Supplementary file

Appendix 1 Search strategy

Example Medline search strategy (Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions (R1946 to May 12, 2021. Filter: Cochrane highly sensitive RCT filter))

Search number	Search term	Results
1	Vaping/	1728
2	Electronic Nicotine Delivery Systems/ or E-cigarette vapor/	4469
3	"Nebulizers and Vaporizers"/ and (nicotine or tobacco).mp.	170
4	e-cig$.mp.	5672
5	Ecig$.mp.	136
6	(Vape or vaping or vaper or vapers).mp.	3065
7	(Vapori#e$ adj3 (cigarette$ or nicotine)).mp.	105
8	((electric or electronic) adj2 (cig$ or nicotine or tobacco or smoking)).mp.	6400
9	(e-sigaret$ or "e-sígarett$" or een sigaret$ or E-Zigarette$ or "cigarette$ électronique$" or "L'e-cigarette" or vapoteuse$ or "cigarrill$ electrónico$" or sigarett$ elettronic$ or sigarett$ elettronik$ or sigarett$ elettroniche$ or elektronik$ sigar$ or e-savuke$ or e-rokok$ or rokok$ elektronik$ or e-papieros$ or e-ugwayi).mp.	92
10	(mods adj5 (tobacco or nicotine)).mp.	3
11	Juul$.mp.	221
12	(e-juice$ or e-liquid$).mp.	701
13	(cig-a-like$ or cigalike$ or ciga-like$).mp.	61
14	(e-hookah$ or electronic hookah$ or "hookah pens").mp.	28
15	(ENNDS or electronic non-nicotine delivery).mp.	7
16	((NMNDS and nicotin$) or non-medicinal nicotine delivery system$).mp.	0
17	or/1-16	8362
18	(Heated tobacco product$ or tobacco heating product$ or tobacco heating system$).mp.	285
19	("heat-not-burn" or "heat not burn" or "heat notburn" or "heatnot burn").mp.	169
20	(Heatsticks or heat-sticks or tobacco sticks or Neosticks).mp.	27
21	((HEETS or Fiit or glo) adj3 (tobacco or nicotine or smok$)).mp.	6
22	(IQOS or iFuse or Ploom).mp.	153
23	(electrically-heated smoking system and (nicotin$ or tobacco$)).mp.	1
24	(Vapotage or "tabac chauffé" or "verhitte tabak" or "riscaldatori di tabacco" or "tabacco riscaldato" or "erhitzter Tabak" or "verhit tabak" or "zahřátý tabák" or "opvarmet tobak" or "oppvarmet tobakk" or "uppvärmd tobak" or "kuumutatud tubakas" or "pinainit na tabako" or "lämmitetty tupakka" or "shan taba mai tsanani" or "hitað tóbak" or "apsildāmā tabaka" or "tembakau dipanaskan" or "šildomas tabakas" or "tembakau yang dipanaskan" or "te taakapa" or "podgrzewany tytoń" or "tabaco aquecido" or "încălzit tutunul" or "zahriaty tabak" or "ogrevani tobak" or "tabaco caliente" or "ısıtılmış tütün" or "ugwayi ovuthayo" or "thuốc lá nóng").mp.	23
25	or/18-24	476
26	17 or 25	8567
27	((randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo or randomly or trial or groups).ab. or drug therapy.fs.) not exp animals/ not humans.sh.	605775
28	26 and 27	379

