Cochrane Library

Cochrane Database of Systematic Reviews

Pharmacological interventions for promoting smoking cessation during pregnancy (Review)

Claire R, Chamberlain C, Davey MA, Cooper SE, Berlin I, Leonardi-Bee J, Coleman T

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.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Pharmacological interventions for promoting smoking cessation during pregnancy

Ravinder Claire[1], Catherine Chamberlain[2], Mary-Ann Davey[3], Sue E Cooper[1], Ivan Berlin[4], Jo Leonardi-Bee[5], Tim Coleman[1]

[1]Division of Primary Care, University of Nottingham, Nottingham, UK. [2]Judith Lumley Centre, La Trobe University, Melbourne, Australia. [3]Department of Obstetrics and Gynaecology, Monash University, Clayton, Australia. [4]Department of Pharmacology, Sorbonne Université, Faculté de medicine-Hopital Pitie-Salpetriere, Paris, France. [5]Centre for Evidence Based Healthcare, Division of Epidemiology and Public Health, Clinical Sciences Building Phase 2, University of Nottingham, Nottingham, UK

Contact address: Tim Coleman, Division of Primary Care, University of Nottingham, Room 1502, Tower Building, University Park, Nottingham, Nottinghamshire, NG7 2RD, UK. tim.coleman@nottingham.ac.uk.

Editorial group: Cochrane Tobacco Addiction Group
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 3, 2020.

Citation: 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.

ABSTRACT

Background

Tobacco smoking in pregnancy causes serious health problems for the developing fetus and mother. When used by non-pregnant smokers, pharmacotherapies (nicotine replacement therapy (NRT), bupropion, and varenicline) are effective for increasing smoking cessation, however their efficacy and safety in pregnancy remains unknown. Electronic cigarettes (ECs) are becoming widely used, but their efficacy and safety when used for smoking cessation in pregnancy are also unknown.

Objectives

To determine the efficacy and safety of smoking cessation pharmacotherapies and ECs used during pregnancy for smoking cessation in later pregnancy and after childbirth, and to determine adherence to smoking cessation pharmacotherapies and ECs for smoking cessation during pregnancy.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (20 May 2019), trial registers, and grey literature, and checked references of retrieved studies.

Selection criteria

Randomised controlled trials (RCTs) conducted in pregnant women, comparing smoking cessation pharmacotherapy or EC use with either placebo or no pharmacotherapy/EC control. We excluded quasi-randomised, cross-over, and within-participant designs, and RCTs with additional intervention components not matched between trial arms.

Data collection and analysis

We followed standard Cochrane methods. The primary efficacy outcome was smoking cessation in later pregnancy; safety was assessed by 11 outcomes (principally birth outcomes) that indicated neonatal and infant well-being. We also collated data on adherence to trial treatments. We calculated the risk ratio (RR) or mean difference (MD) and the 95% confidence intervals (CI) for each outcome for each study, where possible. We grouped eligible studies according to the type of comparison. We carried out meta-analyses where appropriate.

Main results

We included 11 trials that enrolled a total of 2412 pregnant women who smoked at enrolment, nine trials of NRT and two trials of bupropion as adjuncts to behavioural support, with comparable behavioural support provided in the control arms. No trials investigated varenicline or ECs. We assessed four trials as at low risk of bias overall. The overall certainty of the evidence was low across outcomes and comparisons as assessed using GRADE, with reductions in confidence due to risk of bias, imprecision, and inconsistency.

Compared to placebo and non-placebo (behavioural support only) controls, there was low-certainty evidence that NRT increased the likelihood of smoking abstinence in later pregnancy (RR 1.37, 95% CI 1.08 to 1.74; I^2 = 34%, 9 studies, 2336 women). However, in subgroup analysis by comparator type, there was a subgroup difference between placebo-controlled and non-placebo controlled RCTs (test for subgroup differences P = 0.008). There was unclear evidence of an effect in placebo-controlled RCTs (RR 1.21, 95% CI 0.95 to 1.55; I^2 = 0%, 6 studies, 2063 women), whereas non-placebo-controlled trials showed clearer evidence of a benefit (RR 8.55, 95% CI 2.05 to 35.71; I^2 = 0%, 3 studies, 273 women). An additional subgroup analysis in which studies were grouped by the type of NRT used found no difference in the effectiveness of NRT in those using patches or fast-acting NRT (test for subgroup differences P = 0.08).

There was no evidence of a difference between NRT and control groups in rates of miscarriage, stillbirth, premature birth, birthweight, low birthweight, admissions to neonatal intensive care, caesarean section, congenital abnormalities, or neonatal death. In one study infants born to women who had been randomised to NRT had higher rates of 'survival without developmental impairment' at two years of age compared to the placebo group. Non-serious adverse effects observed with NRT included headache, nausea, and local reactions (e.g. skin irritation from patches or foul taste from gum), but data could not be pooled. Adherence to NRT treatment regimens was generally low.

We identified low-certainty evidence that there was no difference in smoking abstinence rates observed in later pregnancy in women using bupropion when compared to placebo control (RR 0.74, 95% CI 0.21 to 2.64; I^2 = 0%, 2 studies, 76 women). Evidence investigating the safety outcomes of bupropion use was sparse, but the existing evidence showed no difference between the bupropion and control group.

Authors' conclusions

NRT used for smoking cessation in pregnancy may increase smoking cessation rates in late pregnancy. However, this evidence is of low certainty, as the effect was not evident when potentially biased, non-placebo-controlled RCTs were excluded from the analysis. Future studies may therefore change this conclusion. We found no evidence that NRT has either positive or negative impacts on birth outcomes; however, the evidence for some of these outcomes was also judged to be of low certainty due to imprecision and inconsistency. We found no evidence that bupropion may be an effective aid for smoking cessation during pregnancy, and there was little evidence evaluating its safety in this population. Further research evidence on the efficacy and safety of pharmacotherapy and EC use for smoking cessation in pregnancy is needed, ideally from placebo-controlled RCTs that achieve higher adherence rates and that monitor infants' outcomes into childhood. Future RCTs of NRT should investigate higher doses than those tested in the studies included in this review.

PLAIN LANGUAGE SUMMARY

Drug treatments and electronic cigarettes for stopping smoking in pregnancy

What is the issue?

Smoking during pregnancy harms women and infants. However, many women who smoke struggle to stop whilst pregnant. Medication for smoking cessation reduces the intensity of cravings, meaning that people trying to stop smoking are more likely to succeed in the long term. Providing pregnant women who smoke with these treatments could help them to stop smoking and have a positive impact on both their own health and the health of their infants.

Why is this important?

Medications commonly used to help people to stop smoking include nicotine replacement therapy (NRT), bupropion, and varenicline. Electronic cigarettes containing nicotine are also used by some who smoke to help avoid smoking. However, the safety and effectiveness of smoking cessation drugs and electronic cigarettes in pregnant women is unknown. We searched for studies looking at how good these aids were at helping pregnant women stop smoking and how safe they were when used during pregnancy.

What evidence did we find?

We searched for evidence on 20 May 2019 and identified 11 randomised studies (studies in which participants are assigned to one of two or more treatment groups using a random method) that enrolled a total of 2412 women. Nine studies tested NRT used alongside counselling to stop smoking, whilst the other two studies tested bupropion.

Low-quality evidence suggests that NRT combined with behavioural support might help women to stop smoking in later pregnancy more than behavioural support alone. Medication trials often use placebos, that is tablets or patches that look like the drug but do not actually include it, so that each comparison group has equal expectation of success and there is a fairer test of the benefits of the medicine itself. When just the higher-quality, placebo-controlled trials were analysed, the evidence suggested that NRT was more effective than placebo NRT. There was no evidence that either nicotine patches or fast-acting NRT (such as gum or lozenge) was more effective than the other.

Low-quality evidence suggests that bupropion may be no more effective than placebo in helping women quit smoking later in pregnancy. We found no trials investigating other smoking cessation pharmacotherapies or electronic cigarettes.

There was insufficient evidence to conclude whether NRT had either positive or negative impacts on rates of miscarriage, stillbirth, preterm birth (less than 37 weeks), mean birthweight, low birthweight (less than 2500 g), admissions of babies to neonatal intensive care, or newborn deaths. However, in one trial where infants were followed until two years of age, those infants born to women who had been randomised to NRT were more likely to have healthy development. Similarly, it is unclear whether bupropion had a positive or negative impact on birth outcomes.

Studies that looked at whether women used their stop smoking medications as instructed found that use was generally low, and the majority of women used little of the NRT they were given.

What does this mean?

More research evidence is needed, in particular placebo-controlled trials that test higher doses of NRT, encourage women to use sufficient medication, and follow infants into childhood. Furthermore, more studies are required investigating the effect and safety of bupropion, electronic cigarettes, and varenicline for giving up smoking during pregnancy.

Summary of findings for the main comparison. Nicotine replacement therapy compared to control for smoking cessation during pregnancy

Nicotine replacement therapy compared to control for smoking cessation during pregnancy

Patient or population: pregnant women who smoke
Setting: public hospitals and antenatal clinics (Australia, Canada, Denmark, France, the UK, the USA)

Intervention: nicotine replacement therapy
Comparison: placebo plus similar/matched behavioural support or similar/matched behavioural support only

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/no NRT	Risk with NRT				
Biochemically validated smoking cessation at the latest point in pregnancy (20 weeks' gestation or more)	Study population		RR 1.37 (1.08 to 1.74)	2336 (9 RCTs)	⊕⊕⊖⊖ LOW [1 2]	
	9 per 100	12 per 100 (10 to 16)				
Mean birthweight (g)	Study population		MD 99.73 g (−6.65 g to 206.10 g)	2202 (7 RCTs)	⊕⊕⊖⊖ LOW [4 5]	
	3139 g [3]	3239 g (3132 g to 3345 g)				
Miscarriage and spontaneous abortion	Study population		RR 1.60 (0.53 to 4.83)	1916 (5 RCTs)	⊕⊕⊖⊖ LOW [6]	
	0 per 100	1 per 100 (0 to 2)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **NRT:** nicotine replacement therapy; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one level due to serious risk of bias: in the subgroup of studies at low or unclear risk of bias the effect was no longer statistically significant, and there were significant subgroup differences when comparing these studies to the three studies judged to be at high risk of bias (P = 0.008).
[2]Downgraded one level due to serious imprecision: there were only 253 events in total (300 to 400 recommended for dichotomous outcomes), and confidence intervals span both minimal clinical benefit and considerable clinical benefit.
[3]Control risk based on observed birthweights in the control arms.
[4]Downgraded one level due to serious inconsistency: I^2 = 70%, not explained by subgroup differences.
[5]Downgraded one level due to serious imprecision: confidence intervals encompass no difference as well as a clinically significant benefit.
[6]Downgraded two levels due to very serious imprecision: there were only 12 events in total (300 to 400 recommended for dichotomous outcomes), and confidence intervals encompass both no difference and potential harm.

Summary of findings 2. Bupropion compared to control for smoking cessation during pregnancy

Bupropion compared to control for smoking cessation during pregnancy

Patient or population: pregnant women who smoke
Setting: antenatal clinics (USA)
Intervention: bupropion
Comparison: placebo plus similar/matched behavioural support

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with bupropion				
Biochemically validated smoking cessation at the latest point in pregnancy (20 weeks' gestation or more)	Study population		RR 0.74 (0.21 to 2.64)	76 (2 RCTs)	⊕⊕⊖⊖ LOW [1]	
	12 per 100	9 per 100 (3 to 32)				
Mean birthweight (g)	Study population		MD 122.64 g (−98.82 g to 344.10 g)	68 (2 RCTs)	⊕⊕⊖⊖ LOW [3]	
	3090 g [2]	3212 g (2991 g to 3434 g)				
Miscarriage and spontaneous abortion	Study population		n/a	n/a	n/a	No studies reported this outcome.
	n/a	n/a				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **n/a:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

---

[1]Downgraded two levels due to very serious imprecision: very few events and participants, so very likely to be underpowered. Confidence intervals are wide and incorporate both clinically significant benefit and clinically significant harm.
[2]Control risk based on observed birthweights in the control arms.
[3]Downgraded two levels due to very serious imprecision: very few participants (< 400).

BACKGROUND

Description of the condition

Risks associated with smoking in pregnancy

Tobacco smoking during pregnancy is one of the most significant, potentially preventable causes of a range of adverse pregnancy outcomes, including placental abruption, miscarriage, stillbirth, preterm birth (less than 37 weeks' gestation), and low birthweight (less than 2500 g) (Hammoud 2005; Marufu 2015; Salihu 2007; US DHHS 2004). Smoking causes intrauterine growth restriction, probably through a reduction in the supply of oxygen and other essential fetal nutrients (Crawford 2008), and is associated with poorer fetal neurodevelopment (Herrmann 2008). Preterm birth is the leading cause of neonatal mortality and morbidity (Hammoud 2005; Kramer 1987; Liu 2016), with up to half of all paediatric neurodevelopmental problems ascribed to preterm birth (Bentley 2016; Green 2005). Low birthweight is a surrogate measure of the harmful impact of tobacco smoking on fetal development, and there is evidence of an association between low birthweight and adult morbidities, including coronary heart disease and type 2 diabetes mellitus (Belbasis 2016; Gluckman 2008). Tobacco smoking also has many long-term health impacts for women, and is a major risk factor for six of the eight leading causes of death globally (WHO 2019).

Epidemiology of smoking in pregnancy

Tobacco smoking is frequently associated with low socioeconomic status and has been cited as one of the principal causes of health inequality between rich and poor (Wanless 2004).

Overall, it is estimated that 29 of 174 countries have a prevalence of smoking during pregnancy greater than 10%, and 12 countries have a prevalence greater than 20% (Lange 2018). Ireland (38%), Uruguay (30%), and Bulgaria (29%) are the three countries estimated to have the highest prevalence of smoking during pregnancy (Lange 2018). In high-income countries such as the USA, Denmark, and Sweden, the prevalence of smoking in pregnancy declined from between 20% and 35% in the 1980s to between 10% and 20% in the 2000s (Al-Sahab 2010; Cnattingius 2004; Dixon 2009; Giovino 2007; Tappin 2010; Tong 2009; US DHHS 2004), and to below 10% in 2010 (Lanting 2012). However, the decline has not been consistent across all sectors of society, with lower rates of decline in lower socioeconomic groups (Graham 2010; Lanting 2012; Pickett 2009; US DHHS 2004). There are marked socioeconomic differences between women who continue to smoke in pregnancy and those who do not. Compared to women who do not smoke, those who continue to smoke in pregnancy generally have lower incomes, higher parity, lower levels of social support, and more limited education; are younger; receive publicly funded or deficient maternity care; are without a partner or with a partner who smokes; and are more likely to feel criticised by society (Ebert 2007; Frost 1994; Graham 1976; Graham 1996; Schneider 2008; Tappin 1996; US DHHS 2004). There is a significantly higher prevalence of smoking in pregnancy in several indigenous and ethnic minority groups, which is in accord with their social and material deprivation (Chan 2001; Hunt 2003; Kaplan 1997; US DHHS 2004; Wiemann 1994). Despite the high prevalence, there is a paucity of evidence-based literature on interventions to reduce antenatal smoking in indigenous groups (Gilligan 2007). In some migrant groups, cultural differences may cut across this social gradient. Women who are migrants or refugees to the UK, Northern Europe, North America, or Australia and who originate from South East Asia retain a lower prevalence of smoking, despite major social disadvantage (Bush 2003; Potter 1996; Small 2000). However, second-generation migrant women are more likely to smoke during pregnancy (Troe 2008). In the USA, African-American, Hispanic, and Pacific Islander women have a lower prevalence of smoking in pregnancy than white women (Andreski 1995; US DHHS 2004; Wiemann 1994).

The global tobacco smoking epidemic is shifting from high-income countries to low- and middle-income ones, with predictions that 80% of the 8 million annual tobacco-related deaths will be occurring in low-middle income countries within 30 years (Oncken 2010). Worldwide, the prevalence of tobacco smoking and smokeless tobacco use amongst women is increasing, not decreasing, and is expected to rise to 20% by 2025 (Oncken 2010; Richmond 2003; Samet 2001). The World Health Organization (WHO) has identified this rise of tobacco use in young females in low-income, high-population countries as one of the most ominous developments of the tobacco epidemic (WHO 2019). National rates of smoking in pregnancy appear to be associated with economic development: for example, in Spain the prevalence is estimated at 26%, whilst the prevalence in African Region is still very low (Lange 2018). However, given the aggressive nature of tobacco marketing, there is concern that prevalence of smoking in pregnancy will increase with economic development (WHO 2019), with subsequent health impacts on countries with already high disease burdens and limited resources to provide health care, and in particular neonatal care (Cnattingius 2004).

In addition to the socioeconomic factors associated with continued smoking, there is a growing understanding of psychological associations, especially mood disorders, stress, and childhood trauma (Aveyard 2007; Blalock 2005; Blalock 2011; Crittenden 2007). Depressed women are up to four times more likely to smoke during pregnancy than non-depressed women (Blalock 2005), but there is limited information available about the effects of smoking and interventions in pregnant women with psychological symptoms, as these women are often excluded from trials (Blalock 2005). Two reviews in the general population, Stead 2013; Tsoi 2013, and several trials of smoking cessation interventions conducted in pregnant women report higher levels of stress and depression amongst women who continue to smoke during pregnancy (Aveyard 2007; Blalock 2005; Crittenden 2007).

A higher proportion of women stop smoking during pregnancy than at other times in their lives. Up to 45% of women who smoke before pregnancy 'spontaneously quit' or stop before their first antenatal visit (Quinn 1991; The NHS Information Centre 2011; Woodby 1999); this 'quit rate' is substantially higher than reported in the general population (McBride 2003). 'Spontaneous quitters' usually smoke less and are more likely to have temporarily stopped smoking previously; to have a non-smoking partner; to have more support and encouragement at home for quitting; to have stronger beliefs about the dangers of smoking; and to be less seriously addicted (Baric 1977; Ryan 1980). Consequently, women who are eligible for smoking cessation assistance in pregnancy are likely to find it more difficult to quit than those in other populations. However, only a third of women who stop smoking spontaneously remain abstinent after one year (CDC 2002). McBride 2003 hypothesises that pregnancy may be a 'teachable moment' at which women perceive increased risk from smoking and become more motivated to attempt smoking cessation. These factors highlight some of the

major differences between the non-pregnant population included in trials of pharmacotherapy for smoking cessation and pregnant women who continue to smoke after they become pregnant (Oncken 2009b).

Smoking cessation in pregnancy

In addition to acknowledged benefits for maternal health, stopping smoking in pregnancy has positive impacts on infant outcomes. Research studies show that smoking cessation interventions delivered in pregnancy reduce the prevalence of infants born at low birthweight, which is accompanied by substantial infant morbidity and mortality (Chamberlain 2017). Similar findings have been observed in women who stop smoking after receiving standard antenatal care, suggesting that trial findings are probably generalisable to all women who stop smoking in early pregnancy, whether or not they participate in research studies (McCowan 2009).

Some non-pharmacological (psychosocial) interventions are effective in reducing the proportion of women who smoke during pregnancy; the evidence for these can be obtained from an associated review (Chamberlain 2017). For example, compared to usual care (minimal information about smoking risks and advice to quit or a less intensive intervention), smoking cessation counselling was demonstrated to improve smoking abstinence rates in late pregnancy (risk ratio (RR) 1.44, 95% confidence interval (CI) 1.19 to 1.73; I^2 = 49%, 30 studies) (Chamberlain 2017). Financial incentives have also shown evidence of effectiveness, based on 10 trials of 2571 pregnant women (Notley 2019). However, all studies were conducted in the USA or the UK, and incentives used in addition to routine care in other countries may have different effects.

Description of the intervention

We evaluated the effectiveness of any pharmacological intervention used to support women to stop smoking in pregnancy, including electronic cigarettes (ECs).

Nicotine replacement therapy (NRT), bupropion, and varenicline are widely available on prescription for smoking cessation, and NRT is also available as an over-the-counter medication. They are licenced as first-line treatments for smoking cessation in the USA and the European Union, and are widely recommended in many national guidelines for use in the general population. ECs are also freely available to buy in some countries, and many people use them as an aid to smoking cessation (McNeill 2018). We have therefore concentrated on these four treatments; however, any pharmacological intervention used for smoking cessation was eligible for inclusion in the review.

In previous Cochrane Reviews, NRT, bupropion, and varenicline have all been found to improve the chances of quitting smoking in non-pregnant adults who smoke (Cahill 2016; Hartmann-Boyce 2018; Hughes 2014). Another Cochrane Review found evidence from two trials that ECs helped non-pregnant adults stop smoking in the long term compared to placebo ECs; however, due to the small number of trials and low event rates, confidence in the findings was low (Hartmann-Boyce 2016). A more recent randomised trial found that ECs were more effective than NRT for smoking cessation in non-pregnant adults who smoke (Hajek 2019).

The treatments are described as follows.

1. **NRT:** is available as patches in various dosages (absorbed slowly through the skin) and in fast-acting forms, such as chewing gum, lozenges, sublingual tablets, sprays, and inhalers (absorbed through the oral or nasal mucosa).
2. **Bupropion:** this was developed as a non-tricyclic antidepressant, but was licenced as a prescription-only smoking cessation aid in the UK in 2000. The usual dose for smoking cessation is 150 mg once a day for 3 days, increasing to 150 mg twice a day, continued for 7 to 12 weeks. The quit attempt is generally initiated a week after starting pharmacotherapy.
3. **Varenicline:** this is a selective nicotinic receptor partial agonist, licenced as a prescription-only treatment for smoking cessation in the USA in 2006, and in Europe in 2006/2007. The standard regimen is 1 mg twice a day for 12 weeks, with the first week titrated to reduce side effects, and quit date set for the second week of use.
4. **ECs:** these are devices that do not burn tobacco leaves; instead, a nicotine-containing aerosol is released and inhaled by the user (Cobb 2010). The awareness and use of ECs are increasing (Filippidis 2017; Zhu 2017), and there is evidence that some women are using ECs to quit smoking during pregnancy (Oncken 2017). However, both the WHO and Centers for Disease Control and Prevention advise that there is insufficient evidence to recommend e-cigarettes for smoking cessation in adults, including pregnant women (US DHHS 2016; WHO 2019).

How the intervention might work

1. **NRT:** this aims to replace the nicotine inhaled through tobacco smoking with nicotine in a medicinal form. In doing so, the user avoids approximately 4000 toxins that are inhaled with nicotine in tobacco smoke (Stedman 1968); medicinal nicotine is therefore likely to be safer than tobacco smoke nicotine. The nicotine provided through NRT should also reduce motivation to smoke and the physiological and psychomotor withdrawal symptoms often experienced during an attempt to stop smoking, thereby increasing the likelihood of remaining abstinent (West 2001).
2. **Bupropion:** this antidepressant has both dopaminergic and noradrenergic actions, and appears to be a nicotinic acetylcholinergic receptor antagonist (Fryer 1999; Slemmer 2000). Bupropion's mechanism of action for smoking cessation remains uncertain, but it may block nicotine effects, reduce depression, or alleviate withdrawal symptoms (Cryan 2003; Lerman 2002; West 2008).
3. **Varenicline:** this is an alpha 4 beta 2 nicotinic acetylcholine receptor partial agonist. It attaches to the nicotinic acetylcholine receptor and is believed to mimic the pleasurable dopaminergic (dopamine-releasing) effect of nicotine. Varenicline binds more easily to receptors than nicotine, so that when abstinent people who smoke use this drug, receptors become blocked with varenicline. Should varenicline users choose to smoke, varenicline prevents nicotine from attaching to receptors, preventing any pleasurable effects for the person smoking (Coe 2005). Smoking whilst using varenicline is therefore less enjoyable and attractive. Varenicline users also experience fewer cravings or withdrawal symptoms and so are better able to remain abstinent (Coe 2005).
4. **ECs:** similar to NRT, ECs deliver nicotine in order to reduce withdrawal symptoms and motivation to smoke. ECs are thought to address the behavioural as well as the biochemical

aspects of smoking addiction (Barbeau 2013). ECs replace some of the habitual gestures associated with cigarette smoking, such as the hand-to-mouth actions, and this in combination with nicotine delivery could help EC users remain abstinent during a quit attempt (Polosa 2011).

One would expect these interventions to have the same mechanisms of action in pregnant women as they do in non-pregnant people who smoke. However, the metabolism of many drugs, including nicotine, is increased in pregnancy, and any medications that are metabolised more swiftly can become less effective at standard doses. Both nicotine and cotinine, the primary metabolite of nicotine, are metabolised much more quickly in pregnancy, where clearance is 60% and 140% greater, respectively (Dempsey 2001). Consequently, NRT and ECs used by pregnant women would be expected to generate lower blood concentrations of nicotine, and these might not adequately substitute for nicotine received from smoking. One might therefore expect NRT and ECs to be less effective for smoking cessation in pregnancy than when used outside of pregnancy. The metabolism of bupropion and varenicline is not known to be altered in pregnancy.

Safety

A caveat to the use of pharmaceutical treatments for smoking cessation in pregnancy is that of potential fetal harm caused by their use. There are insufficient studies investigating the fetal impacts of either bupropion or varenicline use in pregnancy to draw any conclusions about the safety of using either of these treatments. There are, however, more studies demonstrating the effects of nicotine on the fetus, and these suggest that nicotine is a fetal toxin (Dempsey 2001). Also, nicotine crosses the placenta and accumulates in the developing fetus (Maritz 2009; Rore 2008), causing concerns about both short-term effects on newborns, Gaither 2009, and longer-term impacts on infants, Bruin 2010. However, as tobacco smoke contains nicotine plus many other toxins, and NRT delivers nicotine alone, there is a consensus amongst experts that maternal use of NRT in pregnancy should be safer for the fetus than continued smoking of burnt cigarettes (Benowitz 2000), although there is currently insufficient research evidence to support this view.

Why it is important to do this review

Guidelines from many countries recommend that NRT be offered for smoking cessation in pregnancy to heavy smokers who have been unable to quit smoking using behavioural or psychosocial methods (CAN-ADAPTT 2011; NICE 2010; RACGP 2014; RANZCOG 2014). We have been unable to find any clinical guidelines that recommend using bupropion, varenicline, or ECs in pregnancy. These treatments are not recommended in pregnancy as there is very limited evidence for their safety (Oncken 2017; Rore 2008), and their use could involve fetal exposure to potential additional toxins that could be avoided. In most high-income countries (e.g. Canada, the USA, Australia, New Zealand), guidelines recommend that pregnant women be offered intermittent NRT-delivery formulations (e.g. gum, lozenges, spray - classified as category C drugs in pregnancy), rather than continuous ones (e.g. patches - classified as category D) (Bruin 2010). The theoretical rationale for this is that the overall dose of nicotine delivered by intermittent formulations may be lower than that delivered by continuous ones (Oncken 2009b), and that the peaks in blood nicotine concentrations are more extreme, mimicking the action of smoking. However, some experts recommend patches, as the lower peak nicotine levels associated with these may induce fewer adverse effects, such as throat irritation (Oncken 2009b; Rore 2008).

