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ECONOMIC EVALUATIONS OF SMOKING CESSATION INTERVENTIONS DURING PREGNANCY: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: To identify and critically assess previous economic evaluations of smoking cessation interventions delivered during pregnancy.

Design: Narrative review of studies with primary data collection or hypothetical modelling. Quality assessed using the Quality of Health Economic Studies checklist.

Data sources: Electronic search of 13 databases including Medline, Econlit, Embase, and PubMed, and manual search of National Institute of Health and Care Excellence guidelines and US Surgeon General.

Eligibility criteria for selecting studies: All study designs considered if they were published in English, evaluated a cessation intervention delivered to pregnant women during pregnancy, and reported any relevant economic outcome (e.g. cost per quitter, incremental cost per QALY).

Results: 18 studies were included. Eight evaluations were conducted alongside clinical trials, four were part of observational studies, five were hypothetical decision-analytic models, and one combined modelling with within-trial analysis. Analyses conducted were cost-offset (nine studies), cost-effectiveness (five studies), cost-utility (two studies), and combined cost-effectiveness and cost-utility (two studies). Six studies each were identified as high, fair, and poor quality respectively. All interventions were demonstrated to be cost-effective except motivational interviewing which was dominated by usual care (one study). Areas where the current literature was limited were the robust investigation of uncertainty, including time horizons that included outcomes beyond the end of pregnancy, including major morbidities for both the mother and her infant, and incorporating better estimates of postpartum relapse.

Conclusions: There are relatively few high quality economic evaluations of cessation interventions during pregnancy. The majority of the literature suggests that such interventions offer value for money; however, there are methodological issues that require addressing, including investigating uncertainty more robustly, utilising better estimates for postpartum relapse, extending beyond a within-pregnancy time horizon, and including major morbidities for both the mother and her infant for within-pregnancy and beyond.

STRENGTHS

- The review implies a broad search strategy of 13 electronic databases, so is likely to have captured most, if not all, of the literature
- The use of the QHES checklist has allowed the systematic identification of the short coming of the current literature
- The review is the first in this topic area to employ a narrative synthesis to allow comparison between interventions in common terms

LIMITATIONS

- The QHES is a subjective instrument, and therefore there is possible to be influence by reviewer bias
- Certain QHES were required all the criteria to be met for points to be awarded, however studies often met most but not all, and hence it may have been better to partially award points rather all or none
- The QHES is a good measure of internal validity but cannot measure external validity, so we are unable to use the QHES to determine the generalisability of the included studies

ECONOMIC EVALUATIONS OF SMOKING CESSATION INTERVENTIONS DURING PREGNANCY: A SYSTEMATIC REVIEW

Introduction

Smoking is a major, preventable cause of morbidity and mortality, and is estimated to have cost the UK NHS around £5 billion in 2005-2006. [1] Smoking during pregnancy not only impacts on the health of the mother, but can have serious consequences for offspring [2-5] and it remains a significant international problem. In the UK, 12% of mothers smoked throughout their pregnancy in 2010 [6], estimated to cost the NHS £23.5 million a year. [7] In Australia, the US, and Germany, rates are higher, estimated at 14.5%, 14.1%, and 13% respectively. [8-10] Other countries, such as Spain, report a rate of 39.4%. [11] In Canada, estimates suggest that prevalence is lower, with 10.5% of mothers estimated to have smoked; however, this is still a substantial proportion of the population. [12]

Economic evaluation is an important tool for determining which interventions deliver value for money and is an integral part of the decision-making process for new healthcare technologies; poor quality evaluations are likely to lead to misinformed decisions being made and these could have significant negative impacts on health. While economic evaluations of smoking cessation interventions in the non-pregnant population have demonstrated that cessation is cost-effective [13], economic impact of cessation interventions within pregnancy is less certain. A previous review published in 2008 identified only eight studies which involved economic evaluations of cessation interventions delivered to pregnant smokers [14], and suggested that such interventions could be considered potentially cost-effective. However, a number of major studies have since reported on this, so this review could now be considered out of date; hence the aims of this paper are to identify and critically assess economic evaluations of smoking cessation interventions delivered during pregnancy, and determine which, if any, cessation interventions appear to offer value for money.

Methodology

Database selection

13 databases were searched: ASSIA, CINAHL, Econlit, Embase, Maternity and Infant Care, Medline, NHS EED, PsycArticles, PsycINFO, PubMed, Tufts Cost-Effectiveness Analysis Registry, Web of Knowledge, and Web of Science. Additionally, the websites of National Institute for Health and Care Excellence (NICE) in the UK and the US Surgeon General were searched to identify any evaluations published here. [15 16] Databases were searched from inception through to August 2014.

Search terms

The search strategy was developed using terms from a previous review and the Cochrane Pregnancy and Childbirth Group. [14 17] Search terms and an example search can be found in the supplementary information. For the searches of the NICE and US Surgeon General websites, the terms smoking, smoking cessation, and pregnancy were used.

Inclusion criteria

Studies were included if they were in English, reported a formal economic evaluation, with a direct comparison between costs and outcomes, e.g. 'cost per quitter'.

Population: Women who had experienced a cessation intervention during pregnancy and/or their offspring, or hypothetical cohorts modelling cessation during pregnancy and/or after this.

Interventions: Any interventions or combination of interventions, both real and hypothetical, aimed at encouraging pregnant smokers to quit.

Comparators: No intervention or 'usual care' (UC).

Outcomes: Clinical or economic outcomes considered relevant to the mother and/or child (e.g. smoking status at end of pregnancy, LBW averted, SIDS averted, and QALYs).

Design: Any economic evaluation design was considered.

Exclusion criteria

Exclusion criteria were:

- Studies with no economic analyses.
- Studies which did not include an outcome relevant to both smoking and pregnancy.

Identification of papers and data extraction

The lead reviewer screened titles and abstracts of retrieved citations and potentially-relevant texts were retrieved. If a protocol for an ongoing trial was identified, the trial's Principal Investigator was asked to provide economic analysis details. Two reviewers working independently assessed full texts for inclusion, extracted data, and applied a quality assessment checklist. If the two reviewers disagreed on data extraction or quality assessment, a third was consulted. A manual search was conducted of references from included studies for other potentially-relevant studies. Papers were then identically screened and reviewed. Data extracted from each study is given in Table 1.

Table 1: Data extracted from studies

Area of topic	Data extracted
General study background	Author(s)
	Publication year
	Years of study
	Study question
	Funding source
Study design	Study type and design
	Description of intervention
	Description of comparator
	Outcomes measured
	Study assumptions
Evaluation characteristics	Setting (alongside trial versus hypothetical modelling)
	Type of evaluation
	Modelling assumptions
	Characteristics of resource estimates
	Characteristics of cost estimates
	Discounting
	Sensitivity analyses
Study results	Results of evaluation
	Comparison with other evaluations

Quality assessment

To assess the methodology quality of included studies, the Quality of Health Economic Studies (QHES) checklist was chosen. [18] The QHES has been demonstrated to be a reliable and valid instrument [19-21], and was therefore chosen over other checklists because of its ease of application and the quantitative aspect which would allow comparison across the studies. The QHES contains 16 'yes/no' response questions focusing on the both the methodology of economic evaluations and the broader study, with each question carrying a weighted point score, out of a maximum of 100. The QHES instrument can be found in the supplementary information.

When interpreting QHES questions, points were only awarded if the reviewers believed that the most important criteria for the questions were met; if this was the case all points would be awarded. The reviewers did not award fewer points if the study only met some of the question's criteria, the response to each question either being a 'yes' (therefore full points) or a 'no' (no points). For individual questions on the QHES, there were particular criteria to be met in addition to those included within the QHES question. These were:

- Q5: *How was uncertainty handled?* –Uncertainty required investigating using robust statistical techniques; for within-trial evaluations, this would be by non-parametric bootstrapping, and for modelling evaluations by probabilistic sensitivity analyses. One- and two-way sensitivity analyses were not deemed to capture uncertainty robustly enough for points to be awarded.
- Q8: *Did the time horizon allow for all important outcomes?* – Smoking in pregnancy impacts on the health of mothers and infants both within-pregnancy and across their lifetimes. For points to be awarded, studies had to have included a within-pregnancy and lifetime analysis horizon for both mother and infant.
- Q10: *Were the major short-term, long-term and negative outcomes included?* – A separate scoping review conducted by the research team identified that smoking in pregnancy is potentially causally associated with nine conditions. If any of the following conditions was omitted from the evaluation, no points were awarded:
    - Placenta previa
    - Placental abruption
    - Ectopic pregnancy
    - Pre-eclampsia
    - Pre-term birth
    - Miscarriage and stillbirth
    - Sudden infant death syndrome (SIDS)
    - Low birth weight
    - Respiratory illness

Although there is no established, standardised interpretation of the QHES score, the following grouping was adopted based upon the work by Spiegel et al [22]: 0-24, extremely poor quality; 25-49, poor quality; 50-74; fair quality; 75-100 high quality.

Data Synthesis

No meta-analysis was specified prior to searches because it was uncertain how studies could be combined; however, the intention was to investigate whether or not this approach would be possible after considering included studies. It was anticipated that the review would adopt a narrative synthesis, but that a meta-analysis on a subset of data would be investigated if there was potential. The primary objective of the narrative synthesis would be to discuss the quality of the methods used in identified studies, as determined by the QHES. The results of the assessment from the QHES would be used to demonstrate the strengths and weaknesses of each individual study and of the literature as a whole. To facilitate this QHES scores were allocated to studies as an indicator of overall study quality and qualitatively inspected the components of studies' scores to investigate which aspects of evaluation quality were commonly absent or poor across studies.

Results

Electronic searching of databases conducted on 7th August 2014 identified 8,954 citations, while the manual searches of the NICE and US Surgeon General's websites returned a further 30 and zero studies respectively. Screening identified 23 potential studies, four of which were ongoing randomised control trials (RCTs). [23-26] Contact with the trials' Principal Investigators returned the data for three RCTs [27-29], while for one, data were unavailable. [25] Four studies were excluded during data extraction. Two were conference abstracts which reported insufficient detail, and attempts to contact the authors failed. [30 31] One included no outcomes related to either cessation or pregnancy [32], and another did not test a cessation intervention. [33] The study PRISMA diagram can be found in Figure 1. 14 studies were published in peer reviewed journals [27 34-46], two with NICE guidance [47 48], and two were unpublished RCTs. [28 29] As anticipated, it was decided that a meta-analysis was inappropriate due to the extremely heterogeneous nature of included studies.

Characteristics of Studies

Key characteristics of included studies can be found in the supplementary information. Five studies were conducted in the UK [27-29 47 48], and the remainder in the US. There was

wide variety in cessation interventions, including: counselling-based ones (five studies) [34 35 37 40 44]; self-help materials (two studies) [36 45]; combined self-help materials and counselling (two studies) [42 46]; nicotine replacement therapy (NRT) (one study) [27]; financial incentives (one study) [29]; and physical activity (one study). [28] Two studies used literature based interventions [47 48], while four studies modelled hypothetical interventions. [38 39 41 43] Comparators in all except one study were either no intervention or usual care, defined inconsistently across studies. [27]

Cost-offset evaluations were used in nine studies [34 36-39 41 43 44 46], cost-effectiveness in five, [27 28 35 40 45], cost-utility in two [47 48], and two studies used both cost-utility and cost-effectiveness. [29 42] Eight evaluations were conducted alongside clinical trials [27 28 35-37 42 45 46], four were part of observational studies [34 40 41 44], five were decision analytic models [38 39 43 47 48], and one combined a within-trial analysis with a decision analytic model. [29] 12 studies used a healthcare provider perspective, while six studies reported a societal perspective. [27-29 42 47 48]

Most evaluations adopted a short time horizon, with 12 studies considering only outcomes during pregnancy or immediately afterwards. [27 28 34-38 40 41 43-45] Only six studies reported considering outcomes over the mother's lifetime [29 39 42 46-48], and two studies incorporated outcomes over the infant's lifetime too. [47 48] Cost data was predominantly obtained from micro-costing analyses collected within clinical trials, with other cost estimates taken from literature sources. Six studies reported discount rates, with rates of 3% [42], 3.5% [29 47 48], 4% [39], and 5%. [41]

Measures of smoking cessation were the most frequent primary outcomes (12 studies), while two studies used numbers of low birth weight (LBW) infants prevented [38 39], one used SIDS prevented [41], and three used quality adjusted life years (QALYs). [42 47 48] Secondary outcomes were: LBW infants (six studies) [27 36 37 42 43 46], premature birth (two studies) [36 43], prenatal death (three studies) [27 39 47], life years (one study), [42], and QALYs (one study). [29] When smoking status was used as an outcome in trials, this was biochemically validated in eight studies. [27-29 34 40 42 45 46] Deterministic sensitivity analyses, investigating assumptions made in economic analyses, were performed in ten

studies [29 34 38-40 42 43 45-47]; the most frequently- varied parameters were intervention effectiveness [34 38 39 42 43 46], intervention cost [34 39 40 42 45-47], and background quit rate. [38 43] Four studies used statistical techniques judged robust in sensitivity analyses. [27-29 48]

Findings of studies with primary data collection

10 studies reported collection of cost and effectiveness data. [27-29 35-37 40 42 45 46] All except one study identified cessation during pregnancy as being cost-effective [42], with one UK RCT reporting that the intervention was dominant over usual care. [28] Other UK RCTs found the incremental cost per quitter was £4,926 for NRT [27], and £1,127 for financial incentives. [29] One RCT extended the within-trial results to lifetime horizon for the mother using a previously developed model [49], and estimated an incremental cost per QALY of £482 for financial incentives. [29] The impact of uncertainty was explored in all three UK RCTs. For NRT, the majority of the bootstrapping iterations laid within the north east quadrant, suggesting that NRT was likely to be more effective but more costly. [27] The probability of financial incentives being cost-effective compared to usual care at £20,000-£30,000 per QALY was 70% [29], while for physical activity the probability was approximately 75%. [28]

Amongst US studies, one RCT reported that using a counselling intervention provided no additional benefit in QALYs and was therefore dominated by usual care. [42] However, other studies found cost-benefit ratios estimated from 2:1[37] for self-help materials to 2.8:1[36] for counselling, though one study found the cost-benefit ratio to be between USD 1:17.93 to USD 1:45.83 for combined self-help materials and counselling. [46] Another study found an effectiveness to cost ratio of USD 1:84. [40] The incremental cost per quitter was reported in two studies: USD 298.76 for a counselling intervention [35]; and USD 50.93 and USD 118.83 for two different self-help material interventions. [45]

To allow comparison between these studies, the incremental cost was inflated to 2014 UK pound sterling prices. UK costs were inflated using the Hospital & Community Health

Services Pay and Prices Index [50], while US costs were inflated to 2014 prices using the Department of Labor's Consumer Price Index Calculator [51], and converted to UK pound sterling using the exchange rate of USD1=GBP0.677173 (correct as of April 2015). In addition to the incremental cost per quitter, an incremental cost per QALY was calculated. This was done by assuming a QALY gain of 1.94 which was chosen from previous work, based on the mean age of mothers across the included studies ranging from 24 years to 28 years. [52 53] This allowed an incremental cost per QALY to be calculated. The results of this analysis can be found in Table 2.

Table 2: Narrative synthesis of studies with primary data collection

Study	Intervention	Inc cost (£)	Inc quit rate	ICER per quitter (£)	ICER per QALY (£)
Cooper 2014	Nicotine replacement therapy	98.21*	1.8%	5,456.34*	2,812.55*
Dornelas 2006	Counselling	50.23	18.7%	268.62	138.47
Ershoff 1983	Counselling	149.69	11.6%	1,290.42	665.17
Ershoff 1990	Self-help materials	16.58	13.6%	121.94	62.86
Parker 2007	Counselling	2,357.40	13.4%	17,592.55	9,068.32
Ruger 2008	Counselling + self-help materials	304.04	-1.6%	DOMINATED	DOMINATED
Tappin 2015	Financial incentives	157.36†	14.0%	1,124.00†	579.38†
Ussher 2014	Physical activity	-35.39	1.3%	DOMINANT	DOMINANT
Windsor 1988a	Self-help materials	7.12	4.0%	178.10	91.80
Windsor 1988b	Self-help materials	7.12	12.0%	59.37	30.60
Windsor 1993	Counselling + self-help materials	4.99	5.8%	86.05	44.35

*= 95% CI Inc cost -£214.48 to £410.92, 95% CI ICER per quitter -£11,915.50 to £22,828.78, 95% CI ICER per QALY -£6,142.01 to £11,767.41

†= 95% CI Inc cost £155 to £162, 95% CI ICER per quitter £1,107.14 to £1,157.14, 95% CI ICER per QALY £570.69 to £596.47

Findings from other included studies

Eight studies used previous literature estimates to inform evaluations, with three being evaluations alongside observational studies with assumed quit rates and intervention costs [34 41 44]; five studies were modelling-based. [38 39 43 47 48] All three observational studies found that cessation interventions would generate greater cost savings compared to the cost required to deliver the intervention. Ayadi et al reported that an intervention costing USD 24, if applied to the US population, would generate USD 8 million net saving in healthcare costs, a ratio of approximately 1:333,333. [34] Pollack et al stated that a cessation intervention costing USD 45 would avert 108 SIDs if given to all pregnant smokers in the US, saving USD 210,500, a ratio of approximately 1:4678 [41], while Thorsen et al reported savings of USD 137,592 for an intervention costing USD 15,366 given to low income women in the US, a ratio of approximately 1:9. [44]

Three modelling studies were also conducted in the US, and reported favourable cost-saving estimates. Marks et al reported that taking into account the long-term costs averted, the ratio of cost savings to intervention cost was 1:3.26. [39] Hueston et al estimated that cessation interventions were cost-effective if the intervention costed USD 80 (USD 152.73) or less in 1989 prices (2014 prices) and achieved a 18% quit rate [38], while Shipp et al estimated that an intervention would be cost-neutral if the cost of delivering the intervention in 1989 prices (2014 prices) was USD 32 (USD 61.09) or lower. [43] Using the same exchange rate USD1=GBP0.677173 (correct as of April 2015), the values in UK 2014 prices were £103.42 and £41.37 respectively.

Using a model constructed for informing NICE in the UK, Taylor estimated that rewards (interventions where the participant received a financial or non-financial reward for meeting certain criteria) and 'other interventions' (not cognitive behavioural therapies (CBT), financial, or pharmacological interventions) were dominant over usual care; however other cessation interventions had favourable ICERs, assessed as £4,005 per QALY for CBT, £2,253 per QALY for pharmacotherapies, £1,992 per QALY for feedback, and £2,253 per QALY for stages of change. [47]In another model constructed for NICE to inform guidance on secondary care interventions, Mallender et al reported that even considering short-term

outcomes up to three years post-intervention, behavioural interventions appeared to be cost-effective with ICERs of £5,445 and £1,331 per QALY for high and low intensity, while incentives were less cost-effective with ICERs of £41,088 and £60,409 per QALY for conditional and non-conditional incentives. [48] However, the ICERs decreased as the perspective was increased to include the lifetime for both the mother and her infant, and reported that all the interventions modelled achieved a 100% probability of cost-effectiveness by £31,000 per QALY in the lifetime analysis.

QHES assessment

Table 3 summarises QHES assessment results. Six studies attained a score greater than 75 indicating high quality [27-29 42 43 48], six were deemed of fair quality [35-39 47], and six poor. [34 40 41 44-46] The median score was 58, with a range from 33 to 87, and an inter-quartile range of 38. Areas where studies seemed to perform poorly were: performing a robust analysis of uncertainty (Q5, four studies), inclusion of all major short- and long-term maternal and foetal outcomes (Q10, no studies), and incorporation of a time horizon that included both the effects within-pregnancy and lifetime for both the mother and infant (Q8, one study).

