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Systematic critical review of previous economic evaluations of smoking cessation during pregnancy

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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 (eg, cost per quitter, incremental cost per quality adjusted life year).

Results: 18 studies were included. 18 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 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 the mother and her infant for within-pregnancy and beyond.

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 US$110 million in the USA.2 Not only is the mother exposed to the long-term risks of smoking,3 but has an increased risk of certain pregnancy complications (eg, placentia abruption, ectopic pregnancy),4 while also having serious consequences on her offspring.5,6 The prevalence of smoking during pregnancy among 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), 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, 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 and Emmons has already been done on this topic; 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

Thirteen 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. Search terms and an example search can be found in online 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, for example, ‘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 (eg, smoking status at end of pregnancy, low birth weight (LBW) (birth weight <2500 g) births 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 analyses21 and decision

| 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 (eg, 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 |
analytic models (mathematical techniques to synthesise information from multiple sources)\textsuperscript{23} of economic evaluation were considered.

**Exclusion criteria**

Exclusion criteria were:
\begin{itemize}
  \item Studies with no economic analyses
  \item 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.
\end{itemize}

**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 are given in table 2.

**Quality assessment**

To assess the methodology quality of included studies, the Quality of Health Economic Studies (QHES) checklist was chosen.\textsuperscript{23} The QHES has been demonstrated to be a reliable and valid instrument,\textsuperscript{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 online 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 online supplementary file 2. Although there is no established, standardised interpretation of the QHES score, the following grouping was adopted based on the work by Spiegel et al.\textsuperscript{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

| 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 vs 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              |
| Study results               | Sensitivity analyses     |
|                             | Results of evaluation    |
|                             | Comparison with other evaluations |
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/comparsor costs which may not be comparable with those collected directly from an RCT.

RESULTS
The electronic search (conducted 7 August 2014) identified 8954 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,32–33 while for one, data were unavailable.34 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. Fifteen studies were published in peer reviewed journals,32 35 40–52 two with NICE guidance33 43 and one was an unpublished RCT.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 online supplementary files 3 and 4. Five studies were conducted in the UK,32 33 35 53 54 and the remainder in the USA. There was wide variety in cessation interventions, including: counselling-based (five studies)40–42 46 50; self-help materials (two studies),43 44 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).35 Two studies investigated interventions that had previously been described in the literature,33 54 while four studies modelled hypothetical interventions.14 44 45 49 Comparator interventions among 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 online supplementary file 5 for details) (two studies).33 35 The following were used by one study each, placebo patches with behavioural support,32 no intervention,40 and a cessation programme that 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 55 cost-effectiveness in five,32 33 41 46 51 cost-utility in two33 54 and two studies used 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 Twelve 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 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 were 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 LBW (birth weight <2500 g) prevented,44 45 one used SIDS (unexplained death within the first year of life) prevented,47 and three used 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 Among 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 during and after pregnancy,35 while a two studies calculated QALYs for the mother taking into account whether the mother smoked postpregnancy and suffered from coronary heart disease, chronic obstructive pulmonary disorder, myocardial infarction, lung cancer or stroke.33 54 In addition, one decision analytic model also included QALY losses
associated ectopic pregnancy, spontaneous abortion and pre-eclampsia. For studies including infants, one study used previously published QALY estimates adjusting for the higher mortality rate among children born to smoking women, while a second awarded QALY losses for birth weight below 2500 g, otitis media and asthma.

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; the most frequently varied parameters were intervention effectiveness between high and low quit rates, intervention cost between high and low cost, and background quit rate between high and low rates. Four studies used robust statistical techniques in probabilistic sensitivity analyses.

**QHES assessment**

Table 3 summarises QHES assessment results. Six studies attained a score greater than 75 indicating high quality, six were deemed of fair quality, and six poor. 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-term and long-term maternal and fetal outcomes (Q10, no studies), and incorporation of a time horizon that included the effects within-pregnancy and lifetime for the mother and infant (Q8, one study).