Consensus-based recommendations about using NRT for smoking cessation in pregnancy are underpinned by a belief that medicinal NRT is safer than smoking. (Benowitz 2000) However, to date, individual trials have had inconsistent findings (Pollak 2007; Wisborg 2000), and there is no conclusive evidence that NRT is either effective or safe in pregnancy (Coleman 2015). There are also reports of low adherence to NRT regimens, which could reduce efficacy and suggests that the acceptability of NRT use in pregnancy may be limited (Coleman 2011; Coleman 2012). Furthermore, it is unclear whether efficacy or safety is improved with intermittent NRT administration (fast-acting NRT products) or with continuous administration using nicotine patches.

Given that NRT appears to be widely accepted for cautious use in pregnancy, a Cochrane Review investigating the efficacy and safety of this clinical practice and also the potential for other drugs to be safely used was warranted. Additionally, although ECs are not recognised or regulated as a smoking cessation treatment, as they are widely available in some countries it is possible that they may be used by pregnant women to quit smoking, and therefore clear guidance is needed on this. An up-to-date, robust synthesis of research evidence on the use of pharmacological treatments for cessation in pregnancy will help advance clinical practice in an area of substantial clinical need. This review updates an earlier version of this review published in 2015 (Coleman 2015).

OBJECTIVES

To determine the efficacy and safety of smoking cessation pharmacotherapies and ECs used during pregnancy for smoking cessation in later pregnancy and after childbirth, and to determine adherence to smoking cessation pharmacotherapies and ECs for smoking cessation during pregnancy.

METHODS

Criteria for considering studies for this review

Types of studies

Parallel- or cluster-randomised controlled trials (RCTs) were eligible for inclusion. Quasi-randomised, cross-over, and within-participant designs were not eligible for inclusion due to the potential biases inherent in these designs.

Types of participants

Women who were pregnant and who also smoked tobacco at study baseline.

Types of interventions

Pharmacological treatments (including ECs) aimed at promoting smoking cessation including, but not limited to, treatments that have been proven effective in non-pregnant adults (e.g. NRT (Hartmann-Boyce 2018), bupropion (Hughes 2014), varenicline (Cahill 2016), and ECs used to promote smoking cessation (Hajek 2019)).

Eligible comparators were placebo control or no smoking cessation pharmacotherapy/EC.

Trials could provide behavioural support to participants, however the support provided had to be very similar (ideally identical) across the active drug and comparator trial arms. Behavioural support is effective for smoking cessation in pregnancy (Chamberlain 2017), and differences in its provision would be expected to affect cessation and birth outcomes, potentially rendering findings difficult to interpret.

Types of outcome measures

Primary outcomes

Self-reported abstinence from smoking at the latest time point in pregnancy at which this was 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 ECs), anabasine. When validated abstinence data were available, these were preferred to self-report. Where this information was available, we also used prolonged or continuous abstinence measures, timed from a quit date set in early pregnancy and which allowed temporary lapses to smoking as per the Russell Standard criteria for outcome measurement in cessation studies (West 2005). However, point prevalence abstinence measures were substituted for these as required.

Secondary outcomes

1. Abstinence from smoking after childbirth (with abstinence defined as detailed above)
2. Safety
   a. Miscarriage/spontaneous abortion
   b. Stillbirth
   c. Mean unadjusted birthweight
   d. Low birthweight (less than 2500 g)
   e. Preterm birth (less than 37 weeks' gestation)
   f. Neonatal intensive care unit admissions
   g. Neonatal death
   h. Caesarean section
   i. Congenital anomaly
   j. Maternal hypertension
   k. Infant respiratory symptoms
   l. Infant development
3. Pharmacotherapy/EC adherence
4. Non-serious adverse effects (serious adverse event data contributed to safety outcomes, as described above)
5. Any reported long-term effects of smoking cessation pharmacotherapies on safety

We did not carry out a specific literature search for outcomes 3 to 5, but, if reported, these data were extracted from the included studies and described qualitatively.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting their Information Specialist, who ran the search on 20 May 2019.

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO) (Cumulative Index to Nursing and Allied Health Literature);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts;
7. scoping searches of the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov/) and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/) for unpublished, planned, and ongoing trial reports.

Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections (Included, Excluded, Awaiting Classification, or Ongoing).

Details of the search strategies for CENTRAL, MEDLINE, Embase, and CINAHL; the list of handsearched journals and conference proceedings; and the list of journals reviewed via the current awareness service can be found in the 'PCG Trials Register' section of the Cochrane Pregnancy and Childbirth Group's website.

Searching other resources

We checked relevant cited studies whilst reviewing the trial reports identified by the electronic searches, as well as reference lists from any directly relevant reviews identified. We also searched the following trials registers on 20 May 2019: US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov/) and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/), and OpenGrey, "System for Information on Grey Literature in Europe" (www.opengrey.eu/).

We did not apply any language or date restrictions, and included studies regardless of the publication type (e.g. conference abstract, trial registry entry, journal article).

Data collection and analysis

For methods used in the previous version of this review, see Coleman 2015.

For this update, the following methods were used to assess the 11 reports identified as a result of the updated search.

Selection of studies

This describes the identification of papers published since the last version of this review and added to those included in earlier versions (see Other published versions of this review). Two review

authors (RC and TC) independently inspected the search results, making separate lists of titles and abstracts that were potentially suitable for inclusion. We then retrieved the full texts of reports deemed potentially relevant, and two review authors (RC and TC) assessed these for inclusion in the review. At both stages disagreements were resolved by discussion without the need to involve a third review author.

Data extraction and management

We designed a data extraction form based on that used by Lumley 2009, which two review authors (RC and TC) used to extract data from eligible studies. Extracted data were compared, with any discrepancies being resolved through discussion. RC entered data into Review Manager 5 software (Review Manager 2014), double checking this for accuracy.

When information regarding any of the above was unclear, we contacted authors of the reports to provide further details.

We recorded the following information, where available, in the Characteristics of included studies table.

1. Methods: study design.
2. Participants: number of participants, inclusion criteria, and any relevant exclusion criteria.
3. Interventions: description of intervention and control (treatment, dosage, regimen, behavioural support, duration of intervention), information regarding dose matching if relevant.
4. Outcomes: primary outcomes, time points reported, biochemical validation, and definitions of abstinence.
5. Notes: we recorded dates of the trial, trial funding, and declarations of interest of trial authors where reported.

We created Additional tables for details of twin births and fetal loss in pregnancy (Table 1) and for extracted adherence data (Table 2).

Assessment of risk of bias in included studies

RC and TC independently assessed risk of bias for all studies which they had not authored (the one study led by TC was assessed by another review author), using criteria adapted from those in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). Any disagreements were resolved by discussion with a third review author (JLB).

We assessed the following 'Risk of bias' domains for all included studies.

(1) Random sequence generation (checking for possible selection bias)

We determined whether the method used to generate the allocation sequence was sufficiently described to permit an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We determined the method used to conceal the allocation sequence and whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk of bias.

(3) Blinding (checking for possible performance bias and detection bias)

We determined the methods used, if any, to blind study participants and personnel from knowledge of which intervention was received by the participant. In the previous version of this review, we categorised studies that used placebo as at low risk of bias and those that used a behavioural control only as at high risk of bias. Using this categorisation of bias, findings with respect to efficacy of NRT were different for placebo (low risk of bias) and non-placebo (high risk of bias) RCTs, so we have maintained the same classification for this update. In the 'Risk of bias' table (see Characteristics of included studies) we also note whether or not participants, personnel, and outcome assessors were blinded to outcome assessment and whether the abstinence outcome was biochemically validated. We used cut points derived by expert consensus: 8 parts per million where exhaled carbon monoxide was used for validation and 10 ng/mL for saliva cotinine.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We determined for the primary outcome (i.e. smoking cessation) the completeness of data including attrition and exclusions from the analysis and whether an intention-to-treat analysis (i.e. reporting trial arm cessation rates amongst all participants who were originally randomised to that arm) was reported. We assessed whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes.

(5) Selective reporting bias

We determined the possibility of selective outcome reporting bias and assessed methods as:

- low risk of bias (where it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where a prespecified outcome is not reported and there is evidence that this is due to lack of effect or an effect deemed unfavourable); or
- unclear risk of bias (where not all of the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; or the study fails to include results of a key outcome that would have been

expected to have been reported, however there is no clear evidence that this is a source of bias).

(6) Other risk of bias

We considered whether there were any other additional potential sources of bias in the study.

(7) Overall risk of bias

Where a study was judged to be at low risk for all of the above domains, it was considered to be at overall low risk of bias; where at least one judgement of high risk of bias was made, the study was considered to be at overall high risk of bias; and where there was no judgement of high risk, but at least one judgement of unclear risk, the study was considered to be at overall unclear risk of bias.

Assessment of the certainty of the evidence using the GRADE approach

We used the GRADE approach to assess the certainty of the body of evidence relating to the following outcomes for each comparison (NRT versus control; bupropion versus control) (Schünemann 2013), as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019):

- smoking cessation at the latest point in pregnancy (primary outcome);
- mean birthweight (safety outcome). We chose mean birthweight because it can be used as a marker of multiple infant safety outcomes;
- miscarriage and spontaneous abortion (safety outcome). We chose this alongside mean birthweight because it is an important safety outcome that would not be reflected in the above mean birthweight outcome.

We used GRADEpro GDT to import data from Review Manager 5 in order to create 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2) (GRADEpro GDT; Review Manager 2014). A summary of the intervention effect and a measure of certainty for the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for each outcome. The evidence can be downgraded from 'high certainty' by one level for serious (or two levels for very serious) limitations, depending on each of these considerations.

Measures of treatment effect

Dichotomous data

For dichotomous data (all outcomes except mean birthweight), including smoking cessation, we have presented results as summary risk ratios (RR) with 95% confidence intervals (CI). A RR > 1 for the smoking cessation outcomes indicates benefit of the intervention. For undesirable outcomes, such as preterm births, RR < 1 indicates benefit of the intervention.

Continuous data

For mean birthweight (continuous data), we have presented the mean difference (MD) between control and intervention groups with 95% CI.

Unit of analysis issues

Multiple pregnancies

The unit of analysis for smoking cessation was the trial participant, regardless of whether she had a singleton or multiple pregnancy. For all other outcomes, analyses were conducted amongst singleton births only; this approach was undertaken because adverse pregnancy events/outcomes, adverse infant birth outcomes, and poorer infant development are strongly associated with multiple pregnancy. Hence, analysing multiple and singleton pregnancies together for these outcomes could render review findings difficult to interpret. Outcome data from multiple births were insufficient for these to be analysed separately.

Cluster-randomised trials

This study design was eligible for inclusion, however no cluster-randomised trials were identified. If in future updates such trials are identified, we will include them in the analyses along with individually randomised trials. We will adjust their sample sizes or standard errors using the methods described in Sections 16.3.4 and 16.3.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019), employing an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial, or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually randomised trials, we will synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs, and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For the primary smoking abstinence outcome, we assumed any participants lost to follow-up were still smoking or had relapsed to smoking, using the Russell Standard criteria (West 2005). At all outcome points, participants whose smoking status was unknown were assumed to be smoking.

We used the following denominators for other outcomes.

- For the pre-birth outcomes miscarriage/spontaneous abortion 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 fetuses were excluded from the denominator if terminations were performed on a presumed viable fetus 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 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 (i.e. the only birth outcome measured on a continuous scale), the denominator used was the number of singleton births for which this outcome was recorded.
- For dichotomous birth outcomes (e.g. low birthweight, preterm birth, neonatal intensive care admissions, and neonatal death), the denominator used was the number of live births from singleton pregnancies.
- For infant outcomes, the number of live births was used.

For selected secondary outcomes and where appropriate and feasible, we conducted sensitivity analyses to investigate the impact of missing data on pooled treatment effect estimates.

For all outcomes, we carried out analyses, to the greatest degree possible, on an intention-to-treat basis (caveats outlined above); we attempted to include all participants randomised to each group in analyses, and all participants were analysed in the group to which they had been allocated regardless of whether or not they received the allocated intervention.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis visually by inspecting the overlap of 95% CIs for the individual studies on the forest plots. We quantified heterogeneity using the I^2 statistic (Higgins 2019). We regarded heterogeneity as substantial and hence worthy of further investigation (see Subgroup analysis and investigation of heterogeneity) if the I^2 was greater than 50%, and considerable and incompatible with presenting as pooled analyses if greater than 75%. Where it was not possible to perform a meta-analysis due to considerable levels of heterogeneity (I^2 > 75%), we summarised the data for each trial and conducted subgroup analyses (see Subgroup analysis and investigation of heterogeneity) to explore the reasons for the heterogeneity.

Assessment of reporting biases

As there were fewer than 10 studies in all meta-analyses, we did not draw funnel plots to assess the potential for reporting bias. If in future updates of this review there are 10 or more studies, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually if asymmetry is suggested by a visual assessment, and we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using Review Manager 5 software (Review Manager 2014). Following the standard methods of the Cochrane Tobacco Addiction Group for pharmacological interventions, we elected to use a fixed-effect model for meta-analyses of smoking abstinence data. For meta-analyses of safety and adverse events data, we used random-effects models, as effects are likely to vary across populations due to significant differences in baseline risk. Where it was not possible to perform a meta-analysis due to considerable levels of heterogeneity (I^2 > 75%), we have summarised the data for each trial. If in future updates of the review more than 10 studies are included in a meta-analysis, we may consider performing meta-regression to further explore reasons for heterogeneity or to analyse adherence data. A caveat to using this method for adherence data is that there is currently no standard method for reporting adherence; however, for meta-regression to be undertaken, studies must report adherence data similarly.

Subgroup analysis and investigation of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the I^2 statistic. We performed an exploration of heterogeneity for primary and secondary outcomes where the I^2 was greater than 50%. Where substantial heterogeneity was detected between studies, an overall pooled result was presented; however, readers are advised to use caution in interpreting results due to the presence of heterogeneity.

For smoking cessation outcomes, we explored reasons for heterogeneity between the studies using subgroup analyses based on the following groups.

1. Placebo-controlled versus non-placebo-controlled RCTs
2. Studies using different types of NRT, both alone and in combination (i.e. fast-acting NRT and nicotine patch)
3. Low-dose NRT (< 10 mg/24 hours) versus high-dose NRT (> 10 mg/24 hours)

For secondary outcomes, where the I^2 was greater than 50% (indicating substantial heterogeneity), we also performed these subgroup analyses as an exploration of heterogeneity; however, they were not conducted routinely for all secondary outcomes.

We assessed differences between subgroups statistically using subgroup interaction tests, and have presented the P values from these tests.

Sensitivity analysis

We planned two sensitivity analyses using smoking cessation outcomes, depending on the availability of data.

1. Excluding studies rated at high risk of bias overall.
2. Excluding any studies that reported substantially lower treatment adherence than others. As there is no consensus on what constitutes good or acceptable adherence to NRT in pregnancy, we anticipated defining 'low adherence' after consideration of adherence data reported within the included studies.

We were unable to carry out these analyses for the current review (explanations follow in the Results section); they will be undertaken in future review updates, data permitting.

RESULTS

Description of studies

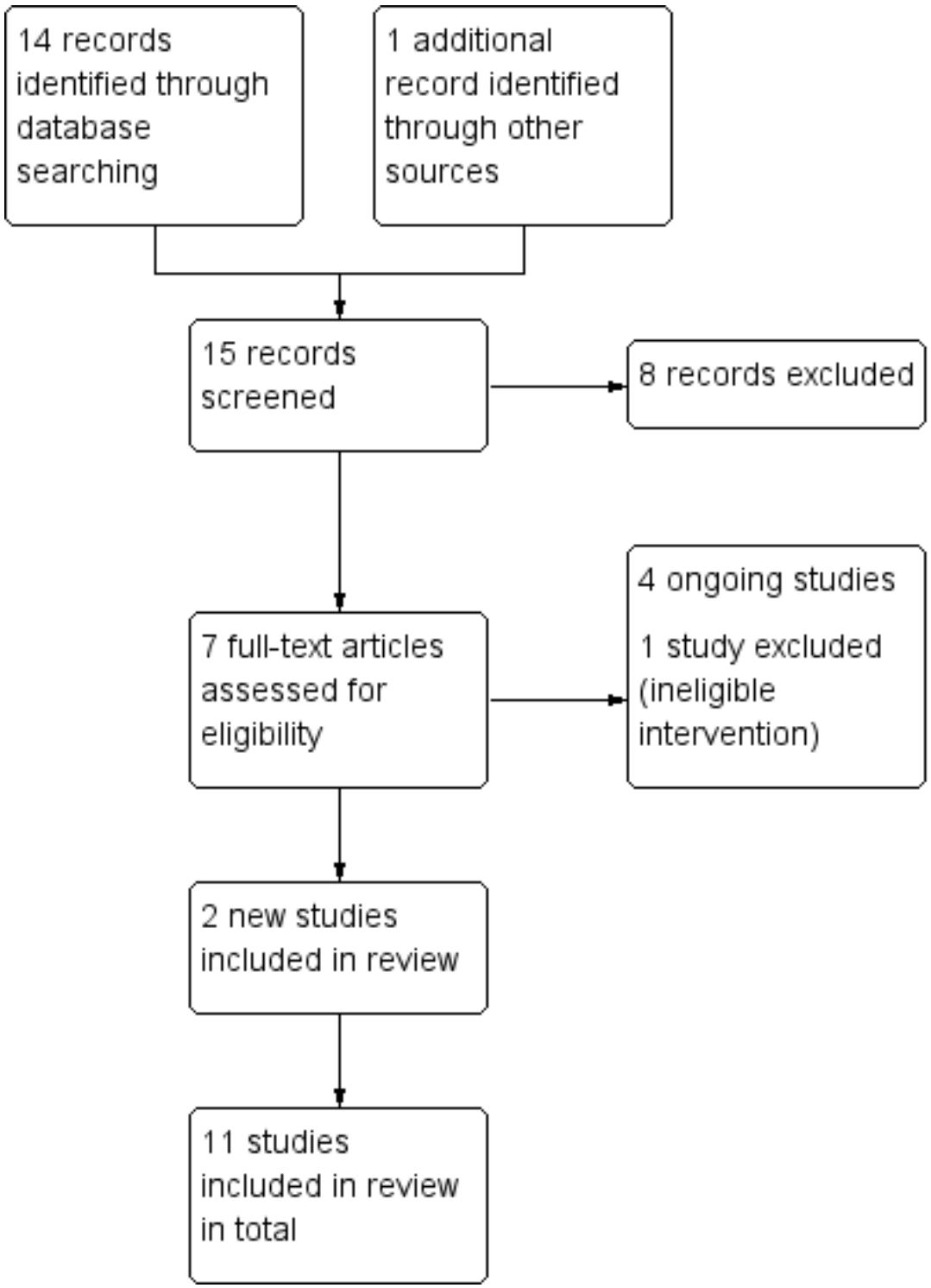
Results of the search

We carried out an updated search of the Cochrane Pregnancy and Childbirth Group's Trials Register on 20 May 2019 and identified 14 trial reports for potential inclusion. We also deemed a further study, which had recently been published and so was not identified by searches, as potentially relevant (Oncken 2019). We identified a total of 15 trial reports for title and abstract screening, of which eight studies were clearly not RCTs and were excluded.

We obtained the full text of the seven remaining records for screening. We excluded one article (Gould 2019), assessed four articles as ongoing studies (see below), and included two articles in this update (Nanovskaya 2017; Oncken 2019). Details of the flow of studies for this update are recorded in a PRISMA diagram in Figure

1. Nine trials included in previous versions of this review are also included in this update (Berlin 2014; Coleman 2012; El-Mohandes 2013; Hotham 2006; Kapur 2001; Oncken 2008; Pollak 2007; Stotts 2015; Wisborg 2000).

Figure 1. Study flow diagram for most recent update.



This updated review therefore includes a total of 11 trials (34 reports). It contains data from two additional trials published since the previous version (Nanovskaya 2017; Oncken 2019), and involves a total of 2412 pregnant women who smoked at study baseline. We added two newly identified reports of Coleman 2012 and two new reports of Berlin 2014. Details of each included study can be found in the Characteristics of included studies table.

Included studies

Interventions

Nine studies investigated the efficacy of different forms of NRT (Berlin 2014; Coleman 2012; El-Mohandes 2013; Hotham 2006; Kapur 2001; Oncken 2008; Oncken 2019; Pollak 2007; Wisborg 2000); two studies investigated bupropion (Nanovskaya 2017; Stotts 2015); and no trials investigated other smoking cessation pharmacotherapies or ECs.

Nicotine replacement therapy studies

All of the included studies investigated the efficacy of NRT provided with behavioural support and compared this with either behavioural support alone or support plus a placebo, therefore studies measured the effect of NRT provided as an adjunct to behavioural support. Seven papers, Berlin 2014; Coleman 2012; Cooper 2014; Kapur 2001; Oncken 2008; Oncken 2019; Wisborg 2000, described six placebo-controlled RCTs (Berlin 2014; Coleman 2012; Kapur 2001; Oncken 2008; Oncken 2019; Wisborg 2000). Three trials compared NRT plus behavioural support with behavioural support alone (El-Mohandes 2013; Hotham 2006; Pollak 2007); participants in these studies could not be blinded to treatment. Two studies used fast-acting NRT, one using nicotine gum, Oncken 2008, and the other nicotine inhalers, Oncken 2019; six trials used nicotine patches (Berlin 2014; Coleman 2012; El-Mohandes 2013; Hotham 2006; Kapur 2001; Wisborg 2000); and one offered a choice of NRT formulations: approximately two-thirds of participants chose patches, whilst the remainder elected to use gum and lozenges (Pollak 2007).

Oncken 2008 used 2 mg nicotine gum, and Oncken 2019 used 4 mg nicotine inhalers. Four studies used 15 mg/16-hour nicotine patches (Coleman 2012; Hotham 2006; Pollak 2007; Wisborg 2000); one of these used a higher nicotine dose (21 mg/24 hours removed at night) for participants who reported smoking more than 15 daily cigarettes (Pollak 2007). Two studies attempted to match nicotine doses prescribed with either saliva, Berlin 2014, or urinary cotinine levels, El-Mohandes 2013, obtained at earlier appointments. Depending on cotinine levels, women in one study were treated with combinations of 10 mg and 15 mg 16-hour patches (Berlin 2014), and in the other study with 21 mg, 14 mg, or 7 mg 24-hour patches, with instructions to remove these at night (El-Mohandes 2013). One trial advised women to use trial treatments from randomisation until childbirth, irrespective of whether or not they had relapsed to smoking (Berlin 2014), and another trial encouraged continued use of treatment for six weeks as long as the woman was actively trying to quit smoking (Oncken 2019). Other trials advised women to stop using NRT if they restarted smoking and had a defined period for use of NRT.

Bupropion studies

Two studies were placebo-controlled RCTs investigating bupropion (Nanovskaya 2017; Stotts 2015). One study experienced recruitment challenges and randomised only 11 women (Stotts 2015). Nanovskaya 2017 initially aimed to randomise 100 women, however after two years the sample size calculation was adjusted as the original calculation was overpowered for craving scores and there was difficulty enrolling participants. The revised sample calculation aimed for 30 participants per treatment group, and 65 were recruited overall. Participants in the Stotts 2015 study were prescribed 150 mg bupropion sustained-release for the first three days of the study, which was then doubled to 300 mg per day (150 mg twice a day) for the remainder of the eight weeks of the trial, whereas Nanovskaya 2017 prescribed participants 300 mg per day (150 mg twice a day) bupropion sustained-release for a duration of 12 weeks.

Setting

Studies were conducted in the USA (n = 6) (El-Mohandes 2013; Nanovskaya 2017; Oncken 2008; Oncken 2019; Pollak 2007; Stotts 2015), Australia (n = 1) (Hotham 2006), Canada (n = 1) (Kapur 2001), Denmark (n = 1) (Wisborg 2000), France (n =1) (Berlin 2014), and England (n = 1) (Coleman 2012). All trials were conducted in public hospitals or antenatal clinics.

Outcomes

The small bupropion trial (n = 11) ascertained smoking cessation at nine weeks after enrolment (mean gestation at enrolment = 16 weeks) (Stotts 2015), and in a small NRT trial (n = 40), smoking cessation was ascertained between 20 and 28 weeks' gestation (Kapur 2001); however, in all other studies this was ascertained at 32 weeks or later. In all of the included studies, biological samples were obtained from participants, and after any required clarification from the authors we determined that all used such samples to validate reported cessation at the primary endpoint: four studies used exhaled carbon monoxide (El-Mohandes 2013; Hotham 2006; Oncken 2008; Oncken 2019); four saliva cotinine (Berlin 2014; Pollak 2007; Stotts 2015; Wisborg 2000); and one used both exhaled carbon monoxide and saliva cotinine (Coleman 2012). One study used both exhaled carbon monoxide and urinary cotinine (Nanovskaya 2017), whilst only one study reported both thiocyanate and cotinine concentrations (cut points are listed in the Characteristics of included studies section) (Kapur 2001). For two studies, cut points were obtained from the trial authors (Pollak 2007; Wisborg 2000), and we obtained further data on biochemical validation from the authors of a trial that used a higher-than-standard cut point for saliva cotinine (26 ng/mL) (Wisborg 2000). This revealed that the cotinine assay used had a lower limit of 20 ng/mL, which was also above the currently accepted cut point of 10 ng/mL, so some women who smoke may have been wrongly categorised as abstinent in this study.

The periods of abstinence from smoking that participants were required to demonstrate varied across studies. For smoking outcomes measured at delivery, three studies reported both seven-day point prevalence abstinence from smoking and a measure of continuous abstinence simultaneously (Berlin 2014; Coleman 2012; Pollak 2007); however, definitions varied. One study, Coleman 2012, permitted a small number of temporary lapses to smoking as recommended by the Russell Standard criteria for outcome measurement in smoking cessation studies (West 2005). The remaining two studies did not permit temporary lapses and defined continuous abstinence as seven-day point prevalence abstinence recorded on three, Pollak 2007, or up to seven occasions (Berlin 2014). Six studies reported only seven-day point prevalence abstinence (Nanovskaya 2017; Oncken 2008; Oncken 2019; Pollak 2007; Stotts 2015; Wisborg 2000), and three reported point prevalence abstinence for an unstated period (El-Mohandes 2013; Hotham 2006; Kapur 2001). Four studies reported seven-day point prevalence abstinence data at time points after childbirth: Wisborg 2000 provided data at three and 12 months postnatally; Coleman 2012 at six, 12, and 24 months; Oncken 2008

at six to 12 weeks (biochemically validated data); and Pollak 2007 at three months. Additionally, Coleman 2012 reported continuous abstinence between a quit date and each time point, allowing for temporary lapses too.

