National Institute for Health and Care Excellence

Final

Tobacco: preventing uptake, promoting quitting and treating dependence: update

[M] Evidence review for long-term health effects of e-cigarettes

NICE guideline NG209

Evidence reviews underpinning recommendations 1.12.1 to 1.12.6, 1.12.13 to 1.12.17, and research recommendations in the NICE guideline

November 2021

Final

These evidence reviews were developed by PH-IGD

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Contents

Long-term health effects of e-cigarettes

Review question

What are the unique long-term health effects of e-cigarette use?

Introduction

Compared with NRT and other cessation and harm reduction aids, e-cigarettes are relatively new devices. They have been in public use for over ten years and it is important to understand what effects they may have on health, aside from their potential as harm reduction or smoking cessation devices. However, the evidence in this area is still developing.

This review aimed to determine whether e-cigarettes are associated with any unique health harms or benefits in the long term.

PICO table

Table 1: PICO inclusion criteria

Population	**Included** People aged 12 and over who are using e-cigarettes and: • Have never smoked OR • Smoke currently OR • Used to smoke (and are using e-cigarettes to stop smoking or using e-cigarettes to prevent relapse). • **Excluded** • People aged 11 and under • People who have not habitually used e-cigarettes
Intervention	**Included:** People who use or have used e-cigarettes habitually[a] Nicotine containing e-cigarettes and e-cigarettes without nicotine will be included. **Excluded:** Use of other nicotine-containing therapies unless present equally in both intervention and control groups.
Comparison	**Included:** Any comparison group where the only difference from the intervention group is use of e-cigarettes.

Outcomes	**Quantitative outcomes**
	Critical outcomes:
	• Risk of or association with long-term health effects using a validated measure:
	  ○ Cancer (e.g. oral cancers, throat cancer)
	  ○ Cardiovascular health effects (cardiovascular disease i.e. coronary heart disease, strokes and transient ischaemic attack, peripheral arterial disease, aortic disease)

[a] Defined as weekly use throughout. Studies will not be required to specify weekly use, as long as participants are defined as e-cigarette users. Explicit occasional or experimental use will be excluded.

	○ Gastrointestinal health effects ○ Mental health outcomes (e.g. anxiety, stress, depression) ○ Mortality ○ Oral health (e.g. gum disease) ○ Respiratory health effects (e.g. asthma, COPD, acute respiratory infection, lung cancer, respiratory tract cancer, interstitial lung diseases) Important outcomes: • Risk factors for disease e.g.: ○ Respiratory health effects (e.g. peak flow measures; FEV1/FVC ratio) ○ Cardiovascular risk factors: (e.g. high blood pressure, high cholesterol). ○ Gingivitis • Health-related quality of life (using validated patient-report measures, for example EQ-5D). **Excluded:** • Outcomes not measured in people who use e-cigarettes. • Outcomes which are not judged to constitute an important change to health, or a proxy for important change to health.
Setting	All settings

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2018). Further methods are detailed in the methods chapter for this guideline. Methods specific to this review are described in 'Synthesis and appraisal of public health studies', and in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

Identification of public health evidence

Included studies

Two studies are included in this review. One is reported on in three separate articles (Flacco 2019, Manzoli 2017, Manzoli 2015). The study will be referred to as Flacco 2019 for the remainder of this review.

Database search

The review presented here is a new review for this guideline. A joint search was used to identify relevant studies for four e-cigarette review questions. One of these is presented in this document. A systematic search was undertaken in January 2019 for studies published since 1998 and in the English language. Website searches were conducted in line with the protocol. Further details on the search strategy are available in Appendix B.

After removal of duplicates 5,280 unique database results were identified. The website searches identified a further 67 results that were screened separately. The surveillance review for this guideline identified 25 studies related to the safety of e-cigarettes. 113 papers in total (including 4 from the surveillance review) were ordered for full-text review. Of these, one paper met the inclusion criteria for this review (Manzoli 2015). The included study has a cohort study design.

Rerun searches were carried out in November 2019. 1,560 articles were identified. Five were requested for full-paper assessment. Two met the inclusion criteria for this review (Manzoli 2017, Flacco 2019); both were linked to the study already identified through the main

searches (Manzoli 2015) and provided longer-term follow-up data at 2 and 4 years. Therefore the Flacco (2019) study was used as this provided the longest follow-up for this study. Of the studies reporting each outcome, the one with the longest follow-up was selected. In all cases, this was Flacco (2019). The other articles are retained as they contribute to study characteristics (see Appendix D for evidence table). The second included study (Bhatta 2019) was identified through wider reading on the topic and was published after the rerun search was conducted.

Rerun searches were carried out in July 2020. 1,382 articles were identified. Three studies were requested for full-paper assessment, none of these met the inclusion criteria for this review.

Call for evidence

A call for evidence was held in January 2020. The call was open from 6th January until 30th January 2020. Four formal responses were received, providing 12 published articles. One was already included in the review, the remaining 11 were excluded based on the protocol for this review.

Excluded studies

See Appendix K for a full list of excluded studies and the reasons for exclusion.

Synthesis and appraisal of public health studies included in the evidence review

Data synthesis

Two studies were identified for inclusion in this review.

Table 2: Summary of studies included in the evidence review

Study	Setting	Population	Intervention	Comparator	Outcome
Flacco 2019 Cohort	Italy Community setting	Adults (30-75)	E-cigarette use (any model, nicotine / no nicotine) AND cigarette smoking	Cigarette smoking only	• Self-reported health • Diagnosed disease*
Bhatta 2019 Longitudinal survey	USA National survey	Adults (18+)	Exposure to e-cigarettes	None	• Association between e-cigarette use and respiratory disease**

*Self-reported chronic obstructive pulmonary diseases, stroke, heart failure, myocardial infarction, angina, pneumonia, cancer of: larynx or oral cavity, lung, stomach, pancreas, cervix, kidney, bladder, myeloid leukaemia as diagnosed by a physician.

**Respiratory disease is chronic obstructive pulmonary disease, chronic bronchitis, emphysema, or asthma.

See appendix D for full evidence tables.

Evidence appraisal

- This review addresses an intervention question. The Flacco cohort study was assessed using the *Risk of Bias in Non-Randomised Studies – of Interventions* (ROBINS-I) tool, according to the NICE Manual.

- The QUIPS checklist for prognostic studies was used to assess the Bhatta longitudinal study.
- All GRADE rating start at 'high' and are downgraded as appropriate.
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See appendix F for full GRADE tables. See methods chapter for details of rationale for GRADE judgements.

Table 3: Minimal Important Differences (MIDs) agreed

Review	Outcome	MID
6.4	Critical outcomes (cancer, cardiovascular health effects, gastrointestinal health effects, mental health outcomes, respiratory health effects like asthma / COPD / interstitial lung diseases)	Statistical significance
6.4	Important outcomes (oral health, respiratory health effects like FEV1; cardiovascular risk factors like blood pressure and cholesterol)	Default RR: 0.8 to 1.25 Continuous: 0.5*SD

See methods chapter for more information on MIDs. See Appendix A for more detail on outcomes.

Economic evidence

No economic evidence was included in the protocol for this review.

Summary of the evidence

This table is a very high-level overview of the results presented in the GRADE tables. These results should not be considered apart from the GRADE tables, which contain more information about confidence in the evidence and limitations.

Table 4: Evidence summary

Outcome	Summary	Confidence	GRADE profile
Diagnosed disease	An effect was not detected of dual use compared with smoking on diagnosed disease either for the full sample or for non-switchers only.	Very low (1 study)	1
Change in health	Full sample: There was no meaningful difference between dual use and smoking for change in self-reported health. Non-switchers only: An effect was not detected of dual use compared with smoking for change in self-reported health	Full sample: Low (1 study) Non-switchers: Low (1 study)	2
Respiratory health effects	In a study where the committee concluded that the evidence was not strong enough to draw any conclusions about the effect of e-cigarettes on respiratory health, exposure to e-cigarettes is associated with an increase in respiratory disease (combined measure for COPD, chronic bronchitis, emphysema and asthma).	Respiratory disease: Low (1 study) Chronic bronchitis, asthma:	3

Outcome	Summary	Confidence	GRADE profile
	In a study where the committee concluded that the evidence was not strong enough to draw any conclusions about the effect of e-cigarettes on respiratory health, of the conditions included in respiratory disease, exposure to e-cigarettes is associated with chronic bronchitis and asthma. An effect of exposure to e-cigarettes was not detected on COPD or emphysema.	Low (1 study) COPD, emphysema: Very Low (1 study)	

Committee discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee discussed the reasons for specifying long-term health effects in the protocol for this review. They acknowledged that considering short-term health effects would be more likely to yield data, but that this would be less informative than data on long-term health effects. This is because, while the presence of short-term health harms (for example inflammation or cytokine levels) might indicate the possibility for long-term health effects, confidence in these proxy measures would not be sufficient to make recommendations about long-term health effects arising from long-term use. Similarly, the absence of short-term health effects does not indicate that there will be no long-term effects. It was also noted that people can experience unpleasant effects in the days and weeks after quitting smoking regardless of the method used for cessation, and this should not be inadvertently attributed to vaping.

The committee noted that, while people using NRT or other cessation treatments to stop smoking tend to stop using them as soon as they are able to and usually within a number of months, people using e-cigarettes to stop smoking may be more likely to use them for a longer period of time. The committee acknowledged that people may be continuing to vape to prevent going back to smoking, but they emphasised that this practice made it especially important to investigate whether extended use may have any longer term effects.

Certainty in the evidence

The committee had serious concerns about both studies included in this review. Flacco (2019) had a large amount of movement between groups (*smokers* and *dual users*), making it difficult to attribute any outcomes to smoking or e-cigarette use status. The “non-switchers only” analysis attempted to mitigate for this, but this analysis of a smaller group reduced precision in the results. The analysis may also have changed the demographics of the participants if those who switched were systematically different, for example had higher nicotine dependence, than those who didn’t switch. This information is not available in the paper so cannot be assessed.

The committee discussed that the respiratory health effect outcomes were of low and very low confidence. They noted that exposure to smoking between the group exposed to e-cigarettes and the group who had never used e-cigarettes was likely to be uneven: it may be that the use of e-cigarettes is associated with heavier smoking and longer duration of smoking. Neither of these aspects of smoking status were controlled for in the analysis, which adjusted for former and current smoking only, meaning that the results are likely to be confounded. The committee discussed that some of the outcomes (particularly emphysema, chronic bronchitis and COPD) have lead times of decades and are caused, in smoking, by long exposure. They were not confident that the study would have been able to detect changes in these outcomes that were due to e-cigarettes even if they were present. Overall,

the committee agreed that the evidence was not strong enough to draw any conclusions about the effect of e-cigarettes on respiratory health.

Based on the paucity of evidence identified from the formal searches, the committee agreed it was appropriate to conduct a call for evidence (see the NICE manual section 5.5 for more information). No further evidence was identified through this route, and the committee agreed that they could not make recommendations based on evidence from the literature searches.

Benefits and harms

The committee referenced recent events around e-cigarettes in the US reported on by the CDC (2019) and others. They noted that the latest findings suggest that the events (which included lung injury and death) have been linked to vaping tetrahydrocannabinol (THC) and vitamin E acetate oil. This compound is not permitted in e-cigarettes in the UK. E-cigarettes containing nicotine are more tightly regulated in the UK than in the US, and "no vaping related cases like in the US have been reported to the EMCDDA [European Monitoring Centre for Drugs and Drug Addiction] by its EU Early Warning System Network to date" (PHE 2019).

The committee noted the importance of weighing up harms and benefits of using e-cigarettes. For smokers, the alternative to using e-cigarettes might be continued smoking. The extensive harms of smoking are well known, and is the commmittee considered it unlikely that use of e-cigarettes could cause similar levels of harm. They also noted the safety scenario analysis suggested that e-cigarettes would need to cause very high number of adverse outcomes before they were considered not to be cost-effective versus placebo. For people who don't smoke, it is unlikely that inhaling vapour from an e-cigarette is as low risk as not doing so, although the extent of that potential risk is not yet known. The current research gaps mean that this exercise can only be undertaken by using a range of assumptions.

Cost effectiveness and resource use

Cost effectiveness evidence was not considered as part of this review. There is cost effectiveness analysis relating to e-cigarette use for smoking cessation in the review on the effectiveness of treatments for smoking cessation (review K).

Other factors the committee took into account

The committee reflected that e-cigarettes are commonly used by individuals directing their own cessation attempts and are increasingly encouraged by stop smoking services as well. They recognised that practice has overtaken research, more of which is required to be able to provide the thorough and evidence-based information on e-cigarettes that practitioners want to be able to deliver and that can enable informed choice about their use.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.12.1 to 1.12.6, 1.12.13 to 1.12.17 and the research recommendation on health effects of e-cigarettes. Other evidence supporting these recommendations can be found in the evidence reviews on barriers and facilitators to e-cigarettes (review L) and cessation and harm-reduction treatments (review K).

References to included studies

Flacco M E, Ferrante M, Fiore M, Marzuillo C, La Vecchia , C , Gualano M R, Liguori G, Fragassi G, Carradori T, Bravi F, Siliquini R, Ricciardi W, Villari P, and Manzoli L (2019) Cohort study of electronic cigarette use: safety and effectiveness after 4 years of follow-up. European review for medical and pharmacological sciences 23(1), 402-41

Manzoli Lamberto, Flacco Maria Elena, Ferrante Margherita, La Vecchia , Carlo , Siliquini Roberta, Ricciardi Walter, Marzuillo Carolina, Villari Paolo, Fiore Maria, and Group Islese Working (2017) Cohort study of electronic cigarette use: effectiveness and safety at 24 months. Tobacco control 26(3), 284-292.

Manzoli Lamberto, Flacco Maria Elena, Fiore Maria et al. (2015) Electronic Cigarettes Efficacy and Safety at 12 Months: Cohort Study. PloS one 10(6), e0129443.

Bhatta, D. N., Glantz, S. A (2019) Association of E-Cigarette Use With Respiratory Disease Among Adults: A Longitudinal Analysis. American Journal of Preventive Medicine 000(000):1−9 (in press).