Table 3: Results of the QHES assessment

Author	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Total
Ayadi	2006	X	X							X			X			X		35
Cooper	2014	X	X	X	X	X	X	X		X		X	X	X	X	X	X	87
Dornelas	2006	X		X			X	X		X		X	X	X		X	X	67
Ershoff	1983	X					X	X		X		X	X	X		X	X	59
Ershoff	1990	X	X	X			X	X		X		X	X	X		X	X	71
Hueston	1994	X					X	X				X	X	X	X	X	X	57
Mallender	2013	X		X		X	X	X	X	X		X	X	X	X	X		86
Marks	1990	X		X				X		X		X	X		X	X		57
Parker	2007		X					X		X		X			X		X	33
Pollack	2001	X						X				X			X	X	X	36
Ruger	2008	X	X	X	X		X	X		X		X	X	X	X	X	X	78
Shipp	1992	X	X	X			X	X		X		X	X	X	X	X	X	77
Tappin	2014	X	X	X	X	X	X	X		X		X	X	X	X	X	X	87
Taylor	2009	X					X	X		X		X	X	X		X		56
Thorsen	2004	X						X		X					X	X	X	37
Ussher	2014	X	X	X	X	X	X	X		X		X	X	X	X	X	X	87
Windsor	1988	X						X		X		X				X		35
Windsor	1993	X		X						X		X	X			X	X	49
Frequency		17	8	10	4	4	11	16	1	16	0	16	14	11	11	17	13	
Percentage		94%	44%	56%	22%	22%	61%	89%	6%	89%	0%	89%	78%	61%	61%	94%	72%	

X = yes on QHES

Discussion

This review found 18 studies which included economic evaluations of cessation interventions delivered during pregnancy, however only six of these (33%) were judged as high quality. 17 studies identified within-pregnancy interventions as being cost-effective, with only one trial reporting that usual care was better than the experimental intervention. [42] The current evaluations were generally well described, utilised appropriate health outcomes and drew realistic conclusions based upon their results. Conversely, aspects where the analyses were in deficit included consideration of all major and relevant foetal and maternal health outcomes, use of an appropriate time horizon, and controlling for uncertainty using statically robust methods.

A limitation of this review is that the QHES is a subjective instrument. This was highlighted by the need for discussion among reviewers to resolve occasional disagreements about how some QHES items related to studies. However, the same issue applies to other checklists and therefore this is likely to have been a problem with any quality checklist utilised. Secondly, there were occasions where the reviewers felt QHES items were difficult to completely address; hence rewarding partial achievement rather than all or none of the available points may have been more appropriate. For example, for QHES question three it might have been appropriate to score in a graded fashion with points awarded being dependant on the different types of study design (e.g. eight points for information from systematic review, seven for information from clinical trial). This could have resulted in the points score calculated for each study better reflecting the overall quality of the methods used, potentially providing a more meaningful comparison. Finally, despite being a good measure of internal validity, the QHES does not measure the external validity. Therefore this review is unable to capture whether the results of the included studies could be generalised to the population, consequently a meaningful comparison across all the studies may not be possible or appropriate. Nevertheless, the reviewers believe that the use of QHES is appropriate to identify, across studies, those aspects of economic evaluations which might require development.

This review also has three important strengths. The broad search strategy has allowed the review to identify the majority of the literature published, and it is unlikely that an evaluation has escaped being identified, while also updating the previous review. [14] Therefore, this review is the most comprehensive in this subject to date. Secondly, the use of the QHES has allowed a systematic identification of the shortcomings in the published evaluations. The important impact of identifying the shortcomings of the current literature is that the review demonstrates that the included studies are potentially inaccurately estimating the cost-effectiveness of cessation interventions, leading to potential misinformation being used in the decision-making process for healthcare interventions. Additionally, this is the first review that has conducted a narrative synthesis on all cessation interventions that have been evaluated as part of clinical trials. This allows the comparison of different within-pregnancy cessation interventions, which is novel in this topic area, and hence permits the decision as to which interventions appear to be the most value for money.

The previous literature currently suggests that cessation interventions may generally be cost-effective, with only one study out of eighteen not supporting that conclusion. [42] From the within-trial evaluations identified, there is evidence that cessation interventions involving physical activity may offer most value for money because they are dominant (saves money and is more effective), however this was only based on the results of one study, which also demonstrates that there is a degree of uncertainty in the results. [28] However, both the ICERs per quitter and ICERs per QALY were relatively low for all other interventions except motivational interviewing, the largest being £17,592.55 per quitter (£9,068.22 per QALY). [40] This was further supported by the evaluations based on models which either returned very favourable cost-offset ratios for the US based studies and ICERs per QALY in UK based models, with one study suggesting that all interventions achieved a 100% probability of cost-effectiveness at a willingness to pay of £31,000 per QALY. [48] Cessation interventions in non-pregnant populations have often been described as 'the gold standard' in cost-effectiveness [13], and this review would suggest that cessation interventions within-pregnancy continue to meet this criteria. However, in the four studies that utilised a probabilistic sensitivity analysis, there was evidence of uncertainty which may warrant further investigation, and could impact on the estimated cost-effectiveness of

cessation interventions. Therefore, it would seem logical that policy makers should continue to fund cessation interventions for pregnant women as current evidence suggest that they offer value for money, however there is some uncertainty in the results of which the policy maker might wish to be aware.

We highlighted several limitations with the economic evaluations in which we identified in the literature. Most studies focused on a within-pregnancy time horizon, with only four studies considering the impacts of smoking during pregnancy on longer term outcomes [29 42 47 48]. However, it is well-established that smoking is associated with serious morbidities that can occur later in life [54], as well as health issues for the infant during its childhood (e.g. respiratory disease). [55] Therefore, to determine the cost-effectiveness of smoking cessation during pregnancy, the time horizon must not only capture within-pregnancy impacts, but also impacts over the lifetime, for both mother and infant. A further issue is that all evaluations omit one or more of the major morbidities which are caused by smoking in pregnancy. Most studies omitted maternal co-morbidities associated with smoking and pregnancy, e.g. placental abruption, placenta previa, pre-eclampsia. [2] These can all lead to severe complications during pregnancy, and in a worst case scenario, death to the infant, the mother, or both. However, many studies included some adverse, smoking-related birth outcomes and infant morbidities (e.g. low birth weight, premature birth, stillbirth), but rarely included more than one-condition and didn't consider any longer term impacts. Some studies attempted to capture the healthcare cost savings for adverse birth outcomes avoided from cessation [34 36-39 41 44 46], but only one included the impact of low birth weight and asthma on the health of the child across their lifetime; yet this study excluded premature birth. [48]

Another limitation of the current literature appears to be a general failure across studies to consider the impact of relapse to smoking after pregnancy; only four studies attempted to allow for this, and there was considerable variation in relapse rates applied within these. [29 42 47 48] Relapse is important since the mother's health risks from smoking increases with relapse, as does the infant's exposure to second-hand smoke. [56 57] Additionally, recent work suggests that if the mother smokes, an infant is over twice as likely to become an adult smoker [58], potentially exposing him or her to the associated lifetime adult health risks.

Hence, by not including a rate of relapse to smoking after childbirth, most economic models are overestimating the number of mothers who remain abstinent after pregnancy, potentially overestimating the benefits of smoking cessation.

One final consideration is the small number of studies which robustly control for uncertainty, with only the four most recently completed incorporating statistically robust techniques. [27-29 48] Controlling for uncertainty appropriately is important since it can demonstrate the level of confidence that the decision resulting from the evaluation is the correct one. Whilst in the past one- and two-way deterministic sensitivity analyses have been considered appropriate for gauging the impact of uncertainty, it is now deemed better to control for all parameter uncertainty through the use of probabilistic sensitivity analysis. [59] By not controlling for uncertainty, decisions made on cessation interventions could be incorrect, leading to a cost in benefits forgone. The present literature does not allow a reviewer to determine how confident they are that cessation interventions are cost-effective.

Conclusions

This review demonstrates that the majority of cessation interventions offered in pregnancy could offer value for money, and physical activity interventions appear to be particularly cost-saving, though there was evidence of uncertainty in the one study evaluating this intervention. However, given that smoking during pregnancy is an important public health issue, there are relatively few high quality economic evaluations demonstrating the cost-effectiveness of cessation interventions, and many of these have methodological shortcomings. To become more comprehensive and to estimate cost-effectiveness more accurately, future economic evaluations of smoking cessation in pregnancy should investigate uncertainty more robustly, use better estimates for the postpartum relapse, extend beyond a within-pregnancy time horizon, and include the major morbidities for both the mother and her infant for within-pregnancy and beyond.

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Declaration of completing interests

We have read and understood BMJ policy on declaration of interests and declare the following interests: Dr. Coleman reports personal fees from Pierre Fabre Laboratories,

France, outside the submitted work; Dr Jones, Dr Lewis, and Dr Parrott have nothing to declare.

Details of contributors

MJ, SL, SP, and TC were involved in the development of the research question. MJ performed the electronic searches and initial screening by title and abstract. MJ, SL, and TC and were responsible reviewing, data extracting identified studies, and applying the QHES checklist. MJ was responsible for conducting the narrative review. MJ, SL, SP, and TC all contributed to the drafting of the final manuscript.

Ethical approval

Ethics approval was not sought as the study did not involve any direct contact with patients or any patient involvement.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Figure Legends

Figure 1: Review PRISMA diagram

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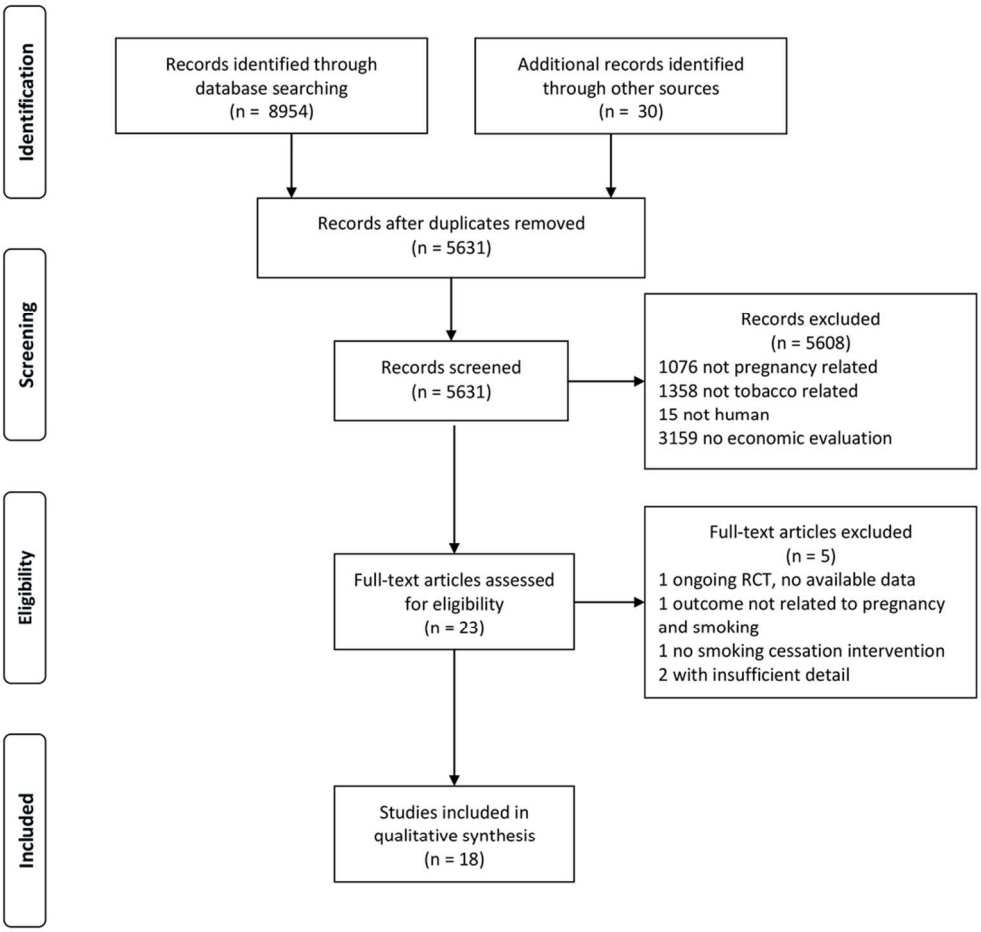

Figure 1: Review PRISMA diagram
46x44mm (600 x 600 DPI)

SUPPLEMENTARY FILE 1: ELECTRONIC SEARCH OF MEDLINE DATABASE

Date of search: 7th August 2014

Search conducted 1946 to July Week 5 2014

Search number	Search terms	Results
1	exp Smoking/	123,716
2	exp Smoking Cessation/	20,581
3	exp Recurrence/	161,774
4	relapse.mp.	76,794
5	relapse prevention.mp.	1,966
6	exp Tobacco/	23,575
7	1 or 2 or 3 or 4 or 5 or 6	366,856
8	exp Pregnant Women/	5,619
9	exp Pregnancy/	720,105
10	exp Prenatal Care/	20,582
11	antenatal.mp.	21,928
12	prenatal.mp.	126,429
13	pregnan*.mp.	774,991
14	exp Fetus/	138,059
15	foetus.mp.	6,248
16	fetal.mp.	291,319
17	foetal.mp.	14,594
18	exp Infant, Newborn/	502,370
19	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	1,275,951
20	exp "Costs and Cost Analysis"/	183,765
21	exp Cost-Benefit Analysis/	61,091
22	cost effectiveness.mp.	33,109
23	cost-effectiveness.mp.	33,109
24	cost benefit.mp.	64,643
25	cost utility.mp.	2,315
26	exp Economics/	497,217
27	economic evaluation.mp.	4,874
28	economic.mp.	141,170
29	exp Quality-Adjusted Life Years/	7,211
30	QALY.mp.	4,032
31	quality adjusted life year.mp.	2,689
32	Quality-adjusted life year.mp.	2,689
33	exp "Quality of Life"/	120,745
34	quality of life.mp.	185,735
35	cost per life year.mp.	538
36	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	748,896
37	7 and 19 and 36	764
38	limit 37 to (english language and humans and yr="2011 - Current")	135

SUPPLEMENTARY FILE 1: THE QHES INSTRUMENT

	Questions	Points	Yes	No
1	Was the study objective presented in a clear, specific, and measurable manner?	7		
2	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4		
3	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial - best, expert opinion - worst)?	8		
4	If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study?	1		
5	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9		
6	Was incremental analysis performed between alternatives for resources and costs?	6		
7	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5		
8	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7		
9	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8		
10	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term, and negative outcomes?	6		
11	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7		
12	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8		
13	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7		
14	Did the author(s) explicitly discuss direction and magnitude of potential biases?	6		
15	Were the conclusions/recommendations of the study justified and based on the study results?	8		
16	Was there a statement disclosing the source of funding for the study?	3		
	Total Points	100		

Reference:
Ofman JJ, Sullivan SD, Neumann PJ, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. J Manag Care Pharm. 2003;9(1):53-61.

SUPPLEMENTARY FILE 3: CHARACTERISTICS OF INCLUDED STUDIES: TYPE OF STUDY, INTERVENTIONS, OUTCOMES, AND COSTS

Author/ Year	Type of study	Intervention / comparator	Primary / secondary outcomes	Characteristics of cost data
Ayadi 2006 **[34]**	Observational with hypothetical modelling	5As intervention in three different settings; clinical trial, quit line, and rural managed care organisation / assumed baseline quit if 14%	Assumed quit rate of intervention 30% – 70% versus 14%	Intervention micro-costing in different settings; neonatal care costs for infants of mothers who smoke estimated from CDC software (SAMMEC)
Cooper 2014 **[27]**	Within-trial analysis alongside RCT	NRT with behavioural support / placebo patches with behavioural support	Sustained biochemically validated abstinence between quit date and end of pregnancy / Self-reported abstinence at six months and two years after delivery; infant outcomes included stillbirth, miscarriage, birth weight, gestation age at birth; EQ-5D scores at six months postpartum	Micro-costing of control and intervention groups, including salary, patches and biochemical validation costs; weighted average NHS reference costs used for HRG data; costs reported for 2009/10 financial year

Dornelas 2006 **[35]**	Within-trial analysis alongside RCT	90 minute psychotherapy session at clinic followed by bi-monthly telephone calls with mental health counsellor / Standard smoking cessation treatment guidelines	Biochemically validated seven-day point prevalence at end of pregnancy and six months postpartum	Cost of training, counselling time, telephone time, clerical staff
Ershoff 1983 **[37]**	Within-trial analysis alongside non-randomised trial	Two 45 minute nutrition counselling sessions. Eight week program with home-correspondence. Three telephone calls with reinforcement message / Standard prenatal care from two sources – random sample who attended in four months before program and random sample who attended maxi-care in different area	Self-reported abstinence at two months postpartum / Nutrition behaviour; complications during pregnancy (toxaemia, infection, hypertension, weight gain); infant birth weight; Apgar scores; abnormalities	In-patient claim forms, cost of hospital stay, staff salaries, program development, implementation costs, overheads
Ershoff 1990 **[36]**	Within-trial analysis alongside non-randomised trial	Self-help intervention, series of booklets / usual care	Biochemically validated point prevalence at end of pregnancy / birth weight and low birth categories; intra-uterine growth restriction; pre-term birth	Overhead, time, materials, postage, health plans costs from computerized claims system, charges to health plan, charges from hospital based providers
Hueston	Decision analytic model	Hypothetical intervention / hypothetical intervention	Intervention quit rate of 3% -	Costs of healthcare for

1994 **[38]**		with assumed level of effectiveness	29% at end of pregnancy versus. background quit rate of 6%, 15% and 37% / rates of LBW amongst smokers estimated from national cohort	LBW infants from literature,
Mallender 2013 **[48]**	Decision analytic model	Interventions come from established literature. Situations modelled were: High intensity versus low intensity behavioural support interventions High intensity behavioural support versus usual care Conditional incentives versus non-conditional incentives	QALYs	Costs for interventions taken from literature; literature based costs used for diseases / conditions; costs reported at 2011 prices
Marks 1990 **[39]**	Decision analytic model	Hypothetical smoking cessation programme / normal care with no cessation intervention	LBW and prenatal deaths prevented	Cost of intervention estimated from 2 previous studies in USD. Short and long-term costs averted taken from 1986 office of technology cost assessment of neonatal intensive care for LBW

				infants.
Parker 2007 **[40]**	Within-trial alongside observational (one arm of trial)	Telephone calls providing motivational interviewing / those receiving no calls (either because they chose not to or because contact could not be made). All received a quit kit	Biochemically validated abstinence at end of pregnancy and six months postpartum	Costs of calls using unit price of staff and non-staff – personnel and training time
Pollack 2001 **[41]**	Case-control with hypothetical modelling	Hypothetical intervention using an average of reported success rates cessation programs across various settings / no intervention, no spontaneous quitting	Abstinence rates at end of pregnancy / number of SIDs averted	Cost of typical intervention per participant in 1998 USD
Ruger 2008 **[42]**	Within-trial analysis alongside RCT	Three 1 hour home visits using motivational interviewing (MI) and self-help manuals. MI targeted: 1) impact of smoking on mothers, foetuses, and newborns; 2) evaluated smoking behaviour; 3) increasing self-efficacy for smoking cessation; 4) setting goals to change smoking; 5) feedback about household nicotine levels / Standard prenatal care: 5-minute intervention outlining the harmful effects of smoking during pregnancy and self-help materials	Abstinence and relapse prevention at six-months postpartum / birth weight; post-delivery status; LYs; QALYs	Intervention costs collected within RCT. From literature: Cost savings for neonatal intensive care, chronic medical conditions, and acute conditions during the first year of life, cost savings for maternal healthcare (cardiovascular and lung diseases)
Shipp 1992 **[43]**	Decision analytic model	Hypothetical intervention / no cessation program	Abstinence at end of pregnancy / number of LBW,	Direct medical charges for maternal care at

			premature births, placental abruptions, haemorrhage, placenta previa, pre-eclampsia cases avoided	delivery and hospital care for newborns.
Tappin 2014 **[29]**	Within-trial analysis alongside RCT, extended using a decision analytic model [117]	Standard care from NHS pregnancy stop smoking services plus financial incentives of vouchers up to £400 for women who quit and remained abstinent throughout pregnancy / standard care from NHS pregnancy stop smoking services which involves, face-to-face appointments, support phone calls, and NRT for up to 12 weeks	Biochemically validated abstinence at end of pregnancy, QALYs	Micro-costing using resource use data within-trial, healthcare costs of birth weight and smoking related diseases from NHS Scotland reference costs and established literature sources
Taylor 2009 **[47]**	Decision analytic model	Interventions identified by Cochrane review: cognitive behaviour strategies; stages of change; feedback; rewards; pharmacotherapies; 'other' interventions / no intervention with spontaneous quit rate	QALYs	Lifetime costs from previously developed model; costs in first five years of life per infant admitted to hospital born to smoking and non-smoking mothers, taken from Oxford Record Linkage study

Thorsen 2004 **[44]**	Within-trial alongside observational study	The 'First Breath' smoking cessation programme / none given	Abstinence rates at end of pregnancy	Costs of: Maternal maternity admissions, inpatient neonatal care and medical costs for first month of life.
Ussher 2014 **[28]**	Within-trial alongside RCT	Intervention to encourage physical activity with behavioural support / standard behavioural support provided by NHS Stop Smoking Services	Biochemically validated abstinence at end of pregnancy	Micro-costing of intervention and control groups, including salaries, physical activity equipment, biochemical validation equipment; weighted average NHS reference costs used for HRG data; costs reported for 2012/13 financial year
Windsor 1988 **[45]**	Within-trial alongside RCT	Two intervention groups: Group 1 given standard information and "Freedom From Smoking in 20 Days"; Group 2 given standard information plus "A Pregnant Woman's Self-Help Guide to Quit Smoking". Both groups received "Because You Love Your Baby", and a 10 minute presentation at the first prenatal visit /	Abstinence at end of pregnancy	Salary estimates in USD , cost of manuals