Infant and fetal safety outcomes were reported in eight studies (Berlin 2014; Coleman 2012; El-Mohandes 2013; Nanovskaya 2017; Oncken 2008; Oncken 2019; Pollak 2007; Wisborg 2000). All eight of these studies reported mean birthweight and mean gestation age at delivery, and all but one reported the incidences of low birthweight births (defined as below 2500 g) (Nanovskaya 2017). Six of these studies reported rates of preterm birth defined as born before 37 weeks' gestation (Berlin 2014; Coleman 2012; Oncken 2008; Oncken 2019; Pollak 2007; Wisborg 2000), with one reporting preterm birth defined as born before 34 weeks' gestation (Nanovskaya 2017). Six studies reported rates of miscarriage/spontaneous abortion and stillbirth (Berlin 2014; Coleman 2012; Oncken 2008; Oncken 2019; Pollak 2007; Wisborg 2000), and five trials also reported infants' rates of special care admission and neonatal death (Berlin 2014; Coleman 2012; Nanovskaya 2017; Oncken 2008; Pollak 2007). Three trials reported data on maternal hypertension in pregnancy or measured arterial blood pressure at each visit (Berlin 2014; Coleman 2012; Nanovskaya 2017), three trials reported rates of congenital malformation (Berlin 2014; Coleman 2012; Oncken 2019); and two of these three trials reported rates of caesarean section (Berlin 2014; Coleman 2012). Details of twin-birth pregnancies in studies where these occurred, and for those trials that reported birth outcomes, details of fetal loss in pregnancy and of subsequent live births within singleton pregnancies, are provided in Table 1. Two trials reported single and multiple pregnancy data together, but authors supplied data for singleton pregnancies separately (Berlin 2014; Pollak 2007).

With regard to the pre-birth fetal outcomes of miscarriage/spontaneous abortion and stillbirth, Oncken 2008 reported that, within singleton pregnancies, three control group participants had terminations that were performed for social reasons (presumed healthy fetus), so these fetuses were removed from the denominator for control group analyses (control group n = 91). Also, Pollak 2007 reported one fetal death prior to randomisation that was documented by ultrasound scanning (i.e. a 'missed abortion') in the NRT group, so this fetus was removed from the denominator for the NRT group (NRT group n = 121). Coleman 2012 reported one termination and one fetal death prior to randomisation in women allocated to NRT, so these two cases were removed from the NRT group denominator (NRT group n = 515). Berlin 2014 reported one termination in each trial group, both of which were conducted for fetal abnormalities that were assessed as not being compatible with survival at birth. Consequently, as these terminations were undertaken at 25 (placebo group) and 32 weeks, they have been counted as stillbirths in the analysis and remained in the denominator as well.

Two studies reported self-reported maternal smoking at 12 months after childbirth (Coleman 2012; Wisborg 2000); Coleman 2012 additionally reported infants' "survival without developmental impairment" and respiratory symptoms at two years of age and self-reported maternal smoking at six and 24 months after childbirth.

Ongoing studies

There were five ongoing studies in the previous version of the review. Two of these were completed with results published and are now included studies (Nanovskaya 2017; Oncken 2019). We excluded one study that stopped due to recruitment problems, NCT00744913, and another that was not an RCT (NCT00888979). The one remaining trial is a trial of bupropion and is still recruiting (NCT02188459). We identified four ongoing studies for this update. There is uncertainty regarding the publication of results for one of these trials (NCT01875172), which was retrospectively registered in 2013, but is listed as completed in January 2004. We attempted to contact the author for clarification but were unable to do so. One study appears to offer NRT as part of a multicomponent intervention (ACTRN12618000972224), which would not be included in this review; however, we will wait for further information to become available before making a decision to exclude. The remaining ongoing studies include an NRT trial, IRCT20181209041904N1, and an EC trial (ISRCTN62025374). For further details, see Characteristics of ongoing studies.

Excluded studies

We excluded one trial following full-text screening in this update (Gould 2019). This was a pilot cluster-randomised step-wedge trial, where NRT was part of a multimodal intervention that provided educational resources to health providers at aboriginal medical services. We judged that due to the study design and the multimodal intervention strategy, it was not possible to identify the independent effect of NRT on smoking cessation from this study. Details and reasons for exclusion are shown in the Characteristics of excluded studies table, alongside the two trials previously categorised as ongoing described above (NCT00744913; NCT00888979), and three other previously excluded studies (Eades 2012; Hegaard 2003; Oncken 2009a).

Risk of bias in included studies

We judged four of the 11 included studies to be at low overall risk of bias (Berlin 2014; Coleman 2012; Oncken 2008; Wisborg 2000), three as at high risk of bias (El-Mohandes 2013; Hotham 2006; Pollak 2007), and the remainder unclear risk of bias (Figure 2; Figure 3).

Figure 2. Methodological bias graph: review authors' judgements about each methodological bias item presented as percentages across all included studies.

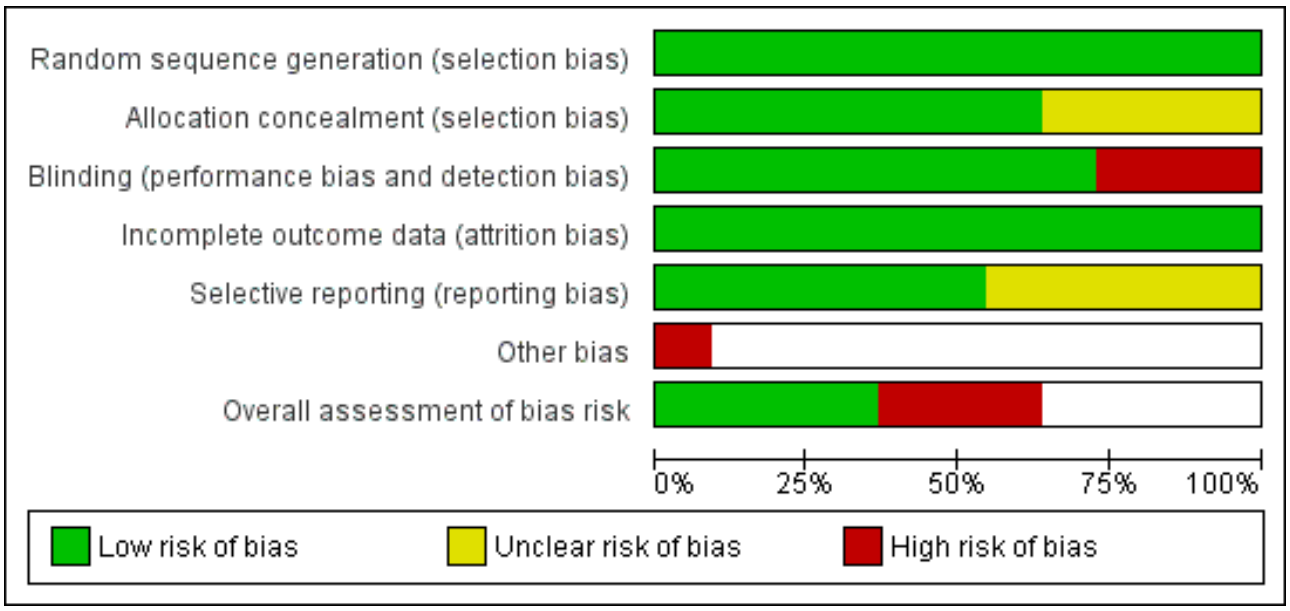
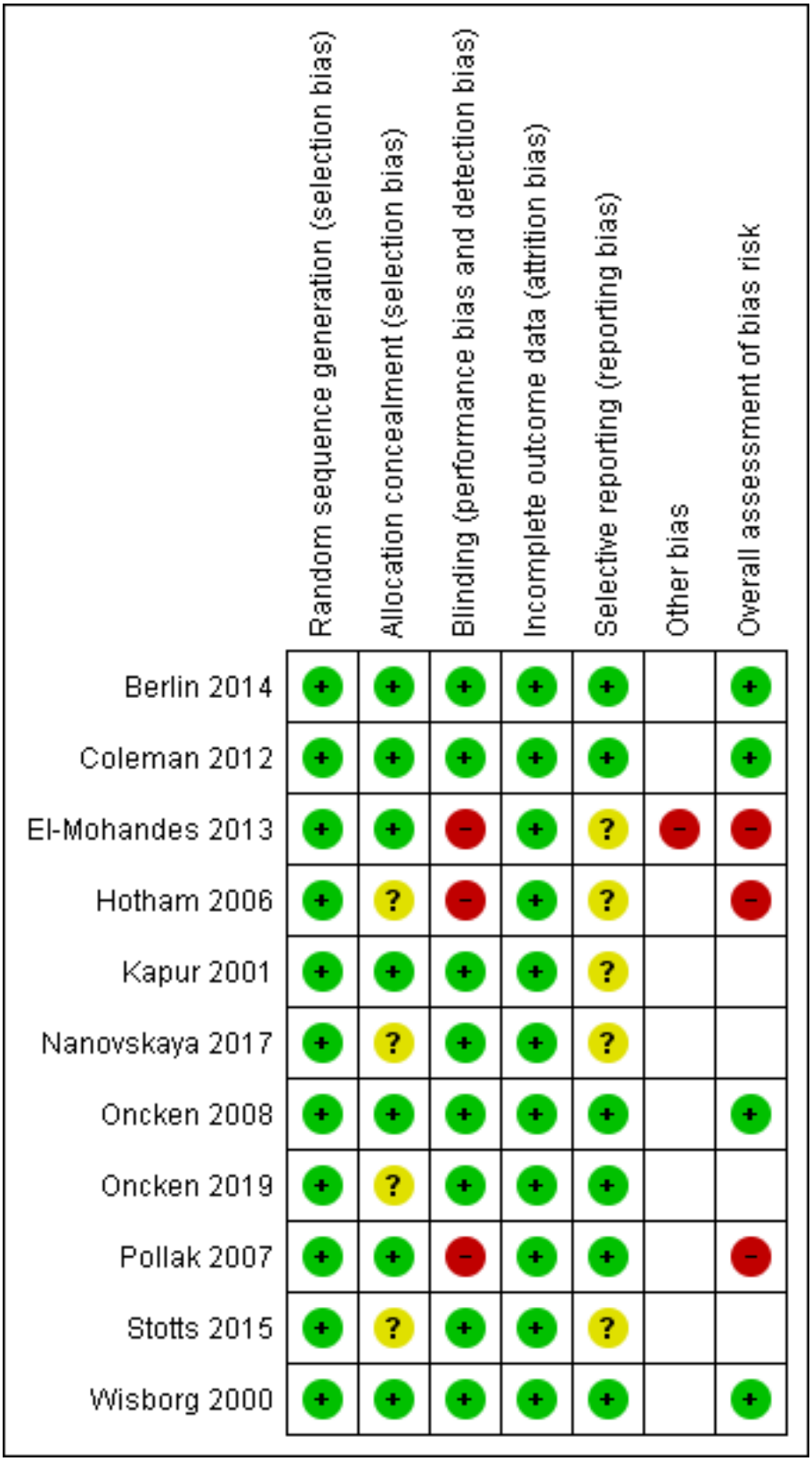


Figure 3. Methodological bias summary: review authors' judgements about each methodological bias item for each included study.



Allocation

Computer-generated random number sequences were used to generate randomisation in most studies. Two studies used urn randomisation methods and were judged to be at low risk of bias for random sequence generation, but were unclear for allocation concealment due to insufficient detail (Nanovskaya 2017; Oncken 2019). One study used sealed envelopes after random numbers had been generated, but it was not clear if these were opaque and sequentially numbered (Hotham 2006), and another study gave no details of how randomisation was operationalised (Stotts 2015); we therefore judged both studies to be unclear at unclear risk of bias for allocation, whilst the others were rated as satisfactory (low risk of bias).

Blinding

We judged studies that had no placebo control to be at a high risk of bias, which was the principal difference between studies that was likely to cause bias. Eight trials were placebo-controlled RCTs (Berlin 2014; Coleman 2012; Kapur 2001; Nanovskaya 2017; Oncken 2008; Oncken 2019; Stotts 2015; Wisborg 2000), and three studies compared behavioural support alone with NRT and behavioural support (El-Mohandes 2013; Hotham 2006; Pollak 2007).

In smoking cessation studies, bias can also occur at outcome ascertainment if trial participants report that they have stopped smoking when actually they have not. Generally, it is perceived that the broadly negative social view of smoking can result in self-perceived pressure on participants in smoking cessation studies to be seen as having successfully stopped smoking, and this may result in false reporting of abstinence from smoking at follow-up. Trialists attempt to minimise this bias (detection bias) through use of biochemical validation of self-reported smoking status data which is collected for trial outcomes. As all included trials biochemically validated self-reported smoking outcomes, this is not a major issue for this review. However, one included study used a cut point for saliva cotinine (26 ng/mL) that was substantially higher than the currently accepted level (10 ng/mL) and, additionally, used an assay with a lower limit of measurement of 20 ng/mL (i.e. samples in the 0 to 20 ng/mL range were reported as 20 ng/mL) (Wisborg 2000). This means that some of those few participants who falsely reported themselves as not smoking in this study might have had their false reports of abstinence validated as true (i.e. some participants who were actually smoking might not have had this detected by the validation process). Of course, no validation process is perfect, and, using any cut point, some false reports of cessation would be accepted to be true, but with a known high cut point as in Wisborg 2000, this would be expected to occur more frequently. However, the use of biochemical validation in this study would still be expected to detect heavier smoking in those who made false reports of abstinence, so validated data from this study were still used in preference to self-report data. One bupropion study also used a relatively high cut point (20 ng/mL), so similar issues are also relevant to that trial (Stotts 2015).

Incomplete outcome data

We judged all studies to be at low risk of bias for smoking abstinence outcomes; all studies carried out an intention-to-treat analysis, so that those participants who could not be contacted at follow-up were assumed to have returned to smoking. It should be noted that this assumption is conservative and is the standard approach taken when assessing the efficacy of smoking cessation interventions. Follow-up for birth outcomes was generally high with one exception: the treatment group allocation for seven women who experienced miscarriage after being randomised within one study could not be ascertained (Wisborg 2000); as this was not the primary outcome, we assessed this trial as at low risk of attrition bias.

Selective reporting

We judged five studies as at unclear risk of reporting bias. Hotham 2006 and Stotts 2015 both collected data on a number of outcomes that were not reported in the trial manuscript; however, it is unclear whether this was a source of bias. We requested birthweight information from Hotham 2006 for our meta-analysis but were unable to obtain it. El-Mohandes 2013 informed us that within their trial, some data on secondary smoking cessation outcomes were collected, but this information was not reported in the trial manuscript; however, primary outcomes were reported. Kapur 2001 did not report any birth outcomes. Nanovskaya 2017 reported measuring low birthweight as an outcome but these data are not presented. Furthermore, this study defined preterm births as any births occurring before 34 weeks' gestation, whereas the current accepted definition is less than 37 weeks' gestation. This means that any births occurring between 34 and 37 weeks' gestation would not be classified as preterm. We judged the remaining six studies to be at low risk of reporting bias.

Other potential sources of bias

We identified an unanticipated potential source of bias in one study (El-Mohandes 2013): two participants were screened and randomised on two separate occasions, with each pregnancy counted as a discrete study participation, and both women included in the trial analysis twice. We considered this as potentially introducing bias into what was a relatively small study, and so judged this study as at high risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Nicotine replacement therapy compared to control for smoking cessation during pregnancy; **Summary of findings 2** Bupropion compared to control for smoking cessation during pregnancy

Data were not identified for all pre-specified outcomes. Where data were available this is summarised below. Where outcomes are not discussed they were not reported.

Primary outcomes (efficacy)

Nicotine replacement therapy

In a pooled analysis of nine included studies and 2336 participants, we found evidence that the use of NRT, as an adjunct to behavioural support, may result in a clinically significant improvement in smoking cessation rates in pregnancy relative to control (risk ratio (RR) 1.37, 95% confidence interval (CI 1.08) to 1.74; I^2 = 34%; Analysis 1.1).

We carried out a subgroup analysis splitting the studies by comparator type - placebo or no placebo- and found evidence of a subgroup difference (P = 0.008; Analysis 1.1). In the subgroup that compared active NRT with placebo, heterogeneity between studies was substantially reduced (I^2 = 0%), however the CIs incorporated the potential for both no effect and a benefit of NRT

for smoking cessation (RR 1.21, 95% CI 0.95 to 1.55; 6 studies, 2063 women; Analysis 1.1), whereas the estimate derived from non-placebo-controlled trials indicated only benefit (RR 8.55, 95% CI 2.05 to 35.71; I^2 = 0%, 3 studies; 273 women), but was limited by substantial imprecision. When analysing the data split into fast-acting and nicotine patch subgroups, the test for subgroup differences provided no evidence that the effect of NRT differed by type (P = 0.08; Analysis 1.2).

We planned to carry out a sensitivity analysis removing all studies judged to be at high risk of bias. The six studies that did not have a high risk of bias for any domain were the same six studies in the placebo-controlled trials subgroup. This analysis and resulting 95% CI found evidence of potentially no clear effect of NRT, as well as the potential for benefit, therefore its interpretation does differ very slightly from that of the overall pooled analysis (Analysis 1.1). We were unable to conduct the planned sensitivity analysis relating to adherence to treatment as trials reported adherence so differently that it was not possible to categorise one or more trials as having substantially worse or better treatment adherence than others.

We investigated the impact of NRT as an adjunct to behavioural support on cessation at time points after childbirth by pooling data from studies that provided postnatal follow-up data on smoking behaviour. In a pooled analysis of studies that reported non-validated seven-day point prevalence smoking abstinence up to six months after childbirth (predominantly at or around three months), there was no clear evidence that NRT compared to placebo or no placebo control was effective for smoking cessation, as CIs incorporated both potential benefit and harm of the intervention (RR 1.22, 95% CI 0.84 to 1.78; I^2 = 0%, 3 studies, 625 women; Analysis 1.3). There was no statistical subgroup difference when comparing studies that were placebo controlled to the one study that was not (P = 0.59). Similarly, the pooled estimate for non-validated seven-day point prevalence smoking abstinence when comparing NRT to placebo at one year after childbirth resulted in CIs that incorporated both a small potentially negative effect of NRT, as well as a potentially positive effect at this time point (RR 1.35, 95% CI 0.97 to 1.88; I^2 = 5%, 2 studies, 1296 women; Analysis 1.4).

The one study that monitored continuous cessation from a quit date set in pregnancy to postnatal time points alongside seven-day point prevalence abstinence data collected at the same time points 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 the NRT group versus 1.7% in the placebo group, adjusted P = 0.12) (Coleman 2012).

Bupropion

In a pooled analysis of the two bupropion studies, we found no clear evidence for an effect of bupropion on smoking cessation during later pregnancy (RR 0.74, 95% CI 0.21 to 2.64; I^2 = 0%, 2 studies, 76 women; Analysis 2.1). However, there was substantial imprecision, with the CIs incorporating both potential benefit and harm, likely due to the small sample size. As neither study was judged to be at high risk of bias, the sensitivity analysis removing studies at high risk of bias was not relevant.

Secondary safety outcomes

Nicotine replacement therapy

Two study papers reported birth outcomes from single- and multiple-birth infants together (Berlin 2014; Pollak 2007); the authors kindly provided data on birth outcomes within singleton pregnancies only. Details of twin births and fetal loss in pregnancy are provided in Table 1.

There was no evidence of a difference in risk of miscarriage/spontaneous abortion between the NRT and control group, and CIs incorporated the possibility of both potential benefit and harm of the intervention (RR 1.60, 95% CI 0.53 to 4.83; I^2 = 0%, 5 studies, 1916 women; Analysis 1.5). However, despite contacting the study authors, we could not determine the treatment allocation for seven miscarriages from one study, which is not included in this comparison (Wisborg 2000). If we assume that all miscarriages from this study occurred in either the NRT or the control group (i.e. the extremes of how these could actually be distributed), this results in the following effect estimates: all assumed in the NRT group: RR 2.15, 95% CI 0.77 to 6.02; all assumed in the control group: RR 1.06, 95% CI 0.38 to 2.97. This has no effect on the interpretation of the results. Similarly, there was no evidence of a clear difference between the numbers of stillbirths in the NRT and control groups (RR 1.24, 95% CI 0.54 to 2.84; I^2 = 0%, 4 studies, 1777 women; Analysis 1.6).

The pooled estimate for birthweight was higher for the NRT group than for the control group, but the CIs incorporated a small decrease in birthweight as well as a more substantial increase (mean difference (MD) 99.73 g, 95% CI −6.65 to 206.10; I^2 = 70%, 7 studies, 2202 women; Analysis 1.7). Heterogeneity was high and on the borderline for presenting pooled estimates; the result for this comparison must therefore be interpreted with caution. The reasons for this heterogeneity are unclear; it is not easily explained by study design as one large placebo-controlled RCT, Coleman 2012, and a smaller non-placebo-controlled one, Pollak 2007, both reported non-significantly lower birthweight in NRT group infants, in contrast to other studies. There was a lower incidence of low birthweight births in women in the NRT group, but again this was not significant and was found in the context of much heterogeneity, so caution is again warranted (RR 0.69, 95% CI 0.39 to 1.20; I^2 = 69%, 7 studies, 2171 women; Analysis 1.8). The pattern of heterogeneity was once again difficult to understand: the same two studies reported non-significantly higher rates of low-birthweight infants in the NRT arm (Coleman 2012; Pollak 2007).

Analyses of rates of preterm births (RR 0.81, 95% CI 0.59 to 1.11; I^2 = 21%, 7 studies, 2182 women; Analysis 1.9), neonatal intensive care unit admissions (RR 0.90, 95% CI 0.64 to 1.27; I^2 = 0%, 4 studies, 1756 women; Analysis 1.10), and neonatal deaths (RR 0.66, 95% CI 0.17 to 2.62; I^2 = 0%, 4 studies, 1746 women; Analysis 1.11) all resulted in CIs spanning one, incorporating the potential for both benefit and harm. We also meta-analysed rates of congenital anomalies and of caesarean birth (2 studies (Berlin 2014; Coleman 2012), 1401 women; Analysis 1.12 and Analysis 1.13, respectively). In both cases the CIs suggested no clear evidence for a benefit or harm of NRT (congenital anomaly: RR 0.73, 95% CI 0.36 to 1.48, I^2 = 0%; caesarean section: RR 1.18, 95% CI 0.83 to 1.69, I^2 = 46%). The three studies that provided data on blood pressure (BP) reported 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 (i.e. BP of greater than 140/90 mmHg) on at least two occasions (no statistical comparison presented). Berlin 2014 reported significantly higher median diastolic BP 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) (P = 0.02). Berlin 2014 also reported an interaction between treatment group and time (i.e. during pregnancy) for increases in diastolic BP, though absolute increases in BP were small.

Coleman 2012 and Berlin 2014 also reported the distribution of other birth outcomes between NRT and placebo groups such as Apgar score at five minutes after birth, cord arterial blood pH, intraventricular haemorrhage, neonatal convulsions, necrotising enterocolitis, mechanical ventilation of infant, assisted vaginal delivery, and maternal death; no statistically significant differences were noted.

Coleman 2012 was the only included study that reported infant outcomes after the neonatal period. Using a composite, self-report outcome based on the Ages and Stages Questionnaire, 3rd edition (ASQ-3) instrument (Squires 2009), significantly better infant developmental outcomes were observed in infants born to women who had been randomised to NRT compared to those in the placebo group. The odds ratio (OR) for infants reaching two years of age 'without developmental impairment' (i.e. normal development) was 1.40 (95% CI 1.05 to 1.86). However, there was no difference in parental reports of infants' respiratory symptoms; the OR for reporting of any respiratory problem in the NRT group was 1.32 (95% CI 0.97 to 1.74).

Bupropion

In the bupropion trials, the pooled estimate for birthweight was higher for the bupropion group than for the control group, but the CIs incorporated evidence for both benefit and harm (MD 122.64 g, 95% CI −98.82 to 344.10; I^2 = 0%, 2 studies, 68 women; Analysis 2.2). Both bupropion studies also found no significant difference in mean length of infants between trial groups (Nanovskaya 2017; Stotts 2015). In the one bupropion study that measured maternal blood pressure (Nanovskaya 2017), there was no difference between the bupropion and placebo groups in systolic (P = 0.46) and diastolic blood pressure (P = 0.40) at the end of pregnancy.

Adherence and adverse effects

Nicotine replacement therapy

Where adherence was reported, this was generally low, as the majority of participants in all studies did not use complete courses of the NRT offered; adherence data reported in trials are summarised in Table 2. Berlin 2014 differed from other studies in that transdermal patches were offered to women between their quit dates and delivery. Much higher self-reported adherence rates were noted in this study; however, it is difficult to reconcile these with reported rates of intervention discontinuation, and direct comparison with other studies was not possible.

Only a narrative reporting of non-serious adverse effect data was possible. Six NRT trials reported non-serious adverse effects (Berlin 2014; Coleman 2012; Hotham 2006; Oncken 2008; Oncken 2019; Wisborg 2000). One trial reported their frequency within women using NRT, noting that five (25%) women in the NRT group experienced minor symptoms, and two women stopped using patches after unpleasant effects (Hotham 2006); however, non-serious adverse effects were not monitored in the control group, so this figure is difficult to interpret. 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. Wisborg 2000 noted that 11 women stated that adverse effects (e.g. skin irritations and headache) made them discontinue patches, but did not report treatment allocations; this trial also reported that five women experienced palpitations and two nausea. Coleman 2012 noted 535 non-serious adverse events reported by 521 NRT group participants and 450 reported by 529 placebo group participants. 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 group suffered a skin reaction at the patch site compared with 4% in the placebo group. Oncken 2019 reported a significantly higher number of adverse effects in women using the nicotine inhaler (11%) than the placebo inhaler (0%) (P = 0.008). These adverse events included throat irritation, cough, and nausea. Furthermore, two women in this study were discontinued from the nicotine inhaler group due to repeated elevations in cotinine concentrations exceeding more than 40% of their baseline cotinine concentration.