Appendices

Appendix A – Review protocols

Review protocol for Tobacco Suite, RQ6.4 Health effects of e-cigarettes

ID	Field (based on PRISMA-P	Content
I	Review question	6.4. What are the unique long-term health effects of e-cigarette use?
II	Type of review question	Intervention review
III	Objective of the review	Evidence suggests that e-cigarettes are substantially less harmful to health than smoking. However, the evidence in this area is still developing, including evidence on the long-term health impact of using e-cigarettes. Compared with NRT and other cessation and harm reduction aids, e-cigarettes are relatively new devices. They have been in public use for over ten years and it is important to understand what effects they may have on health, aside from their potential as harm reduction or smoking cessation devices (their effectiveness in this capacity, as well as any adverse effects, is considered in review question 6.1). This review aims to determine whether e-cigarettes cause any health harms or benefits aside from their potential to reduce smoking-related harm. This does

		not include the potential reduction of harm of e-cigarettes when compared with smoking, but the potential harms and benefits inherent to e-cigarette use alone.
IV	Eligibility criteria – population/disease/condition/issue/domain	Included: People aged 12 and over who are using e-cigarettes and: • Have never smoked OR • Smoke currently OR • Used to smoke (and are using e-cigarettes to stop smoking, or using e-cigarettes to prevent relapse). Excluded: • People aged 11 and under • People who have not habitually used e-cigarettes Setting All settings.
V	Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Included:

		People who use or have used e-cigarettes habitually[2] Nicotine containing e-cigarettes and e-cigarettes without nicotine will be included. Excluded: Use of other nicotine-containing therapies unless present equally in both intervention and control groups.
VI	Eligibility criteria – comparator(s)/control or reference (gold) standard	Included: Any comparison group where the only difference from the intervention group is use of e-cigarettes.
VII	Outcomes and prioritisation	Quantitative outcomes Critical outcomes: - Risk of or association with long-term health effects using a validated measure: • Cancer (e.g. oral cancers, throat cancer)

[2] Defined as weekly use throughout. Studies will not be required to specify weekly use, as long as participants are defined as e-cigarette users. Explicit occasional or experimental use will be excluded.

		• Cardiovascular health effects (cardiovascular disease i.e. coronary heart disease, strokes and transient ischaemic attack, peripheral arterial disease, aortic disease)
		• Gastrointestinal health effects
		• Mental health outcomes (e.g. anxiety, stress, depression)
		• Mortality
		• Oral health (e.g. gum disease)
		• Respiratory health effects (e.g. asthma, COPD, acute respiratory infection, lung cancer, respiratory tract cancer, interstitial lung diseases)
		Important outcomes:
		• Risk factors for disease e.g.:
		  ○ Respiratory health effects (e.g. peak flow measures; FEV1 /FVC ratio)
		  ○ Cardiovascular risk factors: (e.g. high blood pressure, high cholesterol).
		  ○ Gingivitis

		• Health-related quality of life (using validated patient-report measures, for example EQ-5D). Excluded: Outcomes not measured in people who use e-cigarettes. Outcomes which are not judged to constitute an important change to health, or a proxy for important change to health.
VIII	Eligibility criteria – study design	Included study designs: • Systematic reviews of included study designs • RCTs (including cluster RCTs) • Non-randomised controlled trials • Controlled before-and-after studies • Cohort studies If no studies are identified, the following study design will be considered: • Case-control Excluded study designs • Qualitative studies

		• Uncontrolled before-and-after studies • Cost-utility (cost per QALY) • Cost benefit (i.e. net benefit) • Cost-effectiveness (Cost per unit of effect) • Cost minimization • Cost-consequence
IX	Other inclusion exclusion criteria	Studies This is a new review question for this update. Exclusion criteria: Studies with a minimum 1 year follow-up will be included. Only papers published in the English language will be included. Studies carried out in any country will be included. Only studies published in 1998 onwards will be included. Only full published studies (not protocols or summaries, even where they contain some data) will be included. Systematic reviews Relevant systematic reviews (SRs) identified from database searches will be citation searched. Highly relevant systematic reviews may be included as a primary source of

		data. These SRs will be assessed against the inclusion criteria for this protocol, and their quality will be assessed using the ROBIS tool. Where the SR is highly relevant and of high quality, details or data from the systematic review may be used. In addition to any SRs meeting the above criteria, other primary studies will be included if they were published after the publication date of the SR and meet the protocol inclusion criteria.

X	Proposed sensitivity/sub-group analysis, or meta-regression	The following factors will be of interest in any meta-regression or subgroup analysis:
		
		• Age groups
		  o Young people (12-17) vs adults (18+)
		• Chronic conditions at baseline
		  o By system (respiratory, cardiovascular, neurological including cerebrovascular) vs none
		• Nicotine content of e-cigarettes
		  o Nicotine containing e-cigarettes vs e-cigarettes without nicotine

XI	Selection process – duplicate screening/selection/analysis	The review will use the priority screening function within the EPPI-reviewer systematic reviewing software. Double screening will be carried out for 10% of titles and abstracts by a second reviewer. Disagreements will be resolved by discussion. Inter-rater reliability will be assessed and reported. If below 90%, a second round of 10% double screening will be considered. The study inclusion and exclusion lists will be checked with members of the PHAC to ensure no studies are excluded inappropriately.
XII	Data management (software)	EPPI Reviewer will be used:

		• to store lists of citations • to sift studies based on title and abstract • to record decisions about full text papers • to order freely available papers via retrieval function • to request papers via NICE guideline Information Services • to store extracted data Cochrane Review Manager 5 will be used to perform meta-analyses. Any meta-regression analyses will be undertaken using the R software package.
XIII	Information sources – databases and dates	The same search will be used to identify evidence for RQ4.1, RQ6.2, RQ6.3 and RQ 6.4 as the search terms overlap. The results will be updated as appropriate before each review commences. The following methods will be used to identify the evidence: • the databases listed below will be searched with an appropriate strategy. • the websites listed below will be searched or browsed with an appropriate strategy. • selected studies that are potentially relevant to the current review will be identified from the bibliography of any systematic reviews identified during the search process that are not being included in their own right. • forward citation searching and reference harvesting will be done using selected studies prioritised from any scoping searches or relevant papers identified in the search process. Database strategies

		The principal search strategy is listed in Appendix A. The search strategy will take this broad approach: (E-cigarettes OR Vaping) AND Limits Feedback on the principal database strategy will be sought from PHAC members. The principal search strategy will be developed in MEDLINE (Ovid interface) and then adapted, as appropriate, for use in the other sources listed, taking into account their size, search functionality and subject coverage. The databases will be: • Applied Social Science Index and Abstracts (ASSIA) via ProQuest • Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley • Cochrane Database of Systematic Reviews (CDSR) via Wiley • Embase via Ovid • Educational Resources Information Center (ERIC) via ProQuest • Health Management Information Consortium (HMIC) via Ovid • MEDLINE via Ovid • MEDLINE-in-Process (including Epub Ahead-of-Print) via Ovid • PsycINFO via Ovid • Social Policy and Practice (SPP) via Ovid

		Database search limits Database functionality will be used, where available, to exclude: • non-English language papers • animal studies • editorials, letters and commentaries • conference abstracts and posters • registry entries for ongoing or unpublished clinical trials • duplicates. Sources will not be limited by date. The database search strategies will not use any search filters for specific study types. Web of Science Forwards citation searching and reference harvesting will be conducted using Web of Science (WOS) Core Collection. Only those references which NICE can access through its WOS subscription will be added to the search results. Only papers published in the English language will be included in the search results. Duplicates will be removed in WOS before downloading.

		Websites The following websites will be searched with an appropriate strategy: • Health Services/Technology Assessment Texts (HSTAT) https://www.ncbi.nlm.nih.gov/books/NBK16710 • NICE Evidence Search https://www.evidence.nhs.uk The websites of relevant organisations, including the ones below, will be browsed: • Action on Smoking and Health (ASH) http://ash.org.uk/home • Local Government Association https://www.local.gov.uk • National Centre for Smoking Cessation and Training http://www.ncsct.co.uk • NHS Digital https://digital.nhs.uk • Northern Ireland Assembly http://www.niassembly.gov.uk/ • Public Health England https://www.gov.uk/government/organisations/public-health-england • Royal College of Paediatrics and Child Health https://www.rcpch.ac.uk/ • Royal College of Physicians https://www.rcplondon.ac.uk • Scottish Government https://www.gov.scot • Smokefree NHS https://www.nhs.uk/smokefree • Smoking Toolkit Study http://www.smokinginengland.info • Treat Tobacco http://www.treatobacco.net/en/index.php • UK Centre for Tobacco and Alcohol Studies http://ukctas.net/index.html • University of Bath Tobacco Control Research Group https://researchportal.bath.ac.uk/en/organisations/uk-centre-for-tobacco-control-studies

		• University of Stirling Centre for Tobacco Control Research https://www.stir.ac.uk/about/faculties-and-services/health-sciences-sport/research/research-groups/centre-for-tobacco-control-research/publications • Welsh Government https://gov.wales/?lang=en • World Health Organization Europe http://www.euro.who.int/en/health-topics/disease-prevention/tobacco Additional searches will be conducted using Google. It may be necessary to restrict the search results to particular file types (e.g. pdf or Word), to particular countries (e.g. UK), the most recent results (e.g. 2008-current) or to review on screen a limited number pages (e.g. the first 100 results), depending on the number of results retrieved. This will be done in consultation with the review team. • Google https://www.google.co.uk The website results will be reviewed on screen and documents in English and that are potentially relevant will be listed with their title and abstract (if available) in a Word document. The initial screening decision will be made using this Word file. Any items selected for review at full text will be added to EPPI-Reviewer. Quality assurance The guidance Information Services team at NICE will quality assure the principal search strategy and peer review the strategies for the other databases.

		Any revisions or additional steps will be agreed by the review team before being implemented. Any deviations and a rationale for them will be recorded alongside the search strategies. Search results The database search results will be downloaded to EndNote before duplicates are removed using automated and manual processes. The de-duplicated file will be exported in RIS format for loading into EPPI-Reviewer for data screening.
XIV	Identify if an update	This question is a new question for the Tobacco update.
XV	Author contacts	Please see the guideline development page
XVI	Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
XVII	Search strategy – for one database	For details please see appendix B.
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used and published as appendix D (effectiveness evidence tables) or H (economic evidence tables).
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix D (effectiveness evidence tables) or H (economic evidence tables).

XX	Methods for assessing bias at outcome/study level	Standard study checklists will be used to critically appraise individual studies. For details please see Appendix H of Developing NICE guidelines: the manual The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ GRADE will be used to assess confidence in the findings from quantitative evidence synthesis. GRADE-CERQual will be used to assess confidence in the findings from qualitative evidence syntheses.
XXI	Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual Non-randomised studies are at risk of confounding. These studies should adjust for confounders which are decided by the committee to have important potential to affect the result, or the allocation into intervention or control groups. These factors are: - Peer or family smoking - Baseline smoking status (where sample includes people who smoke) - Socioeconomic status Where adjusted results are provided, these will be used in analysis. Where no adjustment has taken place, this will be considered when assessing risk of bias.

XXII	Methods for analysis – combining studies and exploring (in)consistency	Heterogeneity Data from different studies will be pooled in a meta-analysis where they are investigating the same outcome and where the resulting meta-analysis may be useful for decision-making. Cluster and individual randomised controlled trials will be pooled. Randomised and non-randomised controlled studies investigating the same outcomes will be pooled. Results will be stratified by design (cluster, individual, randomised and non-randomised for a maximum of four groups stratified) and the P value of the interaction between study design and effect evaluated. A P value of <0.2 will be considered significant. If interaction is significant, results will be presented separately for each group, but if not, will be presented with one averaged effect estimate. It is anticipated that studies included in the review will be heterogeneous with respect to participants, interventions, comparators, setting and study design. Where significant between study heterogeneity in methodology, population, intervention or comparator is identified by the reviewer in advance of data analysis, random effects models will be used. If methodological heterogeneity is not identified in advance but the I^2 value is ≥50%, random effects models will also be used. If the I^2 value is above 50%, heterogeneity will be judged to be serious and so will be downgraded by one level in GRADE. If the I^2 value is above 75%, heterogeneity will be judged to be very serious and will be downgraded by two levels in GRADE. If the studies are found to be too heterogeneous to be pooled statistically, a narrative synthesis will be conducted. Imprecision

		No minimally important difference (MID) thresholds relevant to this guideline were identified from the COMET database or other published source. MIDs were agreed by committee. Uncertainty is introduced where confidence intervals cross the MID threshold. If the confidence interval crosses one lower MID threshold, this indicates 'serious' risk of imprecision. Crossing both MID thresholds indicates 'very serious' risk of imprecision in the effect estimate. Where the MID is 'any significant change' there is effectively only one threshold (the line of no effect), and so only one opportunity for downgrading. In this instance, outcomes will be downgraded again if they are based on small samples (<300 people). MIDs for outcomes will be included in the methods section of the individual reviews.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see Appendix H of Developing NICE guidelines: the manual.
XXIV	Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee will develop the guideline. The committee will be convened by Public Health Internal Guidelines Development (PH-IGD) team

		and chaired by Sharon Hopkins in line with section 3 of Developing NICE guidelines: the manual. Staff from Public Health Internal Guidelines Development team will undertake systematic literature searches, appraise the evidence, conduct meta-analysis where appropriate and draft the guideline in collaboration with the committee. Cost-effectiveness analysis will be conducted by YHEC where appropriate. For details please see Developing NICE guidelines: the manual.
XXVII	Sources of funding/support	PH-IGD is funded and hosted by NICE
XXVIII	Name of sponsor	PH-IGD is funded and hosted by NICE
XXIX	Roles of sponsor	NICE funds PH-IGD to develop guidelines for those working in the NHS, public health and social care in England.
XXX	PROSPERO registration number	141854

Appendix B – Literature search strategies

Search approach

The strategy comprehensively covered e-cigarettes and vaping, without including any search terms for the population or outcomes. One search was done to cover review questions 4.1, 6.2, 6.3 and 6.4. Review 6.4 is presented in this document.

