ADDICTION

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REVIEW

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Fetal safety of nicotine replacement therapy in pregnancy: systematic review and meta-analysis

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ABSTRACT

Background and aims Smoking in pregnancy causes substantial avoidable harm to mothers and offspring; nicotine replacement therapy (NRT) may prevent this, and is used to help women to quit. A recently updated Cochrane Review of randomized controlled trials (RCTs) investigating impacts of NRT in pregnancy focuses primarily on efficacy data, but also reports adverse impacts from NRT. Here we identify and summarize NRT impacts on adverse pregnancy outcomes reported in non-randomized controlled trials (non-RCTs). **Methods** Systematic reviews and meta-analyses of RCTs and non-RCT studies of NRT in pregnancy, with design-specific risk of bias assessment and grading of recommendations, assessment, development and evaluations (GRADE) criteria applied to selected outcomes. **Findings** Relevant Cochrane Review findings are reported alongside those from this new review. Seven RCTs were included; $n = 2340$. Nine meta-analyses were performed; non-statistically significant estimates indicated potentially reduced risk from NRT compared with smoking for mean birth weight, low birth weight, preterm birth, intensive care admissions, neonatal death, congenital anomalies and caesarean section and potentially increased risks for miscarriage and stillbirth. GRADE assessment for mean birth weight and miscarriage outcomes indicated 'low' confidence in findings. Twenty-three non-RCTs were included; $n = 931163$. Eleven large studies from five routine health-care cohorts reported clinical outcomes; 12 small studies investigated mainly physiological outcomes within in-patient women given NRT. Findings from meta-analyses for congenital anomalies, stillbirth and preterm birth were underpowered and not in a consistent direction; GRADE assessment of confidence in findings was 'very low'. Routine health-care studies were of higher quality, but implications of reported findings were unclear as there was inadequate measurement and reporting of women's smoking. **Conclusions** Available evidence from randomized controlled trials and non-randomized comparative studies does not currently provide clear evidence as to whether maternal use of nicotine replacement therapy during pregnancy is harmful to the fetus.

Keywords Birth outcomes, fetal health, health outcomes, nicotine replacement therapy, pregnancy, smoking, smoking cessation.

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INTRODUCTION

Smoking in pregnancy has adverse effects on the health of pregnant women and their offspring in the pre- and perinatal periods and in later life [1–3]. Smoking rates are highest among younger, socially disadvantaged pregnant women [4,5], and up to 38% of socio-economic inequalities in stillbirths and infant deaths can be attributed to smoking [6]. Stopping smoking in pregnancy improves birth outcomes [7] and reduces the burden of health-care costs to the National Health Service (NHS) [8].

The National Institute for Health and Care Excellence (NICE) recommends nicotine replacement therapy (NRT) in those women who are unable to stop smoking with non-pharmacological interventions [9]. However, even when pregnant women choose NRT, many do not use this

for very long [10] and adherence to NRT by pregnant women tends to be lower than in non-pregnant smokers [10–12]. This poor adherence may at least partially explain why NRT has been found to be less effective when used in pregnancy [13]. One possible reason for poor adherence to NRT in pregnancy is maternal concern about the safety of NRT. Qualitative interviews with pregnant women who sought support from NHS Stop Smoking Services demonstrated that they often reported using NRT intermittently or stopping courses early due to safety concerns [14].

There is a strong theoretical rationale for using NRT to avoid smoking in pregnancy; even if women do not stop smoking completely, cigarette smoke exposes the fetus to numerous toxins whereas NRT exposes them to only nicotine, and so is very likely to be safer [15]. A Cochrane Review investigating the impacts of NRT in pregnancy has recently been updated [13]. RCTs produce the least biased evidence but they also generally have small sample sizes, such that even when they are combined in meta-analyses, small adverse impacts may not be detected. Well-conducted, large non-RCT studies may be still prone to bias, but comprehensive confounder-adjustment could augment RCT data and provide sufficient power to investigate infrequent health outcomes following NRT use in pregnancy. The Cochrane Review focuses primarily on efficacy data, with adverse effects reported as secondary outcomes. Consequently, we conducted a systematic review of non-RCT studies reporting usually adverse fetal or infant health outcomes after pregnant women's use of NRT. Here we report this process alongside the safety-orientated findings from the updated Cochrane Review [13], with the aim of providing a comprehensive, objective and contemporary assessment of whether and how use of NRT during gestation affects pregnancy outcomes.

METHODS

Randomized controlled studies (RCTs)

Standard Cochrane Review (CR) methods used are described in the published review [13]. Searches, for RCTs only, were concluded by 20 May 2019 and from included studies we extracted data on the following outcomes: miscarriage/spontaneous abortion; stillbirth; birth weight; low birth weight (< 2500 g); preterm birth (< 37 weeks' gestation); neonatal intensive care unit admissions; neonatal death; caesarean section; congenital anomalies; infant development; and respiratory symptoms. We assessed study quality using Cochrane's 'risk of bias' tool. A priori, we planned to use grading of recommendations, assessment, development and evaluations (GRADE) criteria for birth weight and miscarriage/spontaneous abortion outcomes, to report studies separately where in meta-analyses $I^2 > 75\%$, and to conduct subgroup analyses for placebo and non-placebo RCTs.

Non-RCTs

A study protocol, written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, was registered on PROSPERO (International Prospective Register of Systematic Reviews) [16,17].

Inclusion criteria

We sought published non-RCT studies, of any design, in any language, reporting empirical data on potentially adverse fetal or infant health outcomes following NRT exposure or nicotine administration in pregnancy. Although we wanted to identify all health outcomes, we anticipated a priori that these would include at least some of the important clinical outcomes in a relevant 2015 Cochrane Review [18] (see below).

Exclusion criteria

We excluded RCTs and studies which reported only smoking-cessation outcomes [18].

Search strategy

A search strategy was developed in MEDLINE and then adapted for the CINAHL, Embase, PsycINFO, CAB Abstracts, Social Sciences Citation Index and Economic and Social Research Council databases. Supporting information, Table S1 gives search terms; we combined those relevant to pregnancy and fetal health with those referring to NRT or nicotine use. NRT became available in the 1980s, so we searched between 1980 and 12 June 2020, hand-searching references from retrieved full texts, including references from texts excluded from the review. Authors were contacted, as required, for study details.

Study selection and data extraction

One reviewer screened titles and abstracts, rejecting those which were not eligible for inclusion and retrieving manuscripts which appeared potentially includable or about which there was uncertainty. Two reviewers independently screened the full texts and a consensus decision was made on inclusion: if consensus was not possible, a third reviewer adjudicated. Study data were extracted by one reviewer and checked by a second, using a piloted form within Covidence (web-based systematic review platform) [19]. Extracted data included: author's details, publication date, study design and objectives, recruitment and data collection methods, participants' characteristics and study outcomes. For NRT exposure, we extracted data concerning when women were issued with or reported using this, and how many times and by what method these data were acquired. We also extracted smoking behaviour data, and particularly any information on smoking before

and after NRT use, including how often and by what means, this was recorded.

Quality assessment

Two researchers independently quality-assessed studies using modified versions of the Newcastle–Ottawa scale (NOS) [20]. Disagreements about scoring were discussed and consensus reached using a third assessor, if necessary. One modified scale was created for studies in which NRT was used as part of routine clinical care; this had a maximum score of eight stars. The other was used for smaller cohorts in which NRT was an experimental intervention (maximum score: seven stars). Both assessed three domains: 'selection', 'design and analysis' and 'outcome', and were modified by removal of the 'demonstration that outcome of interest was not present at start of study' item as pregnancy outcomes could only occur at childbirth. The 'comparability' domain was renamed 'design and analysis', and we removed 'was follow up long enough for outcomes to occur?' from the 'outcome' domain. Supporting information, Appendix S1 details scale modifications and scoring.

Meta-analysis and GRADE criteria

We anticipated substantial variation in study designs and outcomes, so decisions about meta-analyses were made only after consideration of all included studies. Where appropriate, we planned to pool data comparing outcomes following NRT exposure with no NRT exposure. To provide contextual information within the same studies we also compared outcomes following reported NRT exposure with those after smoking.

We created three exposure groups; those women who: (i) were prescribed or reported being given or using NRT, (ii) reported smoking but not being given NRT or (iii) neither reported smoking nor using NRT. As the only indication for using NRT in pregnancy is as a substitute for smoking, we assumed that all women issued with NRT would have smoked prior to this, so where studies categorized women as only having used NRT and not having smoked, we combined these groups with NRT-exposed groups from other studies which did not make this claim. Hence, we assumed that all women issued NRT would have smoked at some point in pregnancy. Review Manager version 5 software generated pooled risk ratios (RR) using a random-effects model and an estimate of heterogeneity using the I^2 statistic from the Mantel–Haenszel model [21]. As non-RCTs and RCTs are subject to very different biases and effects from unmeasured confounding, we decided to present non-RCT and RCT studies in separate meta-analyses. We anticipated that confounding due to women's smoking before, during or after use of NRT was likely to be particularly important to estimates derived from meta-analyses of non-RCTs, as few empirical studies attempted to adjust for this.

Table 1 shows GRADE [22] criteria that were applied to assess strength of evidence for each meta-analysed outcome. These rate the quality or certainty of evidence as 'very low', 'low', 'moderate' or 'high quality'; ratings start at 'high quality' for RCTs and 'low quality' for observational studies and GRADE criteria are used to up/downgrade ratings, as appropriate. Two reviewers independently applied criteria for each meta-analysed outcome; disagreements were resolved by consensus [13].

RESULTS

RCTs

Full results, including the PRISMA diagram, are found in the published CR [13], but of nine RCTs which investigated NRT use in pregnancy, seven reported infant and fetal safety outcomes [23–29] and all were conducted in high-income countries (n = 2340). All RCTs recruited pregnant women who smoked and, as with non-RCTs, pregnancies would have been exposed to tobacco smoke before women joined trials. RCT groups all received either behavioural support alone or with a placebo, or active NRT. Four placebo-RCTs were judged to be at low [23,24,26,29] and two non-placebo RCTs at high risk of bias [25,28]; for the remaining study this was unclear [27]. High bias risk was generally allocated to studies with no placebo control.

All seven studies reported mean birth weight and gestational age at delivery and incidences of low birth weight (below 2500 g). Six reported rates of preterm birth (birth before 37 weeks), miscarriage or spontaneous abortion and stillbirth [23,24,26–29] and four reported rates of infants' admissions to special care and of neonatal death [23,24,26,28]. Three trials reported rates of congenital malformation [23,24,27] and two reported caesarean section rates [23,24]. One study [30] reported infants' 'survival without developmental impairment' and respiratory symptoms at 2 years.

Meta-analysis results: RCTs

Figure 1 shows RCT meta-analyses findings. There was no evidence of a difference in risk of miscarriage/spontaneous abortion between NRT and control groups [RR = 1.60, 95% confidence interval (CI) = 0.53–4.83, I^2 = 0%; Fig. 1.1]. Similarly, there was no evidence of a 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%; Fig. 1.2). The pooled estimate for birth weight was higher for the NRT than for the control group, but the CIs incorporated a small decrease in birth weight as well as a more substantial increase, and heterogeneity was high [mean

Table 1 GRADE criteria for assessing non-RCTs.

GRADE criteria	*Reasons to downgrade*
Risk of bias	Studies scoring < 6/8 for risk of bias in the quality assessment were reviewed and if perceived to have such a high risk of bias that they could threaten findings' accuracy, downgrading by one level occurred
Inconsistency	If I^2 was > 50%, effect estimates for each study in the meta-analysis were assessed. If they were very different, with little-to-no overlap of the confidence intervals around studies' effect estimates, rating was downgraded by one level
Indirectness	This criterion assesses if evidence included in the review directly answers the review question. Quality of evidence was not downgraded based on this criterion due to the problem/patient/population, intervention/indicator, comparison, outcome (PICO) criteria used when searching. We felt our narrow PICO criteria meant that all studies included were reporting data that answered the review question, as we wanted information on all health outcomes reported after NRT exposure in pregnancy
Imprecision	If the confidence interval for the effect estimate was so wide that it could be consistent with having an effect in either direction, this was deemed to be a sign of imprecision and rating was downgraded by one level
Publication bias	Quality of evidence not downgraded based on this criterion due to the types of studies appraised
Upgrading	Quality of evidence not upgraded as there was no supporting evidence for the three recommended reasons to upgrade: large magnitude of effect, the presence of a dose–response gradient or that the effect of all plausible confounding factors would be to reduce the effect seen. It is also not recommended to upgrade a downgraded outcome

Criteria derived from the grading of recommendations, assessment, development and evaluation (GRADE) Working Group Handbook [22]. For all criteria, meta-analysed studies' quality was judged against reasons to downgrade. If there was serious concern regarding any criteria (except 'upgrading'), quality of evidence was downgraded to 'very low' quality, from the starting level of 'low' for observational (non-randomized controlled trial) studies.

difference (MD) = 99.73 g, 95% CI = –6.65 to 206.10, I^2 = 70%; Fig. 1.3]. There was no evidence of a difference in the incidence of low birth weight and there was much heterogeneity in the analysis (RR = 0.69, 95% CI = 0.39–1.20, I^2 = 69%; Fig. 1.4).

Analyses of rates of preterm births (RR = 0.81, 95% CI = 0.59–1.11, I^2 = 21%; Fig. 1.5), neonatal intensive care unit admissions (RR = 0.90, 95% CI = 0.64–1.27; I^2 = 0%; Fig. 1.6) and neonatal deaths (RR = 0.66, 95% CI = 0.17 to 2.62, I^2 = 0%; Fig. 1.7) all resulted in CIs spanning one, incorporating the potential for both benefit and harm. Similarly, meta-analyses of congenital anomalies and caesarean birth suggested no clear evidence for a benefit or harm from NRT (congenital anomalies: RR = 0.73, 95% CI = 0.36–1.48, I^2 = 0%, Fig. 1.8; caesarean section: RR = 1.18, 95% CI = 0.83–1.69, I^2 = 46%, Fig. 1.9).

