NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

Cochrane Tobacco Addiction

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Electronic cigarettes for smoking cessation

Results from the most recent Cochrane Review update

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About Cochrane

WHAT?

- Gathers and combines the best evidence from research to determine the benefits and risks of treatments/interventions

HOW?

- By systematically reviewing the available evidence, with strong emphasis on quality assessment
- Cochrane methods considered gold-standard

WHY?

- To help healthcare providers, patients, carers, researchers, funders, policy makers, guideline developers improve their knowledge and make decisions

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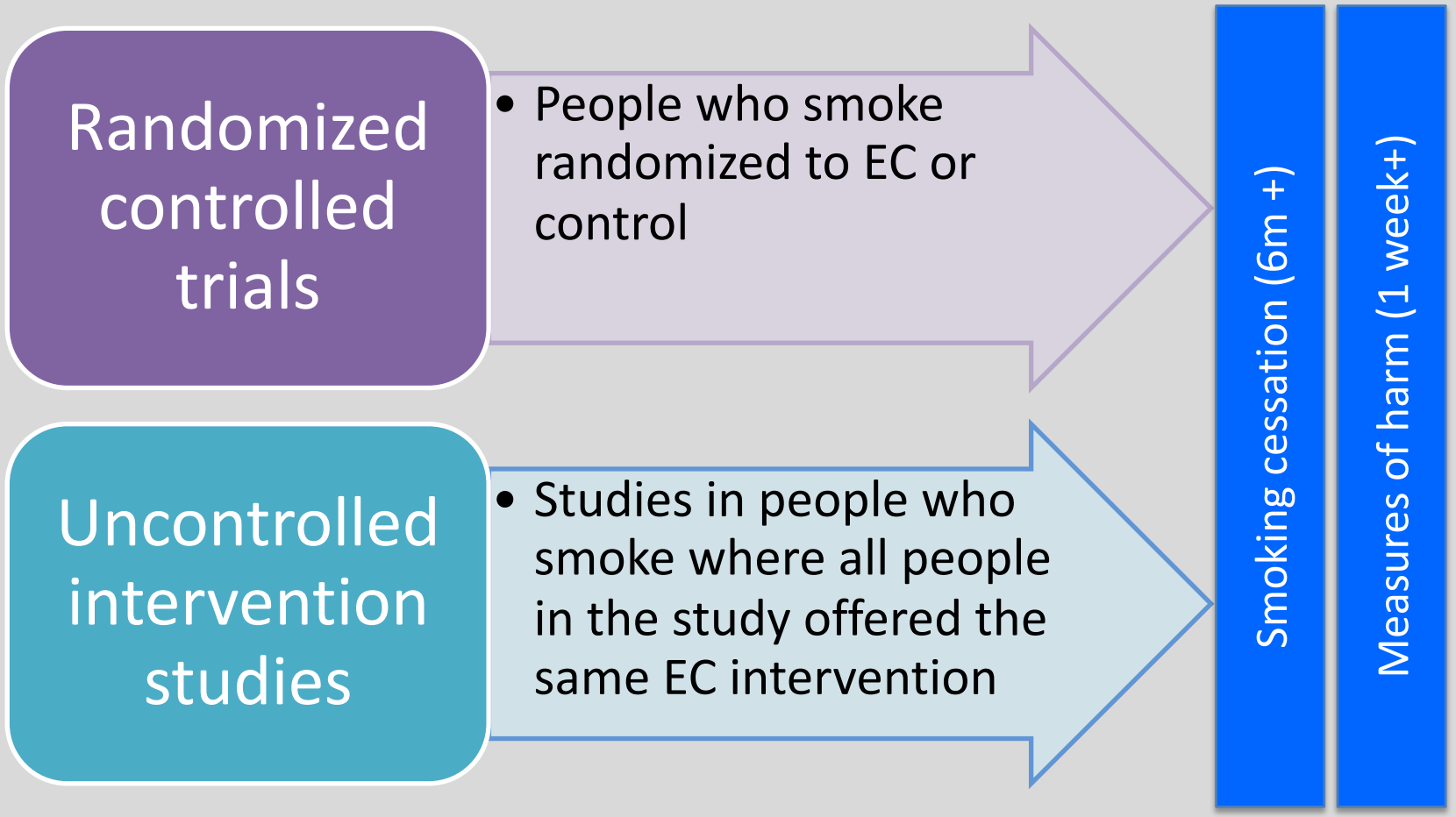
Objective:

