National Institute for Health and Care Excellence

Draft for Consultation

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

[J] Evidence reviews for nicotine replacement therapies and e-cigarettes in pregnancy: update

NICE guideline <number>

Evidence reviews underpinning recommendation 1.20.6 to 1.20.8 and 1.20.10 and research recommendations in the NICE guideline

June 2021

Draft for Consultation

These evidence reviews were developed by PHIGD

NICE accredited

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Contents

Nicotine replacement therapies and e-cigarettes in pregnancy 7
Review questions 7
Introduction 7
PICO table 7
Methods and process 9
Public health evidence for quantitative outcomes 10
Public health evidence for qualitative outcomes 22
Economic evidence 28
Summary of studies included in the economic evidence review 29
Economic model 32
Cost-effectiveness evidence statements 36
The committee's discussion of the evidence 37
Recommendations supported by this evidence review 41
References 42
Appendices 47
Appendix A – Review protocols 47
Review protocol for NRTs and e-cigarettes in pregnancy 47
Appendix B – Literature search strategies 60
Search approach for the updated Cochrane review by Claire (2020) 60
Search approach for the search by NICE for prospective cohort studies that could be relevant to safety outcomes 60
Search approach for the Cochrane review by Campbell 2019 64
Appendix C – Public health study selection 66
Figure 1: Study flow diagram for most recent update of Cochrane review by Claire (2020) 66
Figure 2: Study flow diagram for top-up search by NICE for prospective cohort studies that could be relevant to safety outcomes 67
Figure 3: Study flow diagram for Cochrane review by Campbell 2019 68
Appendix D – Public health evidence tables 69
Quantitative data extraction tables 69
Claire 2020 (Cochrane systematic review) 69
Oncken 2019 72
Quantitative data extraction tables (cohort studies) 73
Berard 2016 73
Dhalwani 2015 77
Dhalwani 2019 81
Strandberg-Larsen 2008 85
Qualitative data extraction tables (Campbell 2019) 88

Ashwin 2010 ... 91
Bauld 2017a ... 92
Borland 2013 ... 94
Bovill 2018 ... 95
Bowker 2016 ... 96
Bowker 2018 ... 97
Butterworth 2014 ... 98
England 2016 ... 100
Fallin 2016a ... 101
Fallin 2016b ... 102
Gamble 2015 ... 103
Glover 2012 ... 104
Grant 2018 ... 105
Hauck 2013 ... 107
Herbec 2014 ... 107
Hotham 2002 ... 109
Mantzari 2012 ... 109
Naughton 2013 ... 110
Pledger 2015 ... 112
Radley 2013 ... 113
Taylor 2010 ... 114
Appendix E – Forest plots ... 116
Appendix F – GRADE tables ... 122
GRADE CERQual tables ... 128
Matrix for integration of qualitative and effectiveness evidence ... 140
Appendix G – Economic evidence study selection ... 141
Appendix H – Economic evidence tables ... 142
Appendix I – Health economic evidence profiles ... 145
Appendix J – Health economic analysis ... 146
Appendix K – Excluded studies ... 147
Public health studies ... 147
Economic studies ... 152
Appendix L – Research recommendations ... 156
Research recommendation 2 ... 156
Why this is important ... 156
Rationale for research recommendation ... 156
Modified PICO table ... 156
Appendix M – Additional information ... 158
Risk of bias for RCTs by domain (Claire 2020) ... 158

Sensitivity analysis removing non-placebo-controlled trials from effectiveness outcomes 158

Nicotine replacement therapies and e-cigarettes in pregnancy

Review questions

Are nicotine replacement therapies (NRT) or e-cigarettes[a] effective and cost effective at helping pregnant women who smoke[b] to quit?

Are NRT and e-cigarettes safe for helping pregnant women who smoke to quit?

What are the barriers or facilitators to women taking up these interventions?

Introduction

Smoking during pregnancy is associated with a variety of health risks for mother and baby. In addition, there are questions around the effectiveness of e-cigarettes – a comparatively new technology – during pregnancy. This review aims to establish whether NRTs and e-cigarettes are effective, cost effective and safe.

Due to these potential harms, cessation rather than harm reduction is the focus of interventions during pregnancy. Reducing harm through cutting down prior to quitting, smoking less, or abstaining from smoking temporarily have uncertain health benefits in and of themselves, and may be mainly beneficial because they may make people more likely to quit in the future. Pregnancy is a short period of time and so emphasis is placed on moving directly to cessation in order that benefits start to be realised for both baby and mother during pregnancy.

The quantitative part of this review was primarily completed by the Cochrane Pregnancy and Childbirth Group (PCG) and the Cochrane Tobacco Addiction Group (TAG) in October 2019 for NICE (Claire 2020[c]). The qualitative part of this review was completed in October 2019 for NICE by Campbell (2019)[d]. Throughout, figures and sections of text have been taken directly from Cochrane work, or had minor amendments to wording, and are presented here in the standard NICE format.

PICO table

Table 1: PICO inclusion criteria

Population	Women who are pregnant and who smoke.
Interventions	Nicotine containing products for the purposes of stopping smoking: • NRT ○ Use of a single mode

[a] E-cigarettes refer throughout to any type of e-cigarette which contains nicotine.
[b] Throughout, smoking refers to the use of all smoked tobacco products.
[c] Claire R, Chamberlain C, Davey MA, Cooper SE, Berlin I, Leonardi-Bee J, Coleman T. Pharmacological interventions for promoting smoking cessation during pregnancy. Cochrane Database of Systematic Reviews 2020, Issue 3. Art. No.: CD010078. DOI: 10.1002/14651858.CD010078.pub3.
[d] Campbell K, Coleman-Haynes T, Bowker K, Cooper S, Connelly SL, Coleman T. Factors that influence the uptake and use of NRT and e-cigarettes by pregnant women who smoke: a qualitative analysis. Cochrane Database of Systematic Reviews 2019.

	○ Use of two or more types of NRT • E-cigarettes Trials with designs that permit the independent effects of NRT and/or e-cigarettes on smoking cessation to be evaluated
Comparator	• CBT, brief advice, behavioural support of similar intensity to any in the intervention. • Placebo • Other included interventions
Outcomes	**Quantitative outcomes (i)** <u>Critical outcomes</u> Smoking status at longest available follow-up prior to birth and longest available follow-up (if after birth). Measured as: • Abstinence from smoking (relative risk) *Where biochemically validated measures are available (i.e. saliva cotinine / carbon monoxide validation), these will be preferred to self-reported measures. Self-reported measures will only be used where no validated measure is reported*. <u>Important outcomes</u> • Adverse or unintended (positive or negative) effects related to the woman's health. For example: ○ Adverse effects such as headaches, nausea, skin or throat irritation or dry mouth. • Health-related quality of life (using validated patient-report measures, for example EQ-5D). **Quantitative outcomes (ii)** <u>Important outcomes</u> • Safety outcomes related to birth or health of the baby: ○ Miscarriage/spontaneous abortion ○ Stillbirth ○ Mean unadjusted birthweight ○ Low birthweight (less than 2500 g) ○ Preterm birth (less than 37 weeks' gestation) Neonatal intensive care unit admissions.

- Neonatal death
- Caesarean section
- Maternal hypertension
- Infant respiratory symptoms
- Infant development

Qualitative outcomes (iii)

Qualitative evidence on NRTs and e-cigarettes for women who smoke and are pregnant will be examined where available. Data will include:

- Barriers or facilitators to pregnant women taking up these interventions.
- Barriers or facilitators to sustained use of these interventions for successful abstinence

Cost/resource use associated with the intervention

The following outcomes will be extracted in reviews of the health economic evidence, where available:

- cost per quality-adjusted life year
- cost per unit of effect
- net benefit
- net present value
- cost/resource impact or use associated with the intervention or its components

Methods and process

This evidence review was developed using the methods and processes 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' sections, and in the review protocol in appendix A.

The following adaptations have been made to ensure the methods for this review are consistent with methods used in other reviews for the Tobacco guideline, and with the protocol for this review:

- Removal of studies assessing varenicline or bupropion
- Application of fixed- or random-effects meta-analysis based on methods described in the methods chapter for this guideline
- Completion of GRADE evidence profiles according to the methods chapter for this guideline

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

Agreed minimally important differences (MIDs) used in this review are presented in Table 2. For one pooled continuous outcome (mean birthweight of infant at delivery), the standard deviation was derived from the control group of the study with the largest weight (Coleman 2012).

Table 2: Minimal Important Differences (MIDs) agreed

Outcome	Importance	MID
Abstinence from smoking during pregnancy	Critical	Statistical significance
Safety outcomes: ○ stillbirth ○ neonatal death	Important	Statistical significance
Safety outcomes: ○ miscarriage / spontaneous abortion, ○ mean unadjusted birthweight, ○ low birthweight (less than 2500g), ○ preterm birth (less than 37 weeks gestation), ○ neonatal intensive care unit admissions, caesarean section, ○ maternal hypertension, ○ infant respiratory symptoms, ○ infant development (congenital abnormalities)	Important	Default ○ Dichotomous outcomes: 25% increase or 20% decrease (RR 0.8 to 1.25) ○ Continuous outcomes: 0.5*standard deviation

Risk of bias

The Cochrane groups used the *Cochrane Risk of Bias tool* to assess risk of bias. This tool assesses random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data, selective reporting and other bias (see appendix M).

Studies which were placebo-controlled (blinding of participants/personnel) were categorised as low risk of performance bias. For studies which were non-placebo controlled and consisted of behavioural control only, blinding was not possible and so studies were judged to be at high risk of bias. Trials were judged to be at high risk of detection bias (blinding of outcomes assessors) when no biochemical validation was used (cut-off points for validation were derived by expert consensus: 8ppm for exhaled carbon monoxide tests, and 10ng/mL for saliva cotinine). Incomplete outcome data was assessed for smoking abstinence outcomes during pregnancy through withdrawals, dropouts and protocol deviations, and studies which had used an intention to treat analysis were judged to be at low risk of attrition bias. Had studies prespecified an outcome which had not been reported, with evidence that was due to a lack of effect or an effect deemed unfavourable, these were judged to be at high risk of selective reporting bias.

Public health evidence for quantitative outcomes

Included studies

NICE guideline PH26 previously considered evidence (5 randomised controlled trials) on nicotine replacement therapy in a briefing paper on the effectiveness of smoking cessation interventions during pregnancy. However, this was not evaluated as part of a complete

formal evidence review. Additionally, no evidence was considered on the use of electronic cigarettes for smoking cessation in pregnancy. As such, the review presented here is a new review for this guideline.

Claire (2020) searched the Cochrane Pregnancy Group's trials register, clinicaltrials.gov, and the ICTRP in May 2019 using the topic number specific for this Cochrane systematic review. No language or date restrictions were applied.

Claire (2020) included studies that looked at the safety and efficacy of smoking cessation pharmacotherapies and electronic cigarettes used during pregnancy, in later pregnancy and after childbirth in women who smoked tobacco at baseline. Such interventions included nicotine replace therapies (NRT), bupropion, varenicline and e-cigarettes. Studies in the Cochrane review which focused on pharmacological interventions such as varenicline and bupropion (which are not licensed for use during pregnancy) are not included in this evidence review, as outlined in the NICE protocol (see appendix A).

Studies included in the Cochrane review had to provide very similar (ideally identical) behavioural support to participants across the active drug and comparator trial arms. A specific literature search was not carried out for secondary outcomes on adherence to interventions and non-serious side effects. Data on these outcomes was extracted, if available, from included studies

Nine randomised controlled trials (2,336 participants) investigating the efficacy of different forms of NRT were included in the Cochrane review, with 1 study (Oncken 2019) being new to this update. Six studies were judged to be at low risk of bias and 3 at high risk of bias. No studies were identified investigating the efficacy or safety of electronic cigarettes. All 5 studies identified in NICE guideline PH26 are included in Claire (2020).

NICE search for cohort studies

A search was completed by NICE for prospective cohort studies that could be relevant to safety outcomes, supplementary to randomised controlled trial (RCT) evidence identified in Claire (2020).

A systematic search was undertaken in April 2019 for relevant studies published and in the English language. No date limits were applied to the search strategy due to the nature of safety outcomes.

No website searches were conducted in line with the protocol. Further details on the search strategy are available in appendix B.

After removal of duplicates 558 unique database results were identified. 12 papers from this search with the potential to answer the safety component of the review question were ordered for full-text review. Of these, 4 papers (4 cohort studies) met the inclusion criteria for this review.

Qualitative studies

A Cochrane qualitative review was completed on the factors that influence the uptake and use of NRT and e-cigarettes by pregnant women who smoke (Campbell 2019). This review included studies that explored views, opinions, and experiences of pregnant women who smoke or smoked in pregnancy on the use of any type of NRT or e-cigarettes in pregnancy for smoking cessation or harm reduction. Six of the studies also examined barriers and facilitators.

The search for this review identified 2449 records after removal of duplicates, 74 papers were screened at full text and 21 papers met the inclusion criteria for this qualitative review.

Excluded studies

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

Table 3: Summary of quantitative public health studies included in the evidence review from Claire 2020 (effectiveness)

Study	Population	Intervention	Comparator	Cessation outcome(s)	Safety outcomes	Risk of bias
Berlin 2014 Double blind, placebo-controlled RCT France	Pregnant women who smoke (between 9-20 weeks gestation) 476 participants	Nicotine transdermal patches (10mg-30mg) + counselling	Placebo transdermal patches + counselling	Continuous abstinence from smoking since quit date (biochemically validated self-report 7-day PPA at each study visit, CO ≤8ppm). Final cessation outcome 1 month prior to delivery	• Mean birthweight • Low birthweight births (<2500g) • Preterm birth (<37 weeks) • Miscarriage/spontaneous abortion • Stillbirth • Neonatal intensive care admissions • Neonatal death • Maternal hypertension in pregnancy • Congenital abnormalities • Caesarean section	Low
Coleman 2012 Double blind, placebo-controlled RCT UK	Pregnant women who smoke (between 12- 24 weeks gestation) 1,050 participants	Nicotine transdermal patches (15mg/16hrs) + behavioural support	Placebo transdermal patches + behavioural support	Self-reported 7-day abstinence at 6, 12 and 24 months after childbirth. Continued abstinence (biochemically validated, CO≤ 7ppm, saliva cotinine ≤9ng/dL) at all follow-up points.	• Mean birthweight • Low birthweight births (<2500g) • Preterm birth (<37 weeks) • Miscarriage/spontaneous abortion • Stillbirth • Neonatal special care admissions • Neonatal death • Maternal hypertension in pregnancy • Congenital abnormalities • Caesarean section. • Infants survival without development impairment	Low

Study	Population	Intervention	Comparator	Cessation outcome(s)	Safety outcomes	Risk of bias
					• Respiratory symptoms at 2 years	
El-Mohandes 2013 USA Non-placebo controlled RCT	Pregnant women who smoke (less than 30 weeks gestation) 52 participants	Nicotine transdermal patches (21, 14 and 7mg dependent on baseline smoking) + cognitive behavioural therapy	Cognitive behavioural therapy	Point prevalence abstinence from smoking (biochemically validated, CO <8ppm) at various time-points during pregnancy. Cessation at last visit before childbirth.	• Mean birthweight • Low birthweight births (<2500g)	High
Hotham 2006 Non-placebo controlled RCT Australia	Pregnant women who smoke (between 12-28 weeks gestation) 40 Participants	Nicotine transdermal patches (15mg/16hrs) + counselling	Counselling	Point prevalence abstinence from smoking (biochemically validated, CO <8ppm) at final antenatal visit.		High
Kapur 2001 Placebo-controlled RCT Canada	Pregnant women who smoke (between 12-24 weeks gestation) 30 participants	Nicotine transdermal patches (15, 10 and 5mg/18hrs) + counselling	Placebo transdermal patches+ counselling	Abstinence from smoking unclear if point prevalence or continuous abstinence (biochemically validated, saliva and serum cotinine- cut off unclear) at 20-32 weeks into pregnancy.		Low
Oncken 2008 Placebo-controlled RCT	Pregnant women who smoke (≤26 weeks' gestation) 194 participants	Nicotine gum (2mg) + counselling	Placebo + counselling	Self-reported 7-day PPA (biochemically validated, CO <8ppm) at 32-35 weeks of pregnancy and at 6-12	• Mean birthweight • Low birthweight births (<2500g) • Preterm birth (<37 weeks)	Low

Study	Population	Intervention	Comparator	Cessation outcome(s)	Safety outcomes	Risk of bias
USA				weeks post-partum	• Miscarriage/spontaneous abortion • Stillbirth • Neonatal intensive care admissions • Neonatal death	
Oncken 2019 Placebo-controlled RCT USA	Pregnant women who smoke (between 13-26 weeks' gestation) 137 participants	Nicotine inhaler (10mg cartridge, 4mg delivered) + counselling	Placebo + counselling	Self-reported 7-day PPA (biochemically validated, CO <4ppm) at 6 weeks after quit date, at 32-36 weeks gestation, 1 and 6 months post-partum.	• Mean birthweight • Low birthweight births (<2500g) • Preterm birth (<37 weeks) • Miscarriage/spontaneous abortion • Stillbirth • Congenital abnormalities	Low
Pollak 2007 Non-placebo controlled RCT USA	Pregnant women who smoke (between 13-25 weeks' gestation) 181 Participants	NRT (Choice of patch- 7, 14 and 21 mg/16hrs, or 2mg gum or 2mg lozenge) +behavioural counselling	Behavioural counselling	Self-reported 7-day PPA at 38 weeks gestation, 7-weeks after randomisation (both (biochemically validated, saliva cotinine ≤10ng/mL) and 3-months post-partum.	• Mean birthweight • Low birthweight births (<2500g) • Preterm birth (<37 weeks) • Miscarriage/spontaneous abortion • Stillbirth • Neonatal intensive care admissions • Neonatal death	High
Wisborg 2000 Placebo-controlled RCT Denmark	Pregnant women who smoke (<22 weeks' gestation) 250 participants	Nicotine transdermal patches (15 reduced to and 10mg/16hrs) + behavioural counselling	Placebo transdermal patches+ behavioural counselling	Self-reported abstinence of >= 7 days at 2nd, 3rd and 4th prenatal visits (4 weeks prior to delivery), 3 and 12 months post-partum. Abstinence biochemically validated (saliva cotinine <26 ng/mL) at 4th visit (4 weeks prior to	• Mean birthweight • Low birthweight births (<2500g) • Preterm birth (<37 weeks) • Miscarriage/spontaneous abortion • Stillbirth	Low

Study	Population	Intervention	Comparator	Cessation outcome(s)	Safety outcomes	Risk of bias
				expected delivery date).		

*All studies were conducted in public hospitals or antenatal clinics.
CO refers to carbon monoxide testing
PPA refers to point prevalence abstinence

Table 4: Summary of quantitative public health studies included in the NICE search (safety cohort studies)

Study	Setting	Population	Intervention	Comparator	Safety outcome(s)
Berard 2016 Prospective cohort study	Quebec pregnancy cohort, Canada	Pregnant women who smoke 1,216 participants	Participants exposed to NRT patches during pregnancy	Participants not exposed to NRT patches during pregnancy	• Preterm birth (<37 weeks gestation) • Small for gestational age
Dhalwani 2015 Prospective cohort study	UK database of electronic primary care records	Pregnant women who smoke 12,657 participants	Participants exposed to NRT during pregnancy	Participants not exposed to NRT during pregnancy	Major congenital anomalies
Dhalwani 2019 Prospective cohort study	UK database of electronic primary care records	Pregnant women who smoke 23,268 participants	Participants exposed to NRT during pregnancy	Participants not exposed to NRT during pregnancy	Stillbirth
Strandberg-Larsen 2009 Prospective cohort study	Danish, National Birth Cohort Denmark	Pregnant women who smoke 14,357 participants	Participants exposed to NRT (gum, patches or inhaled substance) during pregnancy	Participants not exposed to NRT during pregnancy	Stillbirth

Dose of NRT unknown for all cohort studies. Where type of NRT is reported in the study, it is included in the table.

See appendix D for full evidence tables.

Funding information

Cochrane are not aware of any studies included in this review linked to or funded by tobacco organisations.

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

Evidence appraisal

- The systematic review by Claire (2020) was assessed using the Risk of Bias in Systematic Reviews *ROBIS* tool, in accordance with the NICE Manual. Randomised controlled trial (RCT) evidence from this review was not assessed using the *Cochrane Risk of Bias 2.0 tool* recommended by NICE (for risk of bias by domain by Cochrane see appendix M) As such, assessments of overall risk of bias of studies in this review were revised to align with judgments that would be derived from the use of this preferred tool as follows:
    - High risk of bias: The study is judged to be at high risk of bias in at least one domain for this result, or the study is judged to be at unclear risk for multiple domains in a way that substantially lowers confidence in the result.
    - Some concerns: The study is judged to be at unclear risk in at least two domains for this result, but not to be at high risk of bias for any domain.
    - Low risk of bias: The study is not at high risk of bias for any domain and is at unclear risk of bias in no more than one domain.

- Evidence from cohort studies was only included for important outcomes in relation to safety. Studies were assessed using the *ROBINS-I* tool, in accordance with the NICE Manual.
- Assessments for Risk of Bias in GRADE were drawn from the Risk of Bias tool assessment.
- All GRADE ratings start at 'high' and are downgraded as appropriate.
- The Cochrane review (Campbell 2019) applied the Wallace quality appraisal criteria. The CASP tool was applied to this evidence, in accordance with the NICE manual.
- Some of the studies included in the qualitative review included both harm reduction and cessation views, with committee agreement these were combined in the review findings.
- As the committee considered UK based evidence in the qualitative review to be of particular relevance this was particularly noted in the relevance domain in CERQual

See Appendix F for full GRADE tables.

See Methods document for details of rationale for GRADE judgements**.**

Missing data

For abstinence from smoking outcomes, participants lost to follow-up were assumed to still be smoking or had relapsed to smoking. Where smoking status was unknown, participants were also assumed to be smoking.

For pre-birth outcomes (spontaneous abortion/miscarriage and stillbirth), the denominator used was the number of women randomised with viable singleton pregnancies at the time of randomisation. Where terminations occurred after randomisation, terminated foetuses were excluded from the denominator if terminations were performed on a presumed viable foetus for non-medical reasons. Similarly, pregnancies that were documented as non-viable at the point of randomisation were also excluded from this denominator (e.g. missed abortion). Where terminations were undertaken for medical reasons and which were judged incompatible with life, these cases were included in denominators and also within

numerators; they were counted as miscarriages, if performed before 24 weeks and as stillbirths if conducted after this time point.

For mean unadjusted birthweight, the denominator used was the number of singleton births for which this outcome was recorded.

For dichotomous birth outcomes, the denominator used was the number of live births from singleton pregnancies.

For infant outcomes: the number of live births was used.

Unit of analysis

The unit of analysis for smoking cessation was the trial participant, regardless of whether she had a singleton or multiple pregnancy. For safety outcomes, analyses were conducted amongst singleton births only; this approach was taken because adverse pregnancy events/outcomes, adverse infant birth outcomes and poorer infant development are strongly associated with multiple pregnancy.

Heterogeneity

The I^2 statistic was used to quantify heterogeneity. A value greater than 50% indicated substantial heterogeneity. A value greater than 75% indicated considerable heterogeneity which was incompatible with presenting as pooled analyses. In such instances, heterogeneity was explored by conducting subgroup analyses for all primary and selected secondary outcomes:

- Placebo versus non-placebo controlled RCTs
- Studies using different types of NRT both alone and in combination (fast-acting NRT and long-acting NRT)

Meta-Analysis

All meta-analyses are taken from Claire (2020). Amendments were made to comply with the methods chapter for this guideline. Where required, more detail about the meta-analysis (studies excluded, details of pooling etc.) are below:

Adverse effects

Non-serious adverse or unintended effects related to the woman's health were narratively reported by Claire (2020) as they were too diverse to combine, and included 6 studies (Berlin 2014, Coleman 2012; Hotham 2006; Oncken 2008; Oncken 2019; Wisborg 2000).

Hotham 2006 reported that 5 participants in the NRT group experienced minor symptoms and two women stopped using patches after unpleasant effects. However, this trial did not monitor non-serious symptoms in the control group. One study (Oncken 2008) reported that at least 10% of participants experienced headache, dizziness, fatigue, heartburn, nausea or vomiting, with 14 (15%) in the NRT and 12 (12%) in the control groups discontinuing treatment due to adverse effects.

Another study (Wisborg 2000) noted that 11 participants stated that adverse effects (e.g. skin irritations and headache) made them discontinue patches (treatment allocations unknown) also 5 participants reported palpitations and 2 reported nausea. Coleman 2012 noted 535 non-serious adverse events reported by 521 NRT group participants and 450 reported by the 529 placebo group ones.

Berlin 2014 reported a range of non-serious adverse events noting that more non-gynaecological ones occurred in the NRT group, but this was principally due to skin reactions. In this study, 11% of participants in the NRT suffered a skin reaction at the patch site compared with 4% in the placebo one. Oncken 2019 reported a significantly higher number of side effects (throat irritation, cough and nausea) in women using the nicotine inhaler (11%) than the placebo group (0%). Furthermore, two women in this study were discontinued from the nicotine inhaler group due to repeated elevations in cotinine concentrations exceeding >40% of their baseline cotinine concentration.

Cohort data

Claire (2020) conducted meta-analysis using the Mantel-Haenszel method on the outcome *abstinence from smoking* and for *safety outcomes relating to birth or health* or the baby. For *safety outcomes* where cohort studies with adjusted effect estimates were identified, the generic invariance method was used to combine data.

Biochemically validated abstinence from smoking in later pregnancy - (Figures 4 and 5 and GRADE profiles 1 and 2).

Long acting-NRT included all studies which included nicotine transdermal patch interventions, whilst fast acting-NRT studies included nicotine gum or inhaler interventions.

One study (Coleman 2012) reported continuous cessation from a quit date set in pregnancy to postnatal time points alongside 7-day point prevalence abstinence data collected at the same time points. The study reported higher point prevalence than continuous cessation rates at each time point and rates of continuous cessation until two years after childbirth were low (2.9% in NRT group versus 1.7% in placebo, adjusted P = 0.12).

Miscarriage/spontaneous abortion - (Figure 8 and GRADE profile 4).

One study was not included in the pooled analysis due to unclear treatment allocation for 7 miscarriages (Wisborg 2000).

Maternal hypertension

Two studies that provided data on blood pressure gave these in different formats; Coleman 2012 reported that 24 (4.6%) in the NRT group compared to 25 (4.7%) in placebo were noted to have hypertension in pregnancy (blood pressure of greater than 140/90 mmHg) on at least 2 occasions (no statistical comparison presented). Berlin 2014 reported significantly higher median diastolic blood pressure in the NRT group [median BP = 70, interquartile range (IQR) = 60 to 80 mmHg] compared to placebo [median BP = 62, IQR = 60 to 80 mmHg].

Infant development after neonatal period

One study (Coleman 2012) reported an increase in survival to 2 years of age 'without impairment' in infants born to women who had been randomised to NRT, compared to placebo group (OR 1.40, 95% CI 1.05 to 1.86). Coleman 2012 also reported no significant difference in parental reports of infants' respiratory symptoms born to women who had been randomised to NRT, compared with placebo (OR 1.32, 95% CI 0.97 to 1.74). Effect estimates for this outcome were presented in the Cochrane review as odds ratios, rather than risk ratios which is the preferred measure for this guideline.

Summary of the evidence

This table is an overview of the results presented in the GRADE tables. The GRADE tables contain more information about confidence in the evidence and limitations (Appendix F).

Table 5: Evidence summary for quantitative outcomes

Outcome	Summary	Confidence	GRADE profile
Validated abstinence from smoking in later pregnancy	Placebo controlled trials An effect was not detected for NRT provided with behavioural support on abstinence from smoking in later pregnancy (6 studies) compared to placebo *RR 1.21 (0.95 to 1.55)*	Moderate	
	Non-placebo controlled trials NRT provided with behavioural support was effective in increasing abstinence from smoking in later pregnancy (3 studies) compared to behavioural support alone *RR 8.55 (2.05 to 35.71)*	Low	1
	Subgroup analysis by comparator type found statistically significant differences in smoking cessation rates between subgroups.		1
	Subgrouped by NRT type:		
	Long acting-NRT NRT provided with behavioural support was effective in increasing abstinence from smoking in later pregnancy compared with placebo or behavioural support alone (7 studies) *RR 1.53 (1.16 to 2.01)*	Moderate	
	Fast acting-NRT An effect was not detected for NRT provided with behavioural support on abstinence from smoking in later pregnancy compared with placebo (2 studies) *RR 0.91 (0.55 to 1.51)*	Moderate	2
	Subgroup analysis by NRT type found statistically significant differences in smoking cessation rates between subgroups.		2
Self-reported abstinence from smoking at 3 or 6-months post-partum	An effect was not detected for NRT provided with behavioural support on abstinence from smoking at 3 or 6-months post-partum compared with placebo or behavioural support alone (3 studies) *RR 1.22 (0.84 to 1.78)* *Subgroup analysis by comparator type (placebo and no placebo) found no significant differences in abstinence from smoking between subgroups.*	Low	3
Self-reported abstinence from smoking at 12-months post-partum	An effect was not detected for NRT provided with behavioural support on abstinence from smoking at 12-months post-partum compared with placebo (2 studies) *RR 1.35 (0.97 to 1.88)*	Moderate	3

Outcome	Summary	Confidence	GRADE profile
Miscarriage and spontaneous abortion	An effect was not detected for NRT provided with behavioural support on rates of miscarriage and spontaneous abortion compared with placebo or behavioural support alone (5 studies) *RR 1.62 (0.54 to 4.83)*	Low	4
Stillbirth (randomised controlled trials)	An effect was not detected for NRT provided with behavioural support on rates of stillbirth compared with placebo or behavioural support alone (4 studies) *RR 1.28 (0.57 to 2.85)*	Moderate	5
Stillbirth (cohort studies)	An effect was not detected for NRT on rates of stillbirth (2 studies) compared to no NRT *RR 0.86 (0.58 to 1.28)*	Very low	5
Mean birthweight of infant at delivery	There was no meaningful difference in mean infant birthweight at delivery between NRT provided with behavioural support and behavioural support only compared with placebo or behavioural support alone (7 studies) *Mean Difference 99.73 (-6.65 to 206.10)* *Subgroup analysis by comparator type (placebo and no placebo) found no statistically significant differences in mean birthweight of infant at delivery between subgroups.*	Moderate	6
Low birthweight births	**Subgrouped by comparator type:** <u>Placebo-controlled trials</u> An effect was not detected for NRT provided with behavioural support on rates of low birthweight births (5 studies) *RR 0.55 (0.28 to 1.10)* <u>Non-placebo controlled trials (</u>behavioural support alone) An effect was not detected for NRT provided with behavioural support on rates of low birthweight births (2 studies) *RR 1.35 (0.61 to 2.98)* *Subgroup analysis by comparator type found statistically significant differences in low birthweight births between subgroups.*	Very low Low	7 7
Preterm birth (randomised controlled trials)	An effect was not detected for NRT provided with behavioural support on rates of preterm birth compared with placebo or behavioural support alone (7 studies) *RR 0.82 (0.63 to 1.06)*	Moderate	8
Preterm birth (cohort studies)	NRT was effective in reducing the outcome compared to those not exposed to NRT (1 study) *RR 0.27 (0.17 to 0.41)*	Low	8

Outcome	Summary	Confidence	GRADE profile
Neonatal intensive care unit admissions	An effect was not detected for NRT provided with behavioural support on rates of neonatal intensive care unit admissions compared with placebo or behavioural support alone (4 studies) *RR 0.91 (0.64 to 1.28)*	Low	9
Neonatal death	An effect was not detected for NRT provided with behavioural support on rates of neonatal death compared with placebo or behavioural support alone (4 studies) *RR 0.73 (0.22 to 2.37)*	Moderate	10
Congenital abnormalities (randomised controlled trials)	An effect was not detected for NRT provided with behavioural support on rates of congenital abnormalities compared with placebo (2 studies) *RR 0.73 (0.36 to 1.48)*	Low	11
Congenital abnormalities (cohort studies)	An effect was not detected for NRT on rates of congenital abnormalities compared with those not exposed to NRT (1 study) *RR 1.07 (0.79 to 1.45)*	Very low	11
Caesarean section	An effect was not detected for NRT provided with behavioural support on rates of caesarean births compared with placebo (2 studies) *RR 1.24 (0.98 to 1.56)*	Moderate	12
Safety concerns about nicotine	6 studies; believe NRT is safer than smoking 7 studies; concerns that NRT can deliver unsafe amounts of nicotine 12 studies; concern about possible effect of using NRT on the baby in pregnancy 5 studies; belief that e-cigarettes are safer than smoking 3 studies; concern that e-cigarettes can deliver unsafe amounts of nicotine 4 studies; concern that use of e-cigarettes in pregnancy	Moderate Low Moderate Moderate Very low Moderate	GRADE CERQual table
Concerns about the addictiveness of nicotine	4 studies; concerns that nicotine is as addictive as smoking	Moderate	GRADE CERQual table
Beliefs about effectiveness of nicotine-containing products	5 studies; previous experience or reported positive experiences influenced readiness to use NRT 9 studies; previous negative experience or reported negative experiences influenced readiness to use NRT	High Moderate	GRADE CERQual table
Side effects associated with NRT	9 studies; experiencing side-effects of NRT can be a barrier to use in pregnancy	Moderate	GRADE CERQual table
Influence of others	6 studies; reassurance provided by clear, consistent information from health professionals about NRT 11 studies; impact on NRT use of lack of support around NRT use from health professionals 4 studies; impact of views and experiences of others on NRT use	Moderate Low Low	GRADE CERQual table

Outcome	Summary	Confidence	GRADE profile
	5 studies; readiness to use e-cigarettes influenced by the advice from health professionals 3 studies; readiness to use e-cigarettes influenced by the advice from other people	Moderate Moderate	
Characteristics of nicotine-containing products	12 studies; perceived characteristics of NRT can influence uptake and continuous use 5 studies; perceived characteristics of e-cigarettes can influence uptake and continuous use	Moderate Moderate	GRADE CERQual table

Public health evidence for qualitative outcomes

Included studies

This is a new review for this guideline and was completed by in October 2019 for NICE (Campbell 2019).

Campbell 2019 included qualitative studies which explored the views, opinions and experiences of pregnant or recently pregnant women who smoke(d) in pregnancy on the use of NRT of any type or e-cigarettes in pregnancy for smoking cessation or harm reduction (using NRT or e-cigarettes to smoke fewer cigarettes). Participants were not required to have previous experience of using NRT or e-cigarettes, as the focus of the review was on determinants of use. A broad search strategy completed in February 2019 was used to identify relevant studies from several databases and grey literature.

21 studies (497 participants) were included in the Cochrane review by Campbell 2019. Fifteen studies presented data relating to women's views on NRT, 3 studies focused on e-cigarettes and 3 studies included findings on both interventions.

Twelve out of 21 studies were conducted in the UK (Ashwin 2010, Bauld 2017, Bowker 2016, Bowker 2018, Butterworth 2014, Grant 2018, Herbec 2014, Mantzari 2012, Naughton 2013, Pledger 2015, Radley 2013, Taylor 2010) 4 studies were conducted in Australia, 3 studies in the USA, 1 study in New Zealand and 1 study in Canada. The focus of this evidence review is on qualitative studies conducted in the UK context, as indicated in the NICE protocol for this review (see appendix A). Whilst analyses presented in the Cochrane review are derived from both UK and non-UK studies, greater consideration will be placed on findings elicited from UK studies in this evidence review. Out of the 12 UK studies included in the Cochrane view, 8 studies focused on women's views on NRT, 2 studies focused on e-cigarettes and 2 studies reported views on both interventions.

Excluded studies

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

Table 6: Summary of qualitative public health studies included in the evidence review

Study	Setting	Population	Main intervention	Theme(s)
Ashwin 2010	UK, Urban and rural populations covered by a hospital trust	Pregnant women who smoke 10 participants (8	NRT for smoking cessation in pregnancy.	1. Choice of product 2. Thoughts surrounding quit day with NRT 3. Length of time product used 4. Information

Study	Setting	Population	Main intervention	Theme(s)
		using patches, 2 using gum)		5. Anxieties regarding use of NRT
Bauld 2017	Area A: Scotland and Area B: England. Urban and rural populations.	Pregnant or post-partum women who smoke(d) 41 participants (NRT/e-cigarette use not reported)	NRT for smoking cessation in pregnancy.	1. Nicotine replacement therapy 2. Electronic cigarettes
Borland 2013	Canada. Urban and rural populations.	Pregnant or post-partum women who smoke(d) 29 Participants (NRT/e-cigarette use not reported)	NRT for smoking cessation in pregnancy.	1. Inconsistent practice 2. Engagement and acceptability issues
Bovill 2018	Hunter and New England, Australia.	Aboriginal pregnant or post-partum women who smoke(d) 20 Participants (8 current or previous users of NRT/e-cigarettes)	NRT for smoking cessation in pregnancy	1. Attitudes towards NRT
Bowker 2016	UK. context unclear	Pregnant women who smoke(d) 14 Participants (64% using NRT, 36% using e-cigarettes)	NRT and e-cigarettes for smoking cessation in pregnancy	1. Expectations of NRT 2. Experience of using NRT (perceived effects of NRT use, concomitant smoking and side effects) 3. Safety concerns 4. Experience of e-cigarettes
Bowker 2018	UK, range of geographical locations	Pregnant or post-partum women who smoke(d) 30 Participants (9 current users	E-cigarettes for smoking cessation in pregnancy	1. Motivations for use 2. Social stigma 3. Using the e-cigarette 4. Consumer aspects 5. Harm perceptions

Study	Setting	Population	Main intervention	Theme(s)
		of e-cigarettes)		
Butterworth 2014	North Solihull, UK. Urban population.	Pregnant or post-partum women who smoke(d) 19 Participants (NRT/e-cigarette use not reported)	NRT for smoking cessation in pregnancy	1. Advantages of current services: non-judgemental support 2. Initiatives to encourage participation (offering suitable NRT subtheme)
England 2016	Memphis Philadelphia, Oklahoma City Billings, USA. Urban populations.	Pregnant or post-partum women who smoke(d) 59 Participants (19% of quitters (N=27), 28% of smokers (N=32) using other tobacco products	NRT and e-cigarettes for smoking cessation in pregnancy	1. Prior experiences with tobacco and NRT (perceptions related to non-combustible tobacco and NRT, general, subthemes = product familiarly, product appeal), specific and non-specific to pregnant women.
Fallin 2016a	USA, context unclear	Pregnant or post-partum women who smoke 19 Participants (NRT/e-cigarette use not reported)	NRT for smoking cessation in pregnancy	1. Lack of success with NRT
Fallin 2016b	USA, context unclear	Pregnant or post-partum women who smoke(d) cigarettes or e-cigarettes 19 Participants (NRT/e-cigarette use not reported)	E-cigarettes for smoking cessation in pregnancy	1. Attraction to e-cigarette as a harm reduction strategy 2. Uncertainty regarding the health effects of e-cigarettes 3. Ambivalence regarding novel product characteristics 4. Behaviours reflected dual use and often complete relapse to traditional cigarettes
Gamble 2015	Australia. Urban population.	Pregnant women who smoke(d) 6 participants	NRT for smoking cessation in pregnancy	1. What NRT women want

Study	Setting	Population	Main intervention	Theme(s)
Glover 2012	New Zealand. Urban and rural populations.	Pregnant Maori women who smoke(d) 60 Participants (NRT/e-cigarette use not reported)	NRT for smoking cessation in pregnancy	1. Health education resources 2. Nicotine replacement therapy
Grant 2018	South Wales, UK. Context unclear.	Pregnant women who smoke(d) cigarettes 10 Participants (1 using e-cigarettes)	E-cigarettes for smoking cessation in pregnancy	1. Demographics and (self-reported) smoking status, 2. Social networks, hidden smoking during pregnancy and morality, 3. Interaction with maternity healthcare services
Hauck 2013	Australia, urban population.	Pregnant women who smoke 36 Participants (NRT/e-cigarette use not reported)	NRT for smoking cessation in pregnancy	1. Something you could take
Herbec 2014	UK, nationwide recruitment.	Pregnant women who smoke(d) 13 Participants (NRT/e-cigarette use not reported)	NRT for smoking cessation in pregnancy	1. Smoking cessation medication
Hotham 2002	Australia, urban population	Pregnant women who smoke 19 Participants (NRT/e-cigarette use not reported)	NRT for smoking cessation in pregnancy	1. Attitudes of women towards the use of nicotine patches
Mantzari 2012	UK, urban population	Pregnant or post-partum women who smoke(d) 36 Participants (NRT/e-	NRT for smoking cessation in pregnancy	1. Perceived inhibitors

Study	Setting	Population	Main intervention	Theme(s)
		cigarette use not reported)		
Naughton 2013	Cambridgeshire and Suffolk, UK. Urban and rural populations	Pregnant or post-partum women who smoke(d) 20 Participants (NRT/e-cigarette use not reported)	NRT for smoking cessation in pregnancy	1. Uncertainty about the mechanism of harm
Pledger 2015	UK, context unclear	Pregnant or post-partum women who smoke(d) 6 Participants (NRT/e-cigarette use not reported)	NRT for smoking cessation in pregnancy	1. Experiences of using NHS stop smoking support
Radley 2013	Tayside, Scotland, UK. Context unclear.	Pregnant women who smoke(d) 20 Participants (NRT/e-cigarette use not reported)	NRT for smoking cessation in pregnancy	1. Client typology
Taylor 2010	Nottingham, UK. Urban population.	Pregnant or post-partum women who smoke(d) 18 Participants (9past users of NRT)	NRT for smoking cessation in pregnancy	1. Effective for quitting - beliefs about whether or not NRT would be effective in helping with smoking cessation 2. Side effects - beliefs about unwanted side effects accompanying NRT use 3. Improved health - beliefs that using NRT in pregnancy would improve the health of mother and baby 4. Not the same as quitting - beliefs that using NRT would not represent properly quitting smoking 5. Safety - beliefs that NRT might not be safe to use in pregnancy 6. Unsure if allowed - beliefs that NRT might not be allowed in pregnancy 7. Knowledge about products - the amount of knowledge a

Study	Setting	Population	Main intervention	Theme(s)
				pregnant woman has about NRT

See appendix D for full evidence tables.

