

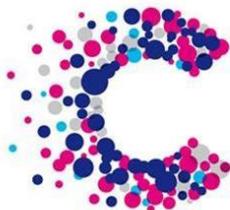
# Cochrane Review on Heated Tobacco: Safety, Effectiveness and Population-level impact

**Harry Tattan-Birch**

*UCL Tobacco and Alcohol Research Group*

*Department of Behavioural Science and Health*

*University College London*



CANCER  
RESEARCH  
UK



Office for Health  
Improvement  
& Disparities

[Full paper](#) published in Cochrane Library:



**Cochrane**  
**Library**

Cochrane Database of Systematic Reviews

## Heated tobacco products for smoking cessation and reducing smoking prevalence (Review)

Tattan-Birch H, Hartmann-Boyce J, Kock L, Simonavicius E, Brose L, Jackson S, Shahab L, Brown J

**1. Our aims**

**2. What we found**

**3. The results**

# **1. Our aims**

- As Tianze discussed, heated tobacco use has grown globally.
- Some people report using heated tobacco as way to help them stop smoking conventional cigarettes. Clinicians need to know what advice to give these people.
- Need to know (1) their **effectiveness** at helping people quit and (2) are **safety/harmfulness** relative to cigarette smoking or no nicotine use.
- Most of the data on these two aims comes from clinical trials. This doesn't reflect the way most people use the product...

- Thus, we also need to understand (3) the population-level **impact** of these products on smoking prevalence.
- To understand the population-level impact, studies must look at what happened to cigarette smoking prevalence and cigarette sales after heated tobacco was introduced, or how prevalence/sales changed as heated tobacco became more popular.
- These types of studies are called **time-series studies**.
- These studies are of most direct relevance to policy and regulation, but they are also more complex and subject to confounding than randomised trials.

## Effectiveness

*Effectiveness at helping people stop smoking conventional cigarettes*

## Safety

*Safety/harmfulness compared with cigarettes or no nicotine use*

## Impact

*Population-level impact of heated tobacco on cigarette smoking*

- Our systematic review aimed to collate the evidence on these three aims.
- **Literature search:** in addition to searching for studies in standard Cochrane databases, we searched in business databases and for “grey literature” such as PMI’s IQOS submission to FDA.
- **Inclusion criteria:** the type of study to be included in our review varied for each of the three aims.
- **Outcomes:** Variety of primary and secondary outcomes.

## Randomised controlled trials (RCTs)

### Effectiveness

*Effectiveness at helping people stop smoking conventional cigarettes*

### Safety

*Safety/harmfulness compared with cigarettes or no nicotine use*

### Impact

*Population-level impact of heated tobacco on cigarette smoking*

## Time-series studies

## Effectiveness

### **Primary outcome:**

Tobacco smoking cessation at  
longest follow-up point available

## Safety

### **Primary outcome:**

Number of people reporting adverse and serious adverse events.

### **Secondary outcomes:**

Biomarkers of toxin and carcinogen exposure. This includes TSNAs, PAHs, VOCs, and carbon monoxide.

Biomarkers of harm. This includes measures of lung function (FEV1, FVC), blood pressure, and heart rate variability.

## Impact

### **Primary outcome:**

Change in smoking prevalence or cigarette sales.

- Where appropriate, we pooled results from different studies using a random-effects model (Mantel-Haenszel for binary outcomes, inverse-variance for continuous)
- We performed subgroup analyses, splitting results based on whether they came from intention-to-treat or per-protocol analyses.
- Caried out sensitivity analyses removing studies:
  1. At high-risk of bias
  2. With <4 weeks follow-up
  3. Using “carbon-tip” products

## **2. What we found**

- 13 studies found.
- Zero studies on **effectiveness** for smoking cessation.
- 11 studies were RCTs – all of which looked at **safety**. In Japan, USA, Poland, UK, and South Korea. All funded by tobacco industry.
- The other 2 were time-series studies looking at **impact** of the introduction of IQOS in Japan on cigarette sales. None looked at smoking prevalence. Not funded by tobacco industry.