**Findings of studies with primary data collection**

Ten studies reported the primary collection of cost and effectiveness data, with all except one study identified cessation interventions during pregnancy as being cost-effective. 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). Other UK RCTs found the incremental cost per additional quitter was £4926 for NRT, and £1127 for financial incentives. One RCT extended the within-trial results to lifetime horizon for the mother using a previously developed model, and estimated an incremental cost per additional QALY of £482 for financial incentives. 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. The probability of financial incentives being cost-effective compared to usual care at £20 000–£30 000 per QALY was 70%, while for physical activity the probability was approximately 75%.
### 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  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | 35    |
| Cooper   | 2014 | X  | 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   | X   | X   | X   | X   | X   | 67    |
| Ershoff  | 1983 | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | 59    |
| Ershoff  | 1990 | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | 71    |
| Hueston  | 1994 | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | 57    |
| Mallender| 2013 | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | 86    |
| Marks    | 1990 | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | 57    |
| Parker   | 2007 | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | 33    |
| Pollack  | 2001 | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | 36    |
| Ruger    | 2008 | X  | X  | 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   | X   | X   | X   | 77    |
| Tappin   | 2015 | X  | 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  | X  | X   | X   | X   | X   | X   | X   | 56    |
| Thorsen  | 2004 | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | 37    |
| Ussher   | 2015 | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | 87    |
| Windsor  | 1988 | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | 35    |
| Windsor  | 1993 | X  | X  | X  | X  | X  | X  | X  | X  | 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.

QHES, Quality of Health Economic Studies.
Among US studies, one RCT reported that using a counselling intervention provided no additional benefit in QALYs and was therefore dominated by usual care.\textsuperscript{48} However, other studies found cost-benefit ratios estimated from 2:1\textsuperscript{42} to self-help materials to 2.8:1\textsuperscript{13} for counselling, though one study found the cost-benefit ratio to be between US$1:17.93 to US$1:45.83 for combined self-help materials and counselling\textsuperscript{52}. Another study found an effectiveness to cost ratio of US$1:84\textsuperscript{46}. The incremental cost per quitter was reported as US $298.76 for a counselling intervention\textsuperscript{41}; while one study found that for two different self-help material interventions the incremental cost per quitter was US$50.93 and US$118.83\textsuperscript{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,\textsuperscript{57} while US costs were inflated to 2014 prices using the Department of Labor’s Consumer Price Index Calculator,\textsuperscript{58} and converted to UK pound sterling using the exchange rate of US$1=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 to 28 years.\textsuperscript{59, 60} The results of this analysis can be found in Table 4.

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.\textsuperscript{40, 47, 50} five studies were modelling-based.\textsuperscript{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\textsuperscript{56} reported that an intervention costing US$24 per person, if applied to the US population, would generate US$ 8 million net saving in healthcare costs, a ratio of approximately 1:333 333. Thorsen et al\textsuperscript{56} reported savings of US$137 592 for an intervention costing US$15 366 given to low-income women in the US, a ratio of approximately 1.9. One observational study conducted by Pollack\textsuperscript{57} found that a cessation intervention costing US$45 per person would avert 108 SIDs if given to all pregnant smokers in the US, suggesting that the cessation service would cost US$210 500 per SID averted.

