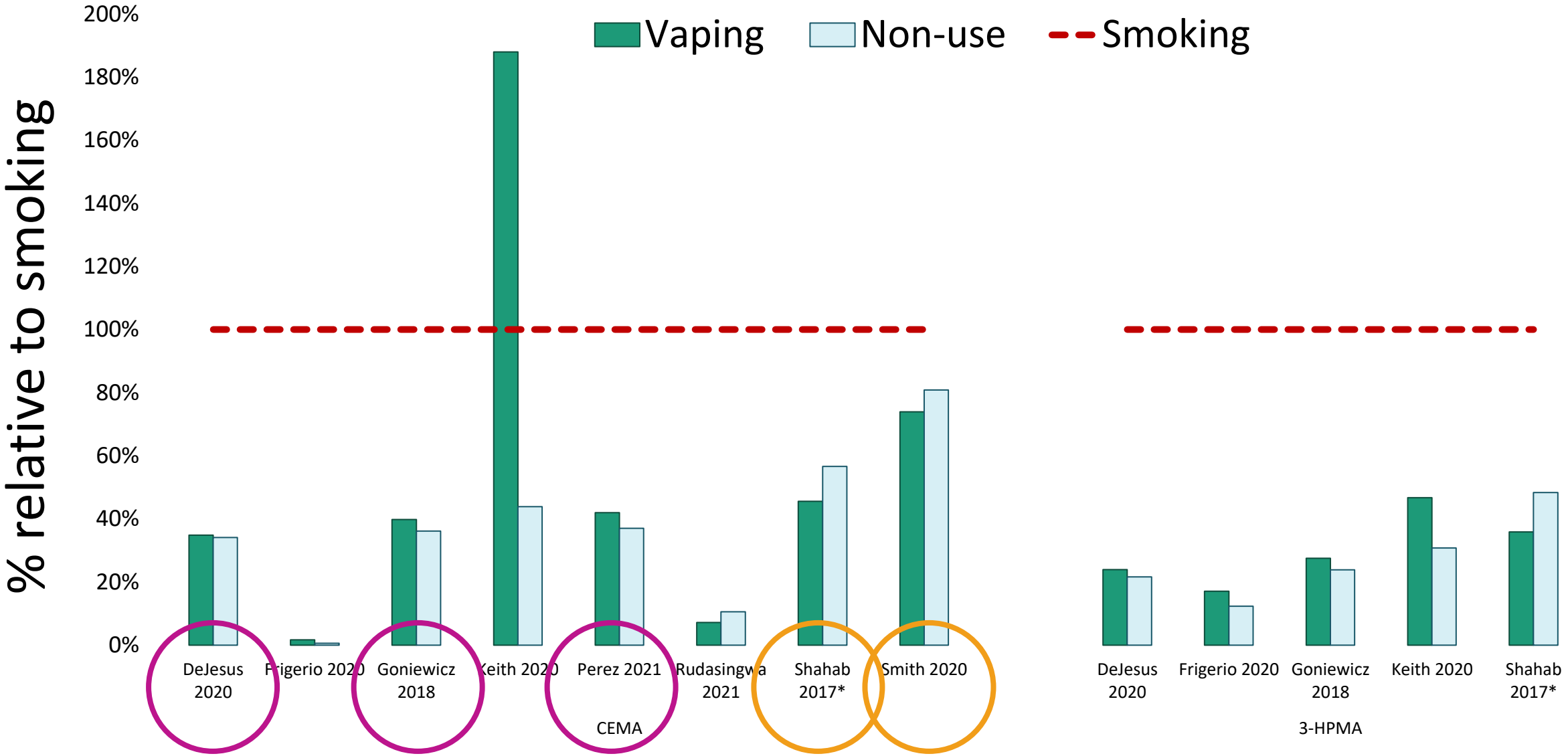
CEMA 8 hours

# Acrolein- cross-sectional



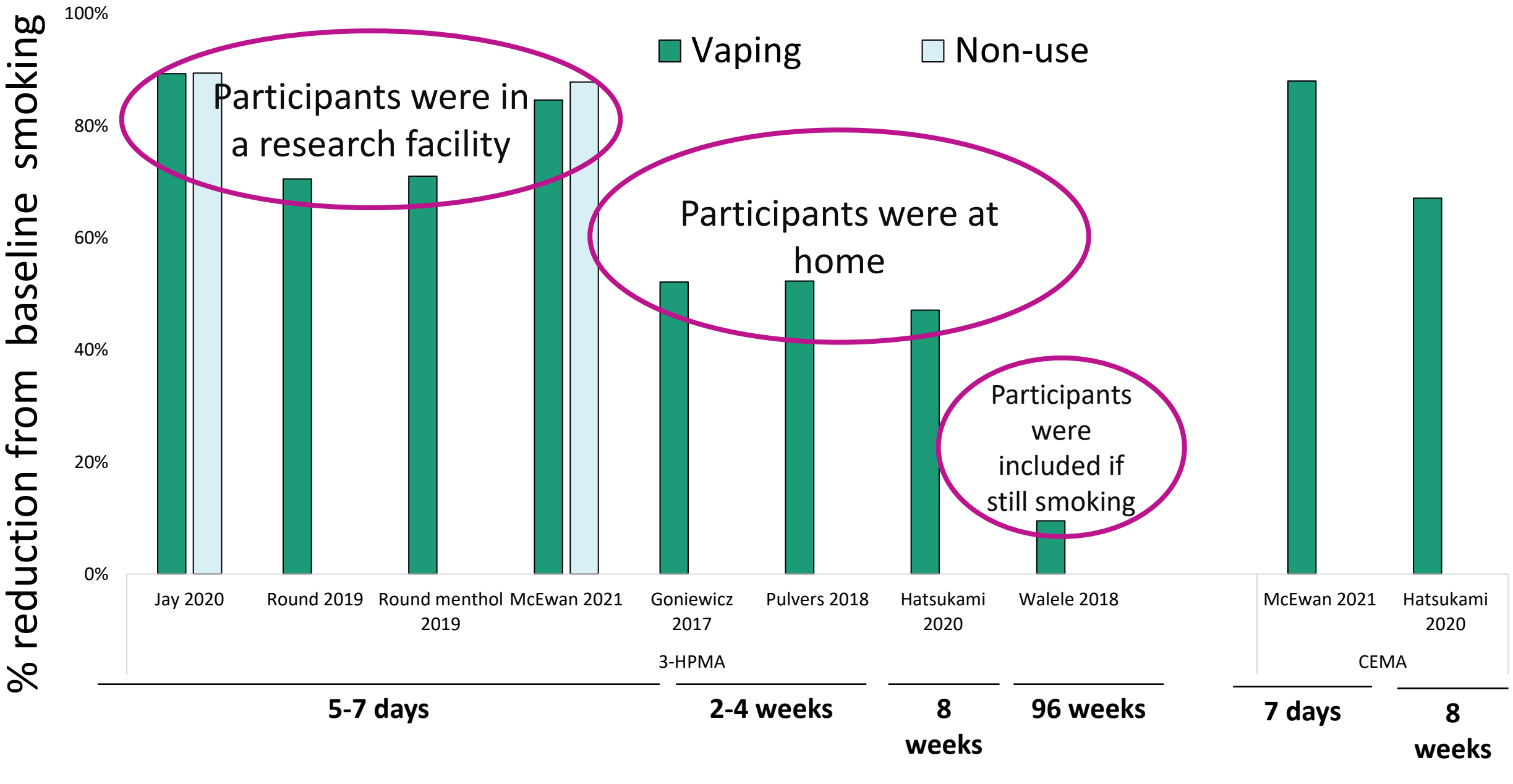

* Non-use participants were using NRT

# Acrolein- cross-sectional




* Non-use participants were using NRT

# Acrolein- longitudinal



# Summary: VOCs

- Most VOCs **significantly lower** among people who **vape compared to smoke.**
- VOCs **reduce significantly** after switching.
- Most VOCs are **similar** among people who **vape compared** to people who **neither vape nor smoke.**

