Effects of antenatal diet and physical activity on maternal and fetal outcomes: individual patient data meta-analysis and health economic evaluation

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PUBLICATION DATE

01-08-2017

HANDLE

10536/DRO/DU:30116640

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HEALTH TECHNOLOGY ASSESSMENT

VOLUME 21 ISSUE 41 AUGUST 2017
ISSN 1366-5278

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NHS
National Institute for Health Research

DOI 10.3310/hta21410

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Declared competing interests of authors: Hans Hauner reports grants from the German Ministry of Education and Research, the Bavarian Ministry of Agriculture and Nutrition, the Bavarian Ministry of Health, the Helmholtz Center Munich, the Else Kröner-Fresenius Foundation, AOK Bavaria (health insurance fund), Amway and the German Research Foundation outside the submitted work. Ben Willem Mol reports other grants from ObsEva during the conduct of the study.

Published August 2017
DOI: 10.3310/hta21410

This report should be referenced as follows:

Rogozińska E, Marlin N, Jackson L, Rayanagoudar G, Ruifrok AE, Dodds J, *et al*. Effects of antenatal diet and physical activity on maternal and fetal outcomes: individual patient data meta-analysis and health economic evaluation. *Health Technol Assess* 2017;**21**(41).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.236

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 12/01/50. The contractual start date was in February 2013. The draft report began editorial review in November 2015 and was accepted for publication in August 2016. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

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Abstract

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Background: Diet- and physical activity-based interventions in pregnancy have the potential to alter maternal and child outcomes.

Objectives: To assess whether or not the effects of diet and lifestyle interventions vary in subgroups of women, based on maternal body mass index (BMI), age, parity, Caucasian ethnicity and underlying medical condition(s), by undertaking an individual patient data (IPD) meta-analysis. We also evaluated the association of gestational weight gain (GWG) with adverse pregnancy outcomes and assessed the cost-effectiveness of the interventions.

Data sources: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects and Health Technology Assessment database were searched from October 2013 to March 2015 (to update a previous search).

Review methods: Researchers from the International Weight Management in Pregnancy Collaborative Network shared the primary data. For each intervention type and outcome, we performed a two-step IPD random-effects meta-analysis, for all women (except underweight) combined and for each subgroup of interest, to obtain summary estimates of effects and 95% confidence intervals (CIs), and synthesised the differences in effects between subgroups. In the first stage, we fitted a linear regression adjusted for baseline (for continuous outcomes) or a logistic regression model (for binary outcomes) in each study separately; estimates were combined across studies using random-effects meta-analysis models. We quantified the relationship between weight gain and complications, and undertook a decision-analytic model-based economic evaluation to assess the cost-effectiveness of the interventions.

Results: Diet and lifestyle interventions reduced GWG by an average of 0.70 kg (95% CI –0.92 to –0.48 kg; 33 studies, 9320 women). The effects on composite maternal outcome [summary odds ratio (OR) 0.90, 95% CI 0.79 to 1.03; 24 studies, 8852 women] and composite fetal/neonatal outcome (summary OR 0.94, 95% CI 0.83 to 1.08; 18 studies, 7981 women) were not significant. The effect did not vary with baseline BMI, age, ethnicity, parity or underlying medical conditions for GWG, and composite maternal and fetal outcomes. Lifestyle interventions reduce Caesarean sections (OR 0.91, 95% CI 0.83 to 0.99), but not other individual maternal outcomes such as gestational diabetes mellitus (OR 0.89, 95% CI 0.72 to 1.10), pre-eclampsia or pregnancy-induced hypertension (OR 0.95, 95% CI 0.78 to 1.16) and preterm birth (OR 0.94, 95% CI 0.78 to 1.13). There was no significant effect on fetal outcomes. The interventions were not cost-effective. GWG, including adherence to the Institute of Medicine-recommended targets, was not associated with a reduction in complications. Predictors of GWG were maternal age (summary estimate –0.10 kg, 95% CI –0.14 to –0.06 kg) and multiparity (summary estimate –0.73 kg, 95% CI –1.24 to –0.23 kg).

Limitations: The findings were limited by the lack of standardisation in the components of intervention, residual heterogeneity in effects across studies for most analyses and the unavailability of IPD in some studies.

Conclusion: Diet and lifestyle interventions in pregnancy are clinically effective in reducing GWG irrespective of risk factors, with no effects on composite maternal and fetal outcomes.

Future work: The differential effects of lifestyle interventions on individual pregnancy outcomes need evaluation.

Study registration: This study is registered as PROSPERO CRD42013003804.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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BMI	body mass index
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
DM	diabetes mellitus
EVPI	expected value of perfect information
GDM	gestational diabetes mellitus
GWG	gestational weight gain
HTA	Health Technology Assessment
HYPITAT	Hypertension and Pre-eclampsia Intervention Trial At near Term
i-WIP	International Weight Management in Pregnancy
ICER	incremental cost-effectiveness ratio
IOM	Institute of Medicine
IPD	individual participant data
IUD	intrauterine death
LGA	large for gestational age
MD	mean difference
NICE	National Institute for Health and Care Excellence
NICU	neonatal intensive care unit
OR	odds ratio
PE	pre-eclampsia
PI	prediction interval
PIH	pregnancy-induced hypertension
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RCT	randomised controlled trial
REML	restricted maximum likelihood
SD	standard deviation
SGA	small for gestational age

Plain English summary

Maternal obesity and excessive weight gain in pregnancy increase complications in the mother and baby. These may be reduced by diet and physical activity. It is possible that benefits are restricted to particular groups of women based on their body mass, age, number of previous children, ethnicity and underlying medical condition(s). We looked at the effects of diet and physical activity on weight gain in pregnancy and on the risk of complications in the mother and baby. We obtained anonymised data of individual participants from multiple studies, and combined them using the technique known as individual patient data meta-analysis. This was intended to allow us to identify particular groups of women who may benefit from diet and physical activity.

We established the International Weight Management in Pregnancy Collaborative Network, comprising anonymised data of 12,343 women from 36 studies. We found that diet, physical activity and mixed methods, individually and when analysed together, effectively reduced weight gain in pregnancy, possibly decreased complications in the mother and had no effect on the baby. The effects were similar in all groups of women.

We did not identify any benefit to mothers or their children when they gained weight within specific targets that are currently recommended in many countries. A mother's age and a history of previous births predicted weight gain in pregnancy.

Diet and physical activity in pregnancy reduced weight gain by 0.7 kg, and had no effect on combined complications. There were with no differences in these benefits between various groups of women. The rate of Caesarean section was reduced by the lifestyle intervention compared with usual care.

Scientific summary

Background

Obesity and excess weight gain in pregnancy are associated with adverse maternal and fetal outcomes. Maternal age, parity, ethnicity and underlying medical conditions influence the risk of complications. Diet and physical activities have the potential to reduce weight gain and alter pregnancy outcomes. Variation in the effect of these interventions across subgroups of women may have implications for clinical management and provision of care. The association of gestational weight gain (GWG) with complications in pregnancy needs evaluation using robust data.

Objectives

Primary

1. To assess if the effects of diet- and physical activity-based interventions on (1) GWG, (2) composite maternal outcomes and (3) composite fetal/neonatal outcomes vary in subgroups of women based on body mass index (BMI) at booking, age, parity, ethnicity and underlying medical conditions.

Secondary

1. To evaluate the association of GWG and adverse pregnancy outcomes in women and their infants.
2. To assess adherence to the Institute of Medicine (IOM)-recommended weight-gain targets in normal weight, overweight and obese pregnant women and rates of maternal and fetal complications.
3. To identify the predictors of GWG in pregnancy based on maternal characteristics such as parity, pre-pregnancy or early pregnancy BMI, ethnicity, smoking, diet, physical activity and socioeconomic status.
4. To evaluate the cost-effectiveness of interventions.
5. To undertake network meta-analysis to determine the rank order of interventions based on effectiveness.

Methods

We undertook individual participant data (IPD) meta-analysis by using a prospective protocol in line with existing recommendations, and complied with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines for IPD meta-analysis in reporting our work. We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects and Health Technology Assessment database, from October 2013 to March 2015, for relevant studies (to update a previous search). Randomised trials that assessed the effects of diet, physical activity or mixed-approach interventions on GWG, composite maternal and fetal/neonatal outcomes were included. The composite maternal outcome included gestational diabetes mellitus (GDM), pre-eclampsia (PE) or pregnancy-induced hypertension (PIH), preterm delivery and Caesarean section. The composite fetal outcomes included intrauterine death, small for gestational age, large for gestational age and admission to the neonatal intensive care unit (NICU). Researchers from the International Weight Management in Pregnancy Collaborative Network shared the primary data.

We obtained summary estimates of effects and 95% confidence intervals (CIs) for each intervention type and outcome, with a two-step IPD random-effects meta-analysis, for all women combined and for each

subgroup of interest. We synthesised the differences in effects between subgroups in a two-step IPD random-effects meta-analysis. In the first stage, we either fitted a linear regression adjusted for baseline (for continuous outcomes) or a logistic regression model (for binary outcomes) in each study separately; in the second stage, the pertinent effect estimates were then combined across studies using a random-effects meta-analysis model estimating via restricted maximum likelihood. We quantified the relationship between weight gain and pregnancy complications. A model-based economic evaluation was undertaken to assess the cost-effectiveness of the interventions.

Results

Of the 74 eligible studies (17,727 women), 36 (12,434 women) contributed data to the IPD meta-analysis: 33 (9320 women) evaluated GWG, 24 (8852 women) reported all four components of the composite maternal outcomes and 18 (7981 women) assessed all four components of the fetal/neonatal composite outcomes.

Effect of diet- and physical activity-based interventions on maternal and fetal outcomes

Diet- and physical activity-based interventions reduced GWG by an average of –0.70 kg [95% CI –0.92 to –0.48 kg, 95% prediction interval (PI) –1.24 to –0.16 kg; 33 studies, 9320 women] compared with the control group in the IPD meta-analysis. The odds of composite adverse maternal outcome were not significantly reduced by the interventions [summary odds ratio (OR) 0.90, 95% CI 0.79 to 1.03, 95% PI 0.68 to 1.20]. The interventions had no effect on fetal/neonatal outcomes (summary OR 0.94, 95% CI 0.83 to 1.08, 95% PI 0.74 to 1.21).

The IPD meta-analysis showed a significant reduction in rates of Caesarean section (OR 0.91, 95% CI 0.83 to 0.99; 32 studies contributing data, 11,410 women). The decreases in rates of other individual maternal outcomes [such as GDM (OR 0.89, 95% CI 0.72 to 1.10; 27 studies contributing data, 9427 women), PE or PIH (OR 0.95, 95% CI 0.78 to 1.16; 22 studies, 9618 women) and preterm birth (OR 0.94, 95% CI 0.78 to 1.13; 32 studies contributing data, 116,876 women)] were not significant.

Sensitivity analysis showed that the beneficial effect on weight gain persisted after adding non-IPD data (summary mean difference –1.13 kg, 95% CI –1.58 to –0.68 kg; 60 studies, 12,895 women). Meta-analysis of published aggregate data showed a significant reduction only in GDM (OR 0.78, 95% CI 0.64 to 0.95; 29 studies, 11,118 women) and Caesarean section (OR 0.90, 95% CI 0.82 to 0.99; 37 studies, 11,340 women) compared with the control group. There were no significant reductions in preterm birth (OR 0.80, 95% CI 0.63 to 1.01; 23 studies, 7480 women) and PE or PIH (OR 0.89, 95% CI 0.75 to 1.05; 20 studies, 9198 women). Both aggregate and IPD meta-analyses did not have an effect on fetal/neonatal outcomes.

Differential effect of interventions on gestational weight gain and pregnancy outcomes

The effect of interventions on GWG did not significantly vary with maternal BMI (–0.02 kg change in intervention effect per 1 kg/m^2 increase in BMI, 95% CI –0.08 to 0.04 kg), age (–0.03 kg change in intervention effect per 1-year increase in age, 95% CI –0.08 to 0.02 kg), parity (0.10 kg change in intervention effect for multiparity vs. nulliparity, 95% CI –0.39 to 0.60 kg), ethnicity (0.05 kg change in intervention effect for non-Caucasian vs. Caucasian, 95% CI –1.27 to 1.37 kg) or underlying medical conditions (1.51 kg change in intervention effect for women with at least one condition vs. none, 95% CI –2.01 to 5.02 kg).

We did not identify any significant change in treatment effect for composite maternal outcomes in subgroups based on maternal BMI (no change in effect for every 1 kg/m^2 increase in BMI, OR 1.00, 95% CI 0.98 to 1.02), age (1% increase in effect for every 1-year increase in age, OR 1.01, 95% CI 0.99 to 1.03), parity (3% increase in effect for multiparity vs. nulliparity, OR 1.03, 95% CI 0.75 to 1.39), ethnicity (7% decrease in effect for non-Caucasian vs. Caucasian, OR 0.93, 95% CI 0.63 to 1.37) or underlying

medical conditions (44% increase in effect for women with at least one condition vs. none, OR 1.44, 95% CI 0.15 to 13.74). For composite fetal/neonatal outcome we observed a 2% lowered effect (OR 0.98, 95% CI 0.95 to 1.00) for every 1 kg/m^2 increase in booking BMI, which was of borderline significance. There was no significant treatment–covariate interaction for other factors and composite fetal/neonatal outcome. There was significant evidence of small-study effects for GWG (Egger's test, $p = 0.038$) and the composite maternal outcome (Peter's test, $p = 0.036$), but not for fetal/neonatal composite outcome ($p = 0.398$).

Gestational weight gain and pregnancy outcomes

We did not identify an association between GWG, booking BMI and risk of maternal (summary OR 1.03, 95% CI 0.93 to 1.15) or fetal/neonatal complications (summary OR 1.02, 95% CI 0.91 to 1.15). Adherence to IOM criteria for GWG did not significantly reduce GWG. Increase in maternal age (–0.1 kg, 95% CI –0.14 to –0.06 kg) and multiparity (–0.73 kg, 95% CI –1.24 to –0.23 kg) were significantly associated with GWG.

We refrained from undertaking network meta-analysis, as there were no differences in estimates of effect for GWG between diet-based, physical activity-based and mixed-approach interventions.

Cost-effectiveness of the intervention

Diet- and physical activity-based interventions in pregnancy are not cost-effective compared with usual care. Although the primary base-case analysis indicated a small reduction in pregnancy-related complications, the probabilistic sensitivity analysis showed no evidence of significant difference between the intervention and the control arms for either cost or clinical effectiveness. Similarly, the results of the secondary analysis for obese, overweight and normal weight women found no evidence that diet- and physical activity-based interventions are more cost-effective than usual care for any of the subgroups.

Conclusions

Interventions based on diet and physical activity in pregnancy reduce GWG, and the effect does not vary by maternal BMI, age, parity, ethnicity or underlying medical conditions. The interventions do not confer any additional benefit for composite maternal and fetal outcomes and are not cost-effective. There is no evidence to support routine use of IOM targets for GWG.

Recommendations for further research

The impact of lifestyle interventions in pregnancy on long-term outcomes (such as postpartum weight retention, future risk of diabetes and hypertension, subsequent pregnancy outcomes and childhood obesity) needs evaluation. Randomised trials are required to evaluate the effect of interventions to optimise the pre-pregnancy health of the mother.

Study registration

This study is registered as PROSPERO CRD42013003804.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Updated data can be found in the meta-analysis by the International Weight Management in Pregnancy (i-WIP) Collaborative Group.[1]

Obesity is an epidemic. In the UK, every other woman of childbearing age is either overweight [body mass index (BMI) of 24.9–29.9 kg/m^2] or obese (BMI of 30 kg/m^2 or more), and one-fifth start pregnancy as obese.[2] The confidential enquiry into maternal and child health identified maternal obesity as a threat to the childbearing population in the UK.[3] The risks for the infant include stillbirth and neonatal death, macrosomia, neonatal unit admission, preterm birth and congenital abnormalities. In the longer term, maternal obesity is associated with an increased risk of childhood obesity and associated complications.[4] A significant proportion of women gain more than the recommended weight during pregnancy,[5] with increased risk of maternal and fetal/neonatal complications.[6] Women who gain excess weight in pregnancy are at increased risk of postpartum weight retention. This predisposes normal weight and overweight women in index pregnancy into entering subsequent pregnancies as overweight or obese. Effective interventions that reduce maternal obesity and excess weight gain in pregnancy could derive significant advantages for the NHS and society.

Clearly defined, effective interventions that target those women at the highest risk in pregnancy are needed. Diet- and physical activity-based interventions have been widely evaluated for their effect on gestational weight gain (GWG) and clinical outcomes. There is limited information on their effects on specific groups of pregnant women known to be at increased risk of complications.

Aggregate meta-analysis of randomised trials on diet- and physical activity-based interventions [Health Technology Assessment (HTA) programme reference number 09/27/06] showed a significant reduction in GWG, with benefit for some clinical outcomes.[7] However, aggregate data meta-analysis was limited because of the inability to explain heterogeneity of effects for important maternal and fetal/neonatal outcomes. This heterogeneity might be a result of variation in maternal characteristics, such as BMI, age, ethnicity and parity with varied weight gain.

Pregnancy during adolescence alters normal growth processes and increases the risk of becoming overweight or obese.[8] Adolescent mothers retain more weight post partum than mature control subjects.[8] Inclusion of a large number of pregnant adolescents may overestimate postpartum weight changes or the risk of becoming overweight, and thus bias estimates for adult women. Migrant groups exhibit less GWG than the local population but similar rates of complications.[9] These aspects need investigation.

The National Institute for Health and Care Excellence (NICE) public health guidance *Weight Management Before, During and After Pregnancy*[10] has prioritised the following areas for research: the clinical effectiveness and cost-effectiveness of weight management interventions in pregnancy for specific groups, such as teenagers, with differing needs and social circumstances; ethnic minorities, such as Asians, in whom comorbidity risk at any particular BMI value is relatively higher than in other ethnic groups; women who enter pregnancy obese; and the effect of adherence to the Institute of Medicine (IOM)'s weight-gain recommendations on pregnancy outcomes.

The paucity of published detail in research on the effects of interventions in particular subgroups of women based on BMI, ethnicity and other relevant factors restricts aggregate data meta-analyses.[11,12] Subgroup effects are rarely reported in sufficient detail, especially to derive differences in intervention effect between subgroups ('treatment–covariate interactions'). Meta-regression examining the across-trial association between overall treatment effect and average patient characteristics (e.g. mean age) has low power to detect genuine subgroup effects and is also prone to study-level confounding.[13,14] Furthermore, the available data could not assess the impact of baseline prognostic factors on the effectiveness of the interventions. Meta-analysis of individual participant data (IPD),[15] in which the raw patient-level data are

obtained and synthesised across trials, overcomes the above limitations. Availability of the raw data substantially increases the power to detect baseline factors that truly modify intervention effect[13] and enables intervention effects to be quantified for clinically relevant groups.[16] It will also allow the magnitude of benefit, due to weight change in pregnancy, to be quantified for both the women and their infants.

We undertook an IPD meta-analysis of randomised trials on diet- and physical activity-based interventions to assess differential effects of interventions in various subgroups of pregnant women.

Chapter 2 Objectives

Primary

1. To assess if the effects of diet- and physical activity-based interventions on (1) GWG, (2) composite maternal and (3) composite fetal/neonatal outcomes vary in subgroups of women based on BMI at booking, age, parity, ethnicity and underlying medical conditions.