The MEDLINE strategy below was run after QA, peer review and consultation with the committee. The strategy was adapted as appropriate to the other databases listed in the protocol (see the sources tables below). The searches were done on 7 January 2019.

Additional search results were identified from the scoping searches for this topic. These were used for forwards citation searching and reference harvesting using Web of Science.

Further searches were undertaken for grey literature using the websites listed in the protocol. 67 results were identified through the websites and these were screened separately in Word.

Full details of all the search strategies are available in a separate document from the NICE guidance Information Services team.

Sources searched to identify the evidence

Database name	Date searched	Database Platform	Database segment or version	No. of records
Applied Social Science Index and Abstracts (ASSIA)	07/01/2019	ProQuest	1987 - current	673
Cochrane Central Register of Controlled Trials (CENTRAL)	07/01/2019	Wiley	Cochrane Central Register of Controlled Trials Issue 1 of 12, January 2019	413
Cochrane Database of Systematic Reviews (CDSR)	07/01/2019	Wiley	Cochrane Database of Systematic Reviews Issue 1 of 12, January 2019	16
Embase	07/01/2019	Ovid	Embase 1974 to 2019 January 04	2493
Educational Resources Information Center (ERIC)	07/01/2019	ProQuest	1966 - current	69
Health Management Information Consortium (HMIC)	07/01/2019	Ovid	HMIC Health Management Information Consortium 1979 to September 2018	117

MEDLINE	07/01/2019	Ovid	Ovid MEDLINE(R) 1946 to January 04, 2019	2530
MEDLINE-in-Process (including Epub Ahead-of-Print)	07/01/2019	Ovid	Ovid MEDLINE(R) Epub Ahead of Print January 04, 2019, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 04, 2019	1278
PsycINFO	07/01/2019	Ovid	PsycINFO 1806 to December Week 5 2018	1387
Social Policy and Practice (SPP)	07/01/2019	Ovid	Social Policy and Practice 201810	5
Scoping searches	07/01/2019	-	-	7
Web of Science	07/01/2019	Clarivate	Web of Science Core Collection (1990-present)	546

Database strategy – main search as run in MEDLINE and adapted for other sources

Database(s): Ovid MEDLINE(R) 1946 to January 04, 2019

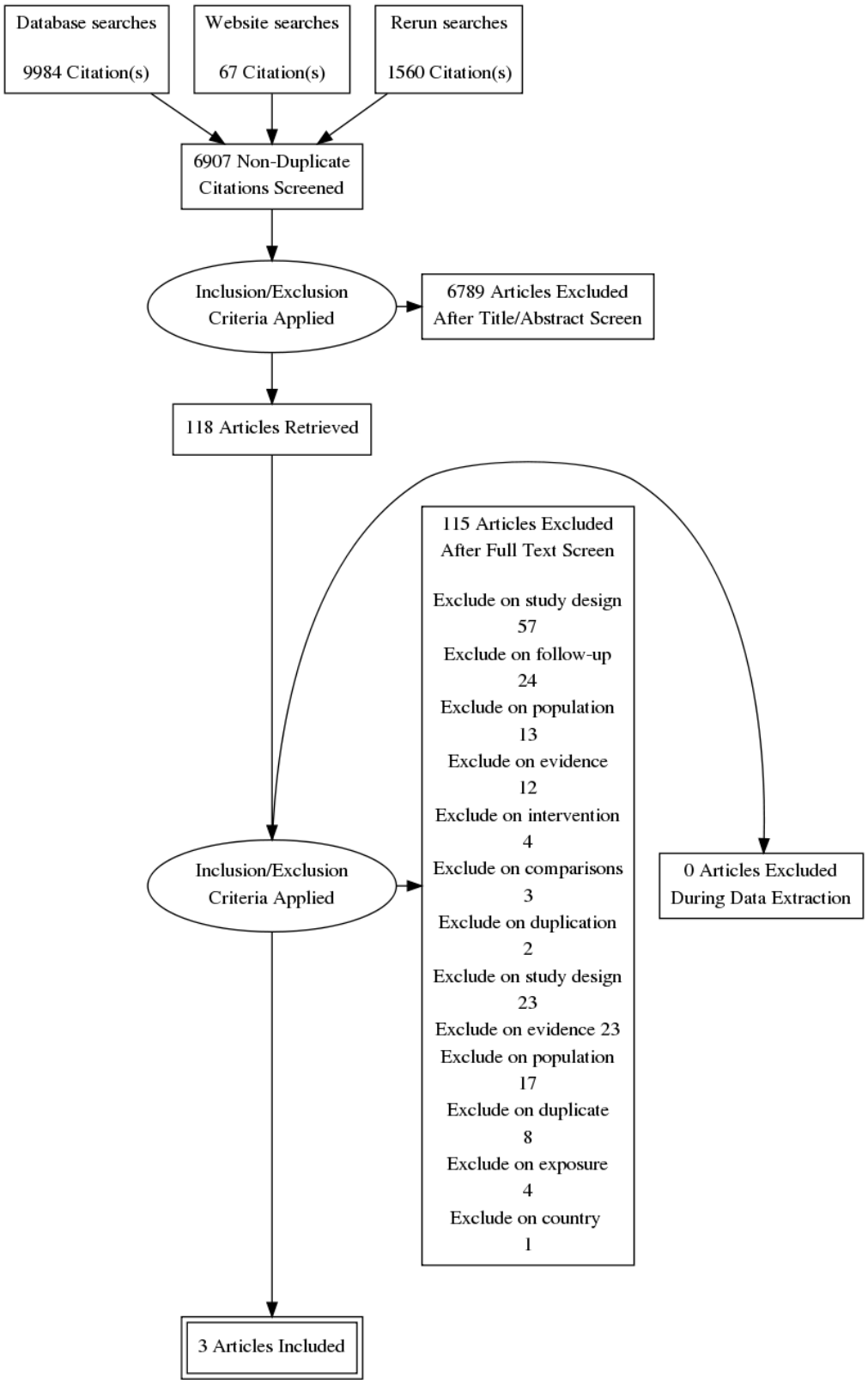
#	Searches	Results
1	Electronic Nicotine Delivery Systems/	2118
2	Vaping/	221
3	(ecig* or e-cig* or e-voke* or juul* or vape* or vaping* or ENNDS).ti,ab.	2000
4	(electronic* adj3 (tobacco* or nicotin* or cigar* or cigs or vapor* or vapour*)).ti,ab.	1596
5	((tobacco* or nicotin* or cigar* or cigs) adj3 (vapor* or vapour* or device* or inhalator* or inhaler*)).ti,ab.	613
6	((tobacco* or nicotin* or cigar* or cigs) adj3 (dual* or multiple* or multi) adj3 ("use" or uses or user* or usage* or using*)).ti,ab.	287
7	(nicotin* and (ENDS or ANDS)).ti,ab.	221
8	(nicotin* adj3 deliver* system*).ti,ab.	251
9	(polytobacco* or poly tobacco* or poly-tobacco* or multitobacco* or multi tobacco* or multi-tobacco*).ti,ab.	68
10	or/1-9	3464
11	Animals/ not (Animals/ and Humans/)	4499580
12	10 not 11	3292

13	limit 12 to (letter or historical article or comment or editorial or news or case reports)	635
14	12 not 13	2657
15	limit 14 to english language	2530

Key to search operators

/	Medical Subject Heading (MeSH) term
.ti	Searches the title field
.ab	Searches the abstract field
*	Truncation symbol (searches all word endings after the stem)
adj*n*	Adjacency operator to retrieve records containing the terms within a specified number (*n*) of words of each other

Appendix C – Public health evidence study selection



Appendix D – Public health evidence tables

Flacco 2019

Bibliographic reference/s	**Flacco M E, Ferrante M, Fiore M, Marzuillo C, La Vecchia , C , Gualano M R, Liguori G, Fragassi G, Carradori T, Bravi F, Siliquini R, Ricciardi W, Villari P, and Manzoli L (2019) Cohort study of electronic cigarette use: safety and effectiveness after 4 years of follow-up. European review for medical and pharmacological sciences 23(1), 402-412**
Study name	Flacco 2019 (supported by Manzoli 2015 and Manzoli 2017)
Registration	Clinicaltrials.gov: NCT01785537
Study type	Prospective cohort study
Study dates	2013-2017
Objective	To evaluate the safety and efficacy as a tool of smoking cessation of electronic cigarettes (e-cigarettes), directly comparing users of e-cigarettes only, smokers of tobacco cigarettes only, and smokers of both. To note: only smokers of tobacco cigarettes and smokers of both e-cigarettes and tobacco cigarettes are extracted (users of e-cigarettes only excluded), as tobacco smoking needs to be consistent across groups to isolate effects of e-cigarettes.
Country/ Setting	Italy (46% of participants are from Abruzzo, remainder not described)
Number of participants / clusters	At 4 year follow-up: Smokers of tobacco cigarettes only: n = 471 Users of tobacco and e-cigarettes: n = 216 Study unlikely to be powered for its primary outcomes (cessation and reduction in cigarettes per day), due to a loss of funding meaning fewer participants recruited than originally planned, but power not explicitly discussed.
Attrition	• Smokers of tobacco cigarettes only: 32.0% (222/693 participants) lost to follow-up / discontinued • Users of tobacco and e-cigarettes: 32.3% (103/319 participants) lost to follow-up / discontinued. Authors report that few differences in baseline characteristics were found between participants completing the study and those who withdrew or were lost to follow-up, but drop-outs were slightly younger than completers. No instances of diagnosed disease were reported by participants who dropped out at 2- or 4-year follow up at their previous follow-up points.
Participant /community characteristics.	Baseline Characteristics relevant to this review:

Characteristic	Tobacco cigarettes only	Dual use	Difference (defined as p<0.01)
Mean age in years (SD)	44.2 (11.9)	44.3 (12.0)	No
Male gender (%)	48.7	64.2	Yes
Employed (%)	79.5	74.4	No
Educational level (%)			
Finished high school	42.5	46.7	No
Bachelor or higher	35.6	31.2	No
Cardiovascular risk and health			
Hypertension (%)	11.6	9.9	No
Diabetes (%)	3.3	4.3	No
Hypercholesterolemia (%)	8.8	10.3	No

Bibliographic reference/s	**Flacco M E, Ferrante M, Fiore M, Marzuillo C, La Vecchia , C , Gualano M R, Liguori G, Fragassi G, Carradori T, Bravi F, Siliquini R, Ricciardi W, Villari P, and Manzoli L (2019) Cohort study of electronic cigarette use: safety and effectiveness after 4 years of follow-up. European review for medical and pharmacological sciences 23(1), 402-412**			
Study name	Flacco 2019 (supported by Manzoli 2015 and Manzoli 2017)			
	Self-reported health (mean, SD)	7.8 (1.3)	7.7 (1.2)	No
	Product use			
	Years of tobacco smoking	22.3 (12.6)	25.2 (12.5)	Yes
	N. cigarettes daily	14.1 (8.1)	14.9 (9.8)	No
	Months of electronic smoking	NA	8.4 (4.5)	NA
	E-cigs without nicotine (%)	NA	5.6	NA
	E-cigs with 10+mg nicotine (%)	NA	41.4	NA
	Representativeness not reported.			
Method of allocation	Participants were recruited through direct contact with general practitioners and e-cigarette shops, via internet advertisement and social networks. Recruitment not random. No allocation to either condition – participants belonged to a group depending on their habits at the time of recruitment.			
Inclusion criteria	Tobacco smokers: must have smoked ≥1 tobacco cigarette per day for the past 6 months. Dual users: must have smoked tobacco cigarettes and used e-cigarettes within the same week for the past 6 months.			
Exclusion criteria	Exclusion criteria were: age <30y and >75y; pregnancy or breastfeeding; illicit drug use, major depression, severe allergies, angina, and past episodes of smoking-related major diseases.			
Intervention	**TIDieR Checklist criteria**	**Details**		
	Brief Name	Dual use		
	Rationale/theory/Goal	NA		
	Materials used	The addition of e-cigarette use on top of smoking. E-cigarettes could be of any model and could either include or not include nicotine. E-cigarettes could be being used for any reason (authors name cessation, reducing tobacco smoking, allowing indoor smoking).		
	Procedures used	NA		
	Provider	E-cigarettes not provided, but used by participants in their usual way (no difference intended between method of use during study compared with before study)		
	Method of delivery	NA		
	Location	Participants used e-cigarettes as they normally did.		
	Duration	Entirety of follow-up period (48 months)		
	Intensity	As decided by participant		
	Tailoring/adaptation	NA		
	Planned treatment fidelity	Intended that participants might change their 'intervention' (or exposure) state throughout the study		

Bibliographic reference/s	**Flacco M E, Ferrante M, Fiore M, Marzuillo C, La Vecchia , C , Gualano M R, Liguori G, Fragassi G, Carradori T, Bravi F, Siliquini R, Ricciardi W, Villari P, and Manzoli L (2019) Cohort study of electronic cigarette use: safety and effectiveness after 4 years of follow-up. European review for medical and pharmacological sciences 23(1), 402-412**	
Study name	Flacco 2019 (supported by Manzoli 2015 and Manzoli 2017)	
		by reducing smoking or quitting smoking. Some might also change their use of e-cigarettes (either taking them up or stopping using them). This reflects natural patterns of use.
	Actual treatment fidelity	At 1 year: Only 24.6% (57/232 participants) in this group were still dual users at follow-up: • 53.4% (124) stopped using e-cigarettes • 11.6% (27) stopped using e-cigs and tobacco cigarettes • 10.3% (24) stopped using tobacco cigarettes At 4 years: • 19.4% had stopped using both tobacco and e-cigarettes • 33.8% had stopped using tobacco cigarettes
	Other details	None
Comparison	**TIDieR Checklist criteria**	**Details**
	Brief Name	Tobacco smokers
	Rationale/theory/Goal	NA
	Materials used	Tobacco smoking as usual for participant
	Procedures used	NA
	Provider	Tobacco cigarettes not provided: purchased as usual by the participant.
	Method of delivery	NA
	Location	Participants used cigarettes as they normally did.
	Duration	Entirety of follow-up period (48 months)
	Intensity	As decided by participant
	Tailoring/adaptation	NA
	Planned treatment fidelity	As for intervention, intended that participants might change their 'intervention' (or exposure) state throughout the study.
	Actual treatment fidelity	At 1 year: 77.6% (381/491 participants) in this group were still sole tobacco smokers at follow-up: • 13.6% (67) stopped using tobacco cigarettes • 6.9% (34) stopped using tobacco cigarettes and started using e-cigarettes • 1.8% (9) became dual users At 4 years: • 20.2% had stopped using both tobacco and e-cigarettes • 26.8% had stopped using tobacco cigarettes (but may have taken up e-cigarettes