Appendix 2 List of articles excluded at full text stage

Original search

	Reference	Reason for exclusion
1	Adriaens K, Van Gucht D, Declerck P, et al. Effectiveness of the electronic cigarette: An eight-week Flemish study with six-month follow-up on smoking reduction, craving and experienced benefits and complaints. *International journal of environmental research and public health* 2014;11(11):11220-48. doi: 10.3390/ijerph111111220 [published Online First: 2014/10/31]	Control (Participants were allowed to continue smoking)
2	Baldassarri SR, Bernstein SL, Chupp GL, et al. Electronic cigarettes for adults with tobacco dependence enrolled in a tobacco treatment program: A pilot study. *Addictive behaviors* 2018;80:1-5. doi: 10.1016/j.addbeh.2017.11.033 [published Online First: 2018/01/06]	Intervention (NRT given in combo with EC)
3	Chaumont M, Bernard A, Pochet S, et al. High-Wattage E-Cigarettes Induce Tissue Hypoxia and Lower Airway Injury: A Randomized Clinical Trial. *American journal of respiratory and critical care medicine* 2018;198(1):123-26. doi: 10.1164/rccm.201711-2198LE [published Online First: 2018/02/17]	Study design (crossover and short duration treatment)
4	4. Harhay MO, Troxel AB, Brophy C, et al. Financial Incentives Promote Smoking Cessation Directly, Not by Increasing Use of Cessation Aids. *Annals of the American Thoracic Society* 2019;16(2):280-82. doi: 10.1513/AnnalsATS.201808-574RL [published Online First: 2018/10/06]	Intervention (Secondary analysis of Halpern trial but only analysing effects of monetary intervention)
5	5. Kumral TL, Salturk Z, Yildirim G, et al. How does electronic cigarette smoking affect sinonasal symptoms and nasal mucociliary clearance? *B-ent* 2016;12(1):17-21. [published Online First: 2016/04/22]	Outcomes
6	6. Lee SM, Tenney R, Wallace A, et al. The end perioperative smoking pilot study: A randomized trial comparing e-cigarettes versus nicotine patch. *Canadian Journal of Anesthesia* 2017;64(1):S48-S49. doi: 10.1007/s12630-017-1003-0	Study design (conference abstract)
7	7. Li J, Hajek P, Pesola F, et al. Cost-effectiveness of e-cigarettes compared with nicotine replacement therapy in stop smoking services in England (TEC study): a randomized controlled trial. *Addiction (Abingdon, England)* 2020;115(3):507-17. doi: 10.1111/add.14829	Study design
8	8. Martin F, Talikka M, Ivanov NV, et al. Evaluation of the tobacco heating system 2.2. Part 9: Application of systems pharmacology to identify exposure response markers in peripheral blood of smokers switching to THS2.2. *Regulatory toxicology and pharmacology : RTP* 2016;81 Suppl 2:S151-	Intervention (too short treatment length)

	s57. doi: 10.1016/j.yrtph.2016.11.011 [published Online First: 2016/11/16]	
9	9. Ogden MW, Marano KM, Jones BA, et al. Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 2. Biomarkers of exposure. *Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals* 2015;20(6-7):391-403. doi: 10.3109/1354750x.2015.1094134 [published Online First: 2015/11/12]	Control
10	10. Ogden MW, Marano KM, Jones BA, et al. Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 3. Biomarkers of biological effect. *Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals* 2015;20(6-7):404-10. doi: 10.3109/1354750x.2015.1094135 [published Online First: 2015/11/04]	Control
11	11. Ogden MW, Marano KM, Jones BA, et al. Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 1. Study design and methodology. *Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals* 2015;20(6-7):382-90. doi: 10.3109/1354750x.2015.1094133 [published Online First: 2015/11/04]	Control
12	1. Picavet P, Haziza C, Lama N, et al. Reduced exposure to harmful and potentially harmful constituents after 90 days of use of tobacco heating system 2.2 in Japan: A comparison with continued combustible cigarette use or smoking abstinence. Toxicology Letters 2016;259:S141. doi: 10.1016/j.toxlet.2016.07.597	Study design (conference abstract)
13	1. Pravettoni G, Masiero M, Lucchiari C, et al. The role of electronic cigarettes in smoking cessation among heavy smokers undergoing a lung cancer screening program: Preliminary results of a randomized controlled study. Psycho-Oncology 2016;25:72. doi: 10.1002/pon.4082	Study design (conference abstract)