Three modelling studies were also conducted in the USA, and reported favourable cost-saving estimates. Marks et al\textsuperscript{45} reported that taking into account the long-term costs averted, the ratio of cost savings to intervention cost was 1:3.26. Hueston et al\textsuperscript{44} estimated that cessation interventions were cost-effective if the intervention costed US$80 or less in 1989 prices (US$152.73 in 2014 prices) and achieved a 18% quit rate, while Shipp et al\textsuperscript{49} estimated that an intervention would be cost-neutral if the cost of delivering the intervention in 1989 prices (2014 prices) was US$32 (US$61.09) or lower. Using the same exchange rate US$1=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\textsuperscript{53} 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 £4005 per additional QALY for CBT, £2253 per additional QALY for pharmacotherapies, £1992 per additional QALY for feedback and £2253 per additional QALY for stages of change. In another model constructed for NICE to inform guidance on secondary care interventions, Mallender et al\textsuperscript{44} reported that even considering short-term outcomes up to 3 years postintervention, behavioural interventions appeared to be cost-effective with incremental cost-effectiveness ratios of £5445 and £1331 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. However, the incremental cost-effectiveness ratios decreased as the perspective was increased to include the lifetime for 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. Seventeen studies identified within-pregnancy interventions as being cost-effective, with only one trial reporting that usual care was better than the experimental intervention.\textsuperscript{48} The current evaluations were generally well described, utilised appropriate health outcomes and drew realistic conclusions based on their results. Conversely, aspects where the analyses were in deficit included consideration of all major and relevant fetal 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, first, the same issue applies to other
### 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 et al | NRT with behavioural support | Placebo with behavioural support | 98.21* | 1.8 | 5456.34* | 2812.55* |
| Tappin et al | Financial incentives with standard NHS care† | Standard NHS care† | 157.36‡ | 14.0 | 1124.00‡ | 579.38‡ |
| Ussher 2015 | Physical activity with standard NHS care† | Standard NHS care† | -35.39 | 1.3 | DOMINANT | DOMINANT |
| Ruger et al | 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 et al | Self-help materials | Self-help materials | 16.58 | 13.6 | 121.94 | 62.86 |
| Dornelas et al | Counselling | Brief advice with self-help materials | 50.23 | 18.7 | 268.62 | 138.47 |
| Ershoff et al | Counselling | Smoking cessation programme (not defined) | 149.69 | 11.6 | 1290.42 | 665.17 |
| **Studies judged poor quality on QHES (≤49)** | | | | | | |
| Windsor et al | Counselling+self-help materials | Self-help materials | 4.99 | 5.8 | 86.05 | 44.35 |
| Windsor et al | Self-help materials | Brief advice | 7.12 | 4.0 | 178.10 | 91.80 |
| Windsor et al | Self-help materials | Brief advice | 7.12 | 12.0 | 59.37 | 30.60 |
| Parker et al | Counselling | No intervention | 2357.40 | 13.4 | 17 592.55 | 9068.32 |

*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 –£6142.01 to £11 767.41.
†Standard NHS care involves face-to-face counselling, telephone support, and up to 12 weeks of NRT.
‡95% CI Inc cost £155 to £162, 95% CI ICER per quitter £1107.14 to £1157.14, 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.

ICER, Incremental Cost-Effectiveness Ratio; NHS, National Health Service; NRT, nicotine replacement therapy; QALY, quality adjusted life years; QHES, Quality of Health Economic Studies.
checklists and therefore this is likely to have been a problem with any quality checklist utilised. Second, 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 dependent on the different types of study design (eg, 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. Therefore, first, this review is the most comprehensive in this subject to date. Second, 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. However, it is well-established that smoking is associated with serious morbidities that can occur later in life, as well as health issues for the infant during its childhood (eg, respiratory disease). 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 comorbidities associated with smoking and pregnancy, for example, placental abruption, placenta praevia, pre-eclampsia. 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 (eg, IBW, premature birth, stillbirth), but rarely included more than one-condition and did not consider any longer term impacts. Some studies have attempted to capture the healthcare cost savings for adverse birth outcomes avoided from cessation, but only one included the impact of LBW and asthma on the health of the child across their lifetime; yet this study excluded premature birth.

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. Relapse is important since the mother’s health risks from smoking increases with relapse, as does the infant’s exposure to secondhand smoke. Additionally, recent work suggests that if the mother smokes, an infant is over twice as likely to become an adult smoker, 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 overemphasising 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. 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. While in the past one-way 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. 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 18 not supporting that...
Conclusion. 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. However, 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 (£9068.22 per additional QALY). 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. Cessation interventions in non-pregnant populations have often been found to be very cost-effective, 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 policymakers 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 policymaker 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 the mother and her infant for within-pregnancy and beyond.

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 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.

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Competing interests We have read and understood BMJ policy on declaration of interests and declare the following interests: TC reports personal fees from Pierre Fabre Laboratories, France, outside the submitted work; MJ, SL and SP have nothing to declare.