<table>
<tr><td>Bibliographic reference/s</td><td colspan="2">Flacco M E, Ferrante M, Fiore M, Marzuillo C, La Vecchia , C , Gualano M R, Liguori G, Fragassi G, Carradori T, Bravi F, Siliquini R, Ricciardi W, Villari P, and Manzoli L (2019) Cohort study of electronic cigarette use: safety and effectiveness after 4 years of follow-up. European review for medical and pharmacological sciences 23(1), 402-412</td></tr>
<tr><td>Study name</td><td colspan="2">Flacco 2019 (supported by Manzoli 2015 and Manzoli 2017)</td></tr>
<tr><td></td><td>Other details</td><td>None</td></tr>
<tr><td>Follow up</td><td colspan="2">48 months</td></tr>
<tr><td>Data collection</td><td colspan="2">Baseline: Data were collected through a structured questionnaire on smoking habits, previous and current diseases, lifestyle behaviour, and quality of life.
Follow-up: The same questionnaire was administered through phone interview and/or by internet (www.ipazienti.it/fumo) after 48 months (proportion by phone vs internet not reported).
Self-reported health: Participants were asked the EuroQol final question, ranging from 1 (feel very bad) to 10 (perfectly healthy): “How would you rate your current overall health status on a scale from 1 (worst imaginable) to 10 (best imaginable)?".
Adverse events (analysed as “diagnosed disease”): Participants were asked to report diseases “diagnosed by a physician”. Self-reported chronic obstructive pulmonary diseases, stroke, heart failure, myocardial infarction, angina, pneumonia, cancer of: larynx or oral cavity, lung, stomach, pancreas, cervix, kidney, bladder, myeloid leukaemia. Combined into one measure (any vs none). This was obtained from direct visits for residents in Sicily (16% of sample) or hospital discharge abstracts for residents of Abruzzo region, (46.6%).
To note: in the protocol, these are called “tobacco-related adverse events”.

Blinding of participants not possible. Blinding of outcome assessors not reported.</td></tr>
<tr><td>Critical outcomes measures and effect size. (time points)</td><td colspan="2">None reported</td></tr>
<tr><td>Important outcomes measures and effect size. (time points)</td><td colspan="2">Difference in self-reported health* at 48-month follow-up compared with baseline
Dual users compared with tobacco cigarette smokers only
<table>
<tr><th></th><th>Within group mean difference between baseline and 48 months in points (SD)</th><th>Between group mean difference (95% CI)</th></tr>
<tr><td>Dual users (n = 216)</td><td>0.0 (1.6)</td><td rowspan="2">0.18 (-0.02, 0.39)</td></tr>
<tr><td>Tobacco cigarette smokers (n = 471)</td><td>-0.2 (1.4)</td></tr>
</table>
*Scale 1 (feel very bad) to 10 (perfectly healthy).
Actual point scores at baseline and follow up for either group not reported.

Non switchers only: Dual users compared with tobacco cigarette smokers only
<table>
<tr><th></th><th>Within group mean difference between baseline and 48 months in points (SD)</th><th>Between group mean difference (95% CI)</th></tr>
<tr><td>Dual users (n = 39)</td><td>0.2 (1.4)</td><td rowspan="2">0.45 (-0.13, 1.04)</td></tr>
<tr><td>Tobacco cigarette smokers (n = 409)</td><td>-0.1 (1.3)</td></tr>
</table>
*Scale 1 (feel very bad) to 10 (perfectly healthy).
Actual point scores at baseline and follow up for either group not reported.</td></tr>
</table>

<table>
<tr><td>Bibliographic reference/s</td><td>Flacco M E, Ferrante M, Fiore M, Marzuillo C, La Vecchia , C , Gualano M R, Liguori G, Fragassi G, Carradori T, Bravi F, Siliquini R, Ricciardi W, Villari P, and Manzoli L (2019) Cohort study of electronic cigarette use: safety and effectiveness after 4 years of follow-up. European review for medical and pharmacological sciences 23(1), 402-412</td></tr>
<tr><td>Study name</td><td>Flacco 2019 (supported by Manzoli 2015 and Manzoli 2017)</td></tr>
<tr><td></td><td>To note: actual point scores not reported for self-reported health outcome.

<u>Difference in diagnosed disease at 48-month follow-up</u>
Dual users compared with tobacco cigarette smokers only
<table>
<tr><td></td><td>Dual users n = 216</td><td>Tobacco only smokers n = 471</td><td>aOR (95% CI)</td><td>aRR (95% CI)*</td></tr>
<tr><td>Number who had any <u>diagnosed disease</u> (%)</td><td>23 (10.7)</td><td>32 (6.8)</td><td>1.57 (0.84, 2.96)</td><td>1.51 [0.86, 2.65]</td></tr>
</table>
*Calculated by analyst, control group prevalence used was 0.068 (reported in paper).

<u>Non switchers only:</u> Dual users compared with tobacco cigarette smokers only
<table>
<tr><td></td><td>Dual users n = 39</td><td>Tobacco only smokers n = 409</td><td>aOR (95% CI)</td><td>aRR (95% CI)*</td></tr>
<tr><td>Number who had any <u>diagnosed disease</u> (%)</td><td>3 (7.7)</td><td>29 (7.1)</td><td>1.31 (0.34, 5.04)</td><td>1.28 [0.39, 4.25]</td></tr>
</table>
*Calculated by analyst, control group prevalence used was 0.071 (reported in paper)

To note: unless the outcome specifies “non switchers only”, the sample is classified by baseline group only regardless of change over time.
All outcomes adjusted for age, gender, self-rated health, years of tobacco smoking, hypertension.</td></tr>
<tr><td>Statistical Analysis</td><td>Multivariate random-effect linear (self-reported health) and logistic (diagnosed disease) regression models used. Geographical region as cluster unit. Two analysis extracted here:
1) exposure group assigned based on baseline smoking / vaping status, including only participants who were followed up to 48 months (those lost to follow-up not included in the results, but no diagnosed disease observed in 12 and 24 month follow up for those who were lost to follow-up).
Exposure group assigned based on baseline smoking / vaping status, with analysis including only those subjects who did not switch smoking / vaping status during 48 month follow-up. Quitting either was not considered a switch.</td></tr>
<tr><td>Risk of bias (ROB) ROBINS-I tool</td><td>Outcome name: self-reported health
<table>
<tr><th>Outcome</th><th>Judgement</th><th>Comments</th></tr>
<tr><td>Pre-intervention: bias due to confounding</td><td>Serious</td><td>Adjustments include years of smoking, age, gender, self-rated health. Likely to be other remaining confounders acting on health which could be related to e-cigarette use.</td></tr>
</table></td></tr>
</table>

Bibliographic reference/s	**Flacco M E, Ferrante M, Fiore M, Marzuillo C, La Vecchia , C , Gualano M R, Liguori G, Fragassi G, Carradori T, Bravi F, Siliquini R, Ricciardi W, Villari P, and Manzoli L (2019) Cohort study of electronic cigarette use: safety and effectiveness after 4 years of follow-up. European review for medical and pharmacological sciences 23(1), 402-412**		
Study name	Flacco 2019 (supported by Manzoli 2015 and Manzoli 2017)		
			Intervention switches could have been to do with (prognostic for) the outcome.
	Pre-intervention: bias in selection of participants into study	Serious	Sample likely to be motivated to quit. Recruited through GPs and e-cig shops, as well as internet adverts. May not be similar to population. Selection bias not controlled for.
	At intervention: Bias in classification of interventions	Low	Exposed and unexposed states relatively well defined. Participants might use different models of e-cig / brands of cigarette and smoke / use at different levels, but this is part of the intentional natural use.
	Post-intervention: bias due to deviations from intended interventions	Critical	Significant changes between groups, low adherence to the baseline state. Although this is part of the intention of the study (expecting people to quit smoking), this may bias the outcome. It is unclear whether the outcome is attributable to baseline state.
	Post-intervention: bias due to missing data	Moderate	32% % of participants lost to follow-up. Missing data similar across groups. No serious health concerns in drop outs.
	Post-intervention: bias in measurement of outcomes	Low	Outcomes measured comparably across groups. Outcome subjective and assessors not blinded – could lead to some bias but unclear in what direction.
	Post-intervention: Bias in selection of the reported result	Low	No indication of bias in selection of reported results
	Overall Risk of Bias	**Critical risk of bias**	
	Other outcome details <u>Diagnosed disease</u>: Bias of selection of participants into study: additional concern that those experiencing diagnosed disease already (as intervention started prior to study) may not have been recruited. Judgement still 'serious' for this domain. Overall risk of bias: **critical risk of bias** <u>Diagnosed disease and self-reported health in non-switchers only</u>**:** Bias due to deviation from intended interventions less because of restriction to non-switchers (moderate). Possibly increased selection bias with this analysis. Overall risk of bias: **serious risk of bias**		

Bibliographic reference/s	**Flacco M E, Ferrante M, Fiore M, Marzuillo C, La Vecchia , C , Gualano M R, Liguori G, Fragassi G, Carradori T, Bravi F, Siliquini R, Ricciardi W, Villari P, and Manzoli L (2019) Cohort study of electronic cigarette use: safety and effectiveness after 4 years of follow-up. European review for medical and pharmacological sciences 23(1), 402-412**
Study name	Flacco 2019 (supported by Manzoli 2015 and Manzoli 2017)
Source of funding	No funding received for this study. Authors state that the report was planned to be funded, but the sponsor withdrew.
Comments	Study reported in three publications (1, 2 and 4 year follow-up). Longest follow-up preferred where same outcomes are reported in multiple publications, • Study is not primarily designed to identify diagnosed disease or QoL as a result of using e-cigarettes. Data extracted here can be used for that purpose but has serious limitations, particularly because participants changed exposure status throughout (although analysis of non-switchers reduces this risk). • Any kind of e-cigarette use / type was permitted, and a small proportion of people used e-cigarettes without nicotine. • Authors conclude that no serious safety concerns emerged among this sample of e-cigarette users.
Additional references	Manzoli Lamberto, Flacco Maria Elena, Fiore Maria et al. (2015) Electronic Cigarettes Efficacy and Safety at 12 Months: Cohort Study. PloS one 10(6), e0129443 Manzoli Lamberto, Flacco Maria Elena, Ferrante Margherita, La Vecchia , Carlo , Siliquini Roberta, Ricciardi Walter, Marzuillo Carolina, Villari Paolo, Fiore Maria, and Group Islese Working (2017) Cohort study of electronic cigarette use: effectiveness and safety at 24 months. Tobacco control 26(3), 284-292.

Bhatta 2019

Bibliographic reference/s	**Bhatta, D. N., Glantz, S. A (2019) Association of E-Cigarette Use With Respiratory Disease Among Adults: A Longitudinal Analysis. American Journal of Preventive Medicine 000(000):1−9 (in press)**
Study name	Bhatta 2019
Registration	Not reported
Study type	Repeat cross-sectional with longitudinal (cohort) analysis
Study dates	2013-2016
Objective	To determine the longitudinal association between e-cigarette use and respiratory diseases (controlling for combustible tobacco use)
Country/ Setting	USA, nationally representative study
Number of participants / clusters	32,320 people in full sample. 19,475 adults completed wave 1, 2 and 3 of PATH survey and did not have respiratory disease at baseline. Of people who are current e-cigarette users at baseline, 85.5% are also current, and 13.9% are former combustible tobacco users. Only 0.6% are never users (weighted percentages).
Cohort name	Population Assessment of Tobacco and Health (PATH)
Attrition	Overall weighted adult retention rates at Waves 2 and 3 were 83.2% and 78.4%, respectively. Unclear retention rate among those who had no respiratory disease at baseline (the subsection of the sample we are interested in)

<table>
<tr><td>Bibliographic reference/s</td><td colspan="2">Bhatta, D. N., Glantz, S. A (2019) Association of E-Cigarette Use With Respiratory Disease Among Adults: A Longitudinal Analysis. American Journal of Preventive Medicine 000(000):1−9 (in press)</td></tr>
<tr><td>Study name</td><td colspan="2">Bhatta 2019</td></tr>
<tr><td>Participant /community characteristics.</td><td colspan="2">Characteristics for those who had no respiratory disease at baseline and are current e-cigarette users not reported separately from full group.
Sample reported as nationally representative.</td></tr>
<tr><td>Method of allocation</td><td colspan="2">No allocation</td></tr>
<tr><td>Inclusion criteria</td><td colspan="2">People answering the PATH survey in wave 1 (Sept 2013-Dec 2014) and in either wave 2 (Oct 2014-Oct 2015) or wave 3 (Oct 2015-Oct 2016).
Sample subsection relevant to this review do not have respiratory disease at baseline, assessed by the following question: “Has a doctor or other health professional ever told you that you had any of the following lung or respiratory conditions? (yes or no): COPD, chronic bronchitis, emphysema, and asthma.”
Sample subsection relevant to this review are current users of e-cigarettes at wave 1 (baseline), defined as people who have ever used an e-cigarette, ever used fairly regularly, and currently used every day or some days (unclear whether people respond yes to all three criteria, or only one of the three, but respondents who have ever used but do not currently use were classed as former users and not included here).</td></tr>
<tr><td>Exclusion criteria</td><td colspan="2">Not reported</td></tr>
<tr><td></td><td>Brief Name</td><td>E-cigarette exposed</td></tr>
<tr><td></td><td>Detail of exposure</td><td>Respondents who ever used an e-cigarette, ever used fairly regularly, and currently used every day or some days were considered current users. Respondents may also be current smokers of tobacco products (cigarettes, traditional cigars, filtered cigars, cigarillos, pipe tobacco, or hookah), former smokers, or never smokers.</td></tr>
<tr><td>Comparison</td><td colspan="2">Never e-cigarette users (respondents who reported that they have never used e-cigarettes, even once or twice and had no respiratory disease at baseline).</td></tr>
<tr><td>Follow up</td><td colspan="2">Minimum -2 months, maximum 3 years 1 month.
Wave 2 and 3 combined. Authors summarise this as 2 year follow-up.</td></tr>
<tr><td>Data collection</td><td colspan="2">PATH household survey</td></tr>
<tr><td>Critical outcomes measures and effect size. (time points)</td><td colspan="2">Respiratory disease
Risk of developing respiratory disease in current e-cigarette users compared with never e-cigarette users at 2 year follow-up (among those with no respiratory disease at baseline, controlling for tobacco smoking):