Update search

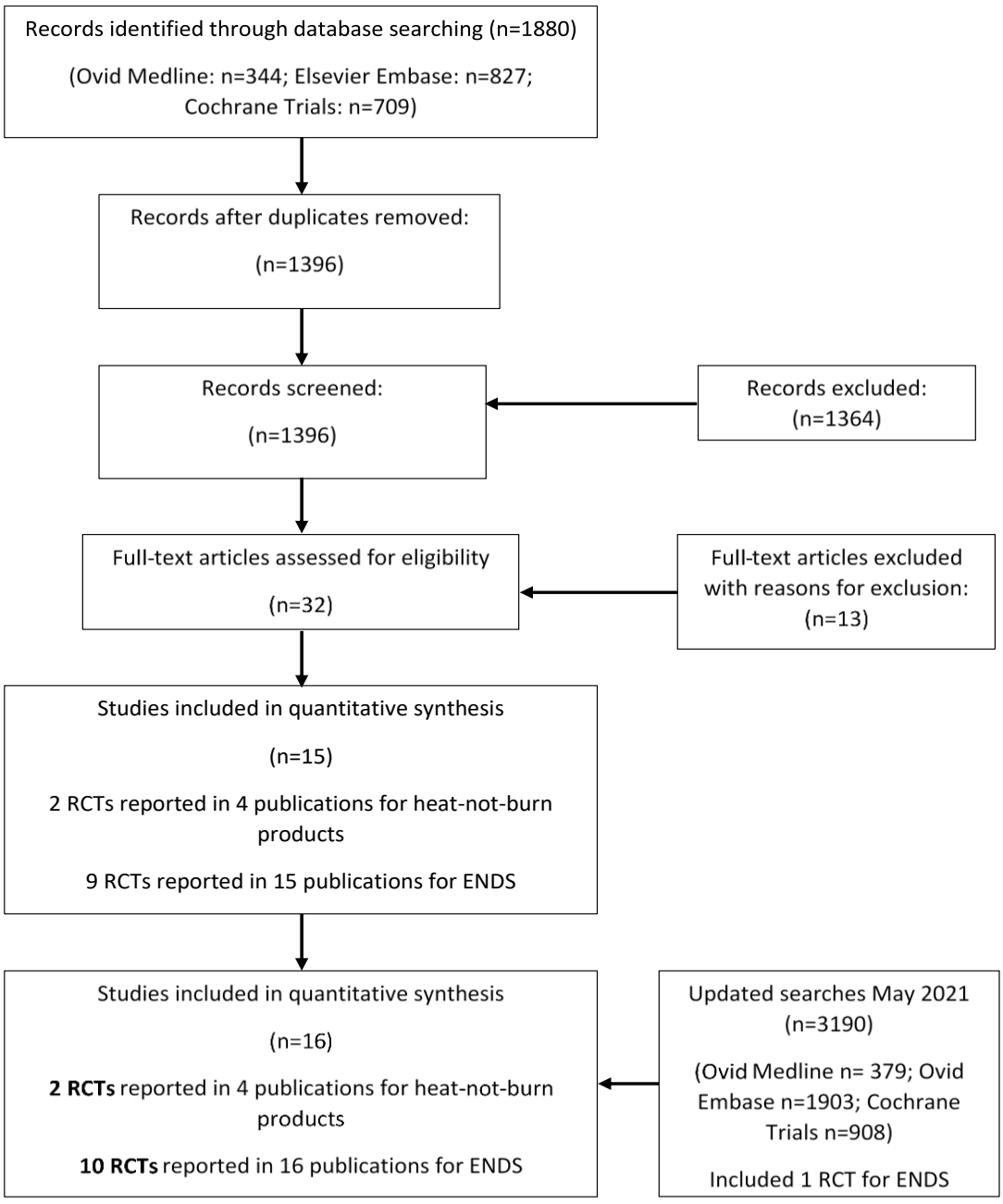
	Reference	Reason for exclusion
1	Watson, N. L., et al. (2021). "The association between frequency of e-cigarette use and long-term smoking cessation outcomes among treatment-seeking smokers receiving a behavioral intervention." Drug and alcohol dependence 218 (no pagination).	Study design (Patient not randomised to e-cigarettes observational data only for this)
2	McRobbie, H. J., et al. (2020). "Nicotine replacement treatment, e-cigarettes and an online behavioural intervention to reduce relapse in recent ex-smokers: a multinational four-arm RCT." Health Technology Assessment (Winchester, England) 24(68): 1-82.	Intervention (Patient choice of NRT or e-cigarettes)

Appendix 3 Model parameters and inconsistency assessment

We specified the following parameters: 250,000 'burn-in' iterations to be discarded, 500,000 iterations for analysis, and three separate chains. Diagnostic tests were run to check model convergence. Thinning of the chains was specified to reduce the risk of autocorrelation. Default priors as specified by the 'gemtc' package were used. For this analysis, we selected NRT as the reference treatment because it is was a common control treatment in the RCTs identified, which is a common standard of care in international clinical guidelines for treatment of tobacco dependence.[1]