		Control group received a non- focused interaction on smoking and pregnancy of 5 minutes during the first prenatal visit		
Windsor 1993 **[46]**	Within-trial alongside RCT	Three components: Self-help materials with brief counselling support with follow-up letters and a buddy system / Normal care – not defined	Abstinence at end of pregnancy / LBWs avoided	Salaries of staff delivering intervention. Costs for the LBW infant at birth, in first year of life and long-term costs

SUPPLEMENTARY FILE 4: CHARACTERISTICS OF INCLUDED STUDIES: TYPE OF EVALUATION, COMPARISON, AND RESULTS

Author/ Year	Type of analysis	Units of comparison	Perspective of analysis / time horizon / discounting (per annum)	Sensitivity analyses	Results
Ayadi 2006 **[34]**	Cost-offset	Neonatal cost savings per quitter	Provider / within-pregnancy / no discounting	Effectiveness (30 to 70%); intervention cost USD 24 to USD 34	Neonatal cost savings of USD 881 per maternal smoker; net savings of up to USD 8 million based on intervention cost of USD 24
Cooper 2014 **[27]**	Cost-effectiveness	Incremental cost per quitter	Societal / within-pregnancy / no discounting	Uncertainty explored by using non-parametric bootstrapping (1000 iterations) on costs and effectiveness; exclusion of multiple births	Mean cost of control £47.75 with a quit rate of 7.6%; mean cost of intervention was £98.31 with a quit rate of 9.4%; ICER £4,926 per quitter (95% CI -£114,128 to £126,747)
Dornelas 2006 **[35]**	Cost-effectiveness	Incremental cost per quitter	Provider (implied) / within-pregnancy and six months postpartum / no discounting	None	Intervention cost USD 56.37 per patient. Incremental quit rate 18.7 (28.3 – 9.6). Incremental cost per quitter USD 298.76
Ershoff 1983 **[37]**	Cost-offset	Benefit-cost ratio	Provider / within-pregnancy and two months postpartum / no discounting	None	Intervention quit rate of 49.1% versus 37.5% of controls; mean birth weight greater in intervention group, 121.34 ounces versus

					113.64; hospital treatment cost differential of USD 183 per delivery; intervention cost USD 93 per patient; benefit cost ratio of 2:1
Ershoff 1990 **[36]**	Cost-offset	Benefit-cost ratio	Provider / within-pregnancy / no discounting	None	Intervention quit rate of 22.2% versus 8.6% for and controls; intervention infants weighed average 57g more; intervention cost per delivery USD 1028 versus USD 1074 in controls; cost savings of USD 5,428; total intervention cost of USD 1,939; benefit: cost ratio of 2.8:1
Hueston 1994 **[38]**	Cost-offset	Intervention cost versus neonatal costs averted	Provider (implied) / within-pregnancy / no discounting	Intervention quit rate between 3% and 29%; spontaneous quit rate of 6%, 15% and 37%	Cessation programmes in pregnancy cost effective for preventing LBW births if they cost $80 or less per participant and achieve quit rates of at least 18% with a spontaneous quit rate of 37%
Mallender 2013 **[48]**	Cost-utility	Incremental cost per QALY	Societal (implied) / up to three years after intervention; lifetime for mother and infant / costs and QALYs at 3.5%	Intervention cost and effectiveness varied in PSA analysis (1000 iterations)	High vs low intensity behavioural: Short term (three years): £5,445, £1,331 Lifetime (mother): £563, £136 Lifetime (mother and infant): £183, £51 High intensity behavioural vs usual care: Short term (three years): £17,827, £157,696, £2,344

					Lifetime (mother): £1,864, £16,515, £244 Lifetime (mother and infant): £528, £4,594, £72 Conditional incentives vs non conditional: Short term (three years): £41,088, £60,409, £43,161 Lifetime (mother): £4,331, £6,441, £4,589 Lifetime (mother and infant): £1,124, £1,488, £1,091
Marks 1990 **[39]**	Cost-offset	Cost per LBW averted; cost per prenatal death averted; benefit-cost ratios for short and long-term hospitalisation costs	Provider (implied) / lifetime / cost of LBW at 4%	Cessation rates from 5% through to 25%; costs programmes varied USD 5-100; percentage of LBW needing neonatal special care 33%-67%; relative risk of LBW 1.5 – 2.5; relative risk of	Note: Also ICERs including productivity estimates, not reproduced here Cost per LBW birth prevented USD 4000; cost per prenatal death prevented USD 695,452; costs averted in terms of short term hospitalization USD 3.31 for every USD 1 spent on cessation; long-term costs averted USD 3.26 per every USD 1 cessation

				prenatal death 1.1 to 1.4	
Parker 2007 **[40]**	Cost-effectiveness	Cost per quitter	Provider / within-pregnancy / no discounting	Varied costs of intervention per patient from USD 20 to USD 30	Quit rate for no calls 9.6% and 3 calls 23%; effectiveness to cost ratio of 1: USD 84 based on 3 calls
Pollack 2001 **[41]**	Cost-offset	Cost per SIDS averted	Provider (implied) / within-pregnancy / 5% per cost of life year	None	Assumed quit rate of 15%; intervention cost USD 45; averts 108 SIDS deaths annually at an estimated cost of USD 210,500 per life saved
Ruger 2008 **[42]**	Cost-effectiveness, cost-utility	Incremental cost per LY; incremental cost per QALY	Societal / lifetime for the mother; first year of life for the infant / costs and QALYs at 3%	Lifetime cost savings due to maternal illness and cost savings due to infant illness in first year of life; varying smoking status data; varying intervention costs; varying QALY weights	For smoking cessation, MI cost more but provided no additional benefit compared to UC, therefore MI was dominated by UC; MI intervention did prevent relapse more effectively than UC with an estimated ICER of USD 628/QALY
Shipp 1992 **[43]**	Cost-offset	Break even cost	Provider / within-pregnancy / no discounting	Prevalence of smoking; intervention quit	Break even cost of USD 32 per pregnant woman; varying between USD 10 and USD 237 in sensitivity analyses

				rate; spontaneous quit rate; probability of LBW; probability of maternal outcomes	
Tappin 2014 **[29]**	Cost-effectiveness, cost-utility	Incremental cost per quitter, incremental cost per QALY	Societal / within-pregnancy and lifetime / discounting costs and QALYs at 3.5%	Inclusion of smoking related disease costs; discount rate of 0%; risk of relapse at three months postpartum varied between 30% and 80%	Intervention quit rate of 23% vs 9% for controls; ICER of £1,127 per quitter; ICER of £482 per QALY for lifetime; 70% of cost-effective at £20,000-£30,000 WTP; additional research cost-effective if less than £3.3 million at £30,000 WTP
Taylor 2009 **[47]**	Cost-utility	Incremental cost per QALY	Societal (implied) / lifetime / discounting costs and QALYs at 3.5%	Varying costs of each intervention between £0 and £1,000	For both mother and infant (per QALY), cognitive behaviour therapy ICER £4,005; stages of change ICER £3,033; feedback ICER £1,992; pharmacotherapies ICER £2,253; rewards and other interventions were dominant over control
Thorsen 2004 **[44]**	Cost-offset	Cost of intervention versus cost saved	Provider (implied) / pregnancy and six months postpartum / no discounting	None	If the intervention costs USD 15,366 it would achieve savings of USD 137,592

Ussher 2014 **[28]**	Cost-effectiveness	Incremental cost per quitter	Societal / within-pregnancy / no discounting	Uncertainty explored by using non-parametric bootstrapping on costs and effects; halving and doubling the number of participants per fixed cost; sub-group analysis on age and cigarette dependence	Intervention quit rate of 7.7% versus 6.4% for controls; intervention cost £35 less per patient than control therefore dominant; high degree of uncertainty with CEAC suggesting that the probability of intervention being cost-effective was 0.8 at £50,000 WTP
Windsor 1988 **[45]**	Cost-effectiveness	Incremental cost per quitter	Provider / within-pregnancy / no discounting	Varying effectiveness of guide; varying cost of staff time; varying of intervention cost	Standard information cost per person USD 2.08; quit rate of 2%; ICER USD 104.00; ALA manual cost per person USD 7.13; quit rate of 6%; ICER USD 118.83; pregnant woman's guide cost per person USD 7.13; quit rate of 14%; ICER USD 50.93
Windsor 1993 **[46]**	Cost-offset	Benefit-cost ratio	Provider (implied) / lifetime / no discounting	Cost of intervention varied USD 4.5 - USD 9.0; smoking attributable risk of	LBW costs USD 9,000 to USD 23,000; cost-benefit ratio low estimate is USD 1:17.93 and high estimate is USD 1:45.83; net benefit minus cost difference is USD 365,728 (low estimate)

	LBW varied from 0.2 to 0.15; low and high estimate of smoking attributable LBWs	and USD 968,320 (high estimate)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No protocol available and not registered
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	See supplementary file 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	None performed
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	See supplementary files 3 and 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	15-16
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	None performed
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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ECONOMIC EVALUATIONS OF SMOKING CESSATION INTERVENTIONS DURING PREGNANCY: A SYSTEMATIC REVIEW

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ECONOMIC EVALUATIONS OF SMOKING CESSATION INTERVENTIONS DURING PREGNANCY: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: To identify and critically assess previous economic evaluations of smoking cessation interventions delivered during pregnancy.

Design: Qualitative review of studies with primary data collection or hypothetical modelling. Quality assessed using the Quality of Health Economic Studies checklist.

Data sources: Electronic search of 13 databases including Medline, Econlit, Embase, and PubMed, and manual search of the UK's National Institute of Health and Care Excellence guidelines and US Surgeon General.

Eligibility criteria for selecting studies: All study designs considered if they were published in English, evaluated a cessation intervention delivered to pregnant women during pregnancy, and reported any relevant economic evaluation metric (e.g. cost per quitter, incremental cost per quality adjusted life year).

Results: 18 studies were included. Eight evaluations were conducted alongside clinical trials, four were part of observational studies, five were hypothetical decision-analytic models, and one combined modelling with within-trial analysis. Analyses conducted were cost-offset (nine studies), cost-effectiveness (five studies), cost-utility (two studies), and combined cost-effectiveness and cost-utility (two studies). Six studies each were identified as high, fair, and poor quality respectively. All interventions were demonstrated to be cost-effective except motivational interviewing which was dominated by usual care (one study). Areas where the current literature was limited were the robust investigation of uncertainty, including time horizons that included outcomes beyond the end of pregnancy, including major morbidities for both the mother and her infant, and incorporating better estimates of postpartum relapse.

Conclusions: There are relatively few high quality economic evaluations of cessation interventions during pregnancy. The majority of the literature suggests that such interventions offer value for money; however, there are methodological issues that require addressing, including investigating uncertainty more robustly, utilising better estimates for postpartum relapse, extending beyond a within-pregnancy time horizon, and including major morbidities for both the mother and her infant for within-pregnancy and beyond.

STRENGTHS

- The review implies a broad search strategy of 13 electronic databases, so is likely to have captured most, if not all, of the published literature
- The use of a quality checklist has allowed the systematic identification of the omissions and limitations of the current literature
- The review is the first in this topic area to employ a qualitative synthesis to allow comparison between interventions in common terms

LIMITATIONS

- The quality assessment could be considered as subjective, and therefore is possibly influenced by reviewer bias
- Unpublished trials with published protocols were included, however, other unpublished work was not identified and therefore some relevant evaluations could have been omitted
- The quality assessment tool is a good judge of studies internal validity but cannot measure external validity, and therefore the tool cannot evaluate the generalisability of the results of included studies

ECONOMIC EVALUATIONS OF SMOKING CESSATION INTERVENTIONS DURING PREGNANCY: A SYSTEMATIC REVIEW

Introduction

A major global public health issue continues to be tobacco smoking during pregnancy, with a per annum economic burden conservatively estimated to be £23.5 million in the UK [1], and USD110 million in the US. [2] Not only is the mother exposed to the long term risks of smoking [3], but has an increased risk of certain pregnancy complications (e.g. placenta abruption, ectopic pregnancy) [4], while also having serious consequences on her offspring. [5-7] The prevalence of smoking during pregnancy amongst countries is highly varied, with approximately 39% in Spain [8], 23% in Canada [9], to 12-14% in the UK, US, Australia and Germany. [10-13] Suggested explanations for the variation in prevalence are that countries with the higher prevalence also had a greater proportion of mothers with low household income, low education levels, and low health literacy levels. [14 15]

Economic evaluation is an important tool for determining which interventions deliver value for money and is an integral part of the decision-making process for new healthcare technologies. However, using the results from poor quality evaluations are likely to lead to misinformed decisions being made and these could have significant negative impacts on health. While economic evaluations of smoking cessation interventions in the non-pregnant population have demonstrated that cessation is cost-effective (offer value for money in terms of effectiveness in relation to cost) [16], it would appear that similar evidence for within-pregnancy cessation interventions is sparse. A previous review published in 2008 identified only eight studies which involved economic evaluations of cessation interventions delivered to pregnant smokers [17], and suggested that such interventions could be considered potentially cost-effective. However, a number of major studies have since been published, so this review could now be considered out of date. The primary aim of this paper was to identify and critically assess economic evaluations of smoking cessation interventions delivered during pregnancy. The secondary aims of this review were to

identify any omissions and limitations within previous evaluations, and to determine, which, if any, cessation interventions appeared to be cost-effective.

Methodology

A previous review conducted by Ruger et al has already been done on this topic [17], however, this review could be considered to be out of date as the search was last performed up to July 2003. Furthermore, this review only searched two electronic databases (PubMed and National Health Service Economic Evaluation Database (NHS EED)), and therefore the authors felt that the previous review's search may have missed relevant articles. Therefore, the authors concluded to expand the electronic search and search terms to ensure that a maximum sensitivity search was conducted and that all the relevant literature had been identified.

Database selection

13 databases were searched: ASSIA, CINAHL, Econlit, Embase, Maternity and Infant Care, Medline, NHS EED, PsycArticles, PsycINFO, PubMed, Tufts Cost-Effectiveness Analysis Registry, Web of Knowledge, and Web of Science. Additionally, the websites of two governmental health guidance bodies, the UK's National Institute for Health and Care Excellence (NICE) and the US Surgeon General, were searched to identify any evaluations published here as part of guideline development. [18 19] Databases were searched from inception through to August 2014.

Search terms

The search strategy was developed using terms from a previous review and the Cochrane Pregnancy and Childbirth Group. [17 20] Search terms and an example search can be found in Supplementary File 1. For the searches of the NICE and US Surgeon General websites, the terms smoking, smoking cessation, and pregnancy were used.

Inclusion criteria

Studies were included if they were in English, reported a formal economic evaluation, with a direct comparison between costs and outcomes, e.g. 'cost per quitter'.

Population: Women who had experienced a cessation intervention during pregnancy, and/or their infants/children whose mother had been exposed to a cessation intervention during pregnancy, or hypothetical cohorts modelling cessation during pregnancy and/or after this.

Interventions: Any interventions or combination of interventions, both real and hypothetical (an intervention with an assumed quit rate), aimed at encouraging pregnant smokers to quit.

Comparators: Any comparator intervention including no intervention and 'usual care' (UC).

Outcomes: Clinical or economic outcomes considered relevant to the mother and/or child (e.g. smoking status at end of pregnancy, low birth weight (birth weight <2500grams) births (LBW) averted, sudden infant deaths (SIDs) averted, and quality adjusted life years (QALYs)).

Design: Any type (see Table 1 for brief definitions) and design (including within-trial analyses [21] and decision analytic models (mathematical techniques to synthesise information from multiple sources) [22])of economic evaluation were considered.

Table 1: Brief definition of the different types of economic evaluation

Type of economic evaluation	Definition
Cost-minimisation (CMA)	Interventions are assumed to have equal effectiveness and are ranked in terms of cost (low to high)
Cost-effectiveness (CEA)	Effectiveness of interventions are measured in their natural scale (e.g. number of quitters)
Cost-utility (CUA)	Effectiveness of interventions are measured using a generic outcome which embodies health related quality of life which captures a patient's preference (utility) for a particular health state/disease
Cost-benefit (CBA)	Effectiveness of interventions are measured in monetary units
Cost-consequence (CCA)	Costs and consequences of an intervention are reported separately
Cost-offset(COA)	Effectiveness of interventions is measured in healthcare cost savings generated by the intervention

Exclusion criteria

Exclusion criteria were:

- Studies with no economic analyses
- Studies which focused on the delivery of a smoking service and did not report an outcome that demonstrated the effectiveness of an intervention in terms of health benefits to the mother/infant or reduction in the number of women smoking by the end of pregnancy; examples of irrelevant outcomes include number of general practitioners delivering a cessation intervention, number of women accessing a cessation intervention

Identification of papers and data extraction

The lead reviewer screened titles and abstracts of retrieved citations and potentially-relevant texts were retrieved. If a protocol for an ongoing trial was identified, the trial's Principal Investigator was asked to provide economic analysis details. Two reviewers working independently assessed full texts for inclusion, extracted data, and applied a quality assessment checklist. If the two reviewers disagreed on data extraction or quality

assessment, a third was consulted. A manual search was conducted of references from included studies for other potentially-relevant studies. Papers were then identically screened and reviewed. Data extracted from each study is given in Table 2.

Table 2: Data extracted from studies

Area of topic	Data extracted
General study background	Author(s) Publication year Years of study Study question Funding source
Study design	Study type and design Description of intervention Description of comparator Outcomes measured Study assumptions
Evaluation characteristics	Setting (alongside trial versus hypothetical modelling) Type of economic evaluation Modelling assumptions Characteristics of resource estimates (staff time, intervention requirements, hospital use) Characteristics of cost estimates (staff cost, itemised costs, total intervention and comparator costs, incremental cost) Discounting Sensitivity analyses
Study results	Results of evaluation Comparison with other evaluations

Quality assessment

To assess the methodology quality of included studies, the Quality of Health Economic Studies (QHES) checklist was chosen. [23] The QHES has been demonstrated to be a reliable and valid instrument [24-26], and was therefore chosen over other checklists because of its ease of application and the quantitative aspect which would allow comparison across the studies. The QHES contains 16 'yes/no' response questions focusing on the both the methodology of economic evaluations and the broader study, with each question carrying a weighted point score, out of a maximum of 100. The QHES instrument can be found in Supplementary File 2.

When interpreting QHES questions, points were only awarded if the reviewers believed that the most important criteria for the questions were met; if this was the case all points would be awarded. The reviewers did not award fewer points if the study only met some of the question's criteria, the response to each question either being a 'yes' (therefore full points) or a 'no' (no points). For three individual questions on the QHES (questions five, eight, and 10), the authors specified further criteria to be met in addition to those included within the QHES question. Details of these additional criteria can be found alongside the QHES instrument in Supplementary File 2. Although there is no established, standardised interpretation of the QHES score, the following grouping was adopted based upon the work by Spiegel et al [27]: 0-24, extremely poor quality; 25-49, poor quality; 50-74; fair quality; 75-100 high quality.

Data Synthesis

No meta-analysis was specified prior to searches because it was uncertain how studies could be combined; however, the intention was to investigate whether or not this approach would be possible after considering included studies. It was anticipated that the review would adopt a qualitative synthesis, but that a meta-analysis on a subset of data would be investigated if there was potential. The primary objective of the qualitative synthesis would be to discuss the quality of the methods used in identified studies, as determined by the QHES. The results of the assessment from the QHES would be used to demonstrate the strengths and weaknesses of each individual study and of the literature as a whole. To facilitate this QHES scores were allocated to studies as an indicator of overall study quality and qualitatively inspected the components of studies' scores to investigate which aspects of evaluation quality were commonly absent or poor across studies.

The secondary objectives of the qualitative synthesis were to determine any omissions and limitations of previous evaluations, and to investigate what evidence there was of the cost-effectiveness of within-pregnancy cessation interventions. To allow comparison between the various evaluations, we grouped studies into those who included primary data collection (e.g. randomised controlled trials (RCTs)) and those who utilised secondary sources (e.g.

hypothetical decision analytic models). We adopted this approach as we anticipated that there would be very different assumptions made within the studies, with RCTs likely to be focusing on a short time horizon while decision analytic models a much longer one. Furthermore, decision analytic models often assume background quit rates or intervention/comparator costs which may not be comparable with those collected directly from a RCT.