GRADE assessment found a 'low' certainty of evidence for mean birth weight and miscarriage/spontaneous abortion outcomes.

Narratively reported outcomes: RCTs

Two RCTs [23,24] reported the distribution of Apgar scores at 5 minutes after birth, cord arterial blood pH, intraventricular haemorrhage, neonatal convulsions, necrotizing enterocolitis, mechanical ventilation of infant, assisted vaginal delivery and maternal death between NRT and placebo groups; no statistically significant differences were noted. One RCT [30] reported infant outcomes after the neonatal period. Using a composite self-report outcome based on the Ages and Stages Questionnaire, 3rd edition instrument [31], significantly better infant developmental outcomes were observed in infants born to women who had been randomized to NRT compared to those in the placebo group. The odds ratio (OR) for infants reaching 2 years of age 'without developmental impairment' (i.e. normal development) was 1.40 (95% CI = 1.05–1.86). 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 = 0.97–1.74).

Non-RCT studies

Study selection, characteristics and outcome measures

A total of 18467 titles and abstracts were identified and, after duplicate removal, 9391 records were screened. Forty-five full text articles were retrieved and 23 were included in the review; Fig. 2 shows the reasons for study exclusion.

Table 2 presents characteristics of the 23 included studies (n = 931 163). Eleven were conducted in health-care settings, used routine clinical data [32–42], compared women prescribed or issued NRT with those who were not and were derived from five discrete birth cohorts. A UK cohort reported outcomes in two manuscripts [32,34] and a PhD [38]; a Danish cohort reported outcomes in five papers [33,35,37,39,42] and Canadian [40], US [36] and Australian [41] cohorts were reported in single studies. Eleven studies described

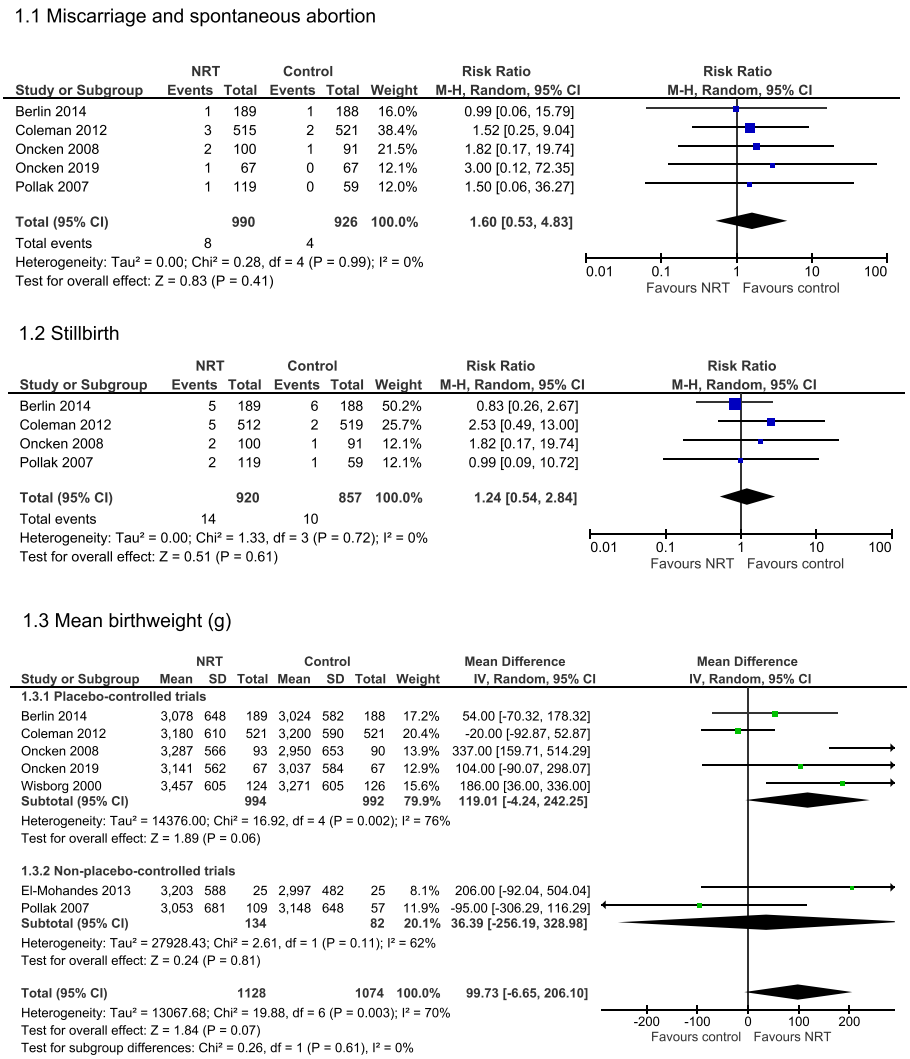


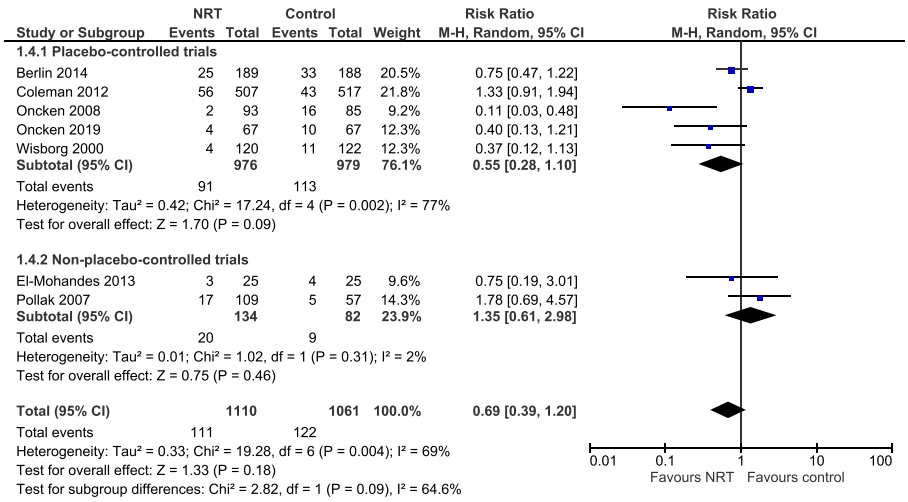
Figure 1 Meta-analyses of randomized controlled trials (RCTs) (from Cochrane Review). [Colour figure can be viewed at wileyonlinelibrary.com]

NRT administration to small, experimental interventional cohorts of inpatient pregnant women who usually smoked but were temporarily abstinent [43–53], and were based in Sweden [43,48], the United States [45,46,49–53], the United Kingdom [44] and Finland [47]. These mainly compared short-term fetal and maternal physiological observations when abstinent and using NRT to those when women smoked. The final Danish study was interventional; participants were a subgroup of women in a quasi-RCT who had been offered and accepted NRT [54].

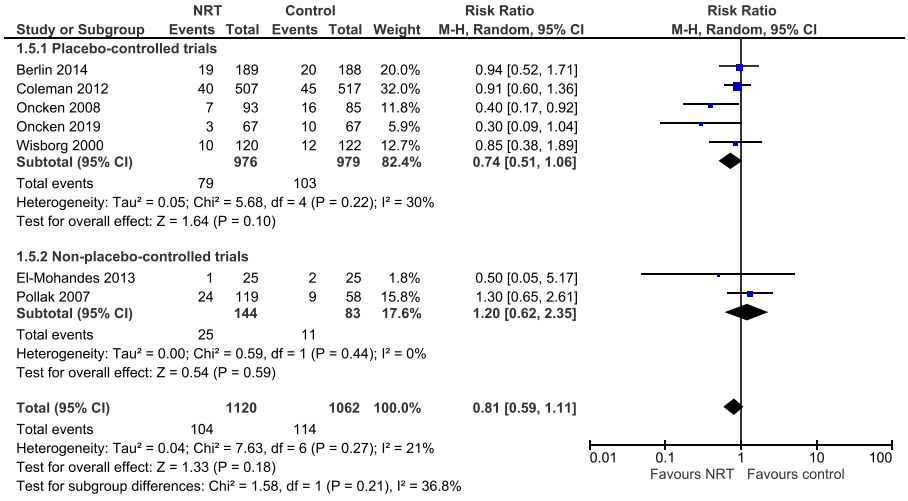
Maternal age was reported by 17 studies [32–36,38–40,43,45,46,48–53] and used as a confounder in analyses, but not reported in three [33,37,41,42]. Socio-economic status or education level was reported by 11 studies [32–40,42,51]. Maternal comorbidities were included as confounders in six routine health-care studies [32,34,37,38,40,41], and as exclusion criteria in five interventional studies [46,50–53]. One interventional study reported comorbidities for each participant and analysed data by condition [44].

NRT exposure data was obtained from electronic medical records or prospectively from telephone interviews in nine routine health-care studies [32–35,37–39,41,42]; two others collected data retrospectively via self-administered postal questionnaires [36,40] sent 3–8 years [40] and 2–3 months [36] after pregnancy. Although women in the Danish cohort were asked in which gestational weeks they had used NRT or smoked, manuscripts did not report the details [33,35,37,39,42] and one routine health-care study reported median duration of NRT use but not when, in pregnancy, this occurred [40]. All 12 interventional studies reported women's gestational ages at NRT administration, with nine providing mean gestational ages at exposure (range = 21.5–35.6 weeks) [45,46,48–54].

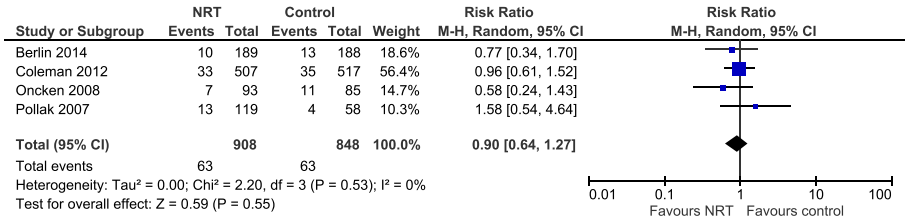
1.4 Low birthweight (<2500g)



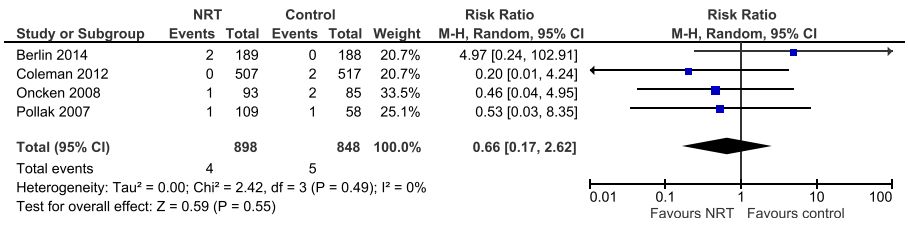
1.5 Preterm birth (birth <37 weeks)



1.6 Neonatal intensive care unit admissions



1.7 Neonatal death



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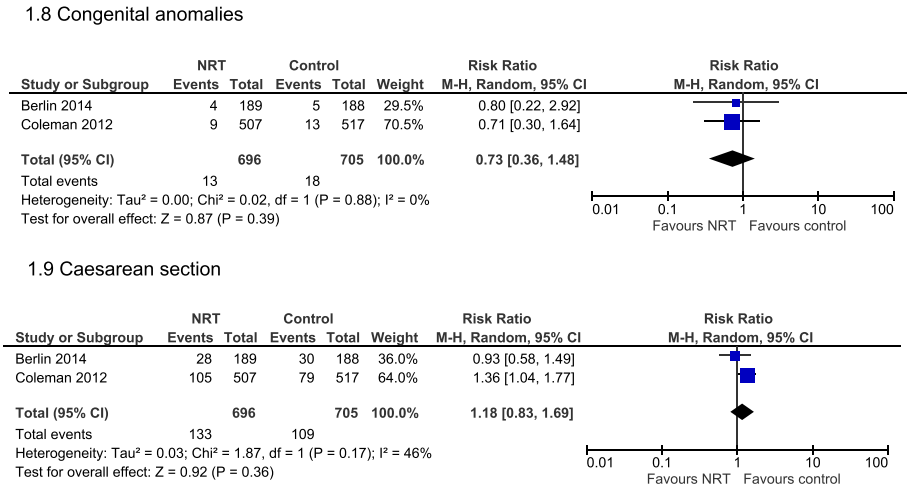

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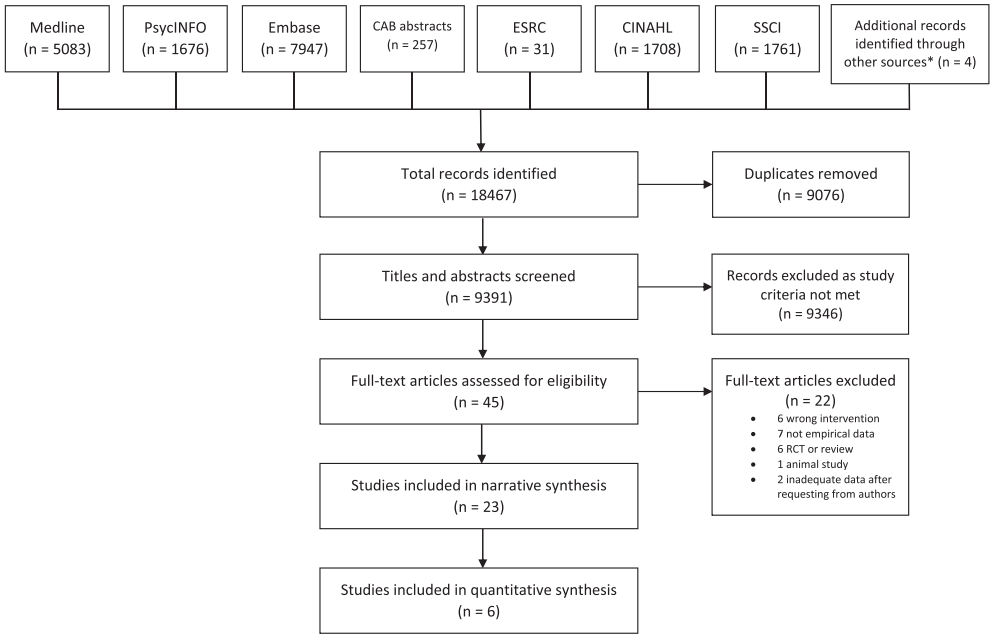

Figure 2 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram: non-RCT review. PRISMA [17] flow diagram showing study selection and reasons for study exclusion. *Hand searches of references located, a PhD thesis and an unpublished study at the time of searching known to the authors.