<table>
<tr><td></td><td>Number developing respiratory disease (%)</td><td>Adjusted odds ratio (95% confidence interval)*</td><td>Adjusted risk ratio (95% confidence interval)**</td></tr>
<tr><td>Current e-cigarette users (n = unclear)</td><td>Unclear</td><td rowspan="2">1.29 (1.03, 1.61)</td><td rowspan="2">1.27 (1.03, 1.56)</td></tr>
<tr><td>Never e-cigarette users (n = unclear)</td><td>Unclear</td></tr>
</table>
*Reported by study.
**Calculated by review team. The unexposed group prevalence used to calculate the aRR was 0.057 (proportion of all participants who had respiratory disease at follow-up)</td></tr>
</table>

Bibliographic reference/s	**Bhatta, D. N., Glantz, S. A (2019) Association of E-Cigarette Use With Respiratory Disease Among Adults: A Longitudinal Analysis. American Journal of Preventive Medicine 000(000):1−9 (in press)**
Study name	Bhatta 2019

COPD

Risk of developing COPD in current e-cigarette users compared with never e-cigarette users at 2 year follow-up (among those with no COPD at baseline, controlling for tobacco smoking):

	Number developing COPD (%)	Adjusted odds ratio (95% confidence interval)*	Adjusted risk ratio (95% confidence interval)**
Current e-cigarette users (n = unclear)	Unclear	1.44 (0.79, 2.62)	1.43 (0.79, 2.56)
Never e-cigarette users (n = unclear)	Unclear		

*Reported by study.

**Calculated by review team. The unexposed group prevalence used to calculate the aRR was 0.014 (quarter of all participants with respiratory disease at follow-up – assumption that there is an even split between the conditions within respiratory disease)

Chronic bronchitis

Risk of developing chronic bronchitis in current e-cigarette users compared with never e-cigarette users at 2 year follow-up (among those with no chronic bronchitis at baseline, controlling for tobacco smoking):

	Number developing chronic bronchitis (%)	Adjusted odds ratio (95% confidence interval)*	Adjusted risk ratio (95% confidence interval)**
Current e-cigarette users (n = unclear)	Unclear	1.60 (1.13, 2.27)	1.59 (1.13, 2.23)
Never e-cigarette users (n = unclear)	Unclear		

*Reported by study.

**Calculated by review team. The unexposed group prevalence used to calculate the aRR was 0.014 (quarter of all participants with respiratory disease at follow-up – assumption that there is an even split between the conditions within respiratory disease)

Emphysema

Risk of developing emphysema in current e-cigarette users compared with never e-cigarette users at 2 year follow-up (among those with no emphysema at baseline, controlling for tobacco smoking):

	Number developing emphysema (%)	Adjusted odds ratio (95%	Adjusted risk ratio (95%

Bibliographic reference/s	**Bhatta, D. N., Glantz, S. A (2019) Association of E-Cigarette Use With Respiratory Disease Among Adults: A Longitudinal Analysis. American Journal of Preventive Medicine 000(000):1−9 (in press)**
Study name	Bhatta 2019

		confidence interval)*	confidence interval)**
Current e-cigarette users (n = unclear)	Unclear	1.60 (0.75, 3.44)	1.59 (0.75, 3.33)
Never e-cigarette users (n = unclear)	Unclear		

*Reported by study.

**Calculated by review team. The unexposed group prevalence used to calculate the aRR was 0.014 (quarter of all participants with respiratory disease at follow-up – assumption that there is an even split between the conditions within respiratory disease)

Asthma

Risk of developing asthma in current e-cigarette users compared with never e-cigarette users at 2 year follow-up (among those with no asthma at baseline, controlling for tobacco smoking):

	Number developing asthma (%)	Adjusted odds ratio (95% confidence interval)*	Adjusted risk ratio (95% confidence interval)**
Current e-cigarette users (n = unclear)	Unclear	1.56 (1.10, 2.22)	1.55 (1.10, 2.18)
Never e-cigarette users (n = unclear)	Unclear		

*Reported by study.

**Calculated by review team. The unexposed group prevalence used to calculate the aRR was 0.014 (quarter of all participants with respiratory disease at follow-up – assumption that there is an even split between the conditions within respiratory disease)

Important outcomes measures and effect size. (time points)	None reported
Statistical Analysis	Among respondents who did not report any respiratory disease at Wave 1, logistic regression was used to quantify the longitudinal association between e-cigarette use at Wave 1 and incident respiratory disease at either Wave 2 or Wave 3 combined, compared with no e-cigarette use. All analysis controlled for combustible tobacco smoking (former and current), age, BMI, sex, poverty level, race/ethnicity, and clinical variables at Wave 1. Waves 2 and 3 were combined to increase the number of events and the power of the study, essentially treating the study as a 2-year longitudinal follow up from baseline when e-cigarette use was assessed.
Risk of bias (ROB)	Outcome name: respiratory disease

Outcome	Judgement	Comments

Bibliographic reference/s	**Bhatta, D. N., Glantz, S. A (2019) Association of E-Cigarette Use With Respiratory Disease Among Adults: A Longitudinal Analysis. American Journal of Preventive Medicine 000(000):1−9 (in press)**		
Study name	Bhatta 2019		
QUIPS	Study participation	Low	PATH study is nationally representative
	Study attrition	Moderate	Cohort – only people who responded at each time point included
	Prognostic factor measurement	Moderate	There is a possibility of recall bias because use of e-cigarettes, conventional cigarettes, and other combustible tobacco products were self-reported as were clinical conditions
	Outcome measurement	High	Possible that outcome (self-reported) is minimally influenced by knowledge of exposure status Possibility of recall bias
	Study confounding	High	Confounding likely as e-cigarette use is associated with smoking. Analysis controlled for combustible tobacco smoking (former and current only, not intensity or duration of use)
	Statistical analysis and reporting	Moderate	Study does not report deviation from baseline exposure status or combustible tobacco status. Likely to have been significant switching which is not taken into account. “
	Overall Risk of Bias	**High**	
	Other outcome: Assessment of bias is the same for each of the four individual conditions (serious risk of bias)		
Source of funding	National Institute on Drug Abuse National Cancer institute US Food and Drug Administration Center for Tobacco Products National Heart, Lung and Blood Institute and the Food and Drug Administration Center for Tobacco Products University of California, San Francisco Helen Diller Family Comprehensive Cancer Center Global Cancer Program. Paper reports that “No financial disclosures were reported by the authors of this paper.”		
Comments	Paper is an analysis of the national PATH cohort study which provides the data for analysis. Minimal information given in this paper about the PATH methodology		
Additional references	None		

Appendix E – Forest plots

No meta-analysis was possible for this review.

Appendix F – GRADE tables

Profile 1: Diagnosed disease

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Dual use	Tobacco only	Relative (95% CI)	Absolute	
Diagnosed disease (follow-up 48 months; assessed with: Self-report of diagnosed disease)											
1 a	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23/216 (10.6%)	32/471 (6.8%)	RR 1.51 (0.86 to 2.65)	35 more per 1000 (from 10 fewer to 112 more)	⊕OOO VERY LOW
Diagnosed disease in non-switchers (follow-up 48 months; assessed with: Self-report of diagnosed disease)											
1 a	cohort studies	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	3/39 (7.7%)	29/409 (7.1%)	RR 1.28 (0.39 to 4.25)	20 more per 1000 (from 43 fewer to 230 more)	⊕OOO VERY LOW

[1] Participants self-selected so may have different health to population. Study concerned with quitting / switching, so deviation from interventions high. Missing data not explored and could be linked to outcome.
[2] CI crosses MID (line of no effect)
[3] Participants self-selected so may have different health to population. Missing data not explored and could be linked to outcome.

* Self-reported chronic obstructive pulmonary diseases, stroke, heart failure, myocardial infarction, angina, pneumonia, cancer of: larynx or oral cavity, lung, stomach, pancreas, cervix, kidney, bladder, myeloid leukaemia. Combined into one measure (any vs none).

a) Flacco 2019

Profile 2: Change in health

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Dual use	Tobacco only	Relative (95% CI)	Absolute	
Change in self-reported health (follow-up 48 months; measured with: EuroQol question; range of scores: 1-10; Better indicated by lower values)											
1 a	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	216	471	-	MD 0.18 higher (0.02 lower to 0.39 higher)	⊕⊕OO LOW
Change in self-reported health in non-switchers (follow-up 48 months; measured with: EuroQol question; range of scores: 1-10; Better indicated by lower values)											
1 a	cohort studies	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	39	409	-	MD 0.45 higher (0.13 lower to 1.04 higher)	⊕⊕OO LOW

[1] Participants self-selected so may have different health to population. Study concerned with quitting / switching, so deviation from interventions high. Missing data not explored and could be linked to outcome.
[2] Confidence intervals are confined within the MIDs (0.5*SD above and below the point estimate; here the MID is 0.7 points)
[3] Participants self-selected so may have different health to population. Missing data not explored and could be linked to outcome.
[4] CI overlaps one MID. MID is 0.5*SD above and below line of no effect. MID here is 0.65 points.

a) Flacco 2019

Profile 3: Respiratory health effects

Quality assessment							No of patients (among those without condition at baseline)		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Baseline current e-cig users	Baseline never e-cig users	Relative (95% CI)	Absolute	
Diagnosis of respiratory disease (follow-up 2 years; measured with self-report)											
1 b	cohort study	Very serious[1]	NA	no serious	no serious	none	Not reported	Not reported	1.27 (1.03, 1.56)	Not calculable	⊕⊕OO LOW
Diagnosis of COPD (follow-up 2 years; measured with self-report)											
1 b	cohort study	Very serious[1]	NA	no serious	Serious[2]	none	Not reported	Not reported	1.43 (0.79, 2.56)	Not calculable	⊕OOO VERY LOW
Diagnosis of chronic bronchitis (follow-up 2 years; measured with self-report)											
1 b	cohort study	Very serious[1]	NA	no serious	no serious		Not reported	Not reported	1.59 (1.13, 2.23)	Not calculable	⊕⊕OO LOW
Diagnosis of emphysema (follow-up 2 years; measured with self-report)											
1 b	cohort study	Very serious[1]	NA	no serious	Serious[2]		Not reported	Not reported	1.59 (0.75, 3.33)	Not calculable	⊕OOO VERY LOW
Diagnosis of asthma (follow-up 2 years; measured with self-report)											
1 b	cohort study	Very serious[1]	NA	no serious	no serious		Not reported	Not reported	1.55 (1.10, 2.18)	Not calculable	⊕⊕OO LOW

[1] Study is at very serious risk of bias for confounding (particularly for smoking) and has some risk of recall bias.
[2] CI includes MID (line of no effect)

b) Bhatta 2019

Appendix G – Economic evidence study selection

No economic evidence was included in the protocol for this review.

Appendix H – Economic evidence tables

No economic evidence was included in the protocol for this review.

Appendix I – Health economic evidence profiles

No economic evidence was included in the protocol for this review.

Appendix J – Health economic analysis

No economic evidence was included in the protocol for this review.