Results

The electronic search (conducted 7th August 2014) identified 8,954 citations, while the manual searches of the UK's National Institute of Health and Care Excellence (NICE) and US Surgeon General's websites returned a further 30 and zero studies respectively. Screening identified 23 potential studies, four of which were ongoing randomised control trials (RCTs) with published protocols. [28-31] Contact with the trials' Principal Investigators returned the data for three RCTs [32-34], while for one, data were unavailable. [30] Four studies were excluded during data extraction. Two were conference abstracts which reported insufficient detail, and attempts to contact the authors failed. [35 36] One included no outcomes related to either cessation or pregnancy [37], and another did not test a cessation intervention. [38] The study PRISMA diagram can be found in Figure 1. 14 studies were published in peer reviewed journals [32 39-51], two with NICE guidance [52 53], and two were unpublished RCTs. [33 34] As anticipated, it was decided that a meta-analysis was inappropriate due to the extremely heterogeneous nature of included studies.

Characteristics of Studies

Key characteristics of included studies can be found in Supplementary Files 3 and 4. Five studies were conducted in the UK [32-34 52 53], and the remainder in the US. There was wide variety in cessation interventions, including: counselling-based (five studies) [39-41 45 49]; self-help materials (two studies) [42 50]; combined self-help materials and counselling (two studies) [47 51]; nicotine replacement therapy (NRT) (one study) [32]; financial incentives (one study) [34]; and physical activity (one study). [33] Two studies investigated

interventions that had previously been described in the literature [52 53], while four studies modelled hypothetical interventions. [43 44 46 48] Comparator interventions amongst studies with primary data collection were self-help materials (four studies) [40 42 47 51]; brief advice (four studies) [40 47 50 51]; and standard UK National Health Service treatment (see Supplementary File 3 for details) (two studies) [33 34]. The following were used by one study each, placebo patches with behavioural support [32]; no intervention [45]; and a cessation program which was not defined. [41] For studies without primary data collection, seven used an assumed or spontaneous background quit rate [39 43 44 48 49 52 54], while one study used multiple comparators which included low intensity behavioural support, non-conditional incentives, and usual care (not defined).[53]

Cost-offset evaluations were used in nine studies [39 41-44 46 48 49 51], cost-effectiveness in five, [32 33 40 45 50], cost-utility in two [52 53], and two studies used both cost-utility and cost-effectiveness. [34 47] Eight evaluations were conducted within clinical trials [32 33 40-42 47 50 51], four were part of observational studies [39 45 46 49], five were decision analytic models [43 44 48 52 53], and one combined a within-trial analysis with a decision analytic model. [34] 12 studies used a healthcare provider perspective (focusing on costs and outcomes directly related to the healthcare provider), while six studies reported a societal perspective (including costs and outcomes both directly and indirectly related to the healthcare provider, patient, and society as a whole). [32-34 47 52 53]

Most evaluations adopted a short time horizon, with 12 studies considering only outcomes during pregnancy or immediately afterwards. [32 33 39-43 45 46 48-50] Only six studies reported considering outcomes over the mother's lifetime [34 44 47 51-53], and two studies incorporated outcomes over the infant's lifetime too. [52 53] Cost data was predominantly obtained from micro-costing analyses (costing individual component parts separately to generate a total cost for the intervention) collected within clinical trials, with other cost estimates taken from literature sources. Six studies reported discount rates (a rate representing how much individuals discount future health and cost), with rates of 3% [47], 3.5% [34 52 53], 4% [44], and 5%. [46]

Measures of smoking cessation were the most frequent primary outcomes (12 studies), while two studies used the number of infants born with low birth weight (LBW) (birth weight <2500 grams) prevented [43 44], one used sudden infant deaths (SIDS) (unexplained death within the first year of life) prevented. [46], and three used quality adjusted life years (QALYs) (a life year weighted by the patient's preference for being in a particular health state). [47 52 53] Secondary outcomes were: LBW infants (six studies) [32 41 42 47 48 51], premature birth (two studies) (birth occurring before 37 weeks gestation) [42 48], prenatal death (three studies) (stillbirths and deaths in the first week of life) [32 44 52], life years (two studies), [47 54], and QALYs (one study). [34] When smoking status was used as an outcome in trials, this was biochemically validated in eight studies. [32-34 39 45 47 50 51] Amongst studies using QALYs, for mothers, one study awarded QALY gains using previously published estimates of QALY gains for quitters [47], a second study awarded QALYs on the basis of the mothers smoking behaviour both during and after pregnancy [34], while a two studies calculated QALYs for the mother taking into account whether the mother smoked post pregnancy and suffered from coronary heart disease, chronic obstructive pulmonary disorder, myocardial infarction, lung cancer, or stroke. [52 53] In addition, one decision analytic model also included QALY losses associated ectopic pregnancy, spontaneous abortion, and pre-eclampsia. [53] For studies including infants, one study used previously published QALY estimates adjusting for the higher mortality rate amongst children born to smoking women [52], while a second awarded QALY losses for birth weight below 2500 grams, otitis media, and asthma. [53]

Deterministic sensitivity analyses were used to investigate the impact of assumptions made within the study on the results of the economic evaluation in 10 studies, [34 39 43-45 47 48 50-52]; the most frequently- varied parameters were intervention effectiveness between high and low quit rates [39 43 44 47 48 51], intervention cost between high and low cost [39 44 45 47 50-52], and background quit rate between high and low rates. [43 48] Four studies used robust statistical techniques in probabilistic sensitivity analyses. [32-34 53]

Quality of Health Economic Studies (QHES) assessment

Table 3 summarises QHES assessment results. Six studies attained a score greater than 75 indicating high quality [32-34 47 48 53], six were deemed of fair quality [40-44 52], and six poor. [39 45 46 49-51] The median score was 58, with a range from 33 to 87, and an inter-quartile range of 38. Areas where studies seemed to perform poorly were: performing a robust analysis of uncertainty (Q5, four studies), inclusion of all major short- and long-term maternal and foetal outcomes (Q10, no studies), and incorporation of a time horizon that included both the effects within-pregnancy and lifetime for both the mother and infant (Q8, one study).

Table 3: Results of the QHES assessment

Author	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Total
Ayadi	2006	X	X							X			X			X		35
Cooper	2014	X	X	X	X	X	X	X		X		X	X	X	X	X	X	87
Dornelas	2006	X		X			X	X		X		X	X	X		X	X	67
Ershoff	1983	X					X	X		X		X	X	X		X	X	59
Ershoff	1990	X	X	X			X	X		X		X	X	X		X	X	71
Hueston	1994	X					X	X				X	X	X	X	X	X	57
Mallender	2013	X		X		X	X	X	X	X		X	X	X	X	X		86
Marks	1990	X		X				X		X		X	X		X	X		57
Parker	2007		X					X		X		X			X		X	33
Pollack	2001	X						X				X			X	X	X	36
Ruger	2008	X	X	X	X		X	X		X		X	X	X	X	X	X	78
Shipp	1992	X	X	X			X	X		X		X	X	X	X	X	X	77
Tappin	2014	X	X	X	X	X	X	X		X		X	X	X	X	X	X	87
Taylor	2009	X					X	X		X		X	X	X		X		56
Thorsen	2004	X						X		X					X	X	X	37
Ussher	2014	X	X	X	X	X	X	X		X		X	X	X	X	X	X	87
Windsor	1988	X						X		X		X				X		35
Windsor	1993	X		X						X		X	X			X	X	49
Frequency		17	8	10	4	4	11	16	1	16	0	16	14	11	11	17	13	
Percentage		94%	44%	56%	22%	22%	61%	89%	6%	89%	0%	89%	78%	61%	61%	94%	72%	

X2= yes on QHES

Findings of studies with primary data collection

10 studies reported the primary collection of cost and effectiveness data [32-34 40-42 45 47 50 51], with all except one study identified cessation interventions during pregnancy as being cost-effective. [47] One UK randomised controlled trial (RCT) reported that the intervention was dominant over usual care (dominance occurs when one intervention costs less and is more effective than another). [33] Other UK RCTs found the incremental cost per additional quitter was £4,926 for NRT [32], and £1,127 for financial incentives. [34] One RCT extended the within-trial results to lifetime horizon for the mother using a previously developed model [55], and estimated an incremental cost per additional QALY of £482 for financial incentives. [34] The impact of uncertainty was explored in all three UK RCTs. For NRT, the majority of the bootstrapping iterations laid within the north east quadrant, suggesting that NRT was likely to be more effective but more costly than the comparator intervention consisting of placebo patches and behavioural support. [32] The probability of financial incentives being cost-effective compared to usual care at £20,000-£30,000 per QALY was 70% [34], while for physical activity the probability was approximately 75%. [33]

Amongst US studies, one RCT reported that using a counselling intervention provided no additional benefit in QALYs and was therefore dominated by usual care. [47] However, other studies found cost-benefit ratios estimated from 2:1[41] for self-help materials to 2.8:1[42] for counselling, though one study found the cost-benefit ratio to be between USD 1:17.93 to USD 1:45.83 for combined self-help materials and counselling. [51] Another study found an effectiveness to cost ratio of USD 1:84. [45] The incremental cost per quitter was reported as USD 298.76 for a counselling intervention [40]; while one study found that for two different self-help material interventions the incremental cost per quitter was USD 50.93 and USD 118.83. [50]

To allow comparison between these studies, the incremental cost was inflated to 2014 UK pound sterling prices. UK costs were inflated using the Hospital & Community Health Services Pay and Prices Index [56], while US costs were inflated to 2014 prices using the Department of Labor's Consumer Price Index Calculator [57], and converted to UK pound sterling using the exchange rate of USD1=GBP0.677173 (correct as of April 2015). In addition

to the incremental cost per additional quitter, an incremental cost per additional quality adjusted life year (QALY) was calculated. This was done by assuming a QALY gain of 1.94 which was chosen from previous work, based on the mean age of mothers across the included studies ranging from 24 years to 28 years. [58 59] The results of this analysis can be found in Table 4.

Table 4: Studies with evaluations informed by primary data collection as grouped by quality as judged by the QHES

Study	Intervention	Comparator	Incremental cost (£)	Incremental quit rate	Incremental cost per additional quitter (£)	Incremental cost per additional QALY (£)
Studies judged high quality on QHES (≥75)						
Cooper 2014	NRT with behavioural support	Placebo with behavioural support	98.21†	1.8%	5,456.34†	2,812.55†
Tappin 2015	Financial incentives with standard NHS care*	Standard NHS care*	157.36‡	14.0%	1,124.00‡	579.38‡
Ussher 2014	Physical activity with standard NHS care*	Standard NHS care*	-35.39	1.3%	DOMINANT	DOMINANT
Ruger 2008	Counselling + self-help materials	Brief advice and self-help materials	304.04	-1.6%	DOMINATED	DOMINATED
Studies judged fair quality on QHES (50-74)						
Ershoff 1990	Self-help materials	Self-help materials	16.58	13.6%	121.94	62.86
Dornelas 2006	Counselling	Brief advice with self-help materials	50.23	18.7%	268.62	138.47
Ershoff 1983	Counselling	Smoking cessation program (not defined)	149.69	11.6%	1,290.42	665.17
Studies judged poor quality on QHES (≤49)						
Windsor 1993	Counselling + self-help materials	Self-help materials	4.99	5.8%	86.05	44.35
Windsor 1988a‡‡	Self-help materials	Brief advice	7.12	4.0%	178.10	91.80
Windsor 1988b‡‡	Self-help materials	Brief advice	7.12	12.0%	59.37	30.60
Parker 2007	Counselling	No intervention	2,357.40	13.4%	17,592.55	9,068.32

* = Standard NHS care involves face-to-face counselling, telephone support, and up to 12 weeks of NRT

†= 95% CI Inc cost -£214.48 to £410.92, 95% CI ICER per quitter -£11,915.50 to £22,828.78, 95% CI ICER per QALY -£6,142.01 to £11,767.41

‡= 95% CI Inc cost £155 to £162, 95% CI ICER per quitter £1,107.14 to £1,157.14, 95% CI ICER per QALY £570.69 to £596.47

‡‡=Windsor 1988 reports two different self-help material interventions versus brief advice, and thus both interventions have been reported separately

Findings from other included studies

Eight studies used previous literature estimates to inform evaluations, with three being evaluations alongside observational studies with assumed quit rates and intervention costs [39 46 49]; five studies were modelling-based. [43 44 48 52 53] Two observational studies found that cessation interventions would generate greater cost savings compared to the cost required to deliver the intervention. Ayadi et al reported that an intervention costing USD 24 per person, if applied to the US population, would generate USD 8 million net saving in healthcare costs, a ratio of approximately 1:333,333. [39] Thorsen et al reported savings of USD 137,592 for an intervention costing USD 15,366 given to low income women in the US, a ratio of approximately 1:9. [49] One observational study conducted by Pollack et al found that a cessation intervention costing USD 45 per person would avert 108 SIDs if given to all pregnant smokers in the US, suggesting that the cessation service would cost USD 210,500 per SID averted. [46]

Three modelling studies were also conducted in the US, and reported favourable cost-saving estimates. Marks et al reported that taking into account the long-term costs averted, the ratio of cost savings to intervention cost was 1:3.26. [44] Hueston et al estimated that cessation interventions were cost-effective if the intervention costed USD 80 or less in 1989 prices (USD 152.73 in 2014 prices) and achieved a 18% quit rate [43], while Shipp et al estimated that an intervention would be cost-neutral if the cost of delivering the intervention in 1989 prices (2014 prices) was USD 32 (USD 61.09) or lower. [48] Using the same exchange rate USD1=GBP0.677173 (correct as of April 2015), the values in UK 2014 prices were £103.42 and £41.37 respectively.

Using a model constructed for informing the National Institute of Health and Care Excellence (NICE) in the UK, Taylor estimated that rewards (interventions where the participant received a financial or non-financial reward for meeting certain criteria) and 'other interventions' (not cognitive behavioural therapies (CBT), financial, or pharmacological interventions) were dominant over usual care; however other cessation interventions had favourable incremental cost-effectiveness ratios (a ratio of the difference in cost over the difference in effectiveness), assessed as £4,005 per additional QALY for CBT,

£2,253 per additional QALY for pharmacotherapies, £1,992 per additional QALY for feedback, and £2,253 per additional QALY for stages of change. [52] In another model constructed for NICE to inform guidance on secondary care interventions, Mallender et al reported that even considering short-term outcomes up to three years post-intervention, behavioural interventions appeared to be cost-effective with incremental cost-effectiveness ratios of £5,445 and £1,331 per additional QALY for high and low intensity, while incentives were less cost-effective with incremental cost-effectiveness ratios of £41,088 and £60,409 per additional QALY for conditional and non-conditional incentives. [53] However, the incremental cost-effectiveness ratios decreased as the perspective was increased to include the lifetime for both the mother and her infant, and reported that all the interventions modelled achieved a 100% probability of cost-effectiveness by £31,000 per additional QALY in the lifetime analysis.

Discussion

This review found 18 studies which included economic evaluations of cessation interventions delivered during pregnancy, however only six of these (33%) were judged as high quality. 17 studies identified within-pregnancy interventions as being cost-effective, with only one trial reporting that usual care was better than the experimental intervention. [47] The current evaluations were generally well described, utilised appropriate health outcomes and drew realistic conclusions based upon their results. Conversely, aspects where the analyses were in deficit included consideration of all major and relevant foetal and maternal health outcomes, use of an appropriate time horizon, and controlling for uncertainty using statically robust methods.

A limitation of this review is that the QHES is a subjective instrument. This was highlighted by the need for discussion among reviewers to resolve occasional disagreements about how some QHES items related to studies. However, the same issue applies to other checklists and therefore this is likely to have been a problem with any quality checklist utilised. Secondly, there were occasions where the reviewers felt QHES items were difficult to completely address; hence rewarding partial achievement rather than all or none of the

available points may have been more appropriate. For example, for QHES question three it might have been appropriate to score in a graded fashion with points awarded being dependant on the different types of study design (e.g. eight points for information from systematic review, seven for information from clinical trial). This could have resulted in the points score calculated for each study better reflecting the overall quality of the methods used, potentially providing a more meaningful comparison. Finally, despite being a good measure of internal validity, the QHES does not measure the external validity. Therefore this review is unable to capture whether the results of the included studies could be generalised to the population, consequently a meaningful comparison across all the studies may not be possible or appropriate. Nevertheless, the reviewers believe that the use of QHES is appropriate to identify, across studies, those aspects of economic evaluations which might require development. Another consideration is that although the review has included several unpublished studies which we identified from published trial protocols, there may be other unpublished studies which have not been included but are relevant to the review; hence this review may not have included all the potential literature.

This review also has three important strengths. The broad search strategy has allowed the review to identify the majority of the literature published, and it is unlikely that an evaluation has escaped being identified, while also updating the previous review. [17] Therefore, this review is the most comprehensive in this subject to date. Secondly, the use of the QHES has allowed a systematic identification of the shortcomings in the published evaluations. The important impact of identifying the shortcomings of the current literature is that the review demonstrates that the included studies have several important omissions and analytical limitations which future evaluations would need to remedy for more accurate estimation of the cost-effectiveness of within-pregnancy cessation interventions. Additionally, this is the first review that has conducted a qualitative synthesis on all cessation interventions that have been evaluated as part of clinical trials. This allows the comparison of different within-pregnancy cessation interventions, which is novel in this topic area, and hence permits the decision as to which interventions appear to be the most value for money.

We highlighted several limitations with the economic evaluations in which we identified in the literature. Most studies focused on a within-pregnancy time horizon, with only four studies considering the impacts of smoking during pregnancy on longer term outcomes [34 47 52 53]. However, it is well-established that smoking is associated with serious morbidities that can occur later in life [3], as well as health issues for the infant during its childhood (e.g. respiratory disease). [60] Therefore, to determine the cost-effectiveness of smoking cessation during pregnancy, the time horizon must not only capture within-pregnancy impacts, but also impacts over the lifetime, for both mother and infant. A further issue is that all evaluations omit one or more of the major morbidities which are caused by smoking in pregnancy. Most studies omitted maternal co-morbidities associated with smoking and pregnancy, e.g. placental abruption, placenta previa, pre-eclampsia. [4] These can all lead to severe complications during pregnancy, and in a worst case scenario, death to the infant, the mother, or both. However, many studies included some adverse, smoking-related birth outcomes and infant morbidities (e.g. low birth weight, premature birth, stillbirth), but rarely included more than one-condition and didn't consider any longer term impacts. Some studies attempted to capture the healthcare cost savings for adverse birth outcomes avoided from cessation [39 41-44 46 49 51], but only one included the impact of low birth weight and asthma on the health of the child across their lifetime; yet this study excluded premature birth. [53]

Another limitation of the current literature appears to be a general failure across studies to consider the impact of relapse to smoking after pregnancy; only four studies attempted to allow for this, and there was considerable variation in relapse rates applied within these. [34 47 52 53] Relapse is important since the mother's health risks from smoking increases with relapse, as does the infant's exposure to second-hand smoke. [61 62] Additionally, recent work suggests that if the mother smokes, an infant is over twice as likely to become an adult smoker [63], potentially exposing him or her to the associated lifetime adult health risks. Hence, by not including a rate of relapse to smoking after childbirth, most economic models are overestimating the number of mothers who remain abstinent after pregnancy, potentially overemphasizing the benefits of smoking cessation.

One final consideration is the small number of studies which robustly control for uncertainty, with only the four most recently completed incorporating statistically robust techniques. [32-34 53] Controlling for uncertainty appropriately is important since it can demonstrate the level of confidence that the decision resulting from the evaluation is the correct one. Whilst in the past one- and two-way deterministic sensitivity analyses have been considered appropriate for gauging the impact of uncertainty, it is now deemed better to control for all parameter uncertainty through the use of probabilistic sensitivity analysis. [64] By not controlling for uncertainty, decisions made on cessation interventions could be incorrect, leading to a cost in benefits forgone. The present literature does not allow a reviewer to determine how confident they are that cessation interventions are cost-effective.

Despite the limitations, included studies suggest that cessation interventions may generally be cost-effective, with only one study out of eighteen not supporting that conclusion. [47] From the within-trial evaluations identified, there is evidence that cessation interventions involving physical activity may offer most value for money because they are dominant (saves money and is more effective), however this was only based on the results of one study, which also demonstrates that there is a degree of uncertainty in the results. [33] However, both the incremental cost per additional quitter and incremental cost per additional quality adjusted life year (QALY) were relatively low for all other interventions except motivational interviewing, the largest being £17,592.55 per additional quitter (£9,068.22 per additional QALY). [45] This was further supported by the evaluations based on models which either returned very favourable cost-offset ratios for the US based studies and the incremental cost per additional QALY ratios in UK based models, with one study suggesting that all interventions achieved a 100% probability of cost-effectiveness at a willingness to pay of £31,000 per QALY. [53] Cessation interventions in non-pregnant populations have often been found to be very cost-effective [16], and this review would suggest that cessation interventions within-pregnancy continue to meet this criteria. However, in the four studies that utilised a probabilistic sensitivity analysis, there was evidence of uncertainty which may warrant further investigation, and could impact on the estimated cost-effectiveness of cessation interventions. Therefore, it would seem logical that policy makers should continue to fund cessation interventions for pregnant women as

current evidence suggest that they offer value for money, however there is some uncertainty in the results of which the policy maker might wish to be aware.

