

# VAPING IN YOUNG PEOPLE: IS THERE A “GATEWAY” EFFECT?

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Marcus Munafò

# Vaping and tobacco harm reduction

- Vaping may serve as a pathway **out** of smoking for established smokers
- Vaping may serve as a pathway **into** smoking for non-smokers (esp. young people)
- The costs and benefits of vaping will in large part depend on the balance of these two possible **causal pathways**

# Vaping and smoking cessation

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

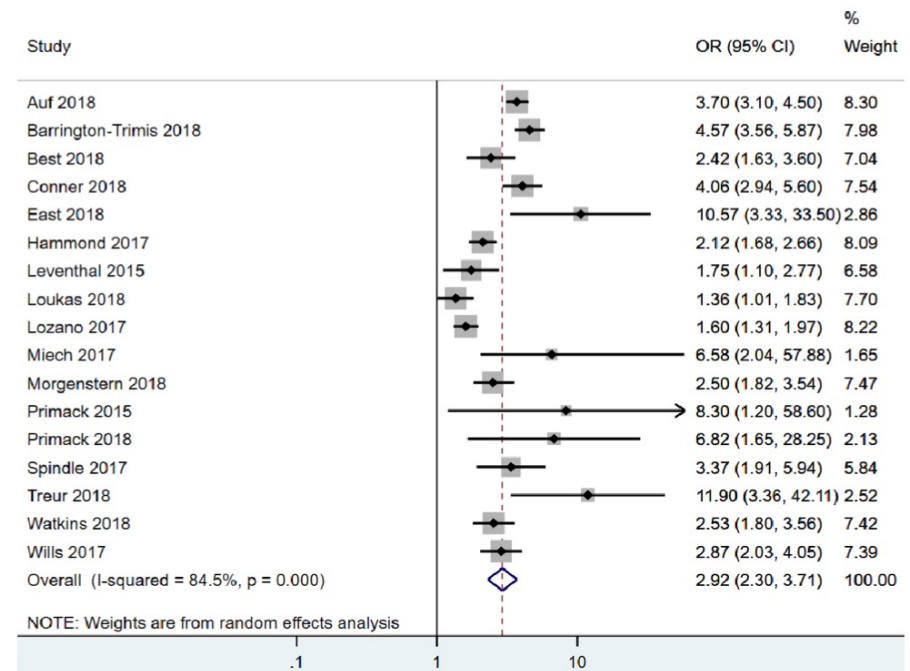
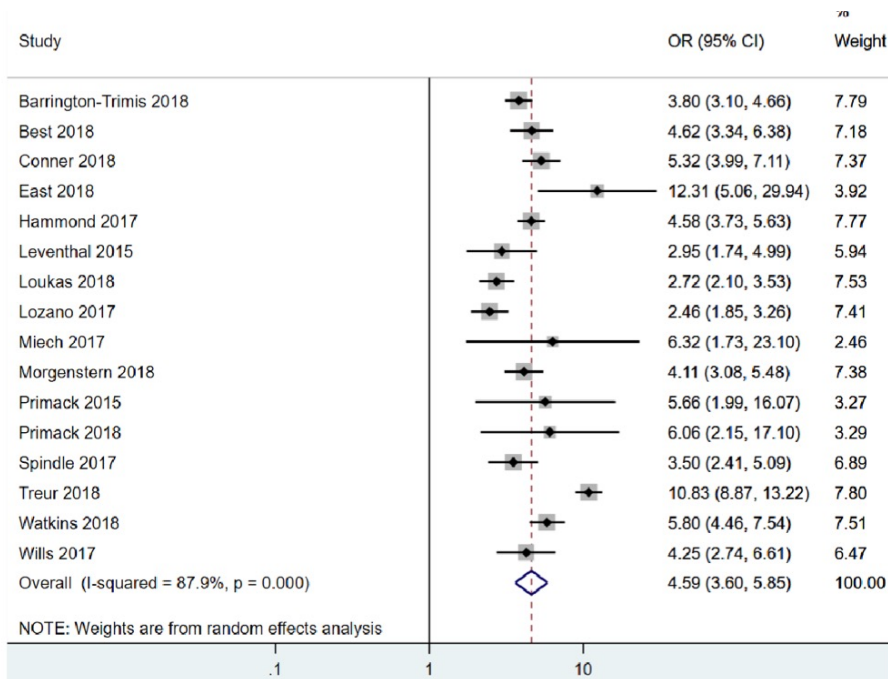
## A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy

**Table 2.** Abstinence Rates at Different Time Points and Smoking Reduction at 52 Weeks.\*

Outcome	E-Cigarettes (N=438)	Nicotine Replacement (N=446)	Primary Analysis: Relative Risk (95% CI)†	Sensitivity Analysis: Adjusted Relative Risk (95% CI)
Primary outcome: abstinence at 52 wk — no. (%)	79 (18.0)	44 (9.9)	1.83 (1.30–2.58)	1.75 (1.24–2.46)‡
Secondary outcomes				
Abstinence between wk 26 and wk 52 — no. (%)	93 (21.2)	53 (11.9)	1.79 (1.32–2.44)	1.82 (1.34–2.47)§
Abstinence at 4 wk after target quit date — no. (%)	192 (43.8)	134 (30.0)	1.45 (1.22–1.74)	1.43 (1.20–1.71)¶
Abstinence at 26 wk after target quit date — no. (%)	155 (35.4)	112 (25.1)	1.40 (1.14–1.72)	1.36 (1.15–1.67)‡
Carbon monoxide–validated reduction in smoking of ≥50% in participants without abstinence between wk 26 and wk 52 — no./total no. (%)	44/345 (12.8)	29/393 (7.4)	1.75 (1.12–2.72)	1.73 (1.11–2.69)

# Vaping and smoking initiation

Is e-cigarette use in non-smoking young adults associated with later smoking? A systematic review and meta-analysis

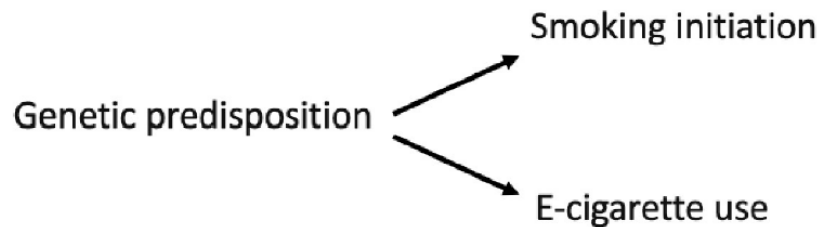


# Correlation or causation?

a) Vertical pleiotropy



b) Horizontal pleiotropy



c) Common risk factor



# Epidemiology

**Daily Mail**  
14 October 2012 (Wednesday), 2012 The Mail Online Group 45p

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**Today's Random Medical News** from the New England Journal of Medicine  
WISZMAN



## Seven cups of tea a day 'raises risk of prostate cancer by 50%'

**Men who drink lots of tea are far more likely to develop prostate cancer, researchers have warned.**  
They found that those who drink seven or more cups a day had a 50 per cent higher risk of developing the disease than men who had three or fewer.  
The finding comes after scientists at the University of Glasgow traced the health of more than 4,000 men for four decades. Their findings run counter to previous research, which had suggested that tea drinking lowers the risk of cancer, as well as heart disease, stroke and Parkinson's disease.  
The study, led by the health researcher James M. Hodge, published online in 2012, followed 4,000 men between 1971 and 1976, were asked to complete a questionnaire about their usual consumption of tea, coffee and alcohol as well as their smoking habits.