Appendix K – Excluded studies

Public health studies

Study Citation	Reason for excluding
Al Rifaiy, Mohammed Q, Qutub Osama A, Alasqah Mohammed N, Al-Sowygh Zeyad H, Mokeem Sameer A, and Alrahlah Ali (2018) Effectiveness of adjunctive antimicrobial photodynamic therapy in reducing peri-implant inflammatory response in individuals vaping electronic cigarettes: A randomized controlled clinical trial. Photodiagnosis and photodynamic therapy 22, 132-136	**Exclude on intervention**: investigates intervention for reducing inflammatory response in e-cig users
Al-Aali Khulud A, Alrabiah Mohammed, ArRejaie Aws S, Abduljabbar Tariq, Vohra Fahim, and Akram Zohaib (2018) Peri-implant parameters, tumor necrosis factor-alpha, and interleukin-1 beta levels in vaping individuals. Clinical implant dentistry and related research 20(3), 410-415	**Exclude on study design**: Cross sectional data
Alanazi Humidah, Park Hyun Jin, Chakir Jamila, Semlali Abdelhabib, and Rouabhia Mahmoud (2018) Comparative study of the effects of cigarette smoke and electronic cigarettes on human gingival fibroblast proliferation, migration and apoptosis. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 118, 390-398	**Exclude on population**: conducted on fibroblasts not humans
Al-Bashaireh Ahmad M, Haddad Linda G, Weaver Michael, Kelly Debra Lynch, Chengguo Xing, and Yoon Saunjoo (2018) The Effect of Tobacco Smoking on Musculoskeletal Health: A Systematic Review. Journal of environmental and public health 2018, 4184190	**Exclude on study design**: systematic review looking at smoking tobacco only
Alharthi Shatha Subhi, BinShabaib Munerah, Akram Zohaib, Rahman Irfan, Romanos Georgios E, and Javed Fawad (2018) Impact of cigarette smoking and vaping on the outcome of full-mouth ultrasonic scaling among patients with gingival inflammation: a prospective study. Clinical oral investigations ,	**Exclude on follow-up**: 6 month follow-up max. dental outcomes.
AlQahtani Mohammed Ayedh, Alayad Abdullah Saeed, Alshihri Abdulmonem, Correa Fernanda Oliveira Bello, and Akram Zohaib (2018) Clinical peri-implant parameters and inflammatory cytokine profile among smokers of cigarette, e-cigarette, and waterpipe. Clinical implant dentistry and related research 20(6), 1016-1021	**Exclude on study design**: case control, also outcomes not relevant
Alzahrani Talal, Pena Ivan, Temesgen Nardos, and Glantz Stanton A (2018) Association Between Electronic Cigarette Use and Myocardial Infarction. American journal of preventive medicine 55(4), 455-461	**Exclude on study design**: cross sectional data
Andrikopoulos G I, Zagoriti Z, Topouzis S, and Poulas K (2018) Oxidative stress induced by electronic nicotine delivery systems (ENDS): Focus on respiratory system. Current Opinion in Toxicology	**Exclude on study design**: non-systematic review
Anonymous (2017) Safety and Efficacy of Electronic Cigarettes: Update for the Clinical Nurse Specialist. Clinical nurse specialist CNS 31(1), E10	**Exclude on evidence**: no evidence to extract, a learning activity only
ArRejaie Aws S, Al-Aali Khulud Abdulrahman, Alrabiah Mohammed, Vohra Fahim, Mokeem Sameer A, Basunbul Ghadeer, Alrahlah Ali, and Abduljabbar Tariq (2018) Proinflammatory cytokine levels and peri-implant parameters among cigarette smokers, individuals vaping electronic cigarettes, and non-smokers. Journal of periodontology ,	**Exclude on study design**: cross sectional data
Badea Mihaela, Luzardo Octavio P, Gonzalez-Antuna Ana, Zumbado Manuel, Rogozea Liliana, Floroian Laura, Alexandrescu Dana, Moga Marius, Gaman Laura, Radoi Mariana, Boada Luis D, and Henriquez-Hernandez Luis Alberto (2018) Body burden of toxic metals and rare	**Exclude on study design**: cross sectional data

earth elements in non-smokers, cigarette smokers and electronic cigarette users. Environmental research 166, 269-275	
Baldassarri Stephen R, Hillmer Ansel T, Anderson Jon Mikael, Jatlow Peter, Nabulsi Nabeel, Labaree David, Cosgrove Kelly P, O'Malley Stephanie S, Eissenberg Thomas, Krishnan-Sarin Suchitra, and Esterlis Irina (2018) Use of Electronic Cigarettes Leads to Significant Beta2-Nicotinic Acetylcholine Receptor Occupancy: Evidence From a PET Imaging Study. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 20(4), 425-433	**Exclude on follow-up**: conducted on same day as exposure
Bandiera Frank C, Loukas Alexandra, Wilkinson Anna V, and Perry Cheryl L (2016) Associations between tobacco and nicotine product use and depressive symptoms among college students in Texas. Addictive behaviors 63, 19-22	**Exclude on study design**: cross sectional data and past 30 day use of e-cigs (not long term use)
Bardellini Elena, Amadori Francesca, Conti Giulio, and Majorana Alessandra (2018) Oral mucosal lesions in electronic cigarettes consumers versus former smokers. Acta odontologica Scandinavica 76(3), 226-228	**Exclude on study design**: case control, smoking not balanced across groups
Battista L, Di Iorio , M , Tancredi M, Acconcia M C, Torromeo C, Barilla F, Paravati V, Gaudio C, and Pannarale G (2013) Cardiovascular Effects Electronic Cigarettes. Circulation 128(22),	**Exclude on evidence**: no data to extract, conference abstract only
Beauval Nicolas, Antherieu Sebastien, Soyez Melissa, Gengler Nicolas, Grova Nathalie, Howsam Michael, Hardy Emilie M, Fischer Marc, Appenzeller Brice M. R, Goossens Jean-Francois, Allorge Delphine, Garcon Guillaume, Lo-Guidice Jean-Marc, and Garat Anne (2017) Chemical Evaluation of Electronic Cigarettes: Multicomponent Analysis of Liquid Refills and their Corresponding Aerosols. Journal of analytical toxicology 41(8), 670-678	**Exclude on population**: machine vaping and vapour content only
Bekki Kanae, Uchiyama Shigehisa, Ohta Kazushi, Inaba Yohei, Nakagome Hideki, and Kunugita Naoki (2014) Carbonyl compounds generated from electronic cigarettes. International journal of environmental research and public health 11(11), 11192-200	**Exclude on population**: study not on people
Bhatnagar Aruni (2017) Are Electronic Cigarette Users at Increased Risk for Cardiovascular Disease?. JAMA cardiology 2(3), 237-238	**Exclude on study design**: non-systematic review
Boas Zachary, Gupta Pawan, Moheimani Roya S, Bhetraratana May, Yin Fen, Peters Kacey M, Gornbein Jeffrey, Araujo Jesus A, Czernin Johannes, and Middlekauff Holly R (2017) Activation of the "Splenocardiac Axis" by electronic and tobacco cigarettes in otherwise healthy young adults. Physiological reports 5(17),	**Exclude on study design**: specifies one year of use but cross-sectional measurement.
Boulay MÈ, Henry C, Bossé Y, Boulet L P, and Morissette M C (2017) Acute effects of nicotine-free and flavour-free electronic cigarette use on lung functions in healthy and asthmatic individuals. Respiratory research 18(1), 33	**Exclude on follow-up**: 1 hour use examined. Letter to editor.
Bowler Russell P, Hansel Nadia N, Jacobson Sean, Graham Barr, R , Make Barry J, Han MeiLan K, O'Neal Wanda K, Oelsner Elizabeth C, Casaburi Richard, Barjaktarevic Igor, Cooper Chris, Foreman Marilyn, Wise Robert A, DeMeo Dawn L, Silverman Edwin K, Bailey William, Harrington Kathleen F, Woodruff Prescott G, Drummond M Bradley, for COPDGene, and Investigators Spiromics (2017) Electronic Cigarette Use in US Adults at Risk for or with COPD: Analysis from Two Observational Cohorts. Journal of general internal medicine 32(12), 1315-1322	**Exclude on population**: ever vapers only, not habitual
Callahan-Lyon Priscilla (2014) Electronic cigarettes: human health effects. Tobacco control 23 Suppl 2, ii36-40	**Exclude on study design**: systematic review, citations checked

Camus M, Gallois G, and Marteau P (2014) Erratum: Ulcerative colitis and electronic cigarette: What's the matter? (American Journal of Gastroenterology (2014) 109 (608-609) DOI: 10.1038 / ajg.2013.439). American Journal of Gastroenterology 109(9), 1504	**Exclude on evidence**: correction only, not publication.
Carnevale Roberto, Sciarretta Sebastiano, Violi Francesco, Nocella Cristina, Loffredo Lorenzo, Perri Ludovica, Peruzzi Mariangela, Marullo Antonino G. M, De Falco , Elena , Chimenti Isotta, Valenti Valentina, Biondi-Zoccai Giuseppe, and Frati Giacomo (2016) Acute Impact of Tobacco vs Electronic Cigarette Smoking on Oxidative Stress and Vascular Function. Chest 150(3), 606-12	**Exclude on follow-up**: one week only. Compares e-cigs with traditional cigarettes
Caruso M, Li Volti, G , Furneri P M, Fuochi V, Emma R, and Polosa R (2018) Commentary: Inflammatory and oxidative responses induced by exposure to commonly used e-cigarette flavoring chemicals and flavored e-liquids without nicotine. Frontiers in Physiology 9(SEP), 1240	**Exclude on study design**: commentary only, not original study.
Chang Y C, Lee Y H, Liu C T, and Shelley M (2019) Patterns of e-cigarette use and self-reported health outcomes among smokers and non-smokers in the United States: A preliminary assessment. Journal of Substance Use 24(1), 79-87	**Exclude on study design**: cross sectional survey data
Chaumont Martin, Bernard Alfred, Pochet Stephanie, Melot Christian, El Khattabi , Charaf , Reye Florence, Boudjeltia Karim Zouaoui, Van Antwerpen , Pierre , Delporte Cedric, van de Borne , and Philippe (2018) High-Wattage E-Cigarettes Induce Tissue Hypoxia and Lower Airway Injury: A Randomized Clinical Trial. American journal of respiratory and critical care medicine 198(1), 123-126	**Exclude on evidence**: letter to editor
Chaumont Martin, de Becker , Benjamin , Zaher Wael, Culie Antoine, Deprez Guillaume, Melot Christian, Reye Florence, Van Antwerpen , Pierre , Delporte Cedric, Debbas Nadia, Boudjeltia Karim Zouaoui, van de Borne , and Philippe (2018) Differential Effects of E-Cigarette on Microvascular Endothelial Function, Arterial Stiffness and Oxidative Stress: A Randomized Crossover Trial. Scientific reports 8(1), 10378	**Exclude on follow-up**: same day, acute outcomes.
Chorti M, Poulianiti K, Jamurtas A, Kostikas K, Tzatzarakis M, Vynias D, Koutedakis Y, Flouris A, and Tsatsakis A (2012) Effects of active and passive electronic and tobacco cigarette smoking on lung function. Toxicology Letters 211, S64-S64	**Exclude on follow-up**: one hour, acute outcomes.
Chun Lauren F, Moazed Farzad, Calfee Carolyn S, Matthay Michael A, and Gotts Jeffrey E (2017) Pulmonary toxicity of e-cigarettes. American journal of physiology. Lung cellular and molecular physiology 313(2), L193-L206	**Exclude on study design**: non-systematic review
Chun L F, Moazed F, Calfee C S, Matthay M A, and Gotts J E (2017) Pulmonary toxicity of e-cigarettes. American Journal of Physiology - Lung Cellular and Molecular Physiology 313(2), L193-L206	**Exclude as duplicate**
Cibella Fabio, Campagna Davide, Caponnetto Pasquale, Amaradio Maria Domenica, Caruso Massimo, Russo Cristina, Cockcroft Donald W, and Polosa Riccardo (2016) Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. Clinical science (London, and England : 1979) 130(21), 1929-37	**Exclude on comparisons**: harm reduction of e-cigs, compares quitters with smokers
Cooke William H, Pokhrel Anusheela, Dowling Colin, Fogt Donovan L, and Rickards Caroline A (2015) Acute inhalation of vaporized nicotine increases arterial pressure in young non-smokers: a pilot study. Clinical autonomic research : official journal of the Clinical Autonomic Research Society 25(4), 267-70	**Exclude on follow-up**: immediate data collection of acute outcomes

Coppeta L, Magrini A, Pietroiusti A, Perrone S, and Grana M (2018) Effects of smoking electronic cigarettes on pulmonary function and environmental parameters. Open Public Health Journal 11(1), 360-368	**Exclude on follow-up**: immediate data collection of acute outcomes
Dicpinigaitis Peter V, Chang Alfredo Lee, Dicpinigaitis Alis J, and Negassa Abdissa (2016) Effect of electronic cigarette use on the urge-to-cough sensation. Nicotine & Tobacco Research 18(8), 1763-1765	**Exclude on follow-up**: immediate data collection of acute outcomes
Dicpinigaitis Peter V, Lee Chang, Alfredo , Dicpinigaitis Alis J, and Negassa Abdissa (2016) Effect of e-Cigarette Use on Cough Reflex Sensitivity. Chest 149(1), 161-5	**Exclude on follow-up**: immediate data collection of acute outcomes
D'Ruiz Carl D, O'Connell Grant, Graff Donald W, and Yan X Sherwin (2017) Measurement of cardiovascular and pulmonary function endpoints and other physiological effects following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers. Regulatory toxicology and pharmacology : RTP 87, 36-53	**Exclude on follow-up**: study lasts 5 days
Eltorai Adam Em, Choi Ariel R, and Eltorai Ashley Szabo (2018) Impact of Electronic Cigarettes on Various Organ Systems. Respiratory care ,	**Exclude on study design**: non-systematic review
Farsalinos Konstantinos E, and Polosa Riccardo (2014) Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. Therapeutic advances in drug safety 5(2), 67-86	**Exclude on study design**: systematic review, citations checked
Farsalinos Konstantinos E, Romagna Giorgio, Tsiapras Dimitris, Kyrzopoulos Stamatis, and Voudris Vassilis (2014) Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers. International journal of environmental research and public health 11(4), 4356-73	**Exclude on study design**: cross-sectional data
Farsalinos Konstantinos E, Tsiapras Dimitris, Kyrzopoulos Stamatis, Savvopoulou Maria, and Voudris Vassilis (2014) Acute effects of using an electronic nicotine-delivery device (electronic cigarette) on myocardial function: comparison with the effects of regular cigarettes. BMC cardiovascular disorders 14, 78	**Exclude on follow-up**: immediate data collection of acute outcomes
Flower Mark, Nandakumar Lakshmy, Singh Mahendra, Wyld David, Windsor Morgan, and Fielding David (2017) Respiratory bronchiolitis-associated interstitial lung disease secondary to electronic nicotine delivery system use confirmed with open lung biopsy. Respirology case reports 5(3), e00230	**Exclude on study design**: case report
Floyd Evan L, Queimado Lurdes, Wang Jun, Regens James L, and Johnson David L (2018) Electronic cigarette power affects count concentration and particle size distribution of vaping aerosol. PloS one 13(12), e0210147	**Exclude on population**: machine vaping only
Franco Teresa, Trapasso Serena, Puzzo Lidia, and Allegra Eugenia (2016) Electronic Cigarette: Role in the Primary Prevention of Oral Cavity Cancer. Clinical medicine insights. Ear, and nose and throat 9, 7-12	**Exclude on study design**: cross sectional data, specifies 6 month use of e-cigs
Franzen Klaas Frederik, Willig Johannes, Cayo Talavera, Silja , Meusel Moritz, Sayk Friedhelm, Reppel Michael, Dalhoff Klaus, Mortensen Kai, and Droemann Daniel (2018) E-cigarettes and cigarettes worsen peripheral and central hemodynamics as well as arterial stiffness: A randomized, double-blinded pilot study. Vascular medicine (London, and England) 23(5), 419-425	**Exclude on follow-up**: immediate data collection of acute outcomes
Fuller Thomas W, Acharya Abhinav P, Meyyappan Thiagarajan, Yu Michelle, Bhaskar Godugu, Little Steven R, and Tarin Tatum V (2018)	**Exclude on study design**: cross-sectional data