Conclusions

This review demonstrates that although smoking during pregnancy is an important public health issue, there are relatively few high quality economic evaluations demonstrating the cost-effectiveness of cessation interventions, and many of these have methodological shortcomings. Although the majority of included studies suggested that within-pregnancy cessation interventions appeared to be cost-effective, the quality of evidence tended to be poor. To become more comprehensive and to estimate cost-effectiveness more accurately, future economic evaluations of smoking cessation in pregnancy should investigate uncertainty more robustly, use better estimates for the postpartum relapse, extend beyond a within-pregnancy time horizon, and include the major morbidities for both the mother and her infant for within-pregnancy and beyond.

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Declaration of completing interests

We have read and understood BMJ policy on declaration of interests and declare the following interests: Dr. Coleman reports personal fees from Pierre Fabre Laboratories,

France, outside the submitted work; Dr Jones, Dr Lewis, and Dr Parrott have nothing to declare.

Details of contributors

MJ, SL, SP, and TC were involved in the development of the research question. MJ performed the electronic searches and initial screening by title and abstract. MJ, SL, and TC and were responsible reviewing, data extracting identified studies, and applying the QHES checklist. MJ was responsible for conducting the qualitative review. MJ, SL, SP, and TC all contributed to the drafting of the final manuscript.

Ethical approval

Ethics approval was not sought as the study did not involve any direct contact with patients or any patient involvement.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing

No additional data available.

Figure Legends

Figure 1: Review PRISMA diagram

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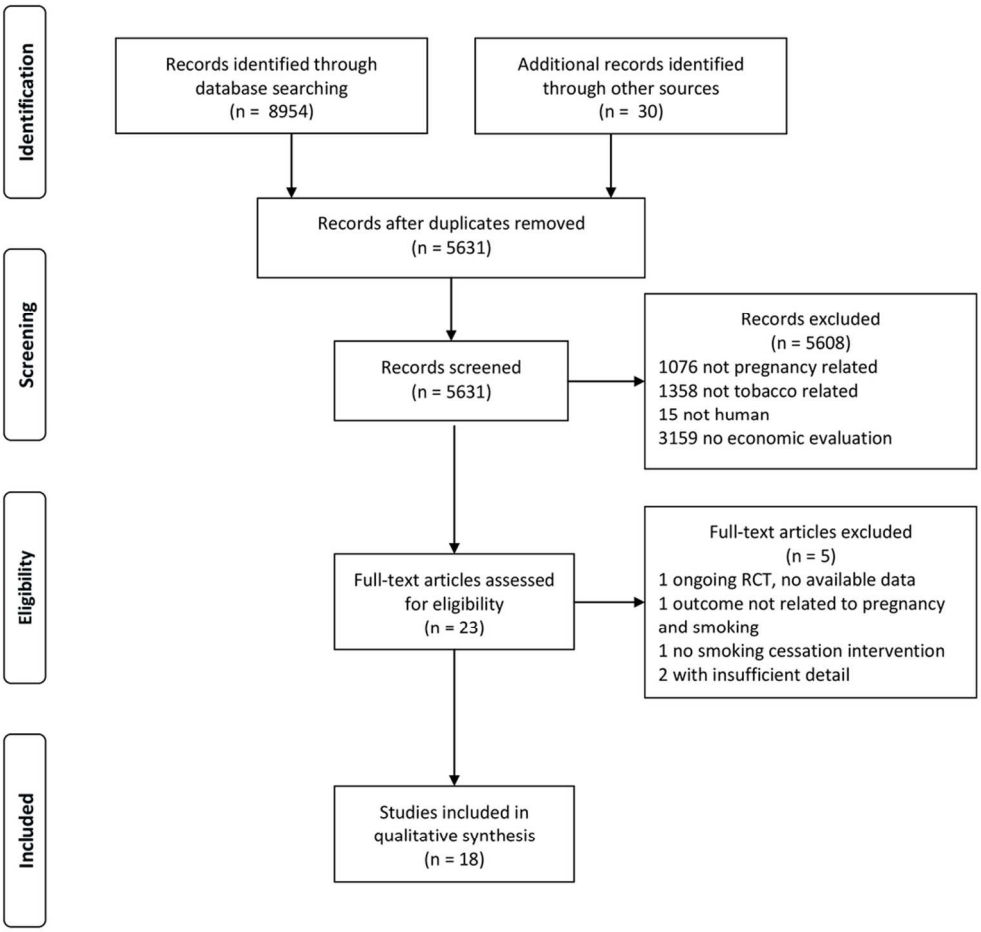

Figure 1: Review PRISMA diagram
46x44mm (600 x 600 DPI)

SUPPLEMENTARY FILE 1: ELECTRONIC SEARCH OF MEDLINE DATABASE

Date of search: 7th August 2014

Search conducted 1946 to July Week 5 2014

Search number	Search terms	Results
1	exp Smoking/	123,716
2	exp Smoking Cessation/	20,581
3	exp Recurrence/	161,774
4	relapse.mp.	76,794
5	relapse prevention.mp.	1,966
6	exp Tobacco/	23,575
7	1 or 2 or 3 or 4 or 5 or 6	366,856
8	exp Pregnant Women/	5,619
9	exp Pregnancy/	720,105
10	exp Prenatal Care/	20,582
11	antenatal.mp.	21,928
12	prenatal.mp.	126,429
13	pregnan*.mp.	774,991
14	exp Fetus/	138,059
15	foetus.mp.	6,248
16	fetal.mp.	291,319
17	foetal.mp.	14,594
18	exp Infant, Newborn/	502,370
19	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	1,275,951
20	exp "Costs and Cost Analysis"/	183,765
21	exp Cost-Benefit Analysis/	61,091
22	cost effectiveness.mp.	33,109
23	cost-effectiveness.mp.	33,109
24	cost benefit.mp.	64,643
25	cost utility.mp.	2,315
26	exp Economics/	497,217
27	economic evaluation.mp.	4,874
28	economic.mp.	141,170
29	exp Quality-Adjusted Life Years/	7,211
30	QALY.mp.	4,032
31	quality adjusted life year.mp.	2,689
32	Quality-adjusted life year.mp.	2,689
33	exp "Quality of Life"/	120,745
34	quality of life.mp.	185,735
35	cost per life year.mp.	538
36	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	748,896
37	7 and 19 and 36	764
38	limit 37 to (english language and humans and yr="2011 - Current")	135

SUPPLEMENTARY FILE 2: THE QUALITY OF HEALTH ECONOMIC STUDIES INSTRUMENT

	Questions	Points	Yes	No
1	Was the study objective presented in a clear, specific, and measurable manner?	7		
2	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4		
3	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial - best, expert opinion - worst)?	8		
4	If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study?	1		
5	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9		
6	Was incremental analysis performed between alternatives for resources and costs?	6		
7	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5		
8	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7		
9	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8		
10	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term, and negative outcomes?	6		
11	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7		
12	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8		
13	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7		
14	Did the author(s) explicitly discuss direction and magnitude of potential biases?	6		
15	Were the conclusions/recommendations of the study justified and based on the study results?	8		
16	Was there a statement disclosing the source of funding for the study?	3		
	Total Points	100		

Reference:
Ofman JJ, Sullivan SD, Neumann PJ, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. J Manag Care Pharm. 2003;9(1):53-61.

Note: The authors added specific criteria to particular questions on the Quality of Health Economic Studies checklist. For points to be awarded to a particular question, these extra criteria had to be met in full. These additional criteria were:

- Q5: *How was uncertainty handled?* –Uncertainty required investigating using robust statistical techniques; for within-trial evaluations, this would be by non-parametric bootstrapping, and for modelling evaluations by probabilistic sensitivity analyses. One- and two-way sensitivity analyses were not deemed to capture uncertainty robustly enough for points to be awarded.

- Q8: *Did the time horizon allow for all important outcomes?* – Smoking in pregnancy impacts on the health of mothers and infants both within-pregnancy and across their lifetimes. For points to be awarded, studies had to have included a within-pregnancy and lifetime analysis horizon for both mother and infant.

- Q10: *Were the major short-term, long-term and negative outcomes included?* – A separate scoping review conducted by the research team identified that smoking in pregnancy is potentially causally associated with nine conditions. If any of the following conditions was omitted from the evaluation, no points were awarded:
    - Placenta previa
    - Placental abruption
    - Ectopic pregnancy
    - Pre-eclampsia
    - Pre-term birth
    - Miscarriage and stillbirth
    - Sudden infant death syndrome (SIDS)
    - Low birth weight
    - Respiratory illness

SUPPLEMENTARY FILE 3: CHARACTERISTICS OF INCLUDED STUDIES: TYPE OF STUDY, INTERVENTIONS, OUTCOMES, AND COSTS

Author/ Year	Type of study	Intervention / comparator	Primary / secondary outcomes	Characteristics of cost data
Ayadi 2006 **[34]**	Observational with hypothetical modelling	5As intervention in three different settings; clinical trial, quit line, and rural managed care organisation / assumed baseline quit if 14%	Assumed quit rate of intervention 30% – 70% versus 14%	Intervention micro-costing in different settings; neonatal care costs for infants of mothers who smoke estimated from CDC software (SAMMEC)
Cooper 2014 **[27]**	Within-trial analysis alongside RCT	NRT with behavioural support / placebo patches with behavioural support	Sustained biochemically validated abstinence between quit date and end of pregnancy / Self-reported abstinence at six months and two years after delivery; infant outcomes included stillbirth, miscarriage, birth weight, gestation age at birth; EQ-5D scores at six months postpartum	Micro-costing of control and intervention groups, including salary, patches and biochemical validation costs; weighted average NHS reference costs used for HRG data; costs reported for 2009/10 financial year

Dornelas 2006 **[35]**	Within-trial analysis alongside RCT	90 minute psychotherapy session at clinic followed by bi-monthly telephone calls with mental health counsellor / Standard smoking cessation treatment guidelines involving brief advice with self-help materials	Biochemically validated seven-day point prevalence at end of pregnancy and six months postpartum	Cost of training, counselling time, telephone time, clerical staff
Ershoff 1983 **[37]**	Within-trial analysis alongside non-randomised trial	Two 45 minute nutrition counselling sessions. Eight week program with home-correspondence. Three telephone calls with reinforcement message / Standard prenatal care from two sources – random sample who attended in four months before program and random sample who attended maxi-care in different area, which involved a group based smoking cessation program (not described) which women could subscribe to	Self-reported abstinence at two months postpartum / Nutrition behaviour; complications during pregnancy (toxaemia, infection, hypertension, weight gain); infant birth weight; Apgar scores; abnormalities	In-patient claim forms, cost of hospital stay, staff salaries, program development, implementation costs, overheads
Ershoff 1990 **[36]**	Within-trial analysis alongside non-randomised trial	Self-help intervention, series of booklets / usual care using self-help materials	Biochemically validated point prevalence at end of pregnancy / birth weight and low birth categories; intra-uterine growth restriction; pre-term birth	Overhead, time, materials, postage, health plans costs from computerized claims system, charges to health plan, charges from hospital based providers

Hueston 1994 **[38]**	Decision analytic model	Hypothetical intervention / hypothetical intervention with assumed level of effectiveness	Intervention quit rate of 3% - 29% at end of pregnancy versus. background quit rate of 6%, 15% and 37% / rates of LBW amongst smokers estimated from national cohort	Costs of healthcare for LBW infants from literature,
Mallender 2013 **[48]**	Decision analytic model	Interventions come from established literature. Situations modelled were: High intensity versus low intensity behavioural support interventions High intensity behavioural support versus usual care Conditional incentives versus non-conditional incentives	QALYs	Costs for interventions taken from literature; literature based costs used for diseases / conditions; costs reported at 2011 prices
Marks 1990 **[39]**	Decision analytic model	Hypothetical smoking cessation programme / normal care with no cessation intervention	LBW and prenatal deaths prevented	Cost of intervention estimated from 2 previous studies in USD. Short and long-term costs averted taken from 1986 office of technology cost assessment of neonatal

				intensive care for LBW infants.
Parker 2007 **[40]**	Within-trial alongside observational (one arm of trial)	Telephone calls providing motivational interviewing / those receiving no calls (either because they chose not to or because contact could not be made). All received a quit kit	Biochemically validated abstinence at end of pregnancy and six months postpartum	Costs of calls using unit price of staff and non-staff – personnel and training time
Pollack 2001 **[41]**	Case-control with hypothetical modelling	Hypothetical intervention using an average of reported success rates cessation programs across various settings / no intervention, no spontaneous quitting	Abstinence rates at end of pregnancy / number of SIDs averted	Cost of typical intervention per participant in 1998 USD
Ruger 2008 **[42]**	Within-trial analysis alongside RCT	Three 1 hour home visits using motivational interviewing (MI) and self-help manuals. MI targeted: 1) impact of smoking on mothers, foetuses, and newborns; 2) evaluated smoking behaviour; 3) increasing self-efficacy for smoking cessation; 4) setting goals to change smoking; 5) feedback about household nicotine levels / Standard prenatal care: 5-minute intervention outlining the harmful effects of smoking during pregnancy and self-help materials	Abstinence and relapse prevention at six-months postpartum / birth weight; post-delivery status; LYs; QALYs	Intervention costs collected within RCT. From literature: Cost savings for neonatal intensive care, chronic medical conditions, and acute conditions during the first year of life, cost savings for maternal healthcare (cardiovascular and lung diseases)
Shipp 1992	Decision analytic model	Hypothetical intervention / no cessation program	Abstinence at end of	Direct medical charges

[43]			pregnancy / number of LBW, premature births, placental abruptions, haemorrhage, placenta previa, pre-eclampsia cases avoided	for maternal care at delivery and hospital care for newborns.
Tappin 2014 **[29]**	Within-trial analysis alongside RCT, extended using a decision analytic model [117]	Standard care from NHS pregnancy stop smoking services plus financial incentives of vouchers up to £400 for women who quit and remained abstinent throughout pregnancy / standard care from NHS pregnancy stop smoking services which involves, face-to-face appointments, support phone calls, and NRT for up to 12 weeks	Biochemically validated abstinence at end of pregnancy, QALYs	Micro-costing using resource use data within-trial, healthcare costs of birth weight and smoking related diseases from NHS Scotland reference costs and established literature sources
Taylor 2009 **[47]**	Decision analytic model	Interventions identified by Cochrane review: cognitive behaviour strategies; stages of change; feedback; rewards; pharmacotherapies; 'other' interventions / no intervention with spontaneous quit rate	QALYs	Lifetime costs from previously developed model; costs in first five years of life per infant admitted to hospital born to smoking and non-smoking mothers, taken from Oxford

Thorsen 2004 **[44]**	Within-trial alongside observational study	The 'First Breath' smoking cessation programme / none given	Abstinence rates at end of pregnancy	Record Linkage study Costs of: Maternal maternity admissions, inpatient neonatal care and medical costs for first month of life.
Ussher 2014 **[28]**	Within-trial alongside RCT	Intervention to encourage physical activity with behavioural support / standard behavioural support provided by NHS Stop Smoking Services	Biochemically validated abstinence at end of pregnancy	Micro-costing of intervention and control groups, including salaries, physical activity equipment, biochemical validation equipment; weighted average NHS reference costs used for HRG data; costs reported for 2012/13 financial year
Windsor 1988 **[45]**	Within-trial alongside RCT	Two intervention groups: Group 1 given standard information and "Freedom From Smoking in 20 Days"; Group 2 given standard information plus "A Pregnant Woman's Self-Help Guide to Quit Smoking". Both groups received "Because You Love Your Baby", and a	Abstinence at end of pregnancy	Salary estimates in USD , cost of manuals

		10 minute presentation at the first prenatal visit / Control group received a non- focused interaction on smoking and pregnancy of 5 minutes during the first prenatal visit		
Windsor 1993 **[46]**	Within-trial alongside RCT	Three components: Self-help materials with brief counselling support with follow-up letters and a buddy system / Brief advice with self-help materials	Abstinence at end of pregnancy / LBWs avoided	Salaries of staff delivering intervention. Costs for the LBW infant at birth, in first year of life and long-term costs

SUPPLEMENTARY FILE 4: CHARACTERISTICS OF INCLUDED STUDIES: TYPE OF EVALUATION, COMPARISON, AND RESULTS

Author/ Year	Type of analysis	Units of comparison	Perspective of analysis / time horizon / discounting (per annum)	Sensitivity analyses	Results
Ayadi 2006 **[34]**	Cost-offset	Neonatal cost savings per quitter	Provider / within-pregnancy / no discounting	Effectiveness (30 to 70%); intervention cost USD 24 to USD 34	Neonatal cost savings of USD 881 per maternal smoker; net savings of up to USD 8 million based on intervention cost of USD 24
Cooper 2014 **[27]**	Cost-effectiveness	Incremental cost per quitter	Societal / within-pregnancy / no discounting	Uncertainty explored by using non-parametric bootstrapping (1000 iterations) on costs and effectiveness; exclusion of multiple births	Mean cost of control £47.75 with a quit rate of 7.6%; mean cost of intervention was £98.31 with a quit rate of 9.4%; ICER £4,926 per quitter (95% CI -£114,128 to £126,747)
Dornelas 2006 **[35]**	Cost-effectiveness	Incremental cost per quitter	Provider (implied) / within-pregnancy and six months postpartum / no discounting	None	Intervention cost USD 56.37 per patient. Incremental quit rate 18.7 (28.3 – 9.6). Incremental cost per quitter USD 298.76
Ershoff 1983 **[37]**	Cost-offset	Benefit-cost ratio	Provider / within-pregnancy and two months postpartum / no discounting	None	Intervention quit rate of 49.1% versus 37.5% of controls; mean birth weight greater in intervention group, 121.34 ounces versus

					113.64; hospital treatment cost differential of USD 183 per delivery; intervention cost USD 93 per patient; benefit cost ratio of 2:1
Ershoff 1990 **[36]**	Cost-offset	Benefit-cost ratio	Provider / within-pregnancy / no discounting	None	Intervention quit rate of 22.2% versus 8.6% for and controls; intervention infants weighed average 57g more; intervention cost per delivery USD 1028 versus USD 1074 in controls; cost savings of USD 5,428; total intervention cost of USD 1,939; benefit: cost ratio of 2.8:1
Hueston 1994 **[38]**	Cost-offset	Intervention cost versus neonatal costs averted	Provider (implied) / within-pregnancy / no discounting	Intervention quit rate between 3% and 29%; spontaneous quit rate of 6%, 15% and 37%	Cessation programmes in pregnancy cost effective for preventing LBW births if they cost $80 or less per participant and achieve quit rates of at least 18% with a spontaneous quit rate of 37%
Mallender 2013 **[48]**	Cost-utility	Incremental cost per QALY	Societal (implied) / up to three years after intervention; lifetime for mother and infant / costs and QALYs at 3.5%	Intervention cost and effectiveness varied in PSA analysis (1000 iterations)	High vs low intensity behavioural: Short term (three years): £5,445, £1,331 Lifetime (mother): £563, £136 Lifetime (mother and infant): £183, £51 High intensity behavioural vs usual care: Short term (three years): £17,827, £157,696, £2,344