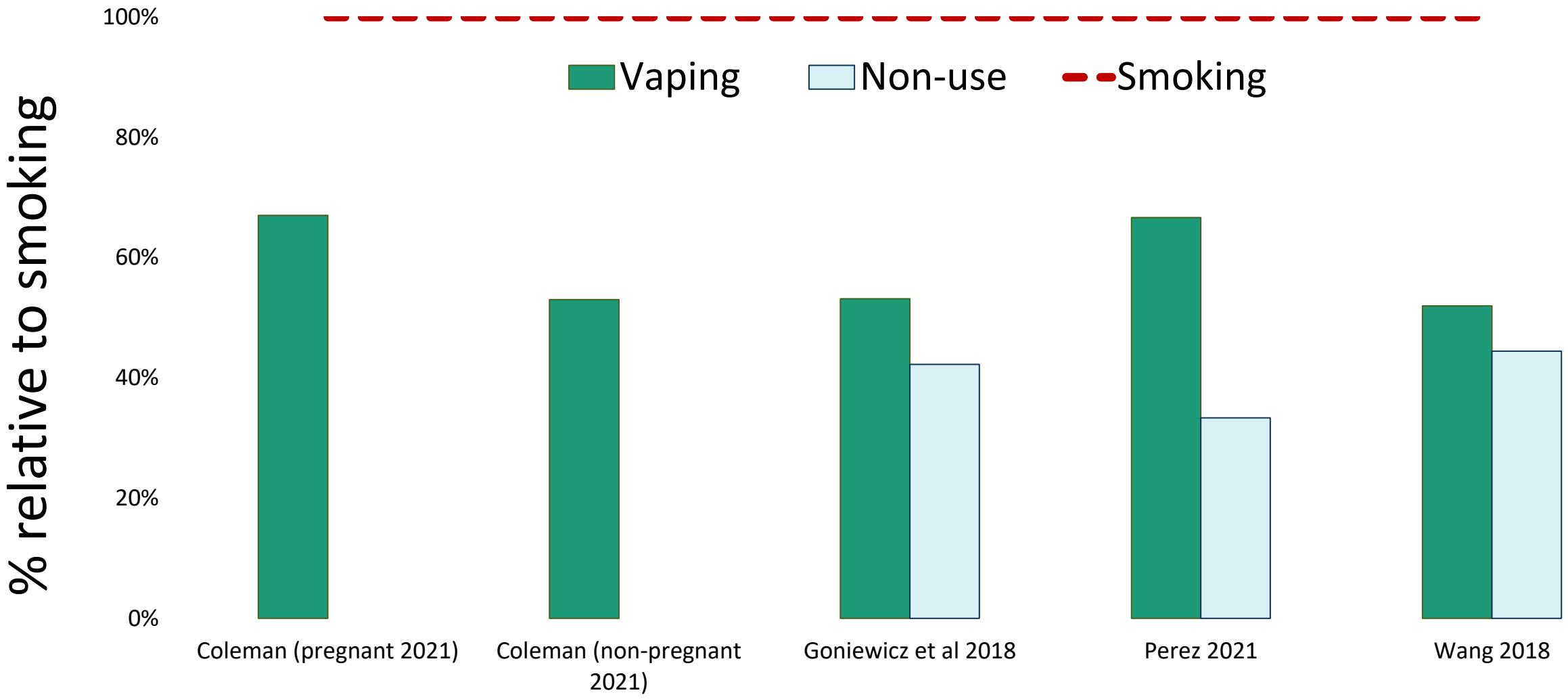
# Pyrene (1-HOP)

Health effects: Not carcinogenic itself, but marker of presence of other carcinogenic PAHs.

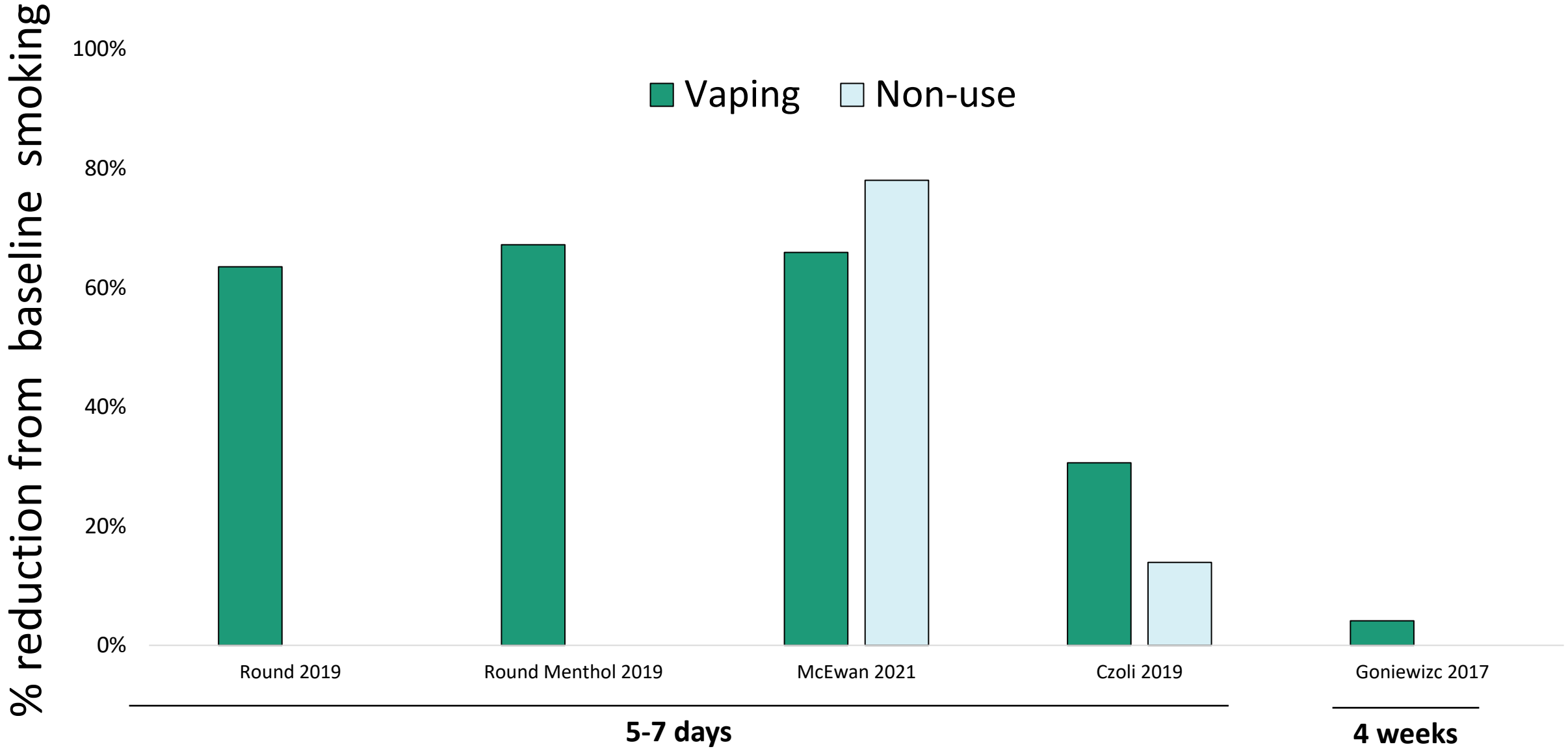
Known exposures: Tobacco curing and smoking, food, fuel combustion, industrial emissions, air pollution.

Half-life: 18-20 hours

# PAH (1-HOP)- cross-sectional



# PAH (1-HOP)- longitudinal



# Summary PAHs

- PAHs **significantly lower** among **vapers compared** to **smokers**.
- Longitudinal studies in a research facility find significant reductions after switching from smoking to vaping, other do not.
- Levels were reported to be higher among vapers compared to non-users, however **findings were not consistent**.

# Metals

Arsenic
Cadmium
Lead

Health effects: Carcinogenic, cardiovascular and respiratory effects.

Known exposures: tobacco, possibly degraded vaping components. Air, water and soil pollution.

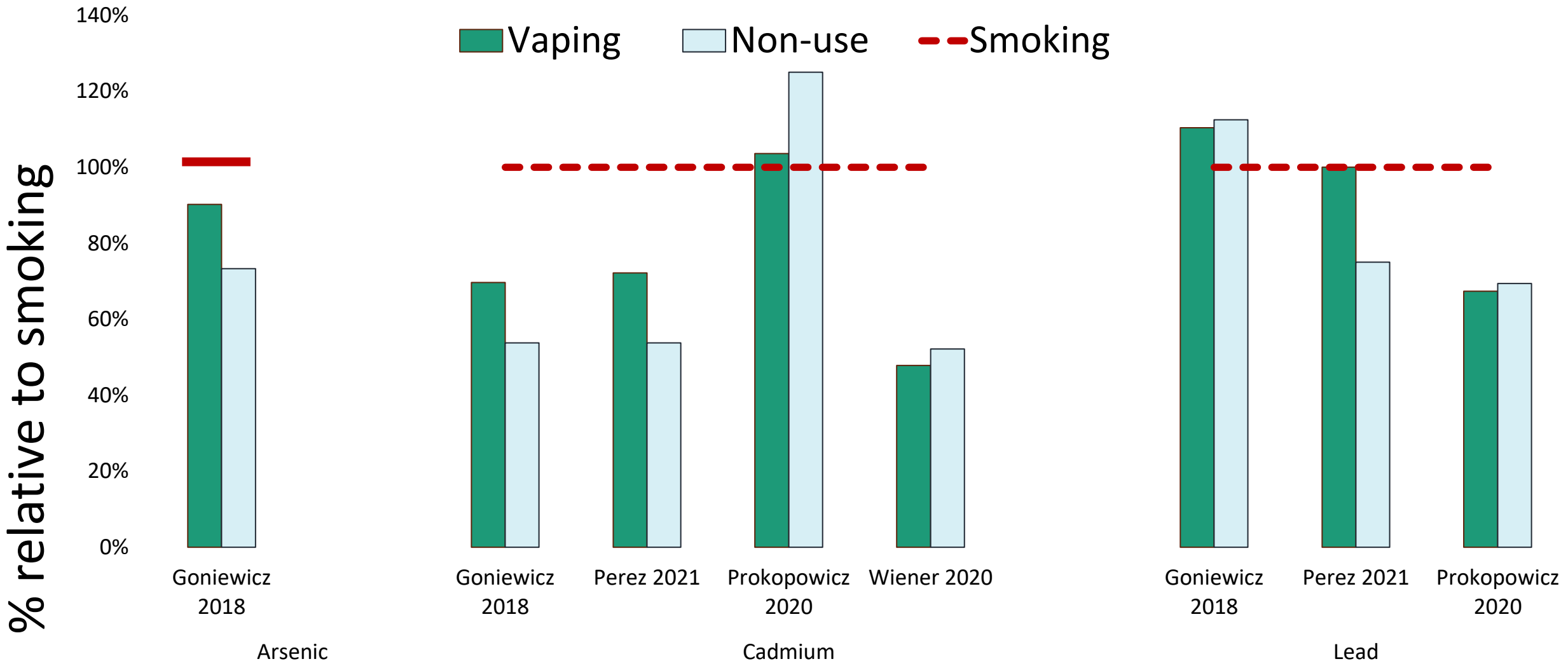
Half-life:

Arsenic  10 hours

Cadmium 13.6 years

Lead 1-2 months

# Metals – Cross-sectional



# Summary Metals

- **Similar** levels of other metals **among people who vape, smoke or do neither.**

- No longitudinal research.

| Metabolites (toxicants) | Vaping vs Smoking (relative risk) | Vaping vs Non-us (absolute risk) |
|---|---|---|
| ↓ significantly lower, ↑ significantly higher, = no significant difference, – not enough data to meta-analyse | | |
| **Tobacco-specific nitrosamines** | | |
| **NNAL (NNK)** | ↓ | ↑ |
| NNN | ↓ | – |
| NAB | ↓ | ↑ |
| NAT | ↓ | ↑ |
| **Volatile organic compounds** | | |
| AAMA (Acrylamide) | = | = |
| GAMA (Acrylamide) | ↓ | = |
| **CEMA (Acrolein)** | = | = |
| **3-HPMA (Acrolein)** | ↓ | = |
| CNEMA (Acrylonitrile) | ↓ | ↑ |
| S-PMA (Benzene) | = | = |
| MU (Benzene) | = | – |
| MHBMA (1,3-Butadiene) | ↓ | = |
| DHBMA (1,3-Butadiene) | = | = |
| HMPMA (Crotonaldehyde) | ↓ | = |
| S-BMA (Toluene) | = | = |
| **Carbon monoxide** | ↓ | – |

# Conclusions

Biomarkers of toxicant exposure were significantly lower among people who vape compared to smoke, often at similar levels to those who do not vape or smoke

Study design, control and methodology greatly impacted findings and produced heterogeneity

Many BoEs have environmental exposures, so may not be exclusively from smoking or vaping

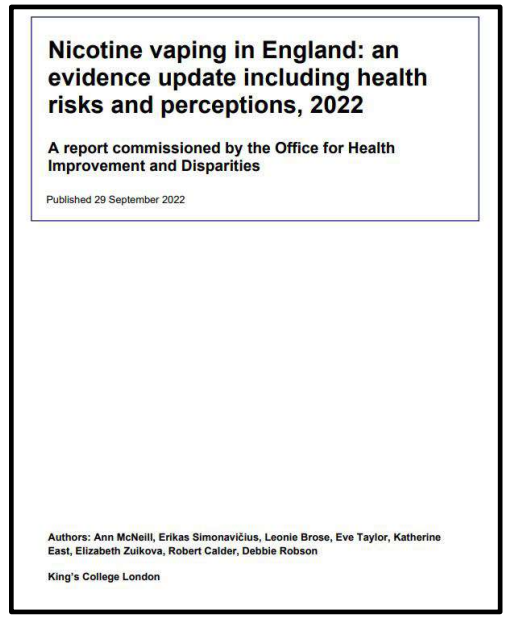
# Cancer, respiratory and cardiovascular diseases

Presenter: Dr Leonie Brose

Twitter for all presenters: @KingsNRG

# Chapters

1. Introduction
2. Methods
3. Vaping among young people
4. Vaping among adults
5. Nicotine
6. Flavours in vaping products
7. Biomarkers of exposure to nicotine and potential toxicants
8. Biomarkers of potential harm cutting across several diseases
9. **Cancers**
10. **Respiratory diseases**
11. **Cardiovascular diseases**
12. Other health outcomes
13. Poisonings, fires & explosions
14. Heated tobacco products
15. Harm perceptions & communications
16. Conclusions



# Aims

1. What effect does vaping (active and second-hand) have on the risk of getting cancers, respiratory disease and cardiovascular disease?

2. Among people with existing health conditions (as above), what are the effects of vaping on disease outcomes?

We assessed, where data were available

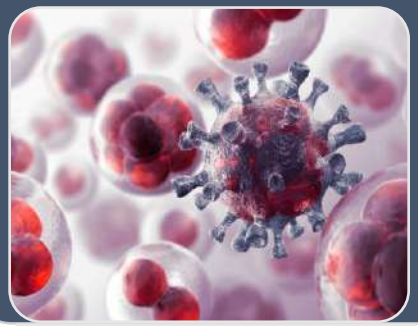
| relative risks (vaping versus smoking) | absolute risks (vaping versus non-use) |
| --- | --- |

# Outcomes

1. Biomarkers of exposure

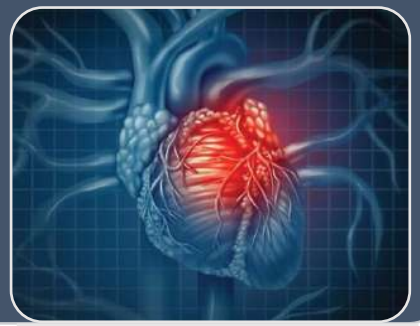
2. Biomarkers of potential harm with relevance across diseases

3. Disease-specific outcomes



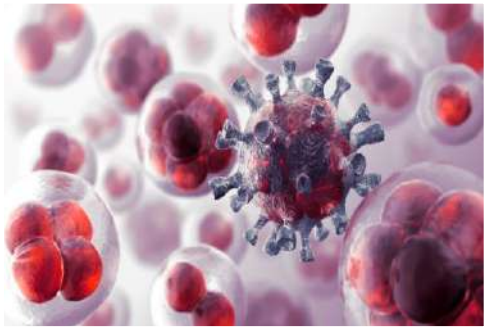
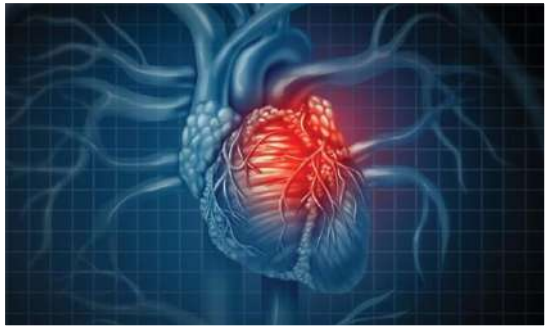
Cancers

Respiratory diseases



Cardiovascular diseases (CVD)

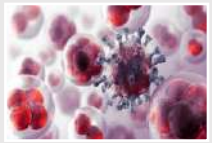
# Biomarkers of **exposure** related to specific diseases

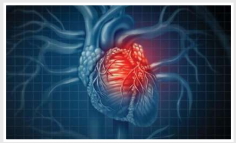
| |  **Cancer** Exposure to carcinogens |  **Respiratory disease** Exposure to related toxicants |  **Cardiovascular disease** Exposure to related toxicants |
|---|---|---|---|
| **Vaping vs smoking** | Significantly lower | Significantly lower | Significantly lower |
| **Vaping vs non use** | Similar<br>Higher for some | Similar for most | Similar |

# Biomarkers of potential harm with relevance across diseases

## Oxidative stress

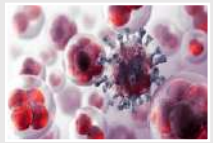
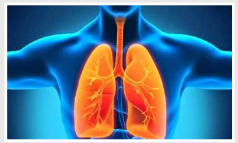
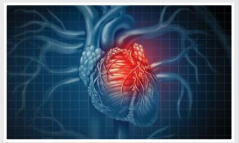
- Overpowering of anti-oxidant defences
- Associated with damage and impaired cellular function
- Examples: Oxidized low-density lipoprotein (LDL), 8-isoprostane





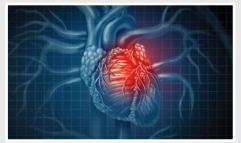
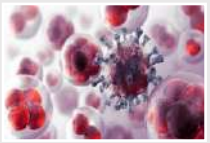
## Inflammation

- Local response to cellular injury
- Examples: C-Reactive Protein, Interleukin-6, soluble intercellular adhesion molecule (sICAM-1)

## Endothelial (dys)function

- Imbalance of vasodilating and vasoconstricting substances
- May elevate blood pressure and play a role in vascular damage
- Examples: Flow mediated dilation, microvesicles

Chang et al (2019) N&TR, https://doi.org/10.1093/ntr/ntx273
Conklin et al (2019), AJP Heart, https://doi.org/10.1152/ajpheart.00591.2018