A key assumption of NMA is that of evidence consistency that is, that estimates of treatment effects from direct and indirect evidence agree. We have compared the main model (consistency model) against an inconsistency model that assumes unrelated mean (relative) effects using a function of the 'gemtc' package. .[2,3] We also compared the direct head-to-head meta-analysis results versus the NMA outputs to further check for potential inconsistency. Meta-analyses for the direct comparisons were run using the metagen function in the 'meta' package for the R programming language .[4,5]

Appendix 4 PRIMSA diagram



Appendix 5 RCT characteristics

Appendix table 1 Eligibility criteria regarding smoking history from included RCTs

Study ID	N (cigarettes smoked per day)	Length of time smoking	Intention to quit smoking	Prior use of smoking cessation aids
ASCEND[6]	≥10	At least 1 year	Those who wanted to stop smoking	Excluding those using cessation drugs
ECLAT[7]	≥10	At least 5 years	Those not currently attempting to quit smoking or wishing to do so in the next 30 days	Use of smokeless tobacco or NRT (no time frame given)
TEC[8]	–	–	–	No strong preference to use or not to use NRT or e-cigarettes, and were currently not using either type of product
Halpern 2018[9]	–	–	–	–
Lee 2019[10]	≥10	At least 3 years	Those who were motivated to stop smoking entirely or to reduce their cigarette consumption	Excluded those who had attempted to stop smoking in the past 12 months by using other NRTs
BETOFREE[11]	≥10	At least 10 years	Those with a high motivation to stop smoking	Excluded any use of NRTs or e-cigarettes
Holliday 2019[12]	≥10	-	Intention to quit was not an inclusion criterion for this study	Included those not currently using an e-cigarette, or not having used one for more than 2 days in the last 30 days
Hatsukami 2019[13]	≥5	At least 1 year	Excluded if planning to quit smoking in the next 3 months	Excluded those currently using NRT or cessation medication
Lee 2018[14]	>2	-	-	Excluded those who were currently using smoking cessation pharmacotherapy or currently used e-cigarettes daily.
Eiseberg 2020[15]	≥10	-	Moderate or strong desire and intention to attempt to quit	Excluded individuals who had used a smoking cessation therapy in the past 30 days, an e-cigarette in the past 60-days, or had ever used an e-cigarette for 7 days consecutively or more.

Appendix table 2 Sociodemographic characteristics of participants

Characteristic	ASCEND[16]	ECLAT[7]	TEC[8]	Halpern 2018[9]	Lee 2019[10]	BETOFREE[11]	Holliday 2019[12]	Lee 2018[14]	Hatsukami 2019[13]	Eisenberg 2020[15]
Age in years										
Median (IQR)	-	-	41 (33–52)	44 (34.4–54)	-	-	-	-	47 (-)	
Mean (SD)	42.4 (12.7)	44 (12.5)	-	-	42.3 (8.3)	62.8 (4.58)	44.3 (10.7)	53.5 (-)	-	52 (13)
Gender (male)	38%	63%	52%	49%	100%	63%		90%	50.8%	53%
Ethnicity	33% Māori	-	-	-	-	-	6.3% Asian or Asian British	6% Latino	37.9% black, 8.7% other non-white	1-6% black *
Education (second level or lower)	49%	31%	-	30%	61%	-	-	-	41.7%	37-39%*
Employed	-	-	70%	100%	100%	-	75%	-	90%	-
Entitled to free prescriptions	-	-	40.7%	-		-	-	-	-	-
Married	-	-	-	-	90%	-	-	-	-	-

*Only reported by treatment arm -range across arms reported
IQR: Interquartile range
SD: Standard deviation

Appendix table 3 Smoking characteristics of the RCT participants

Characteristic	ASCEND[16]	ECLAT[7]	TEC[8]	Halpern 2018[9]	Lee 2019[10]	BETOFREE[11]	Holliday 2019[12]	Lee 2018[14]	Hatsukami 2019[13]	Eisenberg 2020[15]
Age started smoking (years)										
Mean (SD)	15.5 (4.5)	16.8 (3.9)	-	-	-	17.4 (3.7)	15.7 (3.0)	-	-	-
Median (IQR)	-	-	16 (14–18)	-	-	-	-	-	-	-
Number of years smoking continuously										