Bupropion

Both bupropion trials reported non-serious adverse effects (Nanovskaya 2017; Stotts 2015). Stotts 2015 reported that two women suffered from vomiting in the bupropion group. Other adverse effects in the bupropion group included dry mouth, loss of appetite, and agitation. In the placebo group, one woman experienced agitation, and two reported nausea. None of these women decided to discontinue the medication. Nanovskaya 2017 noted that women in both groups reported known adverse effects such as headache (29% bupropion, 11% placebo), difficulty sleeping (25% bupropion, 7% placebo), runny nose (17% bupropion, 7% placebo), dry mouth (37.5% bupropion, 14% placebo), and anxiety (33% bupropion, 18% placebo). However, there was no statistical differences between groups.

DISCUSSION

Summary of main results

Overall there is low-certainty evidence that NRT used alongside behavioural support by pregnant women for smoking cessation may increase smoking abstinence in late pregnancy (Summary of findings for the main comparison). Caution is required when interpreting this pooled estimate, as subgroup analyses revealed potentially different treatment effects when comparing NRT to placebo-controlled versus non-placebo-controlled studies. These findings may be due to unexplained biases potentially within the less robust, non-placebo-controlled trials. The actual efficacy of NRT used for smoking cessation in pregnancy is uncertain and may be lower than the pooled summary estimate (Analysis 1.1). Further subgroup analysis found no evidence that the effect of NRT on abstinence is moderated by the type of NRT used, that is patches versus fast-acting NRT, and there was no consistent evidence of NRT having either a positive or negative impact on birth outcomes.

We identified only two small bupropion trials, which provided no clear evidence that bupropion improved smoking cessation outcomes later in pregnancy. Similarly, we found no evidence that

bupropion has any impact on birth outcomes. Due to the low certainty and scarcity of the evidence, future research is likely to change some of these conclusions.

We identified no eligible trials of varenicline or ECs for inclusion in the review.

Overall completeness and applicability of evidence

All of the included studies were conducted in high-income countries, with only one study specifically recruiting women from ethnic minority backgrounds. These findings may therefore not be applicable to low-middle-income countries if smoking patterns of women or beliefs about using medication in pregnancy differ, and more evidence is needed from these populations.

An exclusion criterion for this review was unmatched additional intervention components in the intervention or comparator arms. As a result the only difference between trial arms was the provision of pharmacotherapy (NRT or bupropion). This means that we can be confident that we have isolated the independent effects of the interventions of interest to our review question.

It has been mandatory since July 2005 for clinical trials to be recorded on a trials register. In this update we searched trials registers from inception, therefore we are confident that we have identified all reported ongoing trials.

The findings reported in this review are based on currently accepted, evidence-based, biochemical verification cut points for determining abstinence from smoking (SRNT 2002), rather than ones that might have been acceptable in the past, enhancing the validity of our findings.

Certainty of the evidence

The included trials had varied 'Risk of bias' ratings, as discussed in the Risk of bias in included studies section. We assessed four of the 11 included studies to be at low risk of bias, three at high risk of bias, and the remainder at unclear risk of bias. We judged the principal difference in studies' propensity to bias to be due to the use/non-use of placebo controls. The reduction in heterogeneity observed after dividing trials according to this criterion seemed to validate this judgement. Trials that were judged to be at an unclear risk of bias lacked information regarding allocation concealment or did not report prespecified outcomes. It is possible, but relatively unlikely, that the lack of information regarding allocation concealment indicates bias.

We assessed the certainty of the evidence using the GRADE approach. Our GRADE assessment of pooled data indicated that the evidence for the smoking cessation outcome in NRT trials was of low certainty (Summary of findings for the main comparison), meaning that the true effect might be markedly different from the estimated effect. The current evidence was downgraded twice, once due to risk of bias: in the subgroup of studies at low or unclear risk of bias the effect was no longer statistically significant, and there were significant subgroup differences when comparing these studies to the three studies judged to be at high risk of bias. We downgraded the evidence further due to imprecision, as there were few events, and confidence intervals spanned both minimal clinical benefit and considerable clinical benefit. We assessed the evidence for the safety outcomes in NRT trials, mean birthweight and miscarriage, to be of low certainty. The mean birthweight outcome was downgraded due to inconsistency where heterogeneity was high and not explained by subgroup differences, and was further downgraded due to imprecision, as the confidence intervals encompassed no difference as well as a clinically significant benefit. The miscarriage and spontaneous abortion outcome was downgraded two levels to low certainty due to imprecision, as there were too few events, and confidence intervals encompassed both no difference and potential harm.

Our GRADE assessment indicated that the evidence for the smoking cessation and mean birthweight outcomes in bupropion trials was of low certainty (Summary of findings 2), meaning that the true effects might be markedly different from the estimated effects. We downgraded the evidence in both cases twice for imprecision due to the small number of events.

The downgrading of the evidence for all outcomes due to imprecision suggests that further research will be beneficial in increasing the reliability and precision of effect estimates and the certainty we are able to place in them.

Potential biases in the review process

We performed the search for studies in this area using the Cochrane Pregnancy and Childbirth Group's Trials Register. It is unlikely that studies that have been conducted have been missed, however it is possible that unpublished studies, or ongoing studies not registered in clinical trial registries, could be missing. Should we identify any such studies, we will include them in future updates of the review. Secondly, we were unable to produce a funnel plot as there were too few studies, and it is possible there was publication bias. In future updates where there are sufficient trials we will be able to assess publication bias more rigorously. Unfortunately, we were unsuccessful in contacting the author for one bupropion trial, where the trial record states that it was completed in 2004 (NCT01875172). This could have had a significant impact on the bupropion results in this review as it states that it enrolled 135 participants, which is larger than both trials included in this review. However, the certainty of the evidence would still likely be downgraded for imprecision. Finally, we aimed to reduce bias wherever possible by having at least two review authors independently conduct study selection, data extraction, and 'Risk of bias' assessment.

Agreements and disagreements with other studies or reviews

This review explicitly assesses the efficacy and safety of pharmacological therapies used for smoking cessation in pregnancy. Some trials of smoking cessation in pregnancy test NRT as part of multimodal intervention strategies, and these are included in an associated review (Chamberlain 2017). However, this review was concerned with the efficacy and safety of pharmacological therapies when used for smoking cessation in pregnancy, and examines the independent safety and efficacy of pharmacological interventions.

We have been unable to identify any other systematic reviews that investigate the efficacy of smoking cessation medications in pregnancy since the previous version of this review was published (Coleman 2015). A systematic review of trials conducted in non-pregnant women has shown that NRT is effective outside of pregnancy (Hartmann-Boyce 2018). The reasons why NRT may not

be as effective in pregnancy are not known; however, variations in adherence to NRT or nicotine metabolism compared to the general population may play a part. Women in trials included in the current review made relatively little use of offered NRT. If this low adherence explains the difference in findings between this and the 'non-pregnancy' NRT review (Hartmann-Boyce 2018), then understanding the phenomenon of low adherence could be important. Lack of efficacy could also be explained by the increased metabolism of nicotine in pregnancy (Dempsey 2001). This may result in NRT generating lower blood nicotine concentration in pregnancy, and this reduced nicotine substitution could, in turn, increase women's experience of withdrawal symptoms, causing them to stop NRT early. A recent systematic review found that pregnant women using NRT were exposed to significantly lower concentrations of nicotine compared to those who continued to smoke tobacco (Hickson 2019). Furthermore, a secondary analysis of a trial included in our review found that pregnant women who both smoke and use nicotine patches had similar cotinine concentrations, smoke less, and exhale less carbon monoxide, therefore they are likely to be exposed to fewer tobacco smoke toxins (Claire 2019a). An increased metabolism of nicotine during pregnancy results in lower exposure, and coupled with the likelihood that nicotine is unlikely to be responsible for the majority of fetal harms caused by tobacco smoke, it is likely that NRT is safer for the fetus than smoking (Kumar 2019). Logically, if in trials to date, increased metabolism underpinned women's low adherence to NRT, higher doses of NRT could be needed for this to be effective in pregnancy.

We were unable to identify any other systematic reviews that investigated the efficacy of smoking cessation medications in pregnancy, and we did not identify any RCTs investigating varenicline for smoking cessation. However, a recent systematic review and meta-analysis assessed the safety of bupropion and varenicline in pregnancy (Turner 2018). This review included cohort, case-control studies, and case reports as well as the two bupropion RCTs included in this review. The authors of Turner 2018 were unable to find any evidence that either bupropion or varenicline was harmful in pregnancy, but neither were they able to identify any strong evidence that they were safe to use in pregnancy.

AUTHORS' CONCLUSIONS

Implications for practice

- The evidence suggests that nicotine replacement therapy (NRT) may be effective for smoking cessation in pregnancy, however there is uncertainty surrounding this evidence. It is also unclear whether NRT affects the risk of adverse pregnancy and infant outcomes, but there is no evidence that it is harmful. One study suggests that NRT improves child development outcomes at two years.
- There is insufficient evidence on either the effectiveness or safety of bupropion, varenicline, or e-cigarettes in pregnancy to guide clinical practice.

Implications for research

- There is a strong case for further trials to examine the effectiveness and safety of NRT against placebo. NRT leads to lower blood nicotine concentrations than when smoking and is effective in the general population (Hartmann-Boyce 2018), however there are also reasons why it may be less effective for pregnant women than for the general population, and the evidence in pregnant women is uncertain.
- As adherence to NRT in pregnant women is low, further research should seek to understand why this is and improve it and use an appropriate behavioural strategy to enhance adherence in future trials of NRT.
- In the general population, there is evidence that 25 mg/16-hour patches are more effective than 15 mg/16-hour patches (Lindson 2019); most studies in this review used 15 mg patches. Consequently, trials are needed in pregnant women using either higher-dose nicotine patches or combination of patch plus rapid-acting forms of NRT, which are also more effective (Lindson 2019).
- Given that NRT may be effective, and there is some evidence for the effectiveness of nicotine-delivering e-cigarettes to support smoking cessation in the general population (Hartmann-Boyce 2016), trials of e-cigarettes to support smoking cessation in pregnancy would be valuable because e-cigarettes are more popular than NRT.
- Trials of bupropion and varenicline for smoking cessation in pregnancy may be justified providing the preclinical data do not raise substantial safety concerns equivalent to the risk of continued smoking in pregnancy.

ACKNOWLEDGEMENTS

Ravinder Claire's PhD is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM). This project was funded through an NIHR Programme for Applied Research (Programme number RP-PG-0615-20003). Professor Coleman is an NIHR Senior Investigator. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

REFERENCES

References to studies included in this review

Berlin 2014 *{published data only}*

Berlin I, Golmard JL, Jacob N, Tanguy ML, Heishman SJ. Cigarette smoking during pregnancy: do complete abstinence and low level cigarette smoking have similar impact on birth weight?. *Nicotine & Tobacco Research* 2017;**19**(5):518-24.

* Berlin I, Grange G, Jacob N, Tanguy ML. Nicotine patches in pregnant smokers: randomised, placebo controlled, multicentre trial of efficacy. *BMJ* 2014;**348**:1622.

Claire R, Coleman T, Leonardi-Bee J, Berlin I. Saliva cotinine concentrations in pregnant women who smoke and use nicotine patches. *Addiction* 2019;**114**(9):1651-8.

NCT00507975. Study of Nicotine Patch in Pregnancy (SNIPP). clinicaltrials.gov/ct2/show/NCT00507975 (first received 27 July 2007).

Coleman 2012 *{published data only}*

Bowker KA, Lewis S, Coleman T, Vaz LR, Cooper S. Comparison of cotinine levels in pregnant women whilst smoking and when using nicotine replacement therapy. *Nicotine & Tobacco Research* 2014;**16**(6):895-8.

* Coleman T, Cooper S, Thornton JG, Grainge MJ, Watts K, Britton J, et al. Smoking, Nicotine, and Pregnancy (SNAP) Trial Team. A randomized trial of nicotine-replacement therapy patches in pregnancy. *New England Journal of Medicine* 2012;**366**:808-18.

Coleman T, Thornton J, Britton J, Lewis S, Watts K, Coughtrie MW, et al. Protocol for the smoking, nicotine and pregnancy (SNAP) trial: double-blind, placebo-randomised, controlled trial of nicotine replacement therapy in pregnancy. *BMC Health Services Research* 2007;**3**(7):2.

Cooper S, Lewis S, Thornton JG, Marlow N, Watts K, Britton J, et al. Smoking, Nicotine and Pregnancy Trial Team. 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 Technology Assessment* 2014;**18**(54):1-128.

Cooper S, Taggar J, Lewis S, Marlow N, Dickinson A, Whitemore R, et al. Smoking, Nicotine and Pregnancy (SNAP) Trial Team. Effect of nicotine patches in pregnancy on infant and maternal outcomes at 2 years: follow-up from the randomised, double-blind, placebo-controlled SNAP trial. *Lancet Respiratory Medicine* 2014;**2**(9):728-37.

Essex HN, Parrott S, Wu Q, Li J, Cooper S, Coleman T. Cost-effectiveness of nicotine patches for smoking cessation in pregnancy: a placebo randomised controlled trial (SNAP). *Nicotine & Tobacco Research* 2014;**17**(6):636-42.

Grainge M, Coleman T, Cooper S, Thornton J, Watts K, Britton J, et al. Double-blind, placebo-controlled randomised trial of nicotine replacement therapy patches in pregnancy. *Journal of Perinatal Medicine* 2012;**39 Suppl**:172.

Thornton JG, Coleman T, Britton J, Cooper S, Watts K, Lewis S, et al. The smoking, nicotine and pregnancy (SNAP) trial: main results. *Archives of Disease in Childhood: Fetal and Neonatal Edition* 2011;**96**(Suppl 1):Fa109.

Vaz LR, Aveyard P, Cooper S, Leonardi-Bee J, Coleman T. The association between treatment adherence to nicotine patches and smoking cessation in pregnancy: a secondary analysis of a randomized controlled trial. *Nicotine & Tobacco Research* 2016;**18**(10):1952-9.

Vaz LR, Coleman T, Cooper S, Aveyard P, Leonardi-Bee J. The nicotine metabolite ratio in pregnancy measured by *trans*-3'-hydroxycotinine to cotinine ratio: characteristics and relationship with smoking cessation. *Nicotine & Tobacco Research* 2015;**17**(11):1318-23.

El-Mohandes 2013 *{published data only}*

* El-Mohandes AAE, Windsor R, Tan S, Perry D, Gantz M, Kiely M. A randomized clinical trial of trans-dermal nicotine replacement in pregnant African-American smokers. *Maternal & Child Health Journal* 2013;**17**(5):897-906.

* NCT00341432. Effectiveness of nicotine replacement therapy in reducing the risk of nicotine exposure in pregnant minority smokers. clinicaltrials.gov/ct2/show/NCT00341432?term=NCT00341432&rank=1) (first received 21 June 2006).

Hotham 2006 *{published data only (unpublished sought but not used)}*

Atkinson E, Hotham L, Baghurst P. Nicotine replacement therapy as an adjunct to smoking cessation counselling in pregnancy: a randomised study to evaluate efficacy in an antenatal clinic setting. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2003;**43**(2):177-87.

* Hotham ED, Gilbert AL, Atkinson ER. A randomised-controlled pilot study using nicotine patches with pregnant women. *Addictive Behaviors* 2006;**31**(4):641-8.

Hotham ED, Gilbert AL, Atkinson ER. Case studies of three pregnant smokers and their use of nicotine replacement therapy. *Midwifery* 2005;**21**(3):224-32.

Kapur 2001 *{published data only}*

Kapur B, Hackman R, Selby P, Klein J, Koren G. Randomized, double-blind, placebo-controlled trial of nicotine replacement therapy in pregnancy. *Current Therapeutic Research - Clinical and Experimental* 2001;**62**(4):274-8.

Nanovskaya 2017 *{published data only}*

Nanovskaya T, Fokina VM, West H, Oncken C, Ahmed MS, Hankins G. Initial assessment of smoking status of pregnant women enrolled in a clinical trial for smoking cessation. *Drug and Alcohol Dependence* 2017;**100**(171):e150-1.

* Nanovskaya TN, Oncken C, Fokina VM, Feinn RS, Clark SM, West H, et al. Bupropion sustained release for pregnant smokers: a randomized, placebo-controlled trial. *American Journal of Obstetrics & Gynecology* 2017;**216**(4):420.e1-e9.

Oncken 2008 *{published data only}*

* Oncken C, Dornelas E, Greene J, Sankey H, Glasmann A, Feinn R, et al. Nicotine gum for pregnant smokers: a randomized controlled trial. *Obstetrics & Gynecology* 2008;**112**(4):859-67.

Oncken C, Dornelas E, Greene J, Sankey H, Glasmann A, Kranzler HR. Nicotine gum for pregnant smokers: a randomized controlled trial. 70th Annual Scientific Meeting of the College on Problems on Drug Dependence; 2008 June 14-19; San Juan, Puerto Rico. 2008:143.

Oncken 2019 *{published data only}*

* Oncken C, Dornelas EA, Kuo CL, Sankey HZ, Kranzler HR, Mead EL, et al. Randomized trial of nicotine inhaler for pregnant smokers. *American Journal of Obstetrics & Gynecology MFM* 2019;**1**(1):19-23. [DOI: 10.1016/j.ajogmf.2019.03.006]

Pollak 2007 *{published data only}*

Fish LJ, Peterson BL, Namenek-Brouwer RJ, Lyna P, Oncken CA, Swamy GK, et al. Adherence to nicotine replacement therapy among pregnant smokers. *Nicotine & Tobacco Research* 2009;**11**(5):514-8.

* Pollak KI, Oncken CA, Lipkus IM, Lyna P, Swamy GK, Pletsch PK, et al. Nicotine replacement and behavioral therapy for smoking cessation in pregnancy. *American Journal of Preventive Medicine* 2007;**33**(4):297-305.

Pollak KI, Oncken CA, Lipkus IM, Peterson BL, Swamy GK, Pletsch PK, et al. Challenges and solutions for recruiting pregnant smokers into a nicotine replacement therapy trial. *Nicotine & Tobacco Research* 2006;**8**(4):547-54.

Pollak KI, Oncken CA, Lipkus IM, Peterson BL, Swamy GK, Pletsch PK, et al. Effectiveness of adding nicotine replacement therapy to cognitive behavioural therapy for smoking cessation in pregnant smokers: the Baby Steps Trial. Society for Research on Nicotine and Tobacco 13th Annual Meeting; 2007 Feb 21-24; Austin, Texas. 2007:25, Abstract no: PA6-3.

Swamy GK, Roelands JJ, Peterson BL, Fish LJ, Oncken CA, Pletsch PK, et al. Predictors of adverse events among pregnant smokers exposed in a nicotine replacement therapy trial. *American Journal of Obstetrics & Gynecology* 2009;**201**:354.e1-e7.

Stotts 2015 *{published data only}*

NCT01286402. Double blind, placebo-controlled pilot study of Bupropion to promote smoking cessation during pregnancy. https://clinicaltrials.gov/ct2/show/NCT01286402 (first received 4 February 2016).

* Stotts AL, Northrup TF, Cinciripini PM, Minnix JA, Blalock JA, Mullen PD, et al. Randomized, controlled pilot trial of bupropion for pregnant smokers: challenges and future directions. *American Journal of Perinatology* 2015;**32**(4):351-6.

Wisborg 2000 *{published data only}*

Wisborg K. Nicotine patches to pregnant smokers - a randomised study. 1st International Conference of the Society for Research on Nicotine and Tobacco; 1998 Aug 22-23; Copenhagen. 1998.

* Wisborg K, Henriksen TB, Jespersen LB, Secher NJ. Nicotine patches for pregnant smokers: a randomized controlled study. *Obstetrics & Gynecology* 2000;**96**(6):967-71.

References to studies excluded from this review

Eades 2012 *{published data only}*

* 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):42-6.

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.

Gould 2019 *{published data only}*

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.

* 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.

Hegaard 2003 *{published data only}*

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.

NCT00744913 *{published data only (unpublished sought but not used)}*

NCT00744913. Study of nicotine replacement therapy in pregnancy [Randomized, controlled open-label study of nicotine replacement therapy in pregnancy]. clinicaltrials.gov/show/NCT00744913 (first received 1 September 2008).

NCT00888979 *{published data only}*

NCT00888979. Pilot study of nicotine replacement for smoking cessation during pregnancy. clinicaltrials.gov/show/NCT00888979 (first received 28 April 2009).

Oncken 2009a *{published data only}*

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.

References to ongoing studies

ACTRN12618000972224 *{published data only}*

ACTRN12618000972224. SISTAQUIT (Supporting Indigenous Smokers to Assist Quitting) [SISTAQUIT (Supporting Indigenous Smokers to Assist Quitting): a cluster randomised controlled trial to improve strategies for the management of smoking cessation in pregnant Aboriginal and/or Torres Strait Islander women]. www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374707 (first received 20 March 2018).

IRCT20181209041904N1 *{published data only}*

IRCT20181209041904N1. Comparison of the effectiveness of treatment with nicotine patches versus support behavior in smoking cessation in pregnant women. en.irct.ir/trial/35928 (first received 21 December 2018).

ISRCTN62025374 *{published data only}*

ISRCTN62025374. Helping pregnant smokers quit: a multi-centre study of electronic cigarettes and nicotine patches [Helping pregnant smokers quit: a multi-centre randomised controlled trial of electronic cigarettes and nicotine patches]. www.isrctn.com/ISRCTN62025374 (first received 20 March 2017).

NCT01875172 *{published data only}*

NCT01875172. Bupropion for smoking cessation in pregnancy [Smoking cessation in pregnancy: a pilot study comparing counseling with and without sustained-release bupropion]. clinicaltrials.gov/show/NCT01875172 (first received 11 June 2013).

NCT02188459 *{published data only}*

NCT02188459. Placebo-controlled trial of bupropion for smoking cessation in pregnant women (BIBS) [Placebo-controlled trial of bupropion for smoking cessation in pregnant women]. clinicaltrials.gov/show/NCT02188459 (first received 11 July 2014).

Additional references

Al-Sahab 2010

Al-Sahab B, Saqib M, Hauser G, Tamim H. Prevalence of smoking during pregnancy and associated risk factors among Canadian women: a national survey. *BMC Pregnancy and Childbirth* 2010;**10**:24. [DOI: 10.1186/1471-2393-10-24]

Andreski 1995

Andreski P, Breslau N. Maternal smoking among blacks and whites. *Social Science and Medicine* 1995;**41**(2):227-33.

Aveyard 2007

Aveyard R, West R. Managing smoking cessation. *BMJ* 2007;**335**:37-41.

Barbeau 2013

Barbeau AM, Burda J, Siegel M. Perceived efficacy of e-cigarettes versus nicotine replacement therapy among successful e-cigarette users: a qualitative approach. *Addiction Science & Clinical Practice* 2013;**8**(1):5.

Baric 1977

Baric L, MacArthur C. Health norms in pregnancy. *British Journal of Preventive and Social Medicine* 1977;**31**(1):30-8.

Belbasis 2016

Belbasis L, Savvidou MD, Kanu C, Evangelou E, Tzoulaki I. Birth weight in relation to health and disease in later life: an umbrella review of systematic reviews and meta-analyses. *BMC Medicine* 2016;**14**(1):147.

Benowitz 2000

Benowitz NL, Dempsey DA, Goldenberg RL, Hughes JR, Dolan-Mullen P, Ogburn PL, et al. The use of pharmacotherapies for smoking cessation during pregnancy. *Tobacco Control* 2000;**9 Suppl 3**(0964-4563):III91-4.

Bentley 2016

Bentley JP, Roberts CL, Bowen JR, Martin AJ, Morris JM, Nassar N. Planned birth before 39 weeks and child development: a population-based study. *Pediatrics* 2016;**138**(6):e20162002.

Blalock 2005

Blalock JA, Fouladi RT, Wetter DW, Cinciripini PM. Depression in pregnant women seeking smoking cessation treatment. *Addictive Behaviors* 2005;**30**(6):1195-208.

Blalock 2011

Blalock JA, Nayak N, Wetter DW, Schreindorfer L, Minnix JA, Canul J, et al. The relationship of childhood trauma to nicotine dependence in pregnant smokers. *Psychology of Addictive Behaviors* 2011;**25**(4):652.

Bruin 2010

Bruin JE, Gerstein HC, Holloway AC. Long-term consequences of fetal and neonatal nicotine exposure: a critical review. *Toxicological Sciences* 2010;**116**(2):364-74.

Bush 2003

Bush J, White M, Kai J, Rankin J, Bhopal R. Understanding influences on smoking in Bangladeshi and Pakistani adults: community based, qualitative study. *BMJ* 2003;**326**:962.

Cahill 2016

Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Systematic Reviews* 2016, Issue 5. [DOI: 10.1002/14651858.CD006103.pub7]

CAN-ADAPTT 2011

CAN-ADAPTT. Canadian smoking cessation clinical practise guideline: summary statements. www.peelregion.ca/health/professionals/events/pdf/2013/canadaptt-summary-statements.pdf.

CDC 2002

Centers for Disease Control and Prevention. Women and smoking: a report of the Surgeon General (executive summary). Morbidity and Mortality Weekly Report 51 (No. RR-12) 2002; Vol. 51, issue RR-12.

Chamberlain 2017

Chamberlain C, O'Mara-Eves A, Porter J, Coleman T, Perlen SM, Thomas J, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. *Cochrane Database of Systematic Reviews* 2017, Issue 2. [DOI: 10.1002/14651858.CD001055.pub5]

Chan 2001

Chan A, Keane RJ, Robinson JS. The contribution of maternal smoking to preterm birth, small for gestational age and low birth weight among aboriginal and non-aboriginal births in South Australia. *Medical Journal of Australia* 2001;**174**(8):389-93.

Claire 2019a

Claire R, Coleman T, Leonardi-Bee J, Berlin I. Saliva cotinine concentrations in pregnant women who smoke and use nicotine patches. *Addiction* 2019;**114**(9):1651-8.

Claire 2019b

Claire R, Cooper SE, Leonardi-Bee J, Coleman T, Davey M-A, Chamberlain C, et al. Pharmacological interventions for promoting smoking cessation during pregnancy. www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019140195.

Cnattingius 2004

Cnattingius S. The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. *Nicotine & Tobacco Research* 2004;**6**(S2):S125-40.

Cobb 2010

Cobb NK, Byron MJ, Abrams DB, Shields PG. Novel nicotine delivery systems and public health: the rise of the "e-cigarette". *American Journal of Public Health* 2010;**100**(12):2340-2.

Coe 2005

Coe JW, Brooks PR, Vetelino MG, Wirtz MC, Arnold EP, Huang J, et al. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. *Journal of Medicinal Chemistry* 2005;**48**(10):3474-7.