Secondary

1. To quantify the relationship between the amount of weight gained in pregnancy and the risk of adverse maternal and fetal/neonatal outcomes for (1) women of normal weight, (2) overweight women and (3) obese women.
2. To assess the relationship between adherence to IOM's guidelines and maternal and fetal complications in normal weight, overweight and obese pregnant women.
3. To identify the predictors of GWG in pregnancy based on patient characteristics such as parity, pre-pregnancy BMI, ethnicity, smoking, diet and lifestyle, and socioeconomic status.
4. To assess the cost-effectiveness of the interventions in pregnancy using model-based full economic evaluation with value of information analysis.
5. To undertake network meta-analysis to determine the rank order of interventions for clinical effectiveness, if appropriate.

Chapter 3 Methods

Our IPD meta-analysis followed existing guidelines and used a prospective protocol registered with PROSPERO (CRD42013003804).[17] Our output complied with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) reporting guidelines for IPD meta-analysis.[18]

Eligibility criteria

Criteria for including studies in individual participant data

We included studies that addressed the components of the structured question presented in *Table 1*.

Randomised trials, with or without clustering, that evaluated the effects of diet- and physical activity-based interventions in pregnancy on maternal, fetal and neonatal outcomes were eligible for inclusion. We included studies on normal, overweight and obese pregnant women. Interventions that addressed mainly diet or mainly physical activity and interventions adopting a mixed approach that combined the two, with or without behavioural modification techniques, were eligible. The control arms included women without any intervention or with routine antenatal care, as defined by local health-care practices. The primary outcomes were maternal weight gain in pregnancy, and composite maternal and composite fetal/neonatal events complications. Studies should have assessed both maternal weight gain and clinical outcomes.

Maternal weight gain was defined as the difference between the weights recorded (kg or lb) at first clinic visit and last weight measured before birth. If weight at first clinic visit was not available, we used pre-pregnancy weight.

The maternal composite outcome included gestational diabetes mellitus (GDM), pre-eclampsia (PE) or pregnancy-induced hypertension (PIH), preterm delivery and Caesarean section. The fetal and neonatal composite outcome comprised intrauterine death (IUD), small for gestational age (SGA), large for gestational age (LGA) and admission to the neonatal intensive care unit (NICU). The components of the composite outcome were identified by a two-round Delphi survey. The final scores of the components are provided in *Appendix 1*. The details of the development of the composite outcomes are published elsewhere.[19]

We excluded studies published before 1990, animal studies and those that evaluated the effects of intervention only on non-clinical outcomes (behaviour change and consumption of particular food groups) or aimed to increase weight gain in pregnancy.

TABLE 1 Structured question for IPD meta-analysis of diet- and physical activity-based interventions on maternal and fetal/neonatal outcomes

Component	Description
Population	Pregnant women with a BMI of ≥ 18.5 kg/m^2
Interventions	Diet-based, physical activity-based and mixed-approach intervention
Comparison	No intervention or routine antenatal care
Main outcomes	GWG, maternal composite outcome, fetal and neonatal composite outcome
Other outcomes	Maternal: gestational diabetes mellitus, pre-eclampsia or pregnancy-induced hypertension, preterm delivery (< 37 weeks), Caesarean section
	Fetal/neonatal: intrauterine death, small for gestational age fetus, large for gestational age fetus, admission to the NICU
Study design	Randomised controlled trial

NICU, neonatal intensive care unit.

Criteria for including participants in individual participant data

We excluded underweight women (BMI of < 18.5 kg/m^2) and women with multiple pregnancies.

Literature search and study identification

We updated our previous literature search (October 2013 to March 2015) to identify new trials published since the completion of our systematic review (HTA number 09/27/06[7]) on effects of diet- and physical activity-based interventions in pregnancy. The following databases were searched from October 2013 to March 2015 to update the search: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects and HTA database without any language restrictions. We used additional sources, such as the internet [general search engines such as Google (Google Inc., Mountain View, CA, USA)], and directly contacted researchers to identify relevant trials. We did not contact authors of trials that were published or identified too close to the analysis stage because of lack of sufficient time to clean and format the data before analysis. The details of the search strategy are provided in *Appendix 2*.

We established the International Weight Management in Pregnancy (i-WIP) IPD Collaborative Network by contacting researchers who had published trials on diet and lifestyle interventions in pregnancy.[20] The network is a global effort in bringing together researchers, clinicians and epidemiologists involved, supported by the World Health Organization, from 16 countries (https://kamolo.org.ar/iwipipd, accessed 1 March 2016).

Study and participant selection

Study selection

We undertook a two-stage study selection process. In the first stage, the abstracts of all citations were evaluated for their eligibility. In the second stage, we studied the identified studies in detail before their inclusion. Two independent reviewers (ER and EM) evaluated all papers. In case of disagreement, an opinion of the third reviewer (ST) was sought. We applied the eligibility criteria provided above for inclusion of studies.

Data collection and storage

We set up a bespoke database and requested authors of the i-WIP Collaborative Network to supply data in any format [Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA), IBM SPSS Statistics versions 22 and 23 (IBM Corporation, Armonk, NY, USA), Stata (StataCorp LP, College Station, TX, USA) and SAS (SAS Institute Inc., Cary, NC, USA)] convenient to them. We sent, on average, three reminders when there was no response. For studies that refused to provide IPD, and for those with which contact could not be established, we extracted the published aggregate data.

We obtained and uploaded the original anonymised data sets using the secure web-based server at Centro Rosarino de Estudios Perinatales, Rosario, Argentina, a World Health Organization Collaborative Centre in Child and Maternal Health. Data manipulations were performed and documented within this environment. The final meta-data set was securely transferred to the Pragmatic Clinical Trials Unit at Queen Mary University of London for final data checks and analysis. An independent data access committee and data access process were established for use of the data in future research.

Data items

We considered all recorded variables for inclusion when appropriate, including those not reported in the published studies. Data were extracted on the study and data set levels. At the study level, we collected information regarding study settings, intervention type, components, format and provider. At the participant level we requested information on individual characteristics including BMI, age, parity, ethnicity, socioeconomic status, pre-existing medical conditions, adherence to intervention and outcome data. The list of final variables collected during the project is available in *Appendix 3*.

Definition and standardisation of variables

Participant characteristics and other measurements were recorded in various different formats within the individual data sets. We chose the meta-data set format by including the variables that were most commonly reported. The standardisation process followed a predefined procedure (*Figure 1*).

Standardisation of baseline variables

Maternal age (years) at baseline was recorded as a continuous variable in most studies except one, in which age at baseline was calculated from the date of first visit and the date of birth. In addition to continuous data, we used the cut-off point of 20 years for age, to dichotomise participants into teenagers and those over 19 years. Race/ethnicity was recorded in a variety of ways and standardisation required a larger number of assumptions to be made. The details of ethnicity coding are available in *Appendix 4*. BMI was recorded both as a continuous measure and categorised into clinically relevant categories as normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese ($\geq$ 30 kg/m^2).

We used the woman's educational status to represent the socioeconomic status by using local standards. After feedback from the study team we defined educational status as 'low' (secondary education completed before A-levels), 'medium' (secondary education to A-level equivalent) or 'high' (any further/higher education) (see *Appendix 4*). Smoking was generally recorded as yes/no, with some studies recording previous habits. If the woman had stopped smoking because of pregnancy or for other reasons at any time point, this was combined into the variable for 'ex-smoker (yes/no)'.

We defined participants as adherent if they completed around 70–80% of the intervention protocol, if the data set provided adherence information in a yes/no format or if non-adherent women were excluded as per study protocol. Parity was defined as the number of times participants had given birth before the index pregnancy and was recorded consistently across the data set. We combined information from physical activity questionnaires, gym attendance, type of work and accelerometer data to standardise the approach

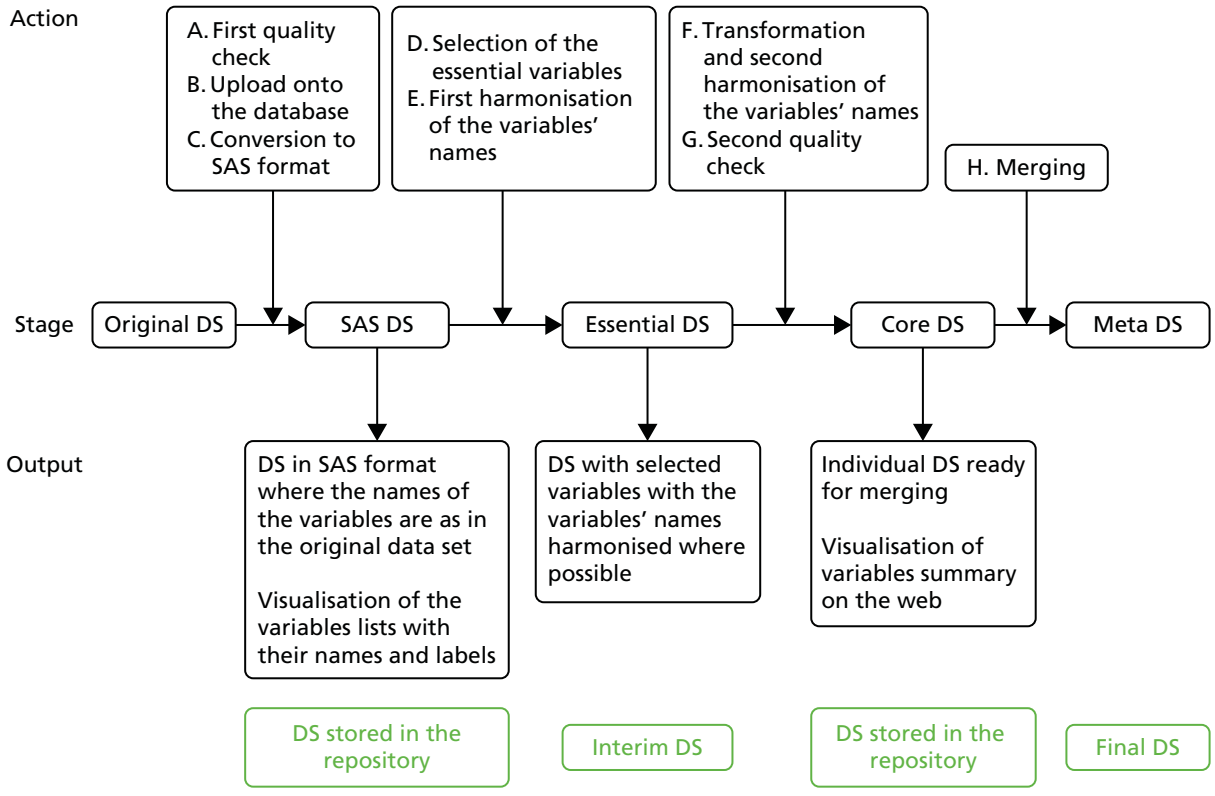

FIGURE 1 Flow diagram of standardisation of variables within the IPD sets. Interim DS refers to a temporary work-in-progress data set that will not be stored onto the database. DS, data set.

for baseline physical activity (for details see *Appendix 4*). Previous macrosomia and GDM were defined as per individual study authors and were recorded in all data sets as 'yes/no'.

Standardisation of outcome variables

Weight was standardised to kilograms and height to centimetres. BMI was defined as weight/height squared (kg/m^2) and was consistently reported across all data sets. Baseline obesity was defined as a BMI of $\geq$ 30 kg/m^2. Adherence to the IOM recommendations for GWG was as follows: 11–16 kg for normal weight women, 7–11 kg for overweight women and 5–9 kg for obese women.[9] We classified women as not reaching the recommendation (i.e. GWG less than the lower limit), adherent (i.e. GWG within limits) or exceeding the recommendation (i.e. GWG more than the upper limit).

Gestational diabetes mellitus, diabetes mellitus (DM), PIH, PE, chronic hypertension and Caesarean section were defined and reported in the data sets in accordance with local standards. IUD and admission to the NICU were analysed as defined in the data set. Outcomes SGA (< 10th centile) and LGA ($\geq$ 90th centile) were generated for all data sets using a bulk birthweight centile calculator [Gestation Related Optimal Weight (GROW) customised centiles (CC) software, version 6.7; Gestation Network, Birmingham, UK, 2013] incorporating data on women's height and baseline weight, parity, gestational age at birth and fetal birthweight.

Data quality (individual participant data integrity)

Data sets included in the i-WIP analysis were expected to be clean on receipt from the original trial team. We performed range checks on the variables used during the analysis and produced summary tables. We focused on checking the randomisation ratio, baseline characteristics and the method of analysis in the IPD data set with the published information. Any major discrepancies were discussed with the trial team.

Risk-of-bias assessment in individual studies

We evaluated the risk of bias in individual studies by considering six items used in the Cochrane risk-of-bias tool: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias.[21] When required, we obtained the full trial protocol and directly contacted the primary investigators to obtain relevant details to assess the study quality. A study was classified as having a high risk of bias if it was assessed as high risk in at least one of the following domains: randomisation, allocation concealment, blinding of outcome assessment, incomplete outcome data and when no single item was assessed as being at low risk of bias.

Handling of trials without individual participant data availability

We explored the potential for publication bias, and the possible impact of unavailable non-IPD data, in accordance with recent guidelines.[22] For each analysis containing 10 or more studies, the potential for publication bias was investigated through contour-enhanced funnel plots, and appropriate statistical tests for 'small-study effects' (i.e. the tendency for small studies to provide more positive findings than large ones).

For all studies in which IPD were not available, we extracted suitable aggregate data from the study publications. When possible, we then incorporated these aggregate data into the second stage of the two-step meta-analysis framework, to combine the IPD trials with the aggregate data from other trials for the outcome of GWG. This allowed us to examine whether or not conclusions (on summary results and potential publication bias) were changed by the inclusion of additional non-IPD trials.[14,23] If the inclusion of studies that did not provide IPD seemed to have an important statistical or clinical impact, we compared the characteristics of the studies with IPD with those without to see if there were any key differences (such as in their quality, follow-up length and statistical methods). This was achievable only when examining the overall treatment effect, as aggregate data for subgroup effects were rarely provided by the non-IPD studies. For individual maternal and fetal/neonatal complications, we compared meta-analyses findings of only aggregate published data with IPD.

Sample size considerations

Although no formal sample size requirements are necessary for the meta-analysis, we have considered the potential power of our IPD meta-analysis in comparison with single trials in this field to detect clinically important effects in each subgroup separately. All calculations relate to a type I error of 5%, a power of 80% and a loss to follow-up of 5%. We chose a reduction of 2.5 kg in GWG as the minimally important difference. We expected the available sample size to be > 9000 women. For maternal weight gain, the sample size required for all subgroups is ≤ 300. For the composite outcome of adverse maternal and fetal/neonatal outcomes, we calculated the sample size needed to detect an intervention effect of a 30% reduction in adverse pregnancy outcomes. Our estimates of the standard deviation (SD) of the control group and the risk of composite pregnancy outcome were obtained from the data of primary studies included in our systematic review.[24]

Given the large sample size available, it is highly likely that the study was powered to detect important differences between subgroups (i.e. to identify genuine factors that modify treatment effect). This allowed us to detect interaction terms as small as about 30% of the size of the overall treatment effect. If the overall intervention effect is a reduction in weight gain of approximately 2.5 kg, then our IPD meta-analysis would have 80% power to detect an interaction term of about $2.5 \times 0.3 = 0.75$ or above (e.g. a difference in intervention effect of 0.75 kg between obese and normal weight women) (*Table 2*).

Data analysis

All analyses were carried out using Stata, version 12.1. Aggregate meta-analyses for components of maternal and fetal/neonatal composites were done using Review Manager, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

TABLE 2 Sample size estimations for various subgroups to evaluate the effect of interventions on weight gain and pregnancy outcomes in a single trial

Subgroups	Control group SD	Sample size required to detect a 2.5-kg reduction in GWG	Control group probability of adverse pregnancy outcome	Sample size required to detect a 30% reduction in adverse pregnancy outcome
BMI category				
Obese	7.5	300	0.30	770
Overweight	7.5	300	0.20	1290
Normal weight	5.1	140	0.12	2330
Age (years)				
< 20	7.12	270		
≥ 20	5.87	184		
Ethnicity				
Caucasian	3.4	64		
Asian	3.8	78		
African	5.1	140		
Parity				
< 1	6.28	212		
≥ 1	6.68	238		
Risk factors such as diabetes				
High risk	6.81	248		
Low risk	6.67	236		

Primary analyses of studies providing individual participant data

For each outcome (i.e. GWG, composite maternal, composite fetal/neonatal) separately, we performed a two-stage IPD meta-analysis to obtain summary estimates and 95% confidence intervals (CIs) for the intervention effects [mean difference (MD) or odds ratios (ORs)] and the interactions (subgroup effects) of interest. All participants were analysed according to the group they were randomised to. We used a two-stage random-effects meta-analysis approach, which allows for between-study heterogeneity in intervention effect (and interaction effect). In any two-stage meta-analysis, the clustering of participants within trials is accounted for by analysing each trial separately in the first stage. Women with confirmed glucose intolerance or hypertensive disorder at baseline, as defined by the primary authors, were excluded in the analysis of composite adverse pregnancy outcomes.

First stage of individual participant data meta-analysis

Continuous outcome measures were checked for normality and log transformed if applicable. Variables (covariates) were kept as continuous as well as defining subgroups for BMI and maternal age. All analyses were performed on complete cases, that is individuals who provided the outcome and (if relevant for the analysis) baseline adjustment factors. When analysing cluster randomised trials, we included a random intercept for the unit of randomisation to account for clustering. For the continuous outcome of weight gain, we used analysis of covariance in each trial to regress the final weight value against the intervention, while adjusting for baseline weight. For the binary outcome of adverse fetal/neonatal or maternal outcome, the binomial nature was modelled using a logistic regression in each trial separately, with intervention as a covariate. Stratification or minimisation factors used in the randomisation of each study were not adjusted for in any analyses. The Sweeting *et al.*[25] approach was applied to include studies into the analysis of composite outcomes that had no information on outcome for one treatment group. This was only done for the primary analysis without interaction terms.

When examining intervention effect modifiers, we extended the models to include interaction terms between participant-level covariates and the intervention. For the interactions, continuous covariates (BMI and age) were analysed on continuous scales and as clinically defined categorical values. In addition, effects were presented within the subgroups defined by the interactions.

All primary analyses were performed on the combined intervention and any multiple treatment arms were combined into one intervention arm. For the secondary analysis of individual intervention types, multiple treatment arms were combined if they belonged to the same type, for example brochure arm and active counselling were grouped as mixed-approach intervention) or analysed separately if the treatment arms were categorised as different types (e.g. exercise and exercise plus dietary counselling).

Second stage of individual participant data meta-analysis

We pooled effect estimates (e.g. relating to treatment effects or treatment–covariate interactions) using a random-effects model using restricted maximum likelihood (REML) to produce a summary effect estimate for the mean (or average) effect across studies. The Knapp–Hartung correction was applied when deriving 95% CIs for each summary effect, to account for the uncertainty of the estimate of between-study heterogeneity (τ^2). Forest plots were generated to display the study-specific and pooled results.

Heterogeneity was summarised using the I^2 statistic and the estimated between-study variance (τ^2) was obtained using REML. To reveal the impact of heterogeneity more clearly, we also calculated approximate 95% prediction intervals (PIs) for the intervention (or interaction) effect in a new study using the formula suggested by Higgins *et al.*[26]

Sensitivity analyses

Small-study effects (and the potential for publication bias) were investigated by using contour-enhanced funnel plots and tests for asymmetry (using either the Egger's test for continuous outcomes or Peter's test for binary outcomes). In order to examine whether or not there may be availability bias in the obtained IPD, we compared summary results when including non-IPD studies with those in our IPD studies.

When possible, we then incorporated this aggregate data into the second stage of the two-step meta-analysis framework (see below), to combine the IPD trials with the aggregate data from other trials, to ascertain if conclusions were robust.