# Number of studies in humans for biomarkers of potential harm and disease-specific outcomes

| Cross-cutting biomarkers | RCT | Cross-over | Longitudinal/ acute exposure | Cross-sectional | Total |
|---|---|---|---|---|---|
| Oxidative stress | 1 | 6 | 5 | 11 | **23** |
| Inflammation | 2 | 3 | 3 | 17 | **25** |
| Endothelial function | 1 | 4 | 3 | 1 | **9** |
| Platelet function | 0 | 1 | 1 | 2 | **4** |

| Disease-specific | RCT | Cross-over | Longitudinal/ acute exposure | Cross-sectional | Total |
|---|---|---|---|---|---|
| Cancers | 2 | 0 | 1 | 5 | **8** |
| Respiratory | 1 | 6 | 13 | 5 | **25** |
| CVD | 3 | 21 | 12 | 6 | **41** |

# Cross-cutting biomarkers - vaping vs smoking

## Oxidative stress

- LDL: no significant differences
- HDL: inconsistent findings
- 8-isoprostane: mixed findings

## Inflammation

- CRP and sICAM-1: lower among vapers in cross-sectional studies, not in all studies

## Endothelial function

- FMD: acutely similar, after 4 weeks vaping improved
- Nitric oxide bioavailability: acutely similar, but associated with length smoked

# Cross-cutting biomarkers - vaping vs non-use

## Oxidative stress

- LDL: no significant differences
- HDL: inconsistent findings
- 8-isoprostane: mixed findings

## Inflammation

- CRP: similar in cross-sectional studies, not in all studies

## Endothelial function

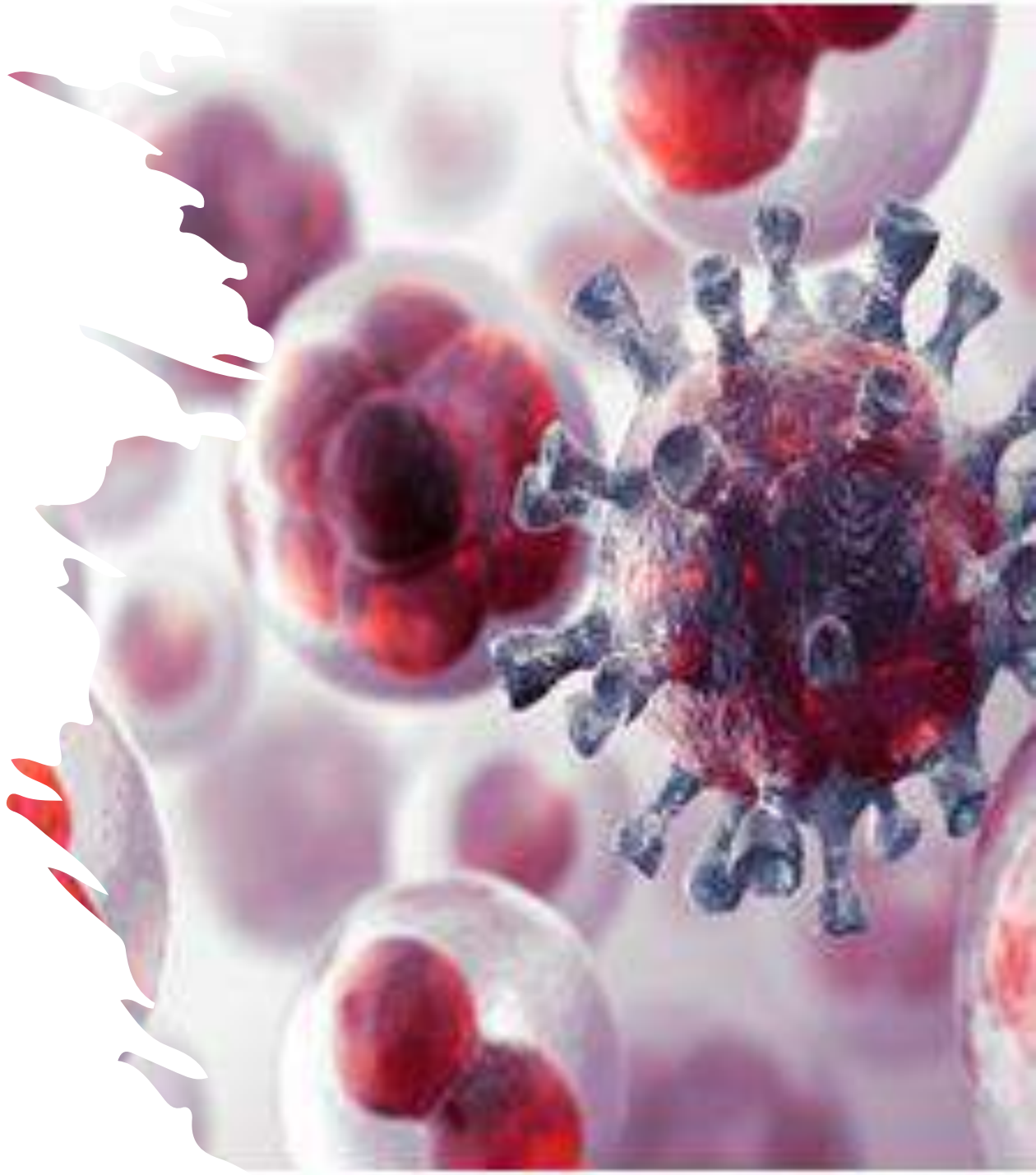
- Microvesicle levels: increased acutely after nicotine vaping

# Cross-cutting biomarkers - summary

| | |
|---|---|
| Oxidative stress | Mostly no difference between vaping and smoking or between vaping and not using tobacco or nicotine |
| Inflammation | Evidence mixed and no definite conclusions could be drawn |
| Endothelial function | Switching from smoking to vaping might improve endothelial function in the short-to-medium term |
| Platelet activation | Evidence insufficient for conclusions |

# Cancer - specific outcomes

- Gene expression and regulation, DNA methylation
- Changes that affect how genes work, e.g.
    1. Smoking leads to specific genes becoming hypermethylated
    2. Uncontrolled cellular division or failure to regulate cell cycle
    3. Cancer



# Cancer - results

## Vaping vs smoking

- Cross-sectional studies: similar or more favourable effects of vaping than smoking
- Other studies no comparison group

## Vaping vs non-use

- Vaping less favourable
- Appears to have some unique effects, separate to smoking

# Respiratory – specific outcomes

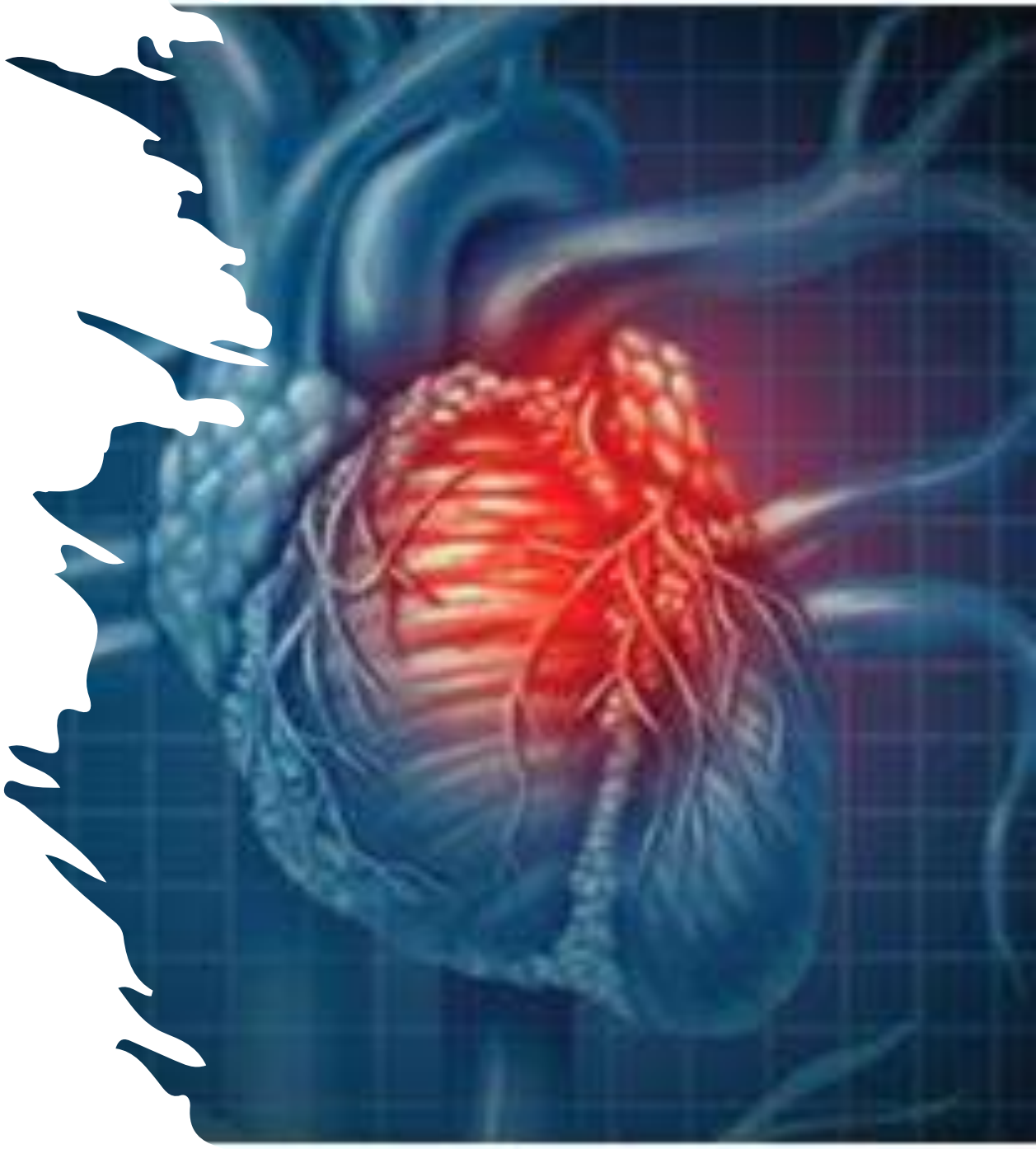
- Spirometry
  - Breath tests assessing airflow obstruction in the lungs, to detect respiratory diseases
- Fractional exhaled nitric oxide (FeNO)
  - Measured in breath, marker of airway inflammation & asthma
- Other outcomes
  - Imaging, bronchoscopies