Table 2 shows which studies reported or adjusted for women's smoking before or after NRT use. Of the six studies in meta-analyses, three reported women's smoking behaviour before NRT use/exposure [33,36,39], but data were collected by questionnaire at set time-points, so no smoking behaviour information was available later in participants' pregnancies. Consequently, many pregnant women in NRT-exposed arms of meta-analyses will also have smoked, and exposures to NRT and smoking are not completely differentiated. Two routine health-care studies adjusted for smoking status during NRT use [33,37]. Two routine health-care studies recruited only pregnant women who smoked, and investigated impacts of using NRT within this group [40,41]. Experimental studies all recorded women's smoking status at the time of recruitment, and nine also validated abstinence just before NRT was given to women [43–46,48–52] and two followed participants until childbirth, collecting some information on smoking after NRT exposure [53,54].

Table 3 summarizes studies' outcomes. Routine health-care cohorts reported pregnancy outcomes such as congenital anomalies [34,35], birth weight [36–40], gestational age at birth [36,37,39,40] and stillbirth [32,33]. Interventional studies generally monitored physiological observations, including biophysical profiles [49,52], umbilical and uterine artery Dopplers

Table 2 Characteristics of included non-RCTs.

First author, Location Date	*Recruitment method (location/setting, eligibility criteria, data collection)*	*Study objectives*	*Baseline characteristics/group differences*
Cohort studies of NRT use during routine health-care – with control/unexposed group for analysis (non-smokers who did not use NRT)			
Outcome: Stillbirth			
Dhalwani UK 2018 [32]	The Health Improvement Network (THIN) database UK database of anonymized electronic primary care records Longitudinally prospectively collected data from 570 GP surgeries, representing 6% of UK population Singleton pregnancies with deliveries between 2000 and 2013	To compare risk of stillbirth between pregnant smokers, non-smokers and those prescribed NRT	220630 singleton pregnancies ~50% in NRT and smoking groups in two most deprived quintiles versus ~25% of controls. Women aged 15–49 years. Higher rates of mental illness in NRT and smoking groups
Strandberg-Larsen Denmark 2008 [33]	Danish National Birth Cohort (DNBC) Population-based cohort of pregnant women and their offspring, recruitment 1996–2002 50% of Danish GPs participated and invited pregnant women to participate. An estimated 60% of invited women took part Eligible if: pregnant, Danish speaker, planned to carry pregnancy to term Computer-assisted telephone interview between 12–16/40 where women self-reported NRT use and smoking behaviours during pregnancy Outcomes identified from Civil Registration System, Danish Medical Birth Registry using record linkage, National Hospital discharge register or by self-report	To examine if NRT use in pregnancy has an association with the risk of stillbirth	Pregnancies 100418 Information from first interview 90165 After exclusion: 87032 singleton pregnancies mean gestational age at: recruitment 11.5 weeks; interview 16.9 weeks. Women using NRT more often at least 35 years, nulliparous, BMI < 25 kg/m^2, alcohol consumption ≥ 2 drinks/week, higher caffeine intake
Outcome: major congenital anomalies (MCAs)			
Dhalwani UK 2015 [34]	THIN database (see Dhalwani 2018) Pregnancy cohort created from all 15–49-year old women in database by linking pregnancy and birth-related codes in women's medical records to live births of children from January 2001 to December 2012 Major congenital anomaly (MCA) diagnoses extracted from European Surveillance of Congenital Anomalies and Twins classification system (EUROCAT). Minor CAs and MCAs specifically attributed to known teratogens excluded	To assess the relationship between early pregnancy exposure to NRT or smoking with MCA in offspring	192498 live-born children. Mothers in smoking group younger compared to NRT group/controls. ~25% mothers in NRT/smoking groups in most deprived quintile. NRT/smoking groups had higher proportions of maternal morbidities (asthma, mental illness)

(*Continues*)

Table 2. (Continued)

First author, Location Date	*Recruitment method (location/setting, eligibility criteria, data collection)*	*Study objectives*	*Baseline characteristics/group differences*
Morales-Suárez-Varela Denmark 2006 [35]	DNBC (see Strandberg-Larsen, 2008). Based on first child in the cohort, women included from January 1997 to December 2003 Included: those who answered first interview smoking questions (11–25 weeks) Excluded: women with ovarian/cervical cancer during pregnancy, multiple pregnancy Congenital malformation data obtained from the Medical Birth Registry and hereditary diseases and chromosome anomalies diagnosed during first year of life obtained from the National Hospital Discharge Registry. Congenital malformations classified as per EUROCAT criteria	To examine whether maternal smoking and use of nicotine substitutes during the first 12 weeks of pregnancy increased the prevalence of congenital malformations	76 768 live-birth singleton pregnancies included Smokers younger, lower body weight, higher alcohol intake and less well educated than non-smokers. NRT members of cohort not described separately
Outcomes: gestational age at birth (including preterm birth), birth weight (including mean and low birth weight)			
Gaither USA 2009 [36]	2004 Phase V Pregnancy Risk Assessment Monitoring System (PRAMS)—population-based surveillance system with information on maternal behaviour before, during and after pregnancy Participating states draw stratified sample of new mothers from birth certificates and send self-administered questionnaires on exposures in pregnancy. Birth outcome information from birth certificates 4 states included in the study—Colorado, Louisiana, Maine, Washington. Excluded if: no prenatal care, missing data on marital status, education, parity, Medicaid, alcohol use	To examine factors associated with the prescription or advisement of NRT during pregnancy and its association with adverse pregnancy outcomes	6041 women aged 18–45 completed questionnaires After exclusion criteria: 5716 women ≤ 24 years less likely to be prescribed/recommended NRT compared to women ≥ 35 years. Women who gained ≤ 15 lbs significantly more likely to be prescribed NRT
Lassen Denmark 2010 [37]	DNBC (see Strandberg-Larsen 2008) Interviews at, on average, 16/40 and 31/40 Included if gave birth to live-born singletons. Excluded if: gave birth before 28 completed weeks; uncertain gestational age/estimated date of delivery; interview before 27 completed weeks; information missing from the variables included in multivariate analysis, did not answer both interviews Information for birth outcomes obtained by linking of cohort to National Patient Registry	To estimate the association between the use of NRT during pregnancy and offspring birth weight	101 042 pregnancies in cohort After exclusion criteria applied: 72 761 Median tobacco use in NRT users was 9.5 pack weeks, 88% of NRT users smoked during 1 or more weeks in first 2 trimesters NRT users had lower socio-economic status than non-smokers but higher than smokers

(***Continues***)

Table 2. (Continued)

First author, Location Date	*Recruitment method (location/setting, eligibility criteria, data collection)*	*Study objectives*	*Baseline characteristics/group differences*
Outcomes: low and mean birth weight, fetal death, mode of delivery			
Dhalwani UK 2014 [38]	Chapter 7 of PhD thesis THIN database (see Dhalwani 2018) Pregnancy cohort created from all 15–49-year-old women in database by linking pregnancy and birth-related codes in women's medical records Low and mean birth weight measured from live births January 2001–December 2009. Stillbirth or fetal death from January 2001–September 2009	To examine the association between NRT and smoking exposure and risk of fetal death, birth weight and mode of delivery	*n* variable for populations depending on outcome—see Results column Approximately 50% mothers in both smoking and NRT groups in 2 most deprived quintiles
Outcome: infantile colic			
Milidou Denmark 2012 [39]	DNBC (see Strandberg-Larsen 2008) 2 computer-assisted telephone interviews in 2nd and 3rd trimesters and at 6 months postpartum concerning infant's behaviour, development, nutrition and frequency and duration of cry episodes Included if completed both 2nd trimester and postnatal interviews. Based on first child in the cohort, so 3695 younger siblings excluded Exposure to nicotine was self-reported smoking or use of NRT during pregnancy	To compare the association between intrauterine exposure to tobacco smoke and infantile colic with the possible association between NRT and infantile colic	101042 pregnancies After exclusion: 63128 mother–infant dyads included Mothers that smoked either with/without NRT tended to be less well educated and slightly younger in age
Cohort studies of routine health care—with no control group for analysis (non-smokers who did not use NRT)			
Outcomes: preterm birth and small for gestational age			
Bérard Canada 2016 [40]	Quebec Pregnancy Cohort (Canada). All pregnancies between January 1998 and December 2009 recorded 1288 women who reported smoking just prior to pregnancy from 6732 of 8505 women selected randomly and contacted annually to fill in a standardized questionnaire (sent in the post, twice, 3– 8 years after pregnancy of interest) on smoking status and information on NRT use NRT usage obtained from Régie de l'Assurance Maladie du Québec medication database. Cross-checked with NRT and smoking status from questionnaire	To quantify the effect of gestational use of bupropion[d] and nicotine patch replacement therapy on the risk of prematurity and small for gestational age	6732 women completed the questionnaire 1288 women were smokers before pregnancy and therefore eligible for inclusion Women aged 15–45 years, NRT initiated in first trimester

(*Continues*)

Table 2. (Continued)

First author, Location Date	*Recruitment method (location/setting, eligibility criteria, data collection)*	*Study objectives*	*Baseline characteristics/group differences*
Tran Australia 2020 [41]	Smoking MUMS study Population-based cohort focused on pharmacotherapies for smoking cessation All pregnancies resulting in a birth (> 20 weeks) across two states, New South Wales and Western Australia, 2004–12 Linked records from 4 data sources—perinatal data, dispensing data for pharmaceuticals subsidized through benefits scheme, hospital admission and deaths Smoking status from perinatal or maternal hospital admission data	To compare risk of adverse perinatal outcomes between pregnancies exposed to pharmacotherapies (NRT, bupropion, varenicline[d]) and pregnancies exposed to smoking but no pharmacotherapy	3608 pregnancies exposed to either NRT or smoking Well-balanced baseline characteristics between groups as pregnancies matched between NRT users and smokers
Outcome: strabismus in infants			
Torp-Pedersen Denmark 2010 [42]	DNBC (see Strandberg-Larsen 2008). Children born between 1996–2003. Interviews ×2 during pregnancy, 6 and 18 months postpartum to obtain information on exposures of potential relevance National Patient Register and Health Security System identified children with strabismus diagnosis, previous strabismus surgery or evaluation for strabismus. Medical records for cases evaluated by 2 experienced orthoptists then linked with information from birth cohort	To investigate the effect of *in-utero* exposure to maternal smoking and consumption of alcohol, coffee and tea on the risk of strabismus	Review of 5655 medical charts yielded 1320 instances of strabismus

(***Continues***)

Table 2. (Continued)

First author, Location Date	*Exposure group(s) (including dose and route of NRT)*	*Non-exposed group*	*Outcome Measures (i.e. adverse fetal/ maternal health outcomes)*	*Main/significant results*
Cohort studies of NRT use during routine health-care – with control/unexposed group for analysis (non-smokers who did not use NRT)				
Outcome: Stillbirth				
Dhalwani UK 2018 [32]	NRT[a], n = 5221, women prescribed NRT during pregnancy or before conception as recorded in primary care record. Average NRT prescription duration 2 weeks (IQR: 6 days–2 weeks), 80% within first 2 trimesters. No quantification of smoking before/during/after NRT exposure. Smokers n = 18407, smoking recorded in medical record with no quantification of exposure	Controls n = 197002, recorded as non-smoker, or not smoked for 3 years in medical records	Stillbirth—baby born with no signs of life at or after 28 weeks gestation	Stillbirth, n = 805 (3.6 in 1000 births) NRT n = 26 (0.5%), smokers n = 96 (0.52%), controls n = 683 (0.35%) When compared with controls: NRT OR = 1.44 (CI = 0.97–2.14), Smokers OR = 1.52 (CI= 1.23–1.89), $P < 0.01$ Similar findings after adjustment for confounders (age, socio-economic status, BMI, diabetes) Higher prevalence of stillbirth if maternal age ≥ 35 years or diabetes
Strandberg-Larsen Denmark 2008 [33]	NRT user[b] n = 1927, any use of NRT between LMP and interview Subcategorized into: NRT user + smoker n = 1091, where participants said they had co-exposure to NRT and smoking at time of interview, by grams of tobacco on average/ day or week NRT user + non-smoker n = 836, non-smokers and those who smoked in pregnancy but were ex-smokers at time of interview and used NRT Smokers n = 13266, those who reported smoking during pregnancy at time of interview (group including ≤ 10 g/ tobacco/day and > 10 g/day) Unclear about smoking behaviour after interview (apart from 836 who were not smoking afterwards)	Non-users of NRT n = 85105 Sub-categorized into: smokers (see previous column) and non-smokers (controls) n = 71 839, non-smokers who were not exposed to NRT, including those who quit before conception, or reported being an ex-smoker at interview but may have smoked in early pregnancy	Stillbirth—any fetus that did not breathe or show any other sign of life at birth > 20 weeks gestation	Stillbirth n = 495 (rate 5.7 in 1000 births) Compared to non-users of NRT, overall NRT user stillbirth hazard ratio (HR) = 0.57 (CI = 0.28–1.16); adjusted for maternal age, household socio-occupational status and smoking habits) Subcategories adjusted for maternal age and socio-occupational status: controls, n = 380 (reference for all HRs) NRT user + smoker—HR = 0.83 (CI = 0.34–2.00) NRT user + non-smoker, HR = 0.67 (CI = 0.21–2.08) Smokers —HR = 1.46 (CI = 1.17–1.82). Definition of stillbirth changed to no signs of life at > 22 weeks—no significant change in results