We investigated the following sources of bias for all or a subset of the primary outcomes by performing the following sensitivity analyses.

Study quality
We excluded studies at high risk of bias in at least one of the following domains: randomisation, allocation concealment, blinding for outcomes assessment or completeness of outcome data, and not a single item of low risk.

Intervention
We analysed the primary outcomes separately for each intervention type (diet, physical activity and mixed) to ensure that the analysis of the combined intervention was valid.

Adherence
We excluded any participants not adherent to their intervention.

Outcome measurement
We analysed BMI change instead of weight change to assess the impact of those studies that reported only on BMI and not weight. The effect of timing of gestational weight measurement on the effects was addressed by excluding weights measured before 37 completed weeks of gestation to exclude systematic differences. We analysed each component separately to ensure validity of the composite outcome.

Secondary analyses
All secondary analyses were performed only on participants in control arms to exclude the effect of treatment.

Quantification of the relationship between gestational weight gain and risk of outcome
For each composite outcome separately, we fitted two-stage meta-analysis models (logistic regression in stage 1, followed by a random-effects meta-analysis in stage 2) to obtain a pooled estimate of how each 1-unit increase in weight gain changed the risk of a poor outcome depending on baseline BMI. Baseline BMI remained a continuous variable.

We assessed if adherence in pregnancy to IOM weight-gain recommendations was associated with a reduced risk of adverse pregnancy outcomes in normal weight, overweight and obese women. We used the two-stage logistic framework as described above, with a covariate for adherence to IOM. Baseline BMI was included as categorical (normal weight/overweight/obese) using the same cut-off points as the definition for IOM adherence. Adherence was defined in three categories as below IOM, adherent to IOM and exceeding IOM recommendations for weight gain.

Evaluation of factors associated with weight change in pregnancy
We evaluated those variables that may be associated with GWG including age, ethnicity, underlying medical conditions like DM, parity and socioeconomic status. To obtain adjusted factor results, a multivariable model was fitted including all variables reported in at least 10 studies to identify those that were independently associated.

Network meta-analysis
We refrained from undertaking network meta-analysis, as there were no differences in estimates of effect for GWG between diet, physical activity and mixed-approach interventions.

Chapter 4 Characteristics and quality of studies included in the individual participant data meta-analysis

Study selection and individual participant data acquisition

Our previous search (until 2013) had identified 44 randomised trials.[7] We identified 3551 potentially relevant citations (*Figure 2*). We also identified 57 potential papers from references of included studies and four from oral communications. Detailed evaluation of the 167 articles led to the final identification of 74 trials ($n = 17,623$) on diet- and physical activity-based interventions in pregnancy (see *Figure 2*).

We invited the authors of 58 trials to join the project and share the IPD. Forty-one researchers from 29 teams, in 16 countries, joined the i-WIP Collaborative Network (until October 2015) and provided access to anonymised individual data on 12,343 women. The collaborators included obstetricians, academics, dietitians, nutritionists, physiotherapists, exercise physiologists, psychologists and clinical epidemiologists.

The most common combined reason for not being able to obtain IPD was difficulty in contacting the authors and contact loss (11/58).[28–38] Reasons for refusal to provide IPD included lack of time,[39,40] problems with data sharing[41] and conflicts of interest.[42,43] Data were lost in two trials.[44,45] Sixteen randomised controlled trials (RCTs) (including 2265 women) were identified too late in the project to be analysed, and thus we refrained from approaching the authors.[46–61] Most of these studies evaluated physical activity-based interventions (10 trials) and/or were conducted in developed countries (10 trials). Details of all 16 studies are provided in *Appendix 5*.

Characteristics of the studies included in the individual participant data analysis

Thirty-six RCTs contributed IPD to this project. Thirty-four trials were randomised trials with individual participant allocation and two were cluster RCTs.[62,63] Twenty-two trials were conducted in Europe, four in each of North America (three in the USA and one in Canada), Australia and South America (Brazil) and one each in Egypt and Iran. The size of the studies ranged from 12 to 2212 women. Eight studies included only obese women,[64–71] three included obese and overweight women,[72–74] one included overweight women[75] and 24 included women of any BMI. Four trials assessed diet-based interventions,[71,76–78] 16 evaluated physical activity,[27,42,67,75,79–89] and 15 trials adopted a mixed approach (diet, physical activity, behaviour-modifying techniques, etc.).[62–66,68,70,72–74,90–94] Four trials had a three-arm design (two interventions and routine care arm).[27,64,66,69] Of these, in three, interventions belonged to the same type (different type of counselling or different exercise routine).[27,64,66] In one trial, one arm of the intervention comprised exercise only and the other a combination of exercise and diet (mixed approach).[69] GWG was reported as an outcome in 57 studies; 33 provided IPD and in 27 studies only aggregate data were available. The numbers of studies reporting rates of individual maternal and fetal/neonatal outcomes are given in *Table 3*.

Overall, 38 eligible studies (38/74, 51.4%) comprising 5280 women did not contribute IPD. *Table 3* compares the characteristics of studies that did and did not share IPD for the meta-analysis. The detailed descriptions of all trials are provided in *Appendix 6*.

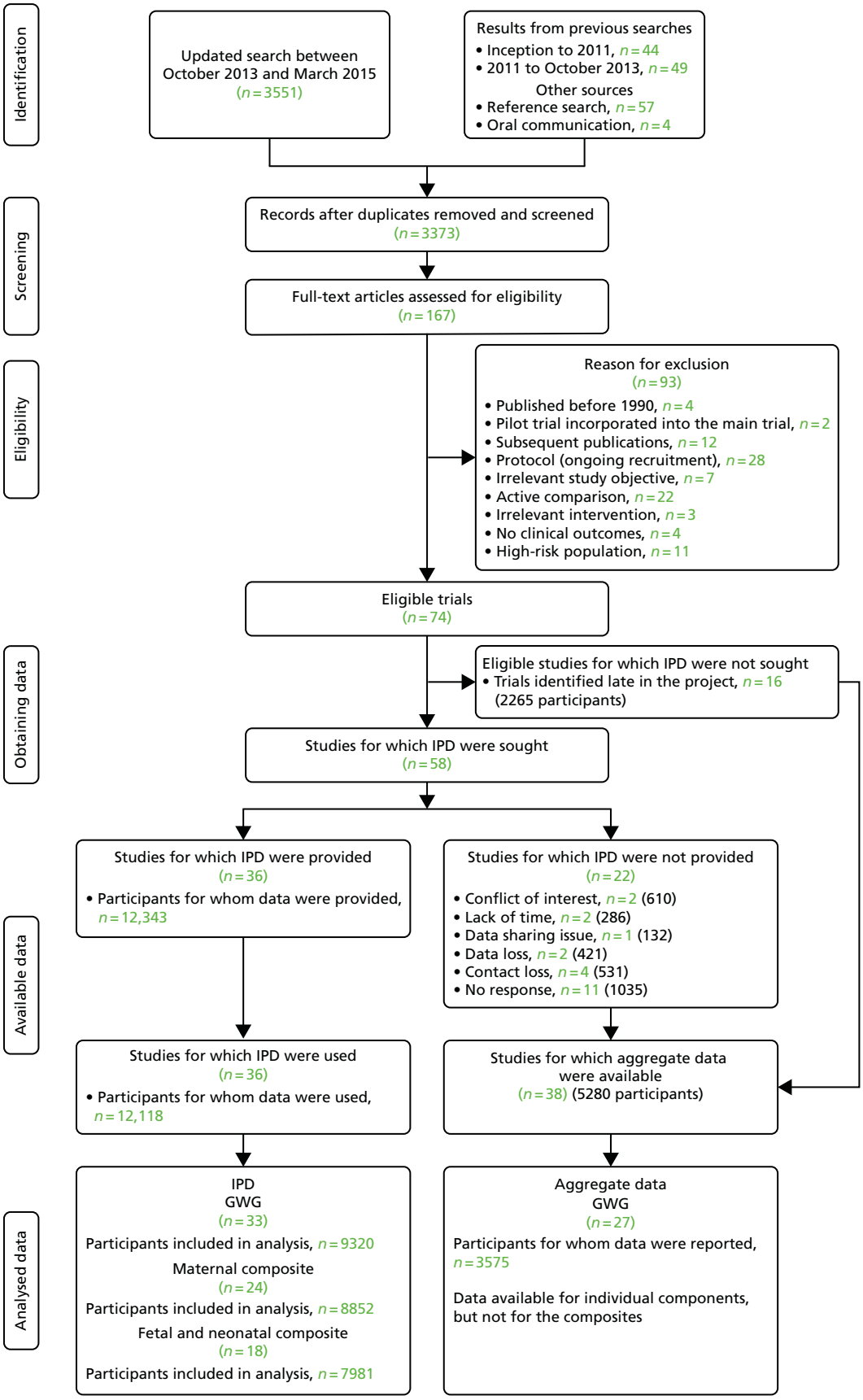

FIGURE 2 Flow diagram of studies in the IPD systematic review, showing the studies included in the review and meta-analysis.[27]

TABLE 3 Brief characteristics of trials available and unavailable for the i-WIP IPD meta-analysis

Characteristics	Availability of IPD (number of studies)	
	Available ($n = 36$ studies, $n = 12{,}526$ women)	Unavailable ($n = 38$ studies, $n = 5280$ women[a])
Population		
Any BMI category	24	27[b]
Obese or overweight	12	11
Intervention type		
Diet based	4	9
Exercise based	16	19
Mixed approach	16[c]	10
Outcomes[a]		
GWG	31	27
GDM	20	11
PE or PIH	15	6
Preterm delivery	16	8
Caesarean section	22	16
IUD	4	0
SGA	6	4
LGA	11	4
Admission to the NICU	4	2
Country of conduct		
Developed	30	26
Developing	6	12

a Based on the numbers given in the published trials reports.
b Li *et al.*[55] recruited women with BMI within normal range.
c Renault *et al.*[69] was classified as a mixed-approach study.

Characteristics of the individual participants in the individual participant data meta-analysis

The average age of participants was 30 years in both arms of the trials. More than 80% of participants were of Caucasian ethnicity. About half of the participants had obtained a higher degree, were nulliparous and were not physically active. *Table 4* shows a detailed comparison of baseline characteristics in both arms of the studies that contributed to the IPD.

The most common outcomes available in studies that contributed IPD were preterm delivery (11,731 women, 34 studies), Caesarean section (11,585 women, 34 studies) and SGA (11,682 women, 34 studies) and LGA (12,078 women, 36 studies) fetuses. This was followed by GWG (9320 women, 33 studies), PE (8350 women, 20 studies), PIH (9065 women, 25 studies) and GDM (9882 women, 30 studies). We were able to obtain maternal and fetal/neonatal outcome based on available individual data of 8852 (24 studies) and 8239 (19 studies) participants, respectively (*Table 5*).

TABLE 4 Baseline characteristics of patients in studies that contributed to the IPD

Baseline characteristics	Number of studies	Number of women	Study arm, mean (SD) or *n* (%)[a]	
			Control	Intervention
Age (years)	35	12,006	30.1 (5.2)	30.0 (5.1)
Height (cm)	31	11,689	165.0 (7.0)	165.4 (6.7)
Race/ethnicity	27	10,020		
Caucasian (including Russia and Australia)			4217 (87.2%)	4562 (88%)
Asian			156 (3.2%)	157 (3%)
Afro-Caribbean			292 (6%)	292 (5.6%)
Central/South American			64 (1.3%)	67 (1.3%)
Middle Eastern (including Iran and Turkey)			37 (0.8%)	37 (0.7%)
Other			68 (1.4%)	71 (1.4%)
Educational status of mother	29	8914		
Low			724 (16.9%)	722 (15.6%)
Medium			1292 (30.2%)	1372 (29.6%)
High			2268 (52.9%)	2536 (54.8%)
Current smoker	29	10,958	865 (16.4%)	875 (15.4%)
Ex-smoker (pre-pregnancy)	13	4099	456 (23.8%)	523 (24%)
Adherence to intervention	18	3321	N/A	2022 (60.9%)
Parity	33	11,805		
0			2692 (47.3%)	3027 (49.5%)
1			2083 (36.6%)	2136 (34.9%)
2			634 (11.1%)	647 (10.6%)
3			165 (2.9%)	179 (2.9%)
≥ 4			113 (2%)	129 (2.1%)
No exercise or sedentary	27	7583	1731 (47.6%)	1761 (44.6%)
Obesity (BMI of ≥ 30 kg/m^2)	34	12,031	2434 (42.0%)	2680 (43.0%)
Previous macrosomia	8	2906	400 (29.1%)	390 (25.5%)
Previous GDM	11	4297	49 (2.4%)	60 (2.9%)
GDM	20	8256	14 (0.4%)	23 (0.6%)
DM	25	9589	9 (0.2%)	6 (0.1%)
Hypertension in pregnancy	20	5695	37 (1.3%)	47 (1.6%)
Hypertension	23	5494	54 (2.1%)	73 (2.5%)

N/A, not applicable.
a Percentage refers to proportion out of observations in control or intervention arms, respectively.

TABLE 5 Details of outcome measures reported in all eligible studies that contributed to the IPD

Outcomes	Number of studies	Number of women
Baseline weight (kg)	33	11,748
Follow-up weight (kg)	33	9326
Change in weight (kg)	33	9320
Baseline BMI	34	12,031
Follow-up BMI	31	9240
Change in BMI	31	9238
PE	20	8350
PIH	25	9065
PE or PIH[a]	27	9915
GDM[a]	30	9882
Preterm delivery (< 37 weeks' gestational age)[a]	34	11,731
All Caesarean section[a]	33	11,585
Emergency Caesarean section	16	7226
Elective Caesarean section	16	7226
Caesarean section unspecified	17	4423
Maternal composite outcome	24	8852
IUD[a]	22	9354
SGA[a]	34	11,682
LGA[a]	36	12,078
Admission to the NICU[a]	21	8749
Fetal/neonatal composite outcome	19	8239

a Components of the composite outcome.

Risk of bias within eligible studies

Two-thirds (52/74, 70.3%) of eligible trials were rated as having a low risk of bias for random sequence generation and selective reporting of outcomes. More than half of the studies (47/74, 63.5%) had complete outcome data, with 18% of the remaining trials (13 studies) being rated as being at high risk of bias. Allocation concealment was adequate in 45% (33/74) of included trials. In all studies the risk of bias for blinding of participants and personnel was rated as either unclear (45/74, 60.8%) or high (29/74, 39.2%). In 27 studies (36.5%) there were no concerns over the rating of risk of bias for blinding of outcome assessment, while 15 studies (20.3%) were assessed as being at high risk of bias. For the remaining studies there was not enough information to assess the risk of bias (32/74, 43.2%). *Figure 3* presents a summary of the risk of bias rating by domain for all eligible RCTs. The detailed assessment and a global risk of bias are presented in *Appendix 7*.

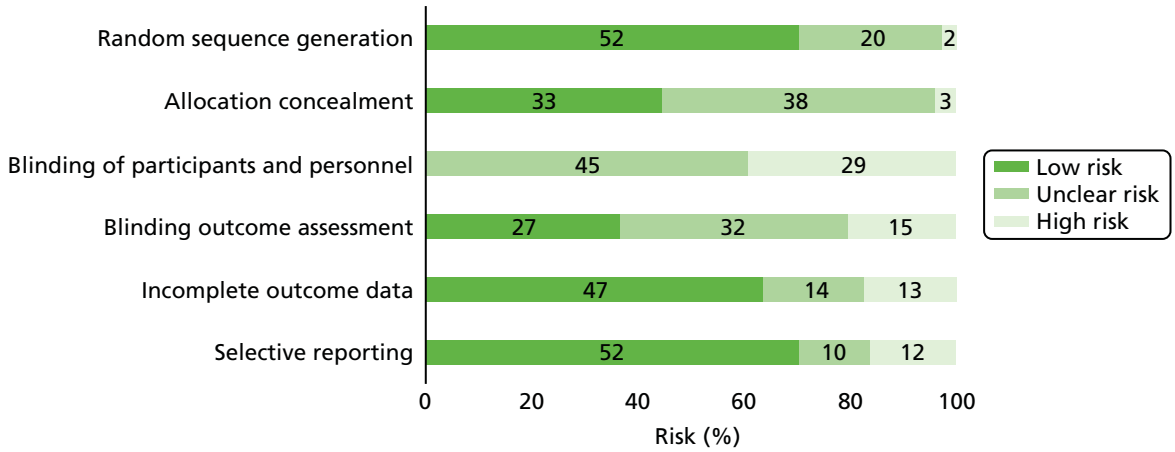

FIGURE 3 Summary of the risk of bias rating for all eligible studies ($n = 74$).

Quality assessment of studies that contributed data to individual participant data meta-analysis

Studies that contributed IPD were rated as being at low risk of bias for random sequence generation (94% vs. 47% among studies with unavailable IPD), allocation concealment (64% vs. 26%) and completeness of outcome data (78% vs. 50%) compared with non-IPD studies. The risk-of-bias rating was similar in both groups for selective reporting of outcomes (*Table 6*).

TABLE 6 Risk-of-bias assessment in IPD studies compared with non-IPD

	Risk-of-bias rating, *n* (%)					
	Low		Unclear		High	
Items	IPD	Non-IPD	IPD	Non-IPD	IPD	Non-IPD
Random sequence generation	34 (94)	18 (47)	2 (6)	18 (47)	0 (0)	2 (5)
Allocation concealment	23 (64)	10 (26)	11 (31)	27 (71)	2 (6)	1 (3)
Blinding of participants and personnel	0 (0)	0 (0)	17 (47)	28 (74)	19 (53)	10 (26)
Blinding of outcome assessment	16 (44)	11 (29)	6 (17)	26 (68)	14 (39)	1 (3)
Incomplete outcome data	28 (78)	19 (50)	3 (8)	11 (29)	5 (14)	8 (21)
Selective reporting of outcomes	23 (64)	29 (76)	6 (17)	4 (11)	7 (19)	5 (13)
Total number of studies	36	38	36	38	36	38

Chapter 5 Effect of diet- and physical activity-based interventions in pregnancy on maternal and fetal outcomes

Gestational weight gain

Overall effect

Overall, diet- and physical activity-based interventions (33 studies, 9320 women) reduced GWG by an average of –0.70 kg (95% CI –0.92 to –0.48 kg; $I^2 = 14.1\%$) (*Figure 4*), after accounting for baseline weight and clustering effect.