- For the 11 **safety** RCTs, they randomised participants to either:

Heated tobacco vs cigarettes

Heated tobacco vs no tobacco

- For three RCTs, participants were held in confinement, so researchers could make sure they only use assigned product.
- For the rest, participants attended regular visits to the clinic for several weeks (three also had confinement period for first five days). Median follow-up was 13 weeks.

- Risk of bias was unclear for 8 RCTs, high for 3.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Bosilkovska 2020	?	+	+	+	+	
Cummings 2020						
Gale 2020	+	?	+	+	+	
Haziza 2019	?	+	+	-	+	?
Lüdicke 2018	?	?	+	+	-	
Lüdicke 2019	?	+	+	+	+	
Martin 2012	?	+	+	+	?	
NCT03364751	?	+	+	+	+	-
Ogden 2015	?	+	+	+	?	
Stoklosa 2020						
Tricker 2012a	?	?	+	?	?	
Tricker 2012b	?	?	+	?	?	
Tricker 2012c	?	?	+	?	?	

- For the 2 time-series studies looking at **impact**, they used an interrupted time-series approach.
- The data came from Japan, before and after the introduction of heated tobacco (IQOS) to market.
- They only looked at cigarette **sales**, not cigarette smoking **prevalence** (I'll come back to this issue).
- They thus essentially compared:

Rate of change in cigarette sales *before* IQOS launched

vs

Rate of change in cigarette sales *after* IQOS launched

# **3. The results**

- As I mentioned, no studies reported of the **effectiveness** of heated tobacco for cigarette smoking cessation.



- For **safety**, we extracted data from 11 studies on a variety of safety outcomes.
- Pooled data from six studies (1713 participants) showed **insufficient evidence** for a difference in adverse events between those randomised to heated tobacco versus cigarette smoking (RR 1.03, 95% CI 0.92 to 1.15;  $I^2 = 0\%$ ).
- Pooled data from two studies (237 participants) showed **insufficient evidence** for a difference in adverse events between those randomised to heated tobacco versus no tobacco (RR 1.03, 95% CI 0.92 to 1.15;  $I^2 = 0\%$ ).

- Removing studies judged to be at high risk of bias or those using carbon-tip products made little difference to results.

- Pooled data from four studies (1472 participants) showed **insufficient evidence** of a difference in serious adverse events reported in people randomised to heated tobacco versus cigarettes (RR 0.79, 95% CI 0.33 to 1.94;  $I^2 = 0\%$ ). There were also five studies where no serious adverse events were reported in either arm.
- Five studies recorded serious adverse events in participants randomised to heated tobacco versus no tobacco, but no such events occurred in either arm in any of these studies.

- Lack of evidence expected given the short length of follow-up.
- Need for large **long-term cohort studies** that investigate this (with proper adjustment for history of cigarette smoking).

## BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 26 1954

---

### THE MORTALITY OF DOCTORS IN RELATION TO THEIR SMOKING HABITS

A 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, C.B.E., F.R.S.**

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

- For the majority of toxins, there was substantial evidence from up to 10 studies (depending on outcome) for **much lower exposure** in those randomised to heated tobacco versus cigarettes.
- These include:
  - Exhaled carbon monoxide
  - 1-OHP
  - COHb
  - 3-HPMA
  - NNAL