(*Continues*)

Table 2. (Continued)

First author, Location Date	*Exposure group(s) (including dose and route of NRT)*	*Non-exposed group*	*Outcome Measures (i.e. adverse fetal/ maternal health outcomes)*	*Main/significant results*
Outcome: major congenital anomalies (MCAs)				
Dhalwani UK 2015 [34]	NRT[a] $n = 2677$, women prescribed NRT either during first trimester of pregnancy or within 4 weeks before estimated conception date according to primary care record. No quantification of smoking before/during/after NRT exposure Smokers $n = 9980$, smoking recorded in medical record with no quantification of exposure	Controls $n = 179841$, recorded as non-smoker, or not smoked for 3 years in medical records	MCAs: heart; limb; genital system; urinary system; chromosomal; musculoskeletal; orofacial cleft; digestive system; nervous system; other malformations; eye; respiratory system; genetic; abdominal wall; ear, face and neck	Maternal age at conception, socio-economic status and preconception BMI similar in women with infants with MCAs and those without. MCA group had a slightly higher proportion of maternal morbidities. At least 1 MCA $n = 5535$ (288 per 10000 live births) All MCAs combined: NRT $n = 90$ (336 of 10000), smokers $n = 314$ (315/10000), controls $n = 5131$ (285 of 10000) when compared with controls across all MCAs (adjusted for maternal age at conception, Townsend deprivation index score, maternal diabetes, asthma, mental illness and multiple births) NRT OR = 1.12 (CI = 0.84–1.48), smokers OR = 1.05 (CI = 0.89–1.23) There were no statistically significant associations between maternal NRT use and system-specific anomalies except for respiratory anomalies OR (compared with controls) = 4.65 (99% CI = 1.76–12.25, $P < 0.001$)
Morales-Suárez-Varela Denmark 2006 [35]	NRT[b] $n = 250$, women who reported during interview using nicotine substitutes in the first 12 weeks of pregnancy but did not smoke. No information available on smoking behaviour after NRT exposure as questionnaire only asked about use in first 12 weeks of pregnancy. Smokers $n = 20603$, women who reported smoking during the first 12 weeks of pregnancy at interview; note $n = 3791$ missing data unaccounted for, so for analysis $n = 16812$ Quantified as ≤ 10/day and > 10/day.	Controls $n = 55915$ women who reported being non-smokers who did not use NRT	Various congenital malformations: nervous system; ear, eye, face and neck; circulatory system; respiratory system; cleft lip and palate; digestive system; genital organs; urinary system; musculoskeletal system; chromosomal anomalies; other	Children born with all congenital malformations $n = 3767$ For major malformations: controls $n = 2186$ [reference for all relative prevalence rate ratios (RPR)] NRT $n = 11$ RPR = 1.13 (CI = 0.62–2.07) Smokers $n = 722 \leq 10$/day $n = 535$, RPR = 1.12 (CI = 1.02–1.23) > 10/day $n = 187$, RPR 1.09 (CI = 0.93–1.27) NRT and major musculoskeletal RPR = 2.05 (CI = 0.91–4.63)

(*Continues*)

Table 2. (Continued)

First author, Location Date	*Exposure group(s) (including dose and route of NRT)*	*Non-exposed group*	*Outcome Measures (i.e. adverse fetal/ maternal health outcomes)*	*Main/significant results*
Outcomes: gestational age at birth (including preterm birth), birth weight (including mean and low birth weight)				
Gaither USA 2009 [36]	NRT[a] n = 225, smoking participants self-reported if a health-care professional prescribed a nicotine spray, inhaler or pill, or recommended using a nicotine patch or gum during prenatal visits as a means of smoking cessation Smokers n = 637 women who reported smoking during pregnancy but no NRT use No quantification of smoking or smoking intensity in either group, before or after NRT exposure.	Non-smokers n = 4854 women who reported not smoking during pregnancy and therefore were not recommended or prescribed NRT	Preterm birth—birth at <37 weeks gestation Low birth weight (LBW) - ≤2500 g at birth	Low birth weight: NRT n = 84 (13.05%), Smokers n = 205 (9.26%), Non-smokers n = 1303 (6.99%) Unadjusted OR when compared with non-smokers: NRT OR = 2.00 (CI = 1.13–3.45), smokers OR = 1.36 (CI = 0.98–1.88). Similar findings after ORs adjusted for age, marital status, education and ethnicity Preterm birth: NRT n = 66 (17.54%), smokers n = 156 (10.19%), non-smokers n = 1165 (9.42%). Unadjusted ORs when compared with non-smokers: NRT OR = 2.05 (CI = 1.16–3.60), smokers OR = 1.09 (CI = 0.76–1.57.) Similar findings after ORs adjusted for age, marital status, education and ethnicity
Lassen Denmark 2010 [37]	NRT[a] n = 1828, women asked if they had used NRT, which type and in which weeks of pregnancy (First 27 weeks was exposure period of interest). Smoking quantified in pack weeks. For analysis, smoking information required, so n without missing smoking info, NRT n = 1753 Smokers n = 15796, women who reported smoking but no NRT use, by pack weeks. Smoking not quantified again after questionnaire completed	Non-smokers n = 53771, self-report of being a non-smoker not using NRT	Gestational age at birth split into: Preterm <259 days Term 259–293 days Post-term >293 days Birth weight (change in mean birth weight in g)	Gestational age at birth: Preterm: NRT 4.1%, smokers 3.9%, non-smokers 3.2%. Term: NRT 87.2%, smokers 87.0%, non-smokers 87.7%. Post-term: NRT 8.8%, smokers 9.1%, non-smokers 9.1% Change in mean birth weight in g after all NRT use within the first 27 completed weeks of gestation 0.25 (CI = 2.31–2.81), adjusted for gestational age, smoking status, partner smoking status, parity, pre-pregnancy BMI, height, alcohol, coffee, exercise, infant sex, socio-economic status, weight loss, eating disorder, fertility problems, vaginal bleeding, nausea, hypertension Subgroups change in mean birth weight in g. Nicotine patch −4.37 (CI = −13.34–4.60). Nicotine gum 0.48 (CI = − 2.51–3.48). Nicotine inhaler 6.19 (CI = − 0.40–12.79) More than one product −10.72 (CI = −26.51–5.05)

(*Continues*)

Table 2. (Continued)

First author, Location Date	*Exposure group(s) (including dose and route of NRT)*	*Non-exposed group*	*Outcome Measures (i.e. adverse fetal/ maternal health outcomes)*	*Main/significant results*
Outcomes: low and mean birth weight, fetal death, mode of delivery				
Dhalwani UK 2014 [38]	NRT[a], women prescribed NRT during pregnancy or before conception according to primary care record. No quantification of smoking before/during/after NRT exposure Smokers, smoking recorded in medical record with no quantification of exposure	Controls, recorded as non-smoker, or not smoked for 3 years in medical records	Low birth weight (<2500 g). Fetal death—combined stillbirth and miscarriage data Mode of delivery Change in mean birth weight	For each outcome: *N* = population. *n* = outcome, adjusted ORs (99% CI), *P*-value, low birth weight [total *N* = 96782 (*n* = 77 939 unknown exposure so excluded)]: NRT *N* = 1223. *n* = 135, OR = 1.88 (1.42–2.49), $P < 0.001$ Smokers *N* = 4622. *n* = 435, OR = 1.73 (1.45–2.06), $P < 0.001$. Non-smoker *N* = 13088, *n* = 740, reference for ORs Fetal death [total *N* = 311802 (*n* = 105750 unknown exposure so excluded)]: NRT *N* = 5234. *n* = 491, OR = 0.44 (0.38–0.50), $P < 0.001$ Smokers *N* = 50643. *n* = 10560, OR = 1.16 (1.11–1.21), $P < 0.001$ Non-smoker *N* = 150175 (*n* = 25962, reference for ORs) Mode of delivery (adjusted RRR relative to normal delivery/non-smokers) NRT Assisted RRR = 0.68 (0.54–0.85), $P < 0.001$; C-section RRR = 0.92, (0.81–1.05), $P = 0.120$ Smokers assisted RRR = 0.76 (0.68–0.86), $P < 0.001$; C-section RRR = 0.88 (0.81–0.95), $P < 0.001$ Mean (SD): birth weight 3.41 kg (0.59). Gestational age for same pregnancies 40 weeks (2.11). Change in mean birth weight with NRT exposure compared with non-smokers $\beta = -168$ g (−214, −122), $P < 0.001$. Change in mean birth weight after smoking compared with non-smokers $\beta = -139$ g, (−165, −113), $P < 0.001$

(*Continues*)

Table 2. (Continued)

First author, Location Date	*Exposure group(s) (including dose and route of NRT)*	*Non-exposed group*	*Outcome Measures (i.e. adverse fetal/ maternal health outcomes)*	*Main/significant results*
Outcome: infantile colic				
Milidou Denmark 2012 [39]	NRT users[b] $n = 207$—those who reported NRT use with no smoking during pregnancy $N = 194$ used one of: gum, patch or inhalator. $N = 13$ used a combination of NRT types Smokers using NRT (in combination) $n = 1245$ Smokers $n = 15016$, those who reported smoking without using NRT Smoking quantified as cigarettes/day, data not given per exposure group. Smoking behaviour elicited at postnatal interview but data not given	Controls $n = 46660$, unexposed i.e. no smoking and no NRT	Infantile colic: Wessel's criteria used—crying or fussing for more than 3 hours a day for more than 3 days a week, starting before age 3 months Preterm birth (gestational age at birth < 37 weeks) and low birth weight (birth weight < 2500 g) also reported for all groups	Preterm birth: controls 4.0%, NRT users 2.9%, smokers 4.9%, smoking and NRT 5.2% Low birth weight: controls 2.4%, NRT users 2.9%, smokers 4.3%, smoking and NRT 4.8% Infantile colic—$n = 4974$ (7.9%) of total infants. Crude unadjusted ORs when compared with controls $n = 3397$: NRT $n = 23$, OR = 1.6; smokers[c] $n = 1417$, OR = 1.3; smoking and NRT $n = 137$, OR 1.6 Similar results (all significant) when adjusted for maternal age, first parity, daily coffee consumption, weekly alcohol consumption, and binge-drinking episodes and when further adjusted for couple's combined educational and occupational status
Cohort studies of routine health care—with no control group for analysis (non-smokers who did not use NRT)				
Outcomes: preterm birth and small for gestational age				
Bérard Canada 2016 [40]	NRT $n = 316$, smokers with prescription for NRT patch filled before 1st day of gestation with duration overlapping beginning of pregnancy, or reporting OTC NRT patch use Some quit smoking during NRT use but no quantification of this in paper Median duration of use 54 days (IQR: 36–72 days) Smokers $n = 900$, pregnant smokers without bupropion or NRT patch exposures during pregnancy. No quantification of smoking	No controls—there was no group exposed to neither NRT nor smoking	Prematurity— birth before the 37th week of gestation Small for gestational age (SGA); lowest 10th percentile of the gestational age-specific birth weight in the cohort	Preterm birth: NRT $n = 25$ (7.9%), smokers $n = 240$ (26.7%) SGA: NRT $n = 44$ (13.9%), smokers $n = 149$ (16.6%) ORs for NRT compared with smoking—adjusted for maternal socio-economic status, health care utilization and comorbidities before pregnancy Preterm birth: NRT OR = 0.21 (CI = 0.13–0.34); SGA: NRT = 0.61 (CI = 0.41–0.90) Mean gestational age in weeks (SD): NRT = 38.9 (1.9), smokers 37.5 (3.3). Mean birth weight in g (SD): NRT = 3257.9 (553.1), smokers 2943.5 (733.5) Smokers had significantly shorter gestation and lower birth weight newborns compared with bupropion or NRT users ($P < 0.05$)

(*Continues*)

Table 2. (Continued)

First author, Location Date	*Exposure group(s) (including dose and route of NRT)*	*Non-exposed group*	*Outcome Measures (i.e. adverse fetal/ maternal health outcomes)*	*Main/significant results*
Tran Australia 2020 [41]	NRT $n = 328$, one or more dispensings of NRT in 100 days prior to conception or in gestation period. Gestational age at exposure calculated. All women assumed to be smokers but degree of smoking alongside NRT use not quantified. Smokers $n = 3280$ (10 : 1 matching), smoking recorded in perinatal data collection ('yes' or smoking > 0 cigarettes in 1st or 2nd halves of pregnancy) or if hospital admission data stated smoked in the last month before delivery	No controls—there was no group exposed to neither NRT nor smoking	Preterm birth, SGA, Apgar at 5 min < 7, admission to neonatal special care, severe neonatal morbidity complications, emergency caesarean, severe maternal morbidity complications, PPROM, placental abruption, perinatal death (stillbirth or neonatal death)	Any adverse perinatal event (composite of all 10 events): NRT $n = 147$, smokers $n = 1520$, HR = 1.02 (CI = 0.84–1.23). Preterm birth: NRT $n = 36$, Smokers $n = 358$, HR = 1.00 (CI = 0.71–1.42) SGA: NRT $n = 47$, Smokers $n = 578$, HR = 0.77 (0.56–1.07) Admission to neonatal special care: NRT $n = 66$, Smokers $n = 692$, HR = 0.97 (CI = 0.74–1.26) Severe neonatal morbidity: NRT $n = 27$, Smokers $n = 345$, HR = 0.82 (CI = 0.55–1.23) Emergency caesarean: NRT $n = 37$, Smokers $n = 421$, HR = 1.01 (CI = 0.70–1.45). Severe maternal morbidity complications: NRT $n = 10$, Smokers $n = 79$, HR = 1.22 (CI = 0.60–2.46). PPROM: NRT $n = 16$, Smokers $n = 139$, HR = 1.15 (CI = 0.68–1.94). Apgar 5 min < 7: NRT $n = 6$, smokers $n = 105$, HR = 0.59 (CI = 0.25–1.37). Placental abruption: NRT $n < 5$,smokers $n = 34$. Perinatal death: NRT $n < 5$, Smokers $n = 30$
Outcome: strabismus in infants				
Torp-Pedersen Denmark 2010 [42]	NRT $n = 61$, NRT use self-reported at least once during pregnancy via maternal interview, smoking status unknown Smokers $n = 415$. Not directly compared with NRT, quantified by average cigarettes/ day during pregnancy	Unexposed to NRT $n = 1239$, women who did not use NRT (although smoking status not reported)	Strabismus in infants	The use of nicotine replacement therapy in pregnancy was associated with a non-significant 22% increase (RR = 1.22, CI = 0.92–1.61) in strabismus risk in comparison with no maternal NRT use Smoking was associated with a significantly increased risk compared with mothers who did not smoke (RR = 1.26, CI = 1.11–1.43). Higher numbers of cigarettes/day associated with higher risk of strabismus