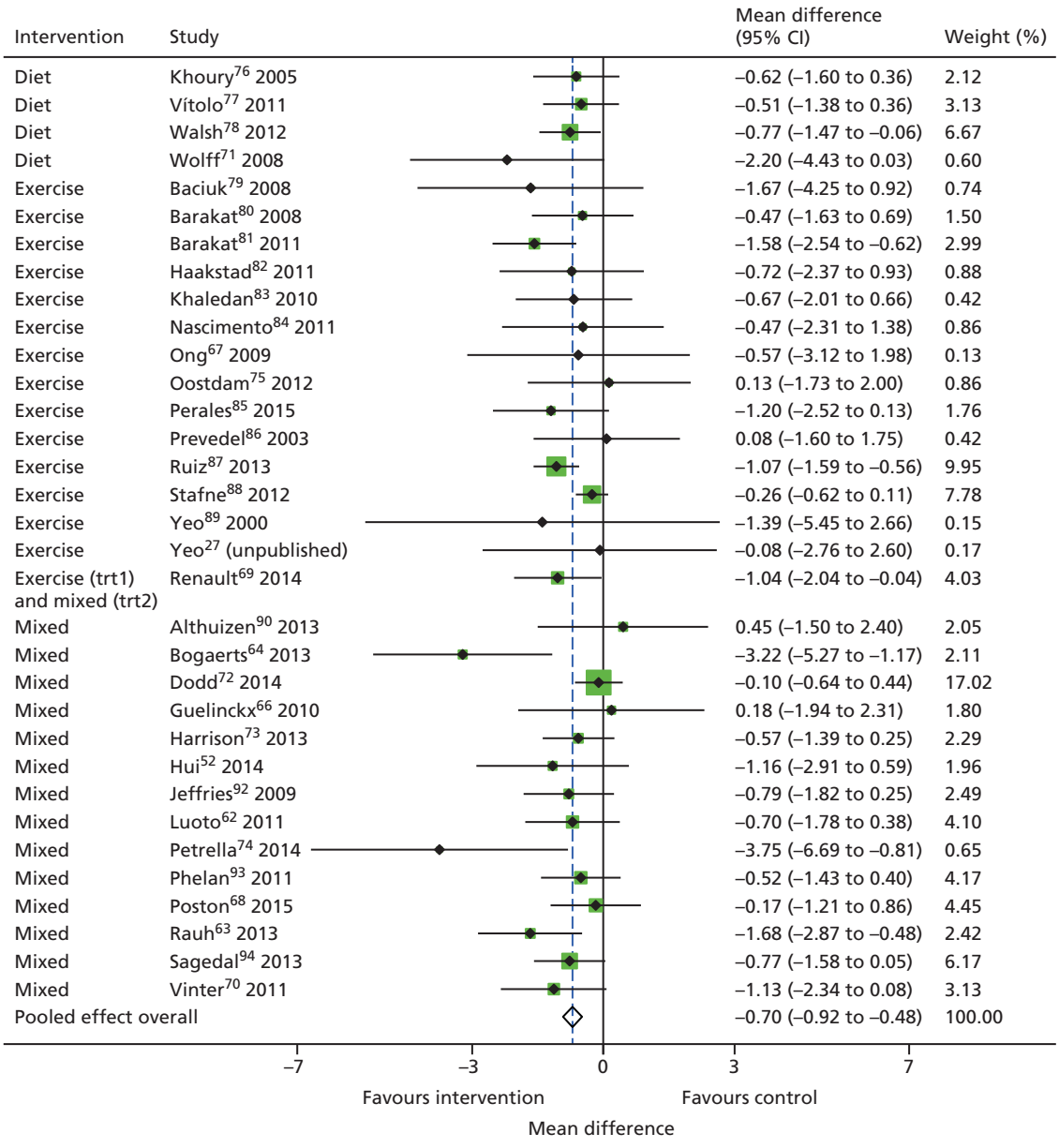

FIGURE 4 Effects of diet- and physical activity-based interventions on GWG (kg). Trt, treatment.

All three individual interventions (diet, physical activity and mixed) had a similar effect on reducing GWG by an average of 0.7 kg (*Table 7*).

Sensitivity analysis

The beneficial effect on GWG was consistent after including all available aggregate data from an additional 27 non-IPD studies (MD –1.13 kg, 95% CI –1.58 to –0.68 kg) by including only IPD studies that were rated as being at low risk of bias (MD –0.67 kg, 95% CI –0.95 to –0.38 kg), excluding women non-adherent to the intervention (MD –0.76 kg, 95% CI –1.00 to –0.52 kg), restricting the IPD analysis to women who were followed up until 37 weeks of gestation (MD –0.91 kg, 95% CI –1.17 to –0.66 kg) and using BMI instead of maternal weight as a measure of weight change in pregnancy (MD –0.30 kg/m^2, 95% CI –0.39 to –0.21 kg/m^2) (see *Appendix 8*).

Differential effect of the intervention on gestational weight gain in various subgroups

Thirty-one studies (9285 women) provided data to evaluate the differential effect of interventions on GWG for women with varied BMI at booking. There was no significant treatment–covariate interaction for baseline BMI (–0.02 kg change in effect per 1 kg/m^2 increase in BMI, 95% CI –0.08 to 0.04 kg change). We did not observe any interaction effect for other effect modifiers such as age (–0.03 kg change in effect per 1-year increase in age, 95% CI –0.08 to 0.02 kg), parity (0.10 kg change in effect for multiparous vs. nulliparous, 95% CI –0.39 to 0.60 kg change), ethnicity (0.05 kg change in effect for non-Caucasian vs. Caucasian, 95% CI –1.27 to 1.37 kg change) and underlying medical condition (1.51 kg change in effect for women with at least one condition vs. none, 95% CI –2.01 to 5.02 kg) (*Table 8*). The findings were consistent when we analysed the continuous covariates as dichotomised measures.

Maternal outcomes

Overall effect

Diet- and physical activity-based interventions (24 studies, 8852 women) reduced the odds of adverse maternal outcomes by 10% (summary OR 0.90, 95% CI 0.79 to 1.03; $I^2 = 26.7\%$). The effect was not statistically significant at the 5% level (*Figure 5*).

The effects on composite maternal outcomes were evaluated in two-thirds of participants in studies of mixed interventions, compared with 4% of participants in studies of diet-based interventions. The effects of physical activity, diet and mixed approaches were not statistically significant (*Table 9*).

TABLE 7 Effects of diet- and physical activity-based interventions on GWG (kg)

Intervention	Number of studies	Number of women	Mean change of weight, mean (SD)		Summary-adjusted MD[a] of weight (95% CI)	95% PI
			Control	Intervention		
Diet	4	1168	11.0 (4.8)	10.2 (4.4)	–0.72 (–1.48 to 0.04)	–1.75 to 0.30
Physical activity	15	2915	10.8 (5.3)	9.8 (4.4)	–0.73 (–1.11 to –0.34)	–1.50 to 0.05
Mixed approach	15	5369	10.4 (5.7)	10.0 (5.8)	–0.71 (–1.10 to –0.31)	–1.42 to 0.01
Overall[b]	33	9320	10.8 (5.4)	10.1 (5.4)	–0.70 (–0.92 to –0.48)	–1.24 to –0.16

a Model accounting for baseline weight and clustering effect.
b The Renault *et al.*[69] trial had two intervention arms (physical activity only and mixed approach).

TABLE 8 Subgroup effects and treatment–covariate interactions for GWG (kg)

Item	Number of studies	Number of women	Summary-adjusted MD[a] of weight (95% CI)	Summary treatment–covariate interaction (95% CI)	95% PI	I^2 (%)
Baseline BMI category						
Normal weight	21	3376	–0.77 (–1.15 to –0.39)		–1.68 to 0.14	33.9
Overweight	28	2574	–0.75 (–1.22 to –0.27)		–2.07 to 0.58	32.7
Obese	31	3335	–0.85 (–1.41 to –0.29)		–2.73 to 1.03	43.9
Per unit of BMI	31	9285		–0.02 (–0.08 to 0.04)	–0.21 to 0.17	39.8
Overweight vs. normal weight	21	6023		–0.11 (–0.77 to 0.55)	–1.48 to 1.25	32.0
Obese vs. normal weight	21	6023		0.06 (–0.90 to 1.01)	–2.23 to 2.34	32.7
Obese vs. overweight	28	8802		–0.09 (–1.05 to 0.86)	–3.2 to 3.01	46.9
Age						
≥ 20 years	32	9045	–0.72 (–0.95 to –0.50)		–1.29 to –0.15	17.0
< 20 years	13	232	0.05 (–1.34 to 1.44)		–2.11 to 2.21	1.0
Per year of age	32	9277		–0.03 (–0.08 to 0.02)	–0.14 to 0.09	25.9
< 20 vs. ≥ 20 years	13	5012		0.65 (–1.11 to 2.41)	–2.66 to 3.97	10.8
Ethnicity						
Caucasian	21	6814	–0.74 (–1.07 to –0.42)		–1.52 to 0.04	41.4
Non-Caucasian	15	621	–0.42 (–1.12 to 0.28)		–1.13 to 0.29	0.0
Non-Caucasian vs. Caucasian	12	4439		0.05 (–1.27 to 1.37)	–1.28 to 1.39	26.1
Parity						
Nulliparous	27	4513	–0.80 (–1.17 to –0.43)		–1.84 to 0.24	38.3
Multiparous	27	4548	–0.62 (–0.88 to –0.37)		–0.88 to –0.37	0.0
Multiparous vs. nulliparous	24	7247		0.10 (–0.39 to 0.60)	–0.83 to 1.04	4.8
Pre-existing medical condition[b]						
No medical condition	18	4335	–0.62 (–0.90 to –0.34)		–1.07 to –0.17	0.0
At least one medical condition	6	128	0.40 (–1.92 to 2.71)		–2.10 to 2.90	14.1
At least one medical condition vs. none	5	1196		1.51 (–2.01 to 5.02)	–4.13 to 7.15	28.4

a Model accounting for baseline weight and clustering effect.
b DM or hypertension.

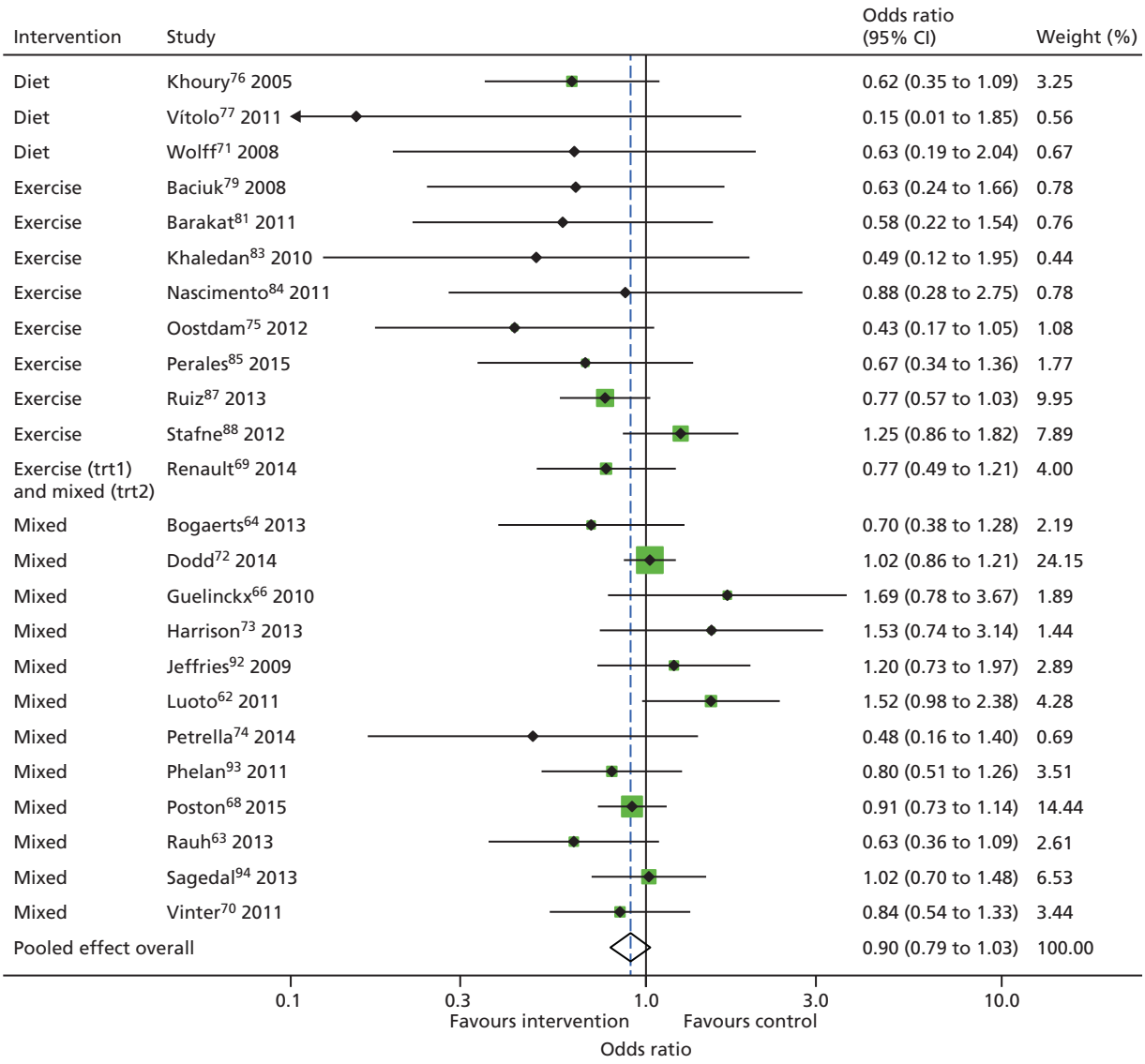

FIGURE 5 Effects of diet- and physical activity-based interventions on composite maternal outcome. Trt, treatment.

TABLE 9 Effects of diet- and physical activity-based interventions on maternal composite outcome

Intervention	Number of studies	Number of women	Study arm (number of events/total number of women)		Summary OR[a] (95% CI)	95% PI
			Control	Intervention		
Diet	3	397	84/218	42/179	0.60 (0.20 to 1.75)	0.02 to 14.27
Physical activity	9	2311	367/1115	346/1196	0.81 (0.61 to 1.09)	0.48 to 1.37
Mixed approach	13	6259	1438/3009	1508/3250	0.97 (0.84 to 1.12)	0.82 to 1.13
Overall[b]	24	8852	1838/4226	1895/4624	0.90 (0.79 to 1.03)	0.68 to 1.20

a Model accounting for baseline weight and clustering effect.
b The Renault *et al.*[69] trial had two intervention arms (physical activity only and mixed approach).

Sensitivity analysis by excluding studies rated as having a high risk of bias (summary OR 0.91, 95% CI 0.77 to 1.08) and women non-adherent to the intervention (summary OR 0.92, 95% CI 0.80 to 1.06) did not affect the findings. The results of all sensitivity analyses are provided in *Appendix 8*.

Effect of interventions on individual maternal outcomes

The odds of Caesarean section were reduced by 9%, which bordered on statistical significance (summary OR 0.91, 95% CI 0.83 to 0.99). For other maternal outcomes, such as GDM (OR 0.89, 95% CI 0.72 to 1.10), PE or PIH (OR 0.95, 95% CI 0.78 to 1.16), and preterm birth (OR 0.94, 95% CI 0.78 to 1.13), there was a trend towards reduction that was not statistically significant. Meta-analysis based on published aggregate data only showed a significant reduction in GDM (OR 0.78, 95% CI 0.64 to 0.95) and Caesarean section (OR 0.90, 95% CI 0.82 to 0.99) compared with the control group. There were no significant reductions in preterm birth (OR 0.80, 95% CI 0.63 to 1.01), PE or PIH (OR 0.89, 95% CI 0.75 to 1.05) (for details see *Appendix 9*). More participants were included in the IPD meta-analysis than in the meta-analysis based on published data for outcomes preterm birth and PE or PIH; the participant numbers were similar for GDM and Caesarean section (*Table 10*).

Differential effects of the intervention for composite maternal outcome in various subgroups

Twenty-four studies (8848 women) contributed IPD to assess the differential effects of interventions on the composite maternal outcome according to maternal BMI category. There was no significant treatment–covariate interaction for baseline BMI (no change in effect for every 1-kg/m^2 increase in BMI, OR 95% CI 0.98 to 1.02). The effects of the interventions were not significantly modified by other relevant covariates such as age (1% increase in effect for every 1-year increase in age, OR 95% CI 0.99 to 1.03), parity (3% increase in effect for multiparity vs. nulliparity, OR 95% CI 0.75 to 1.39), ethnicity (7% decrease in effect for non-Caucasian vs. Caucasian, OR 95% CI 0.63 to 1.37) and underlying medical condition (44% increase in effect for women with none vs. at least one condition, OR 95% CI 0.15 to 13.74). The findings were consistent when continuous covariates were further analysed as categorical values (*Table 11*).

TABLE 10 Intervention effects on the individual components of the composite maternal outcome: IPD meta-analysis and aggregate data meta-analysis

	Data						
	IPD ($n = 36$)			Aggregate ($n = 74$)			
Maternal outcome	Number of studies	Number of women	Summary OR[a] (95% CI)	Number of studies	Number of women	OR[b] (95% CI)	I^2 (%)
GDM[c]	27	9427	0.89 (0.72 to 1.10)	29	11,118	0.77 (0.63 to 0.94)	38
PE or PIH	22	9618	0.95 (0.78 to 1.16)	20	9198	0.89 (0.75 to 1.05)	0
Preterm birth	32	11676	0.94 (0.78 to 1.13)	23	7480	0.80 (0.63 to 1.01)	30
Caesarean section	32	11410	0.91 (0.83 to 0.99)	37	11,340	0.90 (0.82 to 0.99)	2

a IPD meta-analysis adjusted for clustering effect.
b Meta-analysis using aggregate published data, random-effect model.
c As defined in each study.

TABLE 11 Subgroup effects and treatment–covariate interaction for composite maternal outcome

Item	Number of studies	Number of women	Summary OR[a] (95% CI)	Summary treatment–covariate interaction (95% CI)	95% PI	I^2 (%)
Baseline BMI category						
Normal weight	12	2445	0.91 (0.65 to 1.28)		0.42 to 1.96	48.5
Overweight	19	2222	1.04 (0.86 to 1.26)		0.86 to 1.26	0.0
Obese	20	4181	0.92 (0.80 to 1.05)		0.8 to 1.05	0.0
Per unit BMI	24	8848		1.00 (0.98 to 1.02)	0.98 to 1.02	0.0
Overweight vs. normal weight	12	4040		1.02 (0.67 to 1.55)	0.52 to 1.99	20.2
Obese vs. normal weight	12	4040		0.95 (0.57 to 1.59)	0.57 to 1.60	0.0
Obese vs. overweight	20	7400		0.95 (0.71 to 1.26)	0.71 to 1.26	0.0
Age						
≥ 20 years	24	8656	0.91 (0.81 to 1.02)		0.73 to 1.13	20.5
< 20 years	9	172	1.57 (0.66 to 3.71)		0.65 to 3.80	0.0
Per year of age	24	8828		1.01 (0.99 to 1.03)	0.99 to 1.03	0.0
< 20 years vs. ≥ 20 years	8	4720		1.84 (0.74 to 4.57)	0.72 to 4.72	0.0
Ethnicity						
Caucasian	15	6510	0.92 (0.79 to 1.07)		0.67 to 1.25	26.8
Non-Caucasian	11	917	0.86 (0.63 to 1.17)		0.62 to 1.17	0.0
Non-Caucasian vs. Caucasian	9	4851		0.93 (0.63 to 1.37)	0.62 to 1.38	0.0
Parity						
Nulliparous	21	4613	0.87 (0.71 to 1.07)		0.54 to 1.41	39.8
Multiparous	22	4186	0.92 (0.78 to 1.07)		0.78 to 1.07	21.9
Multiparous vs. nulliparous	20	8053		1.03 (0.75 to 1.39)	0.53 to 2.00	34.0
Pre-existing medical condition[b]						
No medical condition	15	3135	0.85 (0.66 to 1.09)		0.46 to 1.57	42.5
At least one medical condition	5	89	1.65 (0.36 to 7.51)		0.29 to 9.37	0.0
None vs. at least one medical condition	4	916		1.44 (0.15 to 13.74)	0.03 to 76.75	24.9

a Model accounting for clustering effect.
b DM or hypertension.

Fetal/neonatal outcomes

Overall effect

Diet- and physical activity-based interventions (18 studies, 7981 women) did not reduce the odds of the composite adverse fetal/neonatal outcome (summary OR 0.94, 95% CI 0.83 to 1.08) (*Figure 6*) after adjusting for clustering.