Evaluate the safety and effect of using EC to help people who smoke achieve long-term smoking abstinence

Inclusion criteria



Searches

- Review update published April 2021
- 56 studies in >12,000 participants (6 new at this update)
- 29 included studies were RCTs
- 23 RCTs contributed to cessation analyses

DEVICE TYPES	RISK OF BIAS	FUNDING SOURCE
• 26 cartridge devices (only one with high nicotine delivery) • 21 refillable devices • 3 used both cartridge & refillable devices • 1 used a pod device • 5 did not report device type	• 5 Low risk • 10 Unclear risk • 41 High risk (including the 25 non-randomized studies)	• 46 studies reported funding information • 32 of these had no EC industry funding or support

Primary comparisons

- Nicotine e-cigarette versus NRT
- Nicotine e-cigarette versus non-nicotine e-cigarette
- Nicotine e-cigarette versus behavioural support only/no-support

Outcomes

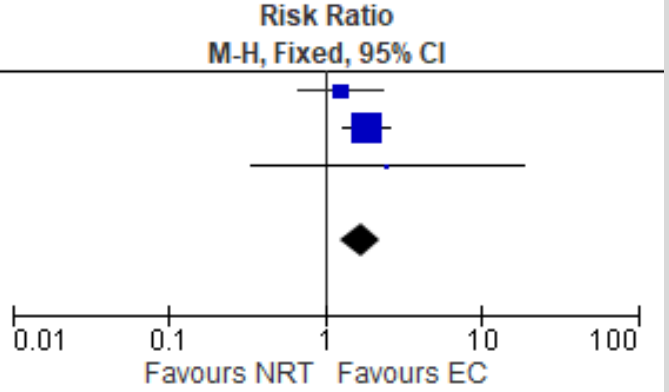
Cessation*	Adverse events (AE)*	Serious adverse events (SAE)*	Changes in relevant biomarkers
• 6 months+ • Intention to treat • Strictest definition of abstinence • Biochemically verified where available • (as per standard Cochrane methods)	• One week or longer of EC use • Defined as any undesirable experience associated with the use of a medical product in a patient	• One week or longer of EC use • Any AE where the patient outcome is death; life-threatening; hospitalization; disability; birth defect; or requires intervention to prevent any of the above	• One week or longer of EC use • Known carcinogens and toxicants • Exhaled carbon monoxide • Airway and lung function • Blood oxygen levels

*primary outcome

Nicotine e-cigarette versus NRT:
Quitting at 6+ months

Study or Subgroup	EC Events	EC Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bullen 2013	21	289	17	295	27.2%	1.26 [0.68, 2.34]
Hajek 2019	79	438	44	446	70.6%	1.83 [1.30, 2.58]
Lee 2018	5	20	1	10	2.2%	2.50 [0.34, 18.63]
Total (95% CI)		**747**		**751**	**100.0%**	**1.69 [1.25, 2.27]**
Total events	105		62			

Heterogeneity: Chi² = 1.21, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 3.46 (P = 0.0005)



GRADE certainty of evidence: MODERATE (downgraded one level due to imprecision)