Coleman 2011

Coleman T, Chamberlain C, Cooper S, Leonardi-Bee J. Efficacy and safety of nicotine replacement therapy for smoking cessation in pregnancy: systematic review and meta-analysis. *Addiction* 2011;**106**(1):52-61.

Cooper 2014

Cooper S, Taggar J, Lewis S, Marlow N, Dickinson A, Whitemore R, et al. Effect of nicotine patches in pregnancy on infant and maternal outcomes at 2 years: follow-up from the randomised, double-blind, placebo-controlled SNAP trial. *Lancet Respiratory Medicine* 2014;**2**(9):728-37.

Crawford 2008

Crawford JT, Tolosa JE, Goldenberg RL. Smoking cessation in pregnancy: why, how, and what next. *Clinical Obstetrics and Gynecology* 2008;**51**(2):419-35.

Crittenden 2007

Crittenden KS, Manfredi C, Cho YI, Dolecek TA. Smoking cessation processes in low-SES women: the impact of time-varying pregnancy status, healthcare messages, stress and health concerns. *Addictive Behaviors* 2007;**32**(7):1347-66.

Cryan 2003

Cryan JF, Bruijnzeel AW, Skjei KL, Markou A. Bupropion enhances brain reward function and reverses the affective and somatic aspects of nicotine withdrawal in the rat. *Psychopharmacology* 2003;**168**(3):347-58.

Dempsey 2001

Dempsey DA, Benowitz NL. Risks and benefits of nicotine to aid smoking cessation in pregnancy. *Drug Safety* 2001;**24**(4):277-322.

Dixon 2009

Dixon L, Aimer P, Fletcher L, Guilliland K, Hendry C. Smoke free outcomes with midwife lead maternity carers: an analysis of smoking during pregnancy from the New Zealand College of Midwives Midwifery database 2004-2007. *New Zealand College of Midwives Journal* 2009;**40**:13-9.

Ebert 2007

Ebert LM, Fahy K. Why do women continue to smoke in pregnancy?. *Women and Birth* 2007;**20**(4):161-8.

Filippidis 2017

Filippidis FT, Laverty AA, Gerovasili V, Vardavas CI. Two-year trends and predictors of e-cigarette use in 27 European Union member states. *Tobacco Control* 2017;**26**(1):98-104.

Fish 2009

Fish LJ, Peterson BL, Namenek Brouwer RJ, Lyna P, Oncken CA, Swamy GK, et al. Adherence to nicotine replacement therapy among pregnant smokers. *Nicotine & Tobacco Research* 2009;**11**(5):514-8.

Frost 1994

Frost FJ, Cawthorn ML, Tollestrup K, Kenny FW, Schrager LS, Nordlund DJ. Smoking prevalence during pregnancy for women who are and women who are not Medicaid-funded. *American Journal of Preventive Medicine* 1994;**10**(2):91-6.

Fryer 1999

Fryer JD, Lukas RJ. Noncompetitive functional inhibition at diverse, human nicotinic acetylcholine receptor subtypes by bupropion, phencyclidine, and ibogaine. *Journal of Pharmacology and Experimental Therapeutics* 1999;**288**(1):88-92.

Gaither 2009

Gaither KH, Brunner-Huber LR, Thompson ME, Huet-Hudson YM. Does the use of nicotine replacement therapy during pregnancy affect pregnancy outcomes. *Maternal and Child Health Journal* 2009;**13**(4):497-504.

Gilligan 2007

Gilligan C, Sanson-Fisher R, Eades S, D'Este C. Antenatal smoking in vulnerable population groups: an area of need. *Journal of Obstetrics and Gynaecology* 2007;**27**(7):664-71.

Giovino 2007

Giovino GA. The tobacco epidemic in the United States. *American Journal of Preventive Medicine* 2007;**33**(6 Suppl):S318-26.

Gluckman 2008

Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in-utero and early life conditions on adult health and disease. *New England Journal of Medicine* 2008;**359**(1):61-73.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEproGDT. Version accessed 13 January 2020. Hamilton (ON): McMaster University (developed by Evidence Prime).

Graham 1976

Graham H. Smoking in pregnancy: the attitudes of pregnant mothers. *Social Science and Medicine* 1976;**10**(7-8):399-405.

Graham 1996

Graham H. Smoking prevalence among women in the European community 1950-1990. *Social Science and Medicine* 1996;**43**(2):243-54.

Graham 2010

Graham H, Hawkins SS, Law C. Lifecourse influences on women's smoking before, during and after pregnancy. *Social Science and Medicine* 2010;**70**(4):582-7.

Green 2005

Green NS, Damus K, Simpson JL, Iams J, Reece EA, Hobel CJ, et al. Research agenda for preterm birth: recommendations from the March of the Dimes. *American Journal of Obstetrics and Gynecology* 2005;**193**(3 Pt 1):626-35.

Hajek 2019

Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *New England Journal of Medicine* 2019;**380**(7):629-37.

Hammoud 2005

Hammoud AO, Bujold E, Sorokin Y, Schild C, Krapp M, Baumann P. Smoking in pregnancy revisited: findings from a large population-based study. *American Journal of Obstetrics & Gynecology* 2005;**192**(6):1856-63.

Hartmann-Boyce 2016

Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews* 2016, Issue 9. [DOI: 10.1002/14651858.CD010216.pub3]

Hartmann-Boyce 2018

Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database of Systematic Reviews* 2018, Issue 5. [DOI: 10.1002/14651858.CD000146.pub5]

Herrmann 2008

Herrmann M, King K, Weitzman M. Prenatal tobacco smoke and postnatal secondhand smoke exposure and child neurodevelopment. *Current Opinion in Pediatrics* 2008;**20**(2):184-90.

Hickson 2019

Hickson C, Lewis S, Campbell KA, Cooper S, Berlin I, Claire R, et al. Comparison of nicotine exposure during pregnancy when smoking and abstinent with nicotine replacement therapy: systematic review and meta-analysis. *Addiction* 2019;**114**(3):406-24.

Higgins 2019

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Hughes 2014

Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database of Systematic Reviews* 2014, Issue 1. [DOI: 10.1002/14651858.CD000031.pub4]

Hunt 2003

Hunt J. Trying to Make a Difference: Improving Pregnancy Outcomes, Care and Services for Australian Indigenous Women [thesis]. Victoria: LaTrobe University, 2003.

Kaplan 1997

Kaplan SD, Lanier AP, Merritt RK, Siegel PZ. Prevalence of tobacco use among Alaska natives: a review. *Preventive Medicine* 1997;**26**(4):460-5.

Kramer 1987

Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. *Bulletin of the World Health Organization* 1987;**65**(5):663-737.

Kumar 2019

Kumar R, Gould GS. Tobacco harm reduction for women who cannot stop smoking during pregnancy - a viable option?. *JAMA Pediatrics* 2019;**173**(7):615-6.

Lange 2018

Lange S, Probst C, Rehm J, Popova S. National, regional, and global prevalence of smoking during pregnancy in the general population: a systematic review and meta-analysis. *Lancet Global Health* 2018;**6**(7):e769-76.

Lanting 2012

Lanting CI, van Wouwe JP, van den Burg I, Segaar D, van der Pal-de Bruin KM. Smoking during pregnancy: trends between 2001 and 2010 [Roken tijdens de zwangerschap: trends in de periode 2001-2010]. *Nederlands Tijdschrift Voor Geneeskunde* 2012;**156**(46):A5092.

Lerman 2002

Lerman C, Roth D, Kaufmann V, Audrain J, Hawk L, Liu A, et al. Mediating mechanisms for the impact of bupropion in smoking cessation treatment. *Drug and Alcohol Dependence* 2002;**67**(2):219-23.

Lindson 2019

Lindson N, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews* 2019, Issue 4. [DOI: 10.1002/14651858.CD013308]

Liu 2016

Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet* 2016;**388**(10063):3027-35.

Maritz 2009

Maritz GS. Are nicotine replacement therapy, varenicline or bupropion options for pregnant mothers to quit smoking? Effects on the respiratory system of the offspring. *Therapeutic Advances in Respiratory Disease* 2009;**3**(4):193-210.

Marufu 2015

Marufu TC, Ahankari A, Coleman T, Lewis S. Maternal smoking and the risk of still birth: systematic review and meta-analysis. *BMC Public Health* 2015;**15**(1):239.

McBride 2003

McBride CM, Emmons KM, Lipkus IM. Understanding the potential of teachable moments: the case of smoking cessation. *Health Education Research* 2003;**18**(2):156-70.

McCowan 2009

McCowan LME, Dekker GA, Chan E, Stewart A, Chappell LC, Hunter M, et al. Spontaneous preterm birth and small for gestational age infants in women who stop smoking early in pregnancy: prospective cohort study. *BMJ* 2009;**338**:b1081.

McNeill 2018

McNeill A, Brose LS, Calder R, Bauld L, Robson D. Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England. London: Public Health England; 2018 February.

NICE 2010

National Institute for Clinical Excellence (NICE). Smoking: stopping in pregnancy and after childbirth [PH26]. London: NICE; 2010 June. London: National Institute for Clinical Excellence.

Notley 2019

Notley C, Gentry S, Livingstone-Banks J, Bauld L, Perera R, Hartmann-Boyce J. Incentives for smoking cessation. *Cochrane Database of Systematic Reviews* 2019, Issue 7. [DOI: 10.1002/14651858.CD004307.pub6]

Oncken 2009b

Oncken CA, Kranzler HR. What do we know about the role of pharmacotherapy for smoking cessation before or during pregnancy?. *Nicotine & Tobacco Research* 2009;**11**(11):1265-73.

Oncken 2010

Oncken CA, Dietz PA, Tong VT, Belizan JM, Tolosa JE, Berghella V, et al. Prenatal tobacco prevention and cessation interventions for women in low- and middle-income countries. *Acta Obstetricia et Gynecologica Scandinavica* 2010;**89**(4):442-53.

Oncken 2017

Oncken C, Ricci KA, Kuo CL, Dornelas E, Kranzler HR, Sankey HZ. Correlates of electronic cigarettes use before and during pregnancy. *Nicotine & Tobacco Research* 2017;**19**(5):585-90.

Pickett 2009

Pickett KE, Wilkinson RG, Wakschlag LS. The psychosocial context of pregnancy smoking and quitting in the Millennium Cohort Study. *Journal of Epidemiology and Community Health* 2009;**63**(6):474-80.

Polosa 2011

Polosa R, Caponnetto P, Morjaria JB, Papale G, Campagna D, Russo C. Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study. *BMC Public Health* 2011;**11**(1):786.

Potter 1996

Potter A, Lumley J, Watson L. The 'new' risk factors for SIDS: is there an association with ethnic and place of birth differences in incidence in Victoria?. *Early Human Development* 1996;**45**:119-31.

Quinn 1991

Quinn VP, Mullen PD, Ershoff DH. Women who stop smoking spontaneously prior to prenatal care and predictors of relapse before delivery. *Addictive Behaviors* 1991;**16**(1-2):29-40.

RACGP 2014

The Royal Australian College of General Practitioners. Supporting smoking cessation: a guide for health professionals. www.racgp.org.au/FSDEDEV/media/documents/Clinical%20Resources/Guidelines/Supporting-smoking-cessation.pdf (accessed prior to 14 February 2020).

RANZCOG 2014

Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Women and smoking. ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Women-and-Smoking-(C-Obs-53)-Review-November-2014_1.pdf?ext=.pdf (accessed prior to 14 February 2020).

Review Manager 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Richmond 2003

Richmond R. You've come a long way baby: women and the tobacco epidemic. *Addiction* 2003;**98**(5):553-7.

Rore 2008

Rore C, Brace V, Danielian P, Williams D. Smoking cessation in pregnancy. *Expert Opinion on Drug Safety* 2008;**7**(6):727-37.

Ryan 1980

Ryan P, Booth R, Coates D, Chapman A, Healy P. Experiences of Pregnancy. Pregnant Pause Campaign. Sydney: Health Commission of New South Wales, Division of Drug and Alcohol Services, 1980.

Salihu 2007

Salihu HM, Wilson RE. Epidemiology of prenatal smoking and perinatal outcomes. *Early Human Development* 2007;**83**(11):713-20.

Samet 2001

Samet JM, Yoon SY. Women and the Tobacco Epidemic: Challenges for the 21st Century. Geneva: World Health Organization, 2001.

Schneider 2008

Schneider S, Schutz J. Who smokes during pregnancy? A systematic literature review of population-based surveys conducted in developed countries between 1997 and 2006. *European Journal of Contraception and Reproductive Health Care* 2008;**13**(2):138-47.

Schünemann 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.guidelinedevelopment.org/app/handbook/handbook.html.

Slemmer 2000

Slemmer JE, Martin BR, Damaj MI, Slemmer JE, Martin BR, Damaj MI. Bupropion is a nicotinic antagonist. *Journal of Pharmacology & Experimental Therapeutics* 2000;**295**(1):321-7.

Small 2000

Small R. Mothers in a New Country (MINC) [thesis]. Victoria: LaTrobe University, 2000.

Squires 2009

Squires J, Twombly E, Bricker D, Potter L. ASQ-3 User's Guide for the Ages and Stages Questionnaires. 3rd Edition. Baltimore: Paul H Brookes Publishing Co, 2009.

SRNT 2002

SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. *Nicotine & Tobacco Research* 2002;**4**(2):149-59.

Stead 2013

Stead LF, Hartmann-Boyce J, Perera R, Lancaster T. Telephone counselling for smoking cessation. *Cochrane Database of Systematic Reviews* 2013, Issue 8. [DOI: 10.1002/14651858.CD002850.pub2]

Stedman 1968

Stedman RL. The chemical composition of tobacco and tobacco smoke. *Chemical Reviews* 1968;**68**(2):153-207.

Tappin 1996

Tappin DM, Ford RP, Nelson KP, Wild CJ. Prevalence of smoking in early pregnancy by census area, measured by anonymous cotinine testing of residual antenatal blood samples. *New Zealand Medical Journal* 1996;**109**(1018):101-3.

Tappin 2010

Tappin DM, MacAskill S, Bauld L, Eadie D, Shipton D, Galbraith L. Smoking prevalence and smoking cessation services for pregnant women in Scotland. *Substance Abuse: Treatment, Prevention, and Policy* 2010;**5**. [DOI: 10.1186/1747-597X-5-1]

The NHS Information Centre 2011

The NHS Information Centre (IFF Research). Infant feeding survey 2010. Early results. Health Care and Social Care Information Centre. London: The National Health Service Information Centre for Health and Social Care, 2011:1-22.

Tong 2009

Tong VT, Jones JR, Dietz PM, D'Angelo D, Bombard JM. Trends in smoking before, during, and after pregnancy - Pregnancy Risk Assessment Monitoring System (PRAMS), United States, 31 sites, 2000-2005. *Morbidity and Mortality Weekly Report* 2009;**58**:1-29.

Troe 2008

Troe EJ, Raat H, Jaddoe VW, Hofman A, Steegers EA, Verhulst FC, et al. Smoking during pregnancy in ethnic populations: the Generation R study. *Nicotine & Tobacco Research* 2008;**10**(8):1373-84. [PUBMED: 18686185]

Tsoi 2013

Tsoi DT, Porwal M, Webster AC. Interventions for smoking cessation and reduction in individuals with schizophrenia. *Cochrane Database of Systematic Reviews* 2013, Issue 2. [DOI: 10.1002/14651858.CD007253.pub3]

Turner 2018

Turner E, Jones M, Vaz LR, Coleman T. Systematic review and meta-analysis to assess the safety of bupropion and varenicline in pregnancy. *Nicotine & Tobacco Research* 2018;**21**(8):1001-10.

US DHHS 2004

US Department of Health and Human Services. The Health Consequences of Smoking. 2004 Surgeon General's Report. US Department of Health and Human Services, 2004.

US DHHS 2016

US Department of Health and Human Services. E-cigarette use among youth and young adults. A report of the Surgeon General. Atlanta (GA): US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2016.

Wanless 2004

Wanless D. Securing Good Health for the Whole Population. London: TSO, 2004.

West 2001

West R, Shiffman S. Effect of oral nicotine dosing forms on cigarette withdrawal symptoms and craving: a systematic review. *Psychopharmacology* 2001;**155**(2):115-22.

West 2005

West R, Hajek P, Stead L, Stapleton J, West R, Hajek P, et al. Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction* 2005;**100**(3):299-303.

West 2008

West R, Baker CL, Cappelleri JC, Bushmakin AG. Effect of varenicline and bupropion SR on craving, nicotine withdrawal symptoms, and rewarding effects of smoking during a quit attempt. *Psychopharmacology* 2008;**197**(3):371-7.

WHO 2019

World Health Organization. WHO Report on the Global Tobacco Epidemic, 2019. www.who.int/tobacco/global_report/en/.

Wiemann 1994

Wiemann CM, Berenson AB, San Miguel VV. Tobacco, alcohol and illicit drug use among pregnant women: age and racial/ethnic differences. *Journal of Reproductive Medicine* 1994;**39**(10):769-76.

Woodby 1999

Woodby LL, Windsor RA, Snyder SW, Kohler CL, Diclemente CC. Predictors of smoking cessation during pregnancy. *Addiction* 1999;**94**(2):283-92.

Zhu 2017

Zhu SH, Zhuang YL, Wong S, Cummins SE, Tedeschi GJ. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. *BMJ* 2017;**358**:j3262.

References to other published versions of this review

Coleman 2012

Coleman T, Chamberlain C, Davey MA, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD010078]

Coleman 2015

Coleman T, Chamberlain C, Davey MA, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database of Systematic Reviews* 2015, Issue 12. [DOI: 10.1002/14651858.CD010078.pub2]

Lumley 1995a

Lumley J. Advice as a strategy for reducing smoking in pregnancy. In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.) Pregnancy and Childbirth Module. In: The Cochrane Pregnancy and Childbirth Database [database on disk and CDROM] The Cochrane Collaboration; Issue 2, Oxford: Update Software; 1995.

Lumley 1995b

Lumley J. Behavioural strategies for reducing smoking in pregnancy. In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.) Pregnancy and Childbirth Module. In: The Cochrane Pregnancy and Childbirth Database [database on disk and CDROM] The Cochrane Collaboration; Issue 2, Oxford: Update Software; 1995.

Lumley 1995c

Lumley J. Counselling for reducing smoking in pregnancy. In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.) Pregnancy and Childbirth Module. In: The Cochrane Pregnancy and Childbirth Database [database on disk and CDROM] The Cochrane Collaboration; Issue 2, Oxford: Update Software; 1995.

Lumley 1995d

Lumley J. Feedback as a strategy for reducing smoking in pregnancy. In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.) Pregnancy and Childbirth Module. In: The Cochrane Pregnancy and Childbirth Database [database on disk and CDROM] The Cochrane Collaboration; Issue 2, Oxford: Update Software; 1995.

Lumley 1995e

Lumley J. Strategies for reducing smoking in pregnancy. In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.) Pregnancy and Childbirth Module. In: The Cochrane Pregnancy and Childbirth Database [database on disk and CDROM] The Cochrane Collaboration; Issue 2, Oxford: Update Software; 1995.

Lumley 1999

Lumley J, Oliver S, Waters E. Interventions for promoting smoking cessation during pregnancy. *Cochrane Database of Systematic Reviews* 1999, Issue 4. [DOI: 10.1002/14651858.CD001055]

Lumley 2004

Lumley J, Oliver S, Chamberlain C, Oakley L. Interventions for promoting smoking cessation in pregnancy. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD001055.pub2]

Lumley 2009

Lumley J, Chamberlain C, Dowswell T, Oliver S, Oakley L, Watson L. Interventions for promoting smoking cessation during pregnancy. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD001055.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Berlin 2014

Methods	Double-blind, placebo-controlled, parallel-group RCT
Participants	476 pregnant women aged ≥ 18 years, between 9 and 20 weeks' gestation who smoked at least 5 daily cigarettes and scored at least 5 on a scale measuring motivation for quitting smoking (range 0 to 10)
Interventions	Intervention and control differed only in the provision of active or visually identical placebo transdermal patches. The intervention patch delivered nicotine as nicotine replacement therapy over a 16-hour period. Both 10 mg and 15 mg patches were used, and women's doses ranged from 10 mg to 30 mg per day. A saliva sample was collected at the woman's first trial visit/contact with the research team. Between this and a second visit/contact, which occurred 2 weeks later, women were instructed to either stop smoking or to reduce this to less than 5 daily cigarettes. Women who managed to reduce or stop smoking in this way were, at their second visit, randomised to either placebo or active patch in a 1:1 ratio. The nicotine dose used for women's first prescription of NRT (made at this 2nd trial visit) was based on their saliva cotinine level obtained from the sample given at visit 1 with the aim being to attempt 100% substitution of nicotine obtained from smoking for that obtained via patches. Women were instructed to use NRT from their quit date until delivery. Smoking and using patches was not encouraged (this is described as a "safety concern"). However, if women did have a temporary lapse to smoking, they were allowed to remain on NRT afterwards. Both groups received counselling on how to use patches.
Outcomes	There were 2 primary outcomes, 1 maternal and 1 relating to infants: complete, continuous abstinence from smoking since the quit date and infant birthweight. A positive abstinence outcome was recorded where women self-reported 7 days abstinence from smoking at each study visit, and this was confirmed by an exhaled CO reading of 8 ppm or less. There were up to 7 study visits with the final visit intended for 1 month prior to delivery; no lapses to smoking were permitted.
Notes	The cessation outcome used was more stringent than in many studies; often some allowance for temporary lapses to smoking is permitted, and many studies assess smoking status as a smaller number of time points in pregnancy. Dates of study: October 2007 to January 2013 Funding sources: "This study was funded by the Ministry of Health, France (grant No MA05 00150) and co-sponsored by Assistance publique-Hôpitaux de Paris (P060604).The Ministry of Health and Assistance publique-Hôpitaux de Paris had no role in the design and conduct of the study; the collection, conduct, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript." Gunnar Gustavsson and McNeil-Johnson & Johnson provided the nicotine and placebo patches free of charge. Declarations of interest: "All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that: none had support of any kind for the submitted work; IB has served as a paid consultant for Pfizer, Novartis, and Ethypharm in the past three years; none of the authors' spouses, partners, or children has financial relationships that may be relevant to the submitted work; and none of the authors has non-financial interests that may be relevant to the submitted work."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation list (allocation ratio 1:1) in blocks of 4 was prepared and kept double-blinded. 60 randomisation numbers were established by centre. In case of more than 60 randomisations by centre, the next randomisation list of 60 was added. The randomisation list by centre was incorporated into the electronic case report form, and the randomisation

Berlin 2014 *(Continued)*

		number was attributed automatically at the completion of the randomisation visit.
Allocation concealment (selection bias)	Low risk	A statistician at the clinical research centre of the Assistance publique-Hôpitaux de Paris, who was fully independent of the trial, prepared the random, computer-generated allocation sequence. The randomisation code was kept in a sealed envelope in a safe. A copy of the randomisation code was kept separately in case of a serious adverse event necessitating exposure of a participant's group assignment. Investigators, members of the co-ordination centre, hospital pharmacists, and the study statistician were kept blinded until the code was opened before witnesses on 19 February 2013.
Blinding (performance bias and detection bias) Women and clinical staff	Low risk	All study staff (investigators, pharmacists, members of the co-ordination centre and of the drug safety monitoring board, laboratory staff, statistician) were double-blinded to treatment allocation. Placebo patches were identical (visually) to active ones. Determination of saliva cotinine levels was carried out blinded, and investigators were not aware of the results. Exhaled CO used with cut point of 8 ppm or less used to validate 7 days' abstinence from smoking.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There are similar rates of attendance for all trial visits, but no data are presented on attendance at individual trial visits. However, for smoking outcomes all women who could not be contacted are assumed to be still smoking, so the potentially low follow-up rates do not affect this. Follow-up rates for birth outcomes are high (e.g. only 3 women had no delivery data).
Selective reporting (reporting bias)	Low risk	All prespecified outcomes appear to have been reported.
Overall assessment of bias risk	Low risk	See all of above; no substantial sources of bias identified.

Coleman 2012

Methods	Double-blind, placebo-controlled RCT – stratified by trial centre only
Participants	Pregnant women (n = 1050) who agreed to set a quit date, were 16 to 50 years of age, were at 12 to 24 weeks of gestation, smoked 10 or more cigarettes daily before pregnancy, currently smoked 5 or more cigarettes daily, and had an exhaled CO concentration of at least 8 ppm
Interventions	Intervention and control conditions differed only in the provision of transdermal patches; the intervention group received active patches and the control group received placebo patches. Research midwives were trained to provide behavioural support according to national standards, with the use of a manual that included guidance from a British expert trainer of smoking-cessation professionals and behavioural approaches from the Smoking Cessation or Reduction in Pregnancy Treatment trials that were believed to be relevant to British people who smoke. At enrolment, research midwives provided behavioural support lasting up to 1 h, and participants agreed to a quit date within the following 2 weeks; follow-up was timed from the quit date. Subsequently, participants were randomly assigned to receive a 4-week supply of transdermal patches for NRT (at a dose of 15 mg per 16 h) or visually identical placebos, which were started on the quit date (all study treatment was purchased at market rates from United Pharmaceuticals). 1 month after the quit date, women who were not smoking, as validated by an exhaled CO concentration of less than 8 ppm, were issued another 4-week supply of patches. In addition to behavioural support at enrolment, research midwives provided 3 sessions of behavioural support by telephone to participants: 1 session on the quit date, 1 session 3 days afterward, and 1 session at 4 weeks. The women who collected a 2nd month's supply of nicotine-replacement or placebo patches also received face-to-face support from the research midwife at the time of collection. Women

Coleman 2012 *(Continued)*

	were offered additional support from local National Health Service smoking cessation services and were encouraged to ask for support from the research midwives or smoking cessation service staff; support was provided according to the manual.
Outcomes	Prolonged smoking cessation between a quit date soon after enrolment and delivery, validated by both exhaled CO monitoring and saliva cotinine estimation. Cut points: exhaled CO, smoking was defined as > 7 ppm; saliva cotinine, smoking defined as > 9 ng/dL. Birth outcomes including Apgar score at 5 min after birth, cord arterial blood pH, intraventricular haemorrhage, neonatal convulsions, congenital abnormalities, necrotising enterocolitis, mechanical ventilation of infant, assisted vaginal delivery, maternal death, and caesarean section. For infants: survival to 2 years of age without developmental impairment, reported respiratory symptoms. Maternal: self-reported abstinence from smoking for at least 7 days reported at 6, 12, and 24 months after childbirth, prolonged abstinence from smoking since a quit date set in pregnancy and until 24-month follow-up (defined as having validate abstinence at delivery followed by reported abstinence at all outcome points listed above).
Notes	Dates of study: May 2007 to February 2010 Funding sources: "Supported by a grant from the NIHR Health Technology Assessment Programme (06/07/01)" Declarations of interest: "No potential conflict of interest relevant to this article was reported."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence, in random permuted blocks of randomly varying size and with stratification by recruiting site
Allocation concealment (selection bias)	Low risk	Allocation and dispensing of treatment/placebo packages by external clinical trials unit, with all study staff and participants unaware of study allocation. “Identically packaged study patches were dispensed, and all participants and study personnel were unaware of the study assignments”
Blinding (performance bias and detection bias) Women and clinical staff	Low risk	It was clear from study text that participants and clinicians were adequately blinded. Although the report does not state that the outcome assessor was adequately blinded, this was confirmed in communication with the Chief Investigator, who stated that the clinicians acted as outcome assessors and were completely blinded. Biochemical validation of smoking cessation conducted at follow-up points prior to and around childbirth but not afterwards.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant excluded postrandomisation due to accidentally being enrolled twice (control group); all other participants were included in intention-to-treat analysis. Intervention: 36 were excluded (24 lost to follow-up, 3 withdrew consent, 9 had fetal or infant death). Control: 33 were excluded (22 lost to follow-up, 7 withdrew consent, 4 had fetal or infant death). Also, groups appeared to be balanced at follow-up, with 60% follow-up rates for smoking outcomes and much higher rates for infant outcomes.