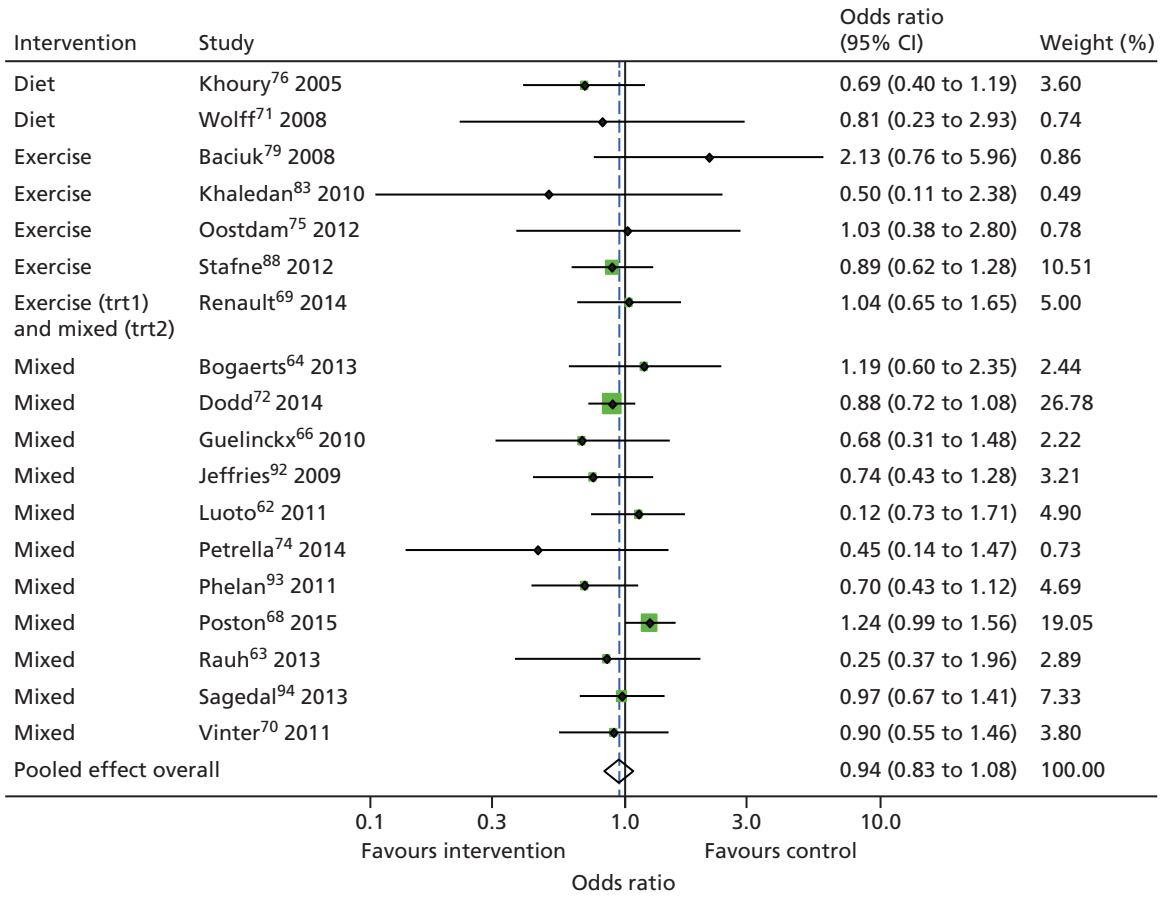

FIGURE 6 Effect of diet- and physical activity-based interventions on composite fetal/neonatal outcome.

Two studies (346 women) evaluated diet-based interventions, five (1274 women) assessed physical activity-based interventions and 12 (6494 women) studied mixed interventions on composite fetal/neonatal outcomes. None of the three interventions reduced composite adverse fetal/neonatal outcome (*Table 12*).

Differential effect of the intervention for composite fetal/neonatal outcome in various subgroups

Eighteen studies (7981 women) provided IPD to assess the differential effects of interventions by maternal baseline BMI on composite fetal/neonatal outcome. There was a 2% decrease in the treatment effect of

TABLE 12 Effects of diet- and physical activity-based interventions on composite fetal/neonatal outcome

Intervention	Number of studies	Number of women	Study arm (number of events/total number of women)		Summary-adjusted OR[a] (95% CI)	95% PI
			Control	Intervention		
Diet	2	346	47/181	31/167	0.64 (0.02 to 18.06)	–
Physical activity	5	1274	156/641	170/634	1.23 (0.72 to 2.10)	0.45 to 3.32
Mixed	12	6494	875/3338	953/3626	1.02 (0.90 to 1.15)	0.87 to 1.19
Overall[b]	18	7981	951/3802	1007/4179	0.94 (0.83 to 1.08)	0.74 to 1.21

a Model accounting for clustering effect.
b The Renault *et al.*[69] trial had two intervention arms (physical activity only and mixed approach).

borderline significance for every 1 kg/m^2 increase in booking BMI for composite fetal/neonatal outcomes (OR 0.98, 95% CI 0.95 to 1.00). There was no treatment–covariate interaction for other variables, such as maternal age of < 20 years (OR 1.05, 95% CI 0.33 to 3.35), ethnicity (12% decrease in effect for non-Caucasian vs. Caucasian, 95% CI 0.75 to 1.68), parity (6% reduction in effect for multiparous vs. nulliparous, 95% CI 0.64 to 1.47), baseline medical conditions (42% increase in effect for women with at least one medical condition vs. none, 95% CI 0.00 to 2440.15) (*Table 13*).

TABLE 13 Subgroup effects and treatment–covariate interaction for fetal/neonatal composite outcome

Item	Number of studies	Number of women	Summary OR[a] (95% CI)	Summary treatment–covariate interaction (95% CI)	95% PI	I^2 (%)
Baseline BMI category						
Normal weight	7	1843	0.93 (0.60 to 1.43)		0.40 to 2.16	31.6
Overweight	12	2065	0.83 (0.61 to 1.13)		0.49 to 1.39	0.0
Obese	13	4327	0.92 (0.72 to 1.19)		0.55 to 1.54	29.7
Per unit BMI	18	7978		0.98 (0.95 to 1.00)	0.94 to 1.02	18.5
Overweight vs. normal weight	8	2827		0.87 (0.40 to 1.92)	0.15 to 4.91	44.0
Obese vs. normal weight	8	2827		0.84 (0.42 to 1.66)	0.41 to 1.70	0.0
Obese vs. overweight	14	6272		0.94 (0.60 to 1.45)	0.51 to 1.71	0.0
Age						
≥ 20 years	16	8061	0.95 (0.82 to 1.09)		0.72 to 1.24	0.0
< 20 years	7	162	1.01 (0.34 to 2.98)		0.32 to 3.14	0.0
Per year of age	18	7965		1.01 (0.98 to 1.04)	0.97 to 1.05	4.1
< 20 vs. ≥ 20 years	6	4941		1.05 (0.33 to 3.35)	0.30 to 3.67	0.0
Ethnicity						
Caucasian	11	6018	0.93 (0.79 to 1.08)		0.75 to 1.14	3.5
Non-Caucasian	9	939	1.10 (0.78 to 1.54)		0.78 to 1.55	0.0
Non-Caucasian vs. Caucasian	9	5146		1.12 (0.75 to 1.68)	0.74 to 1.69	0.0
Parity						
Nulliparous	16	4152	0.97 (0.80 to 1.17)		0.69 to 1.35	21.1
Multiparous	15	4048	0.91 (0.72 to 1.15)		0.56 to 1.48	23.2
Multiparous vs. nulliparous	15	7295		0.94 (0.64 to 1.37)	0.39 to 2.28	35.5
Pre-existing medical condition[b]						
No medical condition	12	3407	0.89 (0.74 to 1.08)		0.74 to 1.08	0.0
At least one medical condition	3	63	0.54 (0.04 to 7.52)		0.00 to 1285.09	0.0
At least one medical condition vs. none	3	925		0.58 (0.03 to 9.81)	0.00 to 2440.15	0.0

a Model accounting for clustering effect.
b DM or hypertension.

None of the sensitivity analyses performed showed a significant impact on the intervention effect (see *Appendix 8*).

Effect of interventions on individual fetal/neonatal outcomes

Compared with published aggregate data, IPD were available for more participants for fetal/neonatal outcomes, such as SG, LGA and admission to the NICU. IPD meta-analysis did not show a significant effect on SGA infants (summary OR 1.06, 95% CI 0.94 to 1.20), LGA infants (summary OR 0.90, 95% CI 0.76 to 1.07) or admission to the NICU (summary OR 1.01, 95% CI 0.84 to 1.23). Aggregate meta-analysis of published data showed similar results of no effect for all fetal outcomes (*Table 14*).

Publication bias

The contour-enhanced funnel plots on small-study effects (potential publication bias) for GWG (*Figure 7*) showed visual and statistical evidence (Egger's test, $p = 0.038$) of asymmetry, indicating that smaller studies were more likely to have large intervention effects. Addition of aggregate data from non-IPD studies to the meta-analysis worsened the symmetry, suggesting that the asymmetry was not caused by availability bias. Exclusion of studies rated as being at high risk of bias to the analysis improved symmetry substantially (Egger's test, $p = 0.608$).

There was significant evidence of small-study effects for the composite maternal (Peter's test, $p = 0.036$), but not for the fetal/neonatal composite outcome ($p = 0.398$) (*Figure 8*). Heterogeneity, which was present in all these meta-analyses, might be the cause (rather than publication bias) of asymmetry in the funnel plots.

TABLE 14 Intervention effects on the individual components of the composite fetal and neonatal outcome: IPD meta-analysis and aggregate meta-analysis

	Data						
	IPD ($n = 35$ studies)			Aggregate ($n = 74$ studies)			
Fetal/neonatal outcome	Number of studies	Number of women	Summary OR[a] (95% CI)	Number of studies	Number of women	Summary OR[b] (95% CI)	I^2 (%)
IUD[c]	–	–	–	4	4857	1.95 (0.55 to 6.90)	0
SGA	33	11,666	1.06 (0.94 to 1.20)	8	2835	1.27 (0.91 to 1.77)	0
LGA	34	12,047	0.90 (0.76 to 1.07)	13	5827	0.88 (0.68 to 1.15)	37
Admission to the NICU	16	8140	1.01 (0.84 to 1.23)	6	5200	0.95 (0.77 to 1.19)	22

a Model accounting for baseline weight and clustering effect.
b Aggregate meta-analysis using published data.
c Insufficient data.

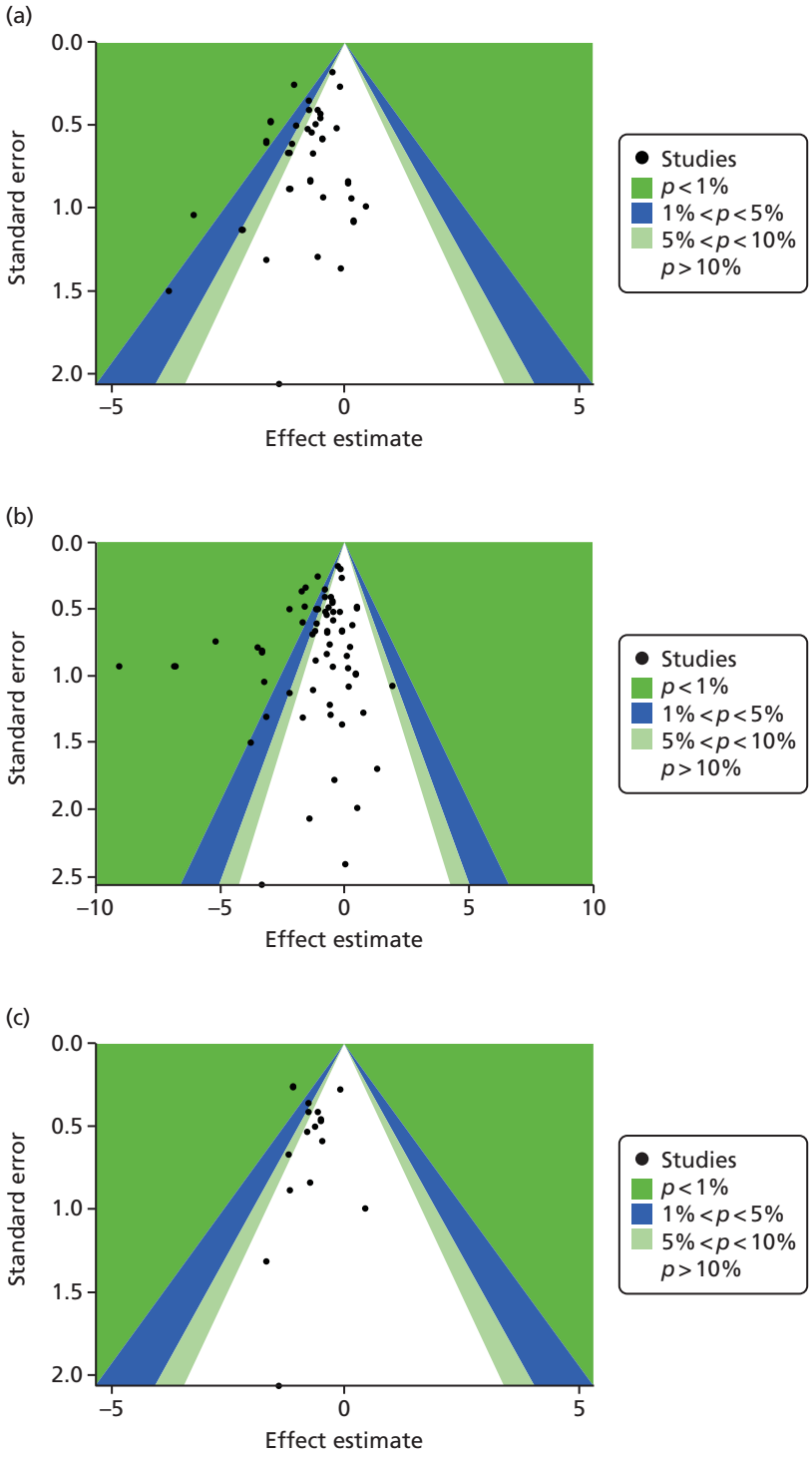

FIGURE 7 Contour-enhanced funnel plot for GWG. (a) IPD data only; (b) IPD and aggregate data; and (c) IPD studies classified as being at low risk of bias.

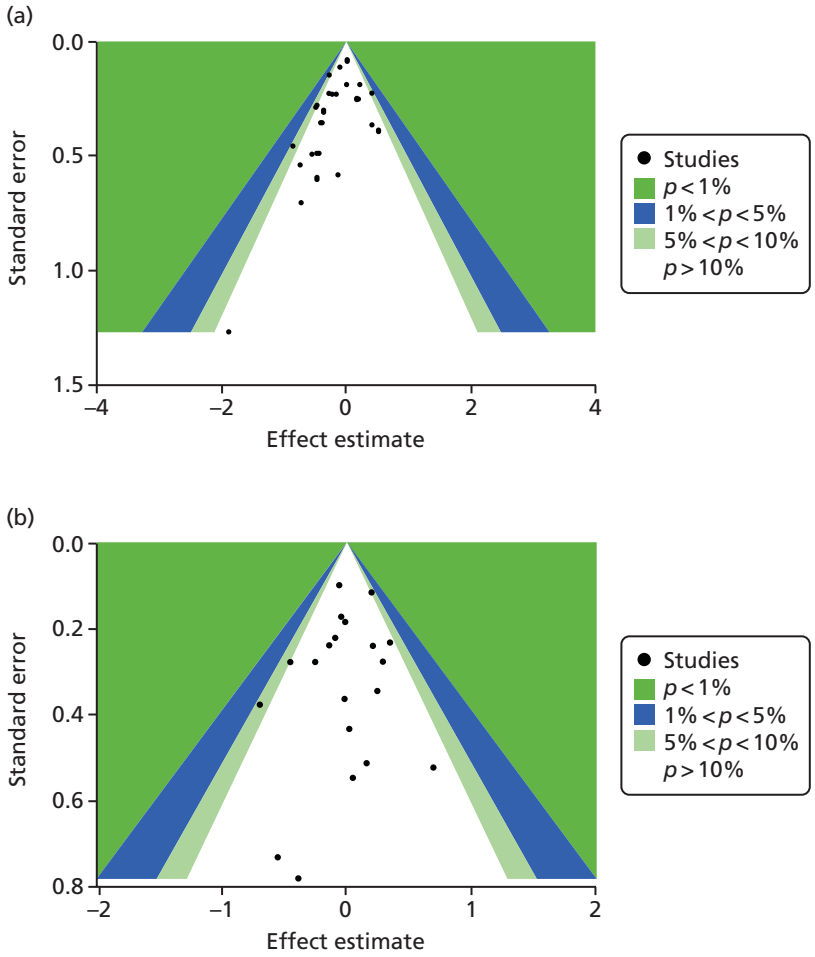

FIGURE 8 Contour-enhanced funnel plot for (a) composite maternal; and (b) fetal/neonatal outcomes.

Chapter 6 Association of maternal weight and weight gain in pregnancy and pregnancy complications

Gestational weight gain, maternal weight at booking and adverse maternal and fetal/neonatal outcomes

Twenty-three trials evaluated the association of GWG, BMI at booking and composite maternal outcomes (3367 women), and 19 trials provided data for composite fetal/neonatal outcomes (3030 women) from women in control groups. There was no association between GWG, booking BMI and risk of adverse maternal (OR 1.03, 95% CI 0.93 to 1.15) or fetal/neonatal complications (OR 1.02, 95% CI 0.91 to 1.15), and this effect does not differ by baseline BMI (*Table 15*).

Figure 9 presents the relationship between presence or absence of adverse maternal and fetal complications for women entering pregnancy with varied BMI, for different values of GWG.

Adherence to the Institute of Medicine's recommendations and risk of adverse pregnancy outcomes

In women who were normal weight at booking, about 40% adhered to the IOM's recommendations and gained up to 16 kg in pregnancy; another 40% gained less than the recommended range, and less than one-fifth exceeded the recommendations. One-third (29%) of overweight and obese (30%) women complied with the recommendations. About half of overweight women and 44% of obese women exceeded the recommended ranges (*Table 16*).

The odds of adverse composite outcome were not significant when normal weight women gained above (summary OR 1.05, 95% CI 0.60, 1.82) and below (summary OR 0.99, 95% CI 0.67, 1.47) the recommended targets. We did not observe any significant additional increase in maternal risks when obese and overweight women did not comply with the recommended targets (*Table 17*). There was no significant increase in the odds of adverse maternal outcomes in overweight and obese women who gained below or above the recommendations.

TABLE 15 Effect of GWG on composite maternal and fetal/neonatal outcomes accounting for the modifying effect of baseline BMI category

Outcomes	Number of studies	Number of women	Effect of GWG, OR[a] (95% CI)	Modifying effect of baseline BMI, OR (95% CI)	I^2 (%)
Composite maternal outcome	23	3367	1.03 (0.93 to 1.15)	N/A[b]	0
Composite fetal and neonatal outcome	19	3030	1.02 (0.91 to 1.15)	1.00 (1.00 to 1.00)	0

N/A, not available.
a Model accounting for clustering effect and for interaction between baseline BMI and GWG.
b Non-convergence during second step of the meta-analysis.