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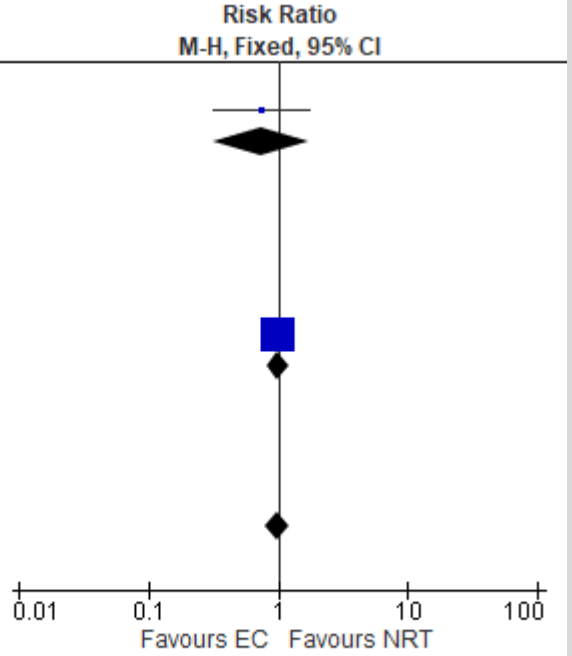
Nicotine e-cigarette versus NRT:

Adverse events at 1+weeks

Study or Subgroup	Nicotine EC Events	Total	NRT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 4 weeks						
Lee 2018 (1)	7	19	5	10	6.1%	0.74 [0.31, 1.73]
Subtotal (95% CI)		**19**		**10**	**6.1%**	**0.74 [0.31, 1.73]**
Total events	7		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
1.2.2 6 months						
Bullen 2013	107	241	96	215	93.9%	0.99 [0.81, 1.22]
Subtotal (95% CI)		**241**		**215**	**93.9%**	**0.99 [0.81, 1.22]**
Total events	107		96			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
Total (95% CI)		**260**		**225**	**100.0%**	**0.98 [0.80, 1.19]**
Total events	114		101			
Heterogeneity: Chi² = 0.45, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.21 (P = 0.83)						
Test for subgroup differences: Chi² = 0.45, df = 1 (P = 0.50), I² = 0%						



Footnotes

(1) Data at 4 weeks post-operation; time from baseline not defined and likely to differ between participants

GRADE certainty of evidence: LOW (downgraded two levels due to imprecision)

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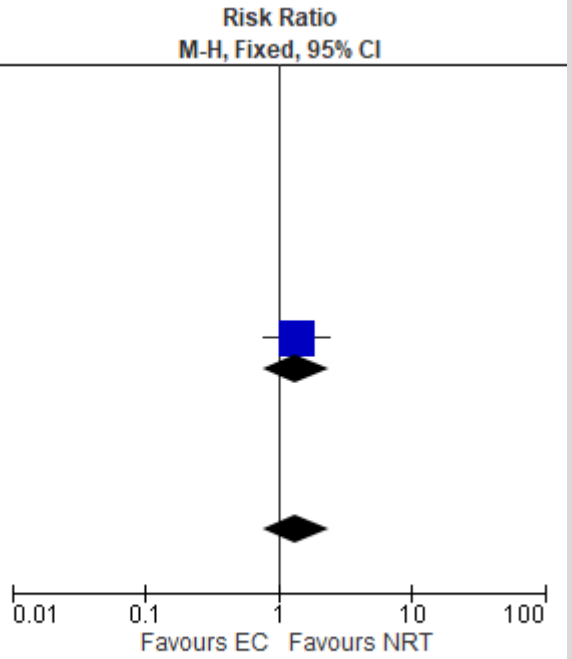
Nicotine e-cigarette versus NRT:

Serious adverse events at 1+weeks

Study or Subgroup	EC Events	EC Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 4 weeks						
Lee 2018 (1)	0	19	0	10		Not estimable
Subtotal (95% CI)		**19**		**10**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.3.2 1 year						
Hajek 2019	27	356	19	342	100.0%	1.37 [0.77, 2.41]
Subtotal (95% CI)		**356**		**342**	**100.0%**	**1.37 [0.77, 2.41]**
Total events	27		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						
Total (95% CI)		**375**		**352**	**100.0%**	**1.37 [0.77, 2.41]**
Total events	27		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						
Test for subgroup differences: Not applicable						