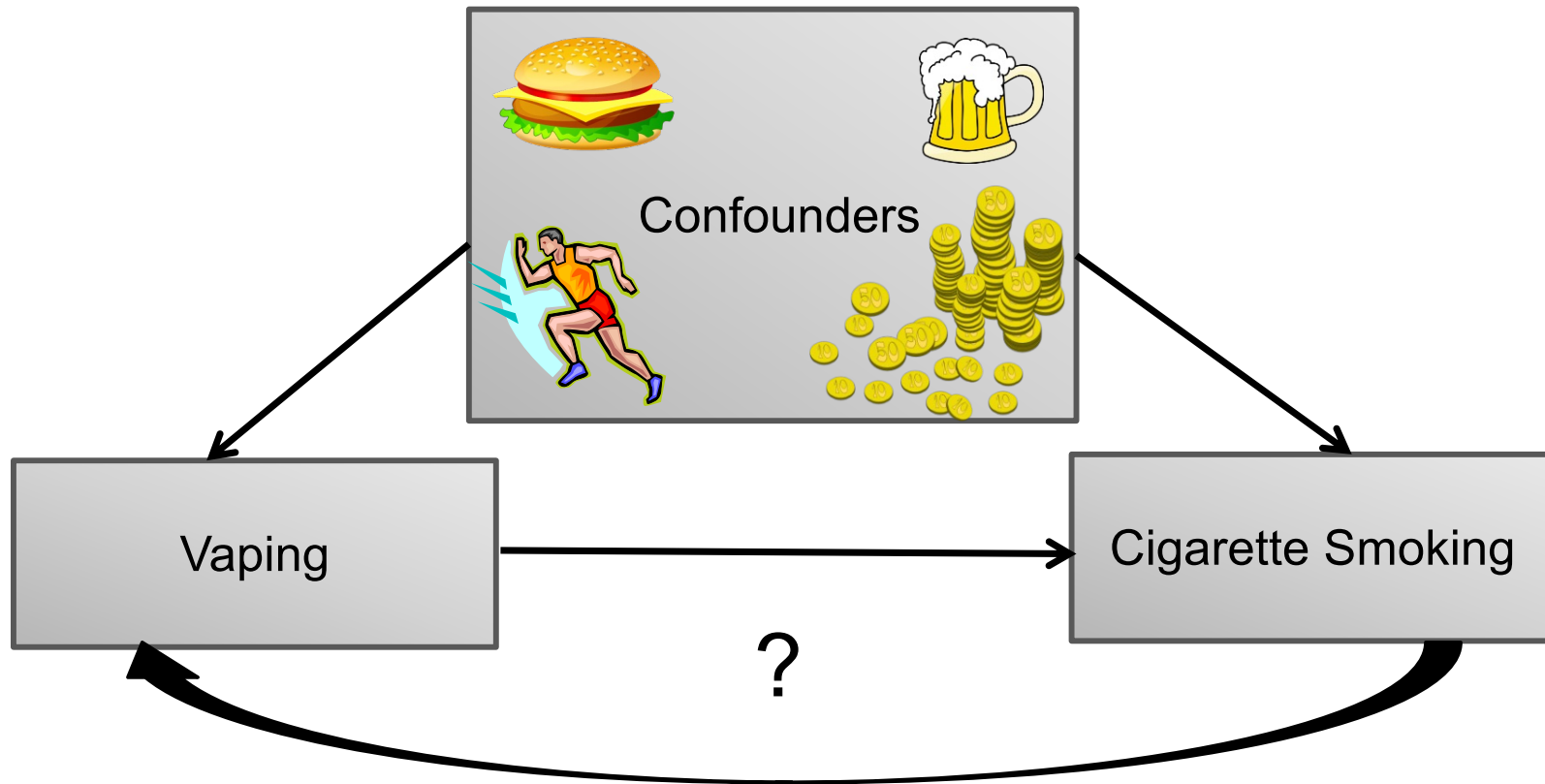
**Coffee and alcohol intake**  
The study found that the subjects who drank the most tea were also the most likely to be smokers. As a result, they had a lower rate of prostate cancer compared to those who drank less tea. However, the researchers found that the risk of prostate cancer was higher for men who drank the most tea and also drank the most alcohol.

Dr David Bates, lead researcher at the Prostate Cancer Charity, said: "While it does appear that those who drink a lot of tea are at a greater risk of developing prostate cancer, this may not be the case if you consider the overall health of the men who drank the most tea. It is clear that those who drank the most tea were also the most likely to be smokers, which may be a greater risk factor for prostate cancer."

The British tea industry is expected to be worth more than £10 billion a year. Dr David Bates of the Prostate Cancer Charity said: "While it does appear that those who drink a lot of tea are at a greater risk of developing prostate cancer, this may not be the case if you consider the overall health of the men who drank the most tea. It is clear that those who drank the most tea were also the most likely to be smokers, which may be a greater risk factor for prostate cancer."

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# Epidemiology



# Reverse causality

RESEARCH ARTICLE

## Investigating the added value of biomarkers compared with self-reported smoking in predicting future e-cigarette use: Evidence from a longitudinal UK cohort study