Funding information

None of the studies included in this review are marked by Cochrane as being funded by tobacco organisations.

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

Data synthesis

Thematic data synthesis was used by Campbell (2019) to identify 6 overarching themes and 18 key review findings relating to factors influencing women's decisions about using, continuing to use or stopping NRT and/or e-cigarettes.

- Theme 1: Safety concerns about nicotine – Women's beliefs about safety of nicotine-containing products influence their readiness to use it in pregnancy
- Theme 2: Concerns about addictiveness of nicotine – women's beliefs about addictiveness of nicotine influence their readiness to use NRT in pregnancy
- Theme 3: Beliefs about effectiveness of nicotine-containing products – women's beliefs about the effectiveness of nicotine-containing products influence their use in pregnancy
- Theme 4: Side effects associated with NRT – Women's beliefs about and experiences with side effects of NRT influence their readiness to use NRT in pregnancy
- Theme 5: Influence of others – Women's readiness to use nicotine-containing products in pregnancy is influenced by the perceived views of and support from other people
- Theme 6: Characteristics of nicotine-containing products – women's views on characteristics of the nicotine-containing products can influence their readiness to use these in pregnancy

Evidence appraisal

- The systematic review by Campbell (2019) was assessed using the Risk of Bias in Systematic Reviews *ROBIS* tool, in accordance with the NICE Manual.
- Qualitative evidence from this review was assessed using the Wallace quality appraisal criteria (Croucher 2003[e]; Wallace 2004[f]), not the *CASP qualitative checklist*, as recommended by NICE. An overall study risk of bias summary was not provided. As such, study specific methodological issues identified in the Cochrane review were used to derive an overall study risk of bias assessment, based on judgments that would be elicited from the use of the *CASP checklist*.
- All GRADE CERQual ratings start at 'high' and are downgraded as appropriate.
- GRADE CERQUal judgements made by Campbell 2019 were reassessed to strengthen review findings that primarily included studies applicable to a UK context, whilst downgrading findings that primarily consisted of non-UK studies.

[e] Croucher K, Quilgars D, Wallace A, Baldwin S, Mather L. Paying the mortgage. A Systematic Literature Review of Safety Nets for Homeowners, York: Department of Social Policy and Social Work. 2003.
[f] Wallace A, Croucher K, Quilgars D, Baldwin S. Meeting the challenge: developing systematic reviewing in social policy. Policy & politics. 2004;32:455-70.

See Appendix F for full GRADE tables.

See Methods document for details of rationale for GRADE judgements.

Economic evidence

Included studies

2,533 records were assessed against the eligibility criteria.

2,473 records were excluded based on information in the title and abstract. One reviewer assessed all of the records and a second reviewer blind-screened 10% of the records. The level of agreement between the two reviewers was 100%.

The full-texts of 60 documents were retrieved and assessed. One study on NRT (in 2 documents) was assessed as meeting the eligibility criteria. One reviewer assessed all of the full texts and a second reviewer blind-screened 10% of the records. The level of agreement between the two reviewers was 100%. 1 study on NRT (in 2 documents) was included.

No studies on e-cigarettes were identified.

Excluded studies

58 full text documents were excluded for this question. The documents and the reasons for their exclusion are listed in Appendix K – Excluded studies. Documents were excluded for the following reasons: ineligible intervention (n=21), ineligible outcomes (n=4), ineligible study design (n=27) and ineligible patient population (n=6). The selection process is shown in Appendix G.

1 Summary of studies included in the economic evidence review

2 Table 7: Summary of the study included in the economic evidence review for NRTs and e-cigarettes in pregnancy

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Cooper 2014 & Essex 2015 (UK) Population: Pregnant smokers Sample size: 1,050 Intervention: NRT + behavioural support: • 4 week NRT supply of 15mg per 16 hours NRT patches, issued on quit date • NRT was renewed at 4 weeks, if patients' non-smoking status was validated by	No limitations [b]	Directly applicable [c]	A life-time analysis was planned but was not performed as there was no difference between short-term costs or outcomes.	Costs per participant NRT + behavioural support: £2,669.87 Placebo + behavioural support: £2,579.06	Verified quit rate at birth NRT + behavioural support: 9.4% Placebo + behavioural support: 7.6% EQ-5D index at 6 months: NRT + behavioural support: 0.896 Placebo + behavioural support: 0.894	£90.81 (not statistically significant [d]) Key incremental cost/resource usage differences: Cost per nicotine patch: NRT + behavioural support £46.07 Placebo + behavioural support £0.00 Caesarean section as mode of delivery: NRT + behavioural support 20.9%	Verified quit rate at birth: 1.8% [e] EQ-5D: 0.002 Neither the difference in quit rate nor EQ-5D were statistically significant Compliance [f]: NRT + behavioural support 7.2% Placebo + behavioural support 2.8%	ICER, per verified quitter: £4,926 Cost per QALY not calculated	PSA was undertaken by bootstrapping the trial results. Bootstrapped ICER: -£114,128 to £126,747 This highlights the uncertainty in the results [g]. Scenario analysis of singleton births, ICER: £4,156 per quitter

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
CO measurement • Behavioural support: 1 hour face to face session with midwife at enrolment • Women received a 15-page manual • A further 3 behavioural support sessions from local NHS stop smoking services, over the course of pregnancy was offered as well as telephone behavioural support Comparators: Placebo + behaviour support: the same as the intervention but with placebo patches [a]						Placebo + behavioural support 16.1%			

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty

NR: not reported; NRT: Nicotine Replacement Therapy; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life-year; UK: United Kingdom

a) *Uptake of behavioural support services were slightly higher in the NRT + behavioural support arm due to higher self-reported quit rates at 4-weeks resulting in additional home visitation for CO monitoring and a face-to-face support session. Overall mean costs of behavioural support and CO monitoring were similar across both arms: NRT + behavioural support £52.25; Placebo + behavioural support £47.75.*
b) *The analysis drew data from appropriate sources and data were analysed in an appropriate manner.*
c) *The study was a high-quality analysis of a UK population and intervention directly relevant to the review question.*
d) *The only statistically significant difference in healthcare resource usage related to mode of delivery where significant increases in Caesarean sections were observed for the NRT + behavioural support arm. The authors could provide no explanation for this increase and suggested it may be a chance outcome. Caesarean section was costed at £3028.66 and was a key driver in higher incremental costs.*
e) *The incremental effect of NRT + behavioural support is lower than observed in previous NICE reviews for the general population. Effect sizes may be lower as general population studies tend to compare NRT + behavioural support to treatment as usual, rather than a placebo patch (with additional behavioural support). A similar study in the general population by Lewis (1998) identified similar absolute cessation rates equal to 4.9% (no intervention), 6.5% (placebo patch + support), and 9.7% (nicotine patch + support). Incremental effects might be lower as the patch may be the least effective form of NRT. Compliance rates are unlikely to explain incremental effect sizes as these were lower in the placebo + behavioural support arm.*
f) *Compliance defined as >1 month continued use of NRT/placebo patch.*
g) *Cost-effectiveness plane illustrates incremental effects predominantly between (-3% and 5%) and costs between (-£700 and £1,000).*

1

Economic model

The evidence review identified 2 published studies relating to 1 randomised controlled trial which compared the use of nicotine replacement therapy (NRT) patches plus behaviour support to placebo patches plus behaviour support. The trial was conducted in a UK setting and was considered directly relevant to the review question. However, the committee considered the evidence from this study too uncertain to judge whether NRT patches plus behaviour support could be considered a cost-effective intervention to reduce smoking during pregnancy and so prioritised it for economic modelling. As no studies on e-cigarettes were identified the potential cost effectiveness of these was explored in a scenario analysis. A scenario analysis was also used to address the committee's concern that NRT might impact foetal loss and use of caesarean section during birth.

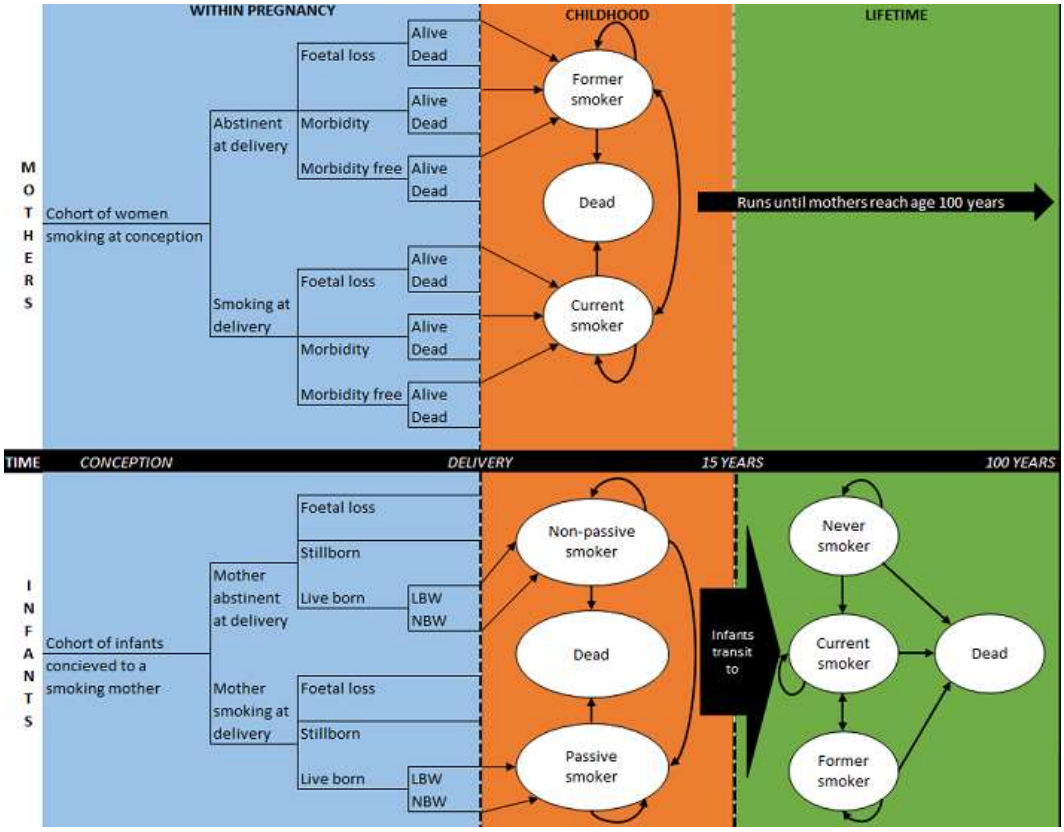
The analyses used a published economic model called the "economics of smoking in pregnancy" or *ESIP* model developed by the Division of Primary Care at the University of Nottingham (ref). The ESIP model estimates the lifetime costs and benefits of maternal smoking cessation during pregnancy for both mother and child. Parameter values, including unit costs and effectiveness rates were updated for each intervention and comparator.

The model adopts an NHS and personal social services (PSS) perspective for costs and incorporates health outcomes as QALYs. It calculates the cost-effectiveness of smoking cessation interventions separately for maternal outcomes only, infant outcomes only, and maternal & infant outcomes combined, each over several time horizons including pregnancy, childhood (<15 years), and lifetime (<100 years). Discount rates of 3.5% for both costs and benefits are applied (Developing NICE guidelines: The manual, 2018). A full description of the ESIP model, including model structure, input parameters, and methods to apply user defined inputs is provided in Jones et al. (2019).

A summary of the model structure and key results is provided below. A detailed report with full results and sensitivity analyses is provided in a separate economic modelling report (evidence review P)

In brief, the ESIP model progresses a cohort of 1000 pregnant women who smoke through an initial decision tree which maps maternal pregnancy outcomes. The cohort then enters a Markov model for the remaining time horizon. For mothers, the Markov component of the ESIP model contains health states related to smoking status, these being "current smoker", "former smoker", "dead". Between birth and 15 years infants enter an initial 'childhood' Markov model which estimates their burden of asthma, factoring in the impact of second-hand exposure to maternal smoking, according to their mothers smoking status. At age 16 years children transition to an 'adulthood' Markov model which estimates their life-time burden of smoking related morbidities and mortality. Different transition probabilities are applied according to the effectiveness of each intervention.

Figure 1 ESIP model structure



Results

NRT l/S

For the mother and child combined analysis, the ICER for NRT l/s vs usual care was £12,426 per QALY which is cost effective at a threshold of £20,000 per QALY. Deterministic analysis showed the results were highly sensitive to changes in intervention effectiveness. When set to the upper 95% CI RR (equal to 1.55) there was a substantial decrease in the ICER to £4,037; in contrast when set to the lower 95% CI RR (equal to 0.95) NRT l/s was not cost-effective being dominated by usual care (costlier and less effective). Similarly, the results were sensitive to changes in the time horizon, where NRT l/s was not cost-effective when limiting the analysis to pregnancy only (ICER vs. usual care =£275,000). Across all other DSA, which included variations to intervention costs, disease costs, utility values and relapse rates, cost effectiveness results were robust. In the probabilistic sensitivity analysis NRT l/s was cost effective in 63% of iterations. For the maternal only analysis, NRT l/s vs usual care was not cost effective with an ICER of £31,889.

Table 8 : NRT l/s Cost-effectiveness results – basecase[a]

Perspective and Intervention	Absolute Costs		Absolute QALYs		Incremental		
	NRT l/S	Usual care[b]	NRT l/s	Usual care	Costs	QALYs	ICER
Maternal + child lifetime outcomes							
NRT l/s vs. usual care	£21,011	£21,110	46.85	46.83	£98	0.019	£5,281
Maternal lifetime outcomes only							
NRT l/s vs. usual care [b]	£10,228	£10,117	23.20	23.20	£111	0.004	£30,056

a: Basecase 0% relapse rate between 20 and 40 weeks
b: Intervention and Usual care include behavioural support

Deterministic Sensitivity Analysis

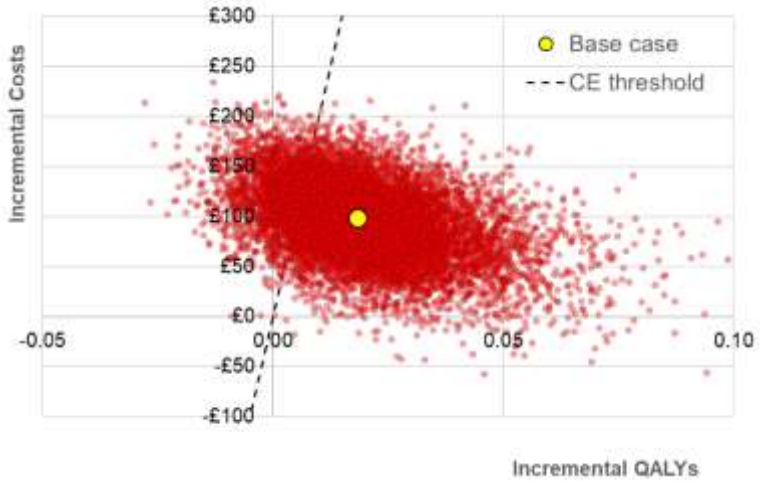
One-way deterministic sensitivity analysis (DSA) was conducted for intervention effectiveness, intervention costs, time horizon, mean age of the population, utility for smokers and non-smokers, disutility per comorbidity and cost per comorbidity.

For the NRT l/s analysis, cost-effectiveness results were highly sensitive to changes in the relative risk of smoking cessation (i.e. intervention effectiveness): when applying the upper 95% CI RR (equal to 1.55) there was a substantial decrease in the ICER from £5,381 to £1,315; In contrast when applying the lower 95% CI RR (equal to 0.95) NRT l/s was not cost-effective being dominated by placebo (costlier and less effective). Similarly, results were sensitive to changes in the time horizon, where NRT l/s was not cost-effective when limiting the analysis to pregnancy only (ICER vs. placebo =£130,000). Cost-effectiveness results were robust across all other DSA, which included variations to intervention costs, disease costs, and utility values.

Probabilistic Sensitivity Analysis

NRT l/s was identified as a cost-effective strategy in 83.1% of PSA iterations, with usual care being cost-effective in the remaining 16.9%27.5%. The results of the PSA are illustrated in Figure 2.

Figure 2: PSA Results NRT l/s



Safety of NRT

The PHAC expressed some concerns regarding the impact of NRT on foetal loss and delivery mode (i.e. the increased requirement for caesarean section during birth) as both of these outcomes had a mean RR in excess of 1 for NRT vs. placebo. To address this concern a threshold analysis was carried out to determine the total number of mothers with NRT dependent foetal loss/caesarean section that would be required to make the NRT l/s intervention not cost-effective vs. usual care.

The analysis demonstrates that cost-effectiveness results are moderately sensitive to changes in caesarean section and highly sensitive to changes in foetal loss (see Fig 2). The

percentage of pregnant women requiring a caesarean section would have to be greater than 10% before NRT l/s becomes not cost-effective. However, any increase in foetal loss would mean NRT l/s was not cost-effective vs. usual care.

Figure 3: Safety analysis NRT l/s

NMB [a]		Absolute % increase in fetal loss (NRT)										
		0%	0.1%	0.2%	0.3%	0.4%	0.5%	0.6%	0.7%	0.8%	0.9%	1.0%
Absolute % increase in c-section (NRT)	0%	£252	-£267	-£787	-£1,306	-£1,826	-£2,345	-£2,864	-£3,384	-£3,903	-£4,423	-£4,942
	2%	£226	-£293	-£812	-£1,332	-£1,851	-£2,371	-£2,890	-£3,409	-£3,929	-£4,448	-£4,968
	4%	£201	-£319	-£838	-£1,358	-£1,877	-£2,396	-£2,916	-£3,435	-£3,955	-£4,474	-£4,993
	6%	£175	-£344	-£864	-£1,383	-£1,903	-£2,422	-£2,941	-£3,461	-£3,980	-£4,500	-£5,019
	8%	£149	-£370	-£889	-£1,409	-£1,928	-£2,448	-£2,967	-£3,486	-£4,006	-£4,525	-£5,045
	10%	£124	-£396	-£915	-£1,435	-£1,954	-£2,473	-£2,993	-£3,512	-£4,032	-£4,551	-£5,070
	12%	£98	-£421	-£941	-£1,460	-£1,980	-£2,499	-£3,018	-£3,538	-£4,057	-£4,577	-£5,096
	14%	£72	-£447	-£967	-£1,486	-£2,005	-£2,525	-£3,044	-£3,567	-£4,083	-£4,602	-£5,122
	16%	£47	-£473	-£992	-£1,512	-£2,031	-£2,550	-£3,070	-£3,589	-£4,109	-£4,628	-£5,147
	18%	£21	-£499	-£1,018	-£1,537	-£2,057	-£2,576	-£3,095	-£3,615	-£4,134	-£4,654	-£5,173
	20%	-£5	-£524	-£1,044	-£1,563	-£2,082	-£2,602	-£3,121	-£3,641	-£4,160	-£4,679	-£5,199

[a]: Results are displayed as incremental net monetary benefit (NMB) vs. placebo. Any NMB greater than zero indicates that the intervention is cost-effective. The cost-effectiveness threshold was set equal to £20,000.

E-cigarettes exploratory analysis

The exploratory analysis assumed the efficacy of e-cigarettes in pregnancy populations vs. the general population would be similar to the efficacy of NRT l/s in pregnancy populations vs. the general population. Applying the assumed effectiveness of a RR of smoking abstinence for e-cigarettes of 1.82, the exploratory analysis found e-cigarettes were cost-effective for both the mother and child and mother only analyses, with ICERs equal to £39 and £3,748 respectively (see Table 9).

Table 9 : Results of E-cigarette exploratory analysis [a]

	Absolute Costs		Absolute QALYs		Incremental		
	E-cigs	Usual care	E-cigs	Usual care	Costs	QALYs	ICER
E-cigarettes vs. usual care							
Mother and child	£21,019	£21,016	46.89	46.82	£2.67	0.069	£39
Mother only	£10,170	£10,119	23.21	23.19	£51.26	0.014	£3,748

a: Exploratory analysis applied assumptions regarding for e-cigarettes, including a proportional relative risk for smoking cessation and equivalent costs as observed in general populations. Parameter values are *not* specific for pregnancy populations.

Because the effectiveness of e-cigarettes in pregnancy populations was based on an assumption a wide range of estimates was used in the deterministic sensitivity analysis. When effectiveness was reduced by 33% the ICER increased from £39 to £3,304. Cost-effectiveness results remained robust when other parameter values were varied including increasing costs, the mean age of mothers, the utility and disutility values, and the cost of the comorbidities. This indicates that e-cigarettes may be cost-effective vs. usual care for a range of plausible parameter values in a population of pregnant women. However, e-cigarettes were not cost-effective when limiting the model time horizon to pregnancy only.

Safety of e-cigarettes

The safety analysis shows e-cigarettes would still be considered cost-effective even if resulting in a 100% of mother's requiring a caesarean section. However, they would not be cost-effective if they resulted in an increase in foetal mortality in more than or equal to 0.3% of the population receiving the intervention (see Fig 4). The impact of foetal mortality is so pronounced due to the extremely high QALY loss per each foetal death, this being equal to the mean QALYs across the entire life expectancy of surviving infants.

Figure 4: Safety Analysis E-cigarettes

NMB [a]		Absolute % increase in fetal loss (e-cigs)										
		0%	0.1%	0.2%	0.3%	0.4%	0.5%	0.6%	0.7%	0.8%	0.9%	1.0%
Absolute % increase in c-section (e-cigs)	0%	£1,365	£845	£326	-£193	-£713	-£1,232	-£1,752	-£2,271	-£2,790	-£3,310	-£3,829
	10%	£1,236	£717	£198	-£322	-£841	-£1,361	-£1,880	-£2,399	-£2,919	-£3,438	-£3,958
	20%	£1,108	£589	£69	-£450	-£970	-£1,489	-£2,008	-£2,528	-£3,047	-£3,567	-£4,086
	30%	£980	£460	-£59	-£579	-£1,098	-£1,617	-£2,137	-£2,656	-£3,176	-£3,695	-£4,214
	40%	£851	£332	-£188	-£707	-£1,226	-£1,746	-£2,265	-£2,785	-£3,304	-£3,823	-£4,343
	50%	£723	£203	-£316	-£835	-£1,355	-£1,874	-£2,394	-£2,913	-£3,432	-£3,952	-£4,471
	60%	£594	£75	-£444	-£964	-£1,483	-£2,003	-£2,522	-£3,041	-£3,561	-£4,080	-£4,600
	70%	£466	-£53	-£573	-£1,092	-£1,612	-£2,131	-£2,650	-£3,170	-£3,689	-£4,209	-£4,728
	80%	£338	-£182	-£701	-£1,221	-£1,740	-£2,250	-£2,779	-£3,298	-£3,818	-£4,337	-£4,856
	90%	£209	-£310	-£830	-£1,349	-£1,868	-£2,388	-£2,907	-£3,427	-£3,946	-£4,465	-£4,985
	100%	£81	-£439	-£958	-£1,477	-£1,997	-£2,516	-£3,036	-£3,555	-£4,074	-£4,594	-£5,113

[a]: Results are displayed as incremental net monetary benefit (NMB) vs. placebo. Any NMB greater than zero indicates that the intervention is cost-effective. The cost-effectiveness threshold was set equal to £20,000.

For detailed results, sensitivity analyses and discussion, including limitations please see the separate health economics appendix.

Cost-effectiveness evidence statements

One cost-effectiveness analysis reported in two studies (Cooper, 2014 & Essex, 2015) on the Smoking, Nicotine and Pregnancy (SNAP) randomised controlled trial found that the use of nicotine patches (nicotine replacement therapy (NRT)) in combination with counselling (behavioural support) made a numerical difference to smoking rates compared to counselling alone, but that this difference was not statistically significant. The incremental cost-effectiveness ratio (ICER), using the numerical difference in quit rate, was £4,156 per quitter. Compliance rates were defined as continued patch use for longer than one month and were very low in the NRT plus counselling (7.2%) arm and even lower in the placebo plus counselling (2.8%) arm. EQ-5D data were collected but were not converted into quality-adjusted life years (QALYs) as the difference between NRT plus counselling and placebo plus counselling was not statistically significant. There was no statistically significant difference in costs between NRT plus counselling and counselling plus placebo. A life-time analysis was planned but not performed as there was no difference between short-term costs or outcomes. Boot strapped ICERs using data from the trial showed ICERs ranged from -£114,128 to £126,747 per quitter. The analysis was assessed as directly applicable to the review question, with no limitations.

One directly applicable cost-utility analysis with minor limitations found that NRT long or short acting plus behavioral support was associated with an ICER of £5,281 per QALY gain compared with usual care comprising behaviour support alone for mother and child combined. The analysis suggested that the cost-effectiveness of NRT l/s is subject to only a small degree of uncertainty, as indicated by the PSA which showed the ICER had a 73% probability of being lower than £20,000. The results of the DSA suggest the uncertainty was driven by the effectiveness of the smoking cessation interventions. For example, when parameter values were set to the lower 95% confidence interval NRT l/s was dominated by usual care, whereas the upper 95% confidence interval resulted in NRT l/s being cost-effective with a very favourable ICER below £1500.

The exploratory analysis of e-cigarettes found they were cost-effective for both the mother and child and mother only analyses, with ICERs equal to £39 and £3,748 respectively. These results were robust when intervention cost and effectiveness were varied across a wide range of parameter values in the DSA.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that not smoking was the most important outcome for this review. They agreed that not smoking during and after pregnancy were both critical outcomes, for several reasons. Firstly, because smoking will have direct health effects for the mother, and also for the child through the inhalation of second-hand smoke. Secondly, it is recognised that parental smoking is a factor in future smoking initiation of children, so that cessation in parents may reduce children's smoking uptake as well.

Confidence in the evidence

Quantitative – effectiveness outcome

There was no effectiveness evidence identified about e-cigarettes in pregnancy. All evidence on NRT measured the treatment as an adjunct to behavioural support. Therefore, all the discussion and recommendations considered NRT in this capacity. The committee agreed, based on the below discussion, that NRT is likely to be an effective method of stopping smoking in pregnancy but the evidence did not show this to be as effective as the committee would have expected. They discussed potential reasons for this, described below.

Risk of bias

The committee had concerns about bias inherent to non-placebo-controlled trials, where results could be inflated due to the placebo effect. This concern was supported by the subgroup analysis which showed that non-placebo-controlled trials had significantly higher effectiveness than placebo-controlled trials. The committee acknowledged that these higher risk of bias studies provided only a small percentage of the weight to the meta-analyses for effectiveness.

To interrogate the data further, the committee considered the sensitivity analyses of the effectiveness outcomes where non-placebo-controlled trials were removed (see Appendix M). This analysis resolved some of the heterogeneity between the NRT type subgroups (long-acting vs. short-acting; I^2 reduced from serious at 68.1% in Figure 5 to not serious at 35.1% in Appendix M). The analysis also slightly shrank the effect estimate of both NRT types combined and caused the confidence interval to include the line of no effect (previous result RR 1.37 95% CI 1.08, 1.74; sensitivity analysis result RR 1.21 95% CI 0.95, 1.55). The

committee recognised the uncertainty in the results and discussed that the detail of the intervention (for example, dose) and adherence to the intervention may be a possible explanation for this.

Detail of intervention

It was noted that a proportion of the studies were conducted more than 10 years ago (5 out of the 9 RCTs in the effectiveness meta-analyses). Most of the included studies prescribed doses of NRT now considered low (5 of the 6 studies giving patches used ≤15mg; 1 study with various NRT mode options used maximum 21mg patch, 2mg gum or 2mg lozenge; 1 study used a 10mg inhalator; 1 gum dose unclear – these doses are mainly those recognised to be for less addicted smokers i.e. those smoking <10 cigarettes per day). The committee acknowledged that this might be a result of cautious approaches to nicotine exposure during pregnancy and discussed that studies using higher doses were needed to strengthen confidence in the effectiveness of NRT.

Adherence

Adherence to NRT courses were noted to be generally low in the studies. The committee agreed that this was reflected in their experiences and pointed out that low adherence could reduce NRT's effect on cessation. The committee further discussed that women's concerns about the impact of NRT on their pregnancy could have contributed to this (see discussion on qualitative evidence below).

Quantitative - safety

Overall confidence

Safety outcomes were of moderate to very low confidence according to GRADE, and results tended to have wide confidence intervals due to events being rare.

The committee discussed several factors relating to the safety outcomes further:

1. The studies were primarily aiming to assess effectiveness outcomes rather than safety outcomes. Therefore, they were often not powered to detect changes in these outcomes, particularly as where events are rare.
2. They agreed that low adherence to the NRT course could mask any potential safety concerns in the randomised studies, as safety events are calculated across the whole of the group randomised to the intervention, regardless of whether or not the intervention was used.
3. The committee also noted that if it is accepted that NRT increases cessation, the safety outcomes from the included RCT designs could be the result of either using NRT or decreased smoking in the intervention group. If NRT is effective and the intervention group had lower levels of smoking, lower levels of harms caused by smoking would be expected. Despite this, there was too much uncertainty about safety outcomes to tell whether the intervention group experienced fewer of these negative events.

The committee also discussed that the placebo effect potentially evident in the non-placebo-controlled trials may have less effect on safety outcomes than on effectiveness outcomes. They also agreed that the direction of effect tended towards a reduction in harmful events in women (and babies of women) in NRT groups, although low event numbers make this very uncertain. This aligned with the committee's experience.

Specific results

The committee discussed the following results:

- Caesarean sections (RR 1.24 [95%CI 0.98 to 1.56]; GRADE profile 12, Figure 17): Although the point estimate indicated an increase, the result was narrowly not statistically significant, and the point estimate was not meaningful according to the MIDs chosen before the review (RR 0.8-1.25). The committee acknowledged that rates of caesarean sections in the general population were potentially higher than those observed in the studies (rates including both elective and emergency caesarean sections were 26% according to NHS Digital, 2018. The studies did not indicate the reason for the result, and the committee suggested that it could be down to chance. The committee also discussed a possible impact of those using NRT having heavier babies as smoking can impact on birth weight and that this may also be a factor in the rates of caesarean sections.
- Miscarriage and spontaneous abortion (RR 1.62 [95%CI 0.54, 4.83]; GRADE profile 4, Figure 8): Concerns about the results around miscarriage and spontaneous abortion were reduced because the confidence intervals were so imprecise, indicating serious uncertainty and a need for further data. The committee also noted that for impact on miscarriage there is additional uncertainty as most miscarriage occurs before 12 weeks, but studies often recruited after this.
- Stillbirth (RCT result RR 1.28 [95% CI 0.57-2.85] and cohort result RR 0.86 [95%CI 0.58-1.28]); GRADE profile 5, Figures 9-10): Concerns about the results around stillbirth were reduced because of wide confidence intervals in the RCT results indicating a non-significant increase in stillbirth and contrasting evidence from cohort studies showing a non-significant decrease in stillbirth.

The committee also pointed out that the MID for mean birthweight of infant at delivery (GRADE profile 6) was high. The MID was arrived at through standard methods (see Methods Chapter) which yielded a result of 295g. The committee agreed this would be considered a very large change in practice and that a smaller change could also be seen as meaningful. They concluded that the mean change in birthweight demonstrated in 7 RCTs (99.73g [95% CI -6.65g, 206.1g]) – although narrowly not statistically significant – gave an indication that NRT groups may have babies with birthweights that are meaningfully higher than those born to women in non-NRT groups. This may be a result of lower smoking in NRT groups, as smoking is known to reduce birthweight.

Qualitative

Overall confidence

The committee discussed the inclusion of non-UK studies in this review before viewing the evidence. They considered that themes about NRT were unlikely to differ significantly between countries. When considering potential e-cigarette themes, they noted that views may have diverged in recent years due to safety events that have taken place in the US and media and regulatory responses to these in both the US and the UK. However, as all non-UK e-cigarette studies (n = 2; England 2016 and Fallin 2016b) were conducted in 2015 or earlier, this was not anticipated in the current data. It was agreed that findings relying heavily on non-UK data, or findings where UK-based and non-UK data showed differences, would be downgraded for relevance in GRADE CERQual (see Appendix F). Once themes were presented and discussed, the committee agreed that most non-UK data was coherent with UK data and differences were minimal.

The committee discussed all of the findings and agreed to focus on findings at high and moderate confidence, but also brought in other findings where relevant.

Findings of importance

The committee agreed that evidence was particularly strong for the following points, which were also supported by their experience:

- The advice of health professionals is an important factor in whether or not products are used (Findings 12, 13, 15). Advice of midwives was considered by the committee to have particular importance for pregnant women. The committee emphasised the importance of clear and consistent messaging to increase likelihood that products are used as directed to gain the best possible effect from them.
- The committee noted the absence of data about the role of partners (and other family members) in the decision of the pregnant woman to use and continue using NRT or e-cigarettes. This might be a function of data which is somewhat thin (not richly described), or might imply the relative importance of health professionals compared with partners or other family members.
- Concerns about effects of NRT or e-cigarettes:
    - Women's fear that the nicotine in NRT is addictive reflects similar findings from the general population (review 6.2) and seems to be a widely held belief.
    - Concerns over safety of NRT or e-cigarettes specifically for the foetus, despite beliefs that these products are safer than smoking for the general population, may be a barrier to using these treatments in pregnancy.
    - Concerns over side effects of NRT and the potential impact of these on the pregnancy, particularly when the woman hasn't been told about and prepared for them, can cause either suboptimal use or discontinuation of use.

Benefits and harms

The committee discussed the benefits of the cessation related to NRT use with the evidence on safety. This evidence was inconclusive and did not clearly suggest safety concerns. They also noted the known adverse effects of smoking during pregnancy. They agreed that offering NRT during pregnancy to women who smoke was likely to have significant benefits. These benefits would be compounded by reducing the rates of relapse after pregnancy. There was no specific evidence on continuing NRT after pregnancy for preventing relapse, but the committee agreed that this was an appropriate option for healthcare providers to give to pregnant women.

The committee discussed that doses of NRT was an area where there was a lack of clarity. While the studies tended to use low doses, the committee agreed that higher doses might deliver more benefits, particularly if paired with higher levels of adherence. Because of uncertainty about any potential harms of higher doses, the committee made a research recommendation in this area.

No effectiveness or safety evidence was identified about using e-cigarettes for cessation during pregnancy was identified. Therefore, although there was evidence on barriers and facilitators to use in the qualitative part of this review, the committee agreed that it was not appropriate to address these in recommendations without knowing whether e-cigarettes work and any benefits or harms of their use.

Cost effectiveness and resource use

The committee discussed evidence from 2 published studies relating to 1 randomised controlled trial which compared the use of nicotine replacement therapy (NRT) patches plus behaviour support to placebo patches plus behaviour support. The trial was conducted in a UK setting and was considered directly relevant to the review question. The committee noted the trial reported a higher cessation rate in the NRT group but that the difference was not statistically different. They also noted the compliance rates in both groups for continued use beyond 1 month was very low and that there was substantial uncertainty around the incremental cost per quitter. A statistically significant difference in healthcare resource usage was reported for mode of delivery where a significant increase in Caesarean sections was observed for the NRT + behavioural support group. The authors could provide no explanation for this increase and suggested it may be a chance outcome. Caesarean section was a key driver in higher incremental costs.

The committee were concerned that the very low cessation rate would mean a large number of pregnant women would be needlessly taking NRT. They were also concerned about the risk of relapse to smoking as well as the resultant exposure to environmental tobacco smoke in the home and elsewhere. However, they were also mindful of the additional benefits of quitting during pregnancy that extend to the foetus and baby and the potential impact on the likelihood of the child taking up smoking if the mother succeeds in quitting. Based on the results from this one study the committee considered the evidence too uncertain to judge whether NRT patches plus behaviour support could be considered a cost-effective intervention to reduce smoking during pregnancy.

The economic analysis sought to address some of the concerns raised by the committee. It showed that NRT l/s plus behavioural support is likely to be cost-effective in the mother and baby combined analysis but not the mother alone analysis. The favourable results of the former occurred due to the combined impact of fewer foetal related mortalities, foetal morbidities and a reduction in the number of maternal smoking related morbidities. As noted above, the committee considered it important to capture the impacts on mother and baby and so placed greater importance on the analyses that combined the two.

The committee's concerns about the high risk of relapse and possible risk of harm to the foetus of using NRT were explored in two separate analyses. For relapse, it was assumed 20% of pregnant women who quit smoking during pregnancy would relapse between 20 and 40 weeks. Although the ICER in this analysis increased, the intervention remained cost effective. For possible risk of harm to the foetus, a threshold analysis was carried out to determine at what level of increase in foetal loss or caesarean section the intervention would no longer be cost effective. This analysis indicated that cost-effectiveness is moderately sensitive to changes in caesarean section and highly sensitive to changes in foetal loss. The NRT l/s intervention would need to increase caesarean section in mothers to over 10% before NRT l/s became not cost-effective whereas any increase in foetal loss would mean NRT l/s was not cost-effective.

Based on the analyses above the committee considered NRT for smoking cessation during pregnancy a reasonable use of public money.