# Respiratory

- Spirometry
  - Acute exposure
    - largely no statistically significant differences in lung function measures between nicotine vaping, non-nicotine vaping, or tobacco smoking
  - Longer-term exposures
    - Switched from smoking to vaping: 3 months – no change, 2 years, some declines (no control group, not in complete switchers)
    - People who vaped and non-users: 3.5 years follow-up, similar between groups
- FeNO
  - Findings mixed, most no significant differences across different user groups

# Cardiovascular diseases – specific outcomes

- Heart rate
- Systolic and diastolic blood pressure
- Other outcomes
  - Pulse wave velocity (Peripheral resistance / arterial stiffness)
  - Oxygen saturation

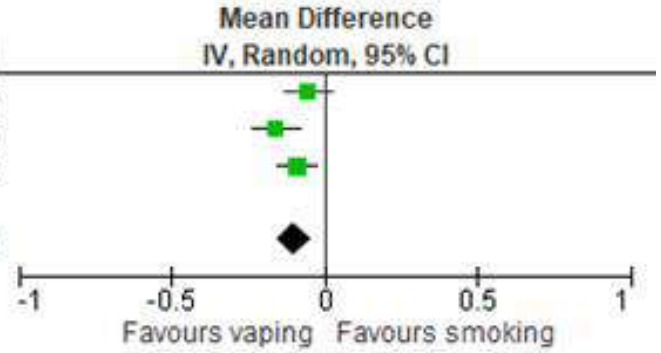


# Meta-analyses heart rate vaping vs smoking

Cross-over studies (acute exposure)

| Study or Subgroup | Vaping Mean | Vaping SD | Vaping Total | Smoking Mean | Smoking SD | Smoking Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Benowitz 2020 | 4.21521163 | 0.17051431 | 36 | 4.26870812 | 0.17250183 | 36 | 30.6% | -0.05 [-0.13, 0.03] |
| Kerr 2019 | 4.28449034 | 0.10926213 | 20 | 4.44305078 | 0.15030979 | 20 | 29.6% | -0.16 [-0.24, -0.08] |
| Maloney 2020 | 4.27785797 | 0.11806103 | 24 | 4.3661345 | 0.10331139 | 24 | 39.8% | -0.09 [-0.15, -0.03] |
| Total (95% CI) | | | 80 | | | 80 | 100.0% | -0.10 [-0.15, -0.04] |

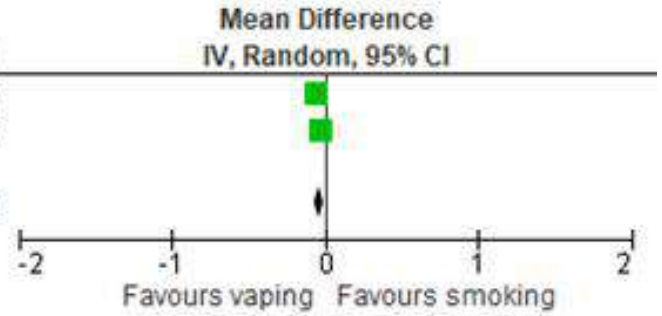
Heterogeneity: Tau² = 0.00; Chi² = 3.43, df = 2 (P = 0.18); I² = 42%
Test for overall effect: Z = 3.45 (P = 0.0006)




Cross-sectional studies (longer-term exposure)

| Study or Subgroup | Vaping Mean | Vaping SD | Vaping Total | Smoking Mean | Smoking SD | Smoking Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Boas 2017 | 4.1116073 | 0.04253395 | 9 | 4.16527781 | 0.05267662 | 9 | 50.8% | -0.05 [-0.10, -0.01] |
| Fetterman 2020 | 4.15113099 | 0.12451581 | 36 | 4.17595525 | 0.16552635 | 285 | 49.2% | -0.02 [-0.07, 0.02] |
| Total (95% CI) | | | 45 | | | 294 | 100.0% | -0.04 [-0.07, -0.01] |

Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 2.45 (P = 0.01)



# Cardiovascular Diseases – vaping vs smoking

## Heart rate

- Acutely, less increase
- Longer-term, lower among those who vaped than those who smoked

## Blood pressure

- Acutely, no differences in meta-analysis, other studies mixed results
- Longer-term, lower among those who vaped

# Cardiovascular Diseases – vaping vs non-use

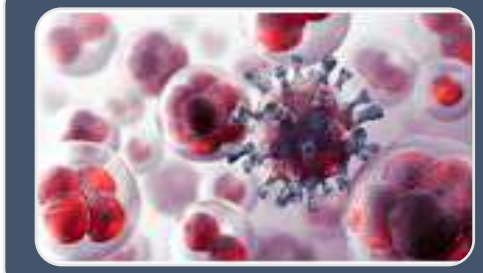
## Heart rate

- Acutely, similar
- Longer-term, lower in meta-analysis, higher in some other studies

## Blood pressure

- Acutely, no difference
- **Longer-term,** only difference for diastolic in cross-sectional studies

# People with existing health conditions



No studies

Asthma: 4 studies - vaping may negatively affect lung function

COPD and smoking: 2 publications from 1 study - switching to vaping may reduce COPD exacerbations

No studies

No studies on clinical outcomes

# Second-hand exposure

## 6 studies overall

- 2 studies exposed people to atypically high levels of vaping emissions
- Lack of second-hand smoking exposure for comparison

## Biomarkers of exposure

- Acute second-hand exposure to vaping aerosol resulted in non-significant changes
- Longer exposure associated with increases

## Biomarkers of potential harm

- Only 2 studies, both at serious risk of bias
- No conclusions can be drawn

# Summary and reflections

Vaping poses only a small fraction of the risks of smoking in the short to medium term

Vaping is not risk-free, particularly for people who have never smoked

And long-term health risks?

- Longest study covered 5-year period; longest UK study had 2-year follow-up
- However, based on substantially lower levels of toxicants of exposure and no major causes of concern for biomarkers of potential harm, we are confident that vaping also poses a fraction of the risk of smoking in long-term
- But we need more long-term studies

KING'S College LONDON

# Methodological limitations and recommendations when assessing vaping effects on health biomarkers

*Presenter:*

*Dr Erikas Simonavičius*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# Chapters