Footnotes

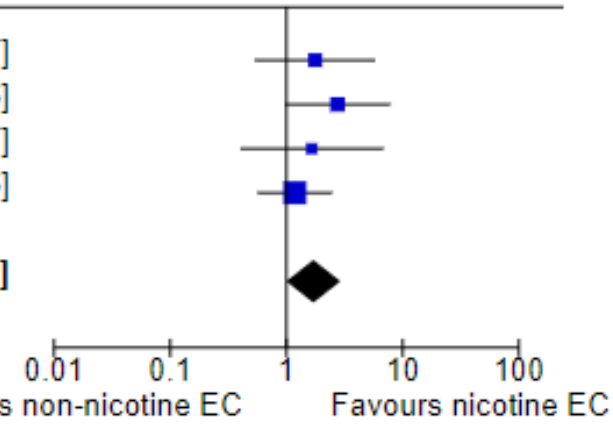
(1) Data at 4 weeks post-operation; time from baseline not defined and likely to differ between participants

GRADE certainty of evidence: LOW (downgraded two levels due to imprecision)

Nicotine e-cigarette versus non-nicotine e-cigarette: Quitting at 6+ months

Study or Subgroup	Nicotine EC Events	Total	Non-nicotine EC Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bullen 2013	21	289	3	73	19.8%	1.77 [0.54 , 5.77]
Caponnetto 2013a	22	200	4	100	22.1%	2.75 [0.97 , 7.76]
Eisenberg 2020	5	128	3	127	12.5%	1.65 [0.40 , 6.77]
Lucchiari 2020	13	70	11	70	45.6%	1.18 [0.57 , 2.46]
Total (95% CI)		**687**		**370**	**100.0%**	**1.70 [1.03 , 2.81]**
Total events:	61		21			

Heterogeneity: Chi² = 1.78, df = 3 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.09 (P = 0.04)
Test for subgroup differences: Not applicable

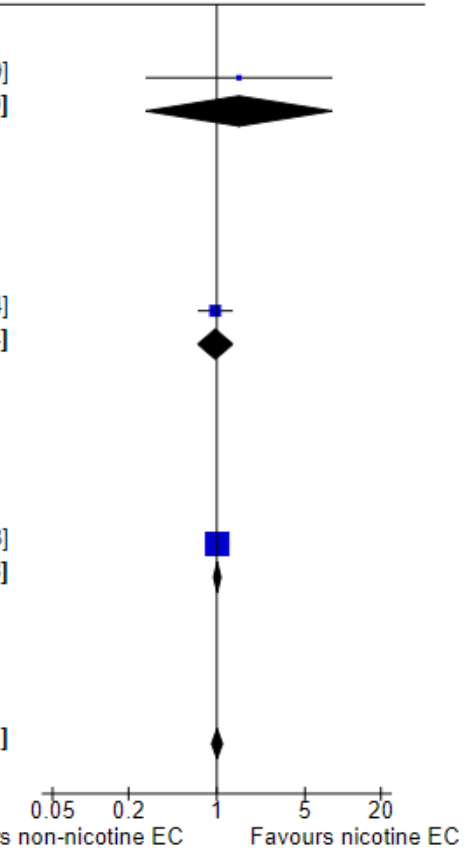


GRADE certainty of evidence: MODERATE (downgraded one level due to imprecision)

Nicotine e-cigarette versus non-nicotine e-cigarette:

Adverse events at 1+ weeks

Study or Subgroup	Nicotine EC Events	Total	Non-nicotine EC Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 1 week						
Meier 2017	3	24	2	24	1.2%	1.50 [0.27 , 8.19]
Subtotal (95% CI)		**24**		**24**	**1.2%**	**1.50 [0.27 , 8.19]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
3.2.2 6 months						
Bullen 2013	107	241	26	57	25.9%	0.97 [0.71 , 1.34]
Subtotal (95% CI)		**241**		**57**	**25.9%**	**0.97 [0.71 , 1.34]**
Total events:	107		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.17 (P = 0.87)						
3.2.3 12 weeks						
Eisenberg 2020	120	128	118	127	72.9%	1.01 [0.94 , 1.08]
Subtotal (95% CI)		**128**		**127**	**72.9%**	**1.01 [0.94 , 1.08]**
Total events:	120		118			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
Total (95% CI)		**393**		**208**	**100.0%**	**1.01 [0.91 , 1.11]**
Total events:	230		146			
Heterogeneity: Chi² = 0.26, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.91)						
Test for subgroup differences: Chi² = 0.26, df = 2 (P = 0.88), I² = 0%						