Characteristic	ASCEND[16]	ECLAT[7]	TEC[8]	Halpern 2018[9]	Lee 2019[10]	BETOFREE[11]	Holliday 2019[12]	Lee 2018[14]	Hatsukami 2019[13]	Eisenberg 2020[15]
Mean (SD)	24.7* (-)	-	-	-	22 (8.8)	-	-	32 (-)	-	35 (14)
Median (IQR)	-	-	-	18 (10–29)	-	-	-		-	-
Number of cigarettes smoked per day										
Mean (SD)	17.9 (6.3)	-	-	-	20* (-)	19.4 (7.8)	17.4 (6.6)	13 (-)		21 (11)
Median (IQR)		20 (15–25)	15 (10–20)	10 (5–15)	-	-	-		15	-
Lives with other smokers	54%	-	-	-	-	-	-	-	-	30-35%**
At least one quit attempt (%)	55% tried in last year	51% ever tried	-	-	90% ever tried	-	-	-	-	89-93% ever tried**
Mean self-efficacy to quit	3.7 of 5-point scale	-	-	-	6 out of 10 confidence about quitting	-	-	-	-	-
Mean FTND score (SD)	5.5 (2.0)	5.8 (2.2)	4.6 (2.4)	-	4.1 (2.2)	4.3 (1.9)	5.0 (2.1)	3.1	3(median)	6 (2)
FTND score >5 (%)	55%	-	-	-	-	-	-	-	-	-
Mean GN-SBQ score (SD)	20 (8.3)	20.0 (7.2)	-	-	-	-	-	-	-	20 (8)
E-cigarette use	-	-	41.5%	34%	-	-	-	-	-	27-43**
Past NRT use	-	-	74.9%	-	-	-	-	-	-	-

*Calculated
**Only reported by treatment arm -range across arms reported
IQR: Interquartile range
FTND: Fagerström Test for Nicotine Dependence
GN-SBQ: Glover-Nilsson Smoking Behavioral Questionnaire
SD: Standard deviation

Appendix 6 RCT cessation results

Appendix table 4 RCT results with smoking cessation at 24 or 26 weeks

Study ID	Treatment	N = cessation events	N = arm total	Quit rate	Verified	Comparison	RR	LCI	UCI	*p*-value
ASCEND[6]	ENDS	21	289	7%	Yes	–	1	–	–	–
ASCEND[6]	NRT	17	295	6%	Yes	ENDS vs NRT	1.26	0.68	2.34	0.46
ASCEND[6]	ENNDS	3	73	4%	Yes	ENDS vs ENNDS	1.77	0.54	5.77	0.44
ECLAT[7]	ENDS	22	200	11%	Yes	–	1	–	–	–
ECLAT[7]	ENNDS	5	100	5%	Yes	ENDS vs ENNDS	2.20	0.86	5.64	0.10
TEC[8]	ENDS	155	438	35%	No*	–	1	–	–	–
TEC[8]	NRT	112	446	25%	No*	ENDS vs NRT	1.40	1.14	1.72	–
Halpern 2018[9]	ENDS	12	1,199	1%	Yes	–	1	–	–	–
Halpern 2018[9]	No additional treatment	1	813	0%	Yes	ENDS vs no additional treatment	8.14	1.06	62.46	0.04**
Lee 2019[10]	ENDS	16	75	21%	Yes	–	1	–	–	–
Lee 2019[10]	NRT	21	75	28%	Yes	ENDS vs NRT	0.76	0.43	1.34	0.34
BETOFREE[11]	ENDS	13	70	19%	Yes	–	1	–	–	–
BETOFREE[11]	ENNDS	11	70	16%	Yes	ENDS vs ENNDS	1.18	0.57	2.46	0.65
BETOFREE[11]	No additional treatment	7	70	10%	Yes	ENDS vs no additional treatment	1.86	0.79	4.38	0.16
Holliday 2019[12]	ENDS	6	40	15%	Yes	-	-	-	-	-
Holliday 2019[12]	No additional treatment	2	40	5%	Yes	ENDS vs no additional treatment	3.00	0.64	13..98	0.16
Eiseberg 2020[15]	ENDS	5	128	4%	Yes	-	-	-	-	-
Eiseberg 2020[15]	ENNDS	3	127	2%	Yes	ENDS vs ENNDS	1.65	0.40	6.77	0.48
Eiseberg 2020[15]	No additional treatment	1	121	1%	Yes	ENDS vs no additional treatment	4.73	0.56	39.88	0.15

*Not verified at this timepoint

**This study intended to use the Holm method to determine significance, however, we report the unadjusted difference here as this is what is extracted for all studies. Using the Holm method, this comparison was not considered significantly different.