The scenario analysis of e-cigarettes plus behavioural support suggested they would be cost-effective if the intervention were prescribed by the NHS and achieved similar levels of effectiveness in pregnant women as have been observed in the general population. However, in the absence of evidence of effectiveness and on potential harms for this population the committee did not recommend them.

Other factors the committee took into account

The committee took into account the licensing indications for various forms of NRT. A range of brands and types of NRT (e.g. patches, gum, inhalers) are licensed for use in pregnancy (EMC website). In addition an Expert Working Group made a recommendation that restrictions on use for all NRT products should be minimised for pregnant and breastfeeding women, as there are no circumstances in which it is safer to smoke than to use NRT (MHRA, 2014).

Recommendations supported by this evidence review

This evidence review supports recommendations 1.20.6 to 1.20.8 and 1.20.10 and the research recommendation on nicotine replacement therapy and e-cigarettes and pregnancy.

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Economic studies

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Appendices

Appendix A – Review protocols

Review protocol for NRTs and e-cigarettes in pregnancy

ID	Field (based on PRISMA-P	Content
I	Review question	5.3a. Are nicotine replacement therapies (NRT) or e-cigarettes[7] effective and cost effective at helping pregnant women who smoke[8] to quit? 5.3b. Are NRT and e-cigarettes safe for helping pregnant women who smoke to quit? 5.3c. What are the barriers or facilitators to women taking up these interventions?
II	Type of review question	Mixed methods
III	Objective of the review	Smoking during pregnancy is associated with a variety of health risks for mother and baby. In addition, there are questions around the effectiveness of e-cigarettes – a comparatively new technology – during pregnancy. The barriers and facilitators to women using these interventions during pregnancy affects how they would be taken up.

[7] E-cigarettes refer throughout to any type of e-cigarette which contains nicotine.
[8] Throughout, smoking refers to the use of all smoked tobacco products.

		This review aims to establish whether NRTs and e-cigarettes are effective, cost effective and safe, and the barriers and facilitators affecting their use. Cessation rather than harm reduction is the focus for during pregnancy. Reducing harm through cutting down prior to quitting, smoking less, or abstaining from smoking temporarily have uncertain health benefits in and of themselves, and are mainly beneficial because they may make people more likely to quit in the future. Pregnancy is a short period of time and so emphasis is placed on moving directly to cessation in order that benefits start to be realised for both baby and mother during pregnancy.
IV	Eligibility criteria – population/disease/condition/issue/domain	**Included**: Women who are pregnant and who smoke. **Excluded**: Women who are trying to conceive or have recently given birth. Women who used to smoke habitually but who have since quit. Women who are trying to stop using other substances (e.g. illicit drugs) or smokeless tobacco products. **Setting** All settings.

V	Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	**Included:**
		
		Nicotine containing products for the purposes of stopping smoking:
		
		• NRT
		  ○ Use of a single mode
		  ○ Use of two or more types of NRT
		• E-cigarettes
		
		Trials with designs that permit the independent effects of NRT and/or e-cigarettes on smoking cessation to be evaluated
		
		Excluded:
		
		Other pharmacotherapies for smoking cessation.
		
		E-cigarettes which do not contain nicotine.

VI	Eligibility criteria – comparator(s)/control or reference (gold) standard	**Included**: CBT, brief advice, behavioural support of similar intensity to any in the intervention. Placebo Other included interventions **Excluded**:

		Pharmacological interventions not included in this review, for example varenicline and bupropion (which are not licensed for use during pregnancy).
VII	Outcomes and prioritisation	**Quantitative outcomes (5.3a)** <u>Critical outcomes</u> Smoking status at longest available follow-up prior to birth and longest available follow-up (if after birth). Measured as: • Abstinence from smoking (relative risk) Where continued abstinence is presented, this is preferred over point-prevalence abstinence. Point prevalence measures will only be used where no continuous measure is reported. Where biochemically validated measures are available (i.e. saliva cotinine / carbon monoxide validation), these will be preferred to self-reported measures. Self-reported measures will only be used where no validated measure is reported. <u>Important outcomes</u> • Adverse or unintended (positive or negative) effects related to the woman's health. For example: o Adverse effects such as headaches, nausea, skin or throat irritation or dry mouth.

		• Health-related quality of life (using validated patient-report measures, for example EQ-5D).
		
		Quantitative outcomes (5.3b)
		
		<u>Important outcomes</u>
		
		• Safety outcomes related to birth or health of the baby:
		  ○ Miscarriage/spontaneous abortion
		  ○ Stillbirth
		  ○ Mean unadjusted birthweight
		  ○ Low birthweight (less than 2500 g)
		  ○ Preterm birth (less than 37 weeks' gestation)
		  ○ Neonatal intensive care unit admissions.
		  ○ Neonatal death
		  ○ Caesarean section
		  ○ Maternal hypertension
		  ○ Infant respiratory symptoms
		  ○ Infant development

		Qualitative outcomes (5.3c) Qualitative evidence on NRTs and e-cigarettes for women who smoke and are pregnant will be examined where available. Data will include: o Barriers or facilitators to pregnant women taking up these interventions. o Barriers or facilitators to sustained use of these interventions for successful abstinence **Cost/resource use associated with the intervention** The following outcomes will be extracted in reviews of the health economic evidence, where available: • cost per quality-adjusted life year • cost per unit of effect • net benefit • net present value • cost/resource impact or use associated with the intervention or its components
VIII	Eligibility criteria – study design	**Included study designs**: 5.3a (effectiveness):

		• Systematic reviews of included study designs • RCTs (including cluster RCTs) 5.3b (safety): • Systematic reviews of included study designs • RCTs (including cluster RCTs) • Cohort studies Economic studies: • Cost-utility (cost per QALY) • Cost benefit (i.e. net benefit) • Cost-effectiveness (Cost per unit of effect) • Cost minimization • Cost-consequence Qualitative studies: • Focus groups or interview-based studies of e-cigarette and NRT interventions for smoking cessation in pregnant women.

		Excluded study designs: • Cross-sectional surveys (except for qualitative data) • Correlation studies • Case control studies.
IX	Other inclusion exclusion criteria	**Studies** This review is a result of a gap identified in PH26 by the 2015 review surveillance report. This is a new review for the Tobacco update. **Systematic Review** This review is being conducted by Cochrane by updating Pharmacological interventions for promoting smoking cessation during pregnancy. No language restriction will be applied to the work being carried out by Cochrane. English language studies only for supplementary work being carried out by NICE (cohort studies for safety analysis). Only studies carried out in OECD countries will be included (for effectiveness data) and in the UK (for qualitative data).
X	Proposed sensitivity/sub-group analysis, or meta-regression	The following factors will be of interest in any meta-regression or subgroup analysis of effectiveness data:

		• Is effectiveness different when comparing placebo-controlled with trials not using a placebo? • How does effectiveness vary according to the socio-economic status or ethnicity of the target audience? • Is effectiveness different when comparing first generation (cig-a-like), second generation (vape pen) and third generation ('mod') devices? To reduce health inequalities, we are particularly interested in effectiveness of the intervention according to the following characteristics: • ethnic group • socio-economic deprivation
XI	Selection process – duplicate screening/selection/analysis	As defined by Cochrane.
XII	Data management (software)	As defined by Cochrane.
XIII	Information sources – databases and dates	As defined by Cochrane. There will be a top-up search for prospective cohort studies that could be relevant to 5.3b (safety) using the following methods: • the databases listed below will be searched with an appropriate strategy. • forward citation searching and reference harvesting will be done using selected studies prioritised from the surveillance reviews, the studies included in PH26, scoping searches or any relevant systematic reviews identified in the search process. The database strategy will be adapted as appropriate from the one used in PH26 in 2009 and the search for the update of the Cochrane review

		The principal top-up search strategy is listed in Appendix A and it will take this approach: (e-cigarettes OR vaping OR NRT) AND ((pregnancy OR maternity services OR obstetrics OR midwifery) OR (embryo OR fetal OR infant health)) AND cohort studies AND Limits 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: • British Nursing Index (BNI) via HDAS • Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley • Cumulative Index to Nursing and Allied Literature (CINAHL) via HDAS • Embase via Ovid • 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: • animal studies • editorials, letters and commentaries • conference abstracts and posters • registry entries for ongoing or unpublished clinical trials • duplicates.

		Web of Science Forward 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. Duplicates will be removed in WOS before downloading. The WOS results will be downloaded to EndNote and then searched for appropriate terms in the title and abstracts e.g. *longitudinal, prospective, cohort*. The results of this operation will then be passed over to the main search results file. **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 in the search history document. **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. **Cost effectiveness evidence** A separate search will be done for cost effectiveness evidence. The following databases will be searched again with agreed study-type search filters applied to a strategy based on the one in Appendix A: • Embase via Ovid • MEDLINE via Ovid

		• MEDLINE-in-Process (including Epub Ahead-of-Print) via Ovid In addition, the following sources will be searched without study-type filters: • Campbell Collaboration via https://campbellcollaboration.org/library.html • EconLit via Ovid • HTA database via CRD https://www.crd.york.ac.uk/CRDWeb/ • NHS EED via CRD https://www.crd.york.ac.uk/CRDWeb
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	As defined by Cochrane. Please see appendix B for details of additional search for cohort studies.
XVIII	Data collection process – forms/duplicate	As defined by Cochrane.
XIX	Data items – define all variables to be collected	As defined by Cochrane.
XX	Methods for assessing bias at outcome/study level	As defined by Cochrane. The Cochrane review provided will be assessed for risk of bias using the ROBIS tool.
XXI	Criteria for quantitative synthesis (where suitable)	As defined by Cochrane.

XXII	Methods for analysis – combining studies and exploring (in)consistency	As defined by Cochrane.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	As defined by Cochrane.
XXIV	Assessment of confidence in cumulative evidence	As defined by Cochrane.
XXV	Rationale/context – Current management	As defined by Cochrane.
XXVI	Describe contributions of authors and guarantor	As defined by Cochrane.
XXVII	Sources of funding/support	As defined by Cochrane.
XXVIII	Name of sponsor	As defined by Cochrane.
XXIX	Roles of sponsor	As defined by Cochrane.
XXX	PROSPERO registration number	As defined by Cochrane.

Appendix B – Literature search strategies

Search approach for the updated Cochrane review by Claire (2020)

The Cochrane groups searched the Cochrane Pregnancy and Childbirth Group's Register of trials, which includes the results of comprehensive searches of electronic bibliographic databases and conference abstracts, and the clinical trials registries clinicaltrials.gov and the ICTRP. Based on the intervention, trials are assigned a number which corresponds to a specific Pregnancy and Childbirth review topic(s) and then are added to the Register. The Register was then searched for this review using a topic number rather than keywords. No language or date restrictions were applied.

At the time of the search in May 2019, the Register included the results of monthly searches of the Cochrane Central Register of Controlled trials (CENTRAL); weekly searches of MEDLINE (via OVID); Embase (via OVID) and monthly searches of CINAHL (via EBSCO). See the 'PCG trials register' section of the Cochrane Pregnancy and Childbirth Group's website for full search strategies and list of other resources searched.

Search approach for the search by NICE for prospective cohort studies that could be relevant to safety outcomes

The MEDLINE searches below were run after QA, peer review and consultation with the committee. The strategies were adapted as appropriate to the other databases listed in the protocol (see the sources table below). No date restrictions were applied. The searches were done between 24-25 April 2019.

Additional search results were obtained from scoping searches and from forwards citation searching and reference checking using Web of Science.

A search for grey literature was not completed as per review protocol.

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
British Nursing Index (BNI)	25/4/2019	ProQuest	(1994-current)	41
Cochrane Central Register of Controlled Trials (CENTRAL)	24/4/2019	Wiley	Cochrane Central Register of Controlled Trials Issue 4 of 12, April 2019	77
Cumulative Index to Nursing and Allied Literature (CINAHL)	24/4/2019	HDAS	1981-present	81
Embase	24/4/2019	Ovid	Embase 1974 to 2019 April 23	114

Health Management Information Consortium (HMIC)	24/4/2019	Ovid	HMIC Health Management Information Consortium 1979 to January 2019	2
MEDLINE	24/4/2019	Ovid	Ovid MEDLINE(R) 1946 to April 23, 2019	91
MEDLINE-in-Process (including Epub Ahead-of-Print)	24/4/2019	Ovid	Ovid MEDLINE(R) Epub Ahead of Print April 22, 2019, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to April 23, 2019	25
PsycINFO	24/4/2019	Ovid	PsycINFO 1806 to April Week 3 2019	28
Social Policy and Practice (SPP)	24/4/2019	Ovid	Social Policy and Practice 201901	0
Forward citation searching	24/4/2019	Clarivate	Web of Science Core Collection (1990-present)	259
Surveillance	24/04/2019	-	-	0
Scoping searches	24/04/2019	-	-	3

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

Database(s): **Ovid MEDLINE(R)** 1946 to April 23, 2019

Search Strategy:

#	Searches	Results
1	Electronic Nicotine Delivery Systems/	2303
2	Vaping/	292
3	(ecig* or e-cig* or e-voke* or juul* or vape* or vaping* or ENNDS).ti,ab.	2170
4	(electronic* adj3 (tobacco* or nicotin* or cigar* or cigs or vapor* or vapour*)).ti,ab.	1705
5	((tobacco* or nicotin* or cigar* or cigs) adj3 (vapor* or vapour* or device* or inhalator* or inhaler*)).ti,ab.	644
6	(nicotin* and (ENDS or ANDS)).ti,ab.	234
7	(nicotin* adj3 deliver* system*).ti,ab.	267
8	((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.	298

9	(polytobacco* or poly tobacco* or poly-tobacco* or multitobacco* or multi tobacco* or multi-tobacco*).ti,ab.	71
10	nicotine chewing gum/	13
11	"tobacco use cessation devices"/	1559
12	Smoking cessation agents/	35
13	(nrt or nicorette* or niquitin* or nicotinell* or nicassist*).ti,ab.	1674
14	(nicotin* adj3 (replacement* or substitut* or gum* or inhaled* or inhaler* or inhalant* or inhalator* or spray* or lozenge* or tablet* or transdermal* or patch* or vaccin* or device* or gel* or pastil* or deliver* or sublingual* or therap* or treatment* or nasal* or microtab* or polacrilex* or product or products*)).ti,ab.	9215
15	or/1-14	13113
16	exp Pregnancy/	859379
17	exp Pregnancy complications/	408186
18	Pregnant Women/	7395
19	exp Maternal Health Services/	45793
20	Midwifery/	18510
21	Doulas/	118
22	obstetrics/	21742
23	obstetric nursing/	2952
24	pregnan*.ti,ab.	430029
25	(ante natal* or ante-natal* or antenatal* or pre natal* or pre-natal* or prenatal* or peri natal* or peri-natal* or perinatal*).ti,ab.	163577
26	(maternity* or maternal* or obstetric* or midwif* or midwiv* or doula*).ti,ab.	301958
27	exp pregnancy outcome/	69630
28	exp Obstetric Surgical Procedures/	127768
29	exp Hypertension, Pregnancy-Induced/	34613
30	Postpartum Period/	23839
31	Peripartum Period/	986
32	exp "Embryonic and Fetal Development"/	258487

33	exp Embryo, Mammalian/	91164
34	Embryo loss/	1339
35	exp fetus/	153638
36	exp Fetal death/	28638
37	Fetal Weight/	1644
38	Fetal distress/	3300
39	Heart Rate, Fetal/	4852
40	Birth weight/	38064
41	exp Infant, Newborn/	582879
42	exp Infant, Newborn, Diseases/	168044
43	exp Infant death/	7575
44	exp Maternal-Child Nursing/	5685
45	Child Development/	43509
46	(miscarr* or stillbirth* or stillborn* or abortion* or fetal* or foetal* or foetus or fetus* or embryo* or childbirth* or child birth* or child-birth* or gestational* or baby* or babies* or neonat* or neo nat* or neo-nat* or infanc* or infant* or newborn* or new born* or "new-born*" or postpartum* or post partum* or post-partum* or peripartum* or peri partum* or peri-partum* or antepartum* or ante partum* or ante-partum* or intrapartum* or intra partum* or intra-partum* or postnatal* or post natal* or post-natal* or puerperium* or puerperal* or parturition* or Caesarean* or Cesarean* or eclampsia* or preeclampsia* or "pre eclampsia*" or pre-eclampsia* or ectopic* or uterine* or fallopian* or SCBU* or NICU* or preterm* or "pre term*" or pre-term* or prematur* or "pre matur*" or pre-matur* or lbw or vlbw or birthweight* or birth weight* or birth-weight*).ti,ab.	1528456
47	or/16-46	2455773
48	15 and 47	976
49	exp Cohort Studies/	1848829
50	((follow up* or followup* or follow-up* or concurrent* or incidence* or population*) adj3 (study* or studies* or analy* or observation* or design* or method*)).ti,ab.	291037
51	(longitudinal* or prospective* or retrospective* or cohort*).ti,ab.	1473903
52	epidemiologic methods/ and (197* or 198*).yr.	10282
53	or/49-52	2465212

54	48 and 53	96
55	Animals/ not (Animals/ and Humans/)	4540337
56	54 not 55	91
57	limit 56 to (letter or historical article or comment or editorial or news or case reports)	0
58	56 not 57	91

Search approach for the Cochrane review by Campbell 2019

The review searched the following databases; MEDLINE(R) ALL 1946 to Present, CINAHL and PsycINFO. Database search strategies were adapted from the main search strategy below for MEDLINE. Additionally, the OpenGrey database was manually searched using terms 'pregnancy' & 'smoking cessation' and 'pregnancy' & 'nicotine replacement' and references of included studies and literature reviews identified by searching were screened. Forward citation searches of included studies were also conducted and no filters for qualitative terms were used. Database searches were completed in February 2019.

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

1. Pregnancy/
2. exp Pregnancy Outcomes/
3. Pregnancy Trimesters/
4. Pregnant Women/
5. Prenatal Care/
6. Postpartum Period/
7. pregnan*.tw,kf.
8. (ante*natal or antenatal).tw,kf.
9. (pre*natal or prenatal).tw,kf.
10. (postpartum or post*partum).tw,kf
11. (postnatal or post*natal).tw,kf.
12. "Tobacco Use Cessation"/
13. "Tobacco Use Cessation Products"/
14. Nicotinic Agonists/
15. Smoking Cessation Agents/
16. Nicotine Chewing Gum/
17. NRT.ti,ab.

18. nicotine replacement.tw,kf.
19. ((nicotine or tobacco) adj2 (gum* or lozenge* or patch* or spray*)).tw,kf.
20. (pharmaco* adj2 (nicotine or tobacco or smoking)).tw,kf.
21. smoking cessation.tw,kf.
22. Electronic Nicotine Delivery Systems/
23. vaping/
24. e-cig*.tw,kf.
25. ecig.tw,kf.
26. electronic cigarette*.tw,kf.
27. electronic nicotine.tw,kf.
28. (nicotine and vap*).tw,kf.
29. exp ANIMALS/ not HUMANS
30. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
31. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
32. 30 and 31
33. 32 not 29

Appendix C – Public health study selection

Figure 1: Study flow diagram for most recent update of Cochrane review by Claire (2020)

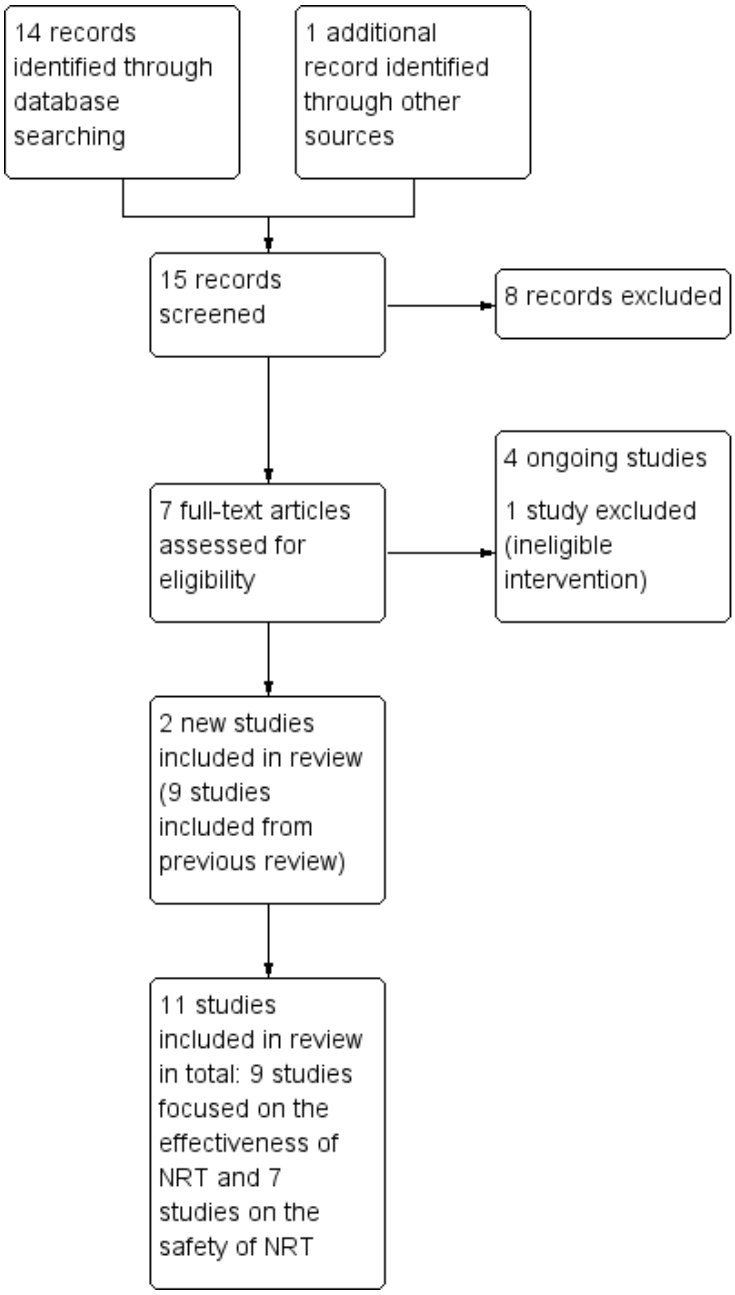


Figure 2: Study flow diagram for top-up search by NICE for prospective cohort studies that could be relevant to safety outcomes

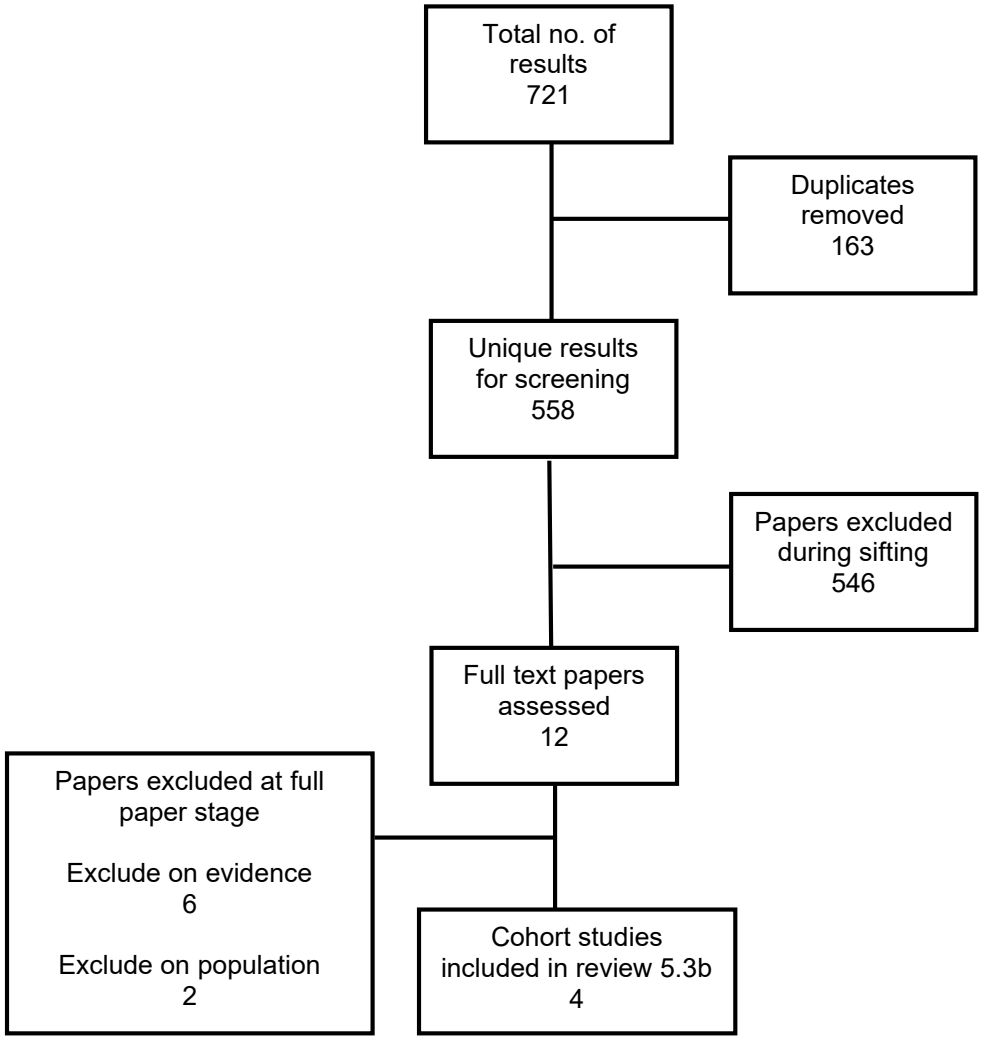
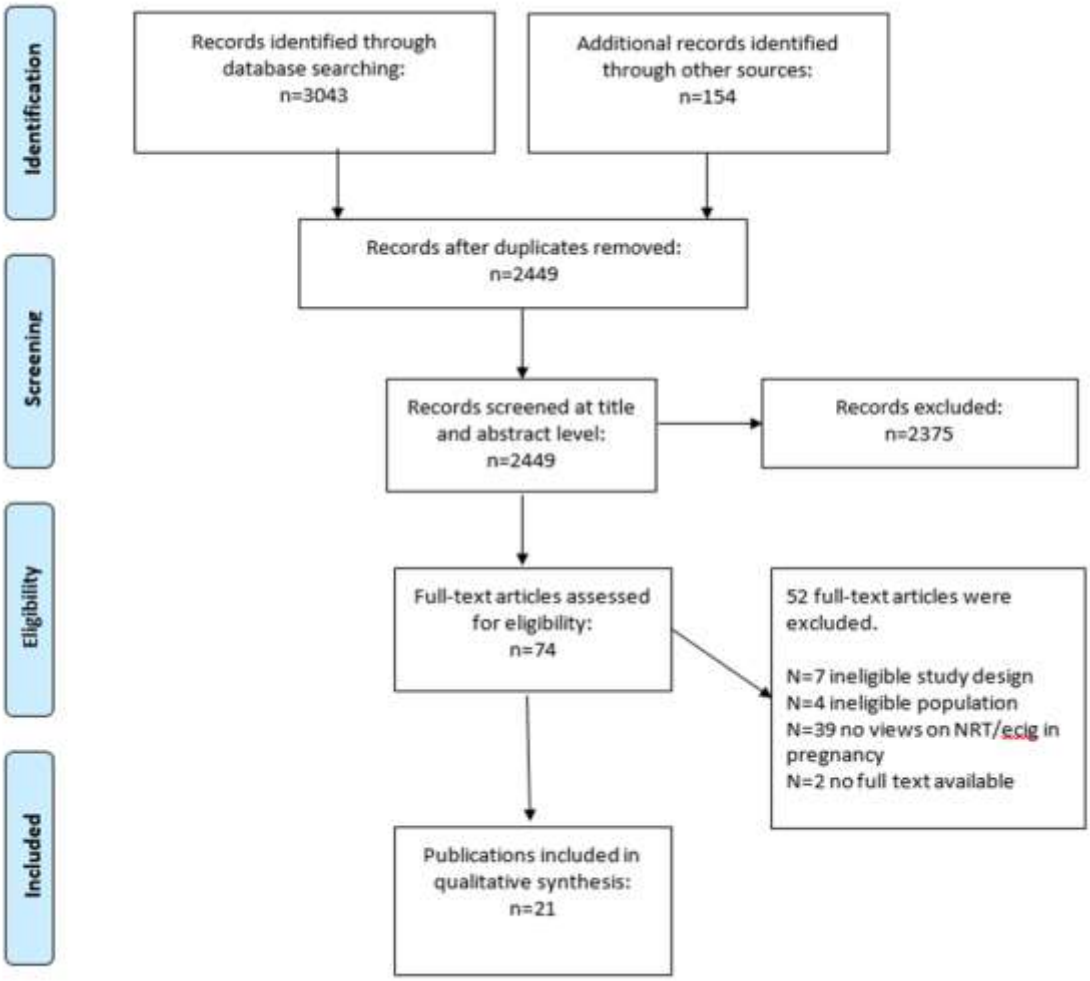


Figure 3: Study flow diagram for Cochrane review by Campbell 2019



Appendix D – Public health evidence tables

Quantitative data extraction tables

Please see *Pharmacological interventions for promoting smoking cessation during pregnancy* for full evidence tables.

Claire 2020 (Cochrane systematic review)

Bibliographic reference	**Claire R, Chamberlain C, Davey MA, Cooper SE, Berlin I, Leonardi-Bee J, Coleman T. Pharmacological interventions for promoting smoking cessation during pregnancy. Cochrane Database of Systematic Reviews 2020, Issue 3. Art. No.: CD010078. DOI: 10.1002/14651858.CD010078.pub3.**
Review question	Cochrane review on pharmacological interventions for promoting smoking cessation during pregnancy This review was updated specifically for use in the NICE Tobacco Update and taking into account the requirements of that update.
Objectives	To determine the efficacy and safety of smoking cessation pharmacotherapies and electronic cigarettes used during pregnancy, for smoking cessation in later pregnancy and after childbirth. In addition, Cochrane investigated adherence to smoking cessation pharmacotherapies and electronic cigarettes for smoking cessation during pregnancy.
Study inclusion characteristics	Parallel- or cluster-randomised controlled trials were eligible for inclusion
Participants	Women who were pregnant and also smoked tobacco at baseline.
Intervention	Pharmacological treatments aimed at promoting smoking cessation including NRT, bupropion, varenicline and electronic cigarettes The NICE evidence review specifically focuses on NRT and electronic cigarettes, and so only studies providing outcomes for these interventions during pregnancy have been detailed in this evidence table.
Comparison	Placebo control or no smoking cessation pharmacotherapy/electronic cigarettes.
Location/setting	Studies were conducted in OECD countries: USA: El-Mohandes 2013, Oncken 2008, Oncken 2019, Pollak 2007 Australia: Hotham 2006 Canada: Kapur 2001 France: Berlin 2014 UK: Coleman 2012 Denmark: Wisborg 2000 Setting included public hospitals or antenatal clinics
Search strategy	Literature searches were conducted in May 2019. The Cochrane Pregnancy and Childbirth Trials Register was searched. No date or language restrictions were applied.
Included studies	9 studies focusing on NRT (Oncken 2019) were included in the review (n = 2,336), including 1 new study for this update. No studies were identified on the safety and efficacy of electronic cigarettes.

Bibliographic reference	**Claire R, Chamberlain C, Davey MA, Cooper SE, Berlin I, Leonardi-Bee J, Coleman T. Pharmacological interventions for promoting smoking cessation during pregnancy. Cochrane Database of Systematic Reviews 2020, Issue 3. Art. No.: CD010078. DOI: 10.1002/14651858.CD010078.pub3.**
Assessment of study quality	Quality assessment criteria (using Cochrane Collaboration's tool) included: • Random sequence generation (selection bias) • Allocation concealment (selection bias) • Blinding of participants and personnel (performance bias) • Blinding of outcome assessment (detection bias) • Incomplete outcome data (attrition bias) • Other potential risks of bias
Outcomes measures and effect size	Primary outcomes Self-reported abstinence from smoking at the latest time point in pregnancy at which this is measured and, where available, validated biochemically using measures such as exhaled carbon monoxide, saliva cotinine or, in those who are not smoking but using nicotine (e.g. from NRT or electronic cigarettes) anabasine. When validated abstinence data were available, these were used in preference to self-report. Prolonged, continuous abstinence measures timed from a quit date set in early pregnancy and which allowed temporary lapses to smoking were preferred. However, point prevalence abstinence measures were substituted for these as required. Secondary outcomes 1. Abstinence from smoking after childbirth 2. Safety 1. Miscarriage/spontaneous abortion 2. Stillbirth 3. Mean unadjusted birthweight 4. Low birthweight (less than 2500 g) 5. Preterm birth (less than 37 weeks' gestation) 6. Neonatal intensive care unit admissions. 7. Neonatal death 8. Caesarean section 9. Congenital anomaly 10. Maternal hypertension 11. Infant respiratory symptoms 12. Infant development 3. Pharmacotherapy/EC adherence 4. Non-serious side effects (serious adverse event data contributed to 'safety' outcomes, above) 5. Any reported long-term effects of smoking cessation pharmacotherapies on safety
Statistical analysis	To investigate heterogeneity, the e I^2 statistic was used. A value greater than 50% may be considered to indicate substantial heterogeneity, whilst a value greater than 75% may be considered to indicate considerable heterogeneity. The reviewers used risk ratios to summarise individual study outcomes and to determine estimates of pooled effect. They estimated a pooled weighted average of risk ratios with 95% confidence intervals, and for pharmacological interventions used a Mantel-Haenszel fixed-effects model for meta-analyses of

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Claire R, Chamberlain C, Davey MA, Cooper SE, Berlin I, Leonardi-Bee J, Coleman T. Pharmacological interventions for promoting smoking cessation during pregnancy. Cochrane Database of Systematic Reviews 2020, Issue 3. Art. No.: CD010078. DOI: 10.1002/14651858.CD010078.pub3.</td></tr>
<tr><td></td><td colspan="3">smoking abstinence data. For meta-analyses of safety and adverse events data, a random-effects model was used as effects are likely to vary across populations due to significant differences in baseline risk.

Predefined subgroups for smoking cessation outcomes:

• Placebo versus non-placebo controlled RCTs
• Studies using different types of NRT both alone and in combination (i.e. fast-acting NRT and nicotine patch)
• Low dose NRT (<10mg/24hr) vs high dose NRT (>10mg/24hr)</td></tr>
<tr><td rowspan="7">Risk of bias (ROB)
Overall ROB</td><td>Domain</td><td>Concerns (Low / High / unclear)</td><td>Rationale for concern</td></tr>
<tr><td>Study eligibility criteria</td><td>Low concern</td><td>Eligibility criteria clear, documented, realistic and appropriate.</td></tr>
<tr><td>Identification and selection of studies</td><td>Low concerns</td><td>Search strategy appropriate and included a range of sources. Two authors identified potentially eligible studies for inclusion</td></tr>
<tr><td>Data collection and study appraisal</td><td>Low concerns</td><td>Duplicate data extraction, clear characteristics extracted. Risk of bias was assessed using Cochrane Collaboration’s tool for assessing risk of bias by two independent authors for all studies which they had not authored.</td></tr>
<tr><td>Synthesis and findings</td><td>Low concerns</td><td>Review addresses heterogeneity appropriately (but differently from pre-specified approach for this guideline). Publication bias not able to be assessed due to insufficient studies. Bias addressed through the GRADE process.</td></tr>
<tr><td>Overall Risk of Bias</td><td colspan="2">Low risk of bias</td></tr>
<tr><td colspan="3">Other details: None</td></tr>
<tr><td>Source of funding</td><td colspan="3">National Institute for Health Research (NIHR), Programme Grant for Applied Research programme (grant number RP-PG 0109–10020), UK, via Cochrane Infrastructure and Cochrane Programme Grant funding to the Cochrane Tobacco Addiction Group.</td></tr>
<tr><td>Comments</td><td colspan="3">- This review included pharmacological therapies, but the NICE protocol specified only NRT and e-cigarettes. Two studies (Stotts 2105, Nanovskaya 2017) investigating efficacy of bupropion on smoking cessation during pregnancy were therefore excluded.
- This review included outcomes on adherence to smoking cessation pharmacotherapies and electronic cigarettes which was not relevant to the NICE protocol, and so this data was not extracted.
- NICE recommends using Cochrane ROB 2.0 to assess risk of bias. The tool used in this review did not contain all the elements of the recommended tool.</td></tr>
</table>

Oncken 2019

Bibliographic reference/s	**Oncken C, Dornelas EA, Kuo CL, Sankey HZ, Kranzler HR, Mead EL, Thurlow SD. Randomized trial of nicotine inhaler for pregnant smokers. American Journal of Obstetrics & Gynecology MFM 2019;1(1):19-23. [DOI: https://doi.org/10.1016/j.ajogmf.2019.03.006]**		
Study type	RCT (placebo-controlled)		
Country/ Setting	USA		
Study dates	August 2012 - January 2017		
Number of participants	137 participants		
Inclusion / exclusion criteria	US English/Spanish-speaking women; smoking at least 5 cigarettes per day; 13–26 weeks' gestation; ≥16 years of age; intending to carry their pregnancy to term; and living in a stable residence		
Intervention	Nicotine inhaler (6-weeks treatment) delivering 4 mg of nicotine from a porous plug containing 10 mg nicotine. At baseline and 1 week after the quit date, participants received 35 minutes of individual smoking-cessation counselling by a study nurse who was trained to deliver the counselling using a motivational interviewing approach.		
Comparator/s	Placebo + counselling (as intervention)		
Outcomes investigated	<u>Cessation</u> Self-reported 7-day point prevalence abstinence at 6 weeks after quit date, at 32-36 weeks of pregnancy, 1 and 6 months after delivery. Exhaled CO of less than 4 ppm used for validation all time points. <u>Safety</u> • Mean birthweight • Mean gestation at delivery • Low birthweight births (<2500g) • Preterm birth (<37 weeks) • Miscarriage/spontaneous abortion and stillbirth • Congenital abnormalities		
Risk of Bias	**Outcome**	**Judgement (Low / High / some concerns)**	**Comments**
	Random sequence generation (selection bias	Low risk	Urn randomisation procedure used, balanced for gestational age, history of preterm delivery and average number of cigarettes smoked per day (<10 vs 10).
	Allocation concealment (selection bias	Unclear	Concealment not explicitly reported
	Blinding of participants and personnel (performance bias)	Low	All study personnel and participants were blinded to treatment assignment. Inhalers were packaged in the same device to maintain blinding integrity.

Bibliographic reference/s	**Oncken C, Dornelas EA, Kuo CL, Sankey HZ, Kranzler HR, Mead EL, Thurlow SD. Randomized trial of nicotine inhaler for pregnant smokers. American Journal of Obstetrics & Gynecology MFM 2019;1(1):19-23. [DOI: https://doi.org/10.1016/j.ajogmf.2019.03.006]**		
	Blinding of outcome assessment (detection bias)	Low	Biochemically validated abstinence using CO at <4ppm.
	Incomplete outcome data (attrition bias)	Low	Follow-up rates for smoking outcomes at 32-36 weeks gestation were 58% in placebo group and 67% in nicotine group. However all women that were lost to follow up were assumed to be smoking and included in the analysis. High follow-up rates for birth outcomes.
	Selective reporting bias	Low	All pre-specified outcomes in the trial registry were reported.
	Other bias	Unclear	
Additional references	None		
Notes	This study planned to recruit 360 subjects, but the trial was stopped after a recommendation from the Sata and Safety Monitoring Board, due to futility in detecting differences in the primary outcome. Funding sources: National Institutes of Health (NIH) of United States and the Lowell P. Weicker Clinical Research at the University of Connecticut School of Medicine. The intervention was provided by Pfizer Pharmaceuticals. Declarations of interest: "Dr Kranzler is a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which was supported in the last 3 years by AbbVie, Alkermes, Ethypharm, Indivior, Lilly, Lundbeck, Otsuka, Pfizer, Arbor, and Amygdala Neurosciences and is named as an inventor on Patent Cooperation Treaty patent application 15/878,640 entitled genotype-guided dosing of opioid agonists, filed Jan. 24, 2018. The other authors report no conflict of interest."		