GRADE certainty of evidence: MODERATE (downgraded one level due to imprecision)

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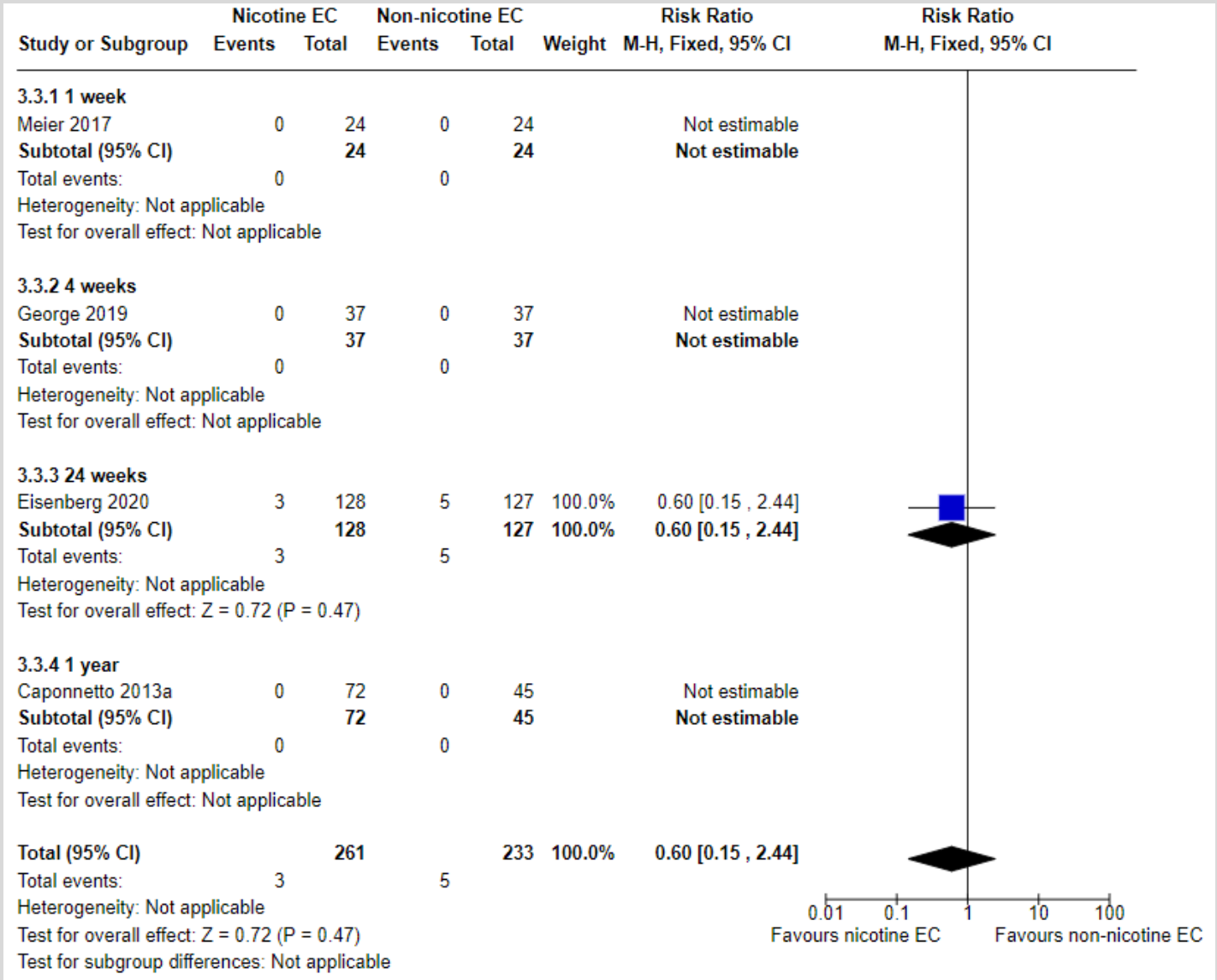
Nicotine e-cigarette versus non-nicotine e-cigarette:

Serious adverse events at 1+weeks

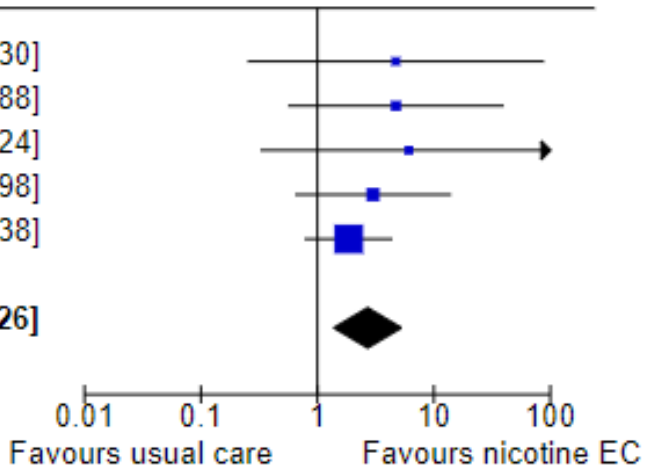
GRADE certainty of evidence: LOW (downgraded two levels due to imprecision)



Nicotine e-cigarette versus behavioural support only/no support: Quitting at 6+ months

Study or Subgroup	Nicotine EC Events	Nicotine EC Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dawkins 2020	3	48	0	32	5.3%	4.71 [0.25 , 88.30]
Eisenberg 2020	5	128	1	121	9.2%	4.73 [0.56 , 39.88]
Halpern 2018	4	1199	0	813	5.3%	6.11 [0.33 , 113.24]
Holliday 2019 (1)	6	40	2	40	17.8%	3.00 [0.64 , 13.98]
Lucchiari 2020	13	70	7	70	62.4%	1.86 [0.79 , 4.38]
Total (95% CI)		**1485**		**1076**	**100.0%**	**2.70 [1.39 , 5.26]**
Total events:	31		10			

Heterogeneity: Chi² = 1.45, df = 4 (P = 0.83); I² = 0%
Test for overall effect: Z = 2.92 (P = 0.003)
Test for subgroup differences: Not applicable



Footnotes

(1) Although participants were given a choice of nicotine concentration including 0 mg, none of the participants chose the non-nicotine e-liq

GRADE certainty of evidence: VERY LOW (downgraded two levels due to risk of bias; one level due to imprecision)

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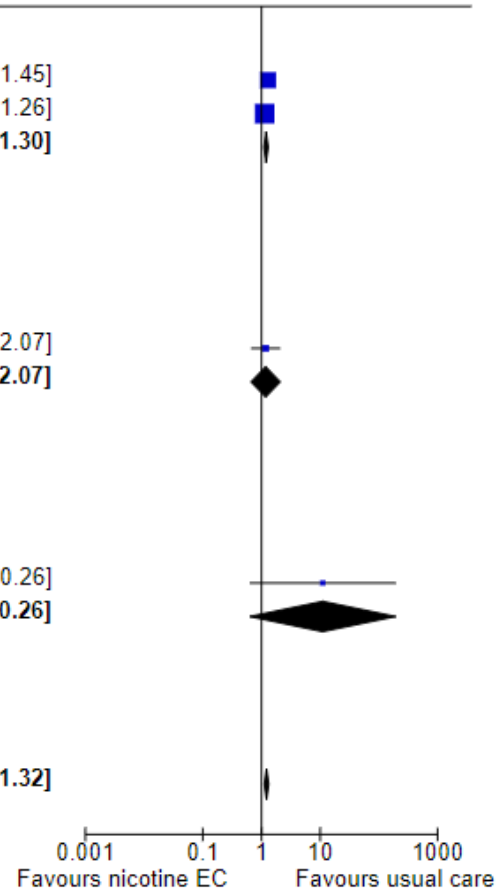
Nicotine e-cigarette versus behavioural support only/no support:

Adverse events at 1+weeks

GRADE certainty of evidence: VERY LOW (downgraded due to risk of bias and imprecision)