					Lifetime (mother): £1,864, £16,515, £244 Lifetime (mother and infant): £528, £4,594, £72 Conditional incentives vs non conditional: Short term (three years): £41,088, £60,409, £43,161 Lifetime (mother): £4,331, £6,441, £4,589 Lifetime (mother and infant): £1,124, £1,488, £1,091 Note: Also ICERs including productivity estimates, not reproduced here
Marks 1990 **[39]**	Cost-offset	Cost per LBW averted; cost per prenatal death averted; benefit-cost ratios for short and long-term hospitalisation costs	Provider (implied) / lifetime / cost of LBW at 4%	Cessation rates from 5% through to 25%; costs programmes varied USD 5-100; percentage of LBW needing neonatal special care 33%-67%; relative risk of LBW 1.5 – 2.5; relative risk of	Cost per LBW birth prevented USD 4000; cost per prenatal death prevented USD 695,452; costs averted in terms of short term hospitalization USD 3.31 for every USD 1 spent on cessation; long-term costs averted USD 3.26 per every USD 1 cessation

				prenatal death 1.1 to 1.4	
Parker 2007 **[40]**	Cost-effectiveness	Cost per quitter	Provider / within-pregnancy / no discounting	Varied costs of intervention per patient from USD 20 to USD 30	Quit rate for no calls 9.6% and 3 calls 23%; effectiveness to cost ratio of 1: USD 84 based on 3 calls
Pollack 2001 **[41]**	Cost-offset	Cost per SIDS averted	Provider (implied) / within-pregnancy / 5% per cost of life year	None	Assumed quit rate of 15%; intervention cost USD 45; averts 108 SIDS deaths; typical cessation service costs USD 210,500 per SID averted and USD 11,000 per discounted life year
Ruger 2008 **[42]**	Cost-effectiveness, cost-utility	Incremental cost per LY; incremental cost per QALY	Societal / lifetime for the mother; first year of life for the infant / costs and QALYs at 3%	Lifetime cost savings due to maternal illness and cost savings due to infant illness in first year of life; varying smoking status data; varying intervention costs; varying QALY weights	For smoking cessation, MI cost more but provided no additional benefit compared to UC, therefore MI was dominated by UC; MI intervention did prevent relapse more effectively than UC with an estimated ICER of USD 628/QALY
Shipp 1992 **[43]**	Cost-offset	Break even cost	Provider / within-pregnancy / no discounting	Prevalence of smoking;	Break even cost of USD 32 per pregnant woman; varying between USD 10 and USD 237 in

				intervention quit rate; spontaneous quit rate; probability of LBW; probability of maternal outcomes	sensitivity analyses
Tappin 2014 **[29]**	Cost-effectiveness, cost-utility	Incremental cost per quitter, incremental cost per QALY	Societal / within-pregnancy and lifetime / discounting costs and QALYs at 3.5%	Inclusion of smoking related disease costs; discount rate of 0%; risk of relapse at three months postpartum varied between 30% and 80%	Intervention quit rate of 23% vs 9% for controls; ICER of £1,127 per quitter; ICER of £482 per QALY for lifetime; 70% of cost-effective at £20,000-30,000 WTP; additional research cost-effective if less than £3.3 million at £30,000 WTP
Taylor 2009 **[47]**	Cost-utility	Incremental cost per QALY	Societal (implied) / lifetime / discounting costs and QALYs at 3.5%	Varying costs of each intervention between £0 and £1,000	For both mother and infant (per QALY), cognitive behaviour therapy ICER £4,005; stages of change ICER £3,033; feedback ICER £1,992; pharmacotherapies ICER £2,253; rewards and other interventions were dominant over control
Thorsen 2004 **[44]**	Cost-offset	Cost of intervention versus cost	Provider (implied) / pregnancy and six months postpartum / no discounting	None	If the intervention costs USD 15,366 it would achieve savings of USD 137,592

		saved			
Ussher 2014 **[28]**	Cost-effectiveness	Incremental cost per quitter	Societal / within-pregnancy / no discounting	Uncertainty explored by using non-parametric bootstrapping on costs and effects; halving and doubling the number of participants per fixed cost; sub-group analysis on age and cigarette dependence	Intervention quit rate of 7.7% versus 6.4% for controls; intervention cost £35 less per patient than control therefore dominant; high degree of uncertainty with CEAC suggesting that the probability of intervention being cost-effective was 0.8 at £50,000 WTP
Windsor 1988 **[45]**	Cost-effectiveness	Incremental cost per quitter	Provider / within-pregnancy / no discounting	Varying effectiveness of guide; varying cost of staff time; varying of intervention cost	Standard information cost per person USD 2.08; quit rate of 2%; ICER USD 104.00; ALA manual cost per person USD 7.13; quit rate of 6%; ICER USD 118.83; pregnant woman's guide cost per person USD 7.13; quit rate of 14%; ICER USD 50.93
Windsor 1993 **[46]**	Cost-offset	Benefit-cost ratio	Provider (implied) / lifetime / no discounting	Cost of intervention varied USD 4.5 - USD 9.0; smoking	LBW costs USD 9,000 to USD 23,000; cost-benefit ratio low estimate is USD 1:17.93 and high estimate is USD 1:45.83; net benefit minus

	attributable risk of LBW varied from 0.2 to 0.15; low and high estimate of smoking attributable LBWs	cost difference is USD 365,728 (low estimate) and USD 768,320 (high estimate)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No protocol available and not registered
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	See supplementary file 4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9 and supplementary file 3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-10

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	None performed
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	See supplementary files 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15-19
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	None performed
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-23
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

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Page 2 of 2

BMJ Open

A SYSTEMATIC CRITICAL REVIEW OF PREVIOUS ECONOMIC EVALUATIONS OF SMOKING CESSATION DURING PREGNANCY

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Secondary Subject Heading:	Smoking and tobacco, Health economics
Keywords:	PRIMARY CARE, HEALTH ECONOMICS, Public health < INFECTIOUS DISEASES, STATISTICS & RESEARCH METHODS, SYSTEMATIC REVIEW

A SYSTEMATIC CRITICAL REVIEW OF PREVIOUS ECONOMIC EVALUATIONS OF SMOKING CESSATION DURING PREGNANCY

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Word count: 5,193 excluding references

Keywords: Smoking, Tobacco, Smoking Cessation, Pregnancy, Economic Evaluation, Cost-Effective.

ABSTRACT

Objective: To identify and critically assess previous economic evaluations of smoking cessation interventions delivered during pregnancy.

Design: Qualitative review of studies with primary data collection or hypothetical modelling. Quality assessed using the Quality of Health Economic Studies checklist.

Data sources: Electronic search of 13 databases including Medline, Econlit, Embase, and PubMed, and manual search of the UK's National Institute of Health and Care Excellence guidelines and US Surgeon General.

Eligibility criteria for selecting studies: All study designs considered if they were published in English, evaluated a cessation intervention delivered to pregnant women during pregnancy, and reported any relevant economic evaluation metric (e.g. cost per quitter, incremental cost per quality adjusted life year).

Results: 18 studies were included. Eight evaluations were conducted alongside clinical trials, four were part of observational studies, five were hypothetical decision-analytic models, and one combined modelling with within-trial analysis. Analyses conducted were cost-offset (nine studies), cost-effectiveness (five studies), cost-utility (two studies), and combined cost-effectiveness and cost-utility (two studies). Six studies each were identified as high, fair, and poor quality respectively. All interventions were demonstrated to be cost-effective except motivational interviewing which was dominated by usual care (one study). Areas where the current literature was limited were the robust investigation of uncertainty, including time horizons that included outcomes beyond the end of pregnancy, including major morbidities for both the mother and her infant, and incorporating better estimates of postpartum relapse.

Conclusions: There are relatively few high quality economic evaluations of cessation interventions during pregnancy. The majority of the literature suggests that such interventions offer value for money; however, there are methodological issues that require addressing, including investigating uncertainty more robustly, utilising better estimates for postpartum relapse, extending beyond a within-pregnancy time horizon, and including major morbidities for both the mother and her infant for within-pregnancy and beyond.

STRENGTHS

- The review implies a broad search strategy of 13 electronic databases, so is likely to have captured most, if not all, of the published literature
- The use of a quality checklist has allowed the systematic identification of the omissions and limitations of the current literature
- The review is the first in this topic area to employ a qualitative synthesis to allow comparison between interventions in common terms

LIMITATIONS

- The quality assessment could be considered as subjective, and therefore is possibly influenced by reviewer bias
- Unpublished trials with published protocols were included, however, other unpublished work was not identified and therefore some relevant evaluations could have been omitted
- The quality assessment tool is a good judge of studies internal validity but cannot measure external validity, and therefore the tool cannot evaluate the generalisability of the results of included studies

A SYSTEMATIC CRITICAL REVIEW OF PREVIOUS ECONOMIC EVALUATIONS OF SMOKING CESSATION DURING PREGNANCY

Introduction

A major global public health issue continues to be tobacco smoking during pregnancy, with a per annum economic burden conservatively estimated to be £23.5 million in the UK [1], and USD110 million in the US. [2] Not only is the mother exposed to the long term risks of smoking [3], but has an increased risk of certain pregnancy complications (e.g. placenta abruption, ectopic pregnancy) [4], while also having serious consequences on her offspring. [5-7] The prevalence of smoking during pregnancy amongst countries is highly varied, with approximately 39% in Spain [8], 23% in Canada [9], to 12-14% in the UK, US, Australia and Germany. [10-13] Suggested explanations for the variation in prevalence are that countries with the higher prevalence also had a greater proportion of mothers with low household income, low education levels, and low health literacy levels. [14 15]

Economic evaluation is an important tool for determining which interventions deliver value for money and is an integral part of the decision-making process for new healthcare technologies. However, using the results from poor quality evaluations are likely to lead to misinformed decisions being made and these could have significant negative impacts on health. While economic evaluations of smoking cessation interventions in the non-pregnant population have demonstrated that cessation is cost-effective (offer value for money in terms of effectiveness in relation to cost) [16], it would appear that similar evidence for within-pregnancy cessation interventions is sparse. A previous review published in 2008 identified only eight studies which involved economic evaluations of cessation interventions delivered to pregnant smokers [17], and suggested that such interventions could be considered potentially cost-effective. However, a number of major studies have since been published, so this review could now be considered out of date. The primary aim of this paper was to identify and critically assess economic evaluations of smoking cessation interventions delivered during pregnancy. The secondary aims of this review were to

identify any omissions and limitations within previous evaluations, and to determine, which, if any, cessation interventions appeared to be cost-effective.

Methodology

A previous review conducted by Ruger et al has already been done on this topic [17], however, this review could be considered to be out of date as the search was last performed up to July 2003. Furthermore, this review only searched two electronic databases (PubMed and National Health Service Economic Evaluation Database (NHS EED)), and therefore the authors felt that the previous review's search may have missed relevant articles. Therefore, the authors concluded to expand the electronic search and search terms to ensure that a maximum sensitivity search was conducted and that all the relevant literature had been identified.

Database selection

13 databases were searched: ASSIA, CINAHL, Econlit, Embase, Maternity and Infant Care, Medline, NHS EED, PsycArticles, PsycINFO, PubMed, Tufts Cost-Effectiveness Analysis Registry, Web of Knowledge, and Web of Science. Additionally, the websites of two governmental health guidance bodies, the UK's National Institute for Health and Care Excellence (NICE) and the US Surgeon General, were searched to identify any evaluations published here as part of guideline development. [18 19] Databases were searched from inception through to August 2014.

Search terms

The search strategy was developed using terms from a previous review and the Cochrane Pregnancy and Childbirth Group. [17 20] Search terms and an example search can be found in Supplementary File 1. For the searches of the NICE and US Surgeon General websites, the terms smoking, smoking cessation, and pregnancy were used.

Inclusion criteria

Studies were included if they were in English, reported a formal economic evaluation, with a direct comparison between costs and outcomes, e.g. 'cost per quitter'.

Population: Women who had experienced a cessation intervention during pregnancy, and/or their infants/children whose mother had been exposed to a cessation intervention during pregnancy, or hypothetical cohorts modelling cessation during pregnancy and/or after this.

Interventions: Any interventions or combination of interventions, both real and hypothetical (an intervention with an assumed quit rate), aimed at encouraging pregnant smokers to quit.

Comparators: Any comparator intervention including no intervention and 'usual care' (UC).

Outcomes: Clinical or economic outcomes considered relevant to the mother and/or child (e.g. smoking status at end of pregnancy, low birth weight (birth weight <2500grams) births (LBW) averted, sudden infant deaths (SIDs) averted, and quality adjusted life years (QALYs)).

Design: Any type (see Table 1 for brief definitions) and design (including within-trial analyses [21] and decision analytic models (mathematical techniques to synthesise information from multiple sources) [22])of economic evaluation were considered.

Table 1: Brief definition of the different types of economic evaluation

Type of economic evaluation	Definition
Cost-minimisation (CMA)	Interventions are assumed to have equal effectiveness and are ranked in terms of cost (low to high)
Cost-effectiveness (CEA)	Effectiveness of interventions are measured in their natural scale (e.g. number of quitters)
Cost-utility (CUA)	Effectiveness of interventions are measured using a generic outcome which embodies health related quality of life which captures a patient's preference (utility) for a particular health state/disease
Cost-benefit (CBA)	Effectiveness of interventions are measured in monetary units
Cost-consequence (CCA)	Costs and consequences of an intervention are reported separately
Cost-offset(COA)	Effectiveness of interventions is measured in healthcare cost savings generated by the intervention

Exclusion criteria

Exclusion criteria were:

- Studies with no economic analyses
- Studies which focused on the delivery of a smoking service and did not report an outcome that demonstrated the effectiveness of an intervention in terms of health benefits to the mother/infant or reduction in the number of women smoking by the end of pregnancy; examples of irrelevant outcomes include number of general practitioners delivering a cessation intervention, number of women accessing a cessation intervention

Identification of papers and data extraction

The lead reviewer screened titles and abstracts of retrieved citations and potentially-relevant texts were retrieved. If a protocol for an ongoing trial was identified, the trial's Principal Investigator was asked to provide economic analysis details. Two reviewers working independently assessed full texts for inclusion, extracted data, and applied a quality assessment checklist. If the two reviewers disagreed on data extraction or quality

assessment, a third was consulted. A manual search was conducted of references from included studies for other potentially-relevant studies. Papers were then identically screened and reviewed. Data extracted from each study is given in Table 2.

Table 2: Data extracted from studies

Area of topic	Data extracted
General study background	Author(s) Publication year Years of study Study question Funding source
Study design	Study type and design Description of intervention Description of comparator Outcomes measured Study assumptions
Evaluation characteristics	Setting (alongside trial versus hypothetical modelling) Type of economic evaluation Modelling assumptions Characteristics of resource estimates (staff time, intervention requirements, hospital use) Characteristics of cost estimates (staff cost, itemised costs, total intervention and comparator costs, incremental cost) Discounting Sensitivity analyses
Study results	Results of evaluation Comparison with other evaluations

Quality assessment

To assess the methodology quality of included studies, the Quality of Health Economic Studies (QHES) checklist was chosen. [23] The QHES has been demonstrated to be a reliable and valid instrument [24-26], and was therefore chosen over other checklists because of its ease of application and the quantitative aspect which would allow comparison across the studies. The QHES contains 16 'yes/no' response questions focusing on the both the methodology of economic evaluations and the broader study, with each question carrying a weighted point score, out of a maximum of 100. The QHES instrument can be found in Supplementary File 2.

When interpreting QHES questions, points were only awarded if the reviewers believed that the most important criteria for the questions were met; if this was the case all points would be awarded. The reviewers did not award fewer points if the study only met some of the question's criteria, the response to each question either being a 'yes' (therefore full points) or a 'no' (no points). For three individual questions on the QHES (questions five, eight, and 10), the authors specified further criteria to be met in addition to those included within the QHES question. Details of these additional criteria can be found alongside the QHES instrument in Supplementary File 2. Although there is no established, standardised interpretation of the QHES score, the following grouping was adopted based upon the work by Spiegel et al [27]: 0-24, extremely poor quality; 25-49, poor quality; 50-74; fair quality; 75-100 high quality.

Data Synthesis

No meta-analysis was specified prior to searches because it was uncertain how studies could be combined; however, the intention was to investigate whether or not this approach would be possible after considering included studies. It was anticipated that the review would adopt a qualitative synthesis, but that a meta-analysis on a subset of data would be investigated if there was potential. The primary objective of the qualitative synthesis would be to discuss the quality of the methods used in identified studies, as determined by the QHES. The results of the assessment from the QHES would be used to demonstrate the strengths and weaknesses of each individual study and of the literature as a whole. To facilitate this QHES scores were allocated to studies as an indicator of overall study quality and qualitatively inspected the components of studies' scores to investigate which aspects of evaluation quality were commonly absent or poor across studies.

The secondary objectives of the qualitative synthesis were to determine any omissions and limitations of previous evaluations, and to investigate what evidence there was of the cost-effectiveness of within-pregnancy cessation interventions. To allow comparison between the various evaluations, we grouped studies into those who included primary data collection (e.g. randomised controlled trials (RCTs)) and those who utilised secondary sources (e.g.

hypothetical decision analytic models). We adopted this approach as we anticipated that there would be very different assumptions made within the studies, with RCTs likely to be focusing on a short time horizon while decision analytic models a much longer one. Furthermore, decision analytic models often assume background quit rates or intervention/comparator costs which may not be comparable with those collected directly from a RCT.

Results

The electronic search (conducted 7th August 2014) identified 8,954 citations, while the manual searches of the UK's National Institute of Health and Care Excellence (NICE) and US Surgeon General's websites returned a further 30 and zero studies respectively. Screening identified 23 potential studies, four of which were ongoing randomised control trials (RCTs) with published protocols. [28-31] Contact with the trials' Principal Investigators returned the data for three RCTs [32-35], while for one, data were unavailable. [30] Four studies were excluded during data extraction. Two were conference abstracts which reported insufficient detail, and attempts to contact the authors failed. [36 37] One included no outcomes related to either cessation or pregnancy [38], and another did not test a cessation intervention. [39] The study PRISMA diagram can be found in Figure 1. 15 studies were published in peer reviewed journals [32 35 40-52], two with NICE guidance [53 54], and one was a unpublished RCTs. [33] As anticipated, it was decided that a meta-analysis was inappropriate due to the extremely heterogeneous nature of included studies.

Characteristics of Studies

Key characteristics of included studies can be found in Supplementary Files 3 and 4. Five studies were conducted in the UK [32 33 35 53 54], and the remainder in the US. There was wide variety in cessation interventions, including: counselling-based (five studies) [40-42 46 50]; self-help materials (two studies) [43 51]; combined self-help materials and counselling (two studies) [48 52]; nicotine replacement therapy (NRT) (one study) [32]; financial incentives (one study) [35]; and physical activity (one study). [33] Two studies investigated

interventions that had previously been described in the literature [53 54], while four studies modelled hypothetical interventions. [44 45 47 49] Comparator interventions amongst studies with primary data collection were self-help materials (four studies) [41 43 48 52]; brief advice (four studies) [41 48 51 52]; and standard UK National Health Service treatment (see Supplementary File 3 for details) (two studies) [33 35]. The following were used by one study each, placebo patches with behavioural support [32]; no intervention [46]; and a cessation program which was not defined. [42] For studies without primary data collection, seven used an assumed or spontaneous background quit rate [40 44 45 49 50 53 55], while one study used multiple comparators which included low intensity behavioural support, non-conditional incentives, and usual care (not defined).[54]

Cost-offset evaluations were used in nine studies [40 42-45 47 49 50 52], cost-effectiveness in five, [32 33 41 46 51], cost-utility in two [53 54], and two studies used both cost-utility and cost-effectiveness. [35 48] Eight evaluations were conducted within clinical trials [32 33 41-43 48 51 52], four were part of observational studies [40 46 47 50], five were decision analytic models [44 45 49 53 54], and one combined a within-trial analysis with a decision analytic model. [35] 12 studies used a healthcare provider perspective (focusing on costs and outcomes directly related to the healthcare provider), while six studies reported a societal perspective (including costs and outcomes both directly and indirectly related to the healthcare provider, patient, and society as a whole). [32 33 35 48 53 54]

Most evaluations adopted a short time horizon, with 12 studies considering only outcomes during pregnancy or immediately afterwards. [32 33 40-44 46 47 49-51] Only six studies reported considering outcomes over the mother's lifetime [35 45 48 52-54], and two studies incorporated outcomes over the infant's lifetime too. [53 54] Cost data was predominantly obtained from micro-costing analyses (costing individual component parts separately to generate a total cost for the intervention) collected within clinical trials, with other cost estimates taken from literature sources. Six studies reported discount rates (a rate representing how much individuals discount future health and cost), with rates of 3% [48], 3.5% [35 53 54], 4% [45], and 5%. [47]

Measures of smoking cessation were the most frequent primary outcomes (12 studies), while two studies used the number of infants born with low birth weight (LBW) (birth weight <2500 grams) prevented [44 45], one used sudden infant deaths (SIDS) (unexplained death within the first year of life) prevented. [47], and three used quality adjusted life years (QALYs) (a life year weighted by the patient's preference for being in a particular health state). [48 53 54] Secondary outcomes were: LBW infants (six studies) [32 42 43 48 49 52], premature birth (two studies) (birth occurring before 37 weeks gestation) [43 49], prenatal death (three studies) (stillbirths and deaths in the first week of life) [32 45 53], life years (two studies), [48 55], and QALYs (one study). [35] When smoking status was used as an outcome in trials, this was biochemically validated in eight studies. [32 33 35 40 46 48 51 52] Amongst studies using QALYs, for mothers, one study awarded QALY gains using previously published estimates of QALY gains for quitters [48], a second study awarded QALYs on the basis of the mothers smoking behaviour both during and after pregnancy [35], while a two studies calculated QALYs for the mother taking into account whether the mother smoked post pregnancy and suffered from coronary heart disease, chronic obstructive pulmonary disorder, myocardial infarction, lung cancer, or stroke. [53 54] In addition, one decision analytic model also included QALY losses associated ectopic pregnancy, spontaneous abortion, and pre-eclampsia. [54] For studies including infants, one study used previously published QALY estimates adjusting for the higher mortality rate amongst children born to smoking women [53], while a second awarded QALY losses for birth weight below 2500 grams, otitis media, and asthma. [54]

Deterministic sensitivity analyses were used to investigate the impact of assumptions made within the study on the results of the economic evaluation in 10 studies, [35 40 44-46 48 49 51-53]; the most frequently- varied parameters were intervention effectiveness between high and low quit rates [40 44 45 48 49 52], intervention cost between high and low cost [40 45 46 48 51-53], and background quit rate between high and low rates. [44 49] Four studies used robust statistical techniques in probabilistic sensitivity analyses. [32 33 35 54]

Quality of Health Economic Studies (QHES) assessment

Table 3 summarises QHES assessment results. Six studies attained a score greater than 75 indicating high quality [32 33 35 48 49 54], six were deemed of fair quality [41-45 53], and six poor. [40 46 47 50-52] The median score was 58, with a range from 33 to 87, and an inter-quartile range of 38. Areas where studies seemed to perform poorly were: performing a robust analysis of uncertainty (Q5, four studies), inclusion of all major short- and long-term maternal and foetal outcomes (Q10, no studies), and incorporation of a time horizon that included both the effects within-pregnancy and lifetime for both the mother and infant (Q8, one study).