1. Introduction
2. Methods
3. Vaping among young people
4. Vaping among adults
5. Nicotine
6. Flavours in vaping products
7. **Biomarkers of exposure to nicotine and potential toxicants**
8. **Biomarkers of potential harm cutting across several diseases**
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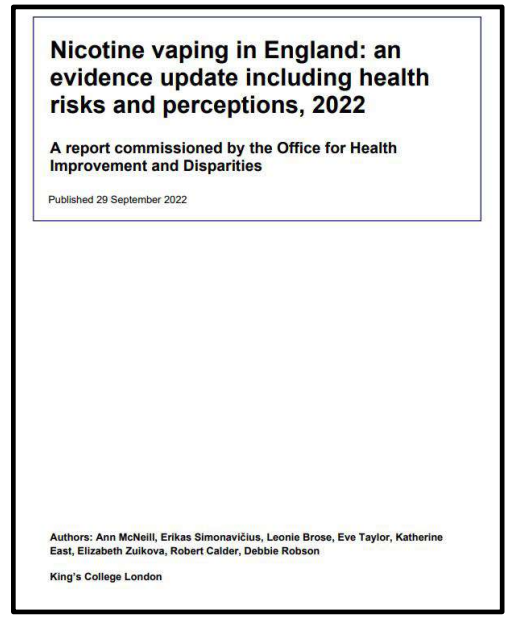
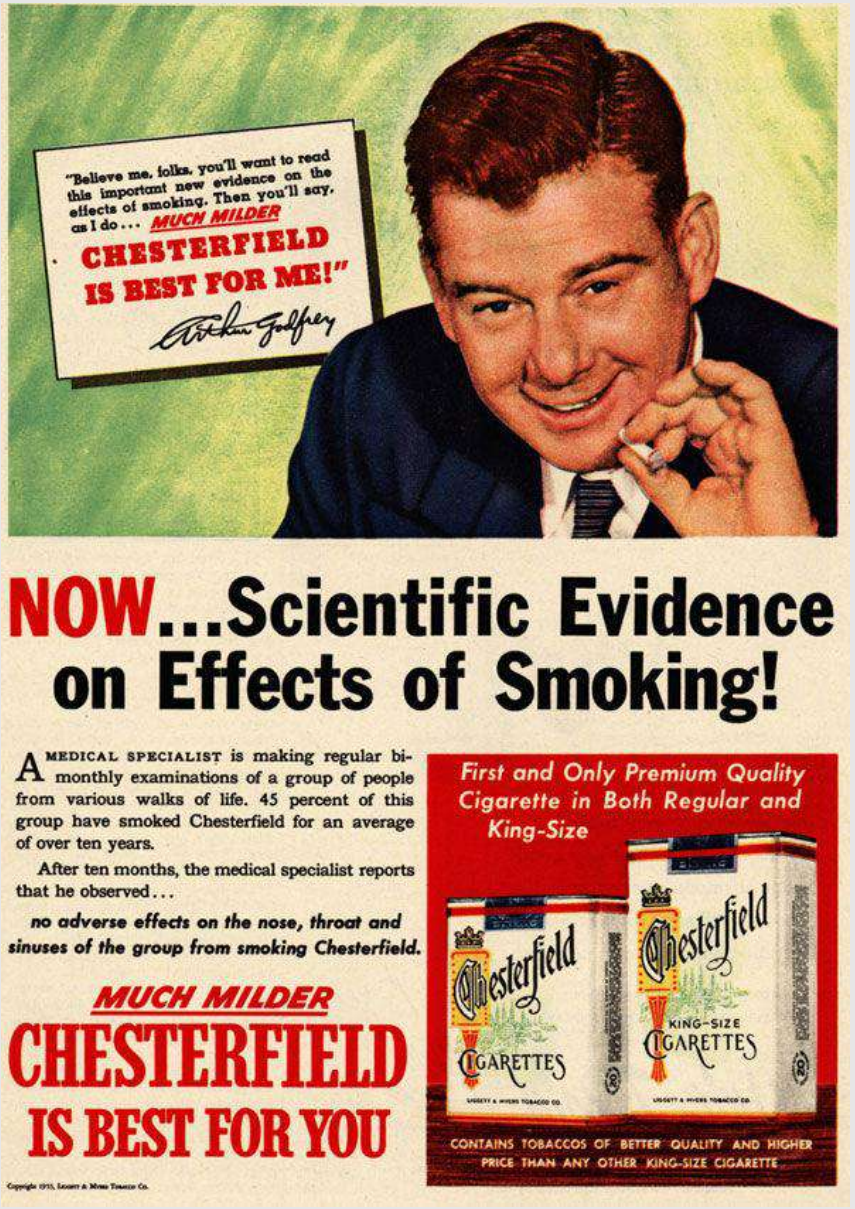
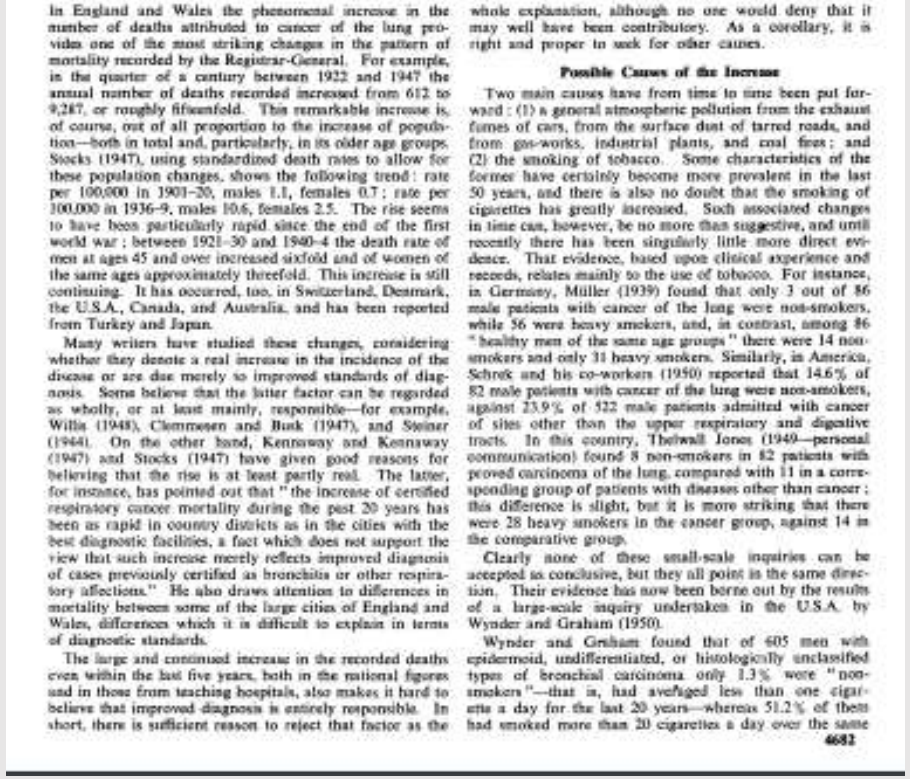


# Years to prove harmful health effects of smoking



BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 30 1950

## SMOKING AND CARCINOMA OF THE LUNG

PRELIMINARY REPORT

BY

RICHARD DOLL, M.D., M.R.C.P.

*Member of the Statistical Research Unit of the Medical Research Council*

AND

A. BRADFORD HILL, Ph.D., D.Sc.

*Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council*

In England and Wales the phenomenal increase in the number of deaths attributed to cancer of the lung provides one of the most striking changes in the pattern of mortality recorded by the Registrar-General. For example, in the quarter of a century between 1922 and 1947 the annual number of deaths recorded increased from 612 to 9,287, or roughly fifteenfold. This remarkable increase is, of course, out of all proportion to the increase of population—both in total and, particularly, in its older age groups. Stocks (1947), using standardized death rates to allow for these population changes, shows the following trend: rate per 100,000 in 1901–20, males 1.1, females 0.7; rate per 100,000 in 1936–9, males 10.6, females 2.5. The rise seems to have been particularly rapid since the end of the first world war; between 1921–30 and 1940–4 the death rate of men at ages 45 and over increased sixfold and of women of the same ages approximately threefold. This increase is still continuing. It has occurred, too, in Switzerland, Denmark, the U.S.A., Canada, and Australia, and has been reported from Turkey and Japan.

Many writers have studied these changes, considering whether they denote a real increase in the incidence of the disease or are due merely to improved standards of diagnosis. Some believe that the latter factor can be regarded as wholly, or at least mainly, responsible—for example, Willis (1948), Clemmesen and Busk (1947), and Steiner (1944). On the other hand, Kennaway and Kennaway (1947) and Stocks (1947) have given good reasons for believing that the rise is at least partly real. The latter, for instance, has pointed out that "the increase of certified respiratory cancer mortality during the past 20 years has been as rapid in country districts as in the cities with the best diagnostic facilities, a fact which does not support the view that such increase merely reflects improved diagnosis of cases previously certified as bronchitis or other respiratory affections." He also draws attention to differences in mortality between some of the large cities of England and Wales, differences which it is difficult to explain in terms of diagnostic standards.

The large and continued increase in the recorded deaths even within the last five years, both in the national figures and in those from teaching hospitals, also makes it hard to believe that improved diagnosis is entirely responsible. In short, there is sufficient reason to reject that factor as the whole explanation, although no one would deny that it may well have been contributory. As a corollary, it is right and proper to seek for other causes.

### Possible Causes of the Increase

Two main causes have from time to time been put forward: (1) a general atmospheric pollution from the exhaust fumes of cars, from the surface dust of tarred roads, and from gas-works, industrial plants, and coal fires; and (2) the smoking of tobacco. Some characteristics of the former have certainly become more prevalent in the last 50 years, and there is also no doubt that the smoking of cigarettes has greatly increased. Such associated changes in time can, however, be no more than suggestive, and until recently there has been singularly little more direct evidence. That evidence, based upon clinical experience and records, relates mainly to the use of tobacco. For instance, in Germany, Müller (1939) found that only 3 out of 86 male patients with cancer of the lung were non-smokers, while 56 were heavy smokers, and, in contrast, among 86 "healthy men of the same age groups" there were 14 non-smokers and only 31 heavy smokers. Similarly, in America, Schrek and his co-workers (1950) reported that 14.6% of 82 male patients with cancer of the lung were non-smokers, against 23.9% of 522 male patients admitted with cancer of sites other than the upper respiratory and digestive tracts. In this country, Thelwall Jones (1949—personal communication) found 8 non-smokers in 82 patients with proved carcinoma of the lung, compared with 11 in a corresponding group of patients with diseases other than cancer; this difference is slight, but it is more striking that there were 28 heavy smokers in the cancer group, against 14 in the comparative group.