Coleman 2012 *(Continued)*

Selective reporting (reporting bias)	Low risk	Very detailed report of all outcomes and adverse outcomes
Overall assessment of bias risk	Low risk	No substantial sources of bias identified.

El-Mohandes 2013

Methods	Non-placebo, parallel-design RCT
Participants	52 English-speaking pregnant women who smoked and were residents of Washington, DC in the USA, of ethnic minority backgrounds, aged at least 18 years, and less than 30 weeks' gestation. Women needed to express a desire to quit and have an expired-air CO reading of 8 ppm or less and a salivary cotinine of 20 ng/mL or less (NB: ClinicalTrials.gov website says 30 ng/mL or less) or a urinary cotinine of 100 ng/mL or less.
Interventions	1:1 ratio randomisation, stratified by site and initial salivary cotinine levels to either 1) cognitive behavioural therapy (CBT) and NRT transdermal patches or 2) CBT alone. NRT: a 10-week course of 24-hour patches was offered, with initial dosing varying with baseline salivary cotinine measurements. Women with levels of ≥ 100 ng/mL were issued 21 mg patches for 2 weeks, 14 mg patches for 4 weeks, and finally 7 mg patches for 4 weeks. Women with levels of ≥ 20 ng/mL and ≤ 100 ng/mL were issued 14 mg patches for 6 weeks and 7 mg patches for 4 weeks. The first batch of patches was issued at the 2nd study visit at which salivary cotinine levels were available. Participants were given clear verbal and written instructions on patch use. They were advised never to smoke whilst using the patch, to remove the patch before going to sleep, and not to use other NRT concurrently. CBT: this was the same for both groups.
Outcomes	Smoking cessation outcome: during the study participants made 6 visits to the study team in the antenatal period. At visit 2 (V2), trial interventions were initiated, and at each of visits V3 to V6 (the last before childbirth), women were asked if they had smoked since their previous clinic visit (e.g. at V3, they were asked if they had smoked since V2). Participants who reported smoking cessation had this validated using exhaled CO, with abstinence viewed as confirmed by a reading of < 8 ppm. The trial manuscript reports point prevalence of abstinence from smoking at each time point, and data from V6 are used in analyses. All data were validated (self-report not available), but the period of abstinence that was validated is unclear and varied with the interval between clinic visits. Secondary outcomes reported in the trial manuscript: premature birth (i.e. at < 37 weeks' gestation); gestational age at birth; mean birthweight and low birthweight < 2500 g. The following outcomes were also collected, as clarified by the authors: ability to not smoke for 24 h or more; longest number of days that the woman was able to go without even a puff of smoking; frequency of smoking at least puff during the last 7 days; number of cigarettes smoked each day; number of cigarettes smoked during the past 24 h; and frequency of use of other forms of tobacco.
Notes	TItle of paper states that it was conducted in "African-American smokers", but in manuscript participants are described as "ethnic minority women", and inclusion criteria on ClinicalTrials.gov includes Hispanic women. Dates of study: July 2006 to May 2010 Funding sources: "This study was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (U10 HD036104 and U18 HD031206-07). This research was supported, in part, by the intramural program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development."

El-Mohandes 2013 *(Continued)*

Declarations of interest: "None of the authors have any competing interests to declare."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation in a 1:1 ratio was stratified by site and initial salivary cotinine levels. A web-based database management system was programmed to randomise after entering the necessary data to verify eligibility.
Allocation concealment (selection bias)	Low risk	Randomisation is remote from research staff, so this seems appropriate (see text from manuscript above).
Blinding (performance bias and detection bias) Women and clinical staff	High risk	No placebo, so participants were not blind to treatment allocation; however, those delivering the behavioural intervention were blind to participants' treatments, and the intensity of interventions/contact with participants was standardised in both groups. Those conducting telephone interviews were blind to allocation, and smoking behaviour data "was collected through a self-administered form, completed and sealed by the participant at the end of visits 2-6 and only available to researchers at the end of the study". Exhaled CO validation using a cut point of < 8 ppm was employed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat appears to have been conducted adequately for smoking outcomes, and there was relatively little data attrition for infant outcomes, so we considered risk of bias to be low.
Selective reporting (reporting bias)	Unclear risk	Adherence data were collected, but these were not reported. Some secondary outcomes (regarding smoking) were not reported.
Other bias	High risk	In addition to the issues highlighted above, 2 women were screened and randomised twice – each pregnancy counted as separate study participation, and both were included in the analysis. Additionally, 1 woman in the NRT and CBT group received no NRT. Given the small size of this trial, both issues could introduce bias.
Overall assessment of bias risk	High risk	

Hotham 2006

Methods	Non-placebo, parallel-design RCT
Participants	40 healthy Australian women between 12 and 28 weeks' pregnant and smoking >= 15 cigarettes daily with an exhaled breath CO reading of > 8 ppm
Interventions	Control group: 5-minute counselling at baseline and further brief counselling (< 2 minutes' duration) at follow-up visits. Intervention: counselling as above plus an element concerning correct use of NRT plus 15 mg/16-hour patches for a maximum of 12 weeks.
Outcomes	Smoking cessation (point prevalence) at final antenatal visit. Women seen "at least monthly during gestation"; also seen within 48 h of delivery when exhaled CO and saliva sample (for cotinine) taken and by telephone at 6 weeks and 3 months.

Hotham 2006 *(Continued)*

Notes	Exhaled CO readings used to validate point prevalence cessation at final antenatal visit. Cut point = 8 ppm CO. Author clarification used to obtain this information as not clear in research report. No data on smoking outcomes after childbirth are reported in the manuscript. Dates of study: not reported Funding sources: "This pilot study was supported by the Health Promotion Branch of the (then) South Australian Health Commission, now the Department of Health (SA). The WCH Perinatal Pathology Fund funded cotinine tests, performed using a competitive micro-plate immuno-assay (COTININE MICRO-PLATE EIA)." Declarations of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Unclear risk	Described as "sealed envelope system". Unclear whether envelopes opaque.
Blinding (performance bias and detection bias) Women and clinical staff	High risk	No placebo was used. Unclear if assessors blinded to allocation of treatments. Exhaled CO and saliva samples used to validate abstinence.
Incomplete outcome data (attrition bias) All outcomes	Low risk	14/40 withdrew from the study (35% attrition). All withdrawals included in this analysis as women who continued to smoke.
Selective reporting (reporting bias)	Unclear risk	Author confirmed that the following outcomes were collected: mode of delivery, labour interventions (if any), birthweight, Apgar scores at 1 and 5 min, results of cord-blood analysis for pH and base excess and also for carboxy-haemoglobin and cotinine. Author asked to provide birthweight data to inform safety analyses.
Overall assessment of bias risk	High risk	

Kapur 2001

Methods	Parallel-design RCT with active and placebo patches and clinicians/researchers and participants unaware of allocation
Participants	30 healthy Canadian women between 12 and 24 weeks' pregnant and smoking >= 15 cigarettes daily who want to quit smoking and could not do so in 1st trimester
Interventions	12-week course of NRT or identical placebo patches: 15 mg/18-hour patch for 8 weeks, then 10 mg/18-hour patch for 2 weeks, and finally 5 mg/18-hour patch for 2 weeks. Behavioural counselling at baseline and at all follow-up points. Counselling at baseline included a video explaining how to use patch; also counselling at all follow-ups. Weekly telephone contact with women. Intervention = active patch, control = placebo

Kapur 2001 *(Continued)*

Outcomes	Smoking cessation (unclear if point prevalence or continuous cessation measured) 8 weeks into programme (20 to 32 weeks into pregnancy). Follow-up also at weeks 1 and 4 into programme with saliva and serum cotinine measured at all time points.
Notes	Primary outcome validated at 8 weeks into programme. Cotinine cut point not reported, but paper states that "in no case was smoking cessation associate with thiocyanate levels of > 1 ug/ml". Dates of study: not reported Funding sources: "This study was supported by a grant from the Canadian lnstitutes of Health Research (CIHR)." Declarations of interest: "Gideon Koren, MD, is a Senior Scientist of the CIHR."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number sequence - confirmed by authors.
Allocation concealment (selection bias)	Low risk	Placebo or active patches packed remotely as per the randomisation sequence - confirmation via contact with author.
Blinding (performance bias and detection bias) Women and clinical staff	Low risk	Described as participants and researchers or clinicians unaware of treatment allocation with identical active and placebo NRT patches, although most women in the placebo group did not complete the programme. Biochemical validation of abstinence using serum thiocyanate and salivary cotinine.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Biochemical validation missing for approximately one-third of the sample. All dropouts and missing data treated in this analysis as women who continued to smoke.
Selective reporting (reporting bias)	Unclear risk	Prespecified birth outcomes were not reported.

Nanovskaya 2017

Methods	Double-blind, placebo-controlled RCT
Participants	65 pregnant women, ≥ 18 years of age, between 13 and 30 weeks' gestation, smoking ≥ 10 cigarettes per day prior to pregnancy and 5 cigarettes per day for the preceding 7 days, English or Spanish speaking, and having the intent to carry to term
Interventions	Participants received bupropion SR orally once daily for 3 days followed by twice daily for a total medication treatment of 12 weeks. Both groups received behavioural interventions, which included 35-minute counselling sessions at each of the first 2 visits (enrolment and on the quit day) and 10 minutes of smoking cessation counselling at subsequent visits. Counselling sessions were delivered by a research nurse using a motivational interviewing approach. Intervention = bupropion SR, control = placebo

Nanovskaya 2017 *(Continued)*

Outcomes	7-day point prevalence abstinence at 12 weeks after the quit date (end of treatment), and 36 to 38 weeks' gestation (end of pregnancy). Defined at each visit as no cigarettes (not even a puff) in the last 7 days, levels of CO in exhaled air < 4 ppm, and concentrations of cotinine in urine < 50 ng/mL.
Notes	Dates of study: July 2011 to December 2016 Funding sources: "The study was supported by National Institute on Drug Abuse grant RO1 DA030998 (to G.H. and T.N.)." Declarations of interest: "The authors report no conflict of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Urn randomisation method. Balanced for 2 variables: gestational age at study entry and number of CPD.
Allocation concealment (selection bias)	Unclear risk	Not explicitly described, so unclear.
Blinding (performance bias and detection bias) Women and clinical staff	Low risk	Participants, primary investigators, and research nurses were blinded to pharmacotherapy group assignment. Implication that drug and placebo were packaged similarly. Research nurses were also those that monitored smoking status and outcomes. Biochemically validated abstinence using CO < 4 ppm and urinary cotinine level of < 50 ng/mL.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced for both groups, for similar reasons. Women lost to follow-up were judged to have returned to smoking.
Selective reporting (reporting bias)	Unclear risk	Paper states that low birthweight was recorded, but no evidence of reporting. Preterm birth defined as < 34 weeks, whereas < 37 weeks is generally used.

Oncken 2008

Methods	Parallel-design RCT with active and placebo NRT gum and clinicians/researchers and participants unaware of allocation
Participants	194 healthy, US English-/Spanish-speaking women <= 26 weeks' pregnant, smoking >= 1 cigarette daily and aged >= 16 years
Interventions	12 weeks treatment with either 2 mg NRT gum or identical placebo. 6 weeks full treatment was followed by 6 weeks tapering of treatment. Instructed not to chew > 20 pieces daily and to use 1 piece of gum for each substituted cigarette. Additionally, all participants received individual counselling at baseline and at all 8 follow-ups: 2, 35-minute counselling sessions at baseline and within 1 week of quit date and shorter sessions at other follow-ups. Intervention = active gum, control = placebo
Outcomes	Self-reported 7-day point prevalence abstinence at 6 weeks after treatment commenced, at 32 to 35 weeks of pregnancy, and at 6 to 12 weeks after delivery. Exhaled CO of less than 8 ppm used for validation all time points.
Notes	Dates of study: July 2003 to April 2007

Oncken 2008 *(Continued)*

Funding sources: "Supported by NIH grants R01 DA15167, GCRC grant M01 RR006192, P50 DA013334, P50 AA015632. Nicotine Gum was provided free of charge from Glaxo-Smith Kline."

Declarations of interest: "Dr. Oncken has received consulting fees and honoraria from Pfizer (New York, NY) for advisory board meetings. She has received at no cost nicotine and/or placebo products from Glaxo-SmithKline (Philadelphia, PA) for smoking cessation studies (i.e., for pregnant women, post-menopausal women). She has received grant funding from Pfizer for smoking cessation studies and from Nabi Biopharmaceuticals (Boca Raton, FL) for a nicotine vaccine study. Dr. Kranzler has received consulting fees from Ortho-McNeil Pharmaceuticals (Raritan, NJ), H. Lundbeck A/S (Copenhagen, Denmark), Forest Pharmaceuticals (St. Louis, MO), elbion NV (Leuven, Belgium), Sanofi-Aventis (Bridgewater, NJ), Solvay Pharmaceuticals (Bruxelles, Belgium), and Alkermes, Inc. (Cambridge, MA). He has received research support from Ortho-McNeil Pharmaceuticals and Bristol-Myers Squibb Company (New York, NY), and honoraria from Forest Pharmaceuticals and Alkermes, Inc. The other authors have no potential conflicts of interest to disclose."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised randomisation program to balance participant assignment into treatment groups based on variables of maternal age, gestational age at study entry, number of cigarettes smoked per day, health insurance (public or private), and use of methadone maintenance
Allocation concealment (selection bias)	Low risk	Computerised allocation
Blinding (performance bias and detection bias) Women and clinical staff	Low risk	Placebo-controlled trial with placebo and treatment packaged in same blister packets. Urine anabasine/anatabine alkaloids from tobacco, which are not altered by NRT, used to validate abstinence.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Perinatal outcomes for 95% of control group and 97% of intervention group (excluding 1 from each group who withdrew consent and others lost to follow-up). Smoking outcomes/participation at end of pregnancy for 64% of control group and 78% of intervention group. All participants with missing data counted in this analysis as women who smoke.
Selective reporting (reporting bias)	Low risk	All adverse events reported.
Overall assessment of bias risk	Low risk	

Oncken 2019

Methods	Parallel-design RCT with active and placebo NRT inhaler and clinicians/researchers and participants unaware of allocation
Participants	137 healthy US English-/Spanish-speaking women smoking at least 5 cigarettes per day, 13 to 26 weeks' gestation, ≥ 16 years of age, intending to carry their pregnancy to term, and living in a stable residence

Oncken 2019 *(Continued)*

Interventions	6 weeks' treatment using NICOTROL inhaler (nicotine inhalation system) delivering 4 mg of nicotine from a porous plug containing 10 mg nicotine. Participants were encouraged to continue the use of the inhaler as long as they were actively trying to quit smoking. Participants instructed to puff on the inhaler 3 to 4 times per minute for up to 20 minutes and to inhale deeply in short breaths as they would normally smoke a cigarette. Participants who smoked ≥ 10 CPD were instructed to begin with 4 to 12 cartridge inhalers per day; women who smoked 5 to 9 CPD were instructed to begin with 1 to 4 cartridge inhalers per day, based on an estimated 1 to 2 mg of nicotine delivery per cigarette, with each cartridge inhaler estimated to release 4 mg of nicotine. At baseline and 1 week after quit date, participants received 35 minutes of individual smoking cessation counselling by a study nurse trained to deliver the counselling using a motivational interviewing approach. Intervention = nicotine inhaler, control = placebo
Outcomes	Self-reported 7-day point prevalence abstinence at 6 weeks after quit date, at 32 to 36 weeks of pregnancy, and at 1 and 6 months after delivery. Exhaled CO of less than 4 ppm used for validation at all time points.
Notes	Study planned to recruit 360 women, but the trial was stopped after a recommendation from the Data and Safety Monitoring Board due to futility in detecting differences in the primary outcome. Dates of study: August 2012 to January 2017 Funding sources: "This study was supported by National Institutes of Health (NIH) of United States grant R01HD069314 and the Lowell P. Weicker Clinical Research at the University of Connecticut School of Medicine. The study medication was donated 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."

Risk of bias

Bias	Authors' judgement	Support for judgement
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 risk	Not explicitly stated whether allocation was concealed from the research pharmacy, so this is rated as unclear.
Blinding (performance bias and detection bias) Women and clinical staff	Low risk	All study personnel and participants were blinded to treatment assignment. Inhalers were packaged in the same device to maintain blinding integrity. Biochemically validated abstinence using CO at < 4 ppm.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up rates for smoking outcomes at 32 to 36 weeks' gestation were 58% in placebo group and 67% in nicotine group. However, all women lost to follow-up were assumed to be smoking and were included in the analysis. High follow-up rates for birth outcomes.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes in the trial registry were reported.

Pollak 2007

Methods	Non-placebo, parallel-design RCT
Participants	181 healthy US English-speaking women between 13 and 25 weeks' pregnant, smoking >= 5 cigarettes daily, and aged >= 18 years. Must have smoked > 100 cigarettes in lifetime.
Interventions	Control group: 5 face-to-face and 1 telephone behavioural counselling sessions with booklet and support materials. Intervention group: counselling as above but with additional focus on use of NRT. Women permitted choice of NRT from patch, gum, or lozenge. Patch dose depended on CPD: < 10 CPD, 7 mg/16 h; 10 to 14 CPD, 14 mg/16 h; >= 15 CPD, 21 mg/16 h. Where gum or lozenge was used, one 2 mg piece was used for each cigarette smoked daily. Maximum of 6 weeks' NRT provided, and no NRT provided when women returned to smoking.
Outcomes	Self-reported 7-day point prevalence abstinence at 38 weeks. Also follow-up at 7 weeks after randomisation and 3 months' postpartum using self-report data. Saliva samples for cotinine validation were collected at the intervention session that coincided with each telephone survey from all women regardless of smoking status. Cut point for primary outcome <= 10 ng/mL. Validation data were collected at all 3 time points, but are only reported for the 2 data collection points within pregnancy.
Notes	Choices of NRT: 72/122 patch = 59%, 32/122 gum = 26.2% and 12/122 lozenge = 9.8%. 19 women chose another formulation as they could not quit with initial selection (changes not recorded). Dates of study: May 2003 to August 2005 Funding sources: "This work was supported by the National Cancer Institute (grant R01CA089053 and operated under IND #67,259)." NRT donated by GlaxoSmithKline. Declarations of interest: "No financial disclosures were reported by the authors of this paper."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random number generation
Allocation concealment (selection bias)	Low risk	Staff responsible for randomising participants used handheld computer devices that kept allocation sequence from them until the point of intervention delivery.
Blinding (performance bias and detection bias) Women and clinical staff	High risk	No placebo used; open-label trial. Assessors blinded to allocation. Biochemical validation of abstinence using salivary cotinine.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up low for perinatal outcomes (10/181 births), but more than 30% attrition for assessment of smoking status at the postnatal follow-up. Women lost to follow-up were included in this analysis as women who continued to smoke.
Selective reporting (reporting bias)	Low risk	All adverse outcomes reported.
Overall assessment of bias risk	High risk	

Stotts 2015

Methods	Placebo-controlled RCT with parallel-group design
Participants	11 pregnant women at least 18 years old; 14 to 26 weeks' gestation; and currently smoking at least 1 daily cigarette. Women were excluded if they had abnormal LFTs; history of or current seizure disorder or closed head injury with loss of consciousness; hypersensitivity to bupropion; any psychiatric disorder requiring psychotropic medication; current anorexia or bulimia; monoamine oxidase use in the past 2 weeks; major depression or risk of suicide; illicit substance use in the past 30 days; > 1 alcoholic drink/week; unstable medical problems; multiple pregnancy; fetal structural anomaly; planned birth at a non-affiliated hospital; communication problems or lack of transport/phone; or current use of NRT, bupropion, or varenicline.
Interventions	Bupropion SR or matching placebo. Bupropion SR was dosed at 150 mg/day for the first 3 days and 300 mg/day thereafter (150 mg twice a day). Placebo appearance, taste, and dosing instructions were identical. Participants and providers were masked to treatment group. Both groups received 4 weekly 15-minute smoking cessation counselling sessions based on Clinical Practice Guidelines delivered by a research nurse.
Outcomes	The primary smoking outcome was self-reported total abstinence in the prior 7 days (7-day point prevalence) with saliva cotinine validation at the end of treatment. Saliva cotinine assays used a cut point of > 20 ng/mL indicating regular smoking. Exhaled CO concentration in ppm was measured at each assessment time point using the EC-50 (Vitalograph Inc, Lenexa, KS) to indicate recent exposure to tobacco smoke in ppm. Maternal, perinatal, and neonatal outcomes assessed included intrauterine fetal death, spontaneous abortion, placental abruption, preterm birth (< 37 weeks, 0 days), pre-eclampsia, maternal weight gain, birthweight, umbilical artery pH, gestational age at delivery, fetal growth restriction (birthweight < 10th percentile), neonatal intensive care unit admission, respiratory complications (per physician notes).
Notes	The cut point for saliva cotinine is higher than the current standard. Dates of study: April 2011 to August 2012 Funding sources: "This study was supported by the Center for Clinical and Translational Sciences (CCTS) funded by CTSA awarded to the University of Texas Health Science Center at Houston (UL1 RR 024148) and the Larry C. Gilstrap MD Center for Perinatal and Women's Health Research of the University of Texas Medical School at Houston." Declarations of interest: "The authors declare that there are no conflicts of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned using permuted block design
Allocation concealment (selection bias)	Unclear risk	There is no description of how randomisation was operationalised, so rated as unclear.
Blinding (performance bias and detection bias) Women and clinical staff	Low risk	Trial used visually identical placebos, therefore participants and those delivering the intervention were blind to treatment. It is not explicitly stated that the outcome assessor was blinded, but this is likely to be an omission, as it seems unlikely given placebo control and randomisation that the assessor would not be blinded. Validated data are presented for cessation outcomes, and although these use a high cut point (20 ng/mL for saliva), individual participant saliva cotinine

Stotts 2015 *(Continued)*

		readings are reported and these could be used to evaluate findings against a lower cut point, if desired.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Use of an intention-to-treat analysis was not specifically stated (this would effectively mean that there was no loss of data); however, at the main outcome point for smoking cessation, outcome data on all 11 participants are reported within the groups to which they had been randomised.
Selective reporting (reporting bias)	Unclear risk	A number of outcomes mentioned in study methods were not reported in the results section.

Wisborg 2000

Methods	Parallel-design RCT with active and placebo patches and clinicians/researchers and participants unaware of allocation
Participants	250 healthy Danish women < 22 weeks' pregnant and smoking >= 10 cigarettes daily
Interventions	11-week course of NRT or identical placebo patches: 15 mg/16 h for 8 weeks then 10 mg/16 h for 3 weeks plus behavioural counselling and information pamphlet. Intervention = active patch, control = placebo
Outcomes	Self-reported abstinence of >= 7 days at 2nd, 3rd, and 4th prenatal visits (4 weeks prior to delivery). Follow-ups at times above and also by telephone at 3 months and 1 year after delivery.
Notes	Saliva cotinine level < 26 ng/mL at the 4th visit (4 weeks prior to expected delivery date) used to validate reported smoking cessation. The test used could not detect lower than 20 ng/mL (data verified by communication with author). Only self-report data were collected after childbirth. Dates of study: October 1995 to October 1997 Funding sources: "This study was supported by the Danish Cancer Society and the Ministry of Health (The National Health Fund supported this study for Research and Development). Pharmacia & Upjohn provided nicotine patches." Declarations of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised list in balanced blocks
Allocation concealment (selection bias)	Low risk	Placebo-controlled trial with allocation coded until the end of data collection
Blinding (performance bias and detection bias) Women and clinical staff	Low risk	Placebo-controlled trial with allocation coded until the end of data collection. Used cut point that is higher than currently accepted and biochemical test that could not detect levels of cotinine of < 20 ng/mL (data obtained from authors). Some respondents reporting smoking cessation may have actually been still smoking, and the biochemical test would not detect this. We dealt with this by using self-report data in primary analyses and investigating the impact of using biochemically validated data in a sensitivity analysis.

Wisborg 2000 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Small loss to follow-up, but missing data treated in this analysis as women who continued to smoke. The treatment allocation of 7 miscarriages could not be determined, though as this was a secondary outcome, the study was deemed to be at low risk of bias for this criterion.
Selective reporting (reporting bias)	Low risk	Adverse outcomes reported.
Overall assessment of bias risk	Low risk	

CO: carbon monoxide
CPD: cigarettes per day
LFTs: liver function tests
NRT: nicotine replacement therapy
ppm: parts per million
RCT: randomised controlled trial
SR: sustained release

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Eades 2012	Quasi-randomised, as women were allocated to intervention or control in 'control' or 'intervention' weeks with the nature of individual weeks determined by random allocation (but outcomes being monitored at the level of individual women). We judged that it was not possible to attribute treatment effects in the intervention arm to NRT because NRT was offered as part of a multimodal intervention that offered more behavioural support (in addition to the NRT) to participants in the intervention group. Additionally, NRT was only offered to those intervention group women who made 2 failed quit attempts after receiving behavioural components of the intervention, and, in the presentation of outcomes from the study, women who accepted the offer of NRT at this stage could not be differentiated from other intervention group women.
Gould 2019	Tested a multimodal intervention, making it impossible to identify the individual effect NRT might have on smoking cessation.
Hegaard 2003	Quasi-random allocation/sequence generation of participants (by birth date). It was not possible to attribute treatment effects in the intervention arm solely to NRT because NRT was offered as part of a multimodal intervention that differed between trial arms. At randomisation, participants did not have to agree to use NRT; of 327 women randomised to the intervention group, only 75 accepted an offer of NRT. Smoking outcomes were not reported within the subgroup of those using NRT, so it was not clear if NRT was responsible for smoking outcomes.
NCT00744913	Trial withdrawn due to recruitment problems.
NCT00888979	Non-randomised study in which all women were provided nicotine inhaler. Feasibility study investigating the impact of nicotine inhaler on smoking cessation.
Oncken 2009a	Non-randomised cohort study that investigated the impacts of nicotine patches or nasal spray on nicotine exposure in pregnant women.