Study or Subgroup	Nicotine EC Events	Nicotine EC Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 12 weeks						
Eisenberg 2020	120	128	88	121	40.8%	1.29 [1.15 , 1.45]
Walele 2018	271	306	80	102	54.1%	1.13 [1.01 , 1.26]
Subtotal (95% CI)		**434**		**223**	**94.9%**	**1.20 [1.11 , 1.30]**
Total events:	391		168			
Heterogeneity: Chi² = 2.61, df = 1 (P = 0.11); I² = 62%						
Test for overall effect: Z = 4.41 (P < 0.0001)						
4.2.2 16 weeks						
Carpenter 2017 (1)	20	34	8	16	4.9%	1.18 [0.67 , 2.07]
Subtotal (95% CI)		**34**		**16**	**4.9%**	**1.18 [0.67 , 2.07]**
Total events:	20		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.57)						
4.2.3 6 months						
Holliday 2019 (2)	5	29	0	29	0.2%	11.00 [0.64 , 190.26]
Subtotal (95% CI)		**29**		**29**	**0.2%**	**11.00 [0.64 , 190.26]**
Total events:	5		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.65 (P = 0.10)						
Total (95% CI)		**497**		**268**	**100.0%**	**1.22 [1.12 , 1.32]**
Total events:	416		176			
Heterogeneity: Chi² = 5.04, df = 3 (P = 0.17); I² = 41%						
Test for overall effect: Z = 4.70 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.33, df = 2 (P = 0.31), I² = 14.1%						



Footnotes

(1) 24mg EC arm included here; 16mg data reported elsewhere

(2) Participants offered choice of nicotine or no-nicotine EC; all chose nicotine-containing EC

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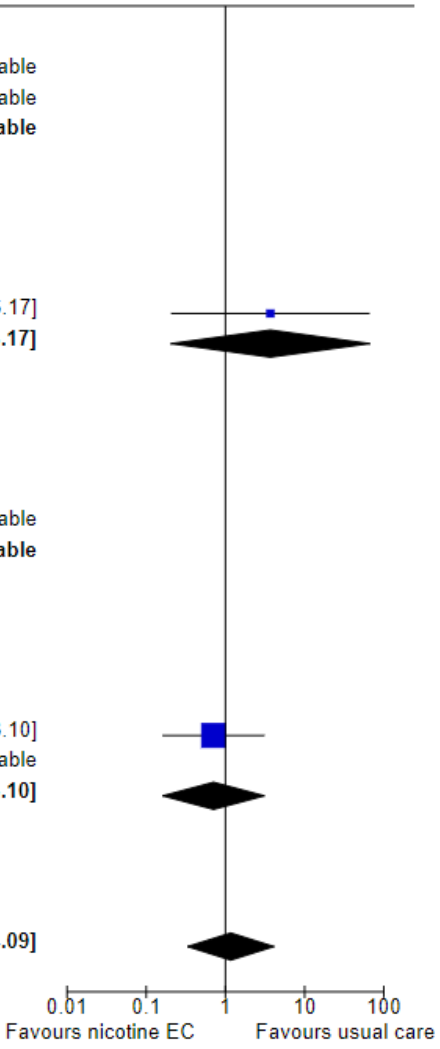
Nicotine e-cigarette versus behavioural support only/no support: Serious adverse events at 1+wks

Study or Subgroup	Nicotine EC Events	Nicotine EC Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 4 to 6 weeks						
George 2019	0	37	0	40		Not estimable
Pulvers 2020	0	115	0	54		Not estimable
Subtotal (95% CI)		**152**		**94**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.3.2 12 weeks						
Walele 2018	5	306	0	102	15.4%	3.69 [0.21 , 66.17]
Subtotal (95% CI)		**306**		**102**	**15.4%**	**3.69 [0.21 , 66.17]**
Total events:	5		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.38)						
4.3.3 16 weeks						
Carpenter 2017 (1)	0	34	0	16		Not estimable
Subtotal (95% CI)		**34**		**16**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.3.4 6 months						
Eisenberg 2020	3	128	4	121	84.6%	0.71 [0.16 , 3.10]
Holliday 2019 (2)	0	29	0	29		Not estimable
Subtotal (95% CI)		**157**		**150**	**84.6%**	**0.71 [0.16 , 3.10]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
Total (95% CI)		**649**		**362**	**100.0%**	**1.17 [0.33 , 4.09]**
Total events:	8		4			
Heterogeneity: Chi² = 1.05, df = 1 (P = 0.31); I² = 5%						
Test for overall effect: Z = 0.24 (P = 0.81)						
Test for subgroup differences: Chi² = 0.99, df = 1 (P = 0.32), I² = 0%						