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

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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REFERENCES
1. Godfrey C, Pickett KE, Parrott S, et al. Estimating the Costs to the NHS of Smoking in Pregnancy for Women and Infants. York: Public Health Research Consortium, University of York, 2010.
2. Mason J, Wheeler W, Brown MJ. The economic burden of exposure to secondhand smoke for child and adult never smokers residing in U.S. public housing. Public Health Rep 2015;130:330–44.
3. Doll R, Petro R, Wheatley K, et al. Mortality in relation to smoking: 40 years’ observations on male British doctors. BMJ 1994;309:901–11.
4. Castles A, Adams EK, Melvin CL, et al. Effects of smoking during pregnancy. Five meta-analyses. Am J Prev Med 1999;16:208–15.
5. DiFranza JR, Lew RA. Effect of maternal cigarette smoking on pregnancy complications and sudden infant death syndrome. J Fam Pract 1995;40:385–94.
6. Shah NR, Bracken MB. A systematic review and meta-analysis of prospective studies on the association between maternal cigarette smoking and preterm delivery. Am J Obstet Gynecol 2000;182:465–72.
7. Jauniaux E, Greenough A. Short and long term outcomes of smoking during pregnancy. Early Hum Dev 2007;83:697–8.
8. Palma S, Perez-Iglesias R, Pardo-Crespo R, et al. Smoking among pregnant women in Cantabria (Spain): trend and determinants of smoking cessation. BMC Public Health 2007;7:65.
9. Cui Y, Shooohlari S, Forget EL, et al. Smoking during pregnancy: findings from the 2009–2010 Canadian Community Health Survey. PLoS ONE 2014;9:e84640.
10. The NHS Information Centre IR. Infant Feeding Survey 2010: Early Results. The Health and Social Care Information Centre, 2011.
11. Tong VT, Dietz PM, Farr SL, et al. Estimates of smoking before and during pregnancy, and smoking cessation during pregnancy: comparing two population-based data sources. Public Health Rep 2013;128:179–88.
12. Schneider S, Maul H, Freerksens N, et al. Who smokes during pregnancy? An analysis of the German Perinatal Quality Survey 2005. Public Health 2008;122:1210–16.
13. Hilder L, Zhichao Z, Parker M, et al. Australia’s mothers and babies 2012. Canberra: The Australian Institute of Health and Welfare, 2014.
14. Boluomar F, Rebagliato M, Hernandez-Aguado I, et al. Smoking and drinking habits before and during pregnancy in Spanish women. J Epidemiol Community Health 1994;48:36–40.
15. Smedberg J, Lupattelli A, Mårdby AC, et al. Characteristics of women who continue smoking during pregnancy: a cross-sectional study of pregnant women and new mothers in 15 European countries. BMC Pregnancy Childbirth 2014;14:213–13.
16. Shearer J, Shanahan M. Cost effectiveness analysis of smoking cessation interventions. Aust N Z J Public Health 2006;30:428–34.
17. Ruget JP, Emmons KM. Economic evaluations of smoking cessation and relapse prevention programs for pregnant women: a systematic review. *Value Health* 2008;11:180–90.

18. National Institute for Health and Care Excellence. National Institute for Health and Care Excellence (homepage). Secondary National Institute for Health and Care Excellence (homepage) 23/07/2014, 2014. http://www.nice.org.uk/

19. US Department of Health & Human Services. Surgeon General.gov.

20. Cochrane Pregnancy and Childbirth Group. *Search methods for identifying trial reports for the Cochrane Pregnancy and Childbirth Group’s Trials Register*. The Cochrane Collaboration, 2012.

21. Petrosi S, Gray A. Economic evaluation alongside randomised controlled trials: design, conduct, analysis, and reporting. *BMJ* 2011;342:d1548.

22. Petrosi S, Gray A. Economic evaluation using decision analytical modelling: design, conduct, analysis, and reporting. *BMJ* 2011;342:d1766.

23. 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;9:53–61.

24. Chiou CF, Hay JW, Wallace JF, et al. Cost-effectiveness of a clinic-based counseling intervention tested in underserved pregnant smokers. *Value Health* 2008;11:191–8.

25. Au F, Prahardhi S, Shiell A. Reliability of two instruments for critical appraisal of economic evaluations in health technology assessments. *J Health Serv Res Policy* 2006;11:128–32.

26. Walker DG, Wilson RF, Sharma R, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. *J Manag Care Pharm* 2003;9:53–61.

27. Walker DG, Wilson RF, Sharma R, et al. Best practices for conducting economic evaluations in health technology assessments review of quality assessment tools. Rockville, MD: Agency for Healthcare Research Quality, U.S. Department of Health and Human Services, 2012.

28. Spiegel BM, Targownik LE, Karwal F, et al. The quality of published health economic analyses in digestive diseases: a systematic review and quantitative appraisal. *Gut* 2004;52:127;403–11.