Quantitative data extraction tables (cohort studies)

Berard 2016

Bibliographic reference/s	**Berard Anick, Zhao Jin-Ping, and Sheehy Odile (2016) Success of smoking cessation interventions during pregnancy. American journal of obstetrics and gynecology 215(5), 611.e1-611.e8**
Study name	Berard 2016
Registration	Not reported
Study type	Cohort study (prospective)
Study dates	Cohort included pregnancies that occurred between January 1998 and December 2009.
Objective	To assess the effect of use of bupropion and nicotine replacement therapy (NRT) during pregnancy on the risk of smoking cessation, prematurity and small for gestational age (SGA)
Country/ Setting	Quebec, Canada

<table>
<tr><td>Bibliographic reference/s</td><td>Berard Anick, Zhao Jin-Ping, and Sheehy Odile (2016) Success of smoking cessation interventions during pregnancy. American journal of obstetrics and gynecology 215(5), 611.e1-611.e8</td></tr>
<tr><td>Study name</td><td>Berard 2016</td></tr>
<tr><td>Cohort source</td><td>Quebec Pregnancy Cohort</td></tr>
<tr><td>Number entering into study (invited)</td><td>8,505 women from the cohort were randomly sampled and contacted annually to complete a questionnaire including smoking status and nicotine patch replacement therapy purchased over the counter. Study lacked statistical power.</td></tr>
<tr><td>Number of participants evaluated</td><td>Women who completed the questionnaire included n=6,732 women, of whom n=1,288 pregnant women met the inclusion criteria (see below). Women were categorised into 3 groups (one has been excluded as focuses on bupropion users which is not of relevance to this review). Numbers of women in the two groups of relevance to the review include:
n= 316 NRT users with/without tobacco use
n= 900 smokers without NRT or bupropion use</td></tr>
<tr><td>Exposure</td><td>Self-reported over-the-counter use of nicotine patch replacement therapy and filling prescriptions for NRT patches during pregnancy or before the first day of gestation and overlapping pregnancy.</td></tr>
<tr><td>Baseline study sample characteristics</td><td>Population included smokers at the beginning of pregnancy who either used bupropion or NRT to stop smoking (NRT of relevance to this review question).

<u>Characteristics of maternal smokers during early pregnancy</u>
<table>
<tr><td></td><td>Exposed to NRT (n = 316)</td><td>Unexposed to NRT (n = 900)</td></tr>
<tr><td>Mean maternal age in years (SD)</td><td>26.7 (5.7)</td><td>27.2 (5.8)</td></tr>
<tr><td>Work status (%)
Working*
Welfare recipients</td><td>
47 (14.9%)
122 (38.6%)</td><td>
120 (13.3)
335 (37.2)</td></tr>
<tr><td>Education level (%)*
High school completed
Postsecondary education</td><td>
61 (19.3)
35 (11.1)</td><td>
517 (57.4)
318 (35.3)</td></tr>
<tr><td>Annual family income (%)*
<30,000 CAN$
30,000-46,000 CAN$
>46,000 CAN$</td><td>
65 (20.1)
18 (5.7)
13 (4.1)</td><td>
586 (65.1)
13 (1.4)
103 (11.4)</td></tr>
<tr><td>Diabetes (%)</td><td>28 (8.9)</td><td>82 (9.1)</td></tr>
<tr><td>Hypertension (%)</td><td>28 (8.9)</td><td>73 (8.1)</td></tr>
<tr><td>Asthma (%)</td><td>92 (29.1)</td><td>279 (31.0)</td></tr>
<tr><td>Depression (%)*</td><td>41 (13.0)</td><td>194 (21.6)</td></tr>
<tr><td>Health service utilisation in the year before pregnancy

Mean physician visits (SD)
Emergency department visits or hospitalisations (%)</td><td>

8.5 (8.5)
57 (18.0)</td><td>

9.6 (9.3)
155 (17.2)</td></tr>
</table>
*Variable with missing values</td></tr>
</table>

<table>
<tr><td>Bibliographic reference/s</td><td>Berard Anick, Zhao Jin-Ping, and Sheehy Odile (2016) Success of smoking cessation interventions during pregnancy. American journal of obstetrics and gynecology 215(5), 611.e1-611.e8</td></tr>
<tr><td>Study name</td><td>Berard 2016</td></tr>
<tr><td>Attrition</td><td>Study used routine data rather than data collected specifically for research, n= 1,773 participants did not return their questionnaire (20.8%).
Responders were similar to non-responders in relation to maternal age, region of residence, marital status, insurance status, gestational age, birthweight and ratio of major congenital anomalies, healthcare use, chronic co-morbidities, multiplicity, new-born sex and year of delivery. Time since delivery was different with responders delivering more recently.</td></tr>
<tr><td>Inclusion and exclusion criteria</td><td>Inclusion criteria: aged between 15-45 years on conception, smokers before pregnancy and live birth
Exclusion criteria: women using both NRT and bupropion, women diagnosed with depression or taking known teratogenic or fetotoxic drugs.</td></tr>
<tr><td>Data collection</td><td>- Quebec Pregnancy cohort was linked to 4 databases: a medical service database, an insurance database, hospitalisation archive database, and a statistics database.
- Quebec Pregnancy cohort includes pregnancies in the hospitalisation archives database, the first day of gestation was defined using gestational age information and was validated against patient charts.
- Data from self-administered questionnaire was linked to the Quebec Pregnancy Cohort.
- Smoking status was self-reported via questionnaire.
- Data on prescription fillings for NRT, captured from insurance database, were validated using maternal reports.
- Demographic data was collected on health service utilisation, specific co-morbidities and use of particular medication (hypertension, diabetes, asthma, depression), socioeconomic variables on the first day of gestation and pregnancy related variables (including multiplicity). Demographic data was either collected from databases or from the self-administered questionnaire.</td></tr>
<tr><td>Outcome measure</td><td>Prematurity was defined as “a birth before the 37th weeks of gestation”.
Small for gestational age (SGA) was defined as “a combined measure of prematurity and low birth weight”
SGA derived from Quebec Pregnancy Cohort were defined as “the lowest 10th percentile of the gestational age-specific birthweight in the cohort”.
Gestational age and birthweight were valuated against patient charts.</td></tr>
<tr><td>Follow up</td><td>From 1 year before the first day of gestation, during pregnancy until December 2009.</td></tr>
<tr><td>Important outcomes measures and effect size. (time points)</td><td>Preterm birth
<u>Risk of preterm birth (<37 weeks gestation) based on maternal exposure to NRT during pregnancy</u>
<table>
<tr><td></td><td>Exposed to NRT n = 316</td><td>Unexposed to NRT n = 900</td><td>aOR* (95% CI)</td><td>aRR**calculated by analyst</td></tr>
<tr><td>Preterm births (%)</td><td>25 (7.9)</td><td>240 (26.7)</td><td>0.21 (0.13 to 0.34)</td><td>0.27 (0.17 to 0.41)</td></tr>
</table>
* Reported by study and unexposed used as reference group. Adjusted for maternal age, work status, place of living, education level, annual family income, welfare status, maternal hypertension, diabetes, asthma, depression and health services utilisation before pregnancy.</td></tr>
</table>

<table>
<tr><td>Bibliographic reference/s</td><td>Berard Anick, Zhao Jin-Ping, and Sheehy Odile (2016) Success of smoking cessation interventions during pregnancy. American journal of obstetrics and gynecology 215(5), 611.e1-611.e8</td></tr>
<tr><td>Study name</td><td>Berard 2016</td></tr>
<tr><td></td><td>**Calculated by review team. The unexposed group prevalence used to calculate the aRR was 0.267.

<u>Risk of small for gestational age (SGA) based on maternal exposure to NRT during pregnancy</u>
<table>
<tr><td></td><td>Exposed to NRT n = 316</td><td>Unexposed to NRT n = 900</td><td>aOR* (95% CI)</td><td>aRR**calculated by analyst</td></tr>
<tr><td>SGA (%)</td><td>44 (13.9)</td><td>149 (16.6)</td><td>0.61 (0.41 to 0.90)</td><td>0.65 (0.45 to 0.92)</td></tr>
</table>
* Reported by study and unexposed used as reference group. Adjusted for maternal age, work status, place of living, education level, annual family income, welfare status, maternal hypertension, diabetes, asthma, depression and health services utilisation before pregnancy.
**Calculated by review team. The unexposed group prevalence used to calculate the aRR was 0.166</td></tr>
<tr><td>Statistical Analysis</td><td>Univariate and multivariate logistic regression models were used to assess risk of preterm birth and SGA, separately, and to adjust for potential confounders.</td></tr>
<tr><td>Risk of bias (ROB)
ROBINS-I tool</td><td>Preterm birth
<table>
<tr><th>Outcome</th><th>Judgement</th><th>Comments</th></tr>
<tr><td>Pre-intervention: bias due to confounding</td><td>Moderate</td><td>Collects data for and adjusts for several confounders including socio-economic deprivation. Does not adjust for ethnic group and potential residual confounding may be present.</td></tr>
<tr><td>Pre-intervention: bias in selection of participants into study</td><td>Serious</td><td>Data was sourced from databases linked to the cohort, cohort coverage is not clear and so may not be generalisable. Study lacked statistical power. Controls may have included some smokers who may have been using NRT.</td></tr>
<tr><td>At intervention: Bias in classification of interventions</td><td>Low</td><td>Intervention is reasonably well defined and primarily based on filled prescriptions as well as self-report of over the counter use of NRT patches.</td></tr>
<tr><td>Post-intervention: bias due to deviations from intended interventions</td><td>Moderate</td><td>NRT prescription fillings were validated using patient reports, however record of prescribed NRT may not necessarily translate to adherence.</td></tr>
<tr><td>Post-intervention: bias due to missing data</td><td>Low</td><td>Study used routine data rather than data collected specifically</td></tr>
</table></td></tr>
</table>

Bibliographic reference/s	**Berard Anick, Zhao Jin-Ping, and Sheehy Odile (2016) Success of smoking cessation interventions during pregnancy. American journal of obstetrics and gynecology 215(5), 611.e1-611.e8**		
Study name	Berard 2016		
			for research. Some women did not complete the questionnaire, however there were no major differences between responders and non-responders.
	Post-intervention: bias in measurement of outcomes	Low	Outcome well defined and defined consistently for exposed and unexposed groups. Outcome measurements were derived from databases and validated against patients' charts.
	Post-intervention: Bias in selection of the reported result	Low	No apparent selective reporting of results.
	Overall Risk of Bias	Serious risk of bias	
	Other outcome details: None		
Source of funding	Fonds de la Reserche du Québec-Santé and the National Cancer Institute of Canada		
Comments	-Questionnaires were sent to participants twice and a free phone line was established to provide further information to women, to increase participation. -Ethics approval was obtained from the Centre Hospitalier Univeristaire Sainte-Justine and the Comission d'Accès a l'Informatiion du Quèbec - Women may have been using NRT as a method to cut-down smoking (smoking cigarettes alongside NRT).		
Additional references	None		

Dhalwani 2015

Bibliographic reference/s	**Dhalwani N N, Szatkowski L, Coleman T, Fiaschi L, and Tata L J (2015) Nicotine Replacement Therapy in Pregnancy and Major Congenital Anomalies in Offspring. Pediatrics 135(5), 859-867**
Study name	Dhalwani 2015
Registration	Not reported
Study type	Cohort study (prospective)
Study dates	Pregnancies with live births between January 2001 and December 2012 were included.
Objective	To assess the relationship between early pregnancy exposure to nicotine replacement therapy (NRT) or smoking with major congenital anomalies (MCA) in offspring. (NRT of relevance to this review question).
Country/ Setting	Study population was from The Health Improvement Network (THIN) being a "UK database of anonymised electronic primary care records with a high validity of recorded diagnoses and prescriptions"
Cohort source	Pregnant women in THIN ("contained longitudinal prospectively collected data from 570 general practices across the United Kingdom, and it covered 6% of the UK population")

<table>
<tr><td>Bibliographic reference/s</td><td>Dhalwani N N, Szatkowski L, Coleman T, Fiaschi L, and Tata L J (2015) Nicotine Replacement Therapy in Pregnancy and Major Congenital Anomalies in Offspring. Pediatrics 135(5), 859-867</td></tr>
<tr><td>Study name</td><td>Dhalwani 2015</td></tr>
<tr><td>Number entering into study (invited)</td><td>Records for n= 192,498 deliveries</td></tr>
<tr><td>Number of participants evaluated</td><td>Total number n= 192,498 deliveries
Maternal smokers exposed to NRT; n=2,677
Maternal smokers not exposed to NRT; n= 9,980
Maternal non-smokers; n=178,841
Study was “underpowered to assess most system-specific anomalies”.</td></tr>
<tr><td>Exposure</td><td>Inclusion in NRT group was based on a primary care record which indicated prescribed NRT during the first trimester of pregnancy or within 4-weeks before their estimated date, as determined by healthcare staff at antenatal appointments.</td></tr>
<tr><td>Baseline study sample characteristics</td><td>Characteristics of maternal smokers during early pregnancy
<table>
<tr><th></th><th>Exposed to NRT (n = 2,677)</th><th>Unexposed to NRT (n = 9,980)</th></tr>
<tr><td>Age at conception (%)
15-19
20-24
25-29
30-34
35-39
40-44
45-49</td><td>
174 (6.5)
630 (23.5)
772 (28.8)
644 (24.1)
370 (13.8)
84 (3.1)
3 (0.1)</td><td>
1,240 (12.4)
2,849 (28.5)
2,632 (26.4)
2,004 (20.1)
1,006 (10.1)
240 (2.4)
9 (0.1)</td></tr>
<tr><td>Deprivation index score (%)
Quintile 1 (most affluent)
Quintile 2
Quintile 3
Quintile 4
Quintile 5 (most deprived)
Missing</td><td>
243 (9.1)
367 (13.7)
564 (21.1)
711 (26.6)
610 (22.8)
182 (6.8)</td><td>
1,036 (10.4)
1,247 (12.5)
1,964 (19.7)
2,562 (25.7)
2,527 (25.3)
644 (6.5)</td></tr>
<tr><td>Pre-conception BMI (%)
Normal (18.5-24.9)
Underweight (<18.5)
Overweight (25-29.9)
Obese (≥30)
Missing</td><td>
780 (29.1)
86 (3.2)
466 (17.4)
385 (14.4)
960 (35.9)</td><td>
2,949 (29.5)
326 (3.3)
1,515 (15.2)
1,230 (12.3)
3,960 (39.7)</td></tr>
<tr><td>Asthma (%)</td><td>389 (14.5)</td><td>1,041 (10.4%)</td></tr>
<tr><td>Hypertension (%)</td><td>63 (2.4)</td><td>183 (1.8)</td></tr>
<tr><td>Diabetes (%)</td><td>91 (3.4)</td><td>215 (2.2)</td></tr>
<tr><td>Mental illness (%)</td><td>555 (20.7)</td><td>1,525 (15.3)</td></tr>
<tr><td>Epilepsy (%)</td><td>11 (0.4)</td><td>68 (0.7)</td></tr>
</table>
*BMI refers to body mass index</td></tr>
</table>

<table>
<tr><td>Bibliographic reference/s</td><td>Dhalwani N N, Szatkowski L, Coleman T, Fiaschi L, and Tata L J (2015) Nicotine Replacement Therapy in Pregnancy and Major Congenital Anomalies in Offspring. Pediatrics 135(5), 859-867</td></tr>
<tr><td>Study name</td><td>Dhalwani 2015</td></tr>
<tr><td>Attrition</td><td>Not applicable as panel data. Study used routine data rather than data collected specifically for research</td></tr>
<tr><td>Inclusion and exclusion criteria</td><td>Pregnant women were recorded in THIN, aged 15-49 and only live-births were examined.
Children with anomalies often related to known teratogens were excluded, including foetal alcohol and valproate syndrome.</td></tr>
<tr><td>Data collection</td><td>Pregnancy and birth-related codes in medical records recorded in THIN were linked to live-births of children registered at the same household at the time of delivery.
Smoking status was self-reported and smokers were classified as “those recorded as smokers at any point from conception until the end of first trimester”.
Control group included women recorded as non-smokers at any point from conception until the end of the first trimester.
Data on children’s major congenital anomalies was collected from the European Surveillance of Congenital Anomalies (EUROCAT) classification system, with all conditions classified using the International Classification of Diseases, 10th Revision (ICD-10).
Minor congenital anomalies were excluded, in line with British registries contributing to EUROCAT.
Data on potential confounders was collected including maternal age at conception, deprivation (Townsend deprivation index), pre-pregnancy body mass index and medical diagnoses before or during pregnancy</td></tr>
<tr><td>Outcome measure</td><td>All major congenital anomalies combined in children including anomalies of the heart, limb, genital system, urinary system, chromosomal, musculoskeletal, orofacial cleft, digestive system, nervous system, other malformations including asplenia and conjoined twins, eye respiratory system, genetic, abdominal wall, ear, face and neck.</td></tr>
<tr><td>Follow up</td><td>Major congenital anomalies in children were recorded at any age during primary care registration in THIN (average length of registration was from birth up to 5 years).</td></tr>
<tr><td>Important outcomes measures and effect size. (time points)</td><td>Major congenital anomalies (infant development)
<u>Major congenital anomalies (MCAs) in children based on maternal exposure to NRT during early pregnancy</u>
<table>
<tr><td></td><td>Maternal smokers exposed to NRT n = 2,677</td><td>Maternal smokers not exposed to NRT
n = 9,980</td><td>aOR* (99% CI)</td><td>aRR** calculated by analyst</td></tr>
<tr><td>All MCAs combined (%)</td><td>90 (3.36%)</td><td>314 (3.15%)</td><td>1.07 (0.78 to 1.47)
P= 0.58</td><td>1.07 (0.79 to 1.45)</td></tr>
</table>
*Reported by study and unexposed group used as reference group. Adjusted for maternal age at conception, deprivation, maternal diabetes, asthma, mental illnesses and multiple births
**Calculated by review team. The unexposed group prevalence used to calculate the aRR was 0.0315.</td></tr>
</table>

<table>
<tr><td>Bibliographic reference/s</td><td>Dhalwani N N, Szatkowski L, Coleman T, Fiaschi L, and Tata L J (2015) Nicotine Replacement Therapy in Pregnancy and Major Congenital Anomalies in Offspring. Pediatrics 135(5), 859-867</td></tr>
<tr><td>Study name</td><td>Dhalwani 2015</td></tr>
<tr><td></td><td><u>Respiratory system major congenital anomalies (MCAs) in children based on maternal exposure to NRT during early pregnancy</u>
<table>
<tr><td></td><td>Maternal smokers exposed to NRT n = 2,677</td><td>Maternal smokers not exposed to NRT
n = 9,980</td><td>aOR* (99% CI)</td><td>aRR** calculated by analyst</td></tr>
<tr><td>Respiratory system MCAs (%)</td><td>10 (0.37%)</td><td>10 (0.10%)</td><td>3.49 (1.05 to 11.62)
P= 0.007</td><td>3.48 (1.05 to 11.50)</td></tr>
</table>
* Reported by study and unexposed group used as reference group. Adjusted for maternal age at conception, deprivation, maternal diabetes, asthma, mental illnesses and multiple births
**Calculated by review team. The unexposed group prevalence used to calculate the aRR was 0.001.</td></tr>
<tr><td>Statistical Analysis</td><td>Analysis adjusted for maternal age at conception, deprivation, diabetes, asthma, mental illnesses and multiple births [co-variates with statistically significant associations (5% significance level) with exposure and outcome were included in the model]</td></tr>
<tr><td>Risk of bias (ROB)
ROBINS-I tool</td><td>Major congenital anomalies (infant development)
<table>
<tr><th>Outcome</th><th>Judgement</th><th>Comments</th></tr>
<tr><td>Pre-intervention: bias due to confounding</td><td>Moderate</td><td>Collects data for and adjusts for several confounders including socio-economic deprivation. Does not adjust for ethnic group and potential residual confounding may be present.</td></tr>
<tr><td>Pre-intervention: bias in selection of participants into study</td><td>Moderate</td><td>Data was sourced from electronic primary care records, which covered 6% of the population. Study participation was “underpowered to assess most system-specific anomalies”.</td></tr>
<tr><td>At intervention: Bias in classification of interventions</td><td>Moderate</td><td>Intervention is reasonably defined and based on recorded GP prescribing. No detail given on type of NRT products evaluated</td></tr>
<tr><td>Post-intervention: bias due to deviations from intended interventions</td><td>Moderate</td><td>Record of prescribed NRT may not necessarily translate to adherence. A small number of women may have accessed NRT through the stop smoking services for pregnancy or from pharmacies, and so may not have been classified as an NRT user. Smoking status was self-reported and so controls may</td></tr>
</table></td></tr>
</table>

			have included some smokers who may have been using NRT.
	Post-intervention: bias due to missing data	Low	Study used routine data rather than data collected specifically for research.
	Post-intervention: bias in measurement of outcomes	Low	Outcome well defined and defined consistently for exposed and unexposed by ICD-10 coding. Clinical coding was validated against GP notes.
	Statistical analysis and reporting	Low	No apparent selective reporting of results.
	Overall Risk of Bias	Moderate risk of bias	
	Other outcome details: None		
Source of funding	British Heart Foundation, Cancer Research UK, Economic and Social Research Council, Medical Research Council, with the approval from the UK Clinical Research Collaboration		
Comments	- MCA linked to pregnancies resulting in miscarriages and stillbirths were not examined - NHS ethical approval for assessment of THIN data was obtained. - A small proportion of women may have been using NRT as a method to cut-down smoking (smoking cigarettes alongside NRT) despite NRT being primarily indicated for smoking cessation.		
Additional references	None		

Dhalwani 2019

Bibliographic reference/s	**Dhalwani Nafeesa N, Szatkowski Lisa, Coleman Tim, Fiaschi Linda, and Tata Laila J (2019) Stillbirth Among Women Prescribed Nicotine Replacement Therapy in Pregnancy: Analysis of a Large UK Pregnancy Cohort. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 21(4), 409-415**
Study name	Dhalwani 2019
Registration	Not reported
Study type	Cohort study (prospective)
Study dates	Pregnancies with births between 2000 and 2013 were extracted
Objective	To compare the risk of stillbirth between maternal smokers and those prescribed nicotine replacement therapy (NRT) during pregnancy.
Country/ Setting	Study population was from The Health Improvement Network (THIN) being a “UK database of anonymised electronic primary care records” and noting that “the validity of recorded diagnoses and prescriptions is high”.
Cohort source	Pregnant women in THIN (“contained longitudinal prospectively collected data from 570 general practices across the United Kingdom, and it covered 6% of the UK population”)
Number entering into study (invited)	Records for n= 220,630 deliveries (of which 805 ended in stillbirth)

<table>
<tr><td>Bibliographic reference/s</td><td>Dhalwani Nafeesa N, Szatkowski Lisa, Coleman Tim, Fiaschi Linda, and Tata Laila J (2019) Stillbirth Among Women Prescribed Nicotine Replacement Therapy in Pregnancy: Analysis of a Large UK Pregnancy Cohort. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 21(4), 409-415</td></tr>
<tr><td>Study name</td><td>Dhalwani 2019</td></tr>
<tr><td>Number of participants evaluated</td><td>Total number n= 220,630 deliveries between 2001 and 2012
Maternal smokers exposed to NRT; n= 5,221
Maternal smokers not exposed to NRT; n= 18,407
Maternal non-smokers; n=197,002
Sample size not large enough to have adequate power.</td></tr>
<tr><td>Exposure</td><td>Inclusion in NRT group was based on a primary care record which indicated prescribed NRT during pregnancy or within 4-weeks before their estimated date, as determined by healthcare staff at antenatal appointments.</td></tr>
<tr><td>Baseline study sample characteristics</td><td>Characteristics of maternal smokers during early pregnancy
<table>
<tr><th></th><th>Exposed to NRT (n = 5,221)</th><th>Unexposed to NRT (n = 18,047)</th></tr>
<tr><td>Age at conception (%)
15-19
20-24
25-29
30-34
35-39
40-44
45-49</td><td>
457 (8.8)
1,279 (24.5)
1,454 (27.8)
1,175 (22.5)
697 (13.3)
153 (2.9)
6 (0.1)</td><td>
2,384 (13.0)
5,211 (28.3)
4,755 (25.8)
3,636 (19.8)
1,931 (10.5)
456 (2.5)
34 (0.2)</td></tr>
<tr><td>Deprivation index score (%)
Quintile 1 (most affluent)
Quintile 2
Quintile 3
Quintile 4
Quintile 5 (most deprived)
Missing</td><td>
513 (9.8)
646 (12.4)
1,019 (19.5)
1,414 (27.1)
1,267 (24.3)
362 (6.9)</td><td>
1,792(9.7)
2,195 (11.9)
3,541 (19.2)
4,805 (26.1)
4,816 (26.2)
1,258 (6.8)</td></tr>
<tr><td>Pre-conception BMI (%)
Normal (18.5-24.9)
Underweight (<18.5)
Overweight (25-29.9)
Obese (≥30)
Missing</td><td>
1,555 (29.8)
158 (3.0)
851 (16.3)
650 (12.4)
2,007 (38.4)</td><td>
5,101 (27.7)
606 (3.3)
2,662 (14.5)
2,214 (12.0)
7,824 (42.5)</td></tr>
<tr><td>Asthma (%)</td><td>652 (12.5)</td><td>2,227 (12.1)</td></tr>
<tr><td>Hypertension (%)</td><td>106 (2.0)</td><td>368 (2.0)</td></tr>
<tr><td>Diabetes (%)</td><td>140 (2.7)</td><td>418 (2.3)</td></tr>
<tr><td>Mental illness (%)</td><td>1,042 (20.0)</td><td>2,952 (16.0)</td></tr>
</table>
*BMI refers to body mass index</td></tr>
<tr><td>Attrition</td><td>Not applicable as panel data. Study used routine data rather than data collected specifically for research</td></tr>
</table>

<table>
<tr><td>Bibliographic reference/s</td><td>Dhalwani Nafeesa N, Szatkowski Lisa, Coleman Tim, Fiaschi Linda, and Tata Laila J (2019) Stillbirth Among Women Prescribed Nicotine Replacement Therapy in Pregnancy: Analysis of a Large UK Pregnancy Cohort. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 21(4), 409-415</td></tr>
<tr><td>Study name</td><td>Dhalwani 2019</td></tr>
<tr><td>Inclusion and exclusion criteria</td><td>Pregnant women were recorded in THIN, aged 15-49.
No specific exclusion criteria.</td></tr>
<tr><td>Data collection</td><td>Smoking status was self-reported and codes were used to classify women as smokers.
Smokers were classified as “those recorded as smokers at any point from conception until delivery”.
Control group included women “recorded as non-smokers at any point from conception until delivery”.
Data on potential confounders was collected including maternal age at conception, deprivation (Townsend deprivation index), pre-pregnancy body mass index and medical diagnoses before or during pregnancy.</td></tr>
<tr><td>Outcome measure</td><td>Stillbirth was defined as “a baby born with no signs of life at or after 28 weeks gestation”</td></tr>
<tr><td>Follow up</td><td>Up to delivery (at least 28-weeks gestation).</td></tr>
<tr><td>Important outcomes measures and effect size. (time points)</td><td>Stillbirth
<u>Risk of stillbirth based on maternal exposure to NRT during pregnancy</u>
<table>
<tr><td></td><td>Maternal smokers exposed to NRT n = 5,221</td><td>Maternal smokers not exposed to NRT
n = 18,047</td><td>aOR* (99% CI)</td><td>aRR** calculated by analyst</td></tr>
<tr><td>Stillbirths (%)</td><td>26 (0.50%)</td><td>96 (0.53%)</td><td>0.95 (0.62 to 1.48)</td><td>0.95 (0.62 to 1.48)</td></tr>
</table>
*Reported by study and unexposed group used as reference group. Adjusted for maternal age, socioeconomic status, pre-pregnancy body mass index and diabetes.
**Calculated by review team. The unexposed group prevalence used to calculate the RR was 0.0053</td></tr>
<tr><td>Statistical Analysis</td><td>Analysis adjusted for maternal age at conception, socioeconomic status, pre-pregnancy body mass index and diabetes. [co-variates with statistically significant associations (5% significance level) with exposure and outcome were included in the model]</td></tr>
<tr><td>Risk of bias (ROB)
QUIPS tool</td><td>Stillbirth
<table>
<tr><th>Outcome</th><th>Judgement</th><th>Comments</th></tr>
<tr><td>Pre-intervention: bias due to confounding</td><td>Moderate</td><td>Collects data for and adjusts for several confounders including socio-economic deprivation. Does not adjust for ethnic group and potential residual confounding may be present.</td></tr>
</table></td></tr>
</table>

Bibliographic reference/s	**Dhalwani Nafeesa N, Szatkowski Lisa, Coleman Tim, Fiaschi Linda, and Tata Laila J (2019) Stillbirth Among Women Prescribed Nicotine Replacement Therapy in Pregnancy: Analysis of a Large UK Pregnancy Cohort. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 21(4), 409-415**		
Study name	Dhalwani 2019		
	Pre-intervention: bias in selection of participants into study	Moderate	Data was sourced from electronic primary care records, which covered 6% of the population. Sample size not large enough to have adequate power.
	At intervention: Bias in classification of interventions	Moderate	Intervention is reasonably defined and based on recorded GP prescribing. No detail given on type of NRT products evaluated.
	Post-intervention: bias due to deviations from intended interventions	Moderate	Record of prescribed NRT may not necessarily translate to adherence. A small number of women may have accessed NRT through the stop smoking services for pregnancy or from pharmacies, and so may not have been classified as an NRT user. Smoking status was self-reported and so controls may have included some smokers who may have been using NRT.
	Post-intervention: bias due to missing data	Low	Study used routine data rather than data collected specifically for research.
	Post-intervention: bias in measurement of outcomes	Moderate	Outcome well defined and defined consistently for exposed and unexposed. Outcome measurement was reliant on recording in primary care records, and so a small proportion of stillbirths may have been missed. There is a small risk that congenital anomalies may have increased the risk of stillbirth.
	Post-intervention: Bias in selection of the reported result	Low	No apparent selective reporting of results.
	Overall Risk of Bias	Moderate risk of bias	
	Other outcome details: None		
Source of funding	National Institute for Health and Research (NIHR)		
Comments	- NHS ethical approval for assessment of THIN data was obtained. - A small proportion of women may have been using NRT as a method to cut-down smoking (smoking cigarettes alongside NRT) despite NRT being primarily indicated for smoking cessation.		
Additional references	None		

Strandberg-Larsen 2008

Bibliographic reference/s	**Strandberg-Larsen K, Tinggaard M, Nybo Andersen, A M, Olsen J, and Gronbaek M (2008) Use of nicotine replacement therapy during pregnancy and stillbirth: a cohort study. BJOG : an international journal of obstetrics and gynaecology 115(11), 1405-10**
Study name	Strandberg-Larsen 2008
Registration	Not reported
Study type	Cohort study (prospective)
Study dates	Recruitment to cohort occurred between 1996 to 2002
Objective	To assess whether NRT use during pregnancy increases the risk of stillbirth
Country/ Setting	Denmark
Cohort source	Danish National Birth Cohort (includes pregnant women and their children)
Number entering into study (invited)	100,418 pregnancies were recruited to the cohort.
Number of participants evaluated	Total number n= 14,357 pregnancies with maternal smokers n= 13,266 maternal smokers not using NRT n= 1,091 maternal smokers using NRT
Exposure	Use of NRT (chewing gum, patches or inhaled substance) was self-reported from their last menstrual period until the time of interview. Women were categorised as either user or non-users.
Baseline study sample characteristics	Characteristics of maternal smokers during early pregnancy

	Exposed to NRT (n = 1,091)	Unexposed to NRT (n = 13,266)	Significant difference
Age at conception (%)			Yes
<20	16 (2)	364 (3)	
21-24	165 (15)	2,285 (17)	
25-29	375 (34)	4,960 (37)	
30-34	367 (34)	4,020 (30)	
≥35	168 (15)	1,631 (12)	
Household socio-occupational status (%)			Yes
Higher-grade professional	184 (17)	1,644 (12)	
Middle-grade professional	317 (29)	2,869 (22)	
Skilled worker	302 (28)	4,720 (36)	
Unskilled worker	240 (22)	3,452 (26)	
Student	31 (3)	320 (2)	
Unemployed for >1 year	17 (2)	261 (2)	
Pre-conception BMI (%)			Yes
<18.5	73 (7)	964 (7)	
18.5-24.9	754 (71)	8,277 (64)	
25-29.9	169 (16)	2,592 (20)	
≥30	72 (7)	1,170 (9)	

Bibliographic reference/s	**Strandberg-Larsen K, Tinggaard M, Nybo Andersen, A M, Olsen J, and Gronbaek M (2008) Use of nicotine replacement therapy during pregnancy and stillbirth: a cohort study. BJOG : an international journal of obstetrics and gynaecology 115(11), 1405-10**
Study name	Strandberg-Larsen 2008
	<table><tr><td></td><td></td><td></td><td></td></tr><tr><td>Alcohol consumption during pregnancy (%) drinks per week Abstainers ½ -1 ½ 2-3½ ≥4</td><td> 573 (53) 331 (30) 127 (12) 58 (5)</td><td> 7,651 (58) 3,727 (28) 1,343 (10) 526 (4)</td><td>Yes</td></tr><tr><td>Coffee consumption during pregnancy (%) cups per day 0 ½ - 7½ ≥8</td><td> 318 (29) 615 (57) 157 (14)</td><td> 4,564 (34) 7,077 (53) 1,613 (13)</td><td>Yes</td></tr><tr><td>Spouse/partner smoking (%) No spouse/partner Non-smoker Smoker</td><td> 54 (5) 645 (59) 391 (36)</td><td> 721 (5) 8,153 (62) 4,378 (33)</td><td>No</td></tr></table> *BMI refers to body mass index
Attrition	Study used routine data rather than data collected specifically for research, with <1% follow-up on outcome of pregnancy obtained from registry-linkage.
Inclusion and exclusion criteria	Pregnant women, who intended to carry the pregnancy to full term were included Multiple births, pregnancies ending in hydatidiform mole, ectopic pregnancy or ending before 20 completed weeks were excluded.
Data collection	Women were asked to take part in a computer-assisted telephone interview between weeks 12-16 gestation. Participants were asked about NRT use and smoking status during pregnancy and at the time of interview, including number of cigarettes. Women who had reported not smoking at interview but smoked during pregnancy were categorised as ex-smokers. Non-smokers included ex-smokers who had quit smoking before conception and those who reported being non-smokers at interview.
Outcome measure	Stillbirth was defined as “any foetus that did not breathe or show any other sign of life at birth after a minimum of 20 weeks of gestation”. Outcomes of pregnancies from the Danish National Cohort were determined for live births and stillbirths using the Civil Registration System and Danish Medical Birth Registry. Miscarriage, termination, pregnancies which were ectopic or resulting in hydatidiform mole and gestational age were determined from the National Hospital Discharge Register. If data could not be obtained, information was sourced from the mother (less than 1% of cases).

<table>
<tr><td>Bibliographic reference/s</td><td>Strandberg-Larsen K, Tinggaard M, Nybo Andersen, A M, Olsen J, and Gronbaek M (2008) Use of nicotine replacement therapy during pregnancy and stillbirth: a cohort study. BJOG : an international journal of obstetrics and gynaecology 115(11), 1405-10</td></tr>
<tr><td>Study name</td><td>Strandberg-Larsen 2008</td></tr>
<tr><td></td><td>Danish National Birth Cohort defined stillbirth as “birth of a death fetus after 28 completed weeks of gestation. Pregnancies coded as miscarriages after 20 or more weeks gestation were also regarded as stillbirths”.</td></tr>
<tr><td>Follow up</td><td>Up to delivery (minimum 20-weeks gestation).</td></tr>
<tr><td>Important outcomes measures and effect size. (time points)</td><td>Stillbirth
<u>Risk of stillbirth based on maternal exposure to NRT during pregnancy</u>
<table>
<tr><td></td><td>Maternal smokers exposed to NRT n = 1,091</td><td>Maternal smokers not exposed to NRT
n = 13,266</td><td>RR* (95% CI) calculated by analyst</td></tr>
<tr><td>Stillbirths (%)</td><td>5 (0.46%)</td><td>107 (0.81%)</td><td rowspan="2">0.57 (0.23 to 1.38)</td></tr>
<tr><td>No stillbirths</td><td>1,086</td><td>13,159</td></tr>
</table>
*Calculated by review team.</td></tr>
<tr><td>Statistical Analysis</td><td>Statistical analysis was performed but not for the comparison of interest for this review</td></tr>
<tr><td>Risk of bias (ROB)
ROBINS-I tool</td><td>Stillbirth
<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>Collects data for several confounders, however for the comparison of interest there is no adjustment of results for potential confounders.</td></tr>
<tr><td>Pre-intervention: bias in selection of participants into study</td><td>Serious</td><td>Cohort coverage is not clear and so may not be generalisable. Participation rate of those invited into the population cohort was 60%, with more non-smokers than smokers compared with source population. Significant differences in demographic data between both groups.</td></tr>
<tr><td>At intervention: Bias in classification of interventions</td><td>Low</td><td>Intervention is reasonably defined and details of the type of NRT products evaluated is provided</td></tr>
<tr><td>Post-intervention: bias due to deviations from intended interventions</td><td>Serious</td><td>NRT use was self-reported so may have been either under/overestimated. Women were asked to self-report their NRT use during pregnancy until interview, which served as an indicator of exposure for the</td></tr>
</table></td></tr>
</table>

Bibliographic reference/s	**Strandberg-Larsen K, Tinggaard M, Nybo Andersen, A M, Olsen J, and Gronbaek M (2008) Use of nicotine replacement therapy during pregnancy and stillbirth: a cohort study. BJOG : an international journal of obstetrics and gynaecology 115(11), 1405-10**		
Study name	Strandberg-Larsen 2008		
			entire pregnancy and so women may have been misclassified.
	Post-intervention: bias due to missing data	Low	Study used routine data rather than data collected specifically for research. Study reports that follow-up was almost complete
	Post-intervention: bias in measurement of outcomes	Low	Outcome well defined and defined consistently for exposed and unexposed groups. Outcome measurement was reliant on records from various registry systems and in a small proportion of cases where data was unobtainable, this was directly sourced from the mother.
	Post-intervention: Bias in selection of the reported result	Low	No apparent selective reporting of results.
	Overall Risk of Bias	Serious risk of bias	
	Other outcome details: None		
Source of funding	Danish Ministry of Health		
Comments	-Women completed a consent form prior to participation in the study -Ethics approval was obtained by the Danish Scientific Ethics Committee and by the Danish Protection Board.		
Additional references	None		

Qualitative data extraction tables (Campbell 2019)

Evidence tables have been reproduced for the 21 qualitative studies included in the Cochrane systematic review by Campbell 2019

Campbell 2019 (Cochrane systematic review)

Bibliographic reference	**Campbell K, Coleman-Haynes T, Bowker K, Cooper S, Connelly SL, Coleman T. Factors that influence the uptake and use of NRT and e-cigarettes by pregnant women who smoke: a qualitative analysis. Cochrane Database of Systematic Reviews 2019.**
Review question	Cochrane review to determine factors that influence the uptake and use of NRT and e-cigarettes by pregnant women who smoke: a qualitative analysis This new review was specifically undertaken for use in the NICE Tobacco Update, taking into account the requirements of that update.
Objectives	To describe:

Bibliographic reference	**Campbell K, Coleman-Haynes T, Bowker K, Cooper S, Connelly SL, Coleman T. Factors that influence the uptake and use of NRT and e-cigarettes by pregnant women who smoke: a qualitative analysis. Cochrane Database of Systematic Reviews 2019.**
	• Factors influencing pregnant women's uptake and use of NRT or e-cigarettes for smoking cessation including acceptability, barriers and facilitators • Factors influencing pregnant women's uptake and use of NRT or e-cigarettes for harm reduction including acceptability, barriers and facilitators • Women's views on and experiences of using NRT or e-cigarettes during pregnancy
Study inclusion characteristics	Qualitative studies either conducted alongside efficacy trials or as 'stand-alone' studies, using any qualitative design and appropriate methods of data collection and data analysis were included. Mixed method studies were included only if they had a distinct section dedicated to qualitative data collection and analysis and reported qualitative data. Studies which explored views, opinions and experiences of pregnant or recently pregnant women who smoke(d) in pregnancy on the use of NRT of any type or e-cigarettes in pregnancy for smoking cessation or harm reduction were included.
Participants	Women who were either pregnant and smoked at any point during pregnancy or were post-partum and had smoked during their pregnancy. Participants were not required to have experience of using NRT or electronic cigarettes.
Phenomenon of interest	Factors influencing the uptake and subsequent use of NRT and e-cigarettes during pregnancy, from the perspectives of pregnant or recently pregnant women.
Location/setting	Studies were conducted in OECD countries: USA: England 2016, Fallin 2016a, Fallin 2016b Australia: Bovill 2018, Gamble 2015, Hauck 2013, Hotham 2002 Canada: Borland 2013 New Zealand: Glover 2012 UK: Ashwin 2010, Bauld 2017, Bowker 2016, Bowker 2018, Butterworth 2014, Grant 2018, Herbec 2014, Mantzari 2012, Naughton 2013, Pledger 2015, Radley 2013, Taylor 2010 Studies recruited via maternity services, children's centres, smoking cessation services or hotlines, local communities, indigenous health services, local or online advertising, a market research company and an opioid dependence clinic. Studies primarily conducted focus groups or face-to-face/ telephone interviews to elicit data. One study used an indigenous yarning method of interviewing (Bovill 2018).
Search strategy	Literature searches were conducted in February 2019. Several databases including MEDLINE, CINAHL, PsychINFO and OpenGrey were searched. Forward citation searches were conducted of included studies.
Included studies	21 studies were included in the review (n = 496) which included a PHD thesis (Taylor 2010), a HTA report (Bauld 2017) and 19 journal articles.