Table 3: Results of the QHES assessment

Author	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Total
Ayadi	2006	X	X							X			X			X		35
Cooper	2014	X	X	X	X	X	X	X		X		X	X	X	X	X	X	87
Dornelas	2006	X		X			X	X		X		X	X	X		X	X	67
Ershoff	1983	X					X	X		X		X	X	X		X	X	59
Ershoff	1990	X	X	X			X	X		X		X	X	X		X	X	71
Hueston	1994	X					X	X				X	X	X	X	X	X	57
Mallender	2013	X		X		X	X	X	X	X		X	X	X	X	X		86
Marks	1990	X		X				X		X		X	X		X	X		57
Parker	2007		X					X		X		X			X		X	33
Pollack	2001	X						X				X			X	X	X	36
Ruger	2008	X	X	X	X		X	X		X		X	X	X	X	X	X	78
Shipp	1992	X	X	X			X	X		X		X	X	X	X	X	X	77
Tappin	2015	X	X	X	X	X	X	X		X		X	X	X	X	X	X	87
Taylor	2009	X					X	X		X		X	X	X		X		56
Thorsen	2004	X						X		X					X	X	X	37
Ussher	2014	X	X	X	X	X	X	X		X		X	X	X	X	X	X	87
Windsor	1988	X						X		X		X				X		35
Windsor	1993	X		X						X		X	X			X	X	49
Frequency		17	8	10	4	4	11	16	1	16	0	16	14	11	11	17	13	
Percentage		94%	44%	56%	22%	22%	61%	89%	6%	89%	0%	89%	78%	61%	61%	94%	72%	

X2= yes on QHES

Findings of studies with primary data collection

10 studies reported the primary collection of cost and effectiveness data [32 33 35 41-43 46 48 51 52], with all except one study identified cessation interventions during pregnancy as being cost-effective. [48] One UK randomised controlled trial (RCT) reported that the intervention was dominant over usual care (dominance occurs when one intervention costs less and is more effective than another). [33] Other UK RCTs found the incremental cost per additional quitter was £4,926 for NRT [32], and £1,127 for financial incentives. [35] One RCT extended the within-trial results to lifetime horizon for the mother using a previously developed model [56], and estimated an incremental cost per additional QALY of £482 for financial incentives. [35] The impact of uncertainty was explored in all three UK RCTs. For NRT, the majority of the bootstrapping iterations laid within the north east quadrant, suggesting that NRT was likely to be more effective but more costly than the comparator intervention consisting of placebo patches and behavioural support. [32] The probability of financial incentives being cost-effective compared to usual care at £20,000-£30,000 per QALY was 70% [34], while for physical activity the probability was approximately 75%. [33]

Amongst US studies, one RCT reported that using a counselling intervention provided no additional benefit in QALYs and was therefore dominated by usual care. [48] However, other studies found cost-benefit ratios estimated from 2:1[42] for self-help materials to 2.8:1[43] for counselling, though one study found the cost-benefit ratio to be between USD 1:17.93 to USD 1:45.83 for combined self-help materials and counselling. [52] Another study found an effectiveness to cost ratio of USD 1:84. [46] The incremental cost per quitter was reported as USD 298.76 for a counselling intervention [41]; while one study found that for two different self-help material interventions the incremental cost per quitter was USD 50.93 and USD 118.83. [51]

To allow comparison between these studies, the incremental cost was inflated to 2014 UK pound sterling prices. UK costs were inflated using the Hospital & Community Health Services Pay and Prices Index [57], while US costs were inflated to 2014 prices using the Department of Labor's Consumer Price Index Calculator [58], and converted to UK pound sterling using the exchange rate of USD1=GBP0.677173 (correct as of April 2015). In addition

to the incremental cost per additional quitter, an incremental cost per additional quality adjusted life year (QALY) was calculated. This was done by assuming a QALY gain of 1.94 which was chosen from previous work, based on the mean age of mothers across the included studies ranging from 24 years to 28 years. [59 60] The results of this analysis can be found in Table 4.

Table 4: Studies with evaluations informed by primary data collection as grouped by quality as judged by the QHES

Study	Intervention	Comparator	Incremental cost (£)	Incremental quit rate	Incremental cost per additional quitter (£)	Incremental cost per additional QALY (£)
Studies judged high quality on QHES (≥75)						
Cooper 2014	NRT with behavioural support	Placebo with behavioural support	98.21†	1.8%	5,456.34†	2,812.55†
Tappin 2015	Financial incentives with standard NHS care*	Standard NHS care*	157.36‡	14.0%	1,124.00‡	579.38‡
Ussher 2014	Physical activity with standard NHS care*	Standard NHS care*	-35.39	1.3%	DOMINANT	DOMINANT
Ruger 2008	Counselling + self-help materials	Brief advice and self-help materials	304.04	-1.6%	DOMINATED	DOMINATED
Studies judged fair quality on QHES (50-74)						
Ershoff 1990	Self-help materials	Self-help materials	16.58	13.6%	121.94	62.86
Dornelas 2006	Counselling	Brief advice with self-help materials	50.23	18.7%	268.62	138.47
Ershoff 1983	Counselling	Smoking cessation program (not defined)	149.69	11.6%	1,290.42	665.17
Studies judged poor quality on QHES (≤49)						
Windsor 1993	Counselling + self-help materials	Self-help materials	4.99	5.8%	86.05	44.35
Windsor 1988a‡‡	Self-help materials	Brief advice	7.12	4.0%	178.10	91.80
Windsor 1988b‡‡	Self-help materials	Brief advice	7.12	12.0%	59.37	30.60
Parker 2007	Counselling	No intervention	2,357.40	13.4%	17,592.55	9,068.32

* = Standard NHS care involves face-to-face counselling, telephone support, and up to 12 weeks of NRT

†= 95% CI Inc cost -£214.48 to £410.92, 95% CI ICER per quitter -£11,915.50 to £22,828.78, 95% CI ICER per QALY -£6,142.01 to £11,767.41

‡= 95% CI Inc cost £155 to £162, 95% CI ICER per quitter £1,107.14 to £1,157.14, 95% CI ICER per QALY £570.69 to £596.47

‡‡=Windsor 1988 reports two different self-help material interventions versus brief advice, and thus both interventions have been reported separately

Findings from other included studies

Eight studies used previous literature estimates to inform evaluations, with three being evaluations alongside observational studies with assumed quit rates and intervention costs [40 47 50]; five studies were modelling-based. [44 45 49 53 54] Two observational studies found that cessation interventions would generate greater cost savings compared to the cost required to deliver the intervention. Ayadi et al reported that an intervention costing USD 24 per person, if applied to the US population, would generate USD 8 million net saving in healthcare costs, a ratio of approximately 1:333,333. [40] Thorsen et al reported savings of USD 137,592 for an intervention costing USD 15,366 given to low income women in the US, a ratio of approximately 1:9. [50] One observational study conducted by Pollack et al found that a cessation intervention costing USD 45 per person would avert 108 SIDs if given to all pregnant smokers in the US, suggesting that the cessation service would cost USD 210,500 per SID averted. [47]

Three modelling studies were also conducted in the US, and reported favourable cost-saving estimates. Marks et al reported that taking into account the long-term costs averted, the ratio of cost savings to intervention cost was 1:3.26. [45] Hueston et al estimated that cessation interventions were cost-effective if the intervention costed USD 80 or less in 1989 prices (USD 152.73 in 2014 prices) and achieved a 18% quit rate [44], while Shipp et al estimated that an intervention would be cost-neutral if the cost of delivering the intervention in 1989 prices (2014 prices) was USD 32 (USD 61.09) or lower. [49] Using the same exchange rate USD1=GBP0.677173 (correct as of April 2015), the values in UK 2014 prices were £103.42 and £41.37 respectively.

Using a model constructed for informing the National Institute of Health and Care Excellence (NICE) in the UK, Taylor estimated that rewards (interventions where the participant received a financial or non-financial reward for meeting certain criteria) and 'other interventions' (not cognitive behavioural therapies (CBT), financial, or pharmacological interventions) were dominant over usual care; however other cessation interventions had favourable incremental cost-effectiveness ratios (a ratio of the difference in cost over the difference in effectiveness), assessed as £4,005 per additional QALY for CBT,

£2,253 per additional QALY for pharmacotherapies, £1,992 per additional QALY for feedback, and £2,253 per additional QALY for stages of change. [53] In another model constructed for NICE to inform guidance on secondary care interventions, Mallender et al reported that even considering short-term outcomes up to three years post-intervention, behavioural interventions appeared to be cost-effective with incremental cost-effectiveness ratios of £5,445 and £1,331 per additional QALY for high and low intensity, while incentives were less cost-effective with incremental cost-effectiveness ratios of £41,088 and £60,409 per additional QALY for conditional and non-conditional incentives. [54] However, the incremental cost-effectiveness ratios decreased as the perspective was increased to include the lifetime for both the mother and her infant, and reported that all the interventions modelled achieved a 100% probability of cost-effectiveness by £31,000 per additional QALY in the lifetime analysis.

Discussion

This review found 18 studies which included economic evaluations of cessation interventions delivered during pregnancy, however only six of these (33%) were judged as high quality. 17 studies identified within-pregnancy interventions as being cost-effective, with only one trial reporting that usual care was better than the experimental intervention. [48] The current evaluations were generally well described, utilised appropriate health outcomes and drew realistic conclusions based upon their results. Conversely, aspects where the analyses were in deficit included consideration of all major and relevant foetal and maternal health outcomes, use of an appropriate time horizon, and controlling for uncertainty using statically robust methods.

A limitation of this review is that the QHES is a subjective instrument. This was highlighted by the need for discussion among reviewers to resolve occasional disagreements about how some QHES items related to studies. However, the same issue applies to other checklists and therefore this is likely to have been a problem with any quality checklist utilised. Secondly, there were occasions where the reviewers felt QHES items were difficult to completely address; hence rewarding partial achievement rather than all or none of the

available points may have been more appropriate. For example, for QHES question three it might have been appropriate to score in a graded fashion with points awarded being dependant on the different types of study design (e.g. eight points for information from systematic review, seven for information from clinical trial). This could have resulted in the points score calculated for each study better reflecting the overall quality of the methods used, potentially providing a more meaningful comparison. Finally, despite being a good measure of internal validity, the QHES does not measure the external validity. Therefore this review is unable to capture whether the results of the included studies could be generalised to the population, consequently a meaningful comparison across all the studies may not be possible or appropriate. Nevertheless, the reviewers believe that the use of QHES is appropriate to identify, across studies, those aspects of economic evaluations which might require development. Another consideration is that although the review has included several unpublished studies which we identified from published trial protocols, there may be other unpublished studies which have not been included but are relevant to the review; hence this review may not have included all the potential literature.

This review also has three important strengths. The broad search strategy has allowed the review to identify the majority of the literature published, and it is unlikely that an evaluation has escaped being identified, while also updating the previous review. [17] Therefore, this review is the most comprehensive in this subject to date. Secondly, the use of the QHES has allowed a systematic identification of the shortcomings in the published evaluations. The important impact of identifying the shortcomings of the current literature is that the review demonstrates that the included studies have several important omissions and analytical limitations which future evaluations would need to remedy for more accurate estimation of the cost-effectiveness of within-pregnancy cessation interventions. Additionally, this is the first review that has conducted a qualitative synthesis on all cessation interventions that have been evaluated as part of clinical trials. This allows the comparison of different within-pregnancy cessation interventions, which is novel in this topic area, and hence permits the decision as to which interventions appear to be the most value for money.

We highlighted several limitations with the economic evaluations in which we identified in the literature. Most studies focused on a within-pregnancy time horizon, with only four studies considering the impacts of smoking during pregnancy on longer term outcomes [35 48 53 54]. However, it is well-established that smoking is associated with serious morbidities that can occur later in life [3], as well as health issues for the infant during its childhood (e.g. respiratory disease). [61] Therefore, to determine the cost-effectiveness of smoking cessation during pregnancy, the time horizon must not only capture within-pregnancy impacts, but also impacts over the lifetime, for both mother and infant. A further issue is that all evaluations omit one or more of the major morbidities which are caused by smoking in pregnancy. Most studies omitted maternal co-morbidities associated with smoking and pregnancy, e.g. placental abruption, placenta previa, pre-eclampsia. [4] These can all lead to severe complications during pregnancy, and in a worst case scenario, death to the infant, the mother, or both. However, many studies included some adverse, smoking-related birth outcomes and infant morbidities (e.g. low birth weight, premature birth, stillbirth), but rarely included more than one-condition and didn't consider any longer term impacts. Some studies attempted to capture the healthcare cost savings for adverse birth outcomes avoided from cessation [40 42-45 47 50 52], but only one included the impact of low birth weight and asthma on the health of the child across their lifetime; yet this study excluded premature birth. [54]

Another limitation of the current literature appears to be a general failure across studies to consider the impact of relapse to smoking after pregnancy; only four studies attempted to allow for this, and there was considerable variation in relapse rates applied within these. [35 48 53 54] Relapse is important since the mother's health risks from smoking increases with relapse, as does the infant's exposure to second-hand smoke. [62 63] Additionally, recent work suggests that if the mother smokes, an infant is over twice as likely to become an adult smoker [64], potentially exposing him or her to the associated lifetime adult health risks. Hence, by not including a rate of relapse to smoking after childbirth, most economic models are overestimating the number of mothers who remain abstinent after pregnancy, potentially overemphasizing the benefits of smoking cessation.

One final consideration is the small number of studies which robustly control for uncertainty, with only the four most recently completed incorporating statistically robust techniques. [32 33 35 54] Controlling for uncertainty appropriately is important since it can demonstrate the level of confidence that the decision resulting from the evaluation is the correct one. Whilst in the past one- and two-way deterministic sensitivity analyses have been considered appropriate for gauging the impact of uncertainty, it is now deemed better to control for all parameter uncertainty through the use of probabilistic sensitivity analysis. [65] By not controlling for uncertainty, decisions made on cessation interventions could be incorrect, leading to a cost in benefits forgone. The present literature does not allow a reviewer to determine how confident they are that cessation interventions are cost-effective.

Despite the limitations, included studies suggest that cessation interventions may generally be cost-effective, with only one study out of eighteen not supporting that conclusion. [48] From the within-trial evaluations identified, there is evidence that cessation interventions involving physical activity may offer most value for money because they are dominant (saves money and is more effective), however this was only based on the results of one study, which also demonstrates that there is a degree of uncertainty in the results. [33] However, both the incremental cost per additional quitter and incremental cost per additional quality adjusted life year (QALY) were relatively low for all other interventions except motivational interviewing, the largest being £17,592.55 per additional quitter (£9,068.22 per additional QALY). [46] This was further supported by the evaluations based on models which either returned very favourable cost-offset ratios for the US based studies and the incremental cost per additional QALY ratios in UK based models, with one study suggesting that all interventions achieved a 100% probability of cost-effectiveness at a willingness to pay of £31,000 per QALY. [54] Cessation interventions in non-pregnant populations have often been found to be very cost-effective [16], and this review would suggest that cessation interventions within-pregnancy continue to meet this criteria. However, in the four studies that utilised a probabilistic sensitivity analysis, there was evidence of uncertainty which may warrant further investigation, and could impact on the estimated cost-effectiveness of cessation interventions. Therefore, it would seem logical that policy makers should continue to fund cessation interventions for pregnant women as

current evidence suggest that they offer value for money, however there is some uncertainty in the results of which the policy maker might wish to be aware.

Conclusions

This review demonstrates that although smoking during pregnancy is an important public health issue, there are relatively few high quality economic evaluations demonstrating the cost-effectiveness of cessation interventions, and many of these have methodological shortcomings. Although the majority of included studies suggested that within-pregnancy cessation interventions appeared to be cost-effective, the quality of evidence tended to be poor. To become more comprehensive and to estimate cost-effectiveness more accurately, future economic evaluations of smoking cessation in pregnancy should investigate uncertainty more robustly, use better estimates for the postpartum relapse, extend beyond a within-pregnancy time horizon, and include the major morbidities for both the mother and her infant for within-pregnancy and beyond.

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Declaration of completing interests

We have read and understood BMJ policy on declaration of interests and declare the following interests: Dr. Coleman reports personal fees from Pierre Fabre Laboratories,

France, outside the submitted work; Dr Jones, Dr Lewis, and Dr Parrott have nothing to declare.

Details of contributors

MJ, SL, SP, and TC were involved in the development of the research question. MJ performed the electronic searches and initial screening by title and abstract. MJ, SL, and TC and were responsible reviewing, data extracting identified studies, and applying the QHES checklist. MJ was responsible for conducting the qualitative review. MJ, SL, SP, and TC all contributed to the drafting of the final manuscript.

Ethical approval

Ethics approval was not sought as the study did not involve any direct contact with patients or any patient involvement.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing

No additional data available.