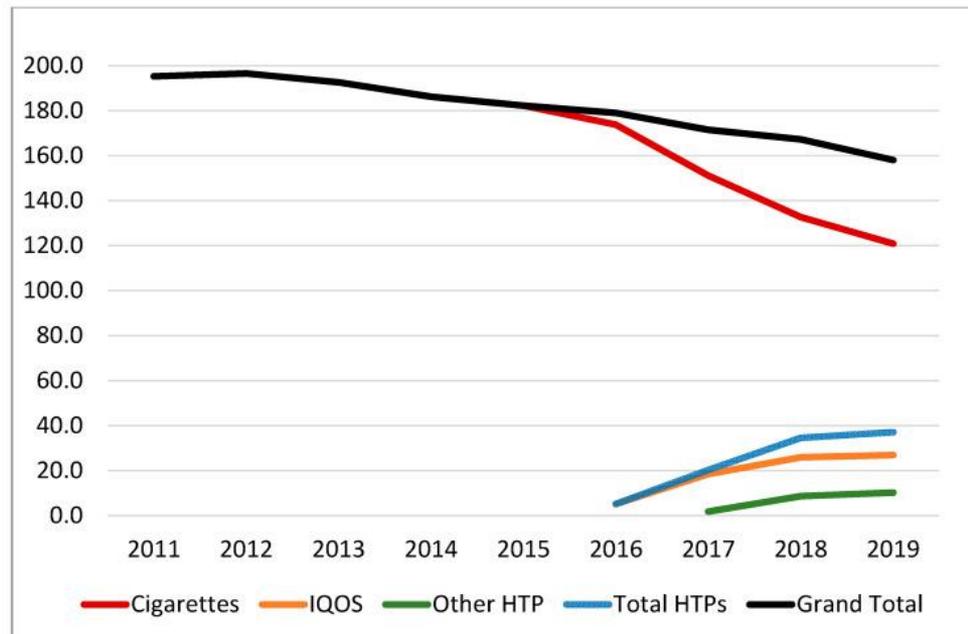
- For some toxins, there was inconsistent evidence from up to 5 studies (depending on outcome) for **higher exposure** in smokers randomised to switch to heated tobacco versus those asked to use no tobacco.
- These include:
  - COHb
  - 3-HPMA
  - NNAL

- Pooled data from five studies (1290 participants) showed some uncertain evidence of **greater** lung function, as measured by FEV1, in those randomised to heated tobacco versus cigarettes (LMD 0.02, 95% CI 0.00 to 0.03;  $I^2 = 0\%$ ).
- Pooled data from two studies (170 participants) showed **insufficient evidence** for a difference in FEV1 (LMD  $-0.00$ , 95% CI  $-0.06$  to  $0.06$ ;  $I^2 = 38\%$ ) in those randomised to heated tobacco versus no tobacco.

- Pooled data from three studies (288 participants) showed **similar** systolic (LMD 0.00, 95% CI -0.02 to 0.02;  $I^2 = 0\%$ ) or diastolic LMD 0.00, 95% CI -0.03 to 0.03;  $I^2 = 0\%$ ) blood pressure in those randomised to heated tobacco versus cigarettes.
- Pooled data from two studies (170 participants) also showed **similar** systolic (LMD 0.02, 95% CI -0.01 to 0.05;  $I^2 = 0\%$ ) or diastolic (LMD 0.00, 95% CI -0.04 to 0.04;  $I^2 = 0\%$ ) blood pressure in those randomised to heated tobacco versus no tobacco.
- No studies reported on heart rate or blood oxygen saturation.