29. Coleman T, Thornton J, Britton J, et al. Protocol for the smoking, nicotine and pregnancy (SNAP) trial: double-blind, placebo-randomised, controlled trial of nicotine replacement therapy in pregnancy. *BMJ Health Serv Res Report* 2007:22.

30. Usher M, Ashcroft P, Manyonda T, et al. Physical activity as an aid to smoking cessation during pregnancy (LEAP) trial: study protocol for a randomized controlled trial. *Trials* 2012;13:186.

31. Lynagh M, Bonesvki S, Sanson-Fisher R, et al. An RCT protocol of varying financial incentive amounts for smoking cessation among pregnant women. *BMJ public health* 2012;12:1032.

32. Tappin DM, Bauld L, Tannahill C, et al. The Cessation in Pregnancy Incentives Trial (CPIT): study protocol for a randomized controlled trial. *Secondary The Cessation in Pregnancy Incentives Trial (CPIT): study protocol for a randomized controlled trial* 2012: http://www.trialjournal.com/content/13/1/113

33. Cooper S, Lewis S, Thornton JG, et al. The SNAP trial: a randomised placebo-controlled trial of nicotine replacement therapy in pregnancy: effectiveness and safety until 2 years after delivery, with economic evaluation. *BMJ Health Technol Assess* 2011;13:1905.

34. Usher M, Lewis S, Aveyard P, et al. The London Exercise And Smoking Incentives Trial (LEAP): a randomised controlled trial of physical activity for smoking cessation in pregnancy with an ethnically diverse sample of pregnant smokers. *Patient Educ Couns* 2006;64:342–9.

35. Boyd KA, Briggs AH, Bauld L, et al. Are financial incentives cost-effective to support smoking cessation during pregnancy? *Addiction* 2015. In press. http://www.ncbi.nlm.nih.gov/pubmed/26370906

36. Barnard M, Price J. Cost-effectiveness of varenicline vs. Existing self-help smoking cessation programs in a HMO. *Public Health Rep* 1990;105:340–7.

37. Li CQ. Behavioral, health, and economic impact of dissemination of smoking cessation interventions for pregnant women in the United States. *Dissertation Abstracts Int* 1991;51:4805.

38. McParlane EC, Mullen PD, DeNino LA. The cost effectiveness of an education outreach representative to OB practitioners to promote smoking cessation counseling. *Patient Educ Couns* 1987;9:263–74.

39. Schramm WM. Weighing costs and benefits of adequate prenatal care for 12,023 births in Missouri’s Medicaid program, 1988. *Public Health Rep* 1992;107:647–52.

40. Ayadi MF, Adams EK, Melvin CL, et al. Costs of a smoking cessation counseling intervention for pregnant women: comparison of three settings. *Public Health Rep* 2006;121:120–6.

41. Dornelas EA, Magnavita J, Bezoglov T, et al. Efficacy and cost-effectiveness of a clinic-based counseling intervention tested in an ethnically diverse sample of pregnant smokers. *Patient Educ Couns* 2006;64:342–9.

42. Ershoff DH, Aaronsen NK, Danaher BG, et al. Behavioral, health, and cost outcomes of an HMO-based prenatal health education program. *Public Health Rep* 2004;119:181–94.

43. Ershoff DH, Quinn VP, Mullen PD, et al. Pregnancy and medical cost outcomes of a self-help prenatal smoking cessation program in a HMO. *Public Health Rep* 1990;105:340–7.

44. Hueston WJ, Mainous AG III, Farrell JB. A cost-benefit analysis of smoking cessation counseling programs during the first trimester of pregnancy for the prevention of low birthweight. *J Fam Pract* 1994;39:353–7.

45. Marks JS, Koplan JP, Hogue CJ, et al. A cost-benefit/cost-effectiveness analysis of smoking cessation for pregnant women. *Am J Prev Med* 1990;6:282

46. Parker DR, Windsor RA, Roberts MB, et al. Feasibility, cost, and cost-effectiveness of a telephone-based motivational intervention for underserved pregnant smokers. *Nicotine Tob Res* 2007;9:1043–51.

47. Pollack HA. Sudden infant death syndrome, maternal smoking during pregnancy, and the cost-effectiveness of smoking cessation interventions. *Am J Public Health* 2001;91:432–8.