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Table 2. (Continued)

Cohorts with NRT administered as an intervention in experimental settings

First author, Location, Date	*Study design*	*Recruitment method (location/setting, eligibility criteria, data gathering)*	*Study objectives*	*Baseline characteristics/group differences*	*Intervention group(s) (including dose and route of NRT)*
Outcome: Fetal breathing movements during nicotine administration					
Gennser Sweden 1975 [43]	Controlled longitudinal cohort study	Department of Obstetrics and Gynecology, University of Lund Performed in morning hours after breakfast following a smoking-free interval of at least 12 hours. Women in recumbent position, with equilibration period of 15 minutes of fetal monitoring before a control period of 30 minutes. Then either tobacco/non-tobacco cigarette or gum smoked over 5 minutes/chewed over 30 minutes, respectively. Fetal breathing movements measured from start to 60 minutes after intervention using ultrasonographic technique, along with maternal breathing and ECG	To study the influence of maternal smoking on the fetal breathing movements and attempts to determine the role of nicotine in this response	12 healthy pregnant women aged 20–31 years between 33rd–39th gestational weeks All smokers, average cigarette consumption 7–20 cigarettes a day	*N* = 6 tested with: ● Standard cigarette (1.7–1.8 mg nicotine) ● Nicotine chewing gum 2 mg ● Nicotine chewing gum 4 mg One substance tested per day on 3 consecutive days
Manning UK 1976 [44]	Uncontrolled longitudinal cohort study	Nuffield Institute for Medical Research, University of Oxford Observations made in morning after patient had eaten normal breakfast and had abstained from smoking overnight. Fetal breathing movements recorded using A-scan ultrasound method for at least 30 minutes before smoking/chewing and for at least 60 minutes afterwards	To determine the factor in cigarette smoke and other substances responsible for the depression of fetal breathing	64 women, all in third trimester, all chronic smokers	Nicotine gum *n* = 12 (chewed vigorously for at least 20 minutes): ● 1 × 4mg nicotine containing gum (*n* = 7) ● 2x4mg nicotine containing gum (*n* = 5)
Outcome: fetal blood flow during nicotine administration					
Bruner USA 1991 [45]	Prospective cross-over cohort study	Obstetric clinics of the Hospital of the University of Pennsylvania. Large, indigent, inner city	Prospective comparison of effects of maternal smoking of a single cigarette and buccal nicotine	47 healthy pregnant women ● Non-smokers (*n* = 16) ● Prior smokers (*n* = 8)	NRT, phase 2: 1–2 weeks after phase 1, same participants chewed one piece of nicotine

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Table 2. (Continued)

Cohorts with NRT administered as an intervention in experimental settings					
First author, Location, Date	*Study design*	*Recruitment method (location/setting, eligibility criteria, data gathering)*	*Study objectives*	*Baseline characteristics/group differences*	*Intervention group(s) (including dose and route of NRT)*
		population of women in late 2nd and 3rd trimesters of pregnancy from menstruation dates and confirmation ultrasound Inclusion criteria specified. Randomly approached, offered written, informed consent. All examinations 8–11 a.m., after abstaining from smoking for 30 minutes. Resting in recumbent position until HR/BP at constant baseline. Uterine/umbilical artery FVWs measured at baseline and after intervention (at 1 minute and 10 minutes) using continuous wave Doppler transducer	exposure on uterine and umbilical artery blood FVWs	● Smokers ($n = 23$, ≤ 10 cigarettes/day $n = 13$, 11–20/day $n = 10$) Mean maternal age 24 years. Mean gestational age at study entry 30/40, 33/40 at gum phase	polacrilex (gum) containing 2 mg nicotine vigorously 15 times and then tucked into cheek until FVWs recorded
Oncken USA 1997 [46]	Prospective cross-over cohort study	Recruitment: April–October 1995 through newspaper advertisements and local physician practices Inclusion and exclusion criteria specified Expired CO measured before patch placement/smoking to verify abstinence, and at 2, 3, 4, 5, 6 and 8 hours. Maternal BP, HR and ultrasound resistance indices (RIs) determined at 2, 3, 4, 6 and 8 hours after patch applied/smoking began. 20-minute FHR monitoring performed at baseline and repeated 4 hours later	To compare nicotine concentrations and fetal middle cerebral artery RIs during transdermal NRT with smoking	23 evaluated for suitability to take part 17 subjects met eligibility criteria 2 exclusions: one because of a single umbilical artery; the other quit smoking after the first session Mean gestational age 28 + 3/40 (SD ±20 days)	Nicotine patch $n = 15$, 21 mg patch applied for 8 hours after abstaining from 8 p.m. the night before the study Women randomized to one intervention and 1 week later crossed over to other study arm
Outcomes: maternal and fetal physiological observations during NRT administration					
Lehtovirta Finland 1983 [47]	Before–after study—two separate cohorts for two interventions	Department of Obstetrics and Gynecology, University Central Hospital, Helsinki, Finland	To determine the effects of nicotine and nicotine-free herbal cigarettes	31 healthy pregnant women: 15 2nd trimester 24–26 weeks 16 3rd trimester 37–40 weeks	NRT $n = 15$ chewed nicotine gum containing 2 mg nicotine

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Table 2. (Continued)

Cohorts with NRT administered as an intervention in experimental settings

First author, Location, Date	*Study design*	*Recruitment method (location/setting, eligibility criteria, data gathering)*	*Study objectives*	*Baseline characteristics/group differences*	*Intervention group(s) (including dose and route of NRT)*
		Subjects rested in 15 degrees left lateral recumbent position. Abdominal fetal electrocardiography recorded by a cardiotocograph. FHR analysis performed after 5-minute period to establish normal variability and measured for 1 minute at 15 minutes before, during and 25 minutes after administration of nicotine chewing gum or smoking a herbal cigarette Baseline FHR estimated visually from cardiogram. Maternal BP/HR also measured for 1-minute periods	on quantitated FHR variability during the antepartum period	8 regular smokers, 23 had stopped smoking before or at the start of pregnancy	for 20 minutes (7 in 2nd trimester, 8 in 3rd)
Lindblad Sweden 1987 [48]	Prospective cross-over cohort study	Recruitment methods not documented. Uncomplicated pregnancies, singleton fetus in cephalic position Women abstained from smoking for at least 12 hours before study. During study, women in left lateral position. Maternal HR, BP, FHR and fetal blood velocity were measured; 3 control measurements taken and then gum chewing started. Recordings were made every 5 minutes for 45 minutes after chewing started	To evaluate maternal and fetal haemodynamics after exposure to nicotine	20 pregnant smokers Mean consumption 12 cigarettes/day (SD = 5.3) Mean maternal age 30.1 years (SD = 3.8), mean gestational age at time of study 35.6 weeks (SD = 2.2), 7 women primiparous	NRT n = 20, chewed nicotine gum containing 4 mg nicotine for 30 minutes Women randomized to one intervention and one day later crossed over to other study arm
Ogburn Jr USA 1999 [49]	Uncontrolled before–after cohort study	Pregnant cigarette smokers in 3rd trimester recruited from Department of Obstetrics at the Mayo Clinic	To determine in abstinent pregnant smokers whether nicotine patch therapy acutely compromised fetal wellbeing	23 women enrolled 2 subjects discontinued before inpatient phase Means at baseline outpatient visit (±SD):	NRT n = 21, 22 mg/24-hour nicotine patch was applied each morning (replaced daily)

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Table 2. (Continued)

Cohorts with NRT administered as an intervention in experimental settings

First author, Location, Date	*Study design*	*Recruitment method (location/setting, eligibility criteria, data gathering)*	*Study objectives*	*Baseline characteristics/group differences*	*Intervention group(s) (including dose and route of NRT)*
		Inclusion and exclusion criteria specified. Data collection: screening questionnaires/consent. Then bloods, urinalysis, ECG, expired CO levels and physician examination, ultrasound for gestational age, fetus size and umbilical artery Doppler studies. On another day, baseline expired CO/bloods, FHR, umbilical artery Doppler and biophysical profile taken before 1st cigarette. Returned after smoking *ad libitum* all day for repeat tests. Within 7 days, admitted in evening after day of smoking, for 4 days/nights to smoke-free setting. Each morning, further tests (as above) and then repeated after 8 hours of NRT patch use		● Age 26.5 years (±5.7) ● Gestational age 27.4 weeks (±2.7) ● Cigarettes/day at time of study 20.5 (±8.7)	1 patient discontinued during 2nd day of hospital stay (excluded from all analyses)
Oncken USA 1996 [50]	Comparison of before–after cohorts	Pregnant smokers recruited through newspaper ads, TV announcements and from local obstetric and family practice clinics Inclusion and exclusion criteria specified. Data collection: screening physical examination, detailed smoking history taken. Then baseline maternal BP/HR, fetal HR and uterine/umbilical artery FVWs and resistance index (RI) measured 30 minutes after refraining from smoking, before and after smoking usual cigarette. Then randomly assigned to either NRT gum/	To evaluate short-term concentrations of nicotine delivered by nicotine gum use versus smoking and maternal and fetal haemodynamic parameters	36 women eligible for screening visit 7 excluded (5 for cotinine concentration too low, 2 urine tox. screen-positive.) 29 remaining Randomly assigned (2 : 1 assignment using simple randomization as anticipated not all gum users would complete study) to smoking versus chewing nicotine gum	NRT n = 19, stop smoking and chew gum containing 2 mg nicotine/piece At least 6 pieces per day and not more than 2 pieces/hour or 30 pieces/day

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Table 2. (Continued)

Cohorts with NRT administered as an intervention in experimental settings

First author, Location, Date	*Study design*	*Recruitment method (location/setting, eligibility criteria, data gathering)*	*Study objectives*	*Baseline characteristics/group differences*	*Intervention group(s) (including dose and route of NRT)*
		smoking and returned daily for monitoring, inc. maternal vital signs, adverse effects, withdrawal symptoms, CO measurements, smoking status and pieces of gum chewed. After 5 days, initial measurements repeated after 30 minutes abstaining			
Oncken USA 2009 [51]	Controlled cross-over cohort study	Recruitment: newspaper advertisements and flyers in local physician offices Inclusion and exclusion criteria specified. Data collection: screening visit for consent, medical history/ physical exam/fetal ultrasound. Advised to reduce smoking to 10–15 cigarettes/day for ≥ 4 days. Session 1: after abstinence for ≥ 8 hours overnight, participants smoked an average of 1 cigarette of their choice/hour in negative pressure room with fetal monitoring. Baseline FHR measured before 1st and after 4th cigarette of day. Then randomly assigned to one of 3 groups (see intervention column). Session 2: on day 5, further monitoring similar to session 1 after 8 hours abstinence, with patch applied at 10 am and 11 doses nasal spray used	To examine the short-term effects of the nicotine patch or nasal spray on measures of nicotine exposure, withdrawal symptoms, and on maternal HR and FHR in pregnant smokers	29 subjects consented 8 did not complete whole study: 1 acted as a pilot subject, 3 did not attend first monitoring session, 2 had pregnancy complications before randomization, 2 dropped out after first day of medication treatment for reasons unrelated to the study. Mean gestational age 31.26 (±2.61)	Women in study n = 21 N = 7 nicotine patch (15 mg/ 16 hours). Used for average 14 hours/day with placebo nasal spray N = 7 nasal spray (recommended regimen of 24 doses per day, each containing 1 mg nicotine) with placebo patch
Wright USA 1997 [52]	Uncontrolled before–after cohort study	Recruited from the University of North Carolina intervention in pregnancy study programme, all	To measure any short-term effects that transdermal NRT may have in pregnancy	6 women Mean maternal age 25.7 (21–31 years)	NRT n = 6, 21 mg nicotine patch applied for 6 hours

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Table 2. (Continued)