Bibliographic reference	**Campbell K, Coleman-Haynes T, Bowker K, Cooper S, Connelly SL, Coleman T. Factors that influence the uptake and use of NRT and e-cigarettes by pregnant women who smoke: a qualitative analysis. Cochrane Database of Systematic Reviews 2019.**		
Assessment of study quality	Quality assessment was undertaken using the Wallace quality appraisal criteria with 13 criteria assessed as being met (responses are either yes, no or can't tell): • Research question clear? • Theoretical perspective clear? • Study design appropriate to answer the question? • Context/setting adequately described? • Sample adequate to explore range of subjects? • Sample drawn from appropriate population? • Data collection adequately described? • Data collection rigorously conducted? • Data analysis rigorously conducted? • Evidence of reflexivity? • Findings substantiated/limitations considered? • Claims to generalisability follow from the data? • Ethical issues addressed? Studies were also assessed for data richness using a tool devised by Ames and colleagues (Ames 2019). The tool uses a 1-5 scale where one means 'very few qualitative data which are relevant to the review, and those presented are fairly descriptive' while 5 means 'a large amount and depth of qualitative data relevant to the review'. Assessment of confidence in the review findings was assessed using GRADE CERQual. Each finding started with a 'high confidence' score which could be downgraded if the CERQual process revealed concerns within CERQual domains.		
Data collection, analysis, synthesis	Identified studies were combined into a database, with duplicates removed before being exported to a screening and data extraction tool. Data was extracted using a specifically designed form including key concepts, summary of findings and supporting quotations from participants. Thematic data synthesis was used for data coding and data exploration to identify key concepts and constructs from within the data and which may not have been predefined. Synthesis included 3 key stages: 1. Line-by-line coding of the findings extracted from the primary studies 2. Developing descriptive themes 3. Developing analytical themes		
Risk of bias (ROB) **Overall ROB**	**Domain**	**Concerns (Low / High / unclear)**	**Rationale for concern**
	Study eligibility criteria	Low concern	Eligibility criteria clear, documented, realistic and appropriate.
	Identification and selection of studies	Low concerns	Search strategy appropriate and included a range of sources. Two authors identified potentially eligible studies for inclusion

Bibliographic reference	**Campbell K, Coleman-Haynes T, Bowker K, Cooper S, Connelly SL, Coleman T. Factors that influence the uptake and use of NRT and e-cigarettes by pregnant women who smoke: a qualitative analysis. Cochrane Database of Systematic Reviews 2019.**		
	Data collection and study appraisal	Low concerns	Data extraction was completed by one review author and checked by another; clear characteristics extracted. Review appraises quality of studies (but differently from pre-specified approach for this guideline) and was undertaken by 2 independent authors.
	Synthesis and findings	Low concerns	Review used thematic data synthesis for data coding, data exploration and development of themes and review findings. Bias addressed through the GRADE CERQual process.
	Overall Risk of Bias	Low risk of bias	
	Other details: None		
Source of funding	National Institute for Health Research (NIHR) Programme for Applied Research (Programme number RP-PG-0615-20003), The National Institute for Health and Care Excellence (NICE).		
Comments	- This review also included views on the use of NRT of any type or e-cigarettes in pregnancy for harm reduction, whereas smoking cessation was the focus in the NICE protocol. - This review included non-UK studies (9 studies), whereas the NICE protocol specified qualitative studies conducted in the UK. - NICE recommends using CASP qualitative checklist to assess risk of bias. The tool used in this review did not contain all the elements of the recommended tool.		

Ashwin 2010

Bibliographic reference	**Ashwin C, Watts K. Exploring the views of women on using nicotine replacement therapy in pregnancy. *Midwifery*. 2010;26:401-6.**
Study type	Qualitative study
Study dates	Not provided
Aim	To raise professional awareness of women's concerns regarding smoking in pregnancy and the use of NRT
Setting/context	Urban and rural populations covered by one hospital trust as the lead provider of maternity care, UK
Participants	Number of participants: 10 NRT/e-cig use: Each participant had used NRT for between 1-180 days (average 45) Maternal status: all pregnant Majority (n=8) used patches (7-15mg), 2 used gum

Bibliographic reference	**Ashwin C, Watts K. Exploring the views of women on using nicotine replacement therapy in pregnancy. *Midwifery*. 2010;26:401-6.**
	Smoking status: no. of cigarettes smoked at the start of pregnancy: 5-20 (range), 5 smoked on average 20 cigarettes per day Most (n=8) participants commenced smoking before age 17 Age range: 25-39 years
Methods	Women were encouraged to offer their views on multiple aspects of NRT use in pregnancy Theoretical perspective: a phenomenological theoretical approach was used. Sampling: a purposive sample of a larger group of women who had previously accessed the local stop smoking service were recruited. Data collection and analysis: semi-structured interviews, thematic analysis
Key themes on NRT or e-cigs	1. Choice of product 2. Thoughts surrounding quit day with NRT 3. Length of time product used 4. Information 5. Anxieties regarding use of NRT
Risk of bias	Data richness: A good amount and depth of qualitative data Concerns regarding: - Data collection: adequate detail not provided regarding interviewer(s), no interview schedule/topic guides. Adequate details of the data collection process not provided (length of interviews, who conducted them) - Data analysis: no second coder and no description of process - Reflexivity is not addressed - Findings substantiated/limitations considered: issues regarding the relevance of quotes to one of the themes identified. Only sample size is discussed as a limitation **Overall risk of bias: Some risk of bias**

Bauld 2017a

Bibliographic reference	**Bauld L, Graham H, Sinclair L, Flemming K, Naughton F, Ford A, et al. Chapter 6. Findings from qualitative study of pregnant and postpartum women's perspectives and experiences of the barriers and facilitators of smoking cessation. In: Assessment HT, editor. Barriers to and facilitators of smoking cessation in pregnancy and following childbirth: literature review and qualitative study 2017a**
Study type	Qualitative study
Study dates	November 2013 – December 2014

Bibliographic reference	**Bauld L, Graham H, Sinclair L, Flemming K, Naughton F, Ford A, et al. Chapter 6. Findings from qualitative study of pregnant and postpartum women's perspectives and experiences of the barriers and facilitators of smoking cessation. In: Assessment HT, editor. Barriers to and facilitators of smoking cessation in pregnancy and following childbirth: literature review and qualitative study 2017a**
Aim	Study objectives: to explore pregnant women's perspectives and experiences of the barriers to and facilitators of smoking cessation, and elicit their views on existing services and interventions to support cessation
Setting/context	Urban and rural, Area A – Scotland; Area B – England, UK
Participants	Number of participants: 41 NRT/e-cig use: not reported Maternal status: all pregnant, 10 interviewed again postpartum Gestation: mean = 19 weeks 15% reported stopping smoking All of area A (n=20) and 20% area B were engaged with stop smoking services by the time of interview 5 participants from each area were interviewed again between 5-12 weeks postpartum but no relevant data Age at interview: mean = 26 years
Methods	Women offered their views on NRT as part of the wider scope of the interviews. Theoretical perspective: a social-ecological framework theoretical perspective was used. Sampling: women were recruited through maternity or stop smoking services. For the second interview, purposive sampling was undertaken, taking into account maternal age, deprivation and smoking status (continuing smokers or quitters). Data collection and analysis: semi-structured interviews, thematic analysis
Key themes on NRT or e-cigs	1. Nicotine replacement therapy 2. Electronic cigarettes
Risk of bias	Data richness: some qualitative data presented Concerns regarding: - Generalisability is not addressed. **Overall risk of bias: Low risk of bias**

Borland 2013

Bibliographic reference	**Borland T, Babayan A, Irfan S, Schwartz R. Exploring the adequacy of smoking cessation support for pregnant and postpartum women. *BMC public health*. 2013;13:472.**
Study type	Qualitative study
Study dates	February 2011 – May 2011
Aim	To examine cessation needs, barriers to the provision and uptake of cessation support and directions for policy, practice and programming
Setting/context	Urban and rural populations, Canada.
Participants	Number of participants: 29 NRT/e-cig use: not reported Maternal status: 10 pregnant, 19 postpartum Smoking status: current/former smokers or making a quit attempt Age: range = 15-49, mean = 22.1 Education: 21 less than high school, 3 high school, 5 more than high school Marital status: 18 had a partner, 11 were single Ethnicity: 11 Aboriginal, 11 White, 4 Black, 1 West Indian, 1 Latin, Central or S. American, 1 not reported Key informants - individuals with insight into the needs or pregnant or postpartum women who smoke – were also interviewed, but are not relevant to this review
Methods	Theoretical perspective: unclear Sampling: participants were purposefully recruited, with promotion through the provincial cessation helpline and gatekeepers working with the target population at local community agencies Data collection and analysis: semi-structured interviews, thematic interpretive analysis
Key themes on NRT or e-cigs	1. Inconsistent practice 2. Engagement and acceptability issues
Risk of bias	Data richness: very few qualitative data presented. Those findings that are presented are fairly descriptive Concerns regarding: - Authors do not state their theoretical perspective - Reflexivity: researcher bias not addressed - Findings substantiated/limitations considered: themes not always substantiated clearly by the data, limited discussion of limitations (consideration of stigma of smoking only) **Overall risk of bias: Low risk of bias**

Bibliographic reference	**Borland T, Babayan A, Irfan S, Schwartz R. Exploring the adequacy of smoking cessation support for pregnant and postpartum women. *BMC public health*. 2013;13:472.**

Bovill 2018

Bibliographic reference	**Bovill M, Gruppetta M, Cadet-James Y, Clarke M, Bonevski B, Gould GS. Wula (Voices) of Aboriginal women on barriers to accepting smoking cessation support during pregnancy: Findings from a qualitative study. *Women and birth : Journal of the Australian College of Midwives*. 2018;31:10-6.**
Study type	Qualitative study
Study dates	August 2015 – January 2016
Aim	To privilege the voices of Aboriginal women, smokers and ex-smokers in the Hunter New England area, collecting their experiences of smoking during pregnancy and of receiving smoking cessation care.
Setting/context	Hunter and New England regions (unclear as to whether urban or rural setting) Australia
Participants	Number of participants: 20 NRT/e-cig use: 8 currently used, or had previously used, medication to help them quit (unclear as to whether this includes NRT) Maternal status: 6 pregnant (1 in first trimester, 2 in second, 3 in the third), 14 recently given birth (2 gave birth 5-12 weeks ago, 7 gave birth 3 months-1 year ago, 2 gave birth over a year ago, 3 = other) Smoking status: 11 current smokers. Cigarettes per day: 8 smoked 10 or less, 3 smoked 11-20 10 participants had made at least 1 quit attempt Age: range = 17-38, mean =27 Ethnicity: 100% Aboriginal or Torres Strait Islander
Methods	Theoretical perspective: unclear Sampling: some participants were recruited through Aboriginal health networks and a smoking cessation trial. The remainder were recruited through use of the researcher's familiarity with Aboriginal community networks, and a university project. Data collection and analysis: therapeutic yarning interviews, inductive thematic analysis
Key themes on NRT or e-cigs	1. Attitudes towards NRT
Risk of bias	Data richness: some qualitative data presented Concerns regarding:

Bibliographic reference	**Bovill M, Gruppetta M, Cadet-James Y, Clarke M, Bonevski B, Gould GS. Wula (Voices) of Aboriginal women on barriers to accepting smoking cessation support during pregnancy: Findings from a qualitative study. *Women and birth : Journal of the Australian College of Midwives*. 2018;31:10-6.**
	- Authors do not state their theoretical perspective - Data collection: unclear as to whether a topic guide was used. The researcher is positioned as 'listener' - Reflexivity: interviews were conducted by a female Aboriginal researcher, but there is no comment on how this affected the study **Overall risk of bias: Low risk of bias**

Bowker 2016

Bibliographic reference	**Bowker K, Campbell KA, Coleman T, Lewis S, Naughton F, Cooper S. Understanding Pregnant Smokers' Adherence to Nicotine Replacement Therapy During a Quit Attempt: A Qualitative Study. *Nicotine Tob Res*. 2016;18:906-12.**
Study type	Qualitative
Study dates	May 2014 – December 2014
Aim	To understand the experience of pregnant women using NRT who discontinue NRT early or do not use the medication as it is recommended
Setting/context	Unclear context, UK
Participants	Number of participants: 14 NRT/e-cig use: 64% using NRT at time of interview. Forms of NRT used: 36% patches, 7% gum, 7% microtab, 43% inhalator, 7% patches, mouth spray and inhalator. E-cig use in pregnancy: 36% of participants Maternal status: all pregnant Gestation: mean = 14 weeks Number of cigarettes smoked before quit attempts: mean = 14 per day Smoking status: all participants smoked during their quit attempt; 72% were smoking at time of the interview Age: mean = 28 Partner smoking status: 64% smoker, 27% non-smoker, 7% no partner Ethnicity: 93% white, 7% mixed British and Caribbean
Methods	Theoretical perspective: unclear Sampling: two stop smoking services were used as participant identification centres. Potentially eligible women – those who had recently been prescribed

Bibliographic reference	**Bowker K, Campbell KA, Coleman T, Lewis S, Naughton F, Cooper S. Understanding Pregnant Smokers' Adherence to Nicotine Replacement Therapy During a Quit Attempt: A Qualitative Study. *Nicotine Tob Res*. 2016;18:906-12.**
	NRT and used it during their quit attempt, but not as recommended – were informed about the study Data collection and analysis: semi-structured interviews, inductive thematic analysis
Key themes on NRT or e-cigs	1. Expectations of NRT 2. Experience of using NRT (perceived effects of NRT use, concomitant smoking and side effects) 3. Safety Concerns 4. Experience of E-Cigarettes
Risk of bias	Data richness: good amount and depth of qualitative data Concerns regarding: - Authors do not state their theoretical perspective - Context/setting: Limited information about the context from which the sample was derived and the specific issues this population might face **Overall risk of bias: Low risk of bias**

Bowker 2018

Bibliographic reference	**Bowker K, Orton S, Cooper S, Naughton F, Whitemore R, Lewis S, et al. Views on and experiences of electronic cigarettes: a qualitative study of women who are pregnant or have recently given birth. *BMC Pregnancy Childbirth*. 2018;18:233.**
Study type	Qualitative
Study dates	October 2015 – October 2016
Aim	To explore pregnant and post-partum women's views and experiences of e-cigarettes
Setting/context	Participants were from a wide range of geographical locations within England and Scotland, UK
Participants	Number of participants: 30 NRT/e-cig use: 9 current e-cig users, 11 ex-users, 10 never users; 7 of the 9 current e-cig users were dual users Maternal status: 15 pregnant (three in 1st trimester, 7 in 2nd trimester, 5 in 3rd trimester), 15 postpartum (6 were 0-3 months postpartum, 9 were 4-6 months postpartum) Smoking status: 16 current smokers, 14 ex-smokers Age: range 21-38 years Education: 70% did not continue education beyond 18 Employed: 83%

Bibliographic reference	**Bowker K, Orton S, Cooper S, Naughton F, Whitemore R, Lewis S, et al. Views on and experiences of electronic cigarettes: a qualitative study of women who are pregnant or have recently given birth. *BMC Pregnancy Childbirth*. 2018;18:233.**
	Living with partner: 70% Ethnicity: 83% White British
Methods	Theoretical perspective: unclear Sampling: participants were purposively sampled from the following groups: e-cig users, e-cig ex-users, each trimester of pregnancy and for varying stages of the postpartum period (up to 6 months). Recruitment adverts were placed on various websites and at stop smoking services, antenatal clinics and health visitor clinics in locations across England and Scotland Data collection and analysis: semi-structured interviews, thematic framework analysis
Key themes on NRT or e-cigs	1. Motivations for use 2. Social stigma 3. Using the e-cig 4. Consumer aspects 5. Harm perceptions
Risk of bias	Data richness: good amount and depth of qualitative data Concerns regarding: - Authors do not state their theoretical perspective - Context/setting: Women were recruited from various settings throughout England and Scotland. No information is provided about the characteristics of the setting or context of the study **Overall risk of bias: Some risk of bias**

Butterworth 2014

Bibliographic reference	**Butterworth SJ, Sparkes E, Trout A, Brown K. Pregnant smokers' perceptions of specialist smoking cessation services. *J Smok Cessat*. 2014;9:85-97.**
Study type	Qualitative
Study dates	January 2011 – May 2011 (recruitment of participants)
Aim	To report on the views held by past and current service users and non-users regarding existing stop smoking services for pregnant women in Solihull, West Midlands.
Setting/context	Urban, North Solihull, England, UK.
Participants	Number of participants: 19 NRT/e-cig use: not reported

Bibliographic reference	**Butterworth SJ, Sparkes E, Trout A, Brown K. Pregnant smokers' perceptions of specialist smoking cessation services. *J Smok Cessat*. 2014;9:85-97.**
	Maternal status: 16 pregnant (5 in 1st trimester, 5 in 2nd trimester, 6 in 3rd trimester, mean gestation = 21 weeks), 3 postpartum (had given birth in the past 10 months) Smoking status: 74% current smokers (smoked between 1-30 cigarettes per day), 26% ex-smokers with experience of 2 weeks – 5 months cessation. All had smoked for all or part of their pregnancy 11% had used a stop smoking service Age: range = 17-35 years, mean = 25 Education: 21% no completed education, 32% completed compulsory education, 47% completed 1-5 years of higher education Employment status: 58% unemployed/never worked, 21% carers, 16% employed, 5% not stated Marital status: 53% parenting with partner, 47% parenting alone Ethnicity: 95% Caucasian British, 5% non-Caucasian/Caribbean
Methods	Theoretical perspective: unclear Sampling: women within two postcode areas were targeted, based on regional statistics indicating high rates of smoking in pregnancy. Participants were invited to participate at their initial contact with smoking cessation services or from community midwife visiting lists
Key themes on NRT or e-cigs	1. Advantages of current services: non-judgemental support 2. Initiatives to encourage participation (offering suitable NRT subtheme)
Risk of bias	Data richness: very few qualitative data presented. Those findings that are presented are fairly descriptive Concerns regarding: - Authors do not state their theoretical perspective - Reflexivity is not adequately addressed - There is no mention regarding obtaining ethical approval, but it is stated that the researcher's complied with relevant ethical standards and the 1975 Helsinki Declaration. **Overall risk of bias: Low risk of bias**

England 2016

Bibliographic reference	**England LJ, Tong VT, Koblitz A, Kish-Doto J, Lynch MM, Southwell BG. Perceptions of emerging tobacco products and nicotine replacement therapy among pregnant women and women planning a pregnancy. *Prev Med Rep*. 2016;4:481-5.**
Study type	Qualitative
Study dates	Not provided
Aim	To assess how women perceive emerging non-combusted tobacco products and NRT use in general and during pregnancy, to assess how women perceive the health risks associated with these.
Setting/context	Memphis (Tennessee), Philadelphia, (Pennsylvania), Oklahoma City (Oklahoma), Billings, (Montana), USA, urban populations
Participants	Number of participants: 59 NRT/e-cig use: 28% of pregnant smokers and 19% of pregnant quitters used other tobacco products', a category including e-cigs Pregnant smokers (n=32): Smoking status: 66% smoked every day, 28% used other tobacco products (including e-cigs, snus, chewing tobacco) Age: 41% 18-23, 44% 24-29, 13% 30-35, 3% 36-40 Education: 19% less than high school, 53% high school or equivalent, 28% some college Ethnicity: 41% Caucasian, 19% African American, 13% Native American, 28% Hispanic Pregnant quitters (n=27): Smoking status: 19% used other tobacco products (including e-cigs, snus, chewing tobacco) Age: 7% 18-23, 22% 24-29, 33% 30-35, 37% 36-40 Education: 15% high school or equivalent, 59% some college, 22% college graduate Ethnicity: 51% Caucasian, 29% African American, 3% Native American, 15% Hispanic The third group, smokers planning a pregnancy, are not relevant to this review
Methods	Theoretical perspective: unclear Sampling: market research facilities recruited participants using their databases. Respondents were then screened for eligibility by telephone
Key themes on NRT or e-cigs	1. Prior experiences with tobacco and NRT (perceptions related to non-combustible tobacco and NRT, general, subthemes = product familiarity, product appeal), specific and non-specific to pregnant
Risk of bias	Data richness: some qualitative data presented (data richness) Concerns regarding: - Authors do not state their theoretical perspective

Bibliographic reference	**England LJ, Tong VT, Koblitz A, Kish-Doto J, Lynch MM, Southwell BG. Perceptions of emerging tobacco products and nicotine replacement therapy among pregnant women and women planning a pregnancy. *Prev Med Rep*. 2016;4:481-5.**
	- Context/setting: no description of context aside from the 4 cities being chosen based on smoking prevalence in pregnancy - Sample: issues regarding the population the sample is drawn from (market research database which is not adequately described) - Data analysis: it is unclear what method is used and the process is not sufficiently described - Reflexivity is not addressed **Overall risk of bias: Some risk of bias**

Fallin 2016a

Bibliographic reference	**Fallin A, Miller A, Ashford K. Smoking Among Pregnant Women in Outpatient Treatment for Opioid Dependence: A Qualitative Inquiry. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*. 2016a;18:1727-32.**
Study type	Qualitative
Study dates	Not provided
Aim	To describe facilitators and barriers to engaging in tobacco treatment among pregnant, opioid dependent women receiving Medication Assisted Treatment (MAT).
Setting/context	Unclear context, USA
Participants	Number of participants: 19 (22 including 3 lifelong non-smokers) NRT/e-cig use: not reported Maternal status: participants ranged from 11 weeks gestation to postpartum (up to 6 weeks) Smoking status: 86% current smokers, 14% lifelong non-smokers Age: range = 22-37, mean = 28 Past pregnancies: range = 1-15, mean = 4, and mean of 2 living children, range = 0-7 Ethnicity: 100% Caucasian
Methods	Theoretical perspective: unclear Sampling: participants were recruited from group prenatal care sessions at a maternal foetal medicine clinic Data collection and analysis: focus groups, thematic analysis
Key themes on NRT or e-cigs	1. Lack of success with NRT
Risk of bias	Data richness: very few qualitative data presented. Those findings that are presented are fairly descriptive Concerns regarding:

Bibliographic reference	**Fallin A, Miller A, Ashford K. Smoking Among Pregnant Women in Outpatient Treatment for Opioid Dependence: A Qualitative Inquiry. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*. 2016a;18:1727-32.**
	- Authors do not state their theoretical perspective - Context/setting: insufficient detail provided - Sample: The inclusion of three lifelong non-smokers in the sample suggests it may have been opportunistic in nature - Data collection: It is not clear who conducted the interviews, and no topic guide is provided. Insufficient details about the data collection process. - Data analysis: insufficient details about the data analysis process - Generalisability: not sufficiently addressed – homogenous sample with no diversity - Ethical issues not addressed **Overall risk of bias: High risk of bias**

Fallin 2016b

Bibliographic reference	**Fallin A, Miller A, Assef S, Ashford K. Perceptions of Electronic Cigarettes Among Medicaid-Eligible Pregnant and Postpartum Women. *Journal of Obstetric, Gynecologic & Neonatal Nursing*. 2016b;45:320-5.**
Study type	Qualitative
Study dates	Not provided
Aim	To describe perceptions and beliefs about e-cigarette use during pregnancy among pregnant and newly postpartum women in Kentucky.
Setting/context	Unclear context, USA
Participants	Number of participants: 12 NRT/e-cig use: not reported, but all participants smoked either cigarettes or e-cigs Maternal status: 8 pregnant, 4 newly postpartum Smoking status: all reported smoking (cigarettes or e-cigs) 3 months before pregnancy or during pregnancy Marital status: 58.3% single Ethnicity: 75% white
Methods	Theoretical perspective: unclear Sampling: women who had taken part in the first phase of the study (a survey completed by a convenience sample of pregnant women), and had consented to being contacted for additional studies, were invited to attend a focus group, providing they met the eligibility criteria

Bibliographic reference	**Fallin A, Miller A, Assef S, Ashford K. Perceptions of Electronic Cigarettes Among Medicaid-Eligible Pregnant and Postpartum Women. *Journal of Obstetric, Gynecologic & Neonatal Nursing*. 2016b;45:320-5.**
	Data collection and analysis: focus groups, content analysis
Key themes on NRT or e-cigs	1. Attraction to e-cig as a harm reduction strategy 2. Uncertainty regarding the health effects of e-cigs 3. Ambivalence regarding novel product characteristics 4. Behaviours reflected dual use and often complete relapse to traditional cigarettes
Risk of bias	Data richness: good amount and depth of qualitative data Concerns regarding: - Authors do not state their theoretical perspective - Sample: small sample size (N=12) for a focus group study, questionable as to whether data saturation was reached as stated by the authors - Data analysis: Insufficient details about the data analysis process - Reflexivity is not addressed **Overall risk of bias: Some risk of bias**

Gamble 2015

Bibliographic reference	**Gamble J, Grant J, Tsourtos G. Missed opportunities: A qualitative exploration of the experiences of smoking cessation interventions among socially disadvantaged pregnant women. *Women Birth*. 2015;28:8-15.**
Study type	Qualitative
Study dates	Not provided
Aim	To explore and describe women's experiences of smoking cessation intervention(s), perceptions of smoking cessation intervention efficacy, and views for improving smoking cessation interventions in pregnancy
Setting/context	Urban, Australia
Participants	Number of participants: 6 NRT/e-cig use: not reported Maternal status: all pregnant Gestation: range 20-35 weeks, mean = 27 weeks Smoking status at recruitment: all daily smokers, with experience of at least one health worker delivered intervention for smoking cessation during their pregnancy Smoking status at interview: 4 smoking, 1 had quit in the last 4 weeks, 1 quit without support

Bibliographic reference	**Gamble J, Grant J, Tsourtos G. Missed opportunities: A qualitative exploration of the experiences of smoking cessation interventions among socially disadvantaged pregnant women. *Women Birth*. 2015;28:8-15.**
	Age: range = 18-38, mean = 24.33 Previous pregnancies: 4 having 1st baby, 1 having 3rd, 1 having 4th All were socio-economically disadvantaged - all held a government health card (indicator of low income). All participants lived in public housing
Methods	Theoretical perspective: feminist Sampling: purposive sample – five women were identified and recruited from a smoking cessation service database. One other was recruited opportunistically via snowball sampling. Data collection and analysis: semi-structured interviews, inductive thematic analysis
Key themes on NRT or e-cigs	1. What NRT women want
Risk of bias	Data richness: very few qualitative data presented. Those findings that are presented are fairly descriptive **Overall risk of bias: Low risk of bias**

Glover 2012

Bibliographic reference	**Glover M, Kira A. Pregnant Māori smokers' perception of cessation support and how it can be more helpful. *J Smok Cessat*. 2012;7:65-71.**
Study type	Qualitative
Study dates	October 2002 – November 2003
Aim	To investigate pregnant Maori smokers' perception of cessation services and products and identify how they may be improved
Setting/context	Urban and rural, New Zealand
Participants	Number of participants: 60 NRT/e-cig use: not reported Maternal status: all pregnant (43% 2nd trimester, 40% 3rd) Smoking status: mostly current smokers (one recently stopped smoking on becoming pregnant) Cigarettes per day: range 1-28, mean = 9, 32% smoked 1st cigarette within 5 minutes of waking Age range: 17-43 Previous pregnancies: 38% having 1st baby

Bibliographic reference	**Glover M, Kira A. Pregnant Māori smokers' perception of cessation support and how it can be more helpful. *J Smok Cessat*. 2012;7:65-71.**
	68% lived in urban centres Education: 23% no formal qualifications Employment status: 38% had some employment, 80% eligible for community services card - an indicator of low income Marital status: 88% with a partner Ethnicity: 100% Maori
Methods	Theoretical perspective: unclear Sampling: Participants were recruited through Maori health services, the researcher's networks and newspaper advertisements from various urban and rural areas of New Zealand's North Island Data collection and analysis: semi-structured interviews, inductive thematic analysis
Key themes on NRT or e-cigs	1. Health education resources 2. Nicotine replacement therapy
Risk of bias	Data richness: very few qualitative data presented. Those findings that are presented are fairly descriptive Concerns regarding: - Authors do not state their theoretical perspective - Context/setting: Does not fully provide the characteristics of the participants or explain the specific issues relating to pregnant Maori women in terms of vulnerability to smoking - Data collection: not clear who carried out the interviews; data collection method is not clear. Does not state how data was recorded. - Data analysis: one very brief statement on the process of data analysis is provided - Reflexivity is not addressed - Ethical issues not addressed **Overall risk of bias: High risk of bias**

Grant 2018

Bibliographic reference	**Grant A, Morgan M, Gallagher D, Mannay D. Smoking during pregnancy, stigma and secrets: Visual methods exploration in the UK. *Women Birth*. 2018.**
Study type	Qualitative
Study dates	March 2016 – August 2016
Aim	To gain an in-depth understanding of the health issues affecting 10 low income pregnant women from deprived areas of south Wales, UK

Bibliographic reference	**Grant A, Morgan M, Gallagher D, Mannay D. Smoking during pregnancy, stigma and secrets: Visual methods exploration in the UK. *Women Birth*. 2018.**
Setting/context	South Wales, UK. Unclear as to whether urban/rural setting
Participants	Number of participants: 10 (9 completed both interview phases). This number of participants was deemed appropriate by the authors due to the highly in-depth nature of the study NRT/e-cig use: 1 participant used an e-cig. Maternal status: all pregnant Gestation: Mean gestation 12.9 weeks (range = 6 weeks - 29 weeks) Smoking status: 2 smoked at time of interview, 1 was using an e-cig, 5 abstinent, 1 did not mention smoking Age: range = 24-34, mean = 28.8 Previous pregnancies: 9 already had children, one participant gave birth as a teenager, another in 30s, rest occurred in 20s
Methods	Theoretical perspective: an interpretivist paradigm guided by feminist principles Sampling: recruitment of participants was achieved through a variety of avenues external to health services, including community settings, online advertising and flyers in deprived areas Data collection and analysis: Three creative tasks based on visual methods, and elicitation interviews, thematic analysis.
Key themes on NRT or e-cigs	1. Demographics and (self-reported) smoking status, 2. Social networks, hidden smoking during pregnancy and morality, 3. Interaction with maternity healthcare services
Risk of bias	Data richness: very few qualitative data presented. Those findings that are presented are fairly descriptive (data richness) Concerns regarding: - Context/setting: insufficient details on current smoking rates, e-cig use, NHS treatment offered in the study setting (South Wales, UK) **Overall risk of bias: Low risk of bias**

Hauck 2013

Bibliographic reference	**Hauck Y, Ronchi F, Lourey B, Lewis L. Challenges and enablers to smoking cessation for young pregnant Australian women: a qualitative study. *Birth (Berkeley, Calif)*. 2013;40:202-8.**
Study type	Qualitative
Study dates	July 2011 – June 2012
Aim	To gain insight into the perceived challenges and enablers young pregnant women encounter when attempting to modify their smoking
Setting/context	Urban, Australia
Participants	Number of participants: 36 NRT/e-cig use: not reported Maternal status: all pregnant Smoking status: all smokers Age: range 16-24 (50% 16-17 years) Parity: 78% in first pregnancy Ethnicity: 14% Aboriginal, all English speaking
Methods	Theoretical perspective: unclear Sampling: participants were recruited by a research assistant whilst attending an antenatal clinic appointment Data collection and analysis: interviews, thematic analysis
Key themes on NRT or e-cigs	1. Something you could take
Risk of bias	Data richness: very few qualitative data presented. Those findings that are presented are fairly descriptive Concerns regarding: - Authors do not state their theoretical perspective - Insufficient details on reflexivity **Overall risk of bias: Low risk of bias**

Herbec 2014

Bibliographic reference	**Herbec A, Beard E, Brown J, Gardner B, Tombor I, West R. The needs and preferences of pregnant smokers regarding tailored Internet-based smoking cessation interventions: a qualitative interview study. *BMC Public Health*. 2014;14:1070.**
Study type	Qualitative
Study dates	Not provided

Bibliographic reference	**Herbec A, Beard E, Brown J, Gardner B, Tombor I, West R. The needs and preferences of pregnant smokers regarding tailored Internet-based smoking cessation interventions: a qualitative interview study. *BMC Public Health*. 2014;14:1070.**
Aim	To explore the needs and preferences of pregnant women seeking online stop smoking support (with an aim to identify features and components of internet-based smoking cessation interventions that might be most attractive to this population)
Setting/context	Nationwide recruitment of participants, UK
Participants	Number of participants: 13. Data saturation appeared to be reached, and no new themes emerged in the final 3 interviews. NRT/e-cig use: not reported Maternal status: all pregnant Smoking status: 54% reported they had quit at time of interview, 69% had previously made a quit attempt Age: range = 20-41, mean = 31 Marital status: 92% married Previous pregnancies: 38% 1st pregnancy, 62% multigravida Ethnicity: 92% white British
Methods	Theoretical perspective: unclear Sampling: participants were women randomised to the intervention arm of a smoking cessation trial (MumsQuit) Data collection and analysis: semi-structured interviews, framework analysis variant
Key themes on NRT or e-cigs	1. Smoking cessation medication
Risk of bias	Data richness: very few qualitative data presented. Those findings that are presented are fairly descriptive Concerns regarding: - Authors do not state their theoretical perspective - Sample: low response rate, a self-selected sample, predominantly white British and married **Overall risk of bias: Low risk of bias**

Hotham 2002

Bibliographic reference	**Hotham ED, Atkinson ER, Gilbert AL. Focus groups with pregnant smokers: barriers to cessation, attitudes to nicotine patch use and perceptions of cessation counselling by care providers. *Drug Alcohol Rev*. 2002;21:163-8.**
Study type	Qualitative
Study dates	To explore barriers to quitting smoking for pregnant women, their attitudes to use of patches and their perceptions of care provider counselling
Aim	Not provided
Setting/context	Urban, Australia
Participants	Number of participants: 19 NRT/e-cig use: not reported (NRT was not approved for use in pregnancy in Australia at the time the study was conducted) Maternal status: all pregnant Smoking status: women who smoked (n= 9) or who had quit before or early in pregnancy (n=10)
Methods	Theoretical perspective: unclear Sampling: convenience sample: a researcher approached women at five successive antenatal clinics at a large obstetrics hospital in South Australia. Over 250 women were approached to take part Data collection and analysis: focus groups, thematic analysis
Key themes on NRT or e-cigs	1. Attitudes of women towards the use of nicotine patches
Risk of bias	A good amount and depth of qualitative data (data richness) Concerns regarding: - Authors do not state their theoretical perspective - Sample: participant characteristics not described - Data analysis: only one of three groups was transcribed in full, the identification of key themes is not described adequately - Reflexivity is not addressed **Overall risk of bias: Some risk of bias**

Mantzari 2012

Bibliographic reference	**Mantzari E, Vogt F, Marteau TM. The effectiveness of financial incentives for smoking cessation during pregnancy: is it from being paid or from the extra aid? *BMC Pregnancy Childbirth*. 2012;12:24.**
Study type	Qualitative
Study dates	September 2009 – May 2010 (recruitment of participants)
Aim	To examine and compare the stop-smoking experiences of pregnant women who were incentivised for smoking cessation and those who were not incentivised for smoking cessation

Bibliographic reference	**Mantzari E, Vogt F, Marteau TM. The effectiveness of financial incentives for smoking cessation during pregnancy: is it from being paid or from the extra aid? *BMC Pregnancy Childbirth*. 2012;12:24.**
Setting/context	Urban, UK
Participants	Number of participants: 36 (20 incentives arm, 16 control arm) NRT/e-cig use: not reported Maternal status: at interview: 24 pregnant, 11 postpartum (6 in incentive group and 5 in control group), 1 participant miscarried Smoking status: at interview: 12 (33%) women smoke free (8 in intervention group, 4 in control group), 24 (66%) smoking Age: range = 17-43, mean = 28 Employment status: mostly unemployed Ethnicity: 94% White
Methods	Theoretical perspective: unclear Sampling: participants were recruited through an opportunistic sampling framework from a population of 115 women living in the greater Birmingham area who had been referred to the NHS Stop Smoking Services by their midwives and were 1) enrolled in a pilot scheme of incentivising smoking cessation or 2) lived in a "comparison" area, and were therefore eligible to be part of a comparison cohort. Data collection and analysis: semi-structured interviews, framework analysis.
Key themes on NRT or e-cigs	1. Perceived inhibitors
Risk of bias	Data richness: some qualitative data presented Concerns regarding: - Authors do not state their theoretical perspective - Data collection: unclear who carried out the interviews, no interview topic guide or broad categories of discussion. Insufficient detail of data collection process - Reflexivity is not addressed - Generalisability is not addressed **Overall risk of bias: Low risk of bias**

Naughton 2013

Bibliographic reference	**Naughton F, Eborall H, Sutton S. Dissonance and disengagement in pregnant smokers: a qualitative study. *J Smok Cessat*. 2013;8:24-32.**
Study type	Qualitative
Study dates	March 2007 – July 2007

Bibliographic reference	**Naughton F, Eborall H, Sutton S. Dissonance and disengagement in pregnant smokers: a qualitative study. *J Smok Cessat*. 2013;8:24-32.**
Aim	To explore the accounts of pregnant smokers and quitters, to investigate the role of their smoking beliefs in influencing their smoking behaviour and the relationships of these with psychosocial factors related to pregnancy and antenatal care
Setting/context	Cambridgeshire and Suffolk, England. Urban and rural setting, UK
Participants	Number of participants: 20 NRT/e-cig use: not reported Maternal status: 15 pregnant (75%), 5 postpartum (25%) Age range: 16-40 Gestation: 5% 1-12 weeks, 30% 13-28 weeks, 40% 29-40 weeks Smoking status: 13 (65%) current smokers Cigarettes per day in pregnancy: 35% 0, 20% 1-4, 30% 5-9, 5% 15-19, 10% 20+ Quit attempts: 1 participant quit during most recent pregnancy (but smoked for first 4), 6 quit when finding out they were pregnant, remaining 13 smoked but had made numerous quit attempts Previous births: 65% had no previous births Socio-economic classification (NS-SEC 1-5): 45% 1, 5% 2, 5% 3, 5% 4, 40% 5 Relationship status: 90% had a partner Partner smoking status: 77.8% smoked
Methods	Theoretical perspective: grounded theory and constant comparative approach Sampling: purposive sampling. Participants were recruited by community midwives from two GP practices in Cambridgeshire and Suffolk, UK. Midwife clinics and a ‘Sure Start’ programme were attended by one of the authors towards the end of recruitment to identify further participants and ensure sample variation Data collection and analysis: semi structured interviews, framework analysis
Key themes on NRT or e-cigs	1. Uncertainty about the mechanism of harm
Risk of bias	Data richness: very few qualitative data presented. Those findings that are presented are fairly descriptive Concerns regarding:

Bibliographic reference	**Naughton F, Eborall H, Sutton S. Dissonance and disengagement in pregnant smokers: a qualitative study. *J Smok Cessat*. 2013;8:24-32.**
	- Context/setting: some description of the issues surrounding smoking in pregnancy, but the setting, Cambridgeshire and Suffolk, is not adequately described - Reflexivity is not addressed - Generalisability is not addressed **Overall risk of bias: Low risk of bias**

Pledger 2015

Bibliographic reference	**Pledger AB. Exploring the experiences of pregnant women using an NHS stop smoking service: a qualitative study. *Perspect Public Health*. 2015;135:138-44.**
Study type	Qualitative
Study dates	August 2013 – September 2013
Aim	To retrospectively examine the needs, motivations and experiences of pregnant women using an NHS stop smoking service. Identify enablers and barriers to stop smoking in expectant mothers
Setting/context	Unclear context, UK
Participants	Number of participants: 6. Data saturation was achieved so no more interviews were carried out. NRT/e-cig use: not reported Maternal status: had been pregnant at time of contact with stop smoking service (between July 2012 and July 2013) Smoking status: smoked at time of referral to stop smoking service Age: range 18-35
Methods	Theoretical perspective: unclear Sampling: purposive sample. The researcher contacted all eligible participants who had contacted an NHS stop smoking service in the preceding 12 months, identifying 82 potential participants Data collection and analysis: semi-structured interviews, comparative analysis.
Key themes on NRT or e-cigs	1. Experiences of using NHS stop smoking support
Risk of bias	Data richness: very few qualitative data presented. Those findings that are presented are fairly descriptive Concerns regarding: - Authors do not state their theoretical perspective - Context/setting: issues of smoking in pregnancy and the role of the NHS are briefly described, but not the specific context and setting

Bibliographic reference	**Pledger AB. Exploring the experiences of pregnant women using an NHS stop smoking service: a qualitative study. *Perspect Public Health*. 2015;135:138-44.**
	- Sample: all participants were from one area. Only 6 of 82 eligible women were interviewed due to the claim that saturation of data had been achieved - Data collection: no topic guide; process not described in sufficient detail - Data analysis: analysis conducted by one researcher; insufficient details of the process - Reflexivity is not addressed **Overall risk of bias: High risk of bias**

Radley 2013

Bibliographic reference	**Radley A, Ballard P, Eadie D, MacAskill S, Donnelly L, Tappin D. Give It Up For Baby: outcomes and factors influencing uptake of a pilot smoking cessation incentive scheme for pregnant women. *BMC Public Health*. 2013;13:343.**
Study type	Qualitative
Study dates	Early 2009
Aim	To seek the views and experiences of two participant groups with divergent levels of engagement to a pilot smoking cessation incentive scheme
Setting/context	Tayside, Scotland, UK. Unclear as to whether it is a rural or urban population.
Participants	Number of participants: 20 NRT/e-cig use: not reported. As part of the financial incentives scheme this study is part of, NRT was provided by a pharmacist at an initial meeting. Maternal status: all pregnant Age: mean = 25.7 Socioeconomic status: majority living in most deprived quintile Previous pregnancies: over half (n=12) of participants were having their 1st child
Methods	Theoretical perspective: unclear Sampling: a cross-sectional sample of participants in the 'Give It Up For Baby' incentives scheme was identified using client databases to represent the two groups of interest: those that engaged regularly with the scheme, and those that registered but did not Data collection and analysis: interviews, thematic analysis
Key themes on NRT or e-cigs	1. Client typology
Risk of bias	Data richness: very few qualitative data presented. Those findings that are presented are fairly descriptive.