48. Ruget JP, Weinstein MC, Hammond SK, et al. Cost-effectiveness of motivational interviewing for smoking cessation and relapse prevention among low-income pregnant women: a randomized controlled trial. *Value Health* 2008;11:191–8.

49. Shipp M, Coughran-Minihane MS, Petitti DB, et al. Estimation of the break-even point for smoking cessation programs in pregnancy. *Am J Public Health* 1992:82:383–90.

50. Thorsen KL, Khali L. Cost savings associated with smoking cessation for pregnant women. *JAMA* 2008;299:89–93.

51. Windsor RA, Warner KE, Cutter GR. A cost-effectiveness analysis of self-help smoking cessation methods for pregnant women. *Public Health Rep* 1988:103:83–8.

52. Windsor RA, Lowe JB, Perkins LL, et al. Health education for pregnant smokers: its behavioral impact and cost benefit. *Am J Public Health* 1993;83:201–6.

53. Taylor M. Economic Analysis of Interventions for Smoking Cessation Aimed at Pregnant Women. In: National Institute for Health and Care Excellence, ed. NICE Guidance PH26, Supplementary Report. York Health Economics Consortium, 2009. https://www.nice.org.uk/guidance/ph26/analysis-economic-analysis-review-376281901

54. Mallender J, Bertranou E, Baceda M, et al. Economic analysis of smoking cessation in secondary care: NICE public health guidance PH48. In: National Institute for Health and Care Excellence, ed: London: Matrix Knowledge, 2013. http://www.clinimatrix.com/ resources/an-economic-analysis-of-smoking-cessation-in-secondary-care.

55. Pollak KI, Oncken CA, Lipkus IM, et al. Estimation of the cost outcomes of a self-help prenatal smoking cessation program in an ethnically diverse sample of pregnant smokers. *Patient Educ Couns* 2008;64:342-9.

56. Fiscella K, Franks P. Cost-effectiveness of the transdermal nicotine patch as an adjunct to physicians’ smoking cessation counseling. *J Health Care Poor Underserved* 1992;3:647–56.

57. Curtis L, Personal Social Services Research Unit. Unit Costs of Health & Social Care 2014. Canterbury: Personal Social Services Research Unit, 2014.

58. US Bureau of Labor Statistics. CPI Inflation Calculator. Secondary NICE Inflation Calculator, 2015. http://www.bis.gov.uk/data/inflation_calculator.htm

59. Antle J, Busch TB, The London Exercise And Smoking Incentives Trial (LEAP) trial: a randomised controlled trial of physical activity for smoking cessation in pregnancy with an ethnically diverse sample of pregnant smokers. *J Public Health* 2003;85:732–5.

60. Fiscella K, Franks P. Cost-effectiveness of the transdermal nicotine patch as an adjunct to physicians’ smoking cessation counseling. *JAMA* 1996;275:1247–51.

61. Jones LL, Hashim A, McKeever T, et al. Cost-effectiveness of the transdermal nicotine patch as an adjunct to physicians’ smoking cessation counseling. *JAMA* 1996;275:1247–51.

62. Jones LS, Hashim A, McKeever T, et al. Parental and household smoking and the increased risk of bronchiolitis, bronchiolitis and other lower respiratory infections and in infants: systematic review and meta-analysis. *Respir Surveill* 2011:12:5.

63. Hofhuis W, de Jongste JC, Merkus PJFM. Adverse health effects of prenatal and postnatal tobacco smoke exposure on children. *Arch Dis Child* 2001;86:986–90.

64. Royal College of Physicians. Passive smoking and children. A report by the Tobacco Advisory Group. London: RCP, 2010.

65. Leonardi-Bee J, Jere ML, Britton J. Exposure to parental and sibling smoking and the risk of smoking uptake in childhood and adolescence: a systematic review and meta-analysis. *Thorax* 2011;66:847–55.