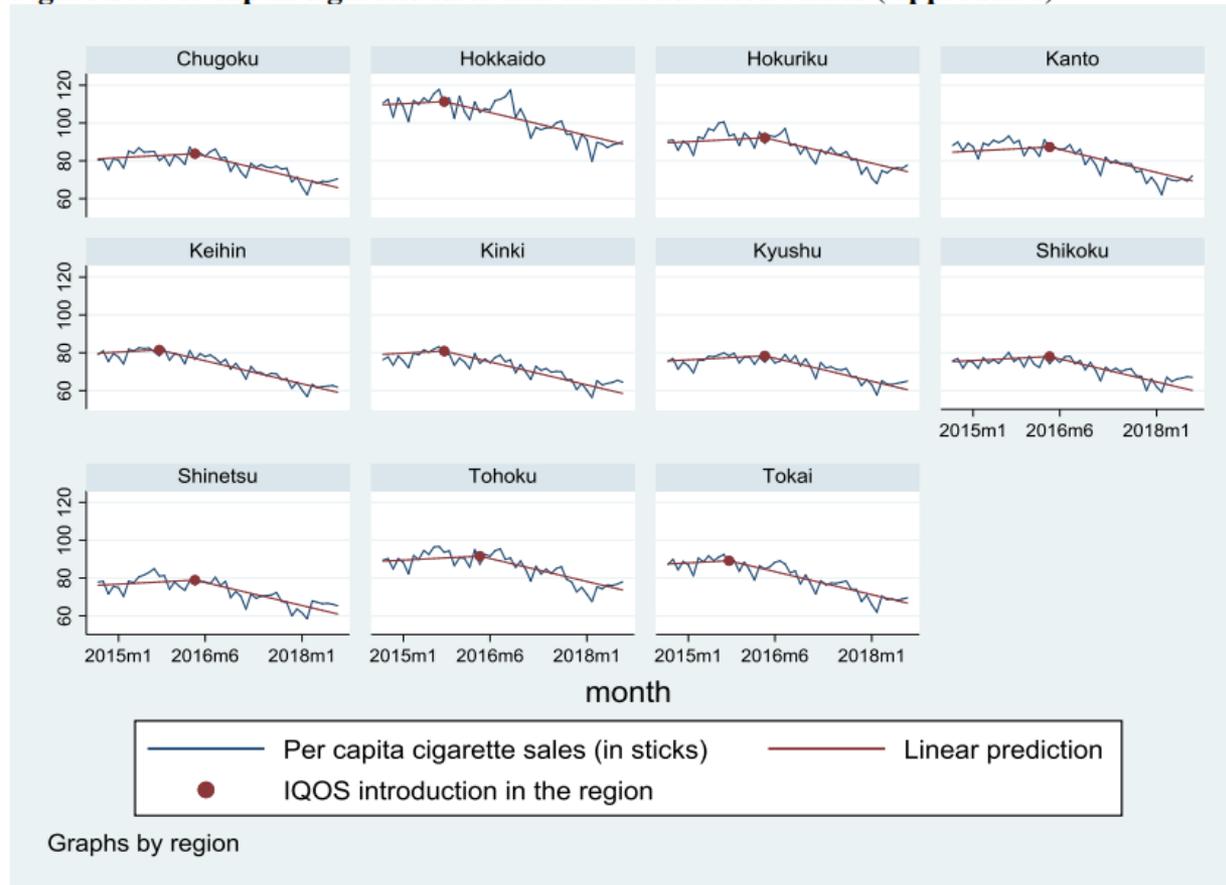
- Results on adverse and serious adverse events were inconclusive. Long-term studies RCTs or cohort studies needed.
- Moderate-certainty evidence that exposure to (measured) toxins was lower in smokers randomised to switch to heated tobacco than continue smoking cigarettes. Very-low to moderate certainty evidence of higher exposures than in those attempting abstinence from all tobacco.
- Uncertain evidence that switching to heated tobacco improves lung function relative to continued cigarette smoking. Little impact of blood pressure.

- Two studies examined the **impact** of IQOS launch in Japan on cigarette sales.
- [Cummings 2020](#) found the launch was associated with an **acceleration in the rate of decline** in cigarette sales



- [Stoklosa 2020](#) used more granular data. Found that the IQOS launch across 11 Japanese regions was associated with **accelerated declines** in cigarette sales.

Figure S1. Per capita cigarette sales and the model fitted values (Approach 1)



- In Japan, IQOS launch probably led to a reduction in cigarette sales.
- Unclear whether this also applies to other countries.
- **Importantly**, falls in cigarette sales do not necessarily imply falls in the percentage of people who smoke.
- People may just cut down on cigarettes, not switch completely to heated tobacco.



- **Effectiveness:** Unlike e-cigarettes, no evidence on their effectiveness at helping people quit smoking ([Hartmann-Boyce 2022](#)).
- **Safety:** Heated tobacco likely pose lower risk to health than cigarettes, but more than not using anything. Need more long-term data directly comparing rates of disease between those using heated tobacco, cigarettes, e-cigarettes, and no nicotine.
- **Impact:** May have reduced cigarette sales in Japan, but need to know impact on smoking prevalence. May be difficult to capture change in surveys given that people often label their IQOS use as “smoking” (to be discussed by Katie).

[Full paper](#) published in Cochrane Library:



**Cochrane  
Library**

Cochrane Database of Systematic Reviews

**Heated tobacco products for smoking cessation and reducing smoking prevalence (Review)**

Tattan-Birch H, Hartmann-Boyce J, Kock L, Simonavicius E, Brose L, Jackson S, Shahab L, Brown J

[Summary article](#) in the Conversation.