Clearly none of these small-scale inquiries can be accepted as conclusive, but they all point in the same direction. Their evidence has now been borne out by the results of a large-scale inquiry undertaken in the U.S.A. by Wynder and Graham (1950).

Wynder and Graham found that of 605 men with epidermoid, undifferentiated, or histologically unclassified types of bronchial carcinoma only 1.3% were "non-smokers"—that is, had averaged less than one cigarette a day for the last 20 years—whereas 51.2% of them had smoked more than 20 cigarettes a day over the same

Public Health England

Protecting and improving the nation's health

## E-cigarettes: an evidence update

A report commissioned by Public Health England


**Authors:**

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UK Centre for Tobacco & Alcohol Studies

**Hajek P, McRobbie H (Chapters 9 and 10)**
Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry Queen Mary, University of London
UK Centre for Tobacco & Alcohol Studies


UKCTAS Queen Mary University of London KING'S College LONDON

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Public Health England

Protecting and improving the nation's health

## Evidence review of e-cigarettes and heated tobacco products 2018

A report commissioned by Public Health England


**Authors:**

**Ann McNeill[1,2], Leonie S Brose[1,2], Robert Calder[1], Linda Bauld[2,3,4], Debbie Robson[1,2]**

[1] King's College London
[2] UK Centre for Tobacco & Alcohol Studies
[3] University of Stirling
[4] Cancer Research UK


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Public Health England

Protecting and improving the nation's health

## Vaping in England: an evidence update February 2019

A report commissioned by Public Health England


**Authors:**

**Ann McNeill[1], Leonie S Brose[1], Robert Calder[1], Linda Bauld[2,3], Debbie Robson[1]**

[1] King's College London
[2] University of Edinburgh
[3] Cancer Research UK


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## 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)**

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Public Health England

Protecting and improving the nation's health

## Vaping in England: an evidence update including mental health and pregnancy, March 2020

A report commissioned by Public Health England


Authors: Ann McNeill[1], Leonie Brose[1], Robert Calder[1], Linda Bauld[2,3], Debbie Robson[1]

[1] King's College London
[2] University of Edinburgh
[3] Cancer Research UK


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Public Health England

## Vaping in England: an evidence update including vaping for smoking cessation, February 2021

A report commissioned by Public Health England


Authors

Ann McNeill, Leonie Brose, Robert Calder, Erikas Simonavicius, Debbie Robson
King's College London


KING'S College LONDON

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**CONSENSUS STUDY REPORT**

## Public Health Consequences of E-Cigarettes

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## Nicotine vaping in England: an evidence update including health risks and perceptions, 2022

**A report commissioned by the Office for Health Improvement and Disparities**

Published 29 September 2022


**Authors: Ann McNeill, Erikas Simonavičius, Leonie Brose, Eve Taylor, Katherine East, Elizabeth Zuikova, Robert Calder, Debbie Robson**

**King's College London**

# Aims

1. Present and illustrate common limitations of vaping biomarker research

2. Provide recommendations for future studies that will explore vaping health risks using biomarkers

# Approaches in assessing health risks of vaping

- Theoretical assumptions
  - No tobacco and no combustion in electronic cigarettes

- Non-human studies[2]
  - Animal and cell studies
  - Laboratory studies assessing vaping emissions

- Human studies
  - Health outcomes in e-cigarette users compared with smokers and non-users
  - Smokers who stop smoking and continue vaping *vs* Smokers who stop smoking
  - Assessing biomarkers of exposure to toxicants and other compounds
  - Assessing biomarkers of potential and actual harm

*2 McNeill et al., 2018. Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by public health England.*

# Biomarkers of exposure to toxicants and other compounds (BoE)

- Measurements of changes in toxicant or their metabolite levels in the body after exposure to tobacco or nicotine products

- Exposure to toxicants and other compounds is associated with developing diseases
- Established lists of tobacco-associated toxicants and other compounds
  - Hoffman and Hecht list[3]
  - Health Canada list[4]
  - US Food & Drug Administration's (FDA) established list of harmful and potentially harmful constituents (HPHC) in tobacco products and tobacco smoke[6]
  - World Health Organisation (WHO) priority toxicant list[5]

*3 Hoffmann & Hecht, 1990. Chemical carcinogenesis and mutagenesis I (pp. 63-102). Springer, Berlin, Heidelberg.*
*4 Hammond & O'Connor, 2008. Tob. Control, 17(Suppl 1), i24-i31.*
*5 WHO TobReg study group (2019). Report on the scientific basis of tobacco product regulation: 7th report of a WHO study group*
*6 US Food & Drug Administration (2012). Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke: Established List.*

# Biomarkers of potential harm to health (BoPH)

- Measurements of biological effects in the body after exposure to tobacco or nicotine products

1) Disease-specific (*e.g., heart rate, FeNO*)
2) Cutting across multiple diseases (*e.g., inflammation, oxidative stress*)

- Multiple pre-clinical BoPH, but no clear categorisation
- We used BoPH from FDA-sponsored public workshop[7]

*7 Chang et al., 2017. Cancer Epidemiol. Biomark. Prev., 26(3), 291-302.*

# Methods of systematic review

- >100 human studies published between August 2017 and July 2021

- Comparison groups
  1) Vaping
  2) Smoking [*Relative risk*]
  3) No use [*Absolute risk*]

- Groups of study designs
  1) Cross-sectional
  2) Longitudinal (*e.g., cross-over, cohort studies and RCTs*)

- Exposure length
  1) Acute: *from single use up to 7 days*
  2) Short-to-medium term: *from 8 days to 12 months*
  3) Long-term: *more than 12 months*

- Algorithm for meta-analyses

# Biomarkers of exposure studies (1)

I. Studies on BoE use lists of tobacco-associated toxicants

- Tobacco cigarettes and vaping devices are different products
- E.g., WHO list includes only 4 metals (*arsenic, cadmium, lead, mercury*) while some included studies[8] reported levels of multiple other metals (*e.g., chromium, nickel, cobalt, vanadium, barium, indium, silver, manganese, barium, strontium, antimony*)

*8 Prokopowicz et al., 2020. Int. J. Environ. Res. Public Health, 17(6), 1877.*

# Biomarkers of exposure studies (2)

II. Some toxicants have a few metabolites with different characteristics

| Metabolites (*toxicants*) | Vaping vs Smoking | Characteristics |
|---|---|---|
| **Volatile organic compounds** | | |
| AAMA (Acrylamide) | = | $t_{1/2}$: 11-17.4 hours[9] |
| GAMA (Acrylamide) | ↓ | $t_{1/2}$: 19-25.1 hours[9] |
| CEMA (Acrolein) | = | $t_{1/2}$: 8 hours[10] |
| 3-HPMA (Acrolein) | ↓ | $t_{1/2}$: 9 hours[11] |

*9 Goniewicz et al., 2018. JAMA Netw Open 1: e185937.*
*10 Jakubowski et al., 1987. Occup. Environ. Med. 44: 834-840.*
*11 St. Helen et al., 2020. Cancer Prev. Res. (Phila.) 13: 153-162.*

# Biomarkers of exposure studies (3)

III. Sensitivity of toxicants' biomarkers (*e.g., MHBMA more sensitive than DHBMA for 1,3-Butadiene*[14])

IV. Toxicants might not have a reliable biomarker (*e.g., formaldehyde & acetaldehyde*)

V. Different measurements of biomarkers

- Biosamples (*urine, blood, saliva, hair, etc.*)
- Sample preparation techniques
- Analytical methods (*gas and liquid chromatography coupled with mass spectrometry (GC-MS, GC-MS/MS and LC-MS/MS), thermal energy analyser (TEA)*[12], *enzyme-linked immunosorbent assays (ELISAs)*[13])

*12 Habibagahi et al., 2020. Anal. Methods, 12(35), 4276-4302.*
*13 Bjercke et al., 1986. J. Immunol. Methods, 90(2), 203-213.*
*14 Chen & Zhang, 2022. Genes Environ. 44(1), 1-22.*