66. Claxton K, Sculpher M, McCabe C, et al. Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. *Health Econ* 2005;14:339–47.
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
| 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 (SAMMEEC) |
| 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 |
| Study          | Type of Analysis | Intervention Details                                                                 | Outcome Measures                                                                 | Costs Included                          |
|---------------|-----------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------|
| 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 |
| Author   | Study Type                  | Intervention Description                                                                 | Intervention Quit Rate | Costs of Healthcare for LBW Infants from Literature |
|----------|-----------------------------|------------------------------------------------------------------------------------------|-------------------------|-----------------------------------------------------|
| Hueston  | 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, |
| 1994 [38]|                             |                                                                                          |                         |                                                     |
| Mallender| Decision analytic model    | Interventions come from established literature.                                           | QALYs                   | Costs for interventions taken from literature; literature based costs used for diseases / conditions; costs reported at 2011 prices |
| 2013 [48]|                             | Situations modelled were:                                                                 |                         |                                                     |
|          |                             | High intensity versus low intensity behavioural support interventions                    |                         |                                                     |
|          |                             | High intensity behavioural support versus usual care                                     |                         |                                                     |
|          |                             | Conditional incentives versus non-conditional incentives                                |                         |                                                     |
| Marks    | 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 |
| 1990 [39]|                             |                                                                                          |                         |                                                     |
| Study | Study Design | Interventions | Outcomes | Costs |
|-------|--------------|---------------|----------|-------|
| 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; Lyps; 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 | Direct medical charges |
| Reference | Methodology | Description | Pregnancy outcomes avoided | Care avoided |
|-----------|-------------|-------------|----------------------------|--------------|
| 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 |
| Reference | Study Design | Intervention | Control | Outcome Measure | Cost Analysis |
|-----------|--------------|--------------|---------|----------------|---------------|
| 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 | | Abstinence at end of pregnancy | Salary estimates in USD, cost of manuals |
| Study Location | Study Design | Intervention Details | Outcomes | Additional Information |
|----------------|--------------|----------------------|----------|------------------------|
| Windsor 1993 [46] | Within-trial alongside RCT | 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 | 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 |
| 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 |

SUPPLEMENTARY FILE 4: CHARACTERISTICS OF INCLUDED STUDIES: TYPE OF EVALUATION, COMPARISON, AND RESULTS
| Study                  | Year | Cost- | Benefit-cost | Provider / within-pregnancy / no discounting | Intervention quit rate | Conclusion |
|------------------------|------|-------|--------------|---------------------------------------------|------------------------|------------|
| Ershoff 1990 [36]     |      | offset| ratio        | 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]     |      | offset| cost versus neonatal costs averted | 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]   |      | utility| cost per QALY | Incremental cost per QALY | Intervention cost and effectiveness varied in PSA analysis (1000 iterations) | High vs low intensity behavioural: Short term (three years): £5,445, £1,331, £2,344 |
|                       |      |       |              | Societal (implied) / up to three years after intervention; lifetime for mother and infant / costs and QALYs at 3.5% | Lifetime (mother): £563, £136 |
|                       |      |       |              | Lifetime (mother and infant): £183, £51 | Lifetime (mother and infant): £183, £51 |

113.64; hospital treatment cost differential of USD 183 per delivery; intervention cost USD 93 per patient; benefit cost ratio of 2:1
| 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 |
|----------------|-------------|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 | 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 |
| Source     | Cost-Effectiveness | Cost per Quitter | Cost per SIDS Averted | Incremental Cost per LY | Societal/Lifetime for the Mother; First Year of Life for the Infant | Prevalence of Smoking | Break Even Cost of USD 32 per Pregnant Woman; Varying between USD 10 and USD 237 in | Notes |
|------------|--------------------|------------------|-----------------------|-------------------------|---------------------------------------------------------------|------------------------|---------------------------------------------------------------------------------|-------|
| 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 | Prevalence of smoking 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 | Prevalence of smoking 1.1 to 1.4 | | 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 SIDS averted and USD 11,000 per discounted life year | Prevalence of smoking 1.1 to 1.4 | | 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 | Prevalence of smoking 1.1 to 1.4 | | 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 | Prevalence of smoking 1.1 to 1.4 |
| Study          | Approach               | 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% |
| 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 |
| Thorsen 2004 [44] | Cost-offset | Cost of intervention versus cost Provider (implied) / pregnancy and six months postpartum / no discounting | None |

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.

If the intervention costs USD 15,366 it would achieve savings of USD 137,592.
| Study        | Cost-Effectiveness | Incremental Cost per Quitter | Analytical Perspective | Uncertainty Explored | Intervention Quit Rate | Benefits-Cost Ratio |
|--------------|--------------------|------------------------------|------------------------|----------------------|------------------------|---------------------|
| 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 968,320 (high estimate) |