Figure Legends

Figure 1: Review PRISMA diagram

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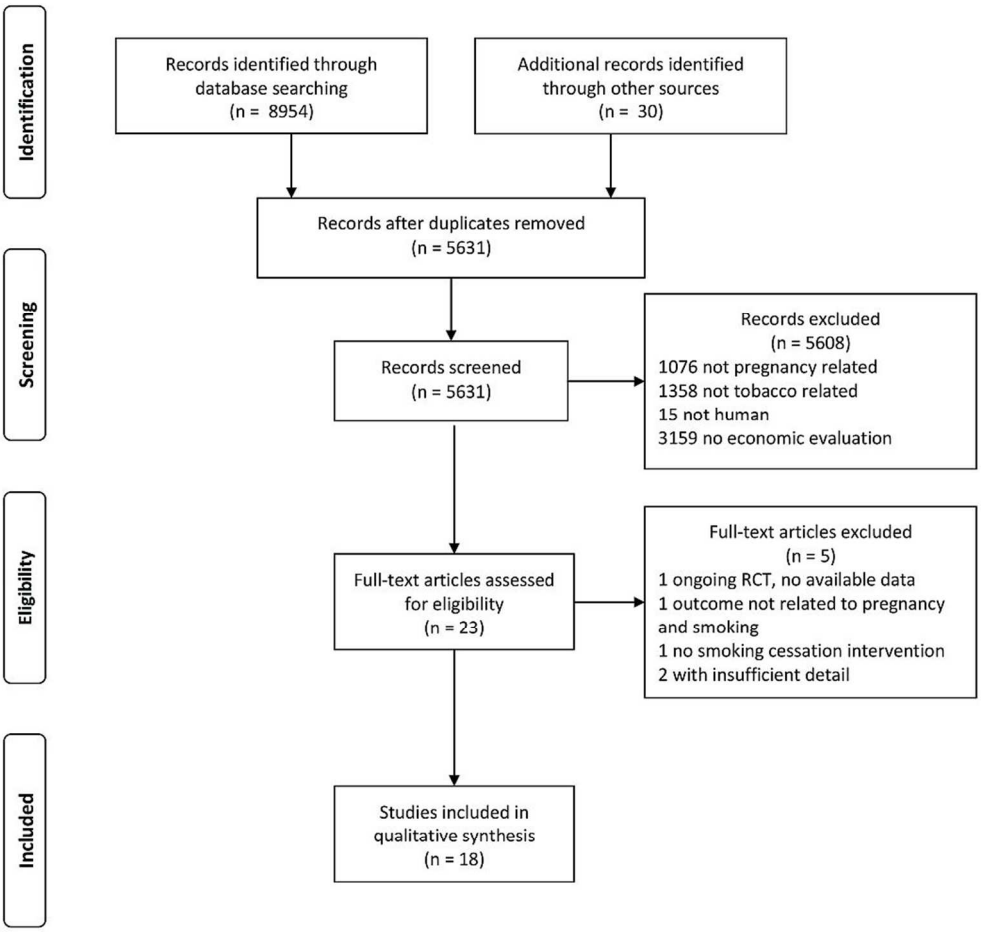

Figure 1: Review PRISMA diagram
90x84mm (300 x 300 DPI)

SUPPLEMENTARY FILE 1: ELECTRONIC SEARCH OF MEDLINE DATABASE

Date of search: 7th August 2014

Search conducted 1946 to July Week 5 2014

Search number	Search terms	Results
1	exp Smoking/	123,716
2	exp Smoking Cessation/	20,581
3	exp Recurrence/	161,774
4	relapse.mp.	76,794
5	relapse prevention.mp.	1,966
6	exp Tobacco/	23,575
7	1 or 2 or 3 or 4 or 5 or 6	366,856
8	exp Pregnant Women/	5,619
9	exp Pregnancy/	720,105
10	exp Prenatal Care/	20,582
11	antenatal.mp.	21,928
12	prenatal.mp.	126,429
13	pregnan*.mp.	774,991
14	exp Fetus/	138,059
15	foetus.mp.	6,248
16	fetal.mp.	291,319
17	foetal.mp.	14,594
18	exp Infant, Newborn/	502,370
19	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	1,275,951
20	exp "Costs and Cost Analysis"/	183,765
21	exp Cost-Benefit Analysis/	61,091
22	cost effectiveness.mp.	33,109
23	cost-effectiveness.mp.	33,109
24	cost benefit.mp.	64,643
25	cost utility.mp.	2,315
26	exp Economics/	497,217
27	economic evaluation.mp.	4,874
28	economic.mp.	141,170
29	exp Quality-Adjusted Life Years/	7,211
30	QALY.mp.	4,032
31	quality adjusted life year.mp.	2,689
32	Quality-adjusted life year.mp.	2,689
33	exp "Quality of Life"/	120,745
34	quality of life.mp.	185,735
35	cost per life year.mp.	538
36	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	748,896
37	7 and 19 and 36	764
38	limit 37 to (english language and humans and yr="2011 - Current")	135

SUPPLEMENTARY FILE 2: THE QUALITY OF HEALTH ECONOMIC STUDIES INSTRUMENT

	Questions	Points	Yes	No
1	Was the study objective presented in a clear, specific, and measurable manner?	7		
2	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4		
3	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial - best, expert opinion - worst)?	8		
4	If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study?	1		
5	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9		
6	Was incremental analysis performed between alternatives for resources and costs?	6		
7	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5		
8	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7		
9	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8		
10	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term, and negative outcomes?	6		
11	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7		
12	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8		
13	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7		
14	Did the author(s) explicitly discuss direction and magnitude of potential biases?	6		
15	Were the conclusions/recommendations of the study justified and based on the study results?	8		
16	Was there a statement disclosing the source of funding for the study?	3		
	Total Points	100		

Reference:
Ofman JJ, Sullivan SD, Neumann PJ, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. J Manag Care Pharm. 2003;9(1):53-61.

Note: The authors added specific criteria to particular questions on the Quality of Health Economic Studies checklist. For points to be awarded to a particular question, these extra criteria had to be met in full. These additional criteria were:

- Q5: *How was uncertainty handled?* –Uncertainty required investigating using robust statistical techniques; for within-trial evaluations, this would be by non-parametric bootstrapping, and for modelling evaluations by probabilistic sensitivity analyses. One- and two-way sensitivity analyses were not deemed to capture uncertainty robustly enough for points to be awarded.

- Q8: *Did the time horizon allow for all important outcomes?* – Smoking in pregnancy impacts on the health of mothers and infants both within-pregnancy and across their lifetimes. For points to be awarded, studies had to have included a within-pregnancy and lifetime analysis horizon for both mother and infant.

- Q10: *Were the major short-term, long-term and negative outcomes included?* – A separate scoping review conducted by the research team identified that smoking in pregnancy is potentially causally associated with nine conditions. If any of the following conditions was omitted from the evaluation, no points were awarded:
    - Placenta previa
    - Placental abruption
    - Ectopic pregnancy
    - Pre-eclampsia
    - Pre-term birth
    - Miscarriage and stillbirth
    - Sudden infant death syndrome (SIDS)
    - Low birth weight
    - Respiratory illness

SUPPLEMENTARY FILE 3: CHARACTERISTICS OF INCLUDED STUDIES: TYPE OF STUDY, INTERVENTIONS, OUTCOMES, AND COSTS

Author/ Year	Type of study	Intervention / comparator	Primary / secondary outcomes	Characteristics of cost data
Ayadi 2006 **[34]**	Observational with hypothetical modelling	5As intervention in three different settings; clinical trial, quit line, and rural managed care organisation / assumed baseline quit if 14%	Assumed quit rate of intervention 30% – 70% versus 14%	Intervention micro-costing in different settings; neonatal care costs for infants of mothers who smoke estimated from CDC software (SAMMEC)
Cooper 2014 **[27]**	Within-trial analysis alongside RCT	NRT with behavioural support / placebo patches with behavioural support	Sustained biochemically validated abstinence between quit date and end of pregnancy / Self-reported abstinence at six months and two years after delivery; infant outcomes included stillbirth, miscarriage, birth weight, gestation age at birth; EQ-5D scores at six months postpartum	Micro-costing of control and intervention groups, including salary, patches and biochemical validation costs; weighted average NHS reference costs used for HRG data; costs reported for 2009/10 financial year

Dornelas 2006 **[35]**	Within-trial analysis alongside RCT	90 minute psychotherapy session at clinic followed by bi-monthly telephone calls with mental health counsellor / Standard smoking cessation treatment guidelines involving brief advice with self-help materials	Biochemically validated seven-day point prevalence at end of pregnancy and six months postpartum	Cost of training, counselling time, telephone time, clerical staff
Ershoff 1983 **[37]**	Within-trial analysis alongside non-randomised trial	Two 45 minute nutrition counselling sessions. Eight week program with home-correspondence. Three telephone calls with reinforcement message / Standard prenatal care from two sources – random sample who attended in four months before program and random sample who attended maxi-care in different area, which involved a group based smoking cessation program (not described) which women could subscribe to	Self-reported abstinence at two months postpartum / Nutrition behaviour; complications during pregnancy (toxaemia, infection, hypertension, weight gain); infant birth weight; Apgar scores; abnormalities	In-patient claim forms, cost of hospital stay, staff salaries, program development, implementation costs, overheads
Ershoff 1990 **[36]**	Within-trial analysis alongside non-randomised trial	Self-help intervention, series of booklets / usual care using self-help materials	Biochemically validated point prevalence at end of pregnancy / birth weight and low birth categories; intra-uterine growth restriction; pre-term birth	Overhead, time, materials, postage, health plans costs from computerized claims system, charges to health plan, charges from hospital based providers

Hueston 1994 **[38]**	Decision analytic model	Hypothetical intervention / hypothetical intervention with assumed level of effectiveness	Intervention quit rate of 3% - 29% at end of pregnancy versus. background quit rate of 6%, 15% and 37% / rates of LBW amongst smokers estimated from national cohort	Costs of healthcare for LBW infants from literature,
Mallender 2013 **[48]**	Decision analytic model	Interventions come from established literature. Situations modelled were: High intensity versus low intensity behavioural support interventions High intensity behavioural support versus usual care Conditional incentives versus non-conditional incentives	QALYs	Costs for interventions taken from literature; literature based costs used for diseases / conditions; costs reported at 2011 prices
Marks 1990 **[39]**	Decision analytic model	Hypothetical smoking cessation programme / normal care with no cessation intervention	LBW and prenatal deaths prevented	Cost of intervention estimated from 2 previous studies in USD. Short and long-term costs averted taken from 1986 office of technology cost assessment of neonatal

				intensive care for LBW infants.
Parker 2007 **[40]**	Within-trial alongside observational (one arm of trial)	Telephone calls providing motivational interviewing / those receiving no calls (either because they chose not to or because contact could not be made). All received a quit kit	Biochemically validated abstinence at end of pregnancy and six months postpartum	Costs of calls using unit price of staff and non-staff – personnel and training time
Pollack 2001 **[41]**	Case-control with hypothetical modelling	Hypothetical intervention using an average of reported success rates cessation programs across various settings / no intervention, no spontaneous quitting	Abstinence rates at end of pregnancy / number of SIDs averted	Cost of typical intervention per participant in 1998 USD
Ruger 2008 **[42]**	Within-trial analysis alongside RCT	Three 1 hour home visits using motivational interviewing (MI) and self-help manuals. MI targeted: 1) impact of smoking on mothers, foetuses, and newborns; 2) evaluated smoking behaviour; 3) increasing self-efficacy for smoking cessation; 4) setting goals to change smoking; 5) feedback about household nicotine levels / Standard prenatal care: 5-minute intervention outlining the harmful effects of smoking during pregnancy and self-help materials	Abstinence and relapse prevention at six-months postpartum / birth weight; post-delivery status; LYs; QALYs	Intervention costs collected within RCT. From literature: Cost savings for neonatal intensive care, chronic medical conditions, and acute conditions during the first year of life, cost savings for maternal healthcare (cardiovascular and lung diseases)
Shipp 1992	Decision analytic model	Hypothetical intervention / no cessation program	Abstinence at end of	Direct medical charges

[43]			pregnancy / number of LBW, premature births, placental abruptions, haemorrhage, placenta previa, pre-eclampsia cases avoided	for maternal care at delivery and hospital care for newborns.
Tappin 2014 **[29]**	Within-trial analysis alongside RCT, extended using a decision analytic model [117]	Standard care from NHS pregnancy stop smoking services plus financial incentives of vouchers up to £400 for women who quit and remained abstinent throughout pregnancy / standard care from NHS pregnancy stop smoking services which involves, face-to-face appointments, support phone calls, and NRT for up to 12 weeks	Biochemically validated abstinence at end of pregnancy, QALYs	Micro-costing using resource use data within-trial, healthcare costs of birth weight and smoking related diseases from NHS Scotland reference costs and established literature sources
Taylor 2009 **[47]**	Decision analytic model	Interventions identified by Cochrane review: cognitive behaviour strategies; stages of change; feedback; rewards; pharmacotherapies; 'other' interventions / no intervention with spontaneous quit rate	QALYs	Lifetime costs from previously developed model; costs in first five years of life per infant admitted to hospital born to smoking and non-smoking mothers, taken from Oxford

Thorsen 2004 **[44]**	Within-trial alongside observational study	The 'First Breath' smoking cessation programme / none given	Abstinence rates at end of pregnancy	Record Linkage study Costs of: Maternal maternity admissions, inpatient neonatal care and medical costs for first month of life.
Ussher 2014 **[28]**	Within-trial alongside RCT	Intervention to encourage physical activity with behavioural support / standard behavioural support provided by NHS Stop Smoking Services	Biochemically validated abstinence at end of pregnancy	Micro-costing of intervention and control groups, including salaries, physical activity equipment, biochemical validation equipment; weighted average NHS reference costs used for HRG data; costs reported for 2012/13 financial year
Windsor 1988 **[45]**	Within-trial alongside RCT	Two intervention groups: Group 1 given standard information and "Freedom From Smoking in 20 Days"; Group 2 given standard information plus "A Pregnant Woman's Self-Help Guide to Quit Smoking". Both groups received "Because You Love Your Baby", and a	Abstinence at end of pregnancy	Salary estimates in USD , cost of manuals

		10 minute presentation at the first prenatal visit / Control group received a non- focused interaction on smoking and pregnancy of 5 minutes during the first prenatal visit		
Windsor 1993 **[46]**	Within-trial alongside RCT	Three components: Self-help materials with brief counselling support with follow-up letters and a buddy system / Brief advice with self-help materials	Abstinence at end of pregnancy / LBWs avoided	Salaries of staff delivering intervention. Costs for the LBW infant at birth, in first year of life and long-term costs

SUPPLEMENTARY FILE 4: CHARACTERISTICS OF INCLUDED STUDIES: TYPE OF EVALUATION, COMPARISON, AND RESULTS

Author/ Year	Type of analysis	Units of comparison	Perspective of analysis / time horizon / discounting (per annum)	Sensitivity analyses	Results
Ayadi 2006 **[34]**	Cost-offset	Neonatal cost savings per quitter	Provider / within-pregnancy / no discounting	Effectiveness (30 to 70%); intervention cost USD 24 to USD 34	Neonatal cost savings of USD 881 per maternal smoker; net savings of up to USD 8 million based on intervention cost of USD 24
Cooper 2014 **[27]**	Cost-effectiveness	Incremental cost per quitter	Societal / within-pregnancy / no discounting	Uncertainty explored by using non-parametric bootstrapping (1000 iterations) on costs and effectiveness; exclusion of multiple births	Mean cost of control £47.75 with a quit rate of 7.6%; mean cost of intervention was £98.31 with a quit rate of 9.4%; ICER £4,926 per quitter (95% CI -£114,128 to £126,747)
Dornelas 2006 **[35]**	Cost-effectiveness	Incremental cost per quitter	Provider (implied) / within-pregnancy and six months postpartum / no discounting	None	Intervention cost USD 56.37 per patient. Incremental quit rate 18.7 (28.3 – 9.6). Incremental cost per quitter USD 298.76
Ershoff 1983 **[37]**	Cost-offset	Benefit-cost ratio	Provider / within-pregnancy and two months postpartum / no discounting	None	Intervention quit rate of 49.1% versus 37.5% of controls; mean birth weight greater in intervention group, 121.34 ounces versus

					113.64; hospital treatment cost differential of USD 183 per delivery; intervention cost USD 93 per patient; benefit cost ratio of 2:1
Ershoff 1990 **[36]**	Cost-offset	Benefit-cost ratio	Provider / within-pregnancy / no discounting	None	Intervention quit rate of 22.2% versus 8.6% for and controls; intervention infants weighed average 57g more; intervention cost per delivery USD 1028 versus USD 1074 in controls; cost savings of USD 5,428; total intervention cost of USD 1,939; benefit: cost ratio of 2.8:1
Hueston 1994 **[38]**	Cost-offset	Intervention cost versus neonatal costs averted	Provider (implied) / within-pregnancy / no discounting	Intervention quit rate between 3% and 29%; spontaneous quit rate of 6%, 15% and 37%	Cessation programmes in pregnancy cost effective for preventing LBW births if they cost $80 or less per participant and achieve quit rates of at least 18% with a spontaneous quit rate of 37%
Mallender 2013 **[48]**	Cost-utility	Incremental cost per QALY	Societal (implied) / up to three years after intervention; lifetime for mother and infant / costs and QALYs at 3.5%	Intervention cost and effectiveness varied in PSA analysis (1000 iterations)	High vs low intensity behavioural: Short term (three years): £5,445, £1,331 Lifetime (mother): £563, £136 Lifetime (mother and infant): £183, £51 High intensity behavioural vs usual care: Short term (three years): £17,827, £157,696, £2,344

					Lifetime (mother): £1,864, £16,515, £244 Lifetime (mother and infant): £528, £4,594, £72 Conditional incentives vs non conditional: Short term (three years): £41,088, £60,409, £43,161 Lifetime (mother): £4,331, £6,441, £4,589 Lifetime (mother and infant): £1,124, £1,488, £1,091 Note: Also ICERs including productivity estimates, not reproduced here
Marks 1990 **[39]**	Cost-offset	Cost per LBW averted; cost per prenatal death averted; benefit-cost ratios for short and long-term hospitalisation costs	Provider (implied) / lifetime / cost of LBW at 4%	Cessation rates from 5% through to 25%; costs programmes varied USD 5-100; percentage of LBW needing neonatal special care 33%-67%; relative risk of LBW 1.5 – 2.5; relative risk of	Cost per LBW birth prevented USD 4000; cost per prenatal death prevented USD 695,452; costs averted in terms of short term hospitalization USD 3.31 for every USD 1 spent on cessation; long-term costs averted USD 3.26 per every USD 1 cessation

				prenatal death 1.1 to 1.4	
Parker 2007 **[40]**	Cost-effectiveness	Cost per quitter	Provider / within-pregnancy / no discounting	Varied costs of intervention per patient from USD 20 to USD 30	Quit rate for no calls 9.6% and 3 calls 23%; effectiveness to cost ratio of 1: USD 84 based on 3 calls
Pollack 2001 **[41]**	Cost-offset	Cost per SIDS averted	Provider (implied) / within-pregnancy / 5% per cost of life year	None	Assumed quit rate of 15%; intervention cost USD 45; averts 108 SIDS deaths; typical cessation service costs USD 210,500 per SID averted and USD 11,000 per discounted life year
Ruger 2008 **[42]**	Cost-effectiveness, cost-utility	Incremental cost per LY; incremental cost per QALY	Societal / lifetime for the mother; first year of life for the infant / costs and QALYs at 3%	Lifetime cost savings due to maternal illness and cost savings due to infant illness in first year of life; varying smoking status data; varying intervention costs; varying QALY weights	For smoking cessation, MI cost more but provided no additional benefit compared to UC, therefore MI was dominated by UC; MI intervention did prevent relapse more effectively than UC with an estimated ICER of USD 628/QALY
Shipp 1992 **[43]**	Cost-offset	Break even cost	Provider / within-pregnancy / no discounting	Prevalence of smoking;	Break even cost of USD 32 per pregnant woman; varying between USD 10 and USD 237 in

				intervention quit rate; spontaneous quit rate; probability of LBW; probability of maternal outcomes	sensitivity analyses
Tappin 2014 **[29]**	Cost-effectiveness, cost-utility	Incremental cost per quitter, incremental cost per QALY	Societal / within-pregnancy and lifetime / discounting costs and QALYs at 3.5%	Inclusion of smoking related disease costs; discount rate of 0%; risk of relapse at three months postpartum varied between 30% and 80%	Intervention quit rate of 23% vs 9% for controls; ICER of £127 per quitter; ICER of £482 per QALY for lifetime; 70% of cost-effective at £20,000-30,000 WTP; additional research cost-effective if less than £3.3 million at £30,000 WTP
Taylor 2009 **[47]**	Cost-utility	Incremental cost per QALY	Societal (implied) / lifetime / discounting costs and QALYs at 3.5%	Varying costs of each intervention between £0 and £1,000	For both mother and infant (per QALY), cognitive behaviour therapy ICER £4,005; stages of change ICER £3,033; feedback ICER £1,992; pharmacotherapies ICER £2,253; rewards and other interventions were dominant over control
Thorsen 2004 **[44]**	Cost-offset	Cost of intervention versus cost	Provider (implied) / pregnancy and six months postpartum / no discounting	None	If the intervention costs USD 15,366 it would achieve savings of USD 137,592

		saved			
Ussher 2014 **[28]**	Cost-effectiveness	Incremental cost per quitter	Societal / within-pregnancy / no discounting	Uncertainty explored by using non-parametric bootstrapping on costs and effects; halving and doubling the number of participants per fixed cost; sub-group analysis on age and cigarette dependence	Intervention quit rate of 7.7% versus 6.4% for controls; intervention cost £35 less per patient than control therefore dominant; high degree of uncertainty with CEAC suggesting that the probability of intervention being cost-effective was 0.8 at £50,000 WTP
Windsor 1988 **[45]**	Cost-effectiveness	Incremental cost per quitter	Provider / within-pregnancy / no discounting	Varying effectiveness of guide; varying cost of staff time; varying of intervention cost	Standard information cost per person USD 2.08; quit rate of 2%; ICER USD 104.00; ALA manual cost per person USD 7.13; quit rate of 6%; ICER USD 118.83; pregnant woman's guide cost per person USD 7.13; quit rate of 14%; ICER USD 50.93
Windsor 1993 **[46]**	Cost-offset	Benefit-cost ratio	Provider (implied) / lifetime / no discounting	Cost of intervention varied USD 4.5 - USD 9.0; smoking	LBW costs USD 9,000 to USD 23,000; cost-benefit ratio low estimate is USD 1:17.93 and high estimate is USD 1:45.83; net benefit minus

	attributable risk of LBW varied from 0.2 to 0.15; low and high estimate of smoking attributable LBWs	cost difference is USD 365,728 (low estimate) and USD 768,320 (high estimate)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No protocol available and not registered
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	See supplementary file 4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9 and supplementary file 3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-10

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	None performed
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	See supplementary files 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15-19
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	None performed
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-23
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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