Cohorts with NRT administered as an intervention in experimental settings					
First author, Location, Date	*Study design*	*Recruitment method (location/setting, eligibility criteria, data gathering)*	*Study objectives*	*Baseline characteristics/group differences*	*Intervention group(s) (including dose and route of NRT)*
		recalcitrant to 'standard of care' for smoking cessation Inclusion and exclusion criteria specified. Admitted for total of 21 hours during which they agreed not to smoke cigarettes or chew gum. Patients continuously observed to ensure not smoking. Day 1, 9 p.m. (baseline): Maternal assessment (weight, BP, HR, RR, and temperature) and fetal assessment (biophysical profile and umbilical artery Doppler). Day 2, 8 a.m.: 21 mg nicotine patch administered. Fetal and maternal assessment repeated at 10 a.m. At 2 p.m., patch removed and further assessment performed		Mean gestational age 34.2 weeks (28.1–37.0 weeks) All reported smoking at least one half-pack per day but no more than two (CO verified)	
Outcomes: fetal effects and delivery outcomes after long-term NRT use in pregnancy					
Schroeder USA 2002 [53]	Within-patient, longitudinal before–after cohort study	Long term follow-up of patients in Ogburn Jr 1999 (see above for details of first part of study) After inpatient phase, subjects continued NRT patch for 8 weeks and returned weekly for follow-up until delivery. At each visit: non-stress testing of FHR, measurement of maternal vital signs and expired CO. Self-reported 7 day abstinence. Additional counselling provided for 5–10-minute sessions with review of personalized nicotine dependence	To describe smoking abstinence, fetal effects and delivery outcomes for pregnant smokers included in Ogburn Jr when treated with 8 weeks of patch therapy	21 pregnant women with singleton pregnancies	NRT n = 21, 22 mg/24-hour patch therapy Continued for 8 weeks Some patients discontinued patch therapy

(*Continues*)

Table 2. (Continued)

Cohorts with NRT administered as an intervention in experimental settings					
First author, Location, Date	*Study design*	*Recruitment method (location/setting, eligibility criteria, data gathering)*	*Study objectives*	*Baseline characteristics/group differences*	*Intervention group(s) (including dose and route of NRT)*
		treatment plan and self-help material. Estimated fetal weight also measured by ultrasound at 4 and 8 weeks. Followed up postnatally at 4 weeks, 6 months and 12 months			
Study reporting cohorts selected from intervention and usual care cohorts of quasi-randomized controlled trial with NRT as one component of study intervention					
Outcomes: pregnancy complications, preterm birth, small for gestational age					
Hegaard Denmark 2004 [54]	Cohort as part of larger quasi-randomized intervention study [55]	Pregnant smokers with uneven birth dates received individual counselling and were invited to join a smoking cessation course offering NRT. Those with even birth dates were offered usual care: routine information on risk of smoking in pregnancy and advice on cessation from midwives without specific cessation training. Women that accepted and suitable for NRT included as cohort intervention group. Comparator group formed by randomly selecting from those offered usual care. Study period November 1996–December 1999. Recruited from a large Copenhagen University Hospital at first prenatal visit. Inclusion/exclusion criteria specified	To describe the effectiveness and safety of NRT in 75 pregnant smokers, comparing with smoking	647 women included in the larger study in total (intervention n = 327, control n = 320) NRT group at baseline: 12.5 ± 5.2 (SD) cigarettes/day 21.5 ± 8.4 (SD) mean gestational age in weeks	NRT n = 75 N = 25 (33.3%) gum only N = 31 (41.3%) patch only N = 19 (25.3%) nicotine patch and gum NRT use was permitted for max. 11 weeks, participants not allowed to smoke. Dose and type based on Fagerström score. Smoking cessation training course provided alongside NRT by trained midwives

(*Continues*)

Table 2. (Continued)

Cohorts with NRT administered as an intervention in experimental settings

First author, Location, Date	*Comparator group(s)*	*Outcome measures (i.e. adverse fetal/maternal health outcomes)*	*Main/significant results*
Outcome: Fetal breathing movements during nicotine administration			
Gennser Sweden 1975 [43]	*N* = 6 tested with: ● Standard cigarette (1.7–1.8 mg nicotine) ● Non-tobacco cigarette (0.75–0.78 µg nicotine) Tested on 2 separate days	Fetal breathing movements—classified per 20 sec period as regular, irregular, periodic or apnoeic breathing patterns and frequency of each movement pattern given for each 5 minute period Maternal HR and RR	Maternal HR: HR significantly increased 5 minutes ($P < 0.001$) and 30 minutes ($P < 0.05$) after smoking standard cigarette, no significant change after smoking non-tobacco cigarette. After 2 mg nicotine gum, HR significantly increased at 30 minutes ($P < 0.05$), not significantly increased at 60 minutes. After 4 mg nicotine gum, HR significantly increased at 30 minutes and 60 minutes ($P < 0.01$). Maternal RR not influenced by any intervention. Fetal breathing movements: Significant increase in frequency of both periodic and apnoeic breathing (i.e. not regular breathing movements) after standard cigarette, max. change during 20–25 minute interval. Dose dependent but non-significant rises of apnoeic/periodic breathing movements was noted after both nicotine gums. No change after non-tobacco cigarette. Proportionally, irregular breathing movements decreased and regular breathing movements were unchanged. Changes independent of fetal age
Manning UK 1976 [44]	Other groups, not directly compared with NRT: smoking ×2 tobacco cigarettes *n* = 47 Smoking ×2 herbal cigarettes *n* = 10 (5 of these also smoked tobacco cigarettes)	Fetal chest wall movements *in utero* Proportion of time during which fetal breathing movements were present were measured at 5-minute intervals	6/7 women given 4 mg gum showed decrease in fetal breathing, 1 showed no difference, not a significant change overall 5/5 women given 8 mg nicotine gum showed decrease in fetal breathing. Mean proportion of time during which fetal breathing movements were present went from pre-chewing level of 75% (±4.93) to 48% (±10.6) at 25 minutes ($P < 0.05$) Gradual recovery noted—35 minutes after chewing started, proportion of fetal breathing movements not significantly different from pre-chewing
Outcome: fetal blood flow during nicotine administration			
Bruner USA 1991 [45]	Smoking, phase 1: smoking one cigarette containing 1.2 mg nicotine over 5 minutes	FVWs analysed by calculation of the ratio of the peak systolic excursion of the maximum velocity envelope to the diastolic trough (S : D ratio). Analysis on	*N* = 35 completed both phases *N* = 12 did not complete phase 2 (4 delivered baby, 5 declined further participation, 3 lost to follow-up)

(***Continues***)

Table 2. (Continued)

Cohorts with NRT administered as an intervention in experimental settings			
First author, Location, Date	*Comparator group(s)*	*Outcome measures (i.e. adverse fetal/maternal health outcomes)*	*Main/significant results*
		average of 5 waveforms recorded from each vessel, insonation performed only during periods of fetal inactivity with apnoea	Significant increase in mean umbilical artery FVW S : D ratio (indicating possible increased fetal cardiac contractility) after smokers chewed gum ($P < 0.01$) and when those who smoked >10/day smoked cigarette ($P < 0.05$) but no significant increase in uterine artery FVW S : D ratios. All changes returned to baseline by 10 minutes No significant difference: between FVW S : D ratios for each group at baseline. Between FVW S : D ratios for non-smokers or prior smokers after phase 1 or 2
Oncken USA 1997 [46]	Smoking $n = 15$ (same women), smoking *ad libitum* for 8 hours, mean cigarettes smoked: 9 ± 2	Maternal plasma nicotine concentrations; changes in the uterine and umbilical artery RIs, FVWs and RIs in the fetal middle cerebral artery; FHR, maternal BP and HR	Between maternal or fetal HRs during any study period Systolic and diastolic BP and maternal HR not significantly different between nicotine patch use/ smoking. Significant time effects for systolic BP and maternal HR (both $P < 0.001$) with max. increases of 5 and 6 mmHg and 10–11 beats/minute 2 hours after baseline measurement in both groups. Diastolic BP also changed significantly over time in both groups ($P = 0.007$). The change in middle cerebral artery RI from baseline to 4 hours later was similar during patch use and smoking. There were no group differences in Doppler measurements of the middle cerebral, umbilical and uterine arteries. Time effects were significant for the middle cerebral artery RI ($P = 0.02$) and the uterine artery RI ($P = 0.02$). Baseline FHR reactivity changes were variable with no significant difference between groups and mean FHR was not significantly different between baseline and 4 hours for either group. No clinically significant adverse effects/pregnancy complications
Outcomes: maternal and fetal physiological observations during NRT administration			
Lehtovirta Finland 1983 [47]	Nicotine-free herbal cigarettes[4] $n = 16$, smoked herbal cigarette (Honeyrose de Luxe) for 5 minutes (8 in 2nd trimester, 8 in 3rd)	Baseline FHR; maternal BP and HR throughout; indices of FHR variability: interval index (II; standard deviation of fetal QRS intervals, long- term	In the 2nd trimester, the DI decreased significantly after 10 minutes chewing ($P < 0.001$), which lasted for 20 minutes after chewing. The II also decreased

(*Continues*)

Table 2. (Continued)

Cohorts with NRT administered as an intervention in experimental settings

First author, Location, Date	*Comparator group(s)*	*Outcome measures (i.e. adverse fetal/maternal health outcomes)*	*Main/significant results*
	Different participants to NRT group	component of FHR variability) and the differential index (DI; SD of interval differences, short term component of FHR variability)	but only significantly for last 5 minutes of chewing ($P < 0.01$). Baseline FHR significantly increased at beginning of chewing ($P < 0.001$) and returned to pre-chewing level 5 minutes after chewing stopped. Maternal HR and diastolic BP increased a little during chewing, but systolic BP remained elevated for 20 minutes after chewing stopped (all significant, but *P*-variable for different time-points). In the 3rd trimester the II decreased ($P < 0.001$), which lasted for 10 minutes after chewing. The DI did not change. Baseline FHR significantly decreased ($P < 0.001$), lasting for 10 minutes after chewing. Maternal HR, systolic and diastolic BP increased during chewing and returned to baseline 5–10 minutes after chewing (all significant, but *P*-variable for different time-points)
Lindblad Sweden 1987 [48]	Placebo chewing gum $n = 20$ (same women), chewed for 30 minutes	Maternal HR; maternal BP; FHR; fetal blood velocity; fetal vessel diameter	Nicotine gum significantly increased maternal HR from 5 to 45 minutes, systolic BP from 5 to 30 minutes and diastolic BP from 5 to 35 minutes, with variable *P*-values for different time-points. FHR and blood flow were not affected There was no change in the waveform of blood velocity in either the fetal aorta or the umbilical artery. One fetus had a supraventricular arrhythmia 15 minutes after gum chewing started which was sustained, but this had a normal heart rhythm the next day Mean gestational age at delivery 39.8 weeks (SD = 1.2). Mean birth weight 3424 g (SD = 445). All newborns had Apgar scores > 8 at 1 and 5 minutes. Mean umbilical arterial and venous pH 7.21 (SD = 0.08) and 7.30 (SD = 0.07) (within normal limits)

(***Continues***)

Table 2. (Continued)

Cohorts with NRT administered as an intervention in experimental settings

First author, Location, Date	*Comparator group(s)*	*Outcome measures (i.e. adverse fetal/maternal health outcomes)*	*Main/significant results*
Ogburn Jr USA 1999 [49]	No comparator group for fetal/maternal observations except baseline measurements	Baseline measurements compared to inpatient phase for FHR, systolic: diastolic ratio in umbilical artery, maternal vital signs, maternal nicotine withdrawal scores	During days 2, 3 and 4 of inpatient phase, morning baseline FHR was significantly reduced relative to baseline when mother was smoking No significant changes in umbilical artery systolic/diastolic ratio from baseline at day 1 or day 4 No changes from baseline in maternal HR Reduction from baseline in overall maternal nicotine withdrawal score each morning
Oncken USA 1996 [50]	Smoking $n = 10$, continued smoking as usual	Maternal and fetal haemodynamic characteristics and nicotine/cotinine levels	No significant difference in any baseline characteristics. Mean maternal age in years ± SD: nicotine gum chewers 28 ± 6, cigarette smokers 27 ± 6. Mean gestational week at entry to study ± SD: nicotine gum chewers 28.1 ± 3.2, smokers 29.6 ± 3.6 Percentage change in haemodynamic parameters usually greater for smokers but when compared to gum, none significant 5 withdrew during study—4 from gum group: 2 unable to maintain abstinence on chewing gum, 2 severe nausea, 1 from smoking group due to acute bronchitis
Oncken USA 2009 [51]	$N = 7$ placebo nasal spray and patch	Nicotine concentration; maternal HR; FHR	Placebo and nicotine nasal spray groups saw a greater reduction in paired differences of the mean maternal HR when compared to session 1 than the nicotine patch group ($P = 0.021$). Baseline FHR decreased in the placebo group throughout session 2, but increased slightly in the patch and nasal spray groups. No serious adverse events during the study
Wright USA 1997 [52]	No comparator group	Maternal HR, BP, RR, temperature Fetal biophysical profile: FHR, amniotic fluid index Narrative birth complications	There were no measurable differences in fetal wellbeing during placement of patch. Maternal vital signs remained stable except for expected low maternal HR in morning after smoking cessation

(*Continues*)

Table 2. (Continued)

Cohorts with NRT administered as an intervention in experimental settings

First author, Location, Date	*Comparator group(s)*	*Outcome measures (i.e. adverse fetal/maternal health outcomes)*	*Main/significant results*
			overnight, which gradually rose after patch applied. FHR baseline, decelerations and umbilical artery Doppler readings were unchanged. No fetus had significant changes in minute variation or accelerations and there were no changes in uterine activity. Ultrasonographic biophysical profiles remained unchanged Mean gestational age at delivery 40 weeks, mean birth weight 3239 g. All deliveries uncomplicated except for 1 which had deep variable decelerations and a low 1 minute Apgar score of 3; at 5 minutes Apgar was 9 5/6 patients denied any nicotine withdrawal symptoms. Symptoms reported: hunger, inadequate sleep, irritability, tobacco craving, impatience, restlessness, headache and drowsiness. All scores ≤ 5/10 on scale from 0 = absent to 10 = severe
Outcomes: fetal effects and delivery outcomes after long-term NRT use in pregnancy			
Schroeder USA 2002 [53]	No comparator group	Infant status at birth Any birth complications Details of remainder of the pregnancy	Only 8 patients finished study according to protocol: 1 withdrew on 2nd inpatient day. After inpatient phase: 7 withdrew within the 1st week, 3 after 5/52 and 2 after 6/52. 7 withdrew due to adverse events, 5 due to resuming smoking. Median time from start of patch therapy to delivery was 12 weeks. Centile weight for gestational age not found to change significantly during study. All weekly non-stress tests reactive initially or with extended observation. All 21 infants born alive. Mean gestational age at birth was 38.9 weeks, SD ± 1.3 (median 39.1), mean birth weight 3439 g, SD ± 570 (length, HC, Apgars also reported). 3 suffered severe neonatal morbidity—1 fetal asystole and HIE, 1 complete transposition of great vessels, 1 mild RDS and seizures within 1 month