Bibliographic reference	**Radley A, Ballard P, Eadie D, MacAskill S, Donnelly L, Tappin D. Give It Up For Baby: outcomes and factors influencing uptake of a pilot smoking cessation incentive scheme for pregnant women. *BMC Public Health*. 2013;13:343.**
	Concerns regarding: - Authors do not state their theoretical perspective - Data collection: no interview topic - Reflexivity is not addressed - Findings substantiated/limitations considered: limitations not sufficiently addressed - Ethical issues not sufficiently addressed (only consent mentioned, no approval) **Overall risk of bias: Some risk of bias**

Taylor 2010

Bibliographic reference	**Taylor JA. Beliefs about NHS stop smoking services and nicotine replacement therapy in pregnancy: exploring the potential role of the theory of planned behaviour in promoting uptake of smoking cessation services [PhD]. Nottingham: University of Nottingham; 2010.**
Study type	Qualitative
Study dates	August 2006 – February 2007
Aim	To elicit salient beliefs women have about NRT
Setting/context	Nottingham, England, UK. Urban population.
Participants	Number of participants: 18 NRT/e-cig use: 7 of the pregnant sample and 2 of the postpartum sample reported past NRT use. Pregnant sample (n=14) Gestation: range = 9-28 weeks Smoking status: 10 smokers, 4 recently quit. Cigarettes per day: average = 8. 3 had used a Stop Smoking Service previously Age: range = 17-36 Marital status: 8 cohabiting with partner, 1 married, 5 single Employment status: 5 employed Education: 7 NVQ/GCSE level, 1 Diploma/HND level, 1 Degree level Ethnicity: 100% White British Postpartum sample (n=4) 6-20 months postpartum Smoking status: 3 smoked throughout pregnancy, 1 quit during pregnancy. Cigarettes per day whilst pregnant: average = 9

Bibliographic reference	**Taylor JA. Beliefs about NHS stop smoking services and nicotine replacement therapy in pregnancy: exploring the potential role of the theory of planned behaviour in promoting uptake of smoking cessation services [PhD]. Nottingham: University of Nottingham; 2010.**
	Age: range = 21-32 Marital status: 3 cohabiting with partner, 1 married Employment status: 2 employed Education: 2 NVQ/GCSE, 1 BTRC/A Level, 1 Degree level Ethnicity: 100% White British The third sample, NHS health professionals, is not relevant to this review
Methods	Theoretical perspective: theory of planned behaviour framework Sampling: purposive sampling (maximum variation sampling strategy) in order to recruit participants from across the social spectrum, recruited from antenatal clinics and Sure Start centres Data collection and analysis: semi-structured interviews, thematic analysis
Key themes on NRT or e-cigs	1. Effective for quitting - beliefs about whether or not NRT would be effective in helping with smoking cessation, 2. Side effects - beliefs about unwanted side effects accompanying NRT use, 3. Improved health - beliefs that using NRT in pregnancy would improve the health of mother and baby, 4. Not the same as quitting - beliefs that using NRT would not represent properly quitting smoking, 5. Safety - beliefs that NRT might not be safe to use in pregnancy, 6. Unsure if allowed - beliefs that NRT might not be allowed in pregnancy, 7. Knowledge about products - the amount of knowledge a pregnant woman has about NRT
Risk of bias	Data richness: a large amount and depth of qualitative data Concerns regarding: - Generalisability: it is inferred that the variety in the sample is sufficient, despite it being small and comprised entirely of white British participants **Overall risk of bias: Low risk of bias**

Appendix E – Forest plots

Nicotine replacement therapy (NRT) compared with control in pregnant women

Figure 4: Biochemically validated abstinence from smoking in later pregnancy (subgrouped by comparator)

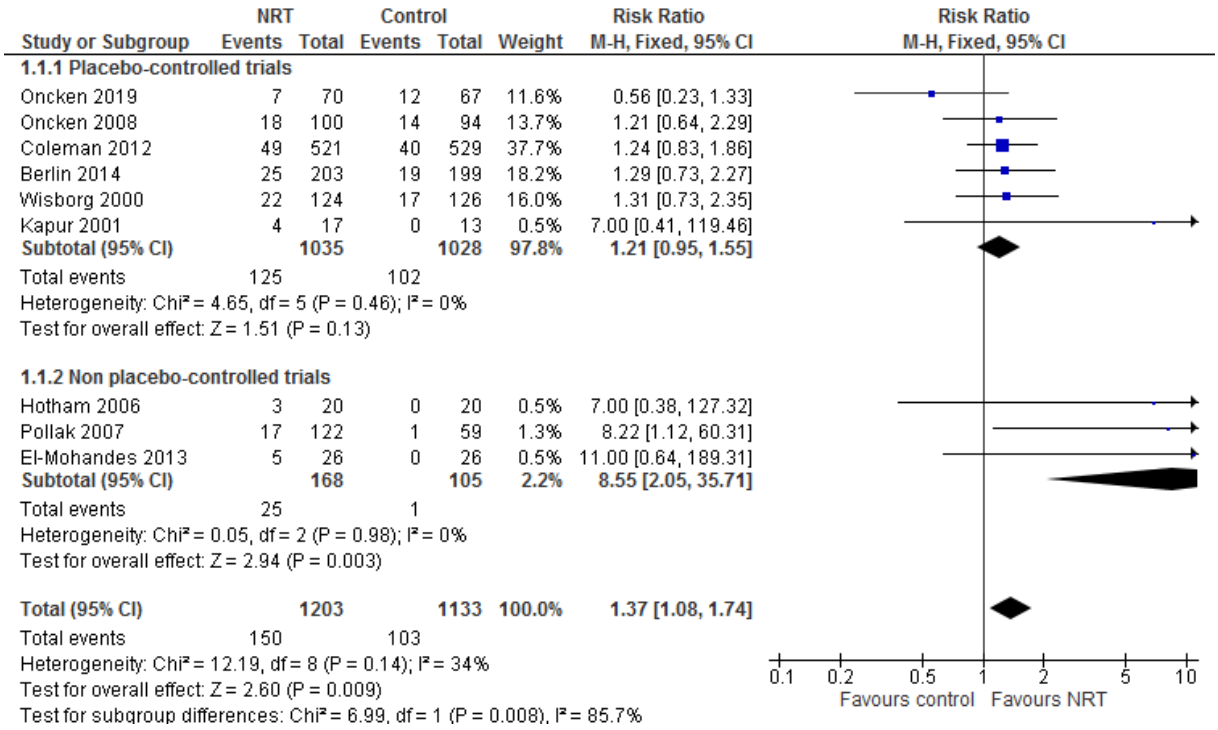


Figure 5: Biochemically validated abstinence from smoking in later pregnancy (subgrouped by NRT type)

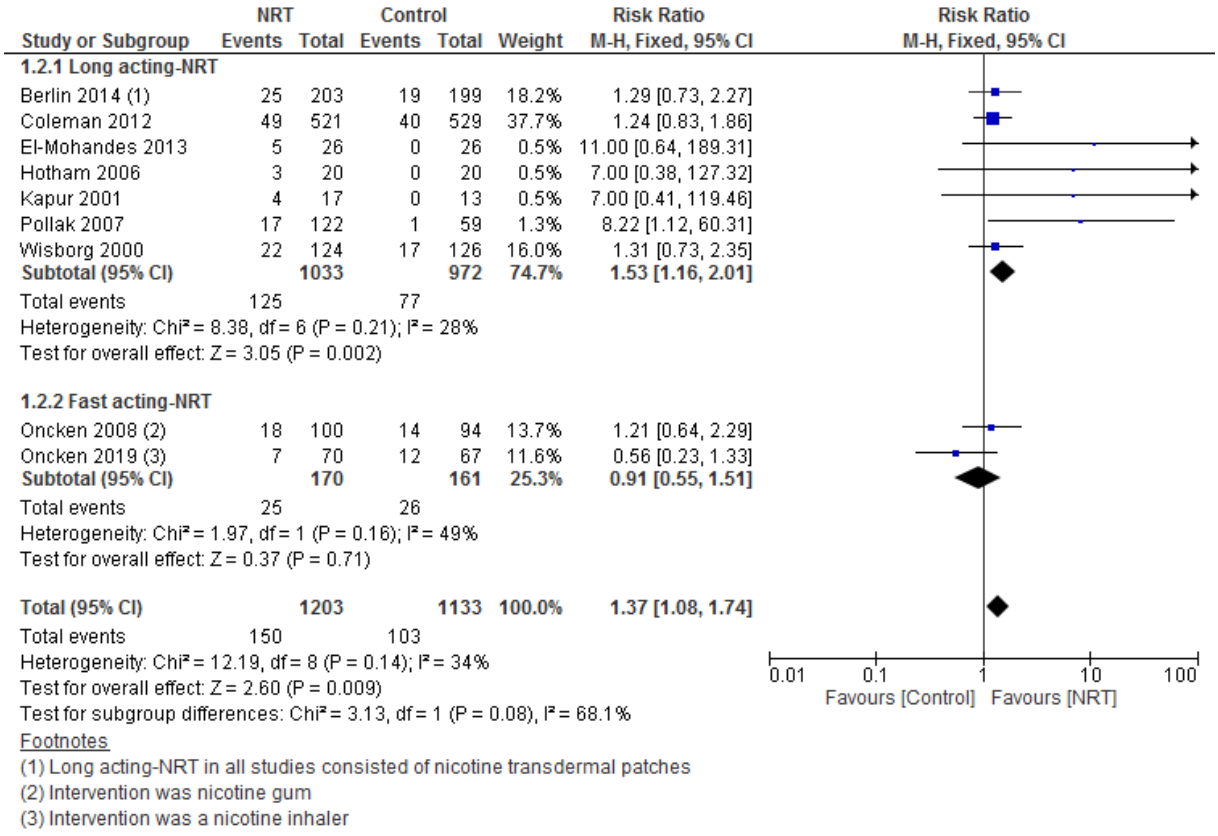


Figure 6: Self-reported abstinence from smoking at 3 or 6-months post-partum (subgrouped by comparator)

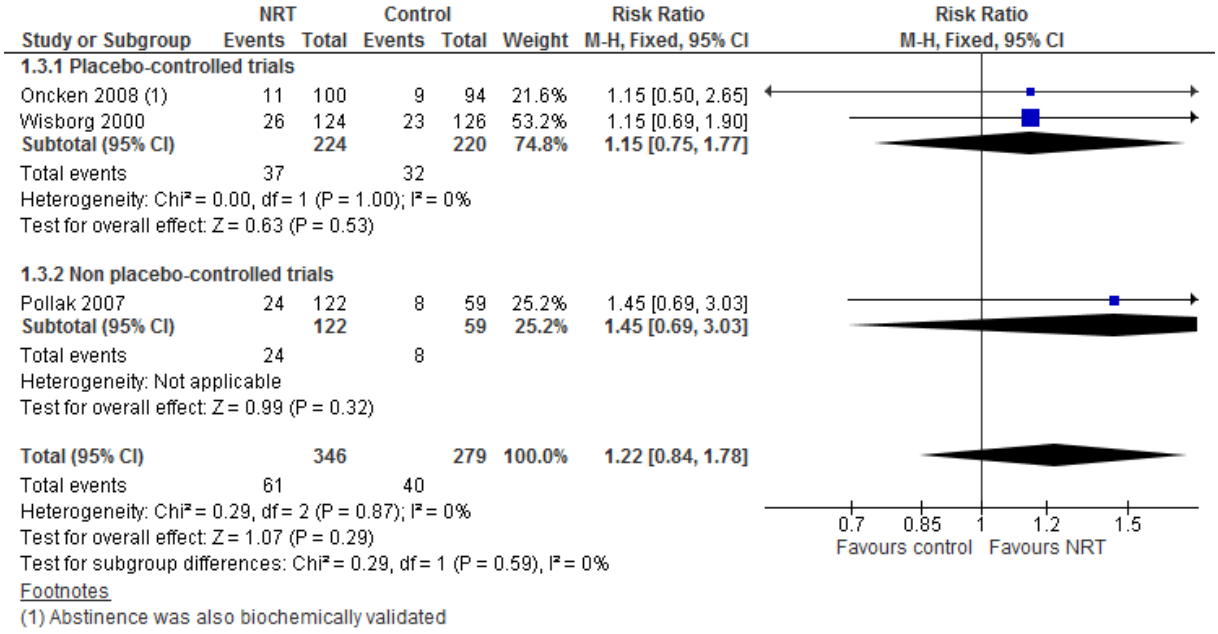


Figure 7: Self-reported abstinence from smoking at 12-months post-partum

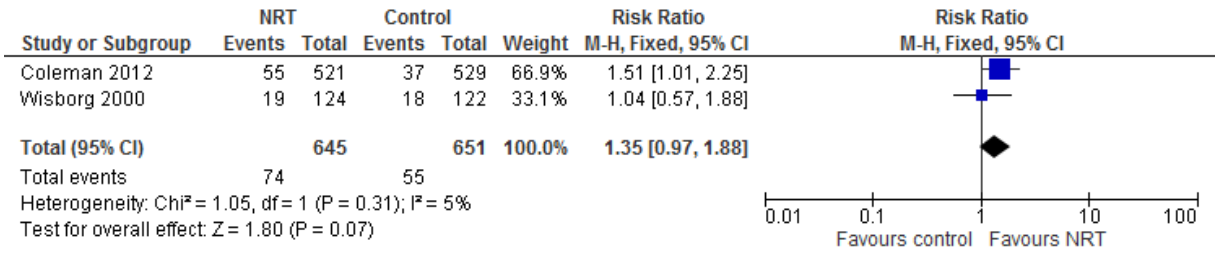


Figure 8: Miscarriage and spontaneous abortion

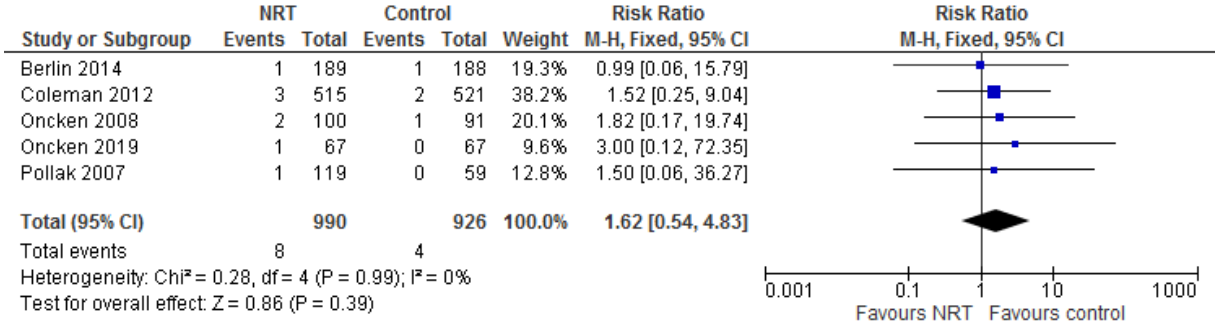


Figure 9: Stillbirth (randomised controlled trials)

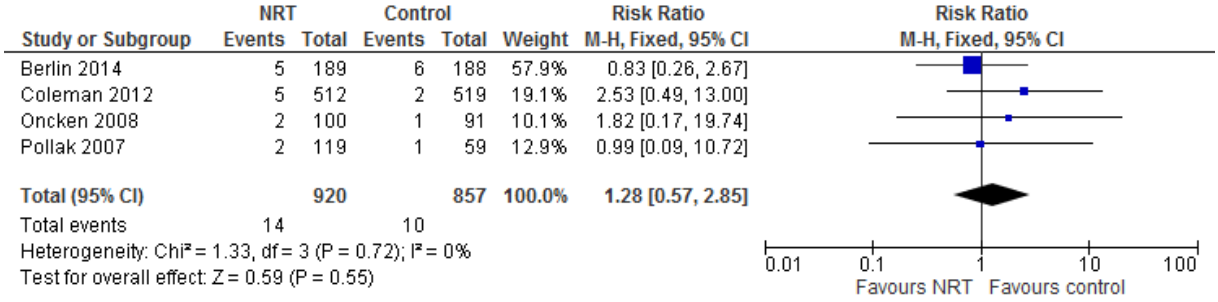


Figure 10: Stillbirth (cohort studies)

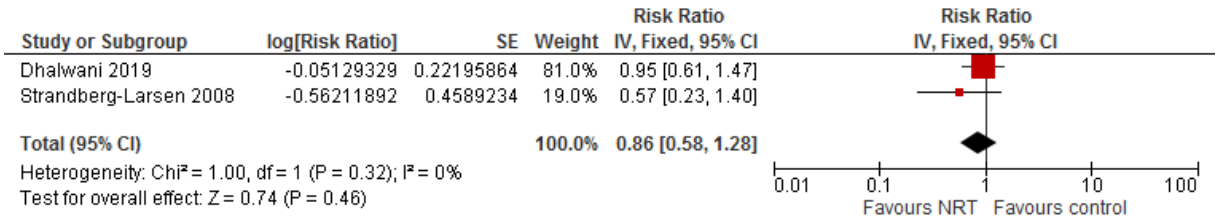


Figure 11: Mean birthweight of infant at delivery (grams)

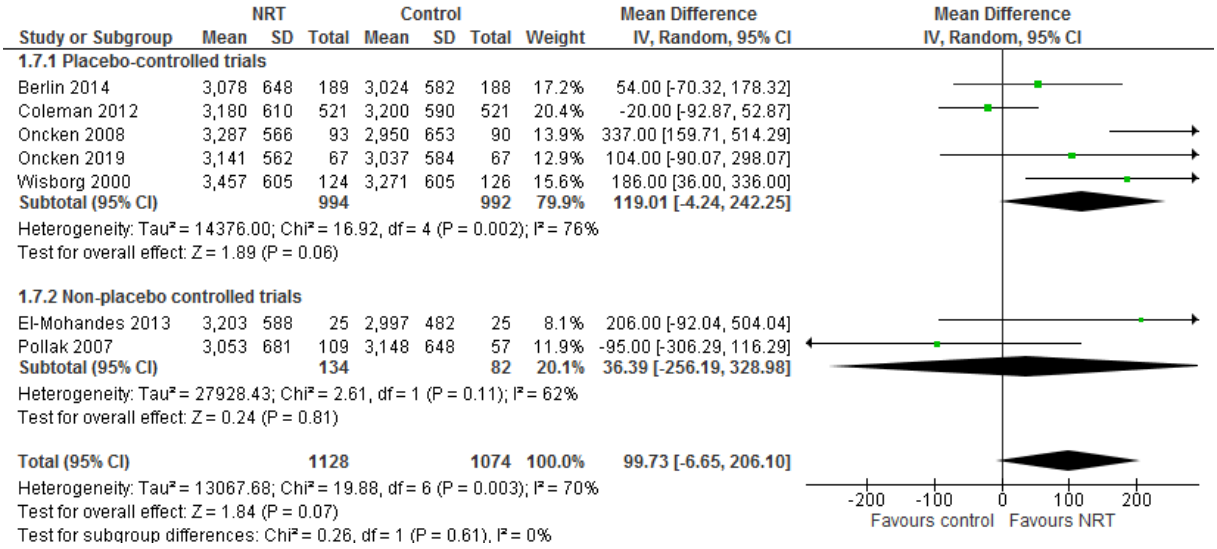


Figure 12: Low birthweight births (< 2500 grams)

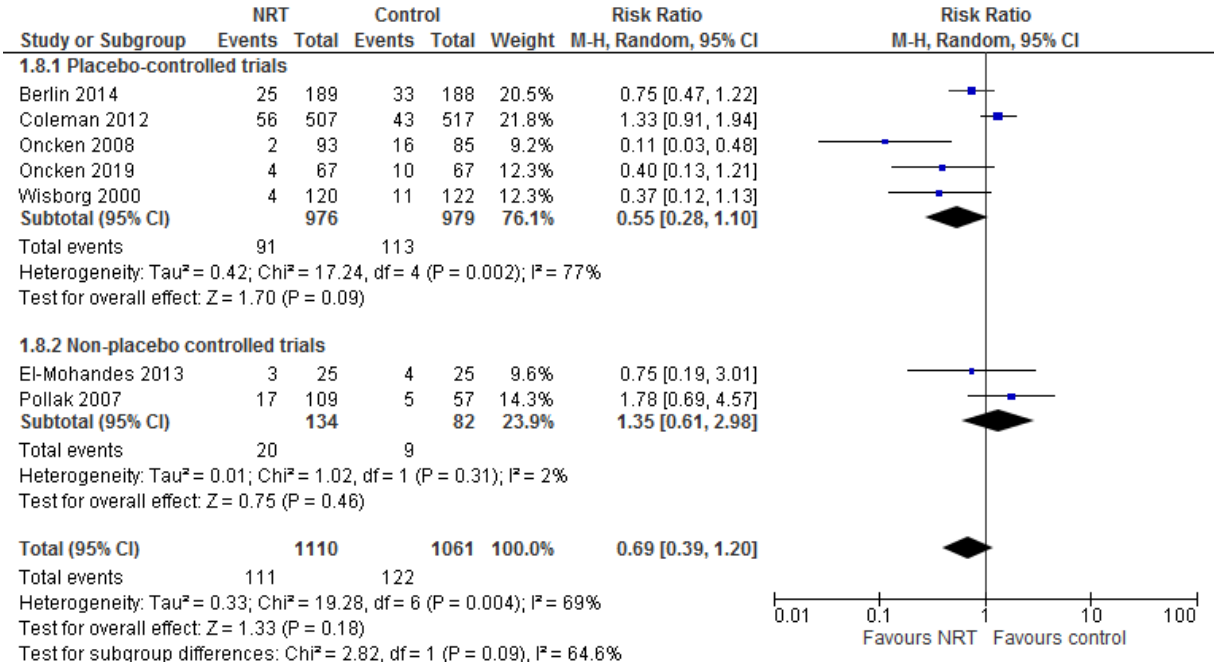


Figure 13: Preterm birth (birth < 37 weeks)

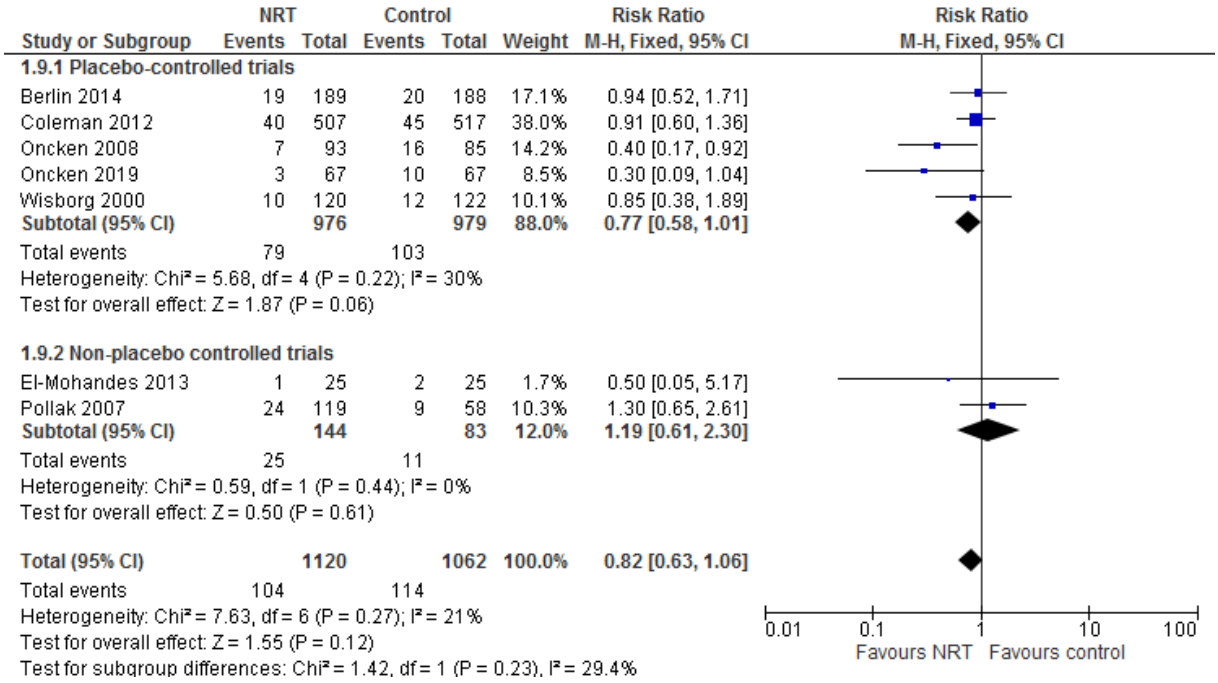


Figure 14: Neonatal intensive care unit admissions

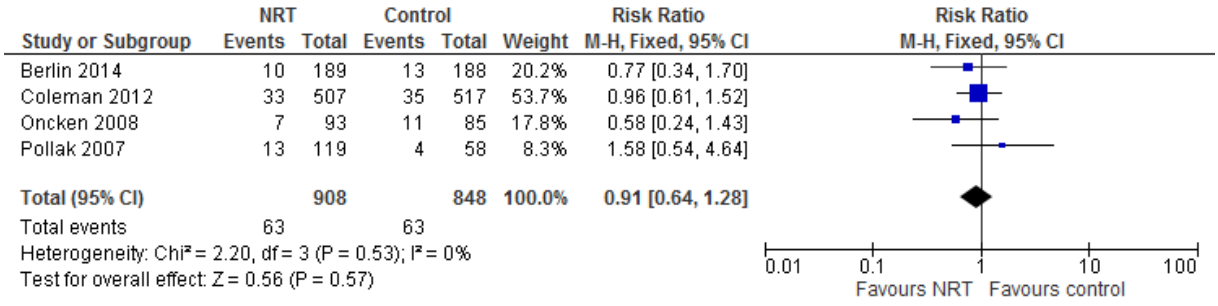


Figure 15: Neonatal death

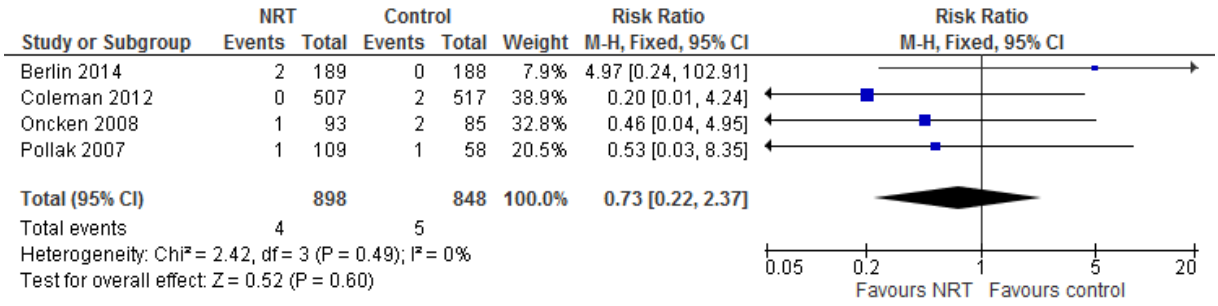
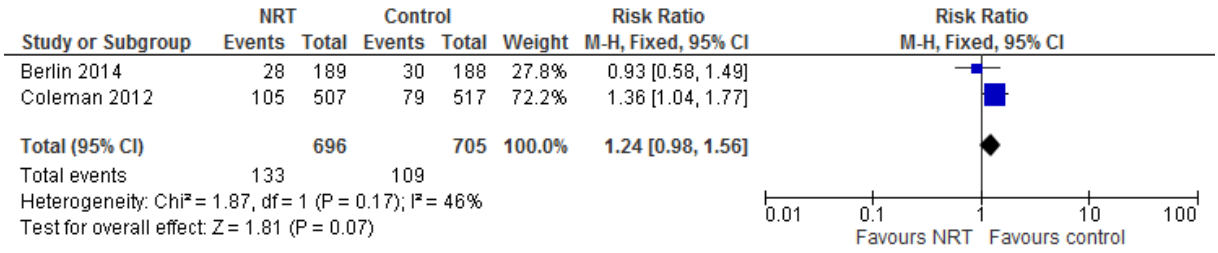


Figure 16: Congenital abnormalities

Figure 17: Caesarean section



Appendix F – GRADE tables

Profile 1: Biochemically validated abstinence from smoking in later pregnancy (subgrouped by comparator type) (Figure 4)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nicotine replacement therapy	Control	Relative (95% CI)	Absolute	
Validated cessation in later pregnancy (subgrouped by comparator type) - Placebo-controlled trials (follow-up 20 weeks[1]; assessed with: biochemically validated)											
6 a-f	randomised trials	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	serious[3]	none	125/1035 (12.1%)	102/1028 (9.9%)	RR 1.21 (0.95 to 1.55)	21 more per 1000 (from 5 fewer to 55 more)	⊕⊕⊕O MODERATE
Validated cessation in later pregnancy (subgrouped by comparator type) - Non placebo-controlled trials (follow-up 20 weeks[1]; assessed with: biochemically validated)											
3 g-i	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25/168 (14.9%)	1/105 (0.95%)	RR 8.55 (2.05 to 35.71)	72 more per 1000 (from 10 more to 331 more)	⊕⊕OO LOW

[1] 20 weeks gestation or more
[2] All studies judged to be at low risk of bias
[3] Confidence interval includes the line of no effect (MID)
[4] All studies judged to be at high risk of bias (participants not blinded to treatment allocation)

Profile 2: Biochemically validated abstinence from smoking in later pregnancy (subgrouped by NRT type) (Figure 5)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nicotine replacement therapy	Control	Relative (95% CI)	Absolute	
Validated cessation in later pregnancy (subgrouped by NRT type) - Long acting-NRT (follow-up 20 weeks[1]; assessed with: biochemically validated)											
7 a-c,g-i,f	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	None	125/1033 (12.1%)	77/972 (7.9%)	RR 1.53 (1.16 to 2.01)	42 more per 1000 (from 13 more to 80 more)	⊕⊕⊕O MODERATE
Validated cessation in later pregnancy (subgrouped by NRT type) - Fast acting-NRT (follow-up 20 weeks[1]; assessed with: biochemically validated)											
2 d-e	randomised trials	no serious risk of bias[3]	no serious inconsistency	no serious indirectness	serious[4]	None	25/170 (14.7%)	26/161 (16.1%)	RR 0.91 (0.55 to 1.51)	15 fewer per 1000 (from 73 fewer to 82 more)	⊕⊕⊕O MODERATE

[1] 20 weeks gestation or more
[2] Three studies judged to be at high risk of bias (participants not blinded to treatment allocation), four studies at low risk of bias
[3] Both studies judged to be at low risk of bias
[4] Confidence interval includes the line of no effect (MID)

Profile 3: Self-reported abstinence from smoking after childbirth (Figure 6 and 7)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nicotine replacement therapy	Control	Relative (95% CI)	Absolute	
Self-report cessation at 3 or 6 months after childbirth											
3 d, f, i	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	61/346 (17.6%)	40/279 (14.3%)	RR 1.22 (0.84 to 1.78)	32 more per 1000 (from 23 fewer to 112 more)	⊕⊕OO LOW
Self-report cessation at 12 months after childbirth											
2 b, f	randomised trials	no serious risk of bias[3]	no serious inconsistency	no serious indirectness	serious[2]	None	74/645 (11.5%)	55/651 (8.4%)	RR 1.35 (0.97 to 1.88)	30 more per 1000 (from 3 fewer to 74 more)	⊕⊕⊕O MODERATE

[1] One study judged to be at high risk of bias (participants not blinded to treatment allocation) and two studies at low risk of bias.
[2] Confidence interval includes the line of no effect (MID)
[3] Both studies judged to be at low risk of bias

Profile 4: Miscarriage and spontaneous abortion (Figure 8)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nicotine replacement therapy	Control	Relative (95% CI)	Absolute	
Miscarriage and spontaneous abortion											
5 a-b,d-e,i	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	None	8/990 (0.81%)	4/926 (0.43%)	RR 1.62 (0.54 to 4.83)	3 more per 1000 (from 2 fewer to 17 more)	⊕⊕OO LOW

[1] Confidence interval crosses both MID thresholds

Profile 5: Stillbirth (Figure 9 and 10)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nicotine replacement therapy	Control	Relative (95% CI)	Absolute	
Stillbirth (randomised controlled trials)											
4 a-b, d, i	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	None	14/920 (1.5%)	10/857 (1.2%)	RR 1.28 (0.57 to 2.85)	3 more per 1000 (from 5 fewer to 22 more)	⊕⊕⊕O MODERATE
Stillbirth (cohort studies)											
2 l-m	cohort studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[1]	None	-	-	RR 0.86 (0.58 to 1.28)	-[3]	⊕OOO VERY LOW

[1] Confidence interval includes the line of no effect (MID)
[2] Concerns about selection bias and bias due to deviation from intended interventions in both studies
[3] Generic inverse variance method used to combine data, calculation of absolute effect not applicable.