GRADE certainty of evidence: VERY LOW (downgraded due to risk of bias and imprecision)

Implications for practice

- Evidence suggesting nicotine EC can aid in smoking cessation is consistent across several comparisons. There was moderate certainty evidence, limited by imprecision, that EC with nicotine increased quit rates at six months or longer compared to non-nicotine EC and compared to NRT. There was very low certainty evidence that EC with nicotine increased quit rates compared to behavioural support only or no support.
- The effect of nicotine EC when added to NRT was unclear.
- None of the included studies (short- to mid-term, up to two years) detected serious adverse events considered possibly related to EC use.
- The most commonly reported adverse effects were throat/mouth irritation, headache, cough, and nausea, which tended to dissipate over time.
- In some studies, reductions in biomarkers were observed in people who smoked who switched to vaping consistent with reductions seen in smoking cessation.

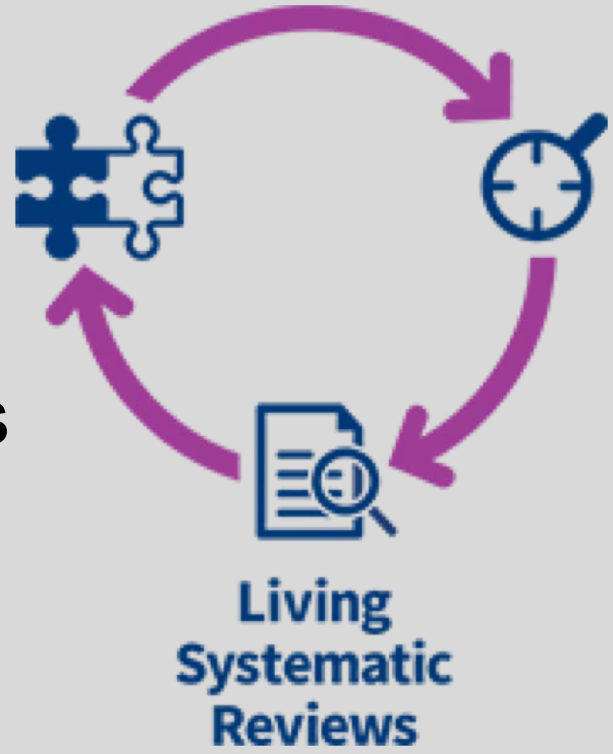
Implications for research

Further trials should:

- Measure cessation at six months or longer.
- Use active comparators
- Assess safety profile for as long as possible
- Be powered to detect differences in safety outcomes
- Present safety in both absolute and relative risk terms (in comparison to the risks of continuing to smoke tobacco).
- Offer recent devices to participants, to be most representative of what will be on the market at the time results are released. Data on pod type EC are particularly lacking. Protocols and statistical analysis plans should be registered in advance and openly available.
- Provide EC in a way that would be used in real-world settings.

Living systematic review (LSR)

- Search for new evidence monthly
- Publish links to new evidence monthly
- Update full review when new data emerges that changes, strengthens, or weakens existing conclusions, or relates to new comparisons or outcomes



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Also as part of the living systematic review project…

See full review for

- More detail on everything that's been presented
- Secondary outcomes
- Other comparisons
- Data from uncontrolled studies
- Comparison with other reviews

Updates to and information on the living systematic review: https://www.cebm.ox.ac.uk/research/electronic-cigarettes-for-smoking-cessation-cochrane-living-systematic-review-1