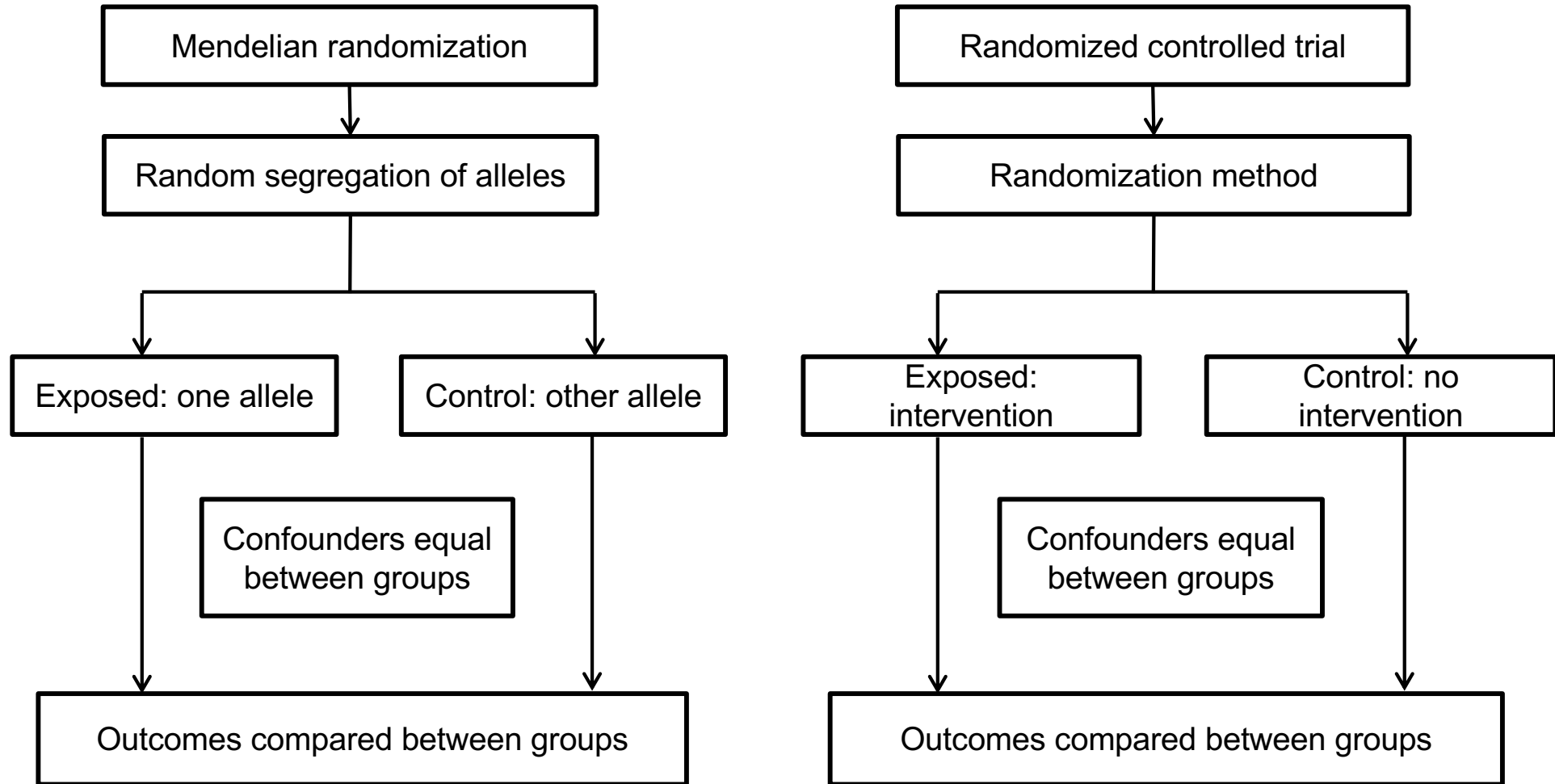
Jasmine N. Khouja<sup>1,2,3\*</sup>, Marcus R. Munafò<sup>1,3,4</sup>, Caroline L. Relton<sup>1,2</sup>, Amy E. Taylor<sup>2,4</sup>, Suzanne H. Gage<sup>5</sup>, Rebecca C. Richmond<sup>1,2</sup>

Model	Active Smoking					
	Self-Report*			Cotinine		
	OR	95% CI	<i>p</i> -value	OR	95% CI	<i>p</i> -value
1	7.77	5.09, 11.85	< .001	10.47	4.88, 22.46	< .001
2	6.99	4.50, 10.86	< .001	8.06	3.69, 17.61	< .001
3	6.34	4.26, 10.34	< .001	7.24	3.29, 15.93	< .001

Self-report reference group = self-reported not current smoking; cotinine reference group = no exposure indicated by cotinine levels; OR = odds ratio; 95% CI = 95% confidence interval. Cotinine was treated as a categorical variable in these analyses. Active exposure is defined as cotinine levels exceeding 10 ng/ml in blood samples; no cotinine exposure is defined as cotinine levels of 0 ng/ml in blood samples. The basic model (model 1) was adjusted for age and sex. Model 2 was additionally adjusted for socioeconomic status, BMI and alcohol. Model 3 was additionally adjusted for passive smoke exposure (maternal smoking at 12 years).