Profile 6: Mean birthweight of infant at delivery (grams) (Figure 11)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nicotine replacement therapy	Control	Relative (95% CI)	Absolute	
Mean birthweight (g) (Better indicated by lower values)											
7 a-b, d-f, g, i	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	1128	1074	-	MD 99.73 higher (6.65 lower to 206.1 higher)	⊕⊕⊕O MODERATE

[1] I^2 is over 50%
MID is 0.5*SD of the control group of the study with the largest weight (also the only UK study). SD is 590g, therefore MID is 0 +/- 295g

Profile 7: Low birthweight (subgrouped by comparator) (Figure 12)

Quality assessment	No of patients	Effect	Confidence

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nicotine replacement therapy	Control	Relative (95% CI)	Absolute	
Low birthweight (< 2500 g) - Placebo-controlled trials											
5 a-b, d-f	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	serious[2]	none	91/976 (9.3%)	113/979 (11.5%)	RR 0.55 (0.28 to 1.1)	52 fewer per 1000 (from 83 fewer to 12 more)	⊕OOO VERY LOW
Low birthweight (< 2500 g) - Non-placebo controlled trials											
2 g,i	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	20/134 (14.9%)	9/82 (11%)	RR 1.35 (0.61 to 2.98)	38 more per 1000 (from 43 fewer to 217 more)	⊕⊕OO LOW

[1] I^2 value over 75%
[2] Confidence interval crosses one MID threshold
[3] Confidence interval crosses both MID thresholds

Profile 8: Preterm birth (Figure 13)

Quality assessment							No of patients		Effect		Quality Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nicotine replacement therapy	Control	Relative (95% CI)	Absolute	
Preterm birth (birth < 37 weeks) - Randomised controlled trials											
7 a-b, d-e, f	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	104/1120 (9.3%)	114/1062 (10.7%)	RR 0.82 (0.63 to 1.06)	19 fewer per 1000 (from 40 fewer to 6 more)	⊕⊕⊕O MODERATE
Preterm birth (birth < 37 weeks) - Cohort studies											
1 j	cohort study	very serious[2]	NA	no serious indirectness	no serious imprecision	none	-	-	RR 0.27 (0.17 to 0.41)	-[3]	⊕⊕OO LOW

[1] Confidence interval crosses one MID threshold
[2] Concerns about selection bias and bias due to deviations from interventions.
[3] Study provides adjusted effect estimate, therefore calculation of absolute effect not applicable

Profile 9: Neonatal intensive care unit admissions (Figure 14)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nicotine replacement therapy	Control	Relative (95% CI)	Absolute	
Neonatal intensive care unit admissions											
4 a-b, d, i	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	63/908 (6.9%)	63/848 (7.4%)	RR 0.91 (0.64 to 1.28)	7 fewer per 1000 (from 27 fewer to 21 more)	⊕⊕OO LOW

[1] Confidence interval crosses both MID thresholds

Profile 10: Neonatal death (Figure 15)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nicotine replacement therapy	Control	Relative (95% CI)	Absolute	
Neonatal death											
4 a-b, d, i	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	4/898 (0.45%)	5/848 (0.59%)	RR 0.73 (0.22 to 2.37)	2 fewer per 1000 (from 5 fewer to 8 more)	⊕⊕⊕O MODERATE

[1] Confidence interval includes line of no effect (MID)

Profile 11: Congenital abnormalities (Figure 16)

Quality assessment							No of patients		Effect		Confidence
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nicotine replacement therapy	Control	Relative (95% CI)	Absolute	
Congenital abnormalities (randomised controlled trials)											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	13/696 (1.9%)	18/705 (2.6%)	RR 0.73 (0.36 to 1.48)	7 fewer per 1000 (from 16 fewer to 12 more)	⊕⊕OO LOW

a-b											
Congenital abnormalities (cohort study)											
1 k	cohort study	very serious[2]	NA	no serious indirectness	very serious[1]	none	-	-	RR 1.07 (0.79 to 1.45)	-[3]	⊕OOO VERY LOW

[1] Confidence interval crosses both MID thresholds
[2] Concerns about selection bias, bias in classification of interventions and bias due to deviations from intended interventions
[3] Study provides adjusted effect estimate, therefore calculation of absolute effect not applicable

Profile 12: Caesarean section (Figure 17)

Quality assessment							No of patients		Effect		Confidence
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nicotine replacement therapy**	**Control**	**Relative (95% CI)**	**Absolute**	
Caesarean section											
2 a-b	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	133/696 (19.1%)	109/705 (15.5%)	RR 1.24 (0.98 to 1.56)	37 more per 1000 (from 3 fewer to 87 more)	⊕⊕⊕O MODERATE

[1] Confidence interval crosses one MID threshold

a) Berlin 2014
b) Coleman 2012
c) Kapur 2001
d) Oncken 2008
e) Oncken 2019
f) Wisborg 2000
g) El-Mohandes 2013
h) Hotham 2006
i) Pollak 2007
j) Berard 2016
k) Dhalwani 2015
l) Dhalwani 2019
m) Strandberg-Larsen 2008

GRADE CERQual tables

Summary of review finding	Studies contributing to the review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
Theme 1: Safety concerns about nicotine – Women's beliefs about safety of nicotine-containing products influence their readiness to use it in pregnancy						
1. NRT Women believe that NRT is safer than smoking in general population; they believe NRT contains fewer harmful chemicals than traditional cigarettes.	(Ashwin 2010, Bauld 2017, Bowker 2016, Hotham 2002, Naughton 2013, Taylor 2010)	Minor concerns 2 studies moderate (unclear sampling adequacy, insufficiently described data collection or insufficiently rigorous data analysis) and all 6 studies had some minor issues.	Minor concerns Some opposing cases in two studies	Moderate concerns 6 studies contributed relatively thin data	Minor concerns The majority of the studies are from the UK (5 out of 6 studies) from diverse settings. 1 non-UK study is from Australia.	Moderate confidence Due to moderate concerns regarding adequacy and minor concerns about methodological issues, coherence, and relevance,
Supporting quotations: "*With nicotine patches, you don't get the chemicals like you do with cigarettes - the things that keep the paper burning and the this and the that they chuck in. They [the patches] are actually better for you - you're just getting the nicotine." [Hotham, 2002]*						
2. NRT Women report concerns that NRT can deliver unsafe amount of nicotine, higher than a traditional cigarette, for example because of constant delivery from a patch or from higher dose patches.	(Borland 2013, Bowker 2016, Butterworth 2014, England 2016, Hotham 2002, Naughton 2013, Taylor 2010)	Minor concerns 2 studies with moderate issues relating to data collection and or/analysis and all 7 with minor methodological issues	No or very minor concerns	Moderate concerns 7 studies contributed, but 3 very thin data	Moderate concerns 4 studies out of 7 are from the UK, 3 are non-UK studies (Canada, USA Australia).	Low confidence Due to moderate concerns about adequacy and relevance and minor concerns about methodical issues

Summary of review finding	Studies contributing to the review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
Supporting quotations: "*The patch can give you a nicotine overdose, so it's scary, smoking and wearing it." (Pregnant smoker). [England, 2016]* *"But with the patch you would wear it all day and there's going to be a constant kind of supply of nicotine going to the body, and I just don't like the thought of that (Pregnant woman, smoker)." [Taylor, 2010]*						
3. NRT Women report concerns that using NRT during pregnancy is unsafe for the baby, due to perceived lack of information about nicotine safety for the foetus.	(Ashwin 2010, Bauld 2017, Borland 2013, Bovill 2018, Bowker 2016, Butterworth 2014, England 2016, Glover 2012, Hotham 2002, Naughton 2013, Radley 2013, Taylor 2010)	Minor concerns 4 studies with moderate (unclear sampling procedure, insufficiently described data collection or analysis) and all 12 studies with minor issues.	No or very minor concerns	Minor concerns 5 studies contributed very thin data, but overall rich data from 7 studies	Moderate concerns 7 studies out of 12 are from the UK, others are non-UK studies (Canada, USA Australia, New Zealand).	Moderate confidence Due to moderate concerns about relevance and minor concerns about adequacy and methodological limitations.
Supporting quotations: *"All I was concerned about was um, was the nicotine being released into your blood stream. I was worried about it affecting the baby." [Ashwin, 2010]* *"I don't think there is a lot of information about NRT in pregnancy and I don't think I had a lot of information about that, but that was probably because it doesn't exist yet. Um, but NRT in general I think I had plenty of information on." [Ashwin, 2010]* *"It seems that patches might have a more direct route to your baby . . . I don't know how they really work. It has to go through your bloodstream somehow. . . I don't know enough about them . . . they [patches] are not really tested and the baby is used to me having a cigarette and she's made it this far. I'll leave it at that." [Hotham, 2002]* *"My main concern was obviously 'smoking passes on horrible chemicals to the child, does this [NRT] still do that' and [the smoking cessation advisor] was like 'no, it's just one main one, it's just the nicotine' so I'd have liked to have known a bit more on how that affects the baby." (Patches). [Bowker 2016]* *"I would rather a cigarette than wear a patch because you still pumping the stuff into your blood wearing a patch . . . at the end of the day if you are going to smoke cigarettes that's not going to be any more harmful than having a patch." (Smoker). [Naughton, 2013]*						

Summary of review finding	Studies contributing to the review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
"They say the nicotine is what stunts the baby's growth and things like that, so I think, well if I can stop smoking [without NRT], then what's the point in me putting a patch on." (Pregnant woman; smoker). [Taylor, 2010]						
4. E-cigarettes Women believe that e-cigarettes are safer than smoking in general population; they believe e-cigarettes contain fewer harmful chemicals than traditional cigarettes	(Bauld 2017, Bowker 2018, England 2016, Fallin 2016b, Grant 2018)	Minor concerns 2 studies with moderate (insufficient description of data analysis and/or data collection), all 5 studies minor issues	Moderate concerns Views varied within studies	Minor concerns Overall moderately rich data but some studies contributed very thin data; one study – data from one participant only	Minor concerns 3 studies out of 5 are from the UK, 2 are non-UK studies (USA).	Moderate confidence Due to moderate concerns about coherence minor concerns about relevance, methodological issues and adequacy
Supporting quotations: *"It [EC] doesn't pass on second-hand smoke, because even if the baby was close-by, which I wouldn't have a baby close-by, it wouldn't be dangerous." (Antenatal ex-smoker and current EC user). [Bowker, 2018]* *"I think the idea behind it—is that because it's water vapor you're not getting some of the tar and some of the other things you get out of a regular cigarette." (Pregnant smoker). [England, 2016]* *"It's just vaper, like you have nothing to lose by using their product." [Fallin, 2016]*						
5. E-cigarettes Women report concerns that e-cigarettes can deliver unsafe amounts of nicotine (higher than a traditional cigarette), for example due to the belief that unlike smoking, vaping has no discernable end point.	(Bowker 2018, England 2016, Fallin 2016b)	Minor concerns 2 studies with moderate (insufficient description of data analysis and/or collection) and all 3 with minor issues	Minor concerns Due to opposing cases	Moderate concerns Data from 3 studies only, thin data	Moderate concerns Data from 3 studies, 2 from USA and 1 from the UK, setting unclear in all studies	Very low confidence Due to moderate concerns about relevance and adequacy, and minor concerns about coherence

Summary of review finding	Studies contributing to the review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
						and methodological issues
Supporting quotations: *"Obviously with a cigarette you can only smoke it for so long till it's finished, but with an e-cigarette you can smoke for as long as you want to. So sometimes, I guess, I was taking in more than the usual nicotine intake that I would have done with a cigarette." (Antenatal ex-smoker and ex-EC user). [Bowker, 2018]* *"Lower milligrams of nicotine is better and if you can get the ones without nicotine in it, that's even better." [Fallin, 2016]*						
6. E-cigarettes Women report concerns that using e-cigarettes during pregnancy is unsafe for the baby, due to perceived lack of information about nicotine safety for the foetus.	(Bauld 2017, Bowker 2016, Bowker 2018, Fallin 2016b)	No or very minor concerns	No or very minor concerns	Minor concerns Data from 4 studies, but overall moderately rich	Moderate concerns Data from 4 studies, 1 from USA and 3 from the UK, setting unclear in all studies	Moderate confidence Due to moderate concerns about relevance and minor concerns about adequacy
Supporting quotations: *"(…) I wasn't allowed anything like that during pregnancy because they have not tested things like that properly yet." (Pregnant woman 18, non-smoker). [Bauld, 2017]*						
Theme 2: Concerns about addictiveness of nicotine – women's beliefs about addictiveness of nicotine influence their readiness to use NRT in pregnancy						
7. NRT Women report concerns that NRT is as addictive as smoking	(Ashwin 2010, Bowker 2016, England 2016, Taylor 2010)	Minor concerns 2 studies with moderate	No or very minor concerns	Moderate concerns	Minor concerns Data from 4 studies, 3 from	Moderate confidence Due to moderate concerns about

Summary of review finding	Studies contributing to the review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
		(insufficient description of data analysis and/or collection) and all 4 with minor issues		4 studies contributed, overall thin data	the UK, in similar setting, 1 from USA	adequacy, minor concerns about methodological issues and relevance.
Supporting quotations: *"Well, all they keep saying is you know it gets rid of the toxins, you still get the nicotine but it gets rid of the toxins, this, that and the other and it's just in that the nicotine you take it in. The nicotine itself is what makes it addictive, so to me the more nicotine that you're taking in anyway, the more you're going to want to smoke or you know you're going to need that nicotine."* (Inhalator). *[Bowker, 2016]* *"I didn't want to be on it too long because I was worried about getting addicted to that. And replacing one addiction with another." [Ashwin, 2010]* *"That's why I decided not to do it [use NRT] personally because you're going to give it [smoking] up, you're prolonging the process by having the nicotine still being put into your body ... you have to believe you can cope without." (Pregnant woman; recent quitter). [Taylor, 2010]*						
Theme 3: Beliefs about effectiveness of nicotine-containing products – women's beliefs about the effectiveness of nicotine-containing products influence their use in pregnancy						
8. NRT Women who had positive experience with NRT, or heard from others about positive experiences with NRT being effective, report greater readiness to use it in pregnancy	(Bauld 2017, Bowker 2016, Butterworth 2014, Pledger 2015, Taylor 2010)	Minor concerns 1 study with moderate issues (insufficiently reported data collection and or/analysis) and all 5 with minor issues.	No or very minor concerns	Minor concerns 5 studies contributing overall thin data	No or very minor concerns All studies from the UK	High confidence Due to minor concerns about adequacy and methodological issues
Supporting quotations: "I swore by those, they were really good . . . you don't even think about a fag when you are on a patch." (Pregnant woman, non-smoker). [Bauld, 2017] *"I mean if I'm stressed or anything, if I get a squirt, once I take my squirt [description of inhalator] it's like a relief, I feel calm, I feel relaxed and that's all it is pretty much. …..But that's how you basically feel, you feel calmer, more relaxed."* (Inhalator). [Bowker, 2016]						

Summary of review finding	Studies contributing to the review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
9. NRT Women who had past negative experiences with NRT or heard from others who had negative experiences with NRT being ineffective were reluctant to use NRT in pregnancy.	(Ashwin 2010, Bauld 2017, Bowker 2016, England 2016, Fallin 2016a, Hotham 2002, Mantzari 2012, Pledger 2015, Taylor 2010)	Moderate concerns 6 studies with moderate (insufficiently rigorous description or conduct of data collection and/or analysis) and all 9 with minor	No or very minor concerns	Minor concerns 3 studies contributed very thin data, but overall moderately rich data from all studies	Minor concerns 6 studies out of 9 are from the UK, 3 are non-UK studies (USA, Australia).	Moderate confidence Due to moderate concerns about methodological issues, and minor concerns about adequacy and relevance
Supporting quotations: *"I was really struggling. It [the patch] was stuck but it felt like I was getting no nicotine. And it didn't matter how much I puffed on the inhalator I was just suffering like really bad. So I started smoking over that weekend."* (Patches, inhalator and mouth spray). [Bowker 2016] *"She did say to put them on and take them off before bedtime to give you and baby a rest. I was finding I was waking up and wanting a cigarette so I took it upon myself to leave them on for 24 hours." (Patches). [Bowker, 2016]* *"I keep thinking to myself, I'll be able to quit if I quit the drugs [heroin] and I had medicine to help me get off of drugs [MAT]. The same thing, nicotine patch….and I still can't quit. I still have the desire to smoke." [Fallin, 2016]* *"I don't think that (gum) had anything to do with it. I think it was just willpower and the fact that that, um, my advisor was coming to see me as well." [Ashwin, 2010]*						
10. E-cigarettes Women present mixed views on effectiveness of e-cigarettes	(Bauld 2017, Bowker 2016, Bowker 2018, Grant 2018)	No or very minor concerns	No or very minor concerns	Serious concerns Overall very thin data from 2 studies and limited contributions from 2 studies	No or very minor concerns All studies from the UK	Low confidence Due to serious concerns about adequacy

Summary of review finding	Studies contributing to the review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
Supporting quotations: *"I smoked and then I quit and then I, when I found out I did quit but then I started smoking again when I was pregnant and then I went onto those e-cig fags and then I stopped on that but now I am pregnant again I've started having a few fags again it's like I've got a craving for smoke or something, it's really weird, I'm not a heavy smoker but if I am in the house I'll fancy like a little cig or something you know." [Grant, 2018]*						
Theme 4: Side effects associated with NRT – Women's beliefs about and experiences with side effects of NRT influence their readiness to use NRT in pregnancy						
11. NRT Women report that experiencing and feeling unable to deal with side-effects of NRT is a barrier to using it in pregnancy	(Ashwin 2010, Bauld 2017, Bovill 2018, Bowker 2016, Butterworth 2014, England 2016, Mantzari 2012, Pledger 2015, Taylor 2010)	Moderate concerns 5 studies with moderate (relating to insufficiently rigorous description or conduct of data collection and/or analysis) and all 9 with minor issues	No or very minor concerns	No or very minor concerns	Moderate concerns 7 studies out of 9 are from the UK, 2 are non-UK studies (USA, Australia).	Moderate confidence Due to moderate concerns about methodological issues and relevance.
Supporting quotations: *"Yeah, totally delayed cos I keep saying oh I don't want to taste it yet, I'll give it another ten minutes you know or I'll give it a bit longer. It is delaying it cos you think I'm not looking forward to the taste of it so I'll just wait a bit longer."* (Inhalator). [Bowker 2016] *"I was just more worried about the side effects obviously because I'm quite early on in pregnancy, and especially with morning sickness anyway, I didn't know that it [NRT] would cause – obviously [it] made me feel more nauseous and [I] vomited quite a few times when I had the gum. So just would have been nice to have a heads up about it that it makes you feel sick." (Gum). [Bowker, 2016]*						

Summary of review finding	Studies contributing to the review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
Theme 5: Influence of others – Women's readiness to use nicotine-containing products in pregnancy is influenced by the perceived views of and support from other people						
12. NRT Women report that receiving clear and consistent reassurance from health professionals about NRT safety in pregnancy can facilitate NRT use.	(Ashwin 2010, Bauld 2017, Bowker 2016, Gamble 2015, Hotham 2002, Taylor 2010)	Minor concerns 2 studies with moderate (insufficient reporting and/or conduct of data collection or analysis) and all 6 with minor issues	No or very minor concerns	Minor concerns Some studies contributed very thin data	Minor concerns 4 studies from the UK, but varied settings, 2 studies from Australia	Moderate confidence Due to minor concerns about relevance, methodological issues and adequacy.
Supporting quotations: "*No, I mean I double checked that everything was okay for me to use it while I was pregnant. Yeah. So I thought it didn't concern me, because I had been told it was safe to use." [Ashwin, 2010]* *"I made doubly sure. I was like 'they are safe?' and she goes, 'I wouldn't be prescribing them to you if they weren't safe in pregnancy." (Pregnant woman, smoker). [Bauld, 2017]* *"I would try, as long as you could convince me it was safe. Have a discussion on it - how it affects the baby - what patches do - the positives and negatives about them. . ." [Hotham, 2002]*						
13. NRT Women report that experiencing lack of support towards NRT use in pregnancy from health professionals is a barrier to NRT use	(Borland 2013, Bovill 2018, Bowker 2016, Gamble 2015, Glover 2012, Hauck 2013, Herbec 2014, Hotham 2002, Mantzari 2012,	Moderate concerns 7 studies with moderate (insufficient reporting and/or conduct of data collection or	No or very minor concerns	No or very minor concerns	Moderate concerns 5 studies out of 11 are from the UK, 6 non-UK studies (Canada, New	Low confidence Due to moderate concerns about relevance and moderate concerns about

Summary of review finding	Studies contributing to the review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
	Pledger 2015, Taylor 2010)	analysis; findings insufficiently substantiated by the data), all 11 studies with minor issues.			Zealand, Australia).	methodological issues.
Supporting quotations: "*I said to her, erm, er, yeah about me being pregnant and still carrying the lozenges she's like "Yeah." I said I've got patches at home can I still use them, like can I start on them again rather than give me more, they're from last year they're still in date though? And she said, "I've never dealt with a pregnant woman before." (Control group). [Mantzari, 2012]* *"They told me here not to do that and they wouldn't give me the patch because I was pregnant." (Postpartum woman). [Borland, 2013]* *"I can remember the conversation we had about it and [the smoking cessation advisor] was letting me know where I can put [the patches] and what not, but to myself I just thought no, that's just a bit too – you know you sit there thinking about it. I don't know, it's weird, I just think it's too close to the baby to be having all that nicotine going in." (Patches). [This participant was not convinced about the safety of using her nicotine patch even after being advised about this; she decided to revert back to smoking as she felt that the harms of using her patch on her lower back would be too dangerous for her baby. Bowker, 2016]* *"They say "do you want to quit smoking?" and you tell them you do but it's like "we'll encourage you to but we're not going to properly support you to do it." [Bovill, 2018]* *"…she gave me the patch where I wanted the highest patch that I could have because I've been smoking 20 24/7, they actually told me the most I could have was a 20 mg patch, which now I've been told by the midwife that's not true .... The patch didn't seem to be working. And then when I told my midwife it didn't work and she said it was, erm, that I could have more than a 20 mg patch. (…) I wouldn't be smoking now if the pharmacist had given me the right amount." (Control group). [Mantzari, 2012]*					
<u>14. NRT</u> Women feel discouraged from NRT use in pregnancy by the perceived views and experiences of other people (non-health-professionals)	(Bovill 2018, England 2016, Hotham 2002, Taylor 2010)	Minor concerns 2 studies with moderate issues relating to data collection and or/analysis and all 4 with minor	No or very minor concerns	Moderate concerns Most data from 1 study, supported by the other 3 (fairly thin data)	Moderate concerns 1 out of 4 studies is from the UK, 3 are non-UK studies (USA, Australia).	Low confidence Due to serious concerns about relevance, moderate concerns about adequacy and minor concerns about

Summary of review finding	Studies contributing to the review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
		methodological issues				methodological issues.
Supporting quotations: "*Everyone I know that has quit smoking has just gone cold turkey, like they haven't used anything." [Bovill, 2018]* *"[I wouldn't want to use NRT] from stories that I've heard off other people nightmares and hot sweats and things like that." (Pregnant woman; recent quitter). [Taylor, 2010]* *"Yes, my family would approve [of me using NRT], definitely." (Pregnant woman; recent quitter). [Taylor, 2010]* *"They see you walking street and you've got that thing in your mouth [inhalator], they'll think, 'hold on a minute, that's not good, she's not allowed to do that, you'd proper get some weird looks... I don't care what people think." (Pregnant woman; smoker). [Taylor, 2010]*						
<u>15. E-cigarettes</u> Women's readiness to use e-cigarettes in pregnancy is influenced by the advice they report receiving from health professionals.	(Bauld 2017, Bowker 2016, Bowker 2018, Fallin 2016b, Grant 2018)	No or very minor concerns	Moderate concerns Some opposing cases where women did not follow health professional's advice	No or very minor concerns	Minor concerns 4 studies out of 5 are from the UK, 1 non-UK studies (USA), context unclear in some	Moderate confidence Due to moderate concerns about coherence and minor concerns about relevance.
Supporting quotations: *"[I tried] an e-cig[arette] which was really good . . . It's good to have this you know the smoke coming out and going through all the motions, but I wasn't allowed anything like that during pregnancy because they have not tested things like that properly yet." (P*regnant woman, non-smoker). [Bauld, 2017] *"Yeah and I think obviously if there was some sort of government stamp on it or you know you don't buy toys without having something, you don't buy anything without, even the bad stuff you know, you buy a packet of cigarettes and the government have put what it can do to you on it, with all the pictures. Whereas there's nothing is there? There's no nothing, no good, no bad, no nothing." (Antenatal smoker and never user) [Bowker, 2018]* *"The doctors and the health visitors all say: 'Are you going to cut down?' And I say: 'No, I don't think it's harming my child' so I am happy to stay on them and that's it really . . . it hasn't got any of the harmful chemicals like tar and all you know . . . it's my decision and I'm happy with this like you know? (…)" [Grant, 2018]*						

Summary of review finding	Studies contributing to the review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
"*And then I completely just quit and picked up the e-cig and worked with it while I was kind of pregnant but I was kind of scared but I talked to my doctor about it and they said it was fine you know so." [Fallin, 2016]*						
16. E-cigarettes Women's readiness to use e-cigarettes in pregnancy is influenced by other people (non-health-professionals)	(Bauld 2017, Bowker 2018, Grant 2018)	No or very minor concerns	No or very minor concerns	Moderate concerns Very thin data from small number of studies	No or very minor concerns All studies from the UK	Moderate confidence Due to moderate concerns about adequacy
Supporting quotations: "*They [family] were a lot happier about me using that [EC] than obviously smoking. My Mum actually bought me the e-cigarette and she never ever bought me cigarettes in my life." (Antenatal smoker and current EC user). [Bowker, 2018]* *"And I smoke my e-cig and some people might not, not that that bothers me at all, but they might look at me and like judge but it doesn't bother me but it's still a factor in the pregnancy." [Grant, 2018]*						
Theme 6: Characteristics of nicotine-containing products – women's views on characteristics of the nicotine-containing products can influence their readiness to use these in pregnancy						
17. NRT Perceived characteristics of the NRT product, such as cost, convenience, ability to mimic a cigarette can influence uptake and continuous use of NRT in pregnancy	(Ashwin 2010, Bauld 2017, Bowker 2016, Bowker 2018, Butterworth 2014, England 2016, Fallin 2016a, Fallin 2016b, Hotham 2002, Pledger 2015,	Moderate concerns 6 studies with moderate issues relating to data collection and or/analysis and all 12 with minor methodological issues	No or very minor concerns	No or very minor concerns	Minor concerns 8 studies out of 12 are from the UK, 4 are non-UK studies (USA, Australia).	Moderate confidence Due to minor concerns about relevance and methodological issues.

Summary of review finding	Studies contributing to the review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
	Radley 2013, Taylor 2010)					
Supporting quotations: "*I don't know what to do with my hands when I'm not smoking – so that's why I used the inhaler [inhalator] because it's something in my hands and it can help – feels like I'm smoking a fag [cigarette] kind of thing." (Inhalator) [Bowker, 2016]* *"The hands thing. You're going to the pub. You're still getting your nicotine, but with your coffee? It's the hands." (About patches) [Hotham, 2002]*						
<u>18. E-cigarettes</u> Perceived characteristics of e-cigarettes, such as cost, convenience, ability to mimic a cigarette can influence uptake and continuous use of e-cigarettes in pregnancy	(Bauld 2017, Bowker 2018, Butterworth 2014, England 2016, Fallin 2016b)	Minor concerns 2 studies with moderate (relating to reporting or conduct of data collection and/or analysis) and all 4 studies with minor issues	No or very minor concerns	Minor concerns Overall moderately rich data, but from four studies only.	Moderate concerns 3 studies out of 5 are from the UK, 2 non-UK studies (Canada, USA), setting often unclear	Moderate confidence Due to moderate concerns about relevance, minor concerns about methodological issues and adequacy
Supporting quotations: "*Today, I feel like a menthol, tomorrow I'll feel like strawberry, the next day I feel like unicorn." [Fallin, 2016b]* *"I had one of them e-cig[arette] things you know the ones with the oil, and it lasted 3 weeks and then I got rid of it because it was rubbish to be fair. It was, you had to charge it all the time and then you had to buy the fluid and then it just ended up costing like the same amount as regular cigarettes. It was – there was no point." (Pregnant woman, smoker) [Bauld, 2016]* *"[I tried] an e-cig[arette] which was really good . . . It's good to have this you know the smoke coming out and going through all the motions." [Bauld, 2017b]* *"I think not smoking at all was less frustrating than trying to get the satisfaction of a real cigarette from an e-cigarette." [Fallin, 2016b]* *"One thing I missed when I have quit smoking is inhaling the smoke, so when I used an e-cigarette obviously you've got that kind of experience of inhaling the vapour. It was too much, it was too similar to having a cigarette, so it made me miss it even more." (Antenatal ex-smoker and ex-EC user) [Bowker, 2018]*						

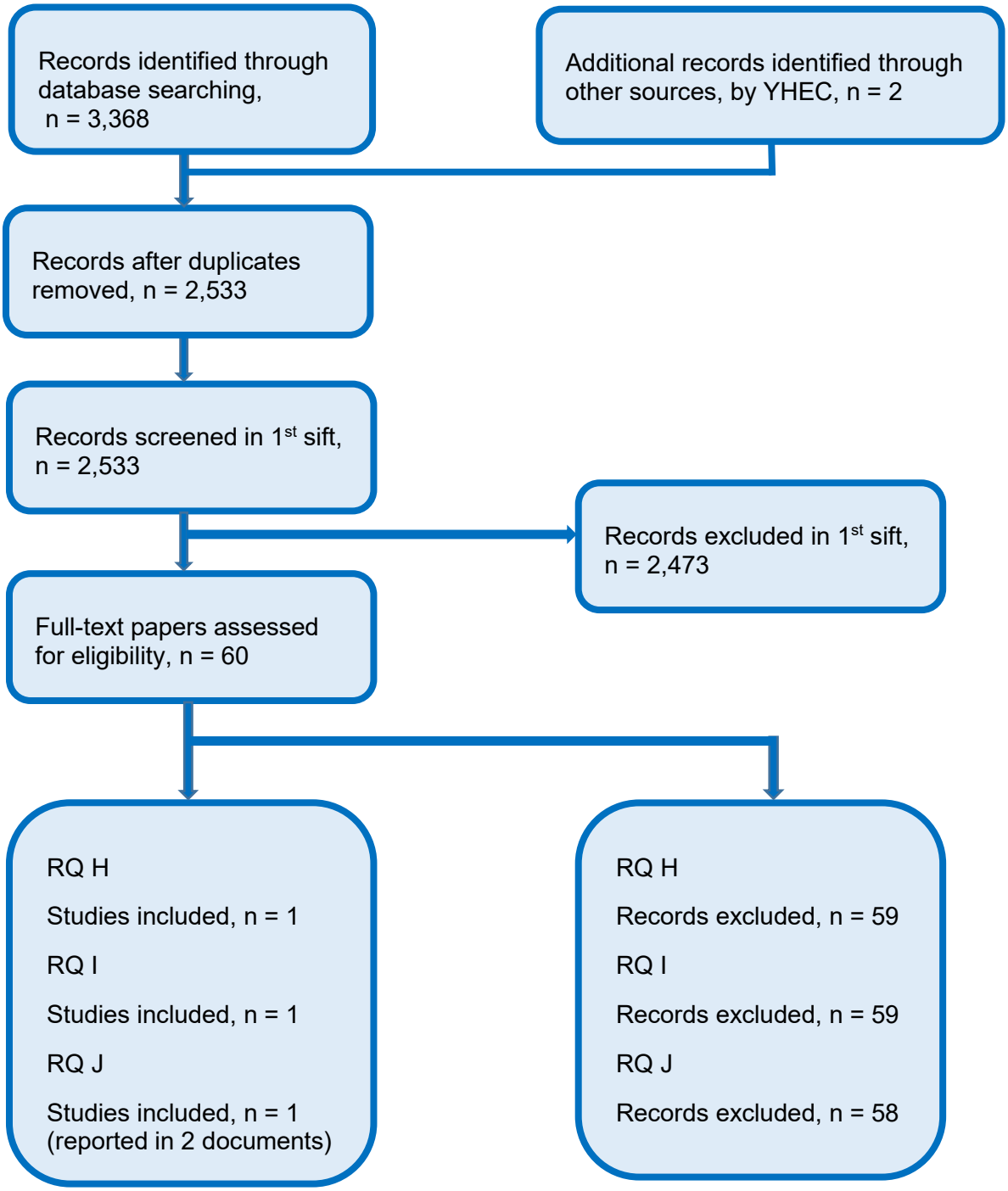
Matrix for integration of qualitative and effectiveness evidence

Quantitative outcomes	Related GRADE profile	Narrative exploration of qualitative review findings in relation to outcome
Abstinence from smoking during pregnancy (NRT products)	Profiles 1 and 2	The effectiveness of NRT with behavioural support at increasing abstinence from smoking could be due to several of the qualitative review findings which included **some** women reporting: • Intrinsic belief that using NRT is safer than cigarette smoking due to delivering nicotine only and not known harmful substances contained in tobacco smoke • Increased motivation to use NRT during pregnancy due to either positive personal or family/peer experiences of using NRT to help quit smoking, including in never users. • Initiating NRT use during pregnancy due to clear and consistent reassurance from health professionals about NRT safety in the antenatal period. • Positive perception of NRT products in relation to the design, ease of use and ability to substitute behaviours associated with smoking cigarettes (hand to mouth action) • NRT patches being positively perceived as visually least likely to remind them of cigarettes. However, the studies do not include sufficient information to determine whether these findings are explicitly linked to the evidence identified for this outcome.

Appendix G – Economic evidence study selection

The following flowchart shows the record selection process for all three review questions.

Flow chart of economic evidence study selection for the guideline



Appendix H – Economic evidence tables

Study	Cooper 2014 & Essex 2015 (UK)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: Cost-effectiveness analysis (CEA) **Study design:** RCT (smoking, nicotine, and pregnancy (SNAP) trial) with costs and resource use collected alongside the trial **Approach to analysis:** Quit rates, resource use and birth outcomes were taken from the RCT. Costs were drawn from the trial and from published sources. EQ-5D was collected at baseline and 6 months. **Perspective:** NHS **Time horizon:** To discharge after birth **Treatment effect duration:** Not applicable – a limited time horizon was used **Discounting:** Not applicable	**Population:** Women aged 16 to 50 years who were 12 to 24 weeks pregnant and smoking at least 10 cigarettes a day before pregnancy and at least 5 a day whilst pregnant. Exhaled carbon monoxide (CO) readings had to be at least 8 ppm. Sample size: 1,050 **Intervention:** NRT + behavioural support: • 4 week NRT supply of 15mg per 16 hours. NRT patches, issued on date women quit smoking • NRT was renewed at 4 weeks, if patients non-smoking status was validated by a CO measurement • Behavioural support: 1 hour face to face	**Mean intervention costs per participant (SD)** NRT + behavioural support: £98.31 (£35.21) Placebo + behavioural support: £47.75 (£19.03) **Mean total costs per participant (standard deviation (SD))** NRT + behavioural support: £2,669.87 (£2,394.09) Placebo + behavioural support: £2,579.06 (£2,385.68) **Cost savings** None reported **Currency & cost year:** £; Cost year not clear (a mix of sources with dates from 2010 to 2013) **Cost components incorporated:** Direct costs: Cessation support, CO monitoring,	**Verified quit rate at birth**: NRT + behavioural support: 9.4% Placebo + behavioural support: 7.6% **EQ-5D index at 6 months**: NRT + behavioural support: 0.896 Placebo + behavioural support: 0.894	**Cost effectiveness ratios** Incremental quit rate was 1.8% which was not statistically significant [b]. ICER, per verified quitter: £4,926 QALYs were not calculated as there was no statistical difference in the EQ-5D. A long term model was considered, but as there was no statistical difference in birth or maternal outcomes, costs, the quit rate or EQ-5D this was not undertaken. **Analysis of uncertainty** PSA undertaken by bootstrapping trial results with a bootstrapped ICER of -£114,128 to £126,747 highlighting the uncertainty in the results [c]. Scenario analysis of singleton births, ICER: £4,156 per quitter

Study	Cooper 2014 & Essex 2015 (UK)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
	session with midwife at enrolment • Women received a 15-page manual • A further 3 behavioural support sessions from local NHS stop smoking services, over the course of pregnancy was offered as well as telephone behavioural support **Comparator:** Placebo + behavioural support: same as the intervention, but with placebo patches [a]	NRT and incentives, antenatal hospital admission, birth including neonatal unit costs.		
Data sources				
Health outcomes: RCT (SNAP trial) (Coleman et al 2012). **Quality-of-life weights:** RCT (SNAP trial). **Cost sources:** Costs were taken directly from the SNAP trial and from published sources.				
Comments				
Source of funding: NIHR. **Limitations:** Compliance rates were very low (7.2% in NRT group and 2.8% in the placebo group); a difference in QALYs with the intervention was not identified; the time horizon was only 7 months. **Other:** None				
Overall applicability: Directly applicable **Overall quality:** No limitations				
Abbreviations: CEA: cost-effectiveness analysis; CO: carbon monoxide; EQ-5D: EuroQoL five dimensions; ICER: Incremental Cost Effectiveness Ratio; NHS: National Health Service; NIHR: National Institute for Health Research; NRT: nicotine replacement therapy; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; RCT: randomised controlled trial; SNAP: smoking, nicotine and pregnancy				
a) Uptake of behavioural support services were slightly higher in the NRT + behavioural support arm due to higher self-reported quit rates at 4-weeks resulting in additional home visitation for CO monitoring and a face-to-face support session. Overall mean costs of behavioural support and CO monitoring were similar across both arms: NRT + behavioural support £52.25; Placebo + behavioural support £47.75.				