RR: Relative risk; LCI: Lower confidence interval; UCI: Upper confidence interval

Appendix table 5 RCT results with smoking cessation at 52 weeks

Study ID	Treatment	N=cessation events	N=arm total	Verified	Comparison	RR	LCI	UCI	*p*-value
ECLAT[7]	ENDS	22	200	Yes	–	1	–	–	–
ECLAT[7]	ENNDS	4	100	Yes	ENDS vs ENNDS	2.75	0.97	7.76	0.06
TEC[8]	ENDS	79	439	Yes	–	1	–	–	–
TEC[8]	NRT	44	447	Yes	ENDS vs NRT	1.83	1.30	2.58	<0.001
Halpern 2018[9]	ENDS	4	1,199	Yes	–	1	–	–	–
Halpern 2018[9]	No additional treatment	0	813	Yes	ENDS vs no additional treatment	6.11	0.33	113.24	0.22

RR: Relative risk
LCI: Lower confidence interval
UCI: Upper confidence interval

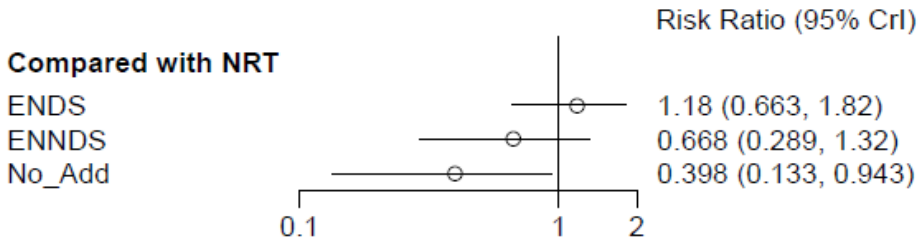
Appendix 7 RCT missing and lost to follow-up data

Appendix table 6 Missing data and lost to follow-up in RCTs

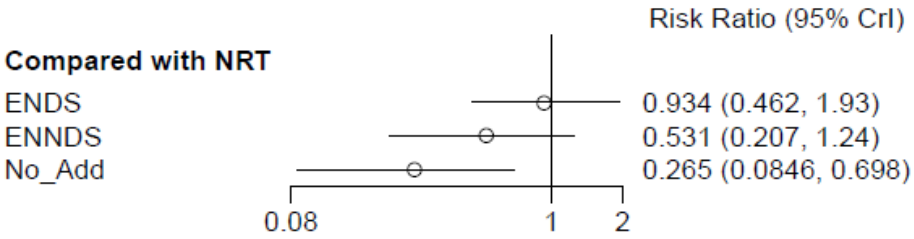
Study ID	How was missing data handled?	Number lost to follow-up/discontinued at 6 months	Number lost to follow-up/discontinued at 12 months
ASCEND	Assumed participants with missing smoking status were smoking	22% in ENDS, 27% in NRT and 22% in ENNDS arm	
ECLAT	Assumed that all those individuals who were lost to follow-up are classified as failures	-	35% in ENDS group A, 37% in ENDS group B and 45% in nicotine e-cigs group
Halpern 2019	Persons with incomplete follow-up data classified as smokers	This trial does not clearly report loss to follow-up although it is clear there was a very large drop-out rate. The study authors defined an engaged cohort as those who had logged on to the trial website at least once. ENDS were only available through logging onto the website so those who were not 'engaged' in the e-cigarette group received no treatment. In the usual care group 15.9% were engaged and 21.1% of the e-cigarette group were engaged	-