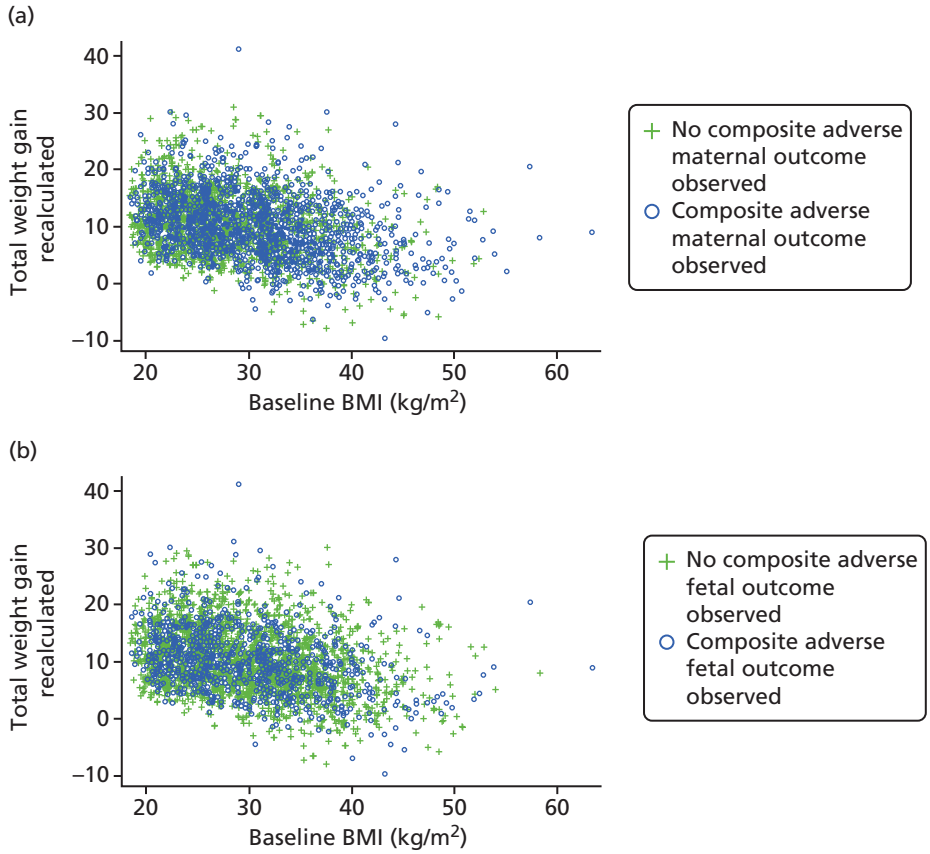

FIGURE 9 Scatterplot of GWG against baseline BMI for adverse (a) maternal; and (b) fetal/neonatal composite outcomes.

TABLE 16 Adherence to IOM's guidelines by baseline BMI category

GWG	Normal weight, *n* (%)	Overweight, *n* (%)	Obese, *n* (%)
Below IOM	649 (40)	242 (19)	400 (26)
Adherent to IOM	663 (41)	362 (29)	467 (30)
Exceeds IOM	310 (19)	641 (51)	695 (44)
Total	1622	1245	1562

TABLE 17 Association between adherence to the IOM-recommended weight-gain targets in pregnancy and composite adverse maternal events within subgroups of BMI category

Adherence to IOM's targets in pregnancy	Number of studies	Number of women	Summary OR[a] (95% CI)	95% PI	I^2 (%)
Normal weight					
Below vs. adherent	12	1092	0.99 (0.67 to 1.46)	0.67 to 1.46	0.0
Exceeds vs. adherent	11	1083	1.05 (0.61 to 1.80)	0.41 to 2.65	0.0
Overweight					
Below vs. adherent	16	889	1.28 (0.79 to 2.08)	0.79 to 2.08	0.0
Exceeds vs. adherent	18	904	0.78 (0.49 to 1.26)	0.34 to 1.80	0.0
Obese					
Below vs. adherent	17	1261	1.38 (0.95 to 2.01)	0.88 to 2.18	0.0
Exceeds vs. adherent	19	1324	1.15 (0.85 to 1.56)	0.85 to 1.56	0.0

a Model adjusted for clustering effect.

Non-adherence to IOM's targets for weight gain in pregnancy did not pose additional risks of fetal complications in normal weight, overweight and obese pregnant women (*Table 18*). The odds of composite adverse fetal outcomes were not significantly increased in normal weight, overweight and obese women who gained more or less than the recommended targets.

TABLE 18 Association between adherence to IOM's guidelines and composite adverse fetal events within subgroups of BMI

Adherence to the IOM-recommended weight-gain targets in pregnancy	Number of studies	Number of women	Summary OR[a] (95% CI)	95% PI	I^2 (%)
Normal weight					
Below vs. adherent	9	821	0.87 (0.40 to 1.90)	0.16 to 4.84	38.4
Exceeds vs. adherent	9	821	1.26 (0.60 to 2.65)	0.35 to 4.57	29.0
Overweight					
Below vs. adherent	10	830	1.07 (0.51 to 2.22)	0.38 to 2.99	0.0
Exceeds vs. adherent	10	830	1.09 (0.68 to 1.74)	0.67 to 1.76	0.0
Obese					
Below vs. adherent	16	1285	1.57 (1.05 to 2.32)	1.05 to 2.33	0.0
Exceeds vs. adherent	15	1271	1.36 (0.89 to 2.06)	0.67 to 2.75	0.0

a Model adjusted for clustering effect.

Chapter 7 Predictors of gestational weight gain

Maternal characteristics, such as increase in age and parity, showed a significant association with reduced GWG, on average, by 0.09 kg (95% CI –0.12 to –0.06 kg) and 0.51 kg (95% CI –0.78 to –0.24 kg), respectively, in univariate (crude) meta-analyses. Non-Caucasian ethnicity was a significant predictor of decreased weight gain (summary-adjusted difference –0.89 kg, 95% CI –1.76 to –0.02 kg). Other maternal characteristics (such as smoking, pre-existing medical conditions, baseline physical activity and maternal education) were not associated with weight gain in pregnancy (*Table 19*).

Multivariable analysis showed that increase in maternal age (–0.1 kg, 95% CI –0.14 to –0.06 kg) and multiparity (–0.73 kg, 95% CI –1.24 to –0.23 kg) were associated with significantly reduced GWG. The details of the multivariable analysis for the association between baseline characteristics and GWG are provided in *Table 20*.

TABLE 19 Univariate analysis of predictors of GWG (kg)

Baseline characteristic	Number of studies	Sample size	Crude summary-adjusted difference[a] in GWG (95% CI)	95% PI	I^2 (%)
Age (years)	32	4424	–0.09 (–0.12 to –0.06)	–0.12 to –0.06	14.7
Non-Caucasian vs. Caucasian	13	2101	–0.89 (–1.76 to –0.02)	–1.83 to 0.05	18.7
Pooled effect ethnicity (reference category: Caucasian)					
Asian	7	1758	–0.53 (–2.24 to 1.18)	–3.42 to 2.36	21.4
Afro-Caribbean	9	1822	–1.17 (–2.65 to 0.30)	–2.69 to 0.34	0.0
Central/South American	1	110	–	–	–
Middle Eastern	4	289	–1.35 (–7.12 to 4.42)	–9.16 to 6.46	0.0
GDM	2	532	–1.43 (–16.58 to 13.72)	–	0.0
DM	3	305	–1.70 (–8.25 to 4.84)	–21.02 to 17.62	0.0
PIH	3	539	–2.08 (–13.71 to 9.55)	–65.15 to 61.00	80.4
Chronic hypertension	5	546	–1.43 (–4.80 to 1.95)	–8.81 to 5.96	52.8
Current smoker	21	3572	–0.07 (–0.98 to 0.84)	–2.39 to 2.25	47.4
Parity (number)	27	3673	–0.51 (–0.78 to –0.24)	–1.42 to 0.40	56.8
Multiparous vs. nulliparous	25[b]	3427	–1.12 (–1.55 to –0.69)	–2.30 to 0.07	32.4
Maternal education (reference category: low)					
Medium	23	3030	0.16 (–0.35 to 0.68)	–0.35 to 0.68	0.0
High	23	3030	–0.09 (–0.71 to 0.53)	–0.71 to 0.53	23.8
Some physical activity vs. physically inactive	22	2697	–0.30 (–0.70 to 0.10)	–0.71 to 0.53	23.8

a Model adjusted for baseline weight and clustering effect.
b Two studies (Harrison *et al.*[73] and Vítolo *et al.*[77]) include only multiparous women and are therefore excluded from this analysis.

TABLE 20 Multivariable analysis of maternal characteristics and GWG (kg)

Baseline characteristic	Number of studies	Sample size	Crude summary-adjusted difference[a] in GWG (95% CI)	95% PI	I^2 (%)
Age (years)	17	2414	–0.10 (–0.14 to –0.06)	–0.14 to –0.06	0.0
Ethnicity: non-Caucasian vs. Caucasian	10	1105	–0.11 (–1.53 to 1.32)	–3.12 to 2.91	34.6
Current smoker	13	2075	–0.06 (–1.65 to 1.52)	–3.93 to 3.81	57.1
Multiparous vs. nulliparous	15	2120	–0.73 (–1.24 to –0.23)	–1.83 to 0.36	15.3
Maternal education (reference category: low)					
Medium	15	2307	–0.07 (–0.91 to 0.77)	–1.88 to 1.74	27.6
High	15	2307	–0.18 (–1.18 to 0.81)	–2.57 to 2.21	36.3
Some physical activity vs. inactive	17	2414	–0.26 (–0.63 to 0.11)	–0.63 to 0.11	0.0

a Model accounting for baseline weight and clustering effect.

Chapter 8 Economic evaluation and decision-analytic modelling

Objectives

The main objective of this model-based economic evaluation was to determine the cost-effectiveness of diet- and exercise-based interventions in pregnancy to improve maternal and fetal clinical outcomes compared with usual care, using the results of the IPD meta-analysis for all women. A secondary objective was to compare the cost-effectiveness of the intervention for women whose pre-pregnancy weight was classed as normal, overweight or obese. The success of any intervention in supporting women to achieve optimum weight gain during pregnancy needs to be balanced against the resources required to achieve this outcome, and additional costs must be assessed in terms of any additional benefits that can be attributed to them.[95] Identification of specific subgroups of women in whom the intervention is cost-effective has the potential to target interventions to particular groups.

Methods

In the economic analysis, diet- and physical activity-based interventions in pregnancy were compared with care as usual (control). The principal clinical data used to populate the model were drawn from the IPD meta-analyses (see *Chapter 5*); this was supplemented with data from other published sources. Resource use was estimated from the published evidence and unit costs were based on published sources such as the *Unit Costs of Health and Social Care 2014*[96] and the *National Schedule of Reference Costs: The Main Schedule*.[97]

Model structure

The appropriate model for this study was a decision tree because of the short-term nature of the decision problem.[98] The model was developed using TreeAge Pro 2014 software (TreeAge Software, Inc., Williamstown, MA, USA). The structure was informed by the objectives of the study, the pathways indicated by the data and trials included in the IPD meta-analysis, clinical input, NICE guidelines on the management of women in pregnancy[10,99,100] and the approaches adopted in previously published model-based economic evaluations in relevant clinical areas.[101–105] For completeness, the model included all the potential pathways that could be followed by the women. Women entered the model at the point of randomisation to receive the intervention or care as usual (control). All women were assumed to follow one of six clinical pathways based on whether or not they developed pregnancy-related complications or experienced miscarriage or maternal death. These pathways were (1) PE, (2) GDM, (3) PIH, (4) no complication, (5) second-trimester miscarriage and (6) maternal death (*Figure 10*). Each pathway included appropriate maternal and fetal outcomes as detailed below.

For the base case, outcomes were considered until the point of discharge from hospital. Once women entered the model, it was assumed that they followed one of the clinical pathways defined in the model, based on whether or not they developed a pregnancy-related condition/complication. Complications were defined in accordance with the definitions used in studies included in the IPD meta-analysis. To illustrate the approach used for each patient pathway, a subset of the model is presented for the PE pathway (*Figure 11*). Women who developed more than one complication were allocated to the most resource-intensive pathway based on an analysis of NICE clinical pathways and clinical opinion.[106] The intensity of pathways was defined as follows (in decreasing order of intensity): (1) PE, (2) GDM[99] and

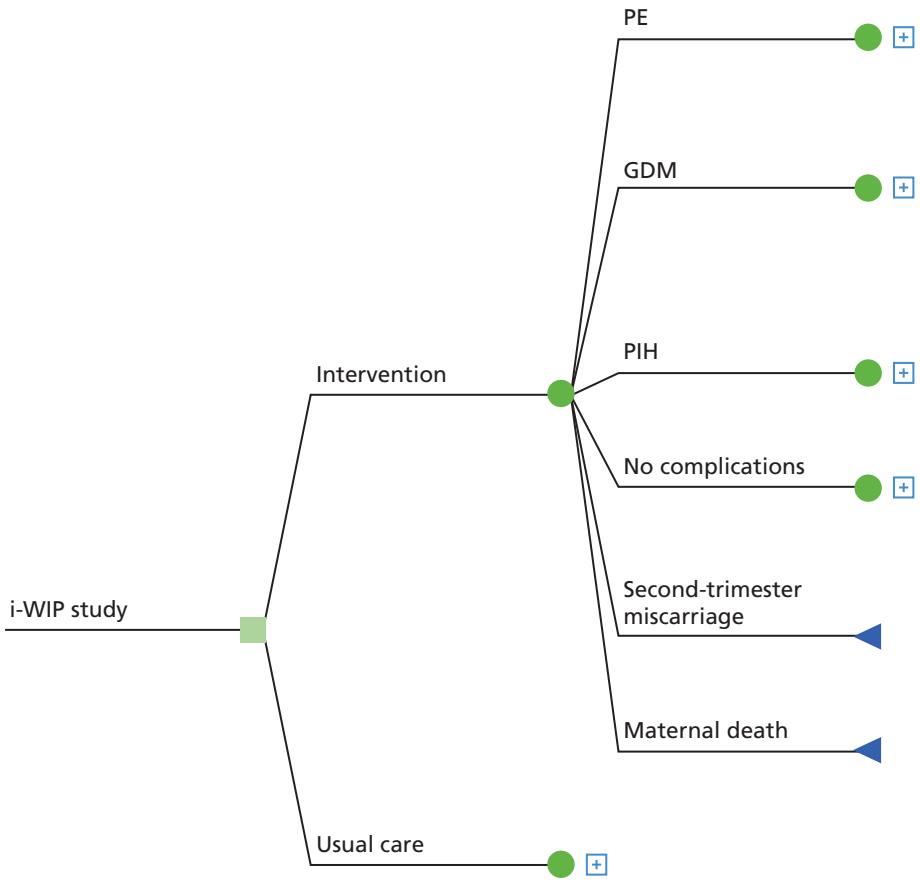

FIGURE 10 Patient pathways incorporated in the model.

(3) PIH.[100] For the purposes of the model it was assumed that once women developed a complication they were treated in accordance with NICE guidelines and incurred associated antenatal health-care costs. Women who did not develop any of the specified conditions were assumed to receive routine antenatal care only. It was assumed that routine antenatal care would be received by all women, irrespective of whether or not they developed a pregnancy-related condition.[107] As the purpose of economic evaluation is to examine the differences in costs and outcomes between alternative courses of action,[95] the costs of routine antenatal care were not included in the model as they would be identical for each arm.

For all clinical pathways, women could either experience a preterm delivery or a delivery at term; preterm delivery was defined as delivery before 37 gestational weeks.[108] Three types of delivery were included in the model: Caesarean section, assisted delivery and vaginal delivery. The outcome of the delivery was either a stillbirth (or IUD) or live baby. Stillbirth was defined as a baby born with no signs of life after 24 weeks of completed pregnancy and IUD as a baby with no signs of life in utero.[109] Women who experienced stillbirth and IUD were assumed to have received appropriate antenatal care for any condition they were recorded as developing during the trial. Additional costs associated with investigations and counselling were included in the total costs for these women.[110]

The model also included pathways for second-trimester miscarriage and maternal death in order to reflect all possible pathways for the women. Second-trimester miscarriage was defined as the spontaneous loss of pregnancy after the 14th week of pregnancy and before the 24 completed weeks. [111] The risk of second-trimester miscarriage and maternal death was based on secondary sources and applied to both arms equally to preserve the face validity of the model.[112] As the purpose of the economic evaluation was

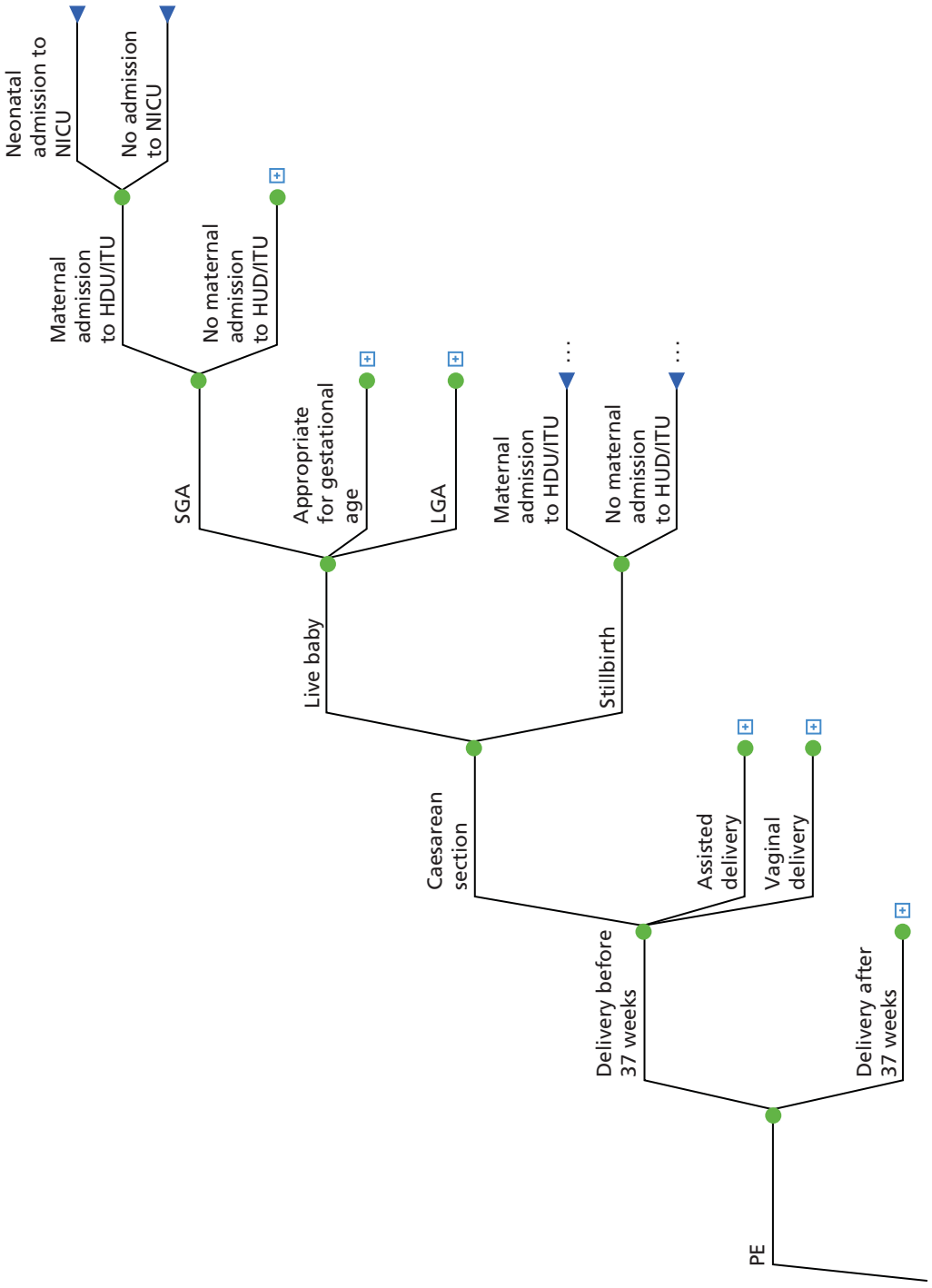

FIGURE 11 Detail for the PE pathway. C-section, Caesarean section.

to examine the differences in costs and outcomes between the intervention and control arms, costs were not included for second-trimester miscarriage and maternal death, as they would be identical for each arm.