Comparison of Bladder Carcinogens in the Urine of E-cigarette Users Versus Non E-cigarette Using Controls. Scientific reports 8(1), 507	
Gaur Sumit, and Agnihotri Rupali (2018) Health Effects of Trace Metals in Electronic Cigarette Aerosols-a Systematic Review. Biological trace element research ,	**Exclude on study design**: systematic review, citations checked
Ghosh Arunava, Coakley Raymond C, Mascenik Teresa, Rowell Temperance R, Davis Eric S, Rogers Keith, Webster Megan J, Dang Hong, Herring Laura E, Sassano M Flori, Livraghi-Butrico Alessandra, Van Buren , Scott K, Graves Lee M, Herman Melissa A, Randell Scott H, Alexis Neil E, and Tarran Robert (2018) Chronic E-Cigarette Exposure Alters the Human Bronchial Epithelial Proteome. American journal of respiratory and critical care medicine 198(1), 67-76	**Exclude on follow-up**: immediate data collection of acute outcomes
Goldenson Nicholas I, Khoddam Rubin, Stone Matthew D, and Leventhal Adam M (2018) Associations of ADHD Symptoms With Smoking and Alternative Tobacco Product Use Initiation During Adolescence. Journal of pediatric psychology 43(6), 613-624	**Exclude on population**: participants don't use e-cigarettes
Goniewicz Maciej L, Gawron Michal, Smith Danielle M, Peng Margaret, Jacob Peyton 3rd, and Benowitz Neal L (2017) Exposure to Nicotine and Selected Toxicants in Cigarette Smokers Who Switched to Electronic Cigarettes: A Longitudinal Within-Subjects Observational Study. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 19(2), 160-167	**Exclude on follow-up**: 2 weeks only
Hajek Peter, Etter Jean-Francois, Benowitz Neal, Eissenberg Thomas, and McRobbie Hayden (2014) Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit. Addiction (Abingdon, and England) 109(11), 1801-10	**Exclude on study design**: systematic review, citations checked
Hobkirk Andrea L, Nichols Travis T, Foulds Jonathan, Yingst Jessica M, Veldheer Susan, Hrabovsky Shari, Richie John, Eissenberg Thomas, and Wilson Stephen J (2018) Changes in resting state functional brain connectivity and withdrawal symptoms are associated with acute electronic cigarette use. Brain research bulletin 138, 56-63	**Exclude on follow-up**: immediate data collection of acute outcomes
Holbrook Bradley D (2016) The effects of nicotine on human fetal development. Birth defects research. Part C, and Embryo today : reviews 108(2), 181-92	**Exclude on study design**: non-systematic review
Huang Shu-Jie, Xu Yan-Ming, and Lau Andy T. Y (2018) Electronic cigarette: A recent update of its toxic effects on humans. Journal of cellular physiology 233(6), 4466-4478	**Exclude on study design**: non-systematic review
Ikonomidis I, Vlastos D, Kourea K, Kostelli G, Varoudi M, Pavlidis G, Efentakis P, Triantafyllidi H, Parissis J, Andreadou I, Iliodromitis E, and Lekakis J (2018) Electronic cigarette smoking increases arterial stiffness and oxidative stress to a lesser extent than a single conventional cigarette. Circulation 137(3), 303-306	**Exclude on follow-up**: immediate data collection of acute outcomes
Jagpal S, Pistun O, and Mikhail J (2014) Pirfenidone for idiopathic pulmonary fibrosis, thrombocytosis in chronic obstructive pulmonary disease exacerbations, and a longitudinal study on e-cigarettes. American Journal of Respiratory and Critical Care Medicine 190(6), 699-700	**Exclude on evidence**: commentary
Javed F, Kellesarian S V, Sundar I K, Romanos G E, and Rahman I (2017) Recent updates on electronic cigarette aerosol and inhaled nicotine effects on periodontal and pulmonary tissues. Oral diseases 23(8), 1052-1057	**Exclude on study design**: non-systematic review
Jiang N, Lee L, Zelikoff J T, and Weitzman M (2018) E-Cigarettes: Effects on the fetus. Pediatrics in Review 39(3), 156-158	**Exclude on study design**: non-systematic review

Kaisar Mohammad A, Sivandzade Farzane, Bhalerao Aditya, and Cucullo Luca (2018) Conventional and electronic cigarettes dysregulate the expression of iron transporters and detoxifying enzymes at the brain vascular endothelium: In vivo evidence of a gender-specific cellular response to chronic cigarette smoke exposure. Neuroscience letters 682, 1-9	**Exclude on population**: conducted in mouse cells
Kaur Gurjot, Muthumalage Thivanka, and Rahman Irfan (2018) Mechanisms of toxicity and biomarkers of flavoring and flavor enhancing chemicals in emerging tobacco and non-tobacco products. Toxicology letters 288, 143-155	**Exclude on study design**: non-systematic review
Khorassani Farah, Kaufman Milena, and Lopez Leonardo V (2018) Supatherapeutic Serum Clozapine Concentration After Transition From Traditional to Electronic Cigarettes. Journal of clinical psychopharmacology 38(4), 391-392	**Exclude on study design**: case report
Kim Shin Ae, Smith Samuel, Beauchamp Carlos, Song Yang, Chiang Martin, Giuseppetti Anthony, Frukhtbeyn Stanislav, Shaffer Ian, Wilhide Joshua, Routkevitch Denis, Ondov John M, and Kim Jeffrey J (2018) Cariogenic potential of sweet flavors in electronic-cigarette liquids. PloS one 13(9), e0203717	**Exclude on population**: machine vaping
Landmesser Anne, Scherer Max, Pluym Nikola, Sarkar Mohammadi, Edmiston Jeffery, Niessner Reinhard, and Scherer Gerhard (2018) Biomarkers of exposure specific to e-vapor products based on stable-isotope labeled ingredients. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco ,	**Exclude on follow-up**: 1 week, and wrong comparison
Lauterstein Dana (2017) Early life exposure to E-cigarettes induces CNS modifications associated with adverse neurobiological and neurobehavioral outcomes. Dissertation Abstracts International: Section B: The Sciences and Engineering 78(5-B(E)), No-Specified	**Exclude on evidence**: abstract only
Lerner Chad A, Sundar Isaac K, Watson Richard M, Elder Alison, Jones Ryan, Done Douglas, Kurtzman Rachel, Ossip Deborah J, Robinson Risa, McIntosh Scott, and Rahman Irfan (2015) Environmental health hazards of e-cigarettes and their components: Oxidants and copper in e-cigarette aerosols. Environmental pollution (Barking, and Essex : 1987) 198, 100-7	**Exclude on population**: machine vaping
Limas Eleuterio F (2018) Combustible cigarette, electronic cigarette, and mental health outcomes among latino college student smokers. Dissertation Abstracts International: Section B: The Sciences and Engineering 79(12-B(E)), No-Specified	**Exclude on evidence**: abstract only
Lippi G, and Sanchis-Gomar F (2018) Is it time to be concerned about the effects of e-cigarettes on cardiovascular health?. Expert Review of Cardiovascular Therapy 16(8), 547-549	**Exclude on evidence**: no data in paper
Lorkiewicz Pawel, Riggs Daniel W, Keith Rachel J, Conklin Daniel J, Xie Zhengzhi, Sutaria Saurin, Lynch Blake, Srivastava Sanjay, and Bhatnagar Aruni (2018) Comparison of Urinary Biomarkers of Exposure in Humans Using Electronic Cigarettes, Combustible Cigarettes, and Smokeless Tobacco. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco ,	**Exclude on follow-up**: 1 day
Manigrasso Maurizio, Buonanno Giorgio, Stabile Luca, Morawska Lidia, and Avino Pasquale (2015) Particle doses in the pulmonary lobes of electronic and conventional cigarette users. Environmental pollution (Barking, and Essex : 1987) 202, 24-31	**Exclude on evidence**: machine used to estimate particle dose
Marini Sara, Buonanno Giorgio, Stabile Luca, and Ficco Giorgio (2014) Short-term effects of electronic and tobacco cigarettes on exhaled nitric oxide. Toxicology and applied pharmacology 278(1), 9-15	**Exclude on follow-up**: short term only

Matz J (2013) Vapendavir significantly improves upper respiratory symptoms of naturally acquired rhinovirus infection in asthmatic adults: results of a phase 2 clinical trial. European respiratory society annual congress, 2013 sept 7-11, barcelona, and spain 42(Suppl 57), 307s [1493]	**Exclude on evidence:** abstract only
McConnell Rob, Barrington-Trimis Jessica L, Wang Kejia, Urman Robert, Hong Hanna, Unger Jennifer, Samet Jonathan, Leventhal Adam, and Berhane Kiros (2017) Electronic Cigarette Use and Respiratory Symptoms in Adolescents. American journal of respiratory and critical care medicine 195(8), 1043-1049	**Exclude on study design**: cross-sectional data only
Meo Sultan Ayoub, Ansary Muhammad Abdullah, Barayan Fahad Rayan, Almusallam Abdulaziz Sulaiman, Almehaid Abdulrahman Muteb, Alarifi Nawaf Saad, Alsohaibani Thamer Abdulnasir, and Zia Inam (2018) Electronic Cigarettes: Impact on Lung Function and Fractional Exhaled Nitric Oxide Among Healthy Adults. American journal of men's health , 1557988318806073	**Exclude on study design**: cross-sectional data only
Middlekauff Holly R, Park Jeanie, and Moheimani Roya S (2014) Adverse effects of cigarette and noncigarette smoke exposure on the autonomic nervous system: mechanisms and implications for cardiovascular risk. Journal of the American College of Cardiology 64(16), 1740-50	**Exclude on study design**: non-systematic review
Middlekauff Holly R. M. D, and Gornbein Jeffrey DrPH (2019) Association of Electronic Cigarette Use With Myocardial Infarction: Persistent Uncertainty. American Journal of Preventive Medicine 56(1), 159	**Exclude on evidence**: no evidence, letter to editor
Moheimani Roya S, Bhetraratana May, Yin Fen, Peters Kacey M, Gornbein Jeffrey, Araujo Jesus A, and Middlekauff Holly R (2017) Increased Cardiac Sympathetic Activity and Oxidative Stress in Habitual Electronic Cigarette Users: Implications for Cardiovascular Risk. JAMA cardiology 2(3), 278-284	**Exclude on study design**: case control, outcomes not relevant
Mokeem Sameer A, Abduljabbar Tariq, Al-Kheraif Abdulaziz A, Alasqah Mohmmed N, Michelogiannakis Dimitrios, Samaranayake Lakshman P, and Javed Fawad (2018) Oral Candida carriage among cigarette- and waterpipe-smokers, and electronic cigarette users. Oral diseases ,	**Exclude on study design**: cross-sectional data only
Morjaria J B, Mondati E, and Polosa R (2017) E-cigarettes in patients with COPD: current perspectives. International journal of chronic obstructive pulmonary disease 12, 3203-3210	**Exclude on study design**: non-systematic review
Munakata Satoru, Ishimori Kanae, Kitamura Nobumasa, Ishikawa Shinkichi, Takanami Yuichiro, and Ito Shigeaki (2018) Oxidative stress responses in human bronchial epithelial cells exposed to cigarette smoke and vapor from tobacco- and nicotine-containing products. Regulatory toxicology and pharmacology : RTP 99, 122-128	**Exclude on population**: machine vaping
Nelluri Bhargava, Murphy Katie, Mookadam Farouk, and Mookadam Martina (2016) The current literature regarding the cardiovascular effects of electronic cigarettes. Future cardiology 12(2), 167-79	**Exclude on study design**: non-systematic review
Oh Anne Y, and Kacker Ashutosh (2014) Do electronic cigarettes impart a lower potential disease burden than conventional tobacco cigarettes? Review on E-cigarette vapor versus tobacco smoke. The Laryngoscope 124(12), 2702-6	**Exclude on study design**: non-systematic review
Park Su Hyun, Lee Lily, Shearston Jenni A, and Weitzman Michael (2017) Patterns of electronic cigarette use and level of psychological distress. PloS one 12(3), e0173625	**Exclude on study design**: cross-sectional data only