NRT: nicotine replacement therapy

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12618000972224

Trial name or title	SISTAQUIT (Supporting Indigenous Smokers to Assist Quitting) A cluster randomised controlled trial to improve strategies for the management of smoking cessation in pregnant Aboriginal and/or Torres Strait Islander women
Methods	Cluster-randomised controlled trial
Participants	Pregnant; up to and including 32 weeks' gestation; Aboriginal and/or Torres Strait Islander (or expectant mothers of an Aboriginal and/or Torres Strait Islander baby); smoke tobacco (any amount); able to provide informed consent; attending antenatal care at 1 of the 30 Aboriginal Medical Services and General Practices participating in SISTAQUIT.
Interventions	• Culturally appropriate training in smoking cessation care for health providers (2 hours) • Health providers include general practitioners, midwives, nurses, Tobacco & Aboriginal Health Workers • Ideally, all health providers at each service/GP practice (especially those who provide care for pregnant women) will undertake the training • Targeted educational resources: participant booklet and flip chart, health provider manual • Oral NRT • Participant smoking cessation information video loop
Outcomes	Smoking cessation status self-report, 4 and 12 weeks after recruitment to the trial, and 36 weeks' gestation
Starting date	July 2018
Contact information	Gillian Gould; gillian.gould@newcastle.edu.au
Notes	Aims to recruit 450 women by July 2020. Multicomponent intervention

IRCT20181209041904N1

Trial name or title	Comparison of the effectiveness of treatment with nicotine patches versus support behavior in smoking cessation in pregnant women
Methods	Placebo-randomised, double-blind, controlled trial
Participants	Pregnant women who agreed to set a quit date, 16 to 50 years of age, 12 to 24 weeks' gestation, smoked 10 or more cigarettes daily before pregnancy, currently smoking 5 or more cigarettes daily
Interventions	Nicotine patches (15 mg/16 hours)
Outcomes	Abstinence from the date of smoking cessation until delivery
Starting date	March 2019
Contact information	Zohre Gozidehkar; zohre.gozidehkar@gmail.com
Notes	Aims to recruit 1050 women by April 2022.

ISRCTN62025374

Trial name or title	Helping pregnant smokers quit: a multi-centre study of electronic cigarettes and nicotine patches
Methods	Multicentre, open-label randomised controlled trial
Participants	Daily smokers; 12 to 24 weeks pregnant; wants help with stopping smoking; willing to be randomised to use either NRT or EC (to avoid selective dropout and contamination); willing to receive 6 weekly support calls over the phone plus 2 follow-up calls; speaks English (to allow data collection via phone); aged 18 years or over
Interventions	Participants randomised (1:1) to receive either nicotine patches for up to 8 weeks (15 mg/16 hours) or an e-cigarette starter pack. Both groups will receive weekly telephone support for 6 weeks from specialist stop-smoking advisors.
Outcomes	Prolonged abstinence rates at the end of pregnancy, defined as per Russell Standard (up to 5 lapses allowed from 2 weeks after the target quit day until end of pregnancy, with no smoking at all during the previous week at the time of follow-up), and verified by salivary cotinine (< 15 ng/mL) for those not reporting using any nicotine product and anabasine (< 1 ng/mL) for those reporting other forms of nicotine use.
Starting date	01 May 2017
Contact information	Dr Dunja Przulj Health and Lifestyle Research Unit Queen Mary University of London 2 Stayner's Road London E1 4AH United Kingdom
Notes	Aims to recruit 1142 and to be completed by May 2021.

NCT01875172

Trial name or title	Bupropion for smoking cessation in pregnancy
Methods	Placebo-randomised, double-blind, controlled trial
Participants	Smoked at least 1 puff in the past 7 days, confirmed viable gestation
Interventions	Study medication (150 mg bupropion SR) daily for 14 days. Women still smoking at 2 and 4 weeks were encouraged to increase their medication to 2 times per day (150 mg twice daily).
Outcomes	Biologically verified smoking cessation or reduction at 8 weeks and at delivery
Starting date	October 2001
Contact information	Hugh S Miller
Notes	The record (updated June 2013) states that the study was completed in January 2004. No results were identified, and we were unable to contact the author.

NCT02188459	
Trial name or title	Placebo-controlled trial of bupropion for smoking cessation in pregnant women (BIBS)
Methods	Placebo-randomised, parallel-group, controlled trial
Participants	Pregnant at 13 to 24 weeks' gestation and > 18 years of age; currently smoking at least 5 cigarettes per day for the preceding 7 days and wants to quit smoking; able to speak and read English at a 6th grade level or higher, using the Slosson Oral Reading Test (SORT); committed to remaining in the geographic area for at least 3 months postpartum; able to sign written informed consent and commit to completing the procedures involved in the study.
Interventions	Bupropion 150 mg twice daily for 10 weeks or a visually identical placebo
Outcomes	7-day point prevalence abstinence from smoking; number of cigarettes smoked; frequency of moderate or severe side effects; birth outcomes; smoking frequency after 10-week treatment phase.
Starting date	October 2014
Contact information	Timothy S Pond; timpond@pennmedicine.upenn.edu Leah Zindel; zindel@pennmedicine.upenn.edu
Notes	Aims to recruit 360 participants by December 2021.

EC: electronic cigarettes
NRT: nicotine replacement therapy
SR: sustained release

DATA AND ANALYSES

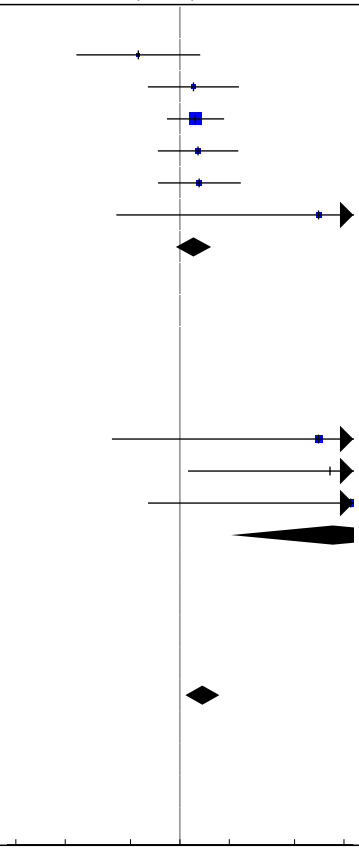
Comparison 1. Nicotine replacement therapy versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Validated cessation in later pregnancy (subgrouped by comparator type)	9	2336	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.08, 1.74]
1.1 Placebo-controlled trials	6	2063	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.95, 1.55]
1.2 Non-placebo-controlled trials	3	273	Risk Ratio (M-H, Fixed, 95% CI)	8.55 [2.05, 35.71]
2 Validated cessation in later pregnancy (subgrouped by NRT type)	9	2336	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.08, 1.74]
2.1 Long-acting NRT	7	2005	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.16, 2.01]
2.2 Fast-acting NRT	2	331	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.55, 1.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Self-report cessation at 3 or 6 months after childbirth	3	625	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.84, 1.78]
3.1 Placebo-controlled trials	2	444	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.75, 1.77]
3.2 Non-placebo-controlled trials	1	181	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.69, 3.03]
4 Self-report cessation at 12 months after childbirth	2	1296	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.97, 1.88]
5 Miscarriage and spontaneous abortion	5	1916	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.53, 4.83]
6 Stillbirth	4	1777	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.54, 2.84]
7 Mean birthweight (g)	7	2202	Mean Difference (IV, Random, 95% CI)	99.73 [-6.65, 206.10]
7.1 Placebo-controlled trials	5	1986	Mean Difference (IV, Random, 95% CI)	119.01 [-4.24, 242.25]
7.2 Non-placebo-controlled trials	2	216	Mean Difference (IV, Random, 95% CI)	36.39 [-256.19, 328.98]
8 Low birthweight (< 2500 g)	7	2171	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.39, 1.20]
8.1 Placebo-controlled trials	5	1955	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.28, 1.10]
8.2 Non-placebo-controlled trials	2	216	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.61, 2.98]
9 Preterm birth (birth < 37 weeks)	7	2182	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.59, 1.11]
9.1 Placebo-controlled trials	5	1955	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.51, 1.06]
9.2 Non-placebo-controlled trials	2	227	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.62, 2.35]
10 Neonatal intensive care unit admissions	4	1756	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.64, 1.27]
11 Neonatal death	4	1746	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.17, 2.62]
12 Congenital abnormalities	2	1401	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.36, 1.48]
13 Caesarean section	2	1401	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.83, 1.69]

Analysis 1.1. Comparison 1 Nicotine replacement therapy versus control, Outcome 1 Validated cessation in later pregnancy (subgrouped by comparator type).

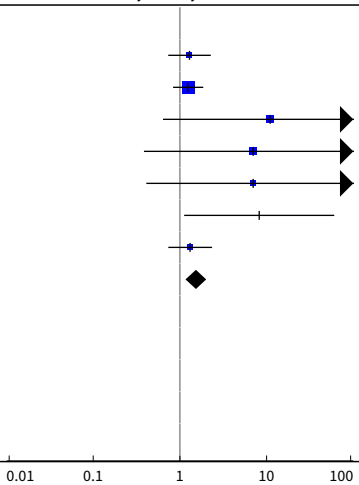
Study or subgroup	NRT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Placebo-controlled trials					
Oncken 2019	7/70	12/67		11.64%	0.56[0.23,1.33]
Oncken 2008	18/100	14/94		13.7%	1.21[0.64,2.29]
Coleman 2012	49/521	40/529		37.68%	1.24[0.83,1.86]
Berlin 2014	25/203	19/199		18.21%	1.29[0.73,2.27]
Wisborg 2000	22/124	17/126		16.01%	1.31[0.73,2.35]
Kapur 2001	4/17	0/13		0.53%	7[0.41,119.46]
Subtotal (95% CI)	**1035**	**1028**		**97.77%**	**1.21[0.95,1.55]**
Total events: 125 (NRT), 102 (Control)					
Heterogeneity: Tau²=0; Chi²=4.65, df=5(P=0.46); I²=0%					
Test for overall effect: Z=1.51(P=0.13)					
1.1.2 Non-placebo-controlled trials					
Hotham 2006	3/20	0/20		0.47%	7[0.38,127.32]
Pollak 2007	17/122	1/59		1.28%	8.22[1.12,60.31]
El-Mohandes 2013	5/26	0/26		0.47%	11[0.64,189.31]
Subtotal (95% CI)	**168**	**105**		**2.23%**	**8.55[2.05,35.71]**
Total events: 25 (NRT), 1 (Control)					
Heterogeneity: Tau²=0; Chi²=0.05, df=2(P=0.98); I²=0%					
Test for overall effect: Z=2.94(P=0)					
Total (95% CI)	**1203**	**1133**		**100%**	**1.37[1.08,1.74]**
Total events: 150 (NRT), 103 (Control)					
Heterogeneity: Tau²=0; Chi²=12.19, df=8(P=0.14); I²=34.4%					
Test for overall effect: Z=2.6(P=0.01)					
Test for subgroup differences: Chi²=6.99, df=1 (P=0.01), I²=85.7%					



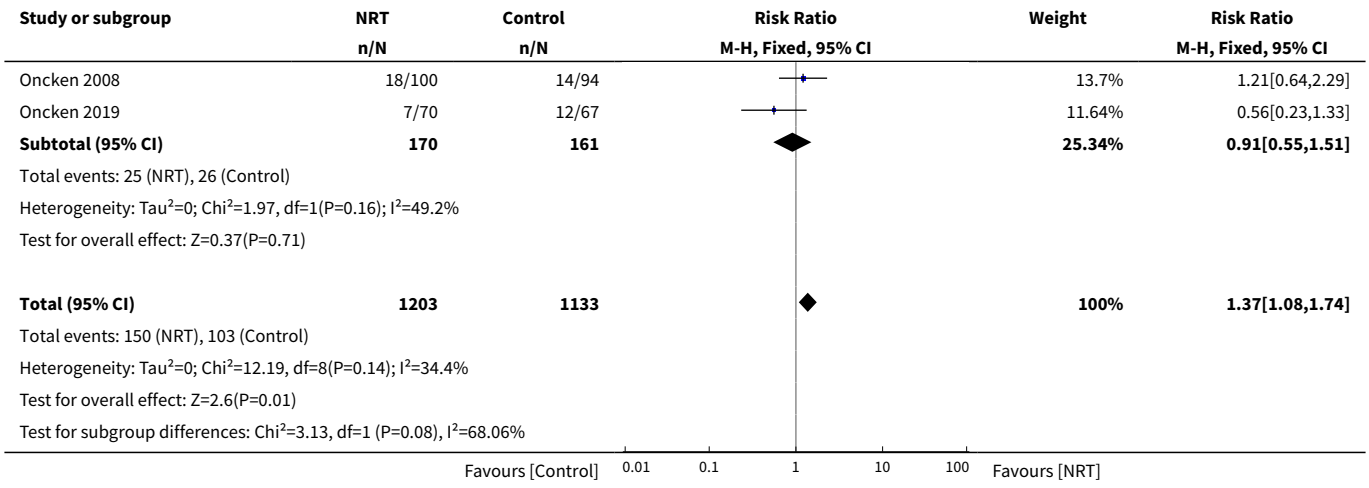
Favours control — Favours NRT

Analysis 1.2. Comparison 1 Nicotine replacement therapy versus control, Outcome 2 Validated cessation in later pregnancy (subgrouped by NRT type).

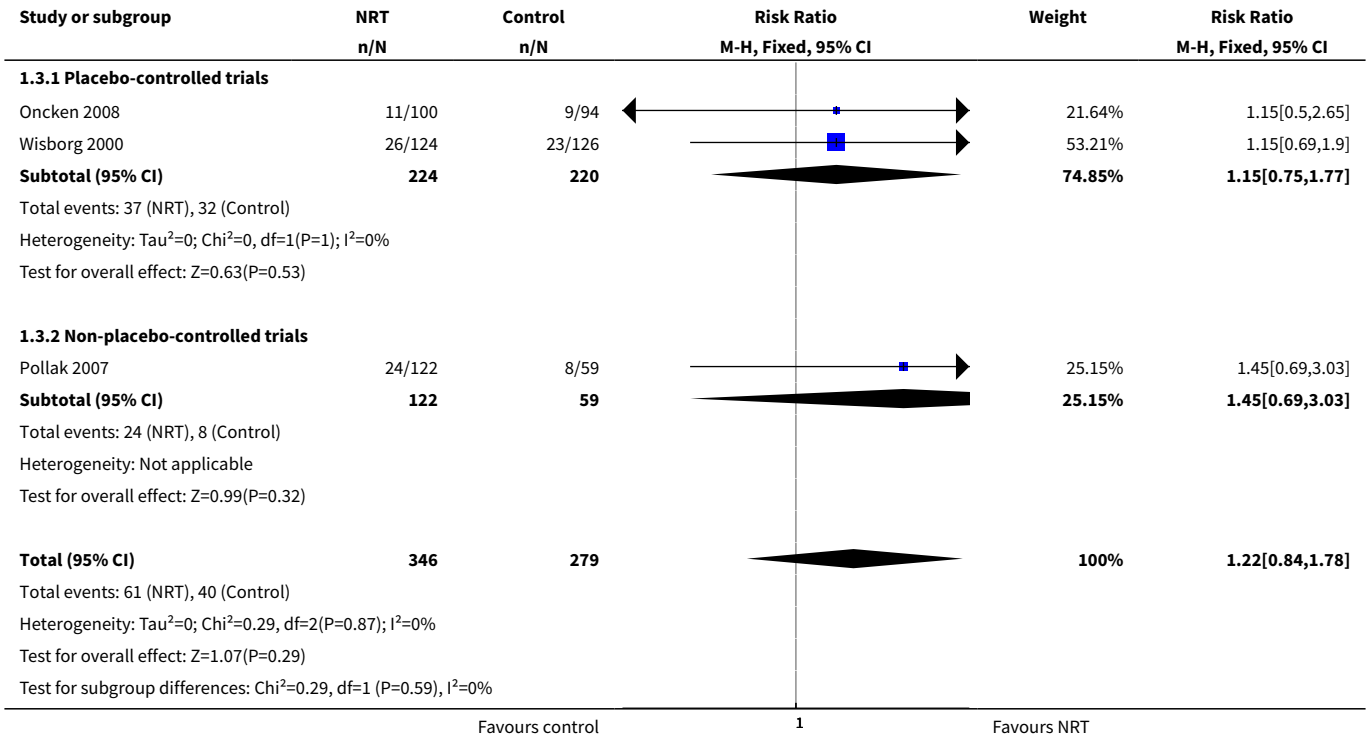
Study or subgroup	NRT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Long-acting NRT					
Berlin 2014	25/203	19/199		18.21%	1.29[0.73,2.27]
Coleman 2012	49/521	40/529		37.68%	1.24[0.83,1.86]
El-Mohandes 2013	5/26	0/26		0.47%	11[0.64,189.31]
Hotham 2006	3/20	0/20		0.47%	7[0.38,127.32]
Kapur 2001	4/17	0/13		0.53%	7[0.41,119.46]
Pollak 2007	17/122	1/59		1.28%	8.22[1.12,60.31]
Wisborg 2000	22/124	17/126		16.01%	1.31[0.73,2.35]
Subtotal (95% CI)	**1033**	**972**		**74.66%**	**1.53[1.16,2.01]**
Total events: 125 (NRT), 77 (Control)					
Heterogeneity: Tau²=0; Chi²=8.38, df=6(P=0.21); I²=28.42%					
Test for overall effect: Z=3.05(P=0)					
1.2.2 Fast-acting NRT					



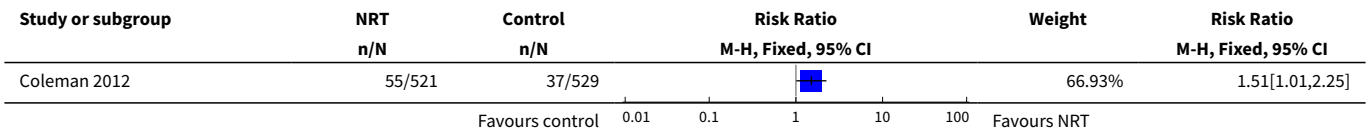
Favours [Control] — Favours [NRT]

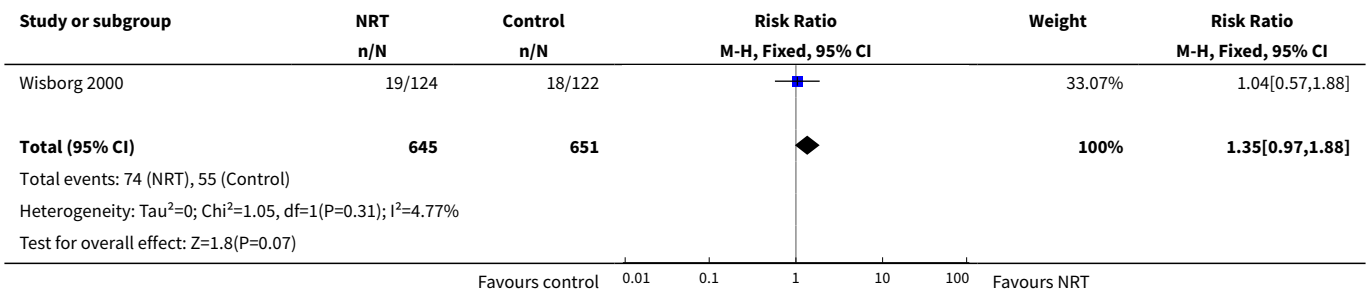


Analysis 1.3. Comparison 1 Nicotine replacement therapy versus control, Outcome 3 Self-report cessation at 3 or 6 months after childbirth.

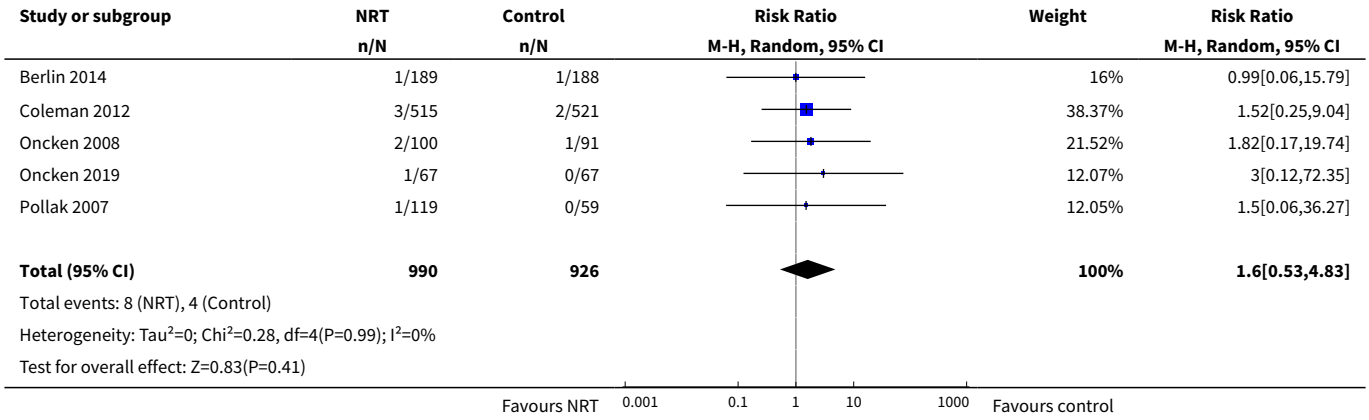


Analysis 1.4. Comparison 1 Nicotine replacement therapy versus control, Outcome 4 Self-report cessation at 12 months after childbirth.

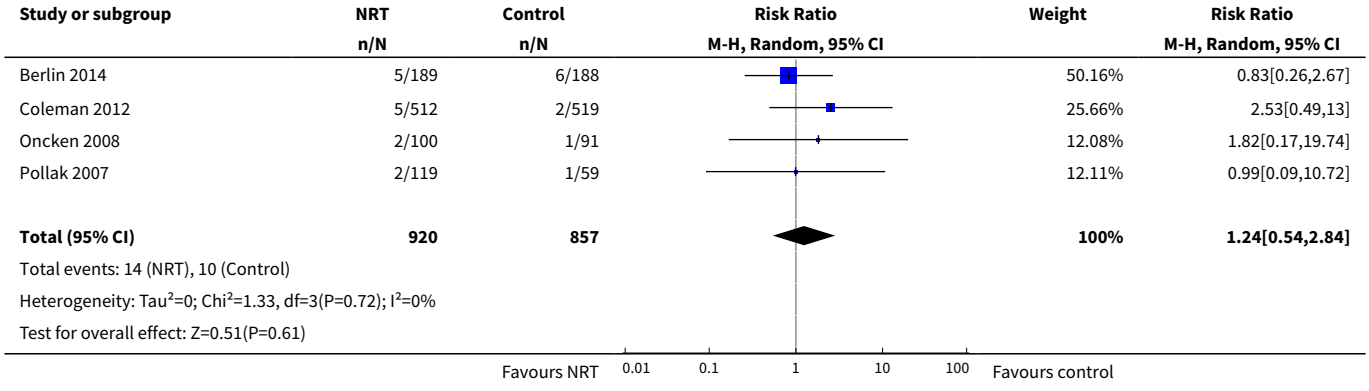




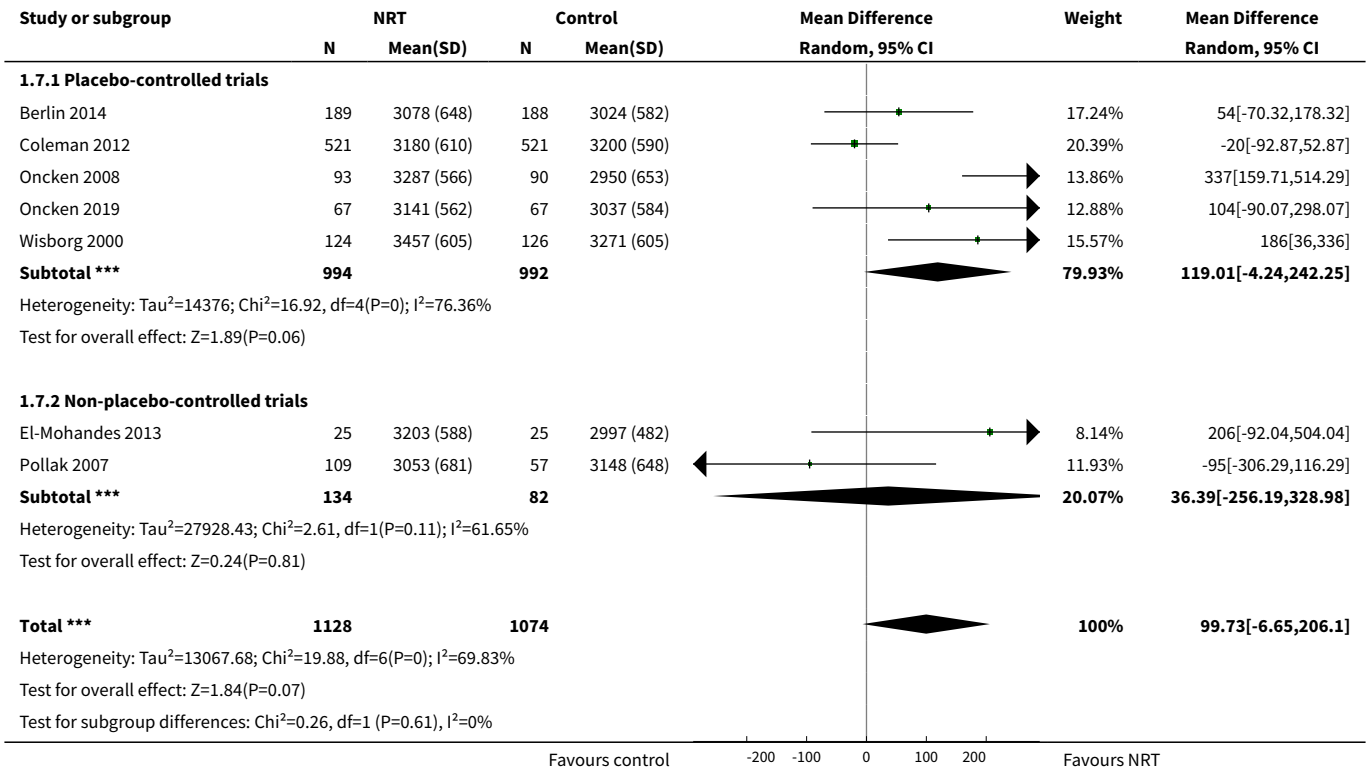
Analysis 1.5. Comparison 1 Nicotine replacement therapy versus control, Outcome 5 Miscarriage and spontaneous abortion.