Model assumptions

To carry out the model-based analysis some further assumptions were required. These are presented below.

Pre-eclampsia pathway

A number of assumptions were made for the PE pathway based on NICE guidelines[100] and the findings of a systematic review that was carried out for this report (see *Appendix 10* for further details). NICE guidance states that before 37 weeks delivery should not be recommended for women with PE unless severe or refractory hypertension is present. In women with PE with mild and moderate hypertension, the offer of delivery will depend on maternal and fetal condition, risk factors and the availability of neonatal intensive care. A systematic review was conducted to identify studies that had considered the costs associated with hypertensive disorders in pregnancy (see *Appendix 10* for further details). Five studies were identified that included primary data on the costs associated with PE in pregnancy.[113–117] Only one study collected primary data on resource use for women who were primarily diagnosed with PE and who were undergoing expectant monitoring.[113] This study was a RCT that compared expectant monitoring and immediate delivery for women with hypertensive disorders between 34 and 37 weeks of gestation [the Hypertension and Pre-eclampsia Intervention Trial At near Term (HYPITAT-II)]. The majority of the women included in the trial had PE (47%) or superimposed PE (13%). The findings of this study were used to inform the modelling of the PE pathway and the following assumptions were made:

- Women develop PE and give birth between 34 and 37 weeks of gestation to reflect the findings of the HYPITAT II study. Other evidence suggests that only a minority of women would give birth before this period; for example, a large clinical trial in this area[118] found that 82% of women with PE gave birth after 34 weeks.
- All women receive expectant monitoring for their condition, in line with NICE guidance.[114]
- Antenatal care was as reported in the HYPITAT-II study. This included maternal admissions, cardiotocography and ultrasounds, outpatient visits, laboratory tests and medication.[113]
- Data from the IPD were used to estimate the timing and type of delivery. The cost of care in the intrapartum phase was estimated using nationally reported average costs. It was assumed that because the women were diagnosed with PE and hypertension that all types of delivery would have a 'complications and comorbidities' score of 2.[119]
- Women receive the postnatal care that was reported in the HYPITAT-II study. This included maternal admissions, neonatal admission, extra care and transfers.[113]
- The costs included in the analysis were a conservative estimate of the costs associated with PE during pregnancy, and the uncertainty around this estimate was explored in the sensitivity analysis (particularly around the inclusion of costs associated with early-onset PE, that is disease occurring before 34 weeks).

Gestational diabetes mellitus pathway

The following assumptions were made for the GDM pathway based on NICE guidelines[99] and a systematic review of the literature conducted for this report. The systematic review identified 10 studies that were concerned with costs and resource use for women with GDM. Only one RCT that recorded primary health-care resource use for women who were diagnosed with GDM was identified.[120] This study included all costs incurred from the start of pregnancy until the final discharge of the mother and her child(ren). As routine antenatal care was included in the costs reported by the economic evaluation of the RCT, the estimate for the cost of antenatal care was based on the results of a modelling study produced to inform the development of for NICE guidelines on DM in pregnancy.[99] This cost was estimated from guideline recommendations for the treatment of women with GDM. The costs associated with delivery were based on national average costs reported in the UK. The costs associated with postnatal care of the

mother and infant were based on the health-care costs reported in the economic analysis conducted alongside the RCT.[120] The following assumptions were made for women with GDM:

- All women were initially treated with diet. After 10 days, if this treatment was not successful, women received insulin treatment (64% patients).
- Health-care professionals instructed women how to undertake self-monitoring of blood glucose levels, provided dietary advice, assessed the success of diet treatment and instructed women who required insulin treatment on this treatment.
- Estimates of the timing and type of delivery were based on data from the IPD. The cost of care in the intrapartum phase reflects nationally reported costs. As women had a diagnosis of GDM, all types of delivery had a complications and comorbidities score of 1.[119]
- The costs of postnatal care were as reported in an economic evaluation undertaken along a RCT.[120] This included NICU costs and costs associated with hospital care following delivery (all of the neonatal care costs and half of the non-delivery hospitalisation costs were incurred after the birth).

Pregnancy-induced hypertension pathway

A number of assumptions were made for the gestational hypertension pathway based on NICE guidelines and the results of a systematic review conducted to inform this report (see *Appendix 10*). For women with gestational hypertension, delivery of the infant should not be offered before 37 weeks and after this point the timing of, and maternal and fetal indications for, birth should be agreed between the woman and senior obstetrician.[114] The systematic review identified very few studies that were concerned with the resource use associated with the expectant monitoring of women with gestational hypertension (without PE) in line with this guidance. An economic evaluation was identified that included costs associated with expectant monitoring for women with hypertensive disorders (the HYPITAT-I[117]). This trial involved a majority of women with gestational hypertension only (65%).[121] The systematic review also identified an economic model developed to support NICE guidelines that was concerned with immediate birth compared with expectant management in women with mild to moderate gestational hypertension after 37 weeks of gestation.[100] However, the model used secondary data and did not involve primary cost collection.

- For the purposes of simplification, it was assumed that women developed gestational hypertension after 37 weeks, as most hypertensive disorders present after 36 weeks of gestation.[121]
- Antenatal care was assumed to follow that recorded in the HYPITAT-I study and included maternal admission, home care, cardiotocography, ultrasound, outpatient visits, assessments, laboratory tests and medication.[117]
- The findings of the IPD meta-analysis were used to estimate the timing and mode of delivery for women with PIH. National data on costs were used to estimate the cost of intrapartum care. Because all women had a diagnosis of hypertension, it was assumed that all types of birth would have a complications and comorbidities score of 1.[119]
- In the postnatal period, just 2% of women were assumed to receive intensive care, while 90% were admitted to the maternity ward for a mean period of 3.4 days. In addition, 3% of infants were assumed to be admitted to the NICU, and 19% to receive medium-level care on the maternal ward, in line with findings from the HYPITAT–I trial.[117]

No complications

A series of assumptions were made for the pathway followed by women who did not develop complications during pregnancy, based on an analysis of NICE guidance:[107]

- Women who did not develop any complications received routine antenatal care only.
- The estimate of the timing and mode of delivery was based on the findings of the IPD meta-analysis. For the purpose of simplification, this means that women would not have any complications and that their delivery would have a complications and comorbidities score of 0.[119]
- Women with no complications would not receive any additional postnatal care.

- The findings of the IPD meta-analysis were used to estimate the probability that infants in this arm would be admitted to the NICU. The findings of a study that reported average length of stay in the NICU by gestational age were used to estimate the length of stay for infants who were born preterm and at term.[119]

Clinical data

The primary focus of the economic evaluation was the effect of the intervention on adverse maternal and fetal outcomes. The maternal outcomes included the development of three pregnancy-related conditions (PE, GDM and PIH), as well as outcomes relating to the timing and mode of delivery (preterm delivery and Caesarean section). Fetal outcomes included IUD, SGA, LGA and admission to the NICU.

Maternal outcomes

The estimates of baseline risk and the effect of the intervention on the development of pregnancy-related conditions were drawn from the IPD meta-analysis. This is shown in *Table 21*. For the intervention effect, data from the IPD meta-analysis were used to estimate pooled effect ORs for the development of PE, GDM and PIH. A two-stage process was used using a REML approach, and CIs were corrected using the Knapp–Hartung correction. The baseline risk for the usual-care group was based on pooled data for the control groups included in the trials. Maternal outcomes were not considered when they were already observed at baseline, that is, we did not count the presence of GDM in women who had DM or GDM at baseline and we did not count PIH in women who had PIH at baseline. The estimate of the risk of second semester miscarriage was based on a review article that summarised evidence on the epidemiology of miscarriage.[122] Data on the risk of maternal death were drawn from the findings of the confidential enquiry into maternal mortality and morbidity in the UK and Ireland 2009–12.[123]

The IPD meta-analysis also considered maternal outcomes that related to the timing and type of delivery (*Table 22*). This included preterm delivery, normal delivery, assisted delivery and Caesarean section. Delivery-related outcomes were estimated for all women with a pregnancy-related condition and for women with no condition (irrespective of whether they received the intervention or care as usual). Women with no complications were defined as those not reported as having PE, GDM or PIH, with at least one of these conditions being reported in the trial. Women were excluded from the analysis if missing data for all of these three outcomes were missing.

TABLE 21 Baseline risk and intervention effect (development of pregnancy-related conditions)

Description	Base-case value	Distribution and values	Source
Baseline risk of PE	0.05	Beta(199, 3786)	IPD
Baseline risk of GDM	0.114	Beta(542, 4205)	IPD
Baseline risk of PIH	0.043	Beta(187, 4133)	IPD
Baseline risk of no complications	0.793	Remainder from above	IPD
OR for PE	0.99	Log-normal(0.79 to 1.24)	IPD
OR for GDM	0.89	Log-normal(0.72 to 1.10)	IPD
OR for PIH	0.93	Log-normal(0.69 to 1.25)	IPD
Risk of second-trimester miscarriage	0.01	Beta(1, 99)	Regan and Rai[122]
Risk of maternal death	0.00010	Beta(10, 99,990)	Knight *et al.*[123]

Note
Values of α and β are given for beta distributions, and 95% confidence limits for log-normal distributions. The base-case values were used to produce deterministic results. The distributions were used to undertake probabilistic sensitivity analysis, produce the probabilistic results and produce the incremental cost-effectiveness scatterplots.

TABLE 22 Timing and mode of delivery for women

Description	Base-case value	Distribution and values	Source
Preterm delivery in women with PE	0.234	Beta(92, 302)	IPD
Preterm delivery in women with GDM	0.076	Beta(82, 1003)	IPD
Preterm delivery in women with PIH	0.049	Beta(19, 366)	IPD
Preterm delivery in women with no complications	0.104	Beta(193, 1671)	IPD
Caesarean section in women with PE	0.46	Beta(180, 211)	IPD
Assisted delivery in women with PE	0.11	Beta(43, 348)	IPD
Normal delivery in women with PE	0.43	Remainder from above	IPD
Caesarean section in women with GDM	0.344	Beta(373, 711)	IPD
Assisted delivery in women with GDM	0.111	Beta(120, 964)	IPD
Normal delivery in women with GDM	0.545	Remainder from above	IPD
Caesarean section in women with PIH	0.279	Beta(107, 276)	IPD
Assisted delivery in women with PIH	0.154	Beta(59, 324)	IPD
Normal delivery in women with PIH	0.567	Remainder from above	IPD
Caesarean section in women with no complications	0.355	Beta(660, 1198)	IPD
Assisted delivery in women with no complications	0.119	Beta(222, 1636)	IPD
Normal delivery in women with no complications	0.525	Remainder from above	IPD

Note
Values of α and β are given for beta distributions. The base-case values were used to produce deterministic results. The distributions were used to undertake probabilistic sensitivity analysis, produce the probabilistic results and produce the incremental cost-effectiveness scatterplots.

Fetal outcomes

Data from the IPD were used to estimate fetal and infant outcomes for all women with a pregnancy-related condition and for women with no condition recorded (irrespective of whether they received the intervention or care as usual). Women were defined as having no pregnancy-related condition if they were not reported as having PE, GDM or PIH, with at least one of these conditions being reported in the trial. Women were excluded from the analysis if data were missing for all of these three outcomes. *Table 23* shows fetal outcomes for women by pregnancy-related condition/no condition.

Cost data

The cost components of the decision model were parameterised with data from NHS reference costs 2013/14[97] and other secondary sources. Costs were calculated in 2013–14 GBP. Costs from secondary sources were inflated to 2013–14 prices using the hospital and community health services pay and prices index.[96] When necessary, costs were converted to GBP using historical annual average rates[124] and then inflated to 2013–14 prices.

The estimate of the cost of the weight management intervention was based on the results of a systematic review of economic evaluations of weight management interventions in pregnancy that was conducted for this report (see *Appendix 10*). The review identified 11 studies that were concerned with the cost-effectiveness of weight management interventions during pregnancy.[68,101,125–133] Four of these involved women who already had DM or GDM and hence the intervention costs included additional monitoring and medication.[125,130,131,133] Two did not report a cost for an intervention.[101,126] Data on the cost of the

TABLE 23 Fetal outcomes

Description	Base-case value	Distribution and values	Source
Intrauterine infant death: women with PE	0.03	Beta(1, 358)	IPD
Intrauterine infant death: women with GDM	0.02	Beta(2, 888)	IPD
Intrauterine infant death: women with PIH	0.03	Beta(1, 332)	IPD
Intrauterine infant death: women with no complications	0.03	Beta(4, 1578)	IPD
LGA: women with PE	0.096	Beta(38, 356)	IPD
LGA: women with GDM	0.156	Beta(171, 928)	IPD
LGA: women with PIH	0.109	Beta(42, 344)	IPD
LGA: women with no complications	0.134	Beta(251, 1628)	IPD
SGA: women with PE	0.193	Beta(76, 318)	IPD
SGA: women with GDM	0.091	Beta(98, 984)	IPD
SGA: women with PIH	0.123	Beta(47, 336)	IPD
SGA: women with no complications	0.119	Beta(221, 1638)	IPD
Infant admission to the NICU: women with PE	0.195	Beta(71, 294)	IPD
Infant admission to the NICU: women with GDM	0.115	Beta(106, 814)	IPD
Infant admission to the NICU: women with PIH	0.057	Beta(19, 312)	IPD
Infant admission to the NICU: women with no complications	0.121	Beta(196, 1420)	IPD

Note
Values of α and β are given for beta distributions. The base-case values were used to produce deterministic results. The distributions were used to undertake probabilistic sensitivity analysis, produce the probabilistic results and produce the incremental cost-effectiveness scatterplots.

intervention were thus extracted for five studies[68,127–129,132] and the median value was used to estimate the cost of the intervention in the model (*Table 24*).

Estimates of antenatal and postnatal care costs were drawn from systematic reviews of the literature (as described in the previous section on assumptions). Delivery costs were based on national average costs in the UK.[97]

Analysis

The decision-analytic model was constructed to compare the cost-effectiveness of diet- and physical activity-based interventions in pregnancy with usual care. Two separate economic analyses were conducted. The main analysis compared costs and outcomes for a hypothetical cohort of 10,000 pregnant women, based on the results of the IPD meta-analysis for all women. The secondary analysis compared costs and outcomes for three subgroups of women based on their pre-pregnancy BMI classification. Women were classified as normal weight (pre-pregnancy BMI of < 25 kg/m^2), overweight (pre-pregnancy BMI 25–29.9 kg/m^2) or obese (pre-pregnancy BMI of ≥ 30 kg/m^2). This allowed an exploration of whether or not a weight management intervention in selective subgroups of women is a more cost-effective strategy than care as usual.

For both the primary and secondary analyses, the relative cost-effectiveness of the intervention was evaluated using effect size estimates from the IPD meta-analysis. An incremental approach was adopted, with a focus on the additional costs and benefits associated with a move from care as usual to diet and lifestyle interventions to manage weight gain in pregnancy. The results were reported in terms of an incremental cost-effectiveness ratio (ICER) of cost per unit benefit gained, measured in clinical outcomes.

TABLE 24 Cost data used in the model

Description	Base-case value (£)	Distribution and values	Source
Intervention to manage weight gain in pregnancy	217	Gamma(1, 413)	Calculated value[a]
Cost of antenatal care: women with PE	2054	Gamma(1, 2054)	van Baaren *et al.*[113]
Cost of antenatal care: women with GDM	1022	Gamma(1, 1022)	NICE[99]
Cost of antenatal care: women with PIH	974	Gamma(1, 974)	Vijgen *et al.*[117]
Cost of preterm delivery, no complications (NZ17B, CC score of 0–1)	642	Gamma(1, 642)	Department of Health[97]
Cost of preterm delivery, with complications (NZ17A, CC score of ≥ 2)	946	Gamma(1, 946)	Department of Health[97]
Cost of normal delivery, with no complications (NZ30C, CC score of 0)	1461	Gamma(1, 1461)	Department of Health[97]
Cost of normal delivery, with minor complications (NZ30B, CC score of 1)	1623	Gamma(1, 1623)	Department of Health[97]
Cost of normal delivery, with major complications (NZ30A, CC score of ≥ 2)	1892	Gamma(1, 1892)	Department of Health[97]
Cost of assisted delivery, without complications (NZ40C, CC score of 0)	1860	Gamma(1, 1860)	Department of Health[97]
Cost of assisted delivery, with minor complications (NZ40C, CC score of 1 or 2)	2153	Gamma(1, 2153)	Department of Health[97]
Cost of assisted delivery, with major complications (NZ40A, CC score of 2)	2625	Gamma(1, 2625)	Department of Health[97]
Cost of Caesarean section, without complications (NZ40C, CC score of 0 or 1)	3363	Gamma(1, 3363)	Department of Health[97]
Cost of Caesarean section, with minor complications (NZ40C, CC score of 2 or 3)	4059	Gamma(1, 4059)	Department of Health[97]
Intensive care (XC04Z, adult critical care, three organs supported)	789	Gamma(1, 789)	Department of Health[97]
Cost of neonatal critical care: intensive care	1118	Gamma(1, 1118)	Department of Health[97]
Cost of postnatal care: women with PE	4987	Gamma(1, 4987)	van Baaren *et al.*[113]
Cost of postnatal care: women with GDM	1899	Gamma(1, 1899)	Kolu *et al.*[120]
Cost of postnatal care: women with PIH	1814	Gamma(1, 1814)	Vijgen *et al.*[117]
Additional cost of IUD (core-recommended investigations and care immediately following miscarriage)	1242	Gamma(1, 1242)	Mistry *et al.*[110]

CC, complications and comorbidity.
a Median value of intervention costs for studies identified in the systematic review.
Note
Values of α and β are given for gamma distributions. The base-case values were used to produce deterministic results. The distributions were used to undertake probabilistic sensitivity analysis, produce the probabilistic results and produce the incremental cost-effectiveness scatterplots.

The IPD meta-analysis was based on a composite outcome, which included maternal and fetal complications. An economic evaluation based on such a composite outcome would not be meaningful, as the full extent of the cost implications based on such an outcome would be lost. The economic analysis therefore examined cost-effectiveness for each of the primary outcomes separately; for example, results are presented in terms of cost per case of PE avoided, cost per case of GDM avoided, etc. Results are also presented in terms of cost per major outcome avoided. The major outcome was predefined to include one

or more of the fetal and maternal outcomes included in the composite measure that was used in the IPD meta-analysis.

The analysis was conducted from the perspective of the health service (NHS) and only direct health service costs were included. The time horizon adopted for both the primary and secondary analyses was from the start of pregnancy until the mother and infant were discharged from hospital following the birth. This was considered appropriate to reflect all key differences in terms of costs and benefits for the options compared, given the time horizon adopted in the trials included in the IPD meta-analysis. The effect of considering a longer time horizon was explored as part of the sensitivity analysis.