Peters Matthew J (2018) E-cigarettes and airways' disease: Behind the smokescreen. Respirology (Carlton, and Vic.) 23(1), 14-15	**Exclude on study design**: commentary of original studies
Polosa Riccardo (2015) Electronic cigarette use and harm reversal: emerging evidence in the lung. BMC medicine 13, 54	**Exclude on study design**: non-systematic review
Polosa Riccardo, Morjaria Jaymin B, Caponnetto Pasquale, Battaglia Eliana, Russo Cristina, Ciampi Claudio, Adams George, and Bruno Cosimo M (2016) Blood Pressure Control in Smokers with Arterial Hypertension Who Switched to Electronic Cigarettes. International journal of environmental research and public health 13(11),	**Exclude on comparisons**: e-cigs' harm reduction potential evaluated – smoking not balanced between groups
Polosa Riccardo, Morjaria Jaymin B, Caponnetto Pasquale, Caruso Massimo, Campagna Davide, Amaradio Maria Domenica, Ciampi Giovanni, Russo Cristina, and Fisichella Alfredo (2016) Persisting long term benefits of smoking abstinence and reduction in asthmatic smokers who have switched to electronic cigarettes. Discovery medicine 21(114), 99-108	**Exclude on study design**: not a controlled study
Polosa Riccardo, Cibella Fabio, Caponnetto Pasquale, Maglia Marilena, Prosperini Umberto, Russo Cristina, and Tashkin Donald (2017) Health impact of E-cigarettes: a prospective 3.5-year study of regular daily users who have never smoked. Scientific reports 7(1), 13825	**Exclude on comparisons**: e-cig users compared to cigarette users, smoking not balanced across groups
Polosa Riccardo, Morjaria Jaymin Bhagwanji, Prosperini Umberto, Russo Cristina, Pennisi Alfio, Puleo Rosario, Caruso Massimo, and Caponnetto Pasquale (2018) Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up. International journal of chronic obstructive pulmonary disease 13, 2533-2542	**Exclude on comparisons**: e-cig users compared to cigarette users, smoking not balanced across groups
Qasim Hanan, Karim Zubair A, Rivera Jose O, Khasawneh Fadi T, and Alshbool Fatima Z (2017) Impact of Electronic Cigarettes on the Cardiovascular System. Journal of the American Heart Association 6(9),	**Exclude on study design**: non-systematic review
Ratajczak Alexsandra, Feleszko Wojciech, Smith Danielle M, and Goniewicz Maciej (2018) How close are we to definitively identifying the respiratory health effects of e-cigarettes?. Expert review of respiratory medicine 12(7), 549-556	**Exclude on study design**: non-systematic review
Reidel Boris, Radicioni Giorgia, Clapp Phillip W, Ford Amina A, Abdelwahab Sabri, Rebuli Meghan E, Haridass Prashamsha, Alexis Neil E, Jaspers Ilona, and Kesimer Mehmet (2018) E-Cigarette Use Causes a Unique Innate Immune Response in the Lung, Involving Increased Neutrophilic Activation and Altered Mucin Secretion. American journal of respiratory and critical care medicine 197(4), 492-501	**Exclude on study design**: cross sectional data
Rong Lingling, Frontera Alfred T, Jr , and Benbadis Selim R (2014) Tobacco smoking, epilepsy, and seizures. Epilepsy & behavior : E&B 31, 210-8	**Exclude on study design**: non-systematic review
Rubenstein D A, Hom S, Ghebrehiwet B, and Yin W (2015) Tobacco and e-cigarette products initiate Kupffer cell inflammatory responses. Molecular Immunology 67(2), 652-660	**Exclude on population**: rat cells
Schweitzer Rebecca J, Wills Thomas A, Tam Elizabeth, Pagano Ian, and Choi Kelvin (2017) E-cigarette use and asthma in a multiethnic sample of adolescents. Preventive medicine 105, 226-231	**Exclude on study design**: cross sectional data
Shahab Lion, Goniewicz Maciej L, Blount Benjamin C, Brown Jamie, McNeill Ann, Alwis K Udeni, Feng June, Wang Lanqing, and West Robert (2017) Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-sectional Study. Annals of internal medicine 166(6), 390-400	**Exclude on study design**: cross sectional data

Sommerfeld Casey G, Weiner Daniel J, Nowalk Andrew, and Larkin Allyson (2018) Hypersensitivity Pneumonitis and Acute Respiratory Distress Syndrome From E-Cigarette Use. Pediatrics 141(6),	**Exclude on study design**: case report
Son Yeongkwon (2018) Estimating the human health risks associated with exposures to harmful constituents emitted from electronic cigarettes. Dissertation Abstracts International: Section B: The Sciences and Engineering 79(10-B(E)), No-Specified St Helen , Gideon , and Eaton David L (2018) Public Health Consequences of e-Cigarette Use. JAMA internal medicine 178(7), 984-986	**Exclude on evidence**: abstract only, no data
Staudt M R, Salit J, Tilley A E, Kaner R J, Agosto-Perez F, and Hollmann C (2016) Acute Exposure to Electronic Cigarettes in Healthy Nonsmokers Leads to Global Transcriptome Changes in Distal Airway Epithelium and Alveolar Macrophages. American journal of respiratory and critical care medicine 193(Meeting Abstracts), A7512	**Exclude on evidence**: abstract only, no data
Staudt Michelle R, Salit Jacqueline, Kaner Robert J, Hollmann Charleen, and Crystal Ronald G (2018) Altered lung biology of healthy never smokers following acute inhalation of E-cigarettes. Respiratory research 19(1), 78	**Exclude on follow-up**: immediate data collection of acute outcomes
Stewart Judith C, Hyde Richard W, Boscia Joseph, Chow Ming-Yan, O'Mara Robert E, Perillo Irene, Pietropaoli Anthony, Smith Carr J, Torres Alfonso, Utell Mark J, and Frampton Mark W (2006) Changes in markers of epithelial permeability and inflammation in chronic smokers switching to a nonburning tobacco device (Eclipse). Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 8(6), 773-83	**Exclude on intervention**: heat not burn
Stewart Christopher J, Auchtung Thomas A, Ajami Nadim J, Velasquez Kenia, Smith Daniel P, De La Garza , Richard , 2nd , Salas Ramiro, and Petrosino Joseph F (2018) Effects of tobacco smoke and electronic cigarette vapor exposure on the oral and gut microbiota in humans: a pilot study. PeerJ 6, e4693	**Exclude on study design**: cross sectional data
Sultan Ahmed S, Jessri Maryam, and Farah Camile S (2018) Electronic nicotine delivery systems: Oral health implications and oral cancer risk. Journal of oral pathology & medicine : official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology ,	**Exclude on study design**: non-systematic review
Sundahl M, Berg E, and Svensson M (2017) Aerodynamic particle size distribution and dynamic properties in aerosols from electronic cigarettes. Journal of Aerosol Science 103, 141-150	**Exclude on population**: machine vaping only
van Staden , Sandri Rachelle, Groenewald Marcelle, Engelbrecht Rifke, Becker Piet Johannes, and Hazelhurst Lynton Tempest (2013) Carboxyhaemoglobin levels, health and lifestyle perceptions in smokers converting from tobacco cigarettes to electronic cigarettes. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde 103(11), 865-8	**Exclude on follow-up**: 2 weeks
Veldheer Susan, Yingst Jessica, Midya Vishal, Hummer Breianna, Lester Courtney, Krebs Nicolle, Hrabovsky Shari, Wilhelm Ashley, Liao Jason, Yen Miao-Shan, Cobb Caroline, Eissenberg Thomas, and Foulds Jonathan (2018) Pulmonary and other health effects of electronic cigarette use among adult smokers participating in a randomized controlled smoking reduction trial. Addictive behaviors ,	**Exclude on follow-up**: 1-3 months
Walele Tanvir, Bush Jim, Koch Annelize, Savioz Rebecca, Martin Claire, and O'Connell Grant (2018) Evaluation of the safety profile of an electronic vapour product used for two years by smokers in a real-	**Exclude on intervention**: e-cig as harm reduction

life setting. Regulatory toxicology and pharmacology : RTP 92, 226-238	
Wang Man Ping, Ho Sai Yin, Leung Lok Tung, and Lam Tai Hing (2016) Electronic Cigarette Use and Respiratory Symptoms in Chinese Adolescents in Hong Kong. JAMA pediatrics 170(1), 89-91	**Exclude on study design**: cross sectional data
Wang Julie B, Olgin Jeffrey E, Nah Gregory, Vittinghoff Eric, Cataldo Janine K, Pletcher Mark J, and Marcus Gregory M (2018) Cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms in the Health eHeart Study. PloS one 13(7), e0198681	**Exclude on study design**: cross sectional data
Warner Kenneth E, and Mendez David (2019) E-cigarettes: Comparing the Possible Risks of Increasing Smoking Initiation with the Potential Benefits of Increasing Smoking Cessation. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 21(1), 41-47	**Exclude on study design**: modelling benefits of cessation in general
Yu Vicky, Rahimy Mehran, Korrapati Avinaash, Xuan Yinan, Zou Angela E, Krishnan Aswini R, Tsui Tzuhan, Aguilera Joseph A, Advani Sunil, Crotty Alexander, Laura E, Brumund Kevin T, Wang-Rodriguez Jessica, and Ongkeko Weg M (2016) Electronic cigarettes induce DNA strand breaks and cell death independently of nicotine in cell lines. Oral oncology 52, 58-65	**Exclude on follow-up**: 8 weeks max
Zhang Guangwei, Wang Zhangli, Zhang Kai, Hou Rui, Xing Chunli, Yu Qi, and Liu Enqi (2018) Safety Assessment of Electronic Cigarettes and Their Relationship with Cardiovascular Disease. International journal of environmental research and public health 15(1),	**Exclude on study design**: systematic review, citations checked

Public health rerun search

Study Citation	Reason for excluding
Akinkugbe A A (2019) Cigarettes, E-cigarettes, and Adolescents' Oral Health: Findings from the Population Assessment of Tobacco and Health (PATH) Study. JDR clinical and translational research 4(3), 276-283	**Exclude as duplicate:** identified in first searches.
Alzahrani T, Pena I, Temesgen N, Glantz SA. Association between electronic cigarette use and myocardial infarction. (2019) Am J Prev Med. 2018;55(4):455–461. American Journal of Preventive Medicine 57(4), 579	**Exclude on study design**: cross-sectional only
Skotsimara Georgia, Antonopoulos Alexios S, Oikonomou Evangelos, Siasos Gerasimos, Ioakeimidis Nikolaos, Tsalamandris Sotirios, Charalambous Georgios, Galiatsatos Nikos, Vlachopoulos Charalambos, and Tousoulis Dimitris (2019) Cardiovascular effects of electronic cigarettes: A systematic review and meta-analysis. European journal of preventive cardiology 26(11), 1219-1228	**Exclude on study design**: systematic review, references checked.

Public health call for evidence

Study Citation	Reason for excluding
Keogan S, Li S, and Clancy L. (2019). Allen Carr's Easyway to Stop Smoking - A randomised clinical trial, Tobacco Control, 28, 414-419.	Exclude on intervention: not e-cigarettes

Frings D, Albery IP, Moss AC, Brunger H, Burghela M, White S, and Wood KV (2020) Comparison of Allen Carr's Easyway programme with a specialist behavioural and pharmacological smoking cessation support service: A randomised controlled trial. Addiction,	Exclude on intervention: not e-cigarettes
Fuller TW, Acharya AP, Meyyappan T, Yu M, Bhasker G, Little SR and Tarin TV. (2018) Comparison of bladder carcinogens in the urine of e-cigarette users versus non e-cigarette using controls. Sci Rep, 8, 507	Exclude on study design: cross-sectional, outcomes not included
Goniewicz ML, Gawron M, Smith DM, Peng M, Jacob P and Benowitz NL. Exposure to nicotine and selected toxicants in cigarette smokers who switched to electronic cigarettes: a longitudinal within-subjects observational study. Nicotine Tob Res, 19, 160-167	Exclude on study design: follow up of 2 weeks
Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L, Ross L and Goniewicz M (2019) A randomized trial of e-cigarettes versus nicotine replacement therapy. N Engl J Med, 380, 629-637	Exclude on study design: effectiveness study
Hajek P, Peerbux S, Phillips-Waller A, Smith C, Pittaccio K and Przulj D. (2019) BMJ Open, e026642	Exclude on participants: all dual users
Manzoli Lamberto, Flacco Maria Elena, Fiore Maria et al. (2015) Electronic Cigarettes Efficacy and Safety at 12 Months: Cohort Study. PloS one 10(6), e0129443	Study already included
Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Udeni Alwis K, Feng J, Wang L and West R. (2017) Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: a cross-sectional study. Ann Intern Med, 21, 390-400	Exclude on study design: cross-sectional, outcomes not included
Nelson WA, Goniewicz ML, Beard E, Brown J, Sheals K, West R and Shahab L. (2015) Comparison of the characteristics of long-term users of electronic cigarettes versus nicotine replacement therapy: a cross-sectional survey of English ex-smokers and current smokers. Drug Alcohol Depend, 153, 300-305	Exclude on study design: same sample as Shahab (2017)
Polosa R, O'Leary R, Tashkin D, Emma R, and Caruso M. (2019) The effect of e-cigarette aerosol emissions on respiratory health: a narrative review. Expert Rev Respir Med, 13, 899-915	Exclude on study design: narrative review

Appendix L – Research recommendations

Research recommendation 1

What are the short or long-term health effects of e-cigarette use? Are there any specific health effects relating to use in pregnancy, or use by children and young people?

Why this is important

The extensive harms of smoking are well known, and it is considered unlikely that use of e-cigarettes could cause similar levels of harm. For people who don't smoke, it is unlikely that inhaling vapour from an e-cigarette is as low risk as not doing so, although the extent of that potential risk is not yet known. E-cigarettes are relatively new devices and it is important to understand whether e-cigarettes cause any health harms or benefits aside from their potential to reduce smoking-related harm.

Rationale for research recommendation

Importance to 'patients' or the population	E-cigarettes are relatively new devices and are a popular choice as a smoking cessation aid. Many users perceive them to be less harmful than cigarettes ('Adult Smoking Habits in the UK: 2017').
Relevance to NICE guidance	It is important to understand whether e-cigarettes cause any health effects aside from their potential to reduce smoking-related harm.
Relevance to the NHS	Although smoking levels have fallen, smoking is linked to over half a million hospital admissions each year (NHS Long Term Plan).
National priorities	The extensive harms of smoking are well known and it is important to identify safe and effective means to support people to quit.
Current evidence base	There is a lack of evidence on the health effects of e-cigarette use.
Equality considerations	More secondary school pupils have tried e-cigarettes at least once (22%) than have tried cigarettes at least once (18%) ('Statistics on smoking, England – 2016'). It is currently estimated that almost a quarter of women smoke in pregnancy. (NHS Long Term Plan)

Modified PICO table

Population	People who use e-cigarettes, (nicotine and non - nicotine containing) including women who are pregnant and children and young people aged 12 and over, and who:

	• Have never smoked • Used to smoke and are using e-cigarettes to stop smoking or to prevent relapse
Intervention	Use of e-cigarettes (nicotine containing and non-nicotine containing)
Comparator	No use of e-cigarettes or tobacco containing products
Outcome	Short and long-term health effects (intended or unintended, positive or negative)