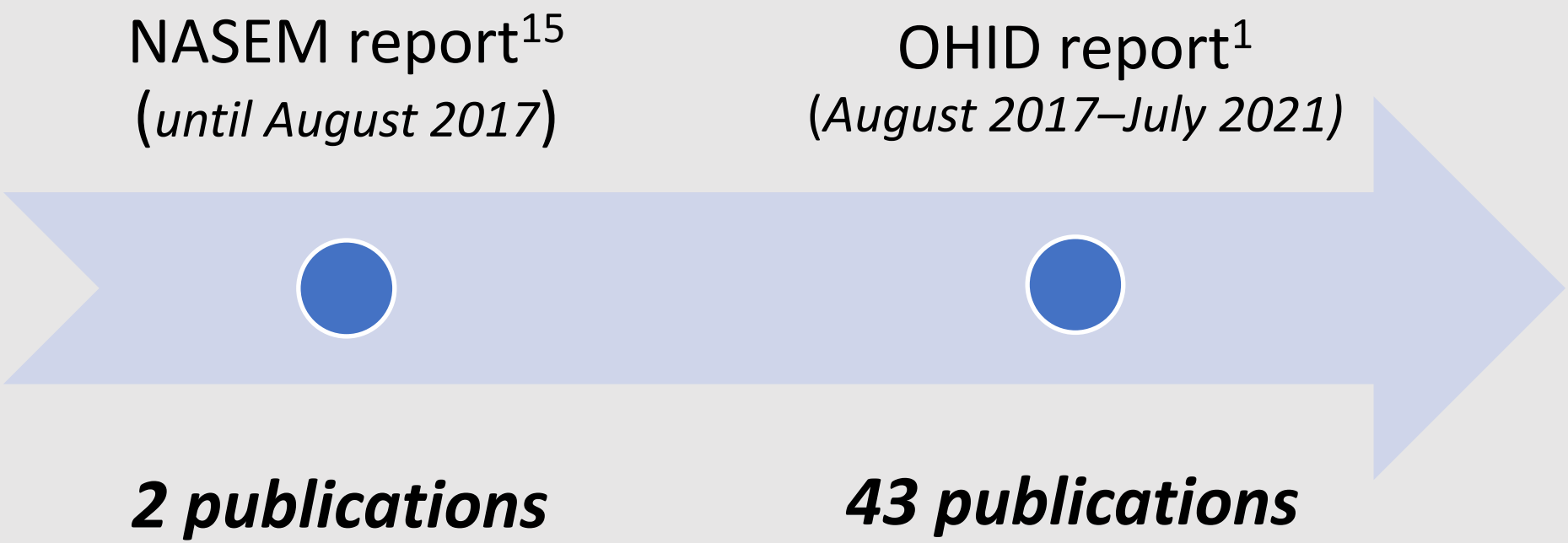
# Biomarkers of exposure studies (4)

## VI. Half-life of biomarkers and length of study follow-up

- NNAL $t_{1/2}$: 10.3 days[9]
- Most metals take months to years to leave human body


*9 Goniewicz et al., 2018. JAMA Netw Open 1: e185937.*

# Biomarkers of potential harm studies (1)




*1 McNeill et al., 2022. Nicotine vaping in England: an evidence update including health risks and perceptions, 2022.*
*15 National Academies of Sciences, Engineering, and Medicine, 2018. Public health consequences of e-cigarettes.*

# Biomarkers of potential harm studies (2)

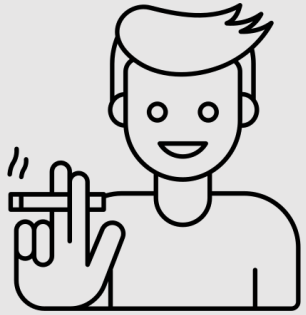
- Sensitivity and validity of biomarkers is not clear
  - Prior research limited to changes after stopping smoking, and it typically takes months to years to normalise after stopping smoking
  - Small sample sizes and lack of control groups (*i.e., non-users*)
  - Confounding (*age, gender, diet, genetics, physical activity*)
  - Associations with diseases often contested
    - *'Single biomarker is unlikely to provide all the information needed'*[16]

*16 Peck et al., 2018. Biomarkers, 23(3), 213-244.*

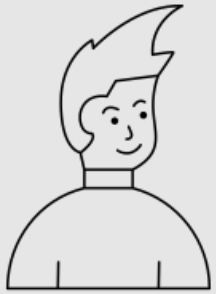
# Things to address in future biomarkers' research (1)

- Definitions of users' groups (*e.g., concurrent/dual users of nicotine and tobacco products*)

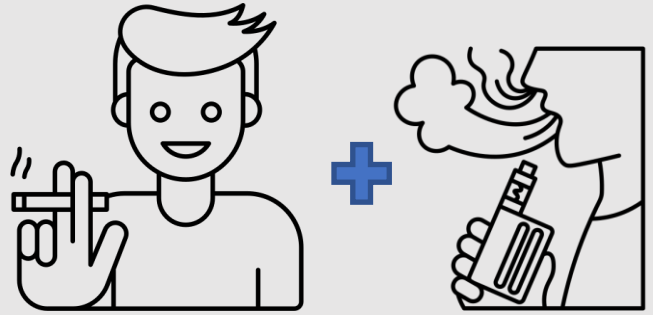
*Vaping*



*Smoking*



*Non-use*



*Concurrent use*

- Environmental and lifestyle confounding, including past smoking history

# Things to address in future biomarkers' research (2)

- Research designs, their benefits and limitations

| Study design | Benefits | Limitations |
|---|---|---|
| **Cross-sectional studies** | • Real-world use accounting for environmental exposure<br>• Large sample sizes | • Definitions<br>• Different (poly)use patterns |
| **Cohort studies** | • Longitudinal changes in real-world settings | • Poly-use, relapses & attrition<br>• Follow-up lengths |
| **Cross-over studies** | • Precise measurements of changes accounting for past use | • Usually acute exposures<br>• Washout periods too short |
| **Randomised controlled trials** | • Precise measurements of changes due to specific exposures | • Do not account for environmental confounders<br>• Non-realistic use of products |

# Future of assessing health risks of vaping

- Standardise methods to study biomarkers (*definitions, interventions, outcomes, measurements, etc.*)
- Address confounding (*bio-verification of smoking, account for environmental and lifestyle confounders*)
- Sensitive, reliable and clinically relevant biomarkers of potential harm should be explored with larger samples, including non-users, and longer follow-ups
- **Address a research gap on vaping among people with most common diseases and how vaping affects progression of these diseases**

# Government-commissioned evidence updates

**2015**
E-cigarettes: an evidence review

**2018**
Evidence review of EC & HTP

Focus on cessation and health risks

**2019**
Vaping in England

Focus on SE indicators

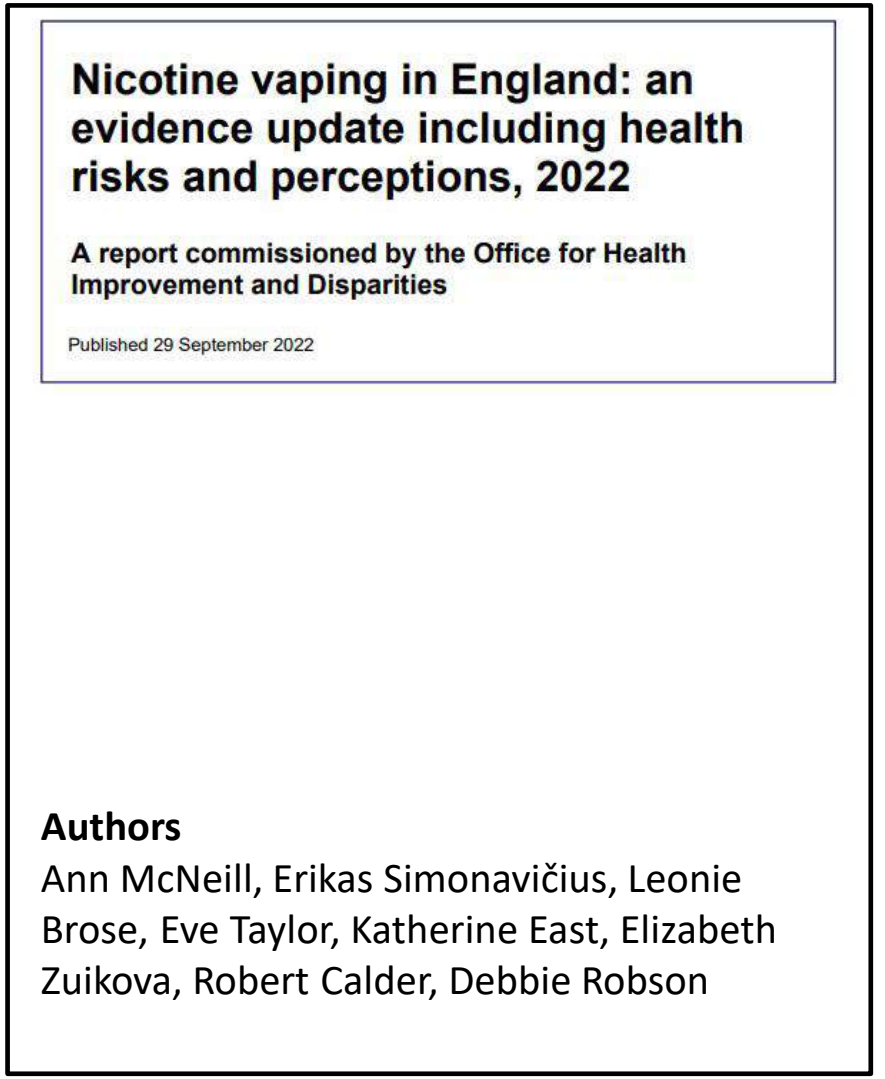
**2020**
Vaping in England

Focus on mental health & pregnancy

**2021**
Vaping in England

Focus on smoking cessation

**2022**



**Nicotine vaping in England: an evidence update including health risks and perceptions, 2022**

**A report commissioned by the Office for Health Improvement and Disparities**

Published 29 September 2022

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# 2023 Annual SRNT-E Conference

## London

11 - 13 Sept 2023

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| Chair of the Scientific Committee | Chair of the Local Organising Committee | Abstract submission | Details |
|---|---|---|---|
| Dr Sharon Cox<br>UCL | Dr Leonie Brose<br>King's College London | From late January | srnt-e.org |