Study ID	How was missing data handled?	Number lost to follow-up/discontinued at 6 months	Number lost to follow-up/discontinued at 12 months
Lee 2019	Method for imputing missing data not reported	5.3% in the ENDS group and 18.6% in the NRT group	-
TEC	To assess the effect of missing data on the primary outcome, the authors conducted four prespecified sensitivity analyses, which excluded participants who did not attend at least one behavioral-support session, excluded participants who used the non-assigned product for at least 5 consecutive days, excluded participants who did not complete the 52-week follow-up, and imputed missing information with the use of multiple imputation by chained equations. Missing data were imputed for 136 participants in each group, and 50 data sets were imputed	19.8% in the ENDS group and 24.6% in the NRT group	18.9% in the ENDS group and 23.5% in the NRT group
BETOFREE	Method for imputing missing data not reported	25.7% in the ENDS group, 27.1% in the NRT group and 25.7% in the no additional treatment group	-
Holliday 2019	Participants with missing smoking outcome data (e.g. those not attending for review) were considered as continuing smokers or to have resumed smoking	27.5% in both groups	-
Hatsukami 2019	Unclear how missing data handled for adverse events	At eight weeks there was 23.7% dropout rate in the ENDS arm and 30.3% in the NRT arm	-
Lee 2018	Unclear how missing data handled for adverse events	20% at eight weeks in NRT and 10% for ENDS	-
Eisenberg 2020	Two methods, primary analysis participants missing data assumed to have returned to smoking at baseline level, sensitivity analysis multiple imputation	12% in ENDS group, 14.1 in ENNDS group, 29.8% in no additional treatment	

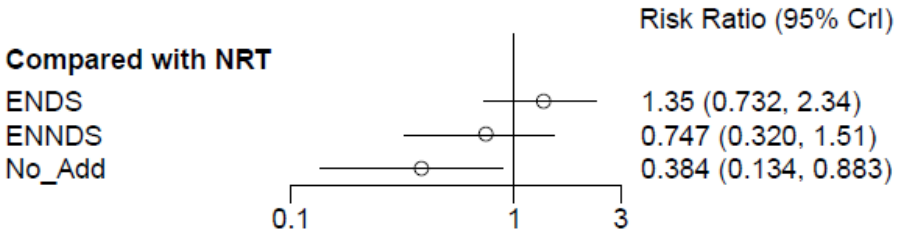
Appendix 8 Sensitivity analyses for NMA at 24—26 weeks



Appendix figure 1 Network meta-analysis of smoking cessation at 24 or 26 weeks: sensitivity analysis 1- excluding light smokers



Appendix figure 2 Network meta-analysis of smoking cessation at 24 or 26 weeks: sensitivity analysis 2-excluding unverified data



Appendix figure 3 Network meta-analysis of smoking cessation at 24 or 26 weeks: sensitivity analysis 3-excluding low dose nicotine e-cigarette

Appendix 9 Adverse events

Appendix table 7 documented adverse events

Study ID	Vital signs	Psychiatric	Cardiovascular	Pulmonary	Rebound and withdrawal and addiction potential	Serious adverse events
ASCEND[6]	N	N	N	N	Y	Y
ECLAT[7]	Y	Y	N	Y	Y	Y
TEC[8]	N	Y	Y	Y	Y	Y
Halpern 2018[9]	N	N	N	N	N	N
Lee 2019[10]	N	N	N	Y	Y	Y
BETOFREE[11]	Y	Y	Y	Y	Y	N
Holliday 2019[12]	N	N	N	N	Y	Y
Lee 2018 [14]	N	N	Y	Y	N	Y
Hatsukami 2019[13]	Y	N	N	Y	N	N
Eisenberg 2020[15]	N	Y	Y	Y	N	Y

Appendix table 8 Pulmonary adverse events documented

Symptom	Study	E-cigarette N events	NRT N events	ENNDS N events	No additional treatment	Total N events
Shortness of breath	TEC[8]	66	64	–	-	130
	ECLAT[7]	12	–	5	-	17
	Lee 2019[10]	–	–	–	-	–
	BETOFREE[11]	92	103	106	-	301
	Eisenberg 2020[15]	53	-	61	43	157
Cough	TEC[8]	97	111	–	-	208
	ECLAT[7]	26	–	11	-	37
	Lee 2019[10]	3	3	–	-	6
	BETOFREE[11]	54	50	36	-	140

	Hatsukami 2019 [13]	15	0	-	-	15
	Lee 2018 [14]	8	1	-	-	9
	Eisenberg 2020[15]	95	-	81	66	242

References

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PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	***2***
ABSTRACT			***2***
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	***3***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	***4***
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one	

		database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	***4***
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	4
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	4 and suppl appendix
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	4 and suppl appendix
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**6/7**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	***8***

RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***8***
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	***7***
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	SUPPL appendix
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Suppl appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	***Suppl appendix***
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	***8***
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	***9***
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	6
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	*Suppl appendix*
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	9-12

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	***5***

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.