Study	Cooper 2014 & Essex 2015 (UK)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
b) *The incremental effect of NRT + behavioural support is lower than observed in previous NICE reviews for the general population. Effect sizes may be lower as general population studies tend to compare NRT + behavioural support to treatment as usual, rather than a placebo patch (with additional behavioural support). A similar study in the general population by Lewis (1998) identified similar absolute cessation rates equal to 4.9% (no intervention), 6.5% (placebo patch + support), and 9.7% (nicotine patch + support). Incremental effects might be lower as the patch may be the least effective form of NRT. Compliance rates are unlikely to explain incremental effect sizes as these were lower in the placebo + behavioural support arm.*				
c) *Cost-effectiveness plane illustrates incremental effects predominantly between (-3% and 5%) and costs between (-£700 and £1,000).*				

Appendix I – Health economic evidence profiles

See Appendix H

Appendix J – Health economic analysis

See separate full modelling report (evidence review P)

Appendix K – Excluded studies

Public health studies

Table 8: Studies excluded from Claire 2020

Study Citation	Reason for excluding
Eades 2012 * Eades SJ, Sanson-Fisher RW, Wenitong M, Panaretto K, D'Este C, Gilligan C, et al. An intensive smoking intervention for pregnant Aboriginal and Torres Strait Islander women: a randomised controlled trial. Medical Journal of Australia 2012;197(1):42- Gilligan C. A pilot randomised controlled trial to test the effectiveness of an intervention to help Aboriginal and Torres Strait Islander women to quit smoking during pregnancy: study design and preliminary results [thesis]. Newcastle, Australia: University of Newcastle 2008	Study was quasi-randomised. NRT was offered as part of a multi-modal intervention which offered more behavioural support (in addition to the NRT) to participants in the intervention group. NRT provision was conditional on 2 failed quit attempts after receiving behavioural components of the intervention.
Gould 2019 * Gould GS, Bovill M, Pollock L, Bonevski B, Gruppetta M, Atkins L, et al. Feasibility and acceptability of Indigenous Counselling and Nicotine (ICAN) QUIT in Pregnancy multicomponent implementation intervention and study design for Australian Indigenous pregnant women: a pilot cluster randomised step-wedge trial. Addictive behaviors 2019;90:176-90. Bar-Zeev Y, Bonevski B, Bovill M, Gruppetta M, Oldmeadow C, Palazzi K, et al. The Indigenous Counselling and Nicotine (ICAN) QUIT in Pregnancy Pilot Study protocol: a feasibility step-wedge cluster randomised trial to improve health providers' management of smoking during pregnancy. BMJ open 2017;7(8):e016095.	Study offered NRT as part of multi-modal intervention.
Hegaard 2003 Hegaard HK, Kjaergaard H, Moller LF, Wachmann H, Ottesen B. Multimodal intervention raises smoking cessation rate during pregnancy. Acta Obstetricia et Gynecologica Scandinavica 2003;82(9):813-9.	Study included quasi-random allocation/sequence generation of participants. NRT was offered as part of multi-modal intervention and differed between groups. Intervention group did not have to agree to use NRT. Smoking outcomes were not reported within the subgroup of those using NRT.
NCT00744913 **Published data only (unpublished sought but not used) [ClinicalTrials.gov: NCT00744913]** NCT00744913. Study of Nicotine Replacement Therapy in Pregnancy [Randomized, Controlled Open-Label Study of Nicotine Replacement Therapy in Pregnancy].	Study withdrawn due to problems with recruitment.

clinicaltrials.gov/show/NCT00744913 (first received 1 September 2008).	
NCT00888979 NCT00888979. Pilot Study of Nicotine Replacement for Smoking Cessation During Pregnancy. clinicaltrials.gov/show/NCT00888979 (first received 28 April 2009).	Study is non-randomised
Oncken 2009a Oncken C, Campbell W, Chan G, Hatsukami D, Kranzler HR. Effects of nicotine patch or nasal spray on nicotine and cotinine concentrations in pregnant smokers. Journal of Maternal-Fetal and Neonatal Medicine 2009;22(9):751-8.	Study is non-randomised

Table 9: Studies excluded from search for cohort studies relevant to safety outcomes

Study Citation	Reason for excluding
Coleman T (2007) Recommendations for the use of pharmacological smoking cessation strategies in pregnant women. Cns Drugs 21(12), 983-993	**Exclude on evidence;** study is a systematic review
Forinash Alicia B, Pitlick Jamie M, Clark Kylie, and Alstat Valerie (2010) Nicotine replacement therapy effect on pregnancy outcomes. The Annals of pharmacotherapy 44(11), 1817-21	**Exclude on evidence;** study is a systematic review
Lancaster T (2014) In pregnant smokers, the nicotine patch did not increase abstinence or birthweight more than placebo. Annals of Internal Medicine 160(12), JC11	**Exclude on evidence;** study is an abstract for an RCT included in Cochrane review (Claire 2020)
Lassen Tina H, Madsen Mia, Skovgaard Lene T, Strandberg-Larsen Katrine, Olsen Jorn, and Andersen Anne-Marie N (2010) Maternal use of nicotine replacement therapy during pregnancy and offspring birthweight: a study within the Danish National Birth Cohort. Paediatric and perinatal epidemiology 24(3), 272-81	**Exclude on target group;** NRT users include non-smokers
Lee P N, and Fariss M W (2017) A systematic review of possible serious adverse health effects of nicotine replacement therapy. Archives of Toxicology 91(4), 1565-1594	**Exclude on evidence;** study is a systematic review
Morales-Suarez-Varela Maria M, Bille Camilla, Christensen Kaare, and Olsen Jorn (2006) Smoking habits, nicotine use, and congenital malformations. Obstetrics and gynecology 107(1), 51-7	**Exclude on target group**; study reports on outcomes in non-smokers using NRT
Oncken C A, and Kranzler H R (2009) What do we know about the role of pharmacotherapy for smoking cessation before or during pregnancy?. Nicotine & Tobacco Research 11(11), 1265-1273	**Exclude on evidence;** study is a systematic review
Seshadri Srividya, Oakeshott Pippa, Nelson-Piercy Catherine, and Chappell Lucy C (2012) Prepregnancy care. BMJ : British Medical Journal (Online) 344,	**Exclude on evidence;** study is a clinical review

Table 10: Studies excluded from Campbell 2019

Study Citation	Reason for excluding
Anderson RH. Making the sale: communicating the importance of smoking cessation to pregnant patients. *The West Virginia medical journal*. 2002;98:18-21.	Not about NRT or e-cigarettes

Ashford K. Successful postpartum smoking abstinence. *Southern Online Journal of Nursing Research*. 2008;8:1p-p.	No full text available
Ashford K, Hahn E, Hall L, Peden AR, Rayens MK. Postpartum smoking abstinence and smoke-free environments. *Health Promotion Practice*. 2011;12:126-34.	Not about NRT or e-cigarettes
Askew DA, Guy J, Lyall V, Egert S, Rogers L, Pokino LA, et al. A mixed methods exploratory study tackling smoking during pregnancy in an urban Aboriginal and Torres Strait Islander primary health care service. *Bmc Public Health*. 2019;19.	Not about NRT or e-cigarettes
Balwicki L, Smith DM, Pierucka M, Goniewicz ML, Zarzeczna-Baran M, Jedrzejczyk T, et al. Factors Associated With Quitting Among Smoking Pregnant Women From Small Town and Rural Areas in Poland. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*. 2017;19:647-51.	Not a qualitative study
Bottorff JL, Kalaw C, Johnson JL, Stewart M, Greaves L, Carey J. Couple dynamics during women's tobacco reduction in pregnancy and postpartum. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*. 2006;8:499-509.	Not about NRT or e-cigarettes
Britton GR, Collier R, McKitrick S, Sprague LM, Rhodes-Keefe J, Feeney A, et al. CE: Original Research: The Experiences of Pregnant Smokers and Their Providers. *The American journal of nursing*. 2017;117:24-34.	Not about NRT or e-cigarettes
Bryce A, Butler C, Gnich W, Sheehy C, Tappin DM. CATCH: development of a home-based midwifery intervention to support young pregnant smokers to quit. *Midwifery*. 2009;25:473-82.	Not about NRT or e-cigarettes
Bull L, Burke R, Walsh S, Whitehead E. Social attitudes towards smoking in pregnancy in East Surrey: a qualitative study of smokers, former smokers and non-smokers. *Journal of Neonatal Nursing*. 2007;13:100-6.	Ineligible patient population
Bull L, Burke R, Walsh S, Whitehead E. The perceived effectiveness of smoking cessation interventions aimed at pregnant women: a qualitative study of smokers, former smokers and non-smokers. *Journal of Neonatal Nursing*. 2008;14:72-8.	Not about NRT or e-cigarettes
Colomar M, Tong VT, Morello P, Farr SL, Lawsin C, Dietz PM, et al. Barriers and promoters of an evidenced-based smoking cessation counseling during prenatal care in Argentina and Uruguay. *Maternal and child health journal*. 2015;19:1481-9.	Not about NRT or e-cigarettes
Constantine NA, Slater JK, Carroll JA, Antin TMJ. Smoking cessation, maintenance, and relapse experiences among pregnant and postpartum adolescents: a qualitative analysis. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine*. 2014;55:216-21.	Not about NRT or e-cigarettes
Cottrell L, Gibson M, Harris C, Rai A, Sobhan S, Berry T, et al. Examining smoking and cessation during pregnancy among an Appalachian sample: A preliminary view. *Substance Abuse Treatment, Prevention, and Policy*. 2007;2.	Not about NRT or e-cigarettes
Davidson-Harden J. Predicting smoking behaviour among pregnant smokers using the reasons model and self-determination theory. *Dissertation Abstracts International: Section B: The Sciences and Engineering*. 2009;69:7126.	Not a qualitative study
Edwards N, Sims-Jones N. Smoking and smoking relapse during pregnancy and postpartum: results of a qualitative study. *Birth (Berkeley, Calif)*. 1998;25:94-100.	Not about NRT or e-cigarettes
Gillam S. Expecting to quit: An implementation evaluation of a smoking cessation intervention for pregnant and parenting women: McGill University (Canada); 2009.	Not about NRT or e-cigarettes

Glover M, Nosa V, Gentles D, Watson D, Paynter J. Do New Zealand Maori and Pacific 'walk the talk' when it comes to stopping smoking? A qualitative study of motivation to quit. *Journal of Smoking Cessation*. 2014;9:68-75.	Ineligible patient population
Goszczynska E, Knol-Michalowska K, Petrykowska A. How do pregnant women justify smoking? A qualitative study with implications for nurses' and midwives' anti-tobacco interventions. *Journal of Advanced Nursing*. 2016;72:1567-78.	Not about NRT or e-cigarettes
Gould GS, Bar-Zeev Y, Bovill M, Atkins L, Gruppetta M, Clarke MJ, et al. Designing an implementation intervention with the Behaviour Change Wheel for health provider smoking cessation care for Australian Indigenous pregnant women. *Implementation science : IS*. 2017a;12:114.	Not a qualitative study
Gould GS, Bovill M, Clarke MJ, Gruppetta M, Cadet-James Y, Bonevski B. Chronological narratives from smoking initiation through to pregnancy of Indigenous Australian women: A qualitative study. *Midwifery*. 2017b;52:27-33.	Not about NRT or e-cigarettes
Gould GS, Munn J, Avuri S, Hoff S, Cadet-James Y, McEwen A, et al. "Nobody smokes in the house if there's a new baby in it": Aboriginal perspectives on tobacco smoking in pregnancy and in the household in regional NSW Australia. *Women and birth : journal of the Australian College of Midwives*. 2013;26:246-53.	Not about NRT or e-cigarettes in pregnancy
Griffis H, Matone M, Kellom K, Concors E, Quarshie W, French B, et al. Home visiting and perinatal smoking: a mixed-methods exploration of cessation and harm reduction strategies. *BMC public health*. 2016;16:764.	Not about NRT or e-cigarettes
Haslam C, Draper ES. A qualitative study of smoking during pregnancy. *Psychology, Health & Medicine*. 2001;6:95-9.	Not about NRT or e-cigarettes
Herberts C, Sykes C. Midwives' perceptions of providing stop-smoking advice and pregnant smokers' perceptions of stop-smoking services within the same deprived area of London. *Journal of Midwifery & Women's Health*. 2012;57:67-73.	Not about NRT or e-cigarettes
Hoek J, Gifford H, Maubach N, Newcombe R. A qualitative analysis of messages to promote smoking cessation among pregnant women. *BMJ open*. 2014;4:e006716.	Not about NRT or e-cigarettes
Homish GG, Eiden RD, Leonard KE, Kozlowski LT. Social-environmental factors related to prenatal smoking. *Addictive behaviors*. 2012;37:73-7.	Not a qualitative study
Hotham ED, Gilbert AL, Atkinson ER. Case studies of three pregnant smokers and their use of nicotine replacement therapy. *Midwifery*. 2005;21:224-32.	Ineligible study design
Howard LM, Bekele D, Rowe M, Demilew J, Bewley S, Marteau TM. Smoking cessation in pregnant women with mental disorders: a cohort and nested qualitative study. *BJOG : an international journal of obstetrics and gynaecology*. 2013;120:362-70.	Not about NRT or e-cigarettes
Kahr MK, Padgett S, Shope CD, Griffin EN, Xie SS, Gonzalez PJ, et al. A qualitative assessment of the perceived risks of electronic cigarette and hookah use in pregnancy. *BMC public health*. 2015;15:1273.	Ineligible patient population
Kennison LH. Smoking and pregnancy: reconciling incompatibilities: University of Florida; 2003.	Not about NRT or e-cigarettes
Koshy P, Mackenzie M, Tappin D, Bauld L. Smoking cessation during pregnancy: the influence of partners, family and friends on quitters and non-quitters. *Health & social care in the community*. 2010;18:500-10.	Not about NRT or e-cigarettes
Lawson EJ. Smoking and smoking cessation among low-income pregnant adolescents. *Dissertation Abstracts International*. 1991;51:3226.	No full text available

Lowry RJ, Hardy S, Jordan C, Wayman G. Using social marketing to increase recruitment of pregnant smokers to smoking cessation service: a success story. *Public health*. 2004;118:239-43.	Not about NRT or e-cigarettes
Mann R, Faflik F. Survey of smoking cessation services and pregnant women's views on use of electronic cigarettes in pregnancy. *Journal of Health Visiting*. 2018;6:32-9.	Not a qualitative study
Maubach N, Hoek JA, Edwards R, Gifford H, Erick S, Newcombe R. 'The times are changing': New Zealand smokers' perceptions of the tobacco endgame. *Tobacco Control: An International Journal*. 2013;22:395-400.	Not about NRT or e-cigarettes
McCurry N, Thompson K, Parahoo K, O'Doherty E, Doherty A. Pregnant women's perception of the implementation of smoking cessation advice. *Health Education Journal*. 2002;61:20-31.	Not about NRT or e-cigarettes
McLeod D, Benn C, Pullon S, Viccars A, White S, Cookson T, et al. The midwife's role in facilitating smoking behaviour change during pregnancy. *Midwifery*. 2003;19:285-97.	Not about NRT or e-cigarettes
Modeste N, Lee J, Lim VJ, Anjejo D. Factors associated with intention to quit smoking among African American pregnant women. *Californian Journal of Health Promotion*. 2004;2:98-106.	Ineligible study design
Naughton F, Jamison J, Sutton S. Attitudes towards SMS text message smoking cessation support: a qualitative study of pregnant smokers. *Health education research*. 2013;28:911-22.	Not about NRT or e-cigarettes
Nguyen SN, Von Kohorn I, Schulman-Green D, Colson ER. The importance of social networks on smoking: perspectives of women who quit smoking during pregnancy. *Maternal and child health journal*. 2012;16:1312-8.	Not about NRT or e-cigarettes
Park ER, Chang Y, Quinn VP, Ross K, Rigotti NA. Perceived support to stay quit: What happens after delivery? *Addictive Behaviors*. 2009;34:1000-4.	Not about NRT or e-cigarettes
Passey ME, Stirling JM. Evaluation of 'Stop Smoking in its Tracks': an intensive smoking cessation program for pregnant Aboriginal women incorporating contingency-based financial rewards. *Public health research & practice*. 2018;28.	Not about NRT or e-cigarettes
Petersen Z, Steyn K, Everett-Murphy K, Emmelin M. Pregnant women's responses to a tailored smoking cessation intervention: turning hopelessness into competence. *Global health action*. 2010;3.	Not about NRT or e-cigarettes
Pletsch PK, Johnson MK. The cigarette smoking experience of pregnant Latinas in the United States. *Health care for women international*. 1996;17:549-62.	Not about NRT or e-cigarettes
Pletsch PK, Kratz AT. Why do women stop smoking during pregnancy? Cigarettes taste and smell bad. *Health care for women international*. 2004;25:671-9.	Not about NRT or e-cigarettes
Pletsch PK, Morgan S, Pieper AF. Context and beliefs about smoking and smoking cessation. *MCN The American journal of maternal child nursing*. 2003;28:320-5.	Not about NRT or e-cigarettes
Quinn G, Ellison BB, Meade C, Roach CN, Lopez E, Albrecht T, et al. Adapting smoking relapse-prevention materials for pregnant and postpartum women: formative research. *Maternal and child health journal*. 2006;10:235-45.	Not about NRT or e-cigarettes
Ronchi F, Lewis L, Hauck YL, Doherty DA. Exploring young pregnant smokers' experiences with a self-nominated non-smoking buddy. *Midwifery*. 2018;59:68-73.	Not about NRT or e-cigarettes
Tod AM. Barriers to smoking cessation in pregnancy: a qualitative study. *British journal of community nursing*. 2003;8:56-64.	Not about NRT or e-cigarettes
Wigginton B, Gartner C, Rowlands IJ. Is It Safe to Vape? Analyzing Online Forums Discussing E-Cigarette Use during	Ineligible patient population

Pregnancy. *Women's health issues : official publication of the Jacobs Institute of Women's Health*. 2017;27:93-9.	
Wood L, France K, Hunt K, Eades S, Slack-Smith L. Indigenous women and smoking during pregnancy: knowledge, cultural contexts and barriers to cessation. *Social science & medicine (1982)*. 2008;66:2378-89.	Not about NRT or e-cigarettes
Wu J, Tombor I, Shahab L, West R. Usability testing of a smoking cessation smartphone application ('SmokeFree Baby'): A think-aloud study with pregnant smokers. *Digital health*. 2017;3:2055207617704273.	Not about NRT or e-cigarettes

Economic studies

Study Citation	Reason for excluding
Antonopoulos MS, Bercume CM. Varenicline (Chantix): A new treatment option for smoking cessation. P and T. 2007;32(1):20.	Ineligible patient population
Askew DA, Guy J, Lyall V, Egert S, Rogers L, Pokino L-A, et al. A mixed methods exploratory study tackling smoking during pregnancy in an urban Aboriginal and Torres Strait Islander primary health care service. BMC Public Health. 2019;19(1):343.	Ineligible study design
Ayadi MF, Adams EK, Melvin CL, Rivera CC, Gaffney CA, Pike J, et al. Costs of a smoking cessation counseling intervention for pregnant women: comparison of three settings. Public Health Rep. 2006;121(2):120-6.	Ineligible intervention
Barker DC. III. Maternal smoking cessation: a cost effective strategy for managed care. Introduction. Tob Control. 2000; 9(Suppl 1): i60. Available from: https://tobaccocontrol.bmj.com/content/9/suppl_1/i60	Ineligible study design
Bauld L, Graham H, Sinclair L, Flemming K, Naughton F, Ford A, et al. Barriers to and facilitators of smoking cessation in pregnancy and following childbirth: literature review and qualitative study. Health Technol Assess. 2017;21(36):1-158.	Ineligible study design
Bell R, Glinianaia SV, Waal Zvd, Close A, Moloney E, Jones S, et al. Evaluation of a complex healthcare intervention to increase smoking cessation in pregnant women: interrupted time series analysis with economic evaluation. Tob Control. 2018;27(1):90-98.	Ineligible intervention
Berlin N, Goldzahl L, Bauld L, Hoddinott P, Berlin I. Public Acceptability of Financial Incentives to Reward Pregnant Smokers Who Quit Smoking: A United Kingdom-France Comparison. Eur J Health Econ. 2018;19(5):697-708.	Ineligible patient population
Boucher J, Konkle ATM. Understanding inequalities of maternal smoking-bridging the gap with adapted intervention strategies. IJERGQ. 2016;13(3):282.	Ineligible study design
Boyd KA, Briggs AH, Bauld L, Sinclair L, Tappin D. Are financial incentives cost-effective to support smoking cessation during pregnancy? Addiction (Abingdon, England). 2016;111(2):360-70.	Ineligible intervention
Buchanan C, Nahhas GJ, Guille C, Cummings KM, Wheeler C, McClure EA. Tobacco Use Prevalence and Outcomes Among Perinatal Patients Assessed Through an "Opt-out" Cessation and Follow-Up Clinical Program. Matern Child Health J. 2017;21(9):1790-97.	Ineligible study design
Canadian Agency for Drugs and Technologies in Health. Smoking cessation interventions for pregnant women and mothers of infants: a review of the clinical effectiveness, safety, and guidelines. Ottawa: CADTH; 2012. Available from: https://www.cadth.ca/smoking-cessation-interventions-pregnant-women-and-mothers-infants-review-clinical-effectiveness.	Ineligible outcomes

Chamberlain C, O'Mara-Eves A, Oliver S, Caird JR, Perlen SM, Eades SJ, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. (CD001055). London: Cochrane Collaboration; 2013. Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001055.pub5/full.	Ineligible study design
Cluss PA, Levine MD, Landsittel D. The Pittsburgh STOP program: disseminating an evidence-informed intervention for low-income pregnant smokers. Am J Health Promot. 2011;25(5 Suppl):S75-81.	Ineligible study design
Cohen D, Barton G. The cost to society of smoking cessation. Thorax. 1998;53(Suppl 2):S38-42.	Ineligible patient population
Coleman T, Cooper S, Thornton JG, Grainge MJ, Watts K, Britton J, et al. A randomized trial of nicotine-replacement therapy patches in pregnancy. N Engl J Med. 2012;366(9):808-18.	Ineligible study design
Cooper S, Lewis S, Thornton JG, Marlow N, Watts K, Britton J, et al. The SNAP trial: A randomised placebo-controlled trial of nicotine replacement therapy in pregnancy - Clinical effectiveness and safety until 2 years after delivery, with economic evaluation. Health Technol Assess. 2014;18(54):1-128.	Ineligible intervention
Crossland N, Thomson G, Morgan H, Dombrowski SU, Hoddinott P. Incentives for breastfeeding and for smoking cessation in pregnancy: An exploration of types and meanings. Soc Sci Med. 2015;128(March):10-17.	Ineligible outcomes
Dornelas EA, Magnavita J, Beazoglou T, Fischer EH, Oncken C, Lando H, et al. Efficacy and cost-effectiveness of a clinic-based counseling intervention tested in an ethnically diverse sample of pregnant smokers. Patient Educ Couns. 2006;64(1-3):342-9.	Ineligible intervention
Emery JL, Coleman T, Sutton S, Cooper S, Leonardi-Bee J, Jones M, et al. Uptake of Tailored Text Message Smoking Cessation Support in Pregnancy When Advertised on the Internet (MiQuit): Observational Study. J Med Internet Res. 2018;20(4):e146.	Ineligible intervention
Ershoff DH, Quinn VP, Boyd NR, Stern J, Gregory M, Wirtschafter D. The Kaiser Permanente prenatal smoking-cessation trial: when more isn't better, what is enough? Am J Prev Med. 1999;17(3):161-8.	Ineligible intervention
Essex HN, Parrott S, Wu Q, Li J, Cooper S, Coleman T. Cost-Effectiveness of Nicotine Patches for Smoking Cessation in Pregnancy: A Placebo Randomized Controlled Trial (SNAP). Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2015;17(6):636-42.	Ineligible intervention
Fitzgerald EM. Evidence-based tobacco cessation strategies with pregnant Latina women. Nurs Clin North Am. 2012;47(1):45-54.	Ineligible study design
Flemming K, Graham H, Heirs M, Fox D, Sowden A. Smoking in pregnancy: a systematic review of qualitative research of women who commence pregnancy as smokers. J Adv Nurs. 2013;69(5):1023-36.	Ineligible patient population
Gamble J, Grant J, Tsourtos G. Missed opportunities: a qualitative exploration of the experiences of smoking cessation interventions among socially disadvantaged pregnant women. Women and Birth. 2015;28(1):8-15.	Ineligible study design
Giatras N, Wanninkhof E, Leontowitsch M, Lewis B, Taylor A, Cooper S, et al. Lessons learned from the London Exercise and Pregnant (LEAP) Smokers randomised controlled trial process evaluation: implications for the design of physical activity for smoking cessation interventions during pregnancy. BMC Public Health. 2017;17(1):85.	Ineligible intervention
Halpern MT, Dirani R, Schmier JK. The cost effectiveness of varenicline for smoking cessation. Manag Care Interface. 2007;20(10):18-25.	Ineligible patient population
Hebert R. What's new in nicotine & tobacco research? Nicotine Tob Res 2007;9(10):983-86.	Ineligible patient population

Higgins ST, Solomon LJ. Some Recent Developments on Financial Incentives for Smoking Cessation Among Pregnant and Newly Postpartum Women. Curr Addict Rep. 2016;3(1):9-18.	Ineligible study design
Higgins ST, Washio Y, Lopez AA, Heil SH, Solomon LJ, Lynch ME, et al. Examining two different schedules of financial incentives for smoking cessation among pregnant women. Prev Med. 2014;68:51-7.	Ineligible study design
Hoekzema L, Werumeus Buning A, Bonevski B, Wolke L, Wong S, Drinkwater P, et al. Smoking rates and smoking cessation preferences of pregnant women attending antenatal clinics of two large Australian maternity hospitals. Aust N Z J Obstet Gynaecol. 2014;54(1):53-8.	Ineligible study design
Jessup MA. Organizational change in a perinatal treatment setting: Integration of clinical practice and policies on tobacco and smoking cessation. J Psychoactive Drugs. 2007;39(4):461-72.	Ineligible study design
Jones M, Lewis S, Parrott S, Coleman T. Systematic critical review of previous economic evaluations of smoking cessation during pregnancy. BMJ Open. 2015;5(11):e008998.	Ineligible study design
Lando HA, Valanis BG, Lichtenstein E, Curry SJ, McBride CM, Pirie PL, et al. Promoting smoking abstinence in pregnant and postpartum patients: a comparison of 2 approaches. Am J Manag Care. 2001;7(7):685-93.	Ineligible intervention
Levine MD, Cheng Y, Cluss PA, Marcus MD, Kalarchian MA. Prenatal smoking cessation intervention and gestational weight gain. Womens Health Issues. 2013;23(6):e389-93.	Ineligible study design
Likis FE, Andrews JC, Fonnesbeck CJ, Hartmann KE, Jerome RN, Potter SA, et al. Smoking cessation interventions in pregnancy and postpartum care. Washington, D.C.: Agency for Healthcare Research and Quality; 2014. Available from: https://www.ncbi.nlm.nih.gov/books/NBK190501/pdf/Bookshelf_NBK190501.pdf.	Ineligible study design
McCallum DM, Fosson GH, Pisu M. Making the case for medicaid funding of smoking cessation treatment programs: an application to state-level health care savings. J Health Care Poor Underserved. 2014;25(4):1922-40.	Ineligible study design
Mejdoubi J, van den Heijkant SCCM, van Leerdam FJM, Crone M, Crijnen A, HiraSing RA. Effects of nurse home visitation on cigarette smoking, pregnancy outcomes and breastfeeding: a randomized controlled trial. Midwifery. 2014;30(6):688-95.	Ineligible intervention
Melvin CL, Dolan-Mullen P, Windsor RA, Whiteside HP, Jr., Goldenberg RL. Recommended cessation counselling for pregnant women who smoke: a review of the evidence. Tob Control. 2000;9(Suppl 3):III80-4.	Ineligible intervention
Miyazaki Y, Hayashi K, Imazeki S. Smoking cessation in pregnancy: Psychosocial interventions and patient-focused perspectives. Int J Women Health. 2015(7):415-27.	Ineligible study design
Moore L, Campbell R, Whelan A, Mills N, Lupton P, Misselbrook E, et al. Self help smoking cessation in pregnancy: Cluster randomised controlled trial. BMJ. 2002;325(7377):1383-86.	Ineligible intervention
Muchowski K, Paladine H. An ounce of prevention: The evidence supporting periconception health care. J Fam Pract. 2004;53(2):126-33.	Ineligible study design
Mullen PD. Maternal smoking during pregnancy and evidence-based intervention to promote cessation. Prim Care. 1999;26(3):577-89.	Ineligible study design
Murthy P, Subodh BN. Current developments in behavioral interventions for tobacco cessation. Curr Opin Psychiatry. 2010;23(2):151-6.	Ineligible intervention
National Institute for Health and Care Excellence. Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities. London: NICE; 2008. Available from: https://www.nice.org.uk/guidance/PH26.	Ineligible study design
Ockene JK, Ma Y, Zapka JG, Pbert LA, Valentine Goins K, Stoddard AM. Spontaneous cessation of smoking and alcohol use among low-income pregnant women. Am J Prev Med. 2002;23(3):150-59.	Ineligible intervention

Oncken C, Dornelas E, Greene J, Sankey H, Glasmann A, Feinn R, et al. Nicotine gum for pregnant smokers: a randomized controlled trial. Obstet Gynecol. 2008;112(4):859-67.	Ineligible study design
Parker DR, Windsor RA, Roberts MB, Hecht J, Hardy NV, Strolla LO, et al. Feasibility, cost, and cost-effectiveness of a telephone-based motivational intervention for underserved pregnant smokers. Nicotine Tob Res 2007;9(10):1043-51.	Ineligible intervention
Patnode CP, Henderson JT, Thompson JH, Senger CA, Fortmann SP, Whitlock EP. Behavioral counseling and pharmacotherapy interventions for tobacco cessation in adults, including pregnant women: a review of reviews for the U.S. Preventive Services Task Force. Washington D.C.: Agency for Healthcare Research and Quality; 2015. Available from: https://www.ncbi.nlm.nih.gov/books/NBK321744/pdf/Bookshelf_NBK321744.pdf.	Ineligible study design
Ruger JP, Emmons KM. Economic evaluations of smoking cessation and relapse prevention programs for pregnant women: a systematic review. Value Health. 2008;11(2):180-90.	Ineligible intervention
Ruger JP, Emmons KM, Kearney MH, Weinstein MC. Measuring the costs of outreach motivational interviewing for smoking cessation and relapse prevention among low-income pregnant women. BMC Pregnancy Childbirth. 2009(9):46.	Ineligible intervention
Ruger JP, Weinstein MC, Hammond SK, Kearney MH, Emmons KM. Cost-effectiveness of motivational interviewing for smoking cessation and relapse prevention among low-income pregnant women: a randomized controlled trial. Value Health. 2008;11(2):191-98.	Ineligible intervention
Sedgwick P. Measuring the benefit of treatment: number needed to treat. BMJ. 2015; (350): h2206. Available from: https://www.bmj.com/content/350/bmj.h2206	Ineligible outcomes
Sloan M, Campbell KA, Bowker K, Coleman T, Cooper S, Brafman-Price B, et al. Pregnant Women's Experiences and Views on an "Opt-Out" Referral Pathway to Specialist Smoking Cessation Support: A Qualitative Evaluation. Nicotine Tob Res 2016;18(5):900-05.	Ineligible study design
Tappin D, Bauld L, Purves D, Boyd K, Sinclair L, MacAskill S, et al. Financial incentives for smoking cessation in pregnancy: Randomised controlled trial. BMJ. 2015; (350): h134. Available from: https://www.bmj.com/content/350/bmj.h134	Ineligible outcomes
Tod AM. Barriers to smoking cessation in pregnancy: a qualitative study. Br J Community Nurs. 2003;8(2):56-64.	Ineligible intervention
Ussher M, Lewis S, Aveyard P, Manyonda I, West R, Lewis B, et al. The London Exercise And Pregnant smokers (LEAP) trial: a randomised controlled trial of physical activity for smoking cessation in pregnancy with an economic evaluation. Health Technol Assess. 2015;19(84):vii-135.	Ineligible intervention
Vaz LR, Coleman T, Fahy SJ, Cooper S, Bauld L, Szatkowski L, et al. Factors associated with the effectiveness and reach of NHS stop smoking services for pregnant women in England. BMC Health Serv Res. 2017;17(1):545.	Ineligible intervention
Washio Y, Cassey H. Systematic Review of Interventions for Racial/Ethnic-Minority Pregnant Smokers. J Smok Cessat. 2016;11(1):12-27.	Ineligible study design
Wisborg K, Henriksen TB, Secher NJ. A prospective intervention study of stopping smoking in pregnancy in a routine antenatal care setting. Br J Obstet Gynaecol. 1998;105(11):1171-6.	Ineligible intervention
Yunzal-Butler C, Joyce TJ, Racine AD. Maternal Smoking and the Timing of WIC Enrollment. Cambridge MA: National Bureau of Economic Research; 2009. Available from: https://www.nber.org/papers/w14728.	Ineligible study design

Appendix L – Research recommendations

Research recommendation 2

Are nicotine replacement therapy (and at what dose) or nicotine-containing e-cigarettes effective to help women stop smoking in pregnancy?

Why this is important

No evidence was found relating to the effectiveness or safety of using nicotine containing e-cigarettes as an aid to smoking cessation in pregnancy. A high proportion of the studies on nicotine replacement therapies included in the effectiveness meta-analysis, were over 10 years old and most included studies used doses of nicotine that would now be considered to be low.

Rationale for research recommendation

Importance to 'patients' or the population	Smoking during pregnancy is associated with a variety of health risks for mother and baby and so it important that pregnant women have safe and effective choices to help them quit smoking.
Relevance to NICE guidance	It is important that pregnant women are provided with clear advice around the efficacy and safety of NRT products and of nicotine containing e-cigarettes as an aid to smoking cessation
Relevance to the NHS	The NHS Long Term Plan commits to offering women who smoke during pregnancy, specialist support to quit.
National priorities	The Tobacco Control Plan aims to reduce smoking among pregnant women to 6% by the end of 2022.
Current evidence base	No evidence was found on the safety or efficacy of nicotine containing e-cigarettes in pregnancy. A high proportion of studies of nicotine replacement therapies used doses of nicotine that would now be considered to be low.
Equality considerations	Smoking prevalence among pregnant women is higher among those aged under 20 than among older women. (Department of Health Tobacco Control Plan for England 2017). Women from more deprived communities are 12 times more likely to smoke (NHS Long Term Plan)

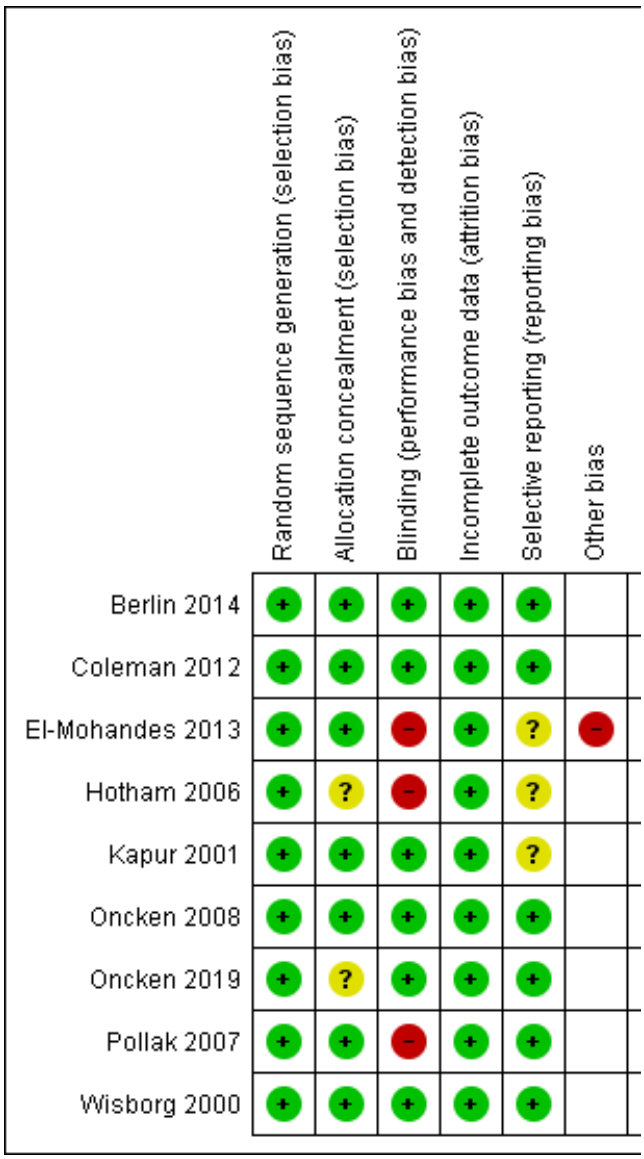
Modified PICO table

Population	Pregnant women who smoke
Intervention	NRT products (patches gums or sprays) intended to aid smoking cessation Nicotine containing e-cigarettes

Comparator	Other smoking cessation interventions
Outcome	Smoking status at longest available follow-up prior to birth and longest available follow-up (if after birth). Adverse or unintended (positive or negative) effects related to the woman's health. Safety outcomes related to birth or health of the baby

Appendix M – Additional information

Risk of bias for RCTs by domain (Claire 2020)



Sensitivity analysis removing non-placebo-controlled trials from effectiveness outcomes

Figure 18: Biochemically validated abstinence from smoking in later pregnancy (subgrouped by NRT type) – Compare with Figure 5

El-Mohandes 2013, Hotham 2016 and Pollack 2007 have been removed. Subgroup differences are now not significant (I^2 was previously 68.1%). Overall effect estimate therefore would be considered. This now includes the line of no effect (RR 1.21 95% CI 0.95, 1.55) where it didn't when high risk of bias studies were included (RR 1.37 95%CI 1.08, 1.74, see Figure 5).

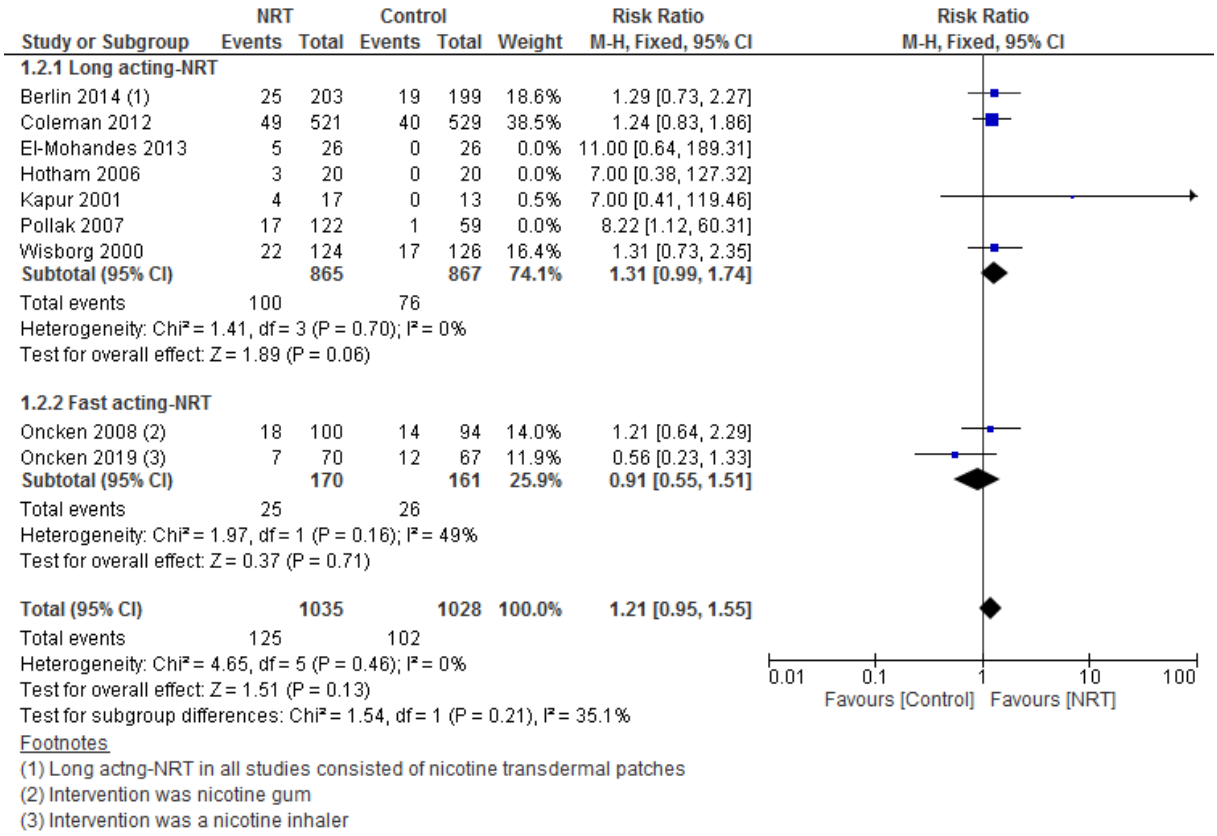
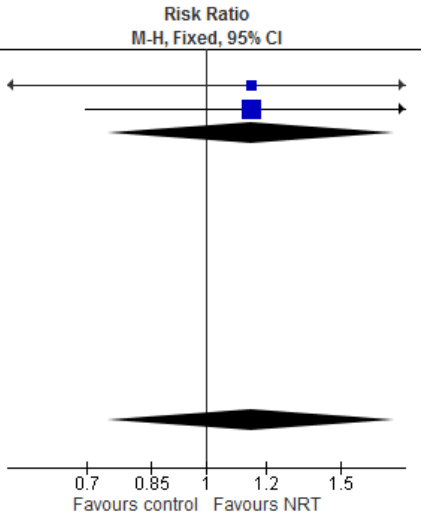


Figure 19: Self-reported abstinence from smoking at 3 or 6-months post-partum (subgrouped by comparator) Compare with Figure 6

The effect estimate for this outcome after removing non-placebo-controlled studies from this meta-analysis is the same as the result for placebo-controlled trials in Figure 6: RR 1.15 (95%CI 0.75, 1.77). The conclusion is therefore unchanged from the previous effect estimate (1.22, 95% CI 0.84, 1.78).

Study or Subgroup	NRT Events	NRT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Placebo-controlled trials						
Oncken 2008 (1)	11	100	9	94	28.9%	1.15 [0.50, 2.65]
Wisborg 2000	26	124	23	126	71.1%	1.15 [0.69, 1.90]
Subtotal (95% CI)		**224**		**220**	**100.0%**	**1.15 [0.75, 1.77]**
Total events	37		32			
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
1.3.2 Non placebo-controlled trials						
Pollak 2007	24	122	8	59	0.0%	1.45 [0.69, 3.03]
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**224**		**220**	**100.0%**	**1.15 [0.75, 1.77]**
Total events	37		32			
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Abstinence was also biochemically validated