# Mendelian Randomization



# Shared genetic liability

RESEARCH ARTICLE

## Association of genetic liability to smoking initiation with e-cigarette use in young adults: A cohort study

Jasmine N. Khouja<sup>1,2,3\*</sup>, Robyn E. Wootton<sup>1,2</sup>, Amy E. Taylor<sup>2,4</sup>, George Davey Smith<sup>1,2</sup>, Marcus R. Munafò<sup>1,3,4</sup>

Outcome	<i>p</i> -value threshold	<i>n</i>	OR	95% CI	<i>p</i>
Ever e-cigarette use by age 24		2,894			
	$5 \times 10^{-8}$		1.24	1.14, 1.34	<0.001
	0.0005		1.27	1.17, 1.38	<0.001
	0.005		1.36	1.26, 1.48	<0.001
	0.05		1.39	1.28, 1.51	<0.001
	0.5		1.39	1.28, 1.51	<0.001

# Epidemiology

## Smoking as “independent” risk factor for suicide: illustration of an artifact from observational epidemiology?

GEORGE DAVEY SMITH    ANDREW N. PHILLIPS    JAMES D. NEATON

It may be argued that smoking is a plausible causal factor for suicide. The risk of being murdered has therefore also been analysed according to smoking status. As there are only 222 deaths due to homicide, smoking has been classified into three groups—no cigarettes, 1–39, and 40+. The relative rates (and 95% CI) of being murdered, adjusted for income and race which are both associated with risk of murder, are: 1.00, 1.71 (1.29–2.28), and 2.04 (1.32–3.15), respectively.

“Unless the provisional wing of the health education lobby has moved on to a direct action phase, during which they shoot smokers, this association is very unlikely to be causal”.

# Shared genetic liability

Outcome	<i>p</i> -value threshold	<i>n</i>	OR	95% CI	<i>p</i>
11 or more sexual partners by age 23*	$5 \times 10^{-8}$	2,505	1.15	1.05, 1.26	0.003
	0.0005		1.12	1.02, 1.23	0.019
	0.005		1.18	1.08, 1.29	<0.001
	0.05		1.25	1.14, 1.37	<0.001
	0.5		1.30	1.19, 1.43	<0.001
Been in trouble with the law since 23rd birthday	$5 \times 10^{-8}$	2,928	1.00	0.79, 1.28	0.988
	0.0005		1.12	0.88, 1.43	0.352
	0.005		1.11	0.87, 1.41	0.407
	0.05		1.04	0.82, 1.33	0.745
	0.5		0.90	0.71, 1.15	0.394
Enjoys taking risks at age 24	$5 \times 10^{-8}$	2,932	1.06	0.98, 1.14	0.154
	0.0005		1.05	0.98, 1.14	0.163
	0.005		1.11	1.03, 1.19	0.005
	0.05		1.09	1.01, 1.17	0.029
	0.5		1.08	1.01, 1.16	0.033

# Shared genetic liability

Outcome	<i>n</i>	OR	95% CI	<i>p</i>
<i>p</i> -value threshold				
Hyperactivity at age 7	5,227			
$5 \times 10^{-8}$		1.02	0.96, 1.08	0.511
0.0005		1.10	1.04, 1.16	0.001
0.005		1.14	1.08, 1.20	<0.001
0.05		1.14	1.08, 1.21	<0.001
0.5		1.15	1.08, 1.21	<0.001
Conduct disorder at age 7	5,334			
$5 \times 10^{-8}$		1.10	1.03, 1.17	0.004
0.0005		1.11	1.04, 1.19	0.001
0.005		1.11	1.04, 1.18	0.002
0.05		1.08	1.01, 1.15	0.021
0.5		1.08	1.01, 1.15	0.017
Oppositional defiant disorder at age 7	5,325			
$5 \times 10^{-8}$		1.02	0.96, 1.08	0.496
0.0005		1.08	1.02, 1.14	0.013
0.005		1.04	0.98, 1.10	0.200
0.05		1.04	0.98, 1.10	0.173
0.5		1.02	0.96, 1.08	0.529

# Conclusions

- There is a robust, replicable association between vaping initiation and smoking initiation
- Whether this represents a causal pathway is less clear; there is evidence for a common underlying phenotype
- Large-scale GWAS of vaping initiation will allow Mendelian randomization studies of vaping outcomes