(*Continues*)

Table 2. (Continued)

Cohorts with NRT administered as an intervention in experimental settings			
First author, Location, Date	*Comparator group(s)*	*Outcome measures (i.e. adverse fetal/maternal health outcomes)*	*Main/significant results*
Study reporting cohorts selected from intervention and usual care cohorts of quasi-randomized controlled trial with NRT as one component of study intervention			
Outcomes: pregnancy complications, preterm birth, small for gestational age			
Hegaard Denmark 2004 [54]	Smokers $n = 150$ Received 'usual care' (see column 3). 2 smokers matched to each NRT user by daily cigarette consumption	Pregnancy related complications: abruption placentae; fetal death; preterm birth (< 37 weeks); small for gestational age	Of the NRT group: $N = 30$ (40%) used NRT for < 2 weeks; $N = 28$ (37%) for 2–6 weeks; $N = 17$ (23%) for 7–11 weeks Complications in pregnancy were similar in the NRT group to the smoking group. There were no fetal deaths in either group and one abruption placentae in the control group. Preterm birth: NRT $n = 4$ (5.3%); control $n = 5$ (3.3%) ($P = 0.5$). Small for gestational age: NRT $n = 5$ (6.7%); control $n = 11$ (7.3%) ($P = 1.0$)

All confidence intervals (CIs) 95% unless stated otherwise. [a]Pregnant women prescribed or issued nicotine replacement therapy (NRT) were assumed to have smoked prior to that point in pregnancy; hence this group was exposed to both smoking and NRT. [b]Pregnant women prescribed or issued NRT were assumed to have smoked prior to that point in pregnancy, so women who reported using NRT 'on its own' were pooled with other NRT users (who smoked concurrently) for analysis. [c]Episodes of infantile colic in smokers were quoted as 11417 in a table in this paper but odds ratio (OR) suggests that this is a typographic error—adjusted to 1417. [d]Data on bupropion/herbal cigarette/varenicline use not displayed here. OTC = over-the-counter; PPROM = preterm premature rupture of membranes; ECG = electrocardiogram; CO = carbon monoxide; HR = heart rate; BP = blood pressure; LMP = labour management partnership; BMI = body mass index; FHR = fetal heart rate; HR = heart rate; BP = blood pressure; HIE = hypoxic–ischaemic encephalopathy; RR = respiratory rate; RRR = resting RR; FVWs = flow velocity waveforms; IQR = interquartile range; GP = general practitioner; MUMS Study = Maternal Use of Medications and Safety; OR = odds ratio.

Table 3 Summary of outcome measures by study: non-RCTs.

First author name and year of study	*Congenital anomalies*	*Low birth weight*	*Mean birth weight*	*Small for gestational age*	*Preterm birth*	*Mean gestational age at birth*	*Stillbirth*	*Fetal death*	*Mode of delivery*	*Birth outcomes*	*Infantile colic*	*Infant strabismus*	*Fetal observations during NRT administration*
Routine health-care studies													
Bérard 2016 [40]			✔	✔	✔	✔							
Dhalwani 2018 [32]							✔						
Dhalwani 2015 [34]	✔												
Dhalwani 2014 [38]		✔	✔					✔	✔				
Gaither 2009 [36]		✔			✔								
Lassen 2010 [37]			✔		✔								
Milidou 2012 [39]		✔			✔						✔		
Morales-Suárez-Varela 2006 [35]	✔												
Strandberg-Larsen 2008 [33]							✔						
Torp-Pedersen 2010 [42]												✔	
Tran 2020 [41]				✔	✔				✔	✔			
Interventional studies													
Bruner 1991 [45]													✔
Gennser 1975 [43]													✔
Hegaard 2004 [54]				✔	✔					✔			
Lehtovirta 1983 [47]													✔
Lindblad 1987 [48]			✔			✔				✔			✔
Manning 1976 [44]													✔
Ogburn Jr 1999 [49]													✔
Oncken 1997 [46]													✔
Oncken 1996 [50]													✔
Oncken 2009 [51]													✔
Schroeder 2002 [53]			✔			✔				✔			✔
Wright 1997 [52]			✔			✔				✔			✔

NRT = nicotine replacement therapy.

Table 4 Modified Newcastle–Ottawa scale quality assessment scores: non-RCTs.

Routine health-care studies	*Selection (max. 5 stars)*	*Design and analysis (max. 1 star)*	*Outcome (max. 2 stars)*	*Total (max. 8 stars)*
Bérard 2016 [40]	★★★	★	★	★★★★★
Dhalwani 2018 [32]	★★★★	★	★	★★★★★★
Dhalwani 2015 [34]	★★★★	★	★	★★★★★★
Dhalwani 2014 [38]	★★★★	★	★	★★★★★★
Gaither 2009 [36]	★★	★	★	★★★★
Lassen 2010 [37]	★★★★	★	★★	★★★★★★★
Milidou 2012 [39]	★★★★	★		★★★★★
Morales-Suárez-Varela 2006 [35]	★★★★	★	★★	★★★★★★★
Strandberg-Larsen 2008 [33]	★★★★	★	★★	★★★★★★★
Torp-Pedersen 2010 [42]	★★★★	★	★★	★★★★★★★
Tran 2020 [41]	★★	★	❖	★★★★
Interventional studies	*Selection (max. 4 stars)*	*Design and analysis (max. 1 star)*	*Outcome (max. 2 stars)*	*Total (max. 7 stars)*
Bruner 1991 [45]	★	★	★★	★★★★
Gennser 1975 [43]	★	★	★★	★★★★
Hegaard 2004 [54]	★			★
Lehtovirta 1983 [47]			★	★
Lindblad 1987 [48]	★★	★	★	★★★★
Manning 1976 [44]	★		★	★★
Ogburn Jr 1999 [49]	★★	★	★★	★★★★★
Oncken 1997 [46]	★★	★	★★	★★★★★
Oncken 1996 [50]	★★		★★	★★★★
Oncken 2009 [51]	★★	★	★★	★★★★★
Schroeder 2002 [53]		★	★★	★★★
Wright 1997 [52]	★		★★	★★★

Quality assessment scores for routine health-care and interventional cohort studies as assessed by the modified Newcastle–Ottawa scale [20]; see Supporting information, Appendix S1 for scales. RCTs = randomized controlled trials.

[45,46,50], fetal breathing [43,44] and heart rate [43,46–48,50,51] and maternal blood pressure and heart rate [43,46–52]; some also reported pregnancy outcomes [48,52–54].

Quality assessment

Table 4 reports quality assessments. Routine health-care studies had a median score of 6/8 stars [interquartile range (IQR) = 5–7] and low scores often reflected a lack of validation of participants' exposures (e.g. NRT use), retrospective exposure assessment or a lack of adverse outcome validation. Interventional studies' median score was 4/7 stars (IQR = 2.5–4.5); these often scored poorly on cohort representativeness but relatively well for having biochemical validation of smoking abstinence.

Meta-analysis outcomes

We performed meta-analyses for congenital anomalies, stillbirth and preterm birth outcomes, but for others this was not possible due to differences in study designs. Analyses only included routine health-care studies. As interventional cohorts used 'before–after' designs without appropriate comparison groups, the few which reported birth outcomes could not be included. The study which investigated a subsample of quasi-RCT intervention group participants selected intervention and comparison groups in very different ways, and was judged unsuitable for inclusion [54].

Major congenital anomalies after first-trimester NRT exposure were reported using the European Surveillance of Congenital Anomalies and Twins (EUROCAT) classification system in two studies [34,35,56]. Stillbirth rate was reported in two; one study defined this as a baby born not showing signs of life at ≥ 28 weeks [32] and the other after 20 weeks [33]; we pooled these, as both represented death in later pregnancy. One interventional study reported fetal deaths but was excluded for the reason outlined above [54]. Preterm birth (at < 37 weeks) was an outcome in six studies, but only two were pooled [36,37]; three were without appropriate comparison groups [40,41,54] and one [39] duplicated findings from another included study [37].

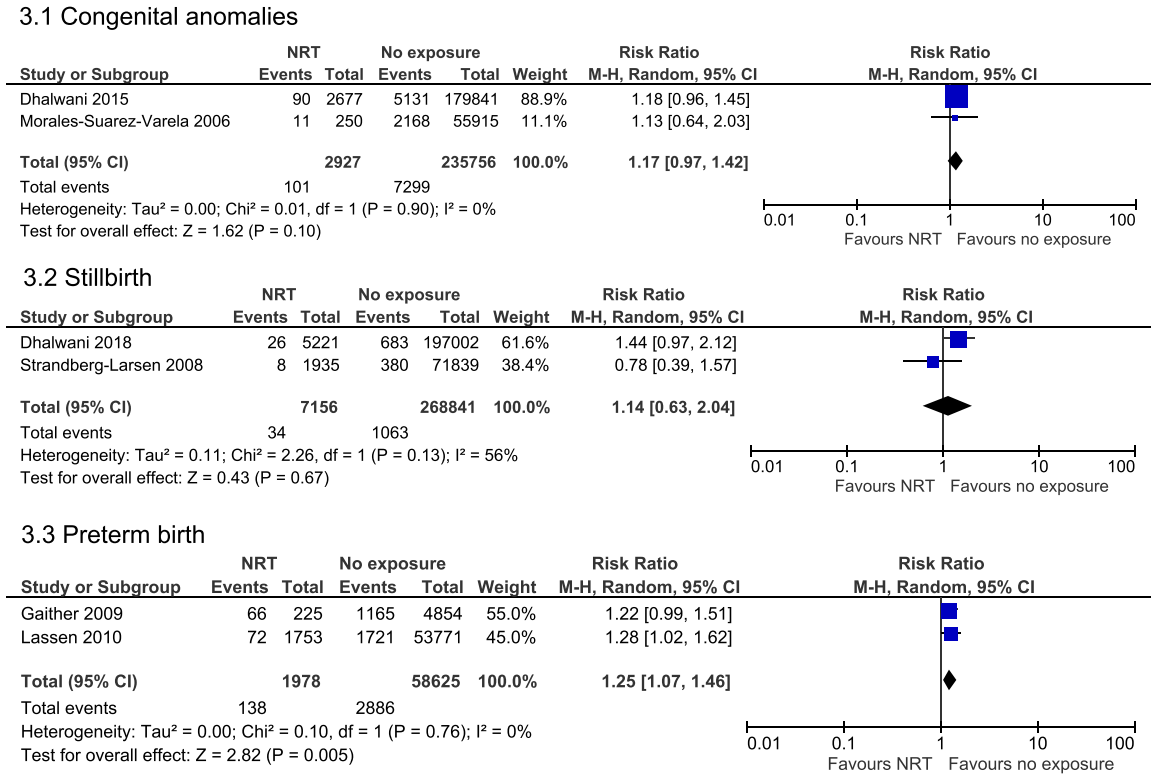

Figure 3 Meta-analyses of non-randomized controlled trials (RCTs). [Colour figure can be viewed at wileyonlinelibrary.com]

Meta-analysis results: non-RCTs

Figure 3 shows non-RCT meta-analysis findings. Compared with no NRT use, there was no evidence for an association between using NRT and risks of congenital anomalies (RR = 1.17, 95% CI = 0.97–1.42, I^2 = 0%; Fig. 3.1) or stillbirth (RR = 1.14, 95% CI = 0.63–2.04, I^2 = 56%; Fig. 3.2). Similarly, when compared to smoking, NRT use was not associated with anomalies (RR = 1.06, 95% CI = 0.86–1.32, I^2 = 0%) or stillbirth (RR = 0.75, 95% CI = 0.41–1.36, I^2 = 54%). Compared with no NRT use, meta-analysis of two studies suggested a slightly increased risk of preterm birth (RR = 1.25, 95% CI = 1.07–1.46, I^2 = 0%; Fig. 3.3) but, compared to smoking, NRT was not associated with greater preterm birth risk (RR = 1.12, 95% CI = 0.95–1.33, I^2 = 0%). For 'NRT versus no NRT' comparisons GRADE criteria certainty of evidence for these outcomes was 'very low'.

Narratively reported outcomes: non-RCTs

Table 3 reports outcomes by study. Two studies excluded from the preterm birth meta-analysis compared risks of preterm birth following NRT use in women who smoked; there was a significantly reduced risk in NRT users compared to non-users in one paper (adjusted OR = 0.21, 95% CI = 0.13–0.34) [40], while the second showed no significant difference (HR = 1.00, 95% CI = 0.71–1.42) [41].

Four studies reported mean gestational age at birth for NRT-exposed women [40,48,52,53] but only one, which enrolled only women who smoked, had a comparison group [40]; with no statistical comparison, this reported a mean (standard deviation (SD)) birth gestational age in NRT users of 38.9 (1.9) weeks and in non-NRT users of 37.5 (3.3).

Three studies reported small for gestational age (SGA) rates [40,41,54]. Two included only women who smoked, with one reporting a significantly reduced risk of SGA in those using NRT compared to those who did not (adjusted OR = 0.61, 95% CI = 0.41–0.90) [40] and the other showing no significant change in risk (HR = 0.77, 95% CI = 0.56–1.07) [41]. The other study used very different methods for selecting exposure groups rendering these non-comparable, but reported no significant difference in SGA rates [54].