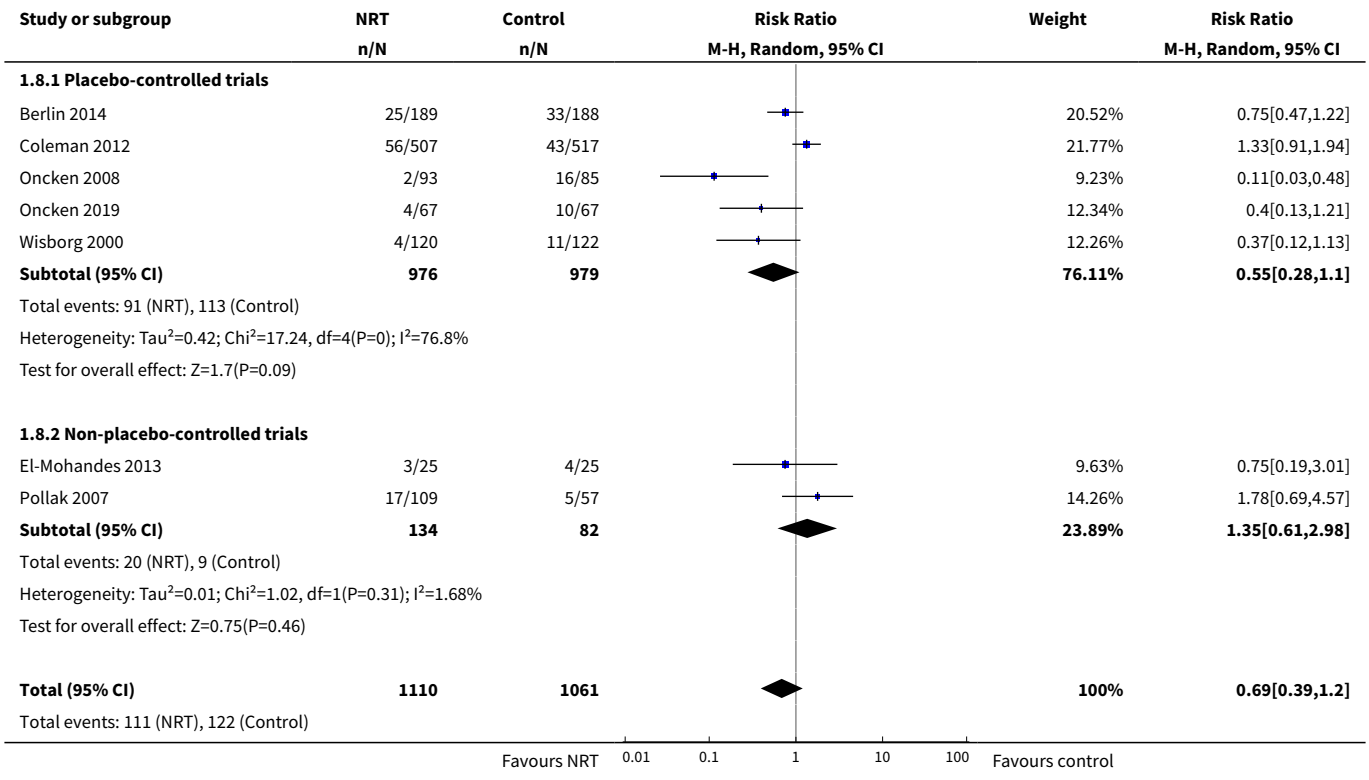
Analysis 1.6. Comparison 1 Nicotine replacement therapy versus control, Outcome 6 Stillbirth.



Analysis 1.7. Comparison 1 Nicotine replacement therapy versus control, Outcome 7 Mean birthweight (g).



Analysis 1.8. Comparison 1 Nicotine replacement therapy versus control, Outcome 8 Low birthweight (< 2500 g).



Study or subgroup	NRT n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.33; Chi²=19.28, df=6(P=0); I²=68.88%					
Test for overall effect: Z=1.33(P=0.18)					
Test for subgroup differences: Chi²=2.82, df=1 (P=0.09), I²=64.56%					

Favours NRT 0.01 0.1 1 10 100 Favours control

Analysis 1.9. Comparison 1 Nicotine replacement therapy versus control, Outcome 9 Preterm birth (birth < 37 weeks).

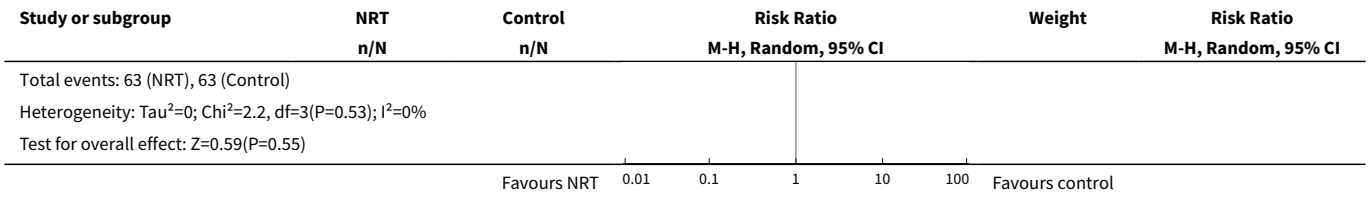
Study or subgroup	NRT n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Placebo-controlled trials					
Berlin 2014	19/189	20/188		20.03%	0.94[0.52,1.71]
Coleman 2012	40/507	45/517		31.97%	0.91[0.6,1.36]
Oncken 2008	7/93	16/85		11.8%	0.4[0.17,0.92]
Oncken 2019	3/67	10/67		5.91%	0.3[0.09,1.04]
Wisborg 2000	10/120	12/122		12.73%	0.85[0.38,1.89]
Subtotal (95% CI)	**976**	**979**		**82.43%**	**0.74[0.51,1.06]**
Total events: 79 (NRT), 103 (Control)					
Heterogeneity: Tau²=0.05; Chi²=5.68, df=4(P=0.22); I²=29.61%					
Test for overall effect: Z=1.64(P=0.1)					
1.9.2 Non-placebo-controlled trials					
El-Mohandes 2013	1/25	2/25		1.79%	0.5[0.05,5.17]
Pollak 2007	24/119	9/58		15.78%	1.3[0.65,2.61]
Subtotal (95% CI)	**144**	**83**		**17.57%**	**1.2[0.62,2.35]**
Total events: 25 (NRT), 11 (Control)					
Heterogeneity: Tau²=0; Chi²=0.59, df=1(P=0.44); I²=0%					
Test for overall effect: Z=0.54(P=0.59)					
Total (95% CI)	**1120**	**1062**		**100%**	**0.81[0.59,1.11]**
Total events: 104 (NRT), 114 (Control)					
Heterogeneity: Tau²=0.04; Chi²=7.63, df=6(P=0.27); I²=21.39%					
Test for overall effect: Z=1.33(P=0.18)					
Test for subgroup differences: Chi²=1.58, df=1 (P=0.21), I²=36.78%					

Favours NRT 0.01 0.1 1 10 100 Favours control

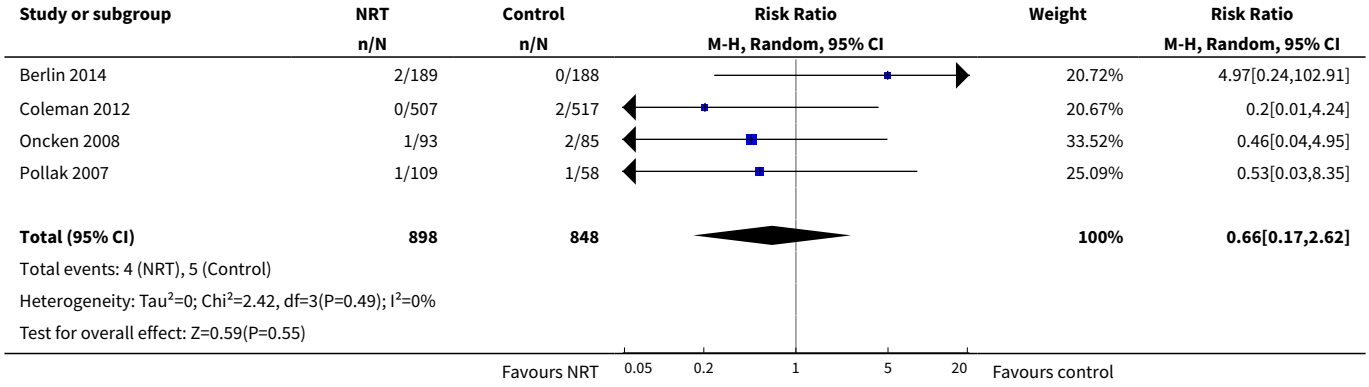
Analysis 1.10. Comparison 1 Nicotine replacement therapy versus control, Outcome 10 Neonatal intensive care unit admissions.

Study or subgroup	NRT n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Berlin 2014	10/189	13/188		18.64%	0.77[0.34,1.7]
Coleman 2012	33/507	35/517		56.4%	0.96[0.61,1.52]
Oncken 2008	7/93	11/85		14.67%	0.58[0.24,1.43]
Pollak 2007	13/119	4/58		10.29%	1.58[0.54,4.64]
Total (95% CI)	**908**	**848**		**100%**	**0.9[0.64,1.27]**

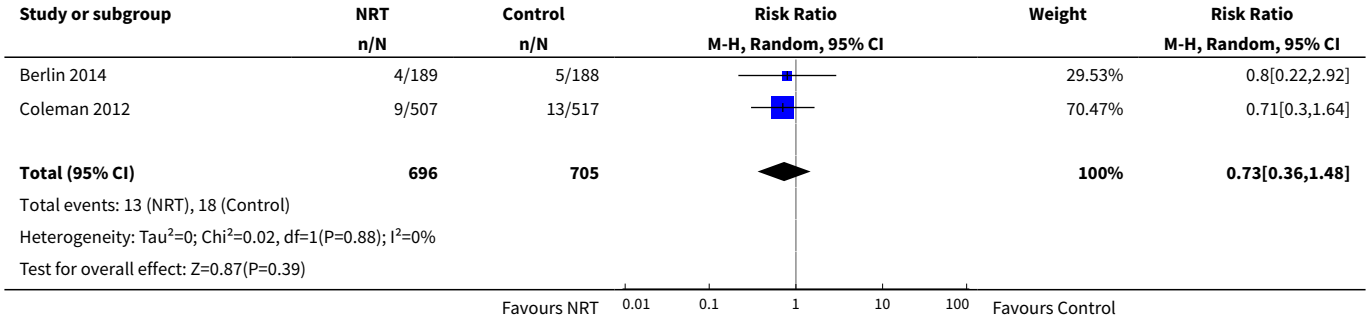
Favours NRT 0.01 0.1 1 10 100 Favours control



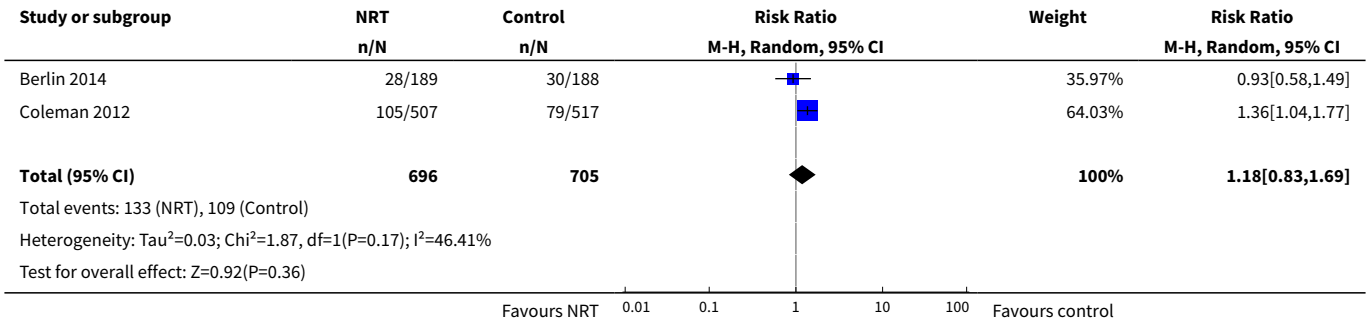
Analysis 1.11. Comparison 1 Nicotine replacement therapy versus control, Outcome 11 Neonatal death.



Analysis 1.12. Comparison 1 Nicotine replacement therapy versus control, Outcome 12 Congenital abnormalities.



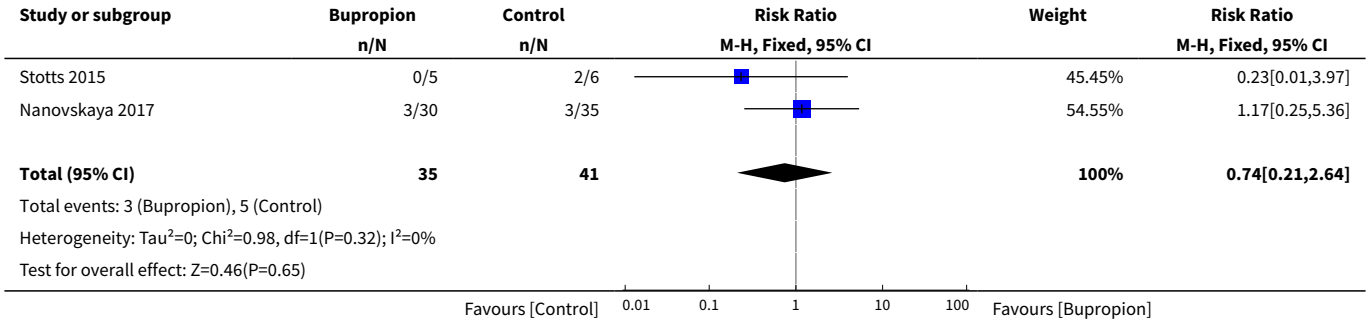
Analysis 1.13. Comparison 1 Nicotine replacement therapy versus control, Outcome 13 Caesarean section.



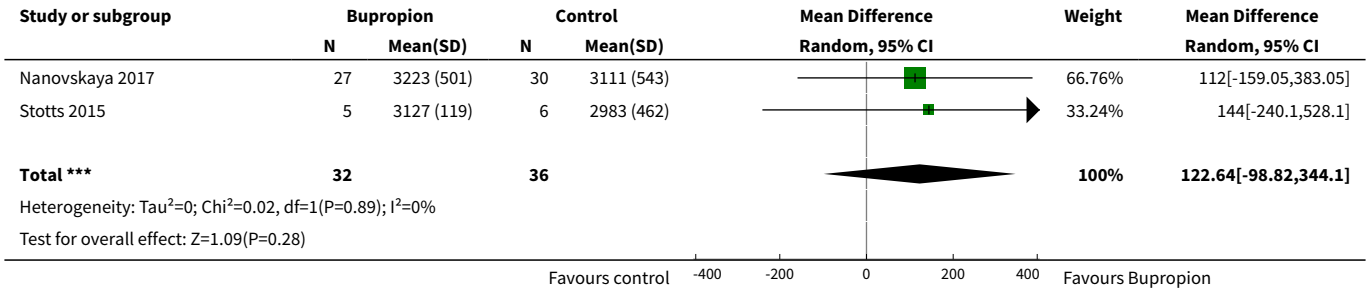
Comparison 2. Bupropion versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Validated cessation in later pregnancy	2	76	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.21, 2.64]
2 Mean birthweight (g)	2	68	Mean Difference (IV, Random, 95% CI)	122.64 [-98.82, 344.10]

Analysis 2.1. Comparison 2 Bupropion versus control, Outcome 1 Validated cessation in later pregnancy.



Analysis 2.2. Comparison 2 Bupropion versus control, Outcome 2 Mean birthweight (g).



ADDITIONAL TABLES

Table 1. Distribution of twin births and fetal losses within singleton pregnancies in nicotine replacement therapy and control groups *(Continued)*

	Twin pregnancies, n		Miscarriage, n		Stillbirth, n		Termination, n		Missing data: birth outcomes/whether birth occurred not known		Non-viable pregnancy at randomisation, n		Known live births from singleton pregnancies, n	
	NRT	Control	NRT	Control	NRT	Control	NRT	Control	NRT	Control	NRT	Control	NRT	Control
Wisborg 2000	1[a]		7[a]		-	-	-	-	-	-	-	-	120	122
Pollak 2007	2	0	1	0	2	1	0	0	8	1	1	0	109	57
Oncken 2008	Women with multiple births were excluded.		2	1	2	1	0	3[b]	3	4	0	0	93	85
Coleman 2012	4	8	3	2	5	2	1	0	4	10	1	0	503	507
El-Mohandes 2013	0	0	0	0	0	0	0	0	1	1	0	0	25	25
Berlin 2014	3	4	1	1	4	5	1[c]	1[c]	3	0	0	0	189[d]	188

NRT: nicotine replacement therapy
[a]The treatment allocation of the twin pregnancy and miscarriages is unknown.
[b]Authors confirmed that all terminations were done for social reasons and that fetus was thought to be normal.
[c]Done for medical problems judged incompatible with birth survival.
[d]Includes two infants who died during childbirth.

Table 2. Adherence with nicotine replacement therapy regimens

Study	Adherence with offered regimen as a percentage of complete course	Adherence with offered regimen in terms of period of use
Wisborg 2000	Complete adherence with 11-week course: nicotine group = 11%, placebo = 7%. Partial adherence (up to 8 weeks' use): nicotine group = 17%, placebo = 8%.	Median number patches (ranges): nicotine group = 14 (0 to 77), median = approximately 2 weeks; placebo = 7 (0 to 77), median = approximately 1 week.
Kapur 2001	In the nicotine group, 4/17 (23.5%) completed the 14-week programme. In the placebo group, no participants completed the programme.	In the nicotine group, 4/17 (23.5%) completed the 14-week programme; 3/17 (17.6%) used the patch for at least 3 weeks; and 10/17 (58.8%) used the patch for less than 1 week. In the placebo group, no participants completed the programme; 3/13 (23%) used the patch for between 4 and 5 weeks; and 10/13 (76.9%) used the patch for < 1 week.
Hotham 2006	25% (5) participants complied fully with protocol: "continuous patch use till 12 weeks or confident that abstinence achieved or adverse reaction experienced".	50% (10) of participants used NRT for 6 weeks or less.
Pollak 2007	Difficult to ascertain from manuscript. A secondary publication reported that 29% of participants used NRT as directed for intended 6-week programme (Fish 2009).	Means of reported periods of use: • Patch = 23.4 patches = 3.3 weeks • Gum = 8 days • Lozenge = 4 days
Oncken 2008	Not clearly reported.	The nicotine group used gum for a mean (SD) of 37.8 (3.8) days (i.e. just > 5 weeks). The placebo group used gum for a mean (SD) of 29.9 (3.4) days (i.e. just > 4 weeks).
Coleman 2012	Limited compliance with the intervention. Only 7.2% of women (35 of 485) assigned to receive NRT and 2.8% (14 of 496) assigned to receive placebo reported using trial medications for more than 1 month (2 months represented a complete course); rates of use of non-study NRT were very low. Most participants had no additional contact, either face-to-face or by text message, with smoking cessation advisors; amongst those who did, the frequency of contact was similar in the 2 groups.	Most participants discontinued patches after using them for only a short period: in the nicotine group 60.1% of participants used patches for no longer than 2 weeks, whilst in the placebo patch group this figure was 76.8%.
Berlin 2014	In contrast to other studies, women were issued with a much longer course of transdermal patches, i.e. from women's quit dates to their delivery. Compliance was measured using self-reported data on patches used between study visits and was obtained at 1016 study visits from 307 (76%) participants: 164 (84%) in the NRT group and 143 (72%) in the placebo group. Median (IQR) reported patch use was 85% (56% to 99%) in the NRT group and 83% (56% to 95%) in the placebo group. However, it is not clear how these figures relate to the rate with which participants discontinued the in-	This was not reported, but it has less meaning for this RCT, as women started using patches at different points in pregnancy and continued until childbirth.

Table 2. Adherence with nicotine replacement therapy regimens *(Continued)*

	tervention. Overall, 225 (60.0%) of participants stopped using trial treatments: 105 (51.7%) in the NRT group and 60.3% in the placebo group.	
Oncken 2019	Not clearly reported.	The nicotine group used the inhaler for a mean (SD) of 36.39 (23.92) days (i.e. just > 5 weeks) and used a mean (SD) of 1.70 (1.19) cartridges per day. The placebo group used the inhaler for a mean (SD) of 34.11 (20.54) days (i.e. just < 5 weeks) and used a mean (SD) of 1.81 (1.62) cartridges per day. Neither of these were statistically significant differences between groups (number of days, P = 0.587; number of cartridges, P = 0.701). Compliance with the inhaler during treatment was 69% in the placebo group and 70% in the nicotine group.

IQR: interquartile range
NRT: nicotine replacement therapy
RCT: randomised controlled trial
SD: standard deviation

WHAT'S NEW

Date	Event	Description
29 August 2019	New citation required but conclusions have not changed	One new study added to nicotine replacement therapy comparison, Oncken 2019, and one new study added to bupropion comparison, Nanovskaya 2017. Neither of these additions led to changes in the overall conclusions.
29 August 2019	New search has been performed	Search updated and two new studies added, one of nicotine replacement therapy, Oncken 2019, and one of bupropion, Nanovskaya 2017.

HISTORY

Review first published: Issue 9, 2012

Date	Event	Description
11 July 2015	New citation required but conclusions have not changed	Review updated. This update looked for both trials of pharmacotherapies and also of Electronic Nicotine Delivery Systems (ENDS) used for smoking cessation in pregnancy; it found mainly nicotine replacement therapy (NRT) trials with one bupropion trial which randomised only 11 pregnant smokers. A total of nine trials are included in this update. The conclusions are largely the same, although there is now more evidence to suggest that NRT used in pregnancy increases smoking cessation rates measured in late pregnancy by approximately 40%. There is evidence, suggesting that when potentially-biased, non-placebo RCTs are excluded from analyses, NRT is no more effective than placebo.

Date	Event	Description
11 July 2015	New search has been performed	Search updated. Three new trials included in this update (Berlin 2014; El-Mohandes 2013; Stotts 2015).

CONTRIBUTIONS OF AUTHORS

All review authors contributed to the refreshed protocol write-up and registration (Claire 2019b). All review authors also commented on the final draft of the updated review after Ravinder Claire (RC) had produced an initial draft, and RC finalised the text. Review authors RC and Tim Coleman (TC) independently inspected the search results and selected papers for inclusion in the review update. RC and TC extracted data from papers newly included in this update, with any disagreements resolved through discussion with Jo Leonardi-Bee (JLB). RC contacted authors of ongoing studies as appropriate and also entered data into Review Manager 5 software. RC and TC assessed the risk of bias for both newly included studies.

DECLARATIONS OF INTEREST

RC has no known conflicts of interest.

CC is a recipient of an Australian National Health and Medical Research Council (NHMRC) Career Development Fellowship to support work around life-course approaches to improving health equity in the perinatal period for Aboriginal parents. She has also received an NHMRC grant to co-design perinatal strategies to support Aboriginal parents experiencing complex trauma. CC is the contact/lead author for a Cochrane Review entitled 'Psychosocial interventions to promote smoking cessation in pregnancy' and co-author on an editorial calling for Australian researchers to oppose tobacco industry funding for smoking research. None of this is deemed to be a conflict of interest.

MD has no known conflicts of interest.

SC is a co-applicant on, and is employed by, funding for a National Institute for Health Research (NIHR) Programme Grant for Applied Research that includes conducting this review. She was previously employed by funding for the SNAP (Smoking Nicotine and Pregnancy) Trial, which is included in this review. She did not assess risk of bias for this trial.

IB declares occasional honoraria from Pfizer Ltd for consultancy, participation in board meeting, and presentations in the last three years fully independent of the current work.

JLB reports personal fees from undertaking independent statistical review for Danone Nutricia Research, and a grant from the Food Standards Agency, both outside of the submitted work.

TC has no known conflicts of interest. He was an investigator on a trial included in this review, but did not assess risk of bias for this trial.

SOURCES OF SUPPORT

Internal sources

- La Trobe University 1996 to date, Australia.
- UK Centre for Tobacco Control Studies: a Public Health Centre of Research Excellence, UK.
- NIHR National School For Primary Care Research, UK.
- Monash University, Australia.

  2016 to present

External sources

- Victorian Health Promotion Foundation, Australia.
- Department of Health, UK funding for EPI-Centre, London University, UK.
- Public Health Branch Victorian Department of Human Services, Australia.
- (TC, SC and JLB) National Institute for Health Research (NIHR), Programme Grant for Applied Research programme (grant number RP-PG-0615-20003), UK.
- Australian National Health and Medical Research Centre, Australia.

  (Fellowship 1161065)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Previous versions of this review used random-effects models for meta-analyses, and the protocol for this review, which was shared with the Cochrane Tobacco Addiction Group, stated that this was the preference of the review authors; however, during editing it was made clear to the review authors that the policy of the Cochrane Tobacco Addiction Group is for fixed-effect models to be used when assessing pharmacotherapies, as it is not expected that relative effects will differ across populations and settings within the pregnant population. We have therefore adopted the fixed-effect approach for smoking abstinence outcomes. The safety outcome analyses remain as random-effects models.

INDEX TERMS

Medical Subject Headings (MeSH)

*Tobacco Use Cessation Devices; Bupropion [therapeutic use]; Nicotinic Agonists [therapeutic use]; Pregnancy Complications [*drug therapy]; Pregnancy Outcome; Randomized Controlled Trials as Topic; Smoking Cessation [*methods]; Varenicline [therapeutic use]

MeSH check words

Female; Humans; Pregnancy