Mean birth weight was reported by six studies [37,38,40,48,52,53], three were interventional [48,52,53] and three had comparison groups which were too dissimilar to be aggregated [37,38,40]. One of these enrolled women who smoked reported, with no statistical comparison, a mean birth weight (SD) in NRT users of 3257.9 g (553.1) and non-users of 2943.5 g (733.5) [40]. A PhD thesis using medical record data compared mean birth weight in NRT users and women who neither smoked nor used NRT in pregnancy and found these were lower (β = −168 g, 99% CI = −214 to −122, $P < 0.001$)

Table 5 Summary of effects of NRT on fetal physiological outcomes: non-RCTs.

Study first author and year	*Participant smoking status at time of baseline measurements*	*Post-baseline exposures: NRT type and dose ± smoking*	*NRT effect on fetal observations*
Fetal breathing movements			
Gennser 1975 [43]	Abstinent for ≥12 hours	NRT gum 2 mg NRT gum 4 mg Smoking (1.7–1.8 mg nicotine cigarette)[c]	↔ Apnoeic/periodic breathing movements after both gums ↑ apnoeic/periodic breathing movements after tobacco cigarette
Manning 1976 [44]	Abstinent overnight	NRT gum 4 mg[d] NRT gum 8mg[d]	↔ Fetal breathing movements after 4 mg gum ↓ Fetal breathing movements after 8 mg gum
Fetal blood flow			
Bruner 1991[a] [45]	Abstinent for ≥ 30 minutes	NRT gum 2 mg smoking (1.2 mg nicotine cigarette)[c]	↑ Umbilical artery flow velocity waveform (FVW) systolic: diastolic (S : D) ratios when all current smokers chewed gum ↑ Umbilical artery FVW S : D ratios when those who smoked > 10/day smoked a cigarette ↔ Uterine artery FVW S : D ratios after current smokers chewed gum ↔ Uterine artery FVW S : D ratios after current smokers smoked a cigarette ↔ Umbilical artery or uterine artery FVW S : D ratios when prior smokers/non-smokers chewed gum ↔ Umbilical artery or uterine artery FVW S : D ratios when prior smokers/non-smokers smoked a cigarette
Oncken 1997 [46]	Abstinent from 8 p.m. the day before the study	NRT patch 21 mg/applied for 8 hours. Smoking cigarettes *ad libitum* for 8 hours[c]	↔ Change from baseline in middle cerebral artery resistance index after patch compared to change after smoking ↔ Change from baseline FHR reactivity after patch compared to after smoking
Fetal physiological observations			
Lehtovirta 1983[b] [47]	Not stated in Methods	NRT gum 2 mg (chewed by women in 2nd and 3rd trimester)	↓ Differential index[e] after 10 minutes of chewing gum in 2nd trimester, ↔ in 3rd trimester ↓ interval index[f] in both 2nd (last 5 minutes of chewing) and 3rd trimesters ↑ FHR at start of chewing in 2nd trimester ↓ FHR in 3rd trimester
Lindblad 1987 [48]	Abstinent for ≥ 2 hours	NRT gum 4 mg	↔ FHR or in waveform of blood velocity in fetal aorta or umbilical artery
Ogburn Jr 1999 [49]	Abstinent in smoke-free setting for 4 days	NRT 22 mg/24 hour patch	↓ Baseline FHR in mornings ↔ In umbilical artery systolic/diastolic ratio
Oncken 1996 [50]	Abstinent for ≥ 30 minutes	NRT 2 mg gum[d]. Smoking[d]	↔ Percentage change from baseline in FHR or umbilical/uterine artery flow velocity waveforms after NRT compared to after smoking. Between-group differences reported

(*Continues*)

Table 5. (Continued)

Study first author and year	*Participant smoking status at time of baseline measurements*	*Post-baseline exposures: NRT type and dose ± smoking*	*NRT effect on fetal observations*
Oncken 2009 [51]	Abstinent for ≥ 8 hours	NRT patch 15 mg/16 hours[d] Nasal spray 24 doses per day 1 mg/dose[d]	↔ FHR in either patch or nasal spray groups compared to placebo
Schroeder 2002 [53]	Smoking alongside NRT use	NRT patch 22 mg/24 hour (over 8 weeks)	Weekly non-stress tests all reactive
Wright 1997 [52]	Abstinent overnight in supervised setting	NRT patch 21 mg applied for 6 hours while abstinent	↔ Baseline FHR, decelerations, umbilical artery Doppler readings or biophysical profile

↔ No significant change; ↑ Significant increase; ↓ Significant decrease.
All participants in these studies were smokers at the start of the study, unless otherwise stated in footnotes.
[a]Participants were: non-smokers, prior smokers, smokers < 10 cigarettes/day, smokers > 10 cigarettes/day.
[b]Smoking status of nicotine replacement therapy (NRT)-exposed women unclear from Methods.
[c]Exposures sequentially in one group of women.
[d]Exposures in different groups of women.
[e]Differential index: short-term component of fetal heart rate (FHR) variability; lower values suggest reduced fetal blood flow [47].
[f]Interval index: long-term component of FHR variability, lower values suggest reduced fetal blood flow.

[38]. Within a multivariate analysis which adjusted for reported smoking behaviour, a population-based cohort found no statistically significant associations between duration of NRT use and mean birth weight (β = 0.25 g per week of NRT use, CI = –2.31 to 2.81) [37].

Low birth weight (less than 2500 g) was reported by three studies which seemed similar enough to be aggregated, but due to heterogeneity (I^2 = 76%) are presented separately [36,38,39]. One reported low birth weight incidences of 2.4% in unexposed women, 2.9% in NRT users, 4.8% of women who smoked and used NRT and 4.3% in smokers [39]. A retrospective questionnaire study found that 13.1% of NRT-exposed women delivered low birth weight infants and rates were 9.26% within women who smoked and 6.99% with neither exposure [36]. Another study reported that NRT exposure was associated with increased risk of low birth weight when compared to no exposure (OR = 1.88, 99% CI = 1.42–2.49, $P < 0.001$) [38]. Two of these studies had the lowest quality scores of all routine health-care studies (see Table 4) [36,39].

Fetal death, a composite of stillbirth and miscarriage [38], delivery mode [38], infantile colic [39] and infant strabismus [42], were reported in single studies and Table 2 reports these findings. Compared with no NRT use, exposure was associated with reduced risk of fetal death (OR = 0.44, 99% CI = 0.38–0.50, $P < 0.001$) [38] and of assisted delivery (relative RR (RRR) = 0.68, 99% CI = 0.54–0.85, $P < 0.001$) but not with increased risk of caesarean section [38]. A study of women who smoked who were exposed to NRT reported a composite outcome: 'any adverse perinatal event', encompassing a number of separate birth outcomes [41]. Table 2 reports the individual outcome HRs, but there was no significant change in overall risk of any adverse perinatal event when comparing women who smoked who were exposed to NRT and those who were not (HR = 1.02, 95% CI = 0.84–1.23).

Table 5 presents physiological outcomes measured by study. In nine studies, fetal physiological observations were recorded at baseline and compared to readings taken when abstinent and using NRT [43–46,48–52]. Three also compared these within-patient changes from baseline with those recorded during or after smoking following a similar period of abstinence [43,45,46]. Results showed no consistent patterns, and most studies did not report significant outcome changes after NRT administration.

DISCUSSION

Key findings

Overall, we found no evidence that NRT used by pregnant women who smoke has adverse impacts on fetal and infant outcomes. Although underpowered, the direction of point-estimates derived from most RCT meta-analyses

suggest that NRT is not likely to have adverse impacts or be more harmful than smoking in pregnancy. The robustness of non-RCT evidence was poor, with meta-analyses' findings affected by imprecision or potential biases, which may explain the inconsistency in the direction of associations found in non-RCT meta-analyses. NRT-exposed women are likely to have smoked at some point in pregnancy but, generally, this was not measured and so could not be adjusted for in non-RCTs, making interpretation of these studies' findings particularly difficult.

Strengths and limitations

Our synthesis meta-analyses of non-RCT studies are limited by the inherent biases in these study designs. An issue was that ascertainment of NRT exposure relied upon maternal self-report or prescription records. Women's recall may not have been perfect and, as some women prescribed NRT will not have used it, using prescription records could overestimate NRT exposure. More importantly, studies generally assessed NRT exposure at only one or two time-points in pregnancy and in most, smoking intensity either before or after NRT use was not reported, despite smoking being known to adversely affect outcomes. The omission of detailed smoking data from non-RCT reports was probably the greatest threat to these studies' validity. It is logical to assume that all women issued NRT would have smoked at least in early pregnancy, and this will have tended to reduce differences between exposure groups' outcomes. Only two non-RCT studies adjusted for smoking behaviour [33,37]; others could be subject to confounding of unknown magnitude. Another important issue was that NRT prescribing involved confounding by indication [57]. In three of the five birth cohorts which provided non-RCT studies' data, women issued with NRT had higher rates of comorbidities and lower socio-economic status than other women who smoked, and so very probably experienced 'higher-risk' pregnancies [10,33,36] which may have substantially affected adverse outcomes. We believe that our modified NOS for non-RCTs' quality assessments and the application of GRADE criteria should help readers to understand the degree to which observed associations might be causal or due to bias, confounding or chance.

For the non-RCT review, only one reviewer screened titles and abstracts and extracted data; although another person checked this, there was no parallel independent screening or extraction by the second researcher, so researcher bias is a possibility. Additionally, some non-RCTs may not have been indexed in databases, but we are confident that our comprehensive search strategy will have found all which were and, hopefully, methods for assessing bias and certainty of non-RCT evidence assist the findings' interpretation.

Strengths of this work include applying 'Cochrane-type' review methods to find all available and relevant RCTs and non-RCTs. We believe this is the first attempt to systematically retrieve and synthesize all studies which report fetal and infant health outcomes after pregnant women have used or been offered NRT, and that we have successfully identified, assessed and presented together all relevant studies. This, coupled with objective methods for assessing studies' biases and the strength of evidence produced by meta-analyses, should provide a thorough report of what is known about the impact of NRT on pregnancy outcomes. Similar reviews have had less thorough search strategies, presented only narrative data or have not attempted to assess bias [15,58,59]. While meta-analyses are underpowered, these remain the strongest currently available data on NRT safety in pregnancy, and strengths and weaknesses of the literature are highlighted. The juxtaposition of non-RCT and RCT meta-analyses is perhaps the most useful feature of the review, and is illustrated by considering findings regarding preterm birth. For this outcome, meta-analysis of two non-RCT studies revealed a statistically significant association between NRT use and higher rates of prematurity in which we have 'very low' certainty. However, meta-analysis of data from seven RCTs provides a non-statistically significant 'best estimate' for this association being in the opposite (protective) direction. This direct comparison helps the reader to more clearly appreciate and consider the quality of available data before drawing conclusions. This disparity might be explained by women's smoking either before, after or alongside NRT exposure, which was generally not adjusted for by non-RCTs. Smoking is well known to contribute to increased risk of pre-term birth [60], and one of the included studies in this meta-analysis acknowledges that the women recommended or prescribed NRT by a health-care professional might be those who smoke more heavily [36] and find it harder to quit [61].

Findings in context of previous literature

The most robust research on the safety of NRT in pregnancy comes from RCTs, and we report meta-analyses for nine safety-orientated outcomes [13]. In RCTs there is no confounding by indication, and randomization ensures that unknown confounders are distributed equally between trial groups, so differences in birth outcomes can be assumed to be caused by NRT. Although meta-analyses were underpowered and there were no significant differences between the NRT and control groups, the trend in non-statistically significant point estimates derived from these analyses is noteworthy. For low birth weight, preterm birth, neonatal intensive care unit admissions, neonatal death and congenital anomalies, point estimates suggest a protective effect of NRT, whereas those for miscarriage

and stillbirth do not. Additionally, caesarean section rates were non-significantly higher following NRT but, in the absence of contextual data, it is not clear if this is an adverse or a positive outcome. This point estimate trend suggests that, with more data from RCTs, NRT could well prove to be less harmful than smoking in pregnancy. Due to design issues, non-RCT meta-analyses are probably not methodologically robust enough to inform clinical practice and their findings do not add to those from RCT meta-analyses. Pregnant women in non-RCT studies are only likely to have been prescribed or offered NRT by clinicians if they smoked. Consequently, to provide valid findings, these studies should have assessed pregnant women's smoking behaviour and adjusted analyses for this. As the probable mechanism for NRT improving birth outcomes is due to women stopping smoking or smoking less, this is particularly important.

Further work

RCTs and robust population-based cohort studies from routine health-care settings are needed to improve the evidence base for the safety of NRT use in pregnancy. Electronic medical records databases offer the potential for valid capture of near-complete pregnancy outcome data. However, to make a valid contribution to the literature, future non-RCT studies need better methods for quantifying exposures to NRT and smoking during the whole of pregnancy and to adjust for the latter in analyses.

CONCLUSIONS

The strongest data on the probable impacts of NRT exposure in pregnancy on birth outcomes comes from RCTs, and these provide no suggestion that NRT might be harmful. Non-RCT studies have less consistent findings, due most probably to inherent design weaknesses, and future observational studies should provide analyses which account for the impact of smoking behaviour within women who also use NRT in pregnancy.

Declaration of interests

None.

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Author contributions

Lauren Taylor: Data curation; formal analysis; investigation; methodology; project administration; validation; visualization. **Ravinder Claire:** Formal analysis; validation; visualization. **Katarzyna Campbell:** Formal analysis; methodology; validation. **Tom Coleman-Haynes:** Data curation; validation. **Sue Cooper:** Conceptualization; funding acquisition; methodology; supervision. **Tim Coleman:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; supervision; validation.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Example search – used in Medline database
Appendix S1. Quality assessment scales and modification