Sensitivity analysis

Deterministic and probabilistic sensitivity analyses were conducted to explore the effects of the inherent uncertainty in the parameter estimates on the results produced by the model.[98] Deterministic sensitivity analysis involves varying one or more parameters while keeping the others at their baseline value. Such analysis can help to identify which model inputs are important in leading to a particular decision from the model, and can help to identify threshold values. A probabilistic sensitivity analysis (PSA) was also undertaken to allow uncertainty to be represented more comprehensively. A PSA involves varying all parameters simultaneously, and multiple sets of parameter values are sampled from defined probability distributions.[134] Monte Carlo simulation was used to sample from these distributions to allow the effect of parameter uncertainty to be evaluated. This involved 1000 repeated random draws from the distributions to indicate how variation in the model parameters would affect the results and hence illustrate the decision uncertainty.[135] Beta distributions were used for binomial data, log-normal distributions for ORs and gamma distributions for costs.[98] Ideally, when there are more than two possibilities at a chance node, a Dirichlet distribution would be applied. But to populate a Dirichlet distribution it is necessary that all included studies have reported data for all the branches from the appropriate chance node. This could be done if all data sources reported results for all possible branches. However, in this case, some studies did not report numbers for all branches in the model. For example, the number of LGA infants born to mothers with GDM was reported in 27 studies, but the numbers of SGA infants was reported in only 26 studies. Therefore, it is feasible to assign separate beta distributions only for the probabilities of each of these two outcomes. For consistency, we considered it appropriate to apply beta distributions throughout. The potential limitation of applying a beta distribution is that some correlation between parameters could be lost. However, in this study, this is unlikely to have had an impact on results.

Using the net monetary benefit for each of the 1000 simulations, the proportion of times the intervention had the highest net monetary benefit was calculated for a range of threshold values for the maximum willingness to pay for a major outcome averted. These values were summarised graphically using a cost-effectiveness acceptability curve (CEAC) to show the uncertainty surrounding the cost-effectiveness of the intervention, for a range of thresholds for cost-effectiveness. A value of information analysis was also conducted to estimate the expected costs of uncertainty. The expected cost of uncertainty is calculated by estimating the probability of making a wrong decision based on existing evidence and the consequences of this wrong decision. The expected value of perfect information (EVPI) estimates the difference between the expected value of the decision made with perfect information and the decision made on the basis of existing evidence.[98] EVPI was calculated based on the methods described in Claxton and Posnett.[136]

Deterministic sensitivity analysis

A range of deterministic sensitivity analyses was carried out for the primary and secondary analyses. Both univariate and multivariate analyses were undertaken to assess how uncertainty around the parameters used in the model would impact on the results achieved. Univariate sensitivity analysis involves varying input values one at a time across a plausible range while holding the remaining values at their baseline values, while multivariate analysis involves varying two or more input values simultaneously.[136] Six univariate and two multivariate analyses were undertaken based on the following justifications.

Univariate analyses

1. The cost of the intervention was varied to reflect the maximum and minimum costs identified in the literature review (£136 and £1023, respectively). The base-case value was estimated based on the median cost reported in the identified studies and these costs were varied to examine the impact on results.
2. The effect of the intervention in increasing or reducing the odds of developing pregnancy-related conditions was varied using 95% CIs for pregnancy-related conditions: PE, 95% CI 0.79 to 1.24; GDM, 95% CI 0.72 to 110; and PIH, 95% CI 0.69 to 1.25.
3. The rate of preterm delivery and Caesarean section varied for each condition separately using 95% CIs calculated using an exact method.[137,138] The rate of preterm delivery varied for women with PE from 19.3% to 27.8%, for those with GDM from 6.1% to 9.3% and for women with PIH from 3% to 7.6%. The rate of Caesarean section varied from 41% to 51.1% for women with PE, from 31.6% to 37.3% for those with GDM and from 23.5% to 32.7% for those with PIH.
4. The costs associated with health care were increased and decreased for each condition. The costs of care before and after the birth were varied drawing on the results of the literature review. The total costs of care for women with PE varied from £4476[104] to £12,052 (this was based on the highest estimate of the costs of PE identified, with a 15% increase[102]). The costs of delivery and postnatal care for women with PIH varied from £2988[104] to £5530 (the higher cost included follow-up care[117]). The total costs associated with care for women with GDM varied between £3105[130] (estimate for women with mild GDM) and £8753.[131]
5. The costs of delivery were varied using the upper- and lower-quartile costs reported for elective and non-elective deliveries reported in the *National Schedule of Reference Costs: The Main Schedule*.[97] Thus, the costs of Caesarean section with a complications and comorbidities score of 0 or 1 varied from £1818 (planned elective delivery, lower-quartile cost) to £4289 (emergency delivery, non-elective patient, upper-quartile cost). The cost of a Caesarean section with a complications and comorbidities score of ≥ 2 varied from £2085 (planned elective delivery, lower-quartile cost) to £4289 (emergency delivery, non-elective patient, upper-quartile cost). For assisted deliveries, the costs of delivery varied for deliveries with no complications (£960–2721, reflecting non-elective short-stay lower-quartile costs and long-stay upper-quartile costs, respectively), a complications score of 1 (£1033–3050, for non-elective short-stay and long-stay costs, respectively) and a complications and comorbidities score of 2 (£1132–3604, non-elective short-stay and long-stay costs, respectively). For normal deliveries, similar variations in costs were explored; costs were varied for deliveries with no complications (£854–2688, reflecting non-elective short-stay lower-quartile costs and long-stay upper-quartile costs, respectively), deliveries with a complications and comorbidities score of 1 (£898–2968, for non-elective short-stay and long-stay costs, respectively) and develieries with a complication score of 2 (£957–3349, non-elective short-stay and long-stay costs, respectively).
6. Increasing the costs of IUD. The costs associated with IUD were increased using estimates provided in a published review of the literature.[110] The costs of IUD were increased to £1804 to reflect the increased costs associated with comprehensive investigations.

Multivariate analyses

Multivariate analyses were undertaken to reflect the fact that a change in the clinical effectiveness of the intervention is likely to affect more than one outcome measure. Hence, multiple parameters were varied simultaneously to examine the impact on the results:

1. Varying the effectiveness for all pregnancy-related conditions. For this analysis, CIs were used to examine the impact on cost-effectiveness using the highest and lowest estimates of effect.
2. Increasing and decreasing the cost of pregnancy-related conditions. All costs associated with pregnancy-related conditions were increased and decreased simultaneously using the estimates from the literature.

Results

Primary analysis

The results of the primary analysis are reported in *Tables 25* and *26*. Care as usual was the least costly arm, with the average cost estimated at £3242 (excluding routine antenatal care). However, the intervention arm was only slightly more expensive, with average costs estimated at £3390 (excluding routine antenatal care). In the base-case model (using point estimates) there was a reduction in pregnancy-related complications in the intervention arm (see *Table 26*). Overall, there were 55 fewer women who experienced any major outcome in the intervention arm, five fewer cases of PE, 113 fewer cases of GDM and 29 fewer women who developed PIH. No reduction was found in other outcomes such as preterm delivery, Caesarean section, IUD, LGA and NICU admission for the intervention arm. The ICERs indicated that there was an additional cost of around £306,000 for each case of PE avoided, £13,000 for each case of GDM avoided and £27,000 for each woman with a major outcome avoided. This means that, if for example, the outcome of interest is the reduction in cases of PE, an additional £306,000 is required for each additional woman who avoids the development of PE compared with usual care. These results taken in isolation would suggest that the intervention would be preferred at any willingness to pay for a case of PE avoided above £306,000.

TABLE 25 Average costs (£) for intervention group compared with care as usual

Group allocation	Total cost (point estimate)[a]	Difference in costs
Intervention	3390	147
No intervention	3242	

a As it was assumed that routine antenatal care was received by all women this was not included in the total costs as there would be no difference in costs between model arms.

TABLE 26 Results for primary base-case analysis for a cohort of 10,000 women

Outcome	Number of women experiencing complications		Number of complications avoided per 10,000 women: outcome averted (point estimate)	Cost (£) per complication avoided[a]
	Intervention (point estimate)	No intervention (point estimate)		
Any major outcome	6981	7036	55	27,000
PE	495	499	5	306,000
GDM	1029	1142	113	13,000
PIH	398	426	29	51,000
Preterm delivery	1037	1033	–4	[b]
Caesarean section	3526	3523	–3	[b]
IUD	25	25	0	[b]
LGA	1608	1605	–4	[b]
SGA	888	891	3	
NICU admission	1202	1200	–2	[b]

a Cost per complication avoided is rounded to the nearest £1000.
b Intervention less clinically effective than care as usual.

These results need to be viewed together with those from the PSA (*Tables 27* and *28*). The PSA results show the modelled uncertainty in the cost and effectiveness between the intervention arm and the care-as-usual arm, from 1000 Monte Carlo simulations. These results show that it is uncertain whether the intervention is more effective than usual care or less effective (with respect to all the outcome measures) and whether the intervention is more costly or less expensive than the alternative. Hence, the most reasonable interpretation is that there is no significant difference between the intervention and control arm results for either cost or clinical effectiveness. This is further illustrated by *Figure 12*. The graph plots the result of each simulation on the cost-effectiveness plane, which gives information about the joint density of differences in cost and effectiveness between the two model arms. It is evident that the data in the scatterplot go into all quadrants of the incremental cost-effectiveness plane and, therefore, it should be assumed that there is no significant difference between the intervention and control arms for either cost or clinical effectiveness. This was the case for all of the outcome measures (for more details see *Appendix 11*). The CEAC (*Figure 13*) shows that the probability that the intervention is cost-effective increases as the willingness to pay for a major outcome averted increases. Thus, if the maximum willingness to pay for a major outcome averted for all pregnant women was £30,000, then the probability that the intervention was cost-effective would be 0.55.

TABLE 27 Results of PSA: average costs (£) for intervention group compared with care as usual[a]

	Cost (95% CI)	
Group allocation	Mean	Difference
Intervention	3457 (1651 to 6408)	151 (–247 to 754)
No intervention[b]	3306 (1432 to 6088)	

a Note that the mean results in the PSA are not the same as the point estimates used in the base-case analysis because of the use of log-normal distributions which create a non-linearity in the model.
b As it was assumed that routine antenatal care was received by all women this was not included in the total costs as there would be no difference in these costs between model arms.

TABLE 28 Results of PSA: primary analysis for a cohort of 10,000 women[a]

	Number of women experiencing complications, mean (95% CI)		
Outcome	Intervention	No intervention	Number of complications avoided per 10,000 women (95% CI)
Any major outcome	6984 (6758 to 7202)	7036 (6875 to 7209)	52 (–88 to 172)
PE	496 (381 to 635)	498 (432 to 567)	3 (–116 to 103)
GDM	1032 (825 to 1278)	1142 (1050 to 1230)	109 (–117 to 307)
PIH	401 (289 to 547)	426 (369 to 491)	25 (–100 to 134)
Preterm delivery	1036 (921 to 1153)	1032 (923 to 1150)	–4 (–15 to 7)
Caesarean section	3529 (3329 to 3718)	3527 (3336 to 3714)	–3 (–17 to 13)
IUD	25 (9 to 52)	25 (9 to 51)	0 (–1 to 1)
LGA	1608 (1474 to 1742)	1605 (1471 to 1739)	–3 (–18 to 12)
SGA	889 (800 to 975)	891 (808 to 975)	2 (–14 to 18)
NICU admission	1201 (1073 to 1333)	1199 (1074 to 1328)	–2 (–13 to 10)

a Note that the mean results in the PSA are not the same as the point estimates used in the base-case analysis because of the use of log-normal distributions which create a non-linearity in the model.

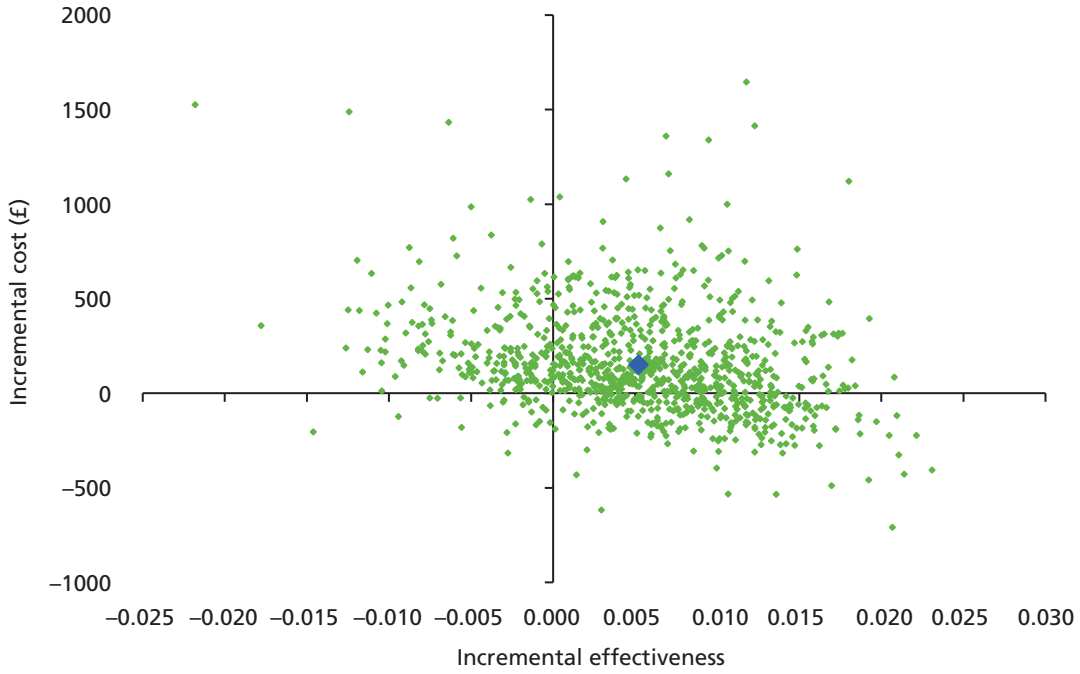

FIGURE 12 Incremental cost-effectiveness scatterplot of intervention compared with care as usual for pregnant women: major outcome averted. The mean of the distribution is highlighted.

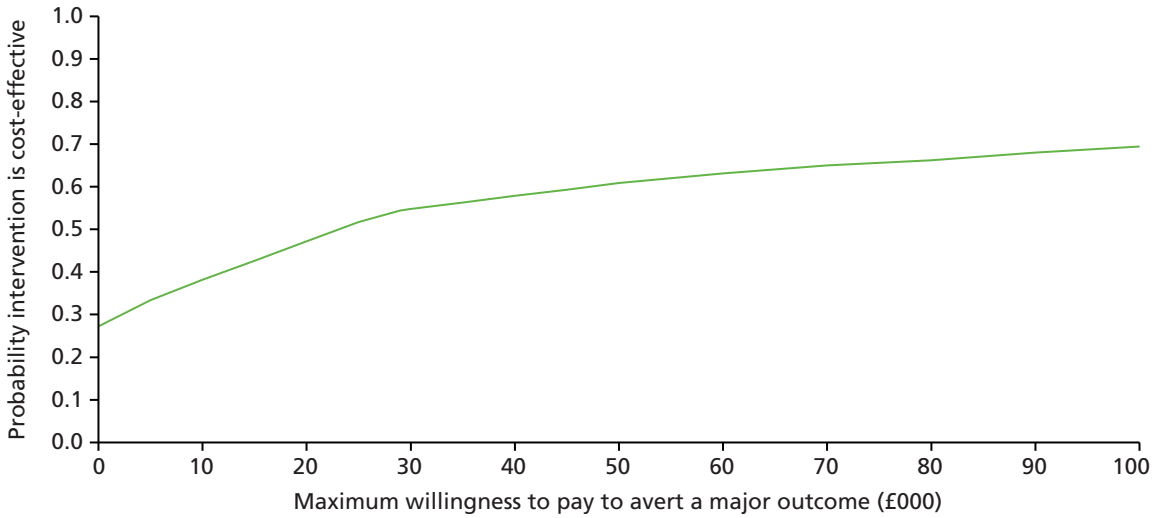

FIGURE 13 Incremental CEAC of intervention for pregnant women: major outcome averted.

The analysis of the EVPI demonstrates that at a willingness-to-pay threshold of £30,000 to avert a major outcome, the expected value of resolving the uncertainty around the decision is £142 per patient to whom the decision would apply (*Figure 14*). Thus, for a cohort of 10,000 women, the EVPI would be £1,420,000.

Secondary analysis

Obese women

The results of the secondary analysis for obese women are reported in *Tables 29* and *30*. Care as usual was the least costly arm for obese women, with an average cost estimated at £3428 (excluding routine antenatal care). However, the intervention arm was only slightly more expensive, with average costs estimated at £3613 (excluding routine antenatal care). In the base-case model (using point estimates)

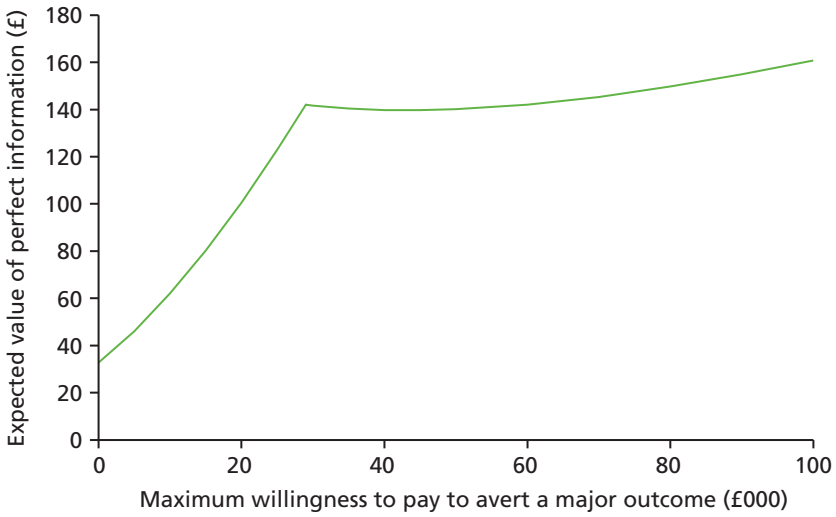

FIGURE 14 Expected value of perfect information: major outcome averted.

TABLE 29 Average costs (£) for intervention group compared with care as usual: obese women

	Cost	
Group allocation	Mean (point estimate)	Difference
Intervention	3613	185
No intervention[a]	3428	

a As it was assumed that routine antenatal care was received by all women this was not included in the total costs, as there would be no difference in these costs between model arms.

TABLE 30 Results for analysis for a cohort of 10,000 obese women

	Number of women experiencing complications (point estimate)		Number of complications avoided per 10,000 women: outcome averted (point estimate)	Cost (£) per complication avoided[a]
Outcome	Intervention	No intervention		
Any major outcome	7248	7269	21	88,000
PE	550	530	–20	[b]
GDM	1512	1637	125	15,000
PIH	562	514	–48	[b]
Preterm delivery	1021	1018	–3	[b]
Caesarean section	3514	3514	0	[b]
IUD	25	25	0	[b]
LGA	1587	1589	3	712,000
SGA	905	902	–3	[b]
NICU admission	1192	1193	1	2,057,000

a Cost per complication avoided is rounded to the nearest £1000.
b Intervention is less clinically effective than care as usual/no difference in clinical effectiveness.

there were 21 fewer obese women who experienced any major outcome in the intervention arm and 125 fewer cases of GDM. No reduction was found in other outcomes such as the development of PE, PIH and rates of preterm delivery, Caesarean section, IUD, LGA and NICU admission. The ICERs indicated that there was an additional cost of around £88,000 for each major outcome avoided and £15,000 for each case of GDM avoided. The PSA results show the modelled uncertainty in the cost and clinical effectiveness between the intervention arm and the care-as-usual arm and demonstrate that it is uncertain whether the intervention is more or less effective than usual care and whether the intervention is more or less costly than the alternative (*Tables 31* and *32*). These results suggest that there is no significant difference between the intervention and the control arm results for either cost or clinical effectiveness for obese women. This is further illustrated by *Figure 15*, which plots the result of each simulation on the cost-effectiveness plane and shows that there is no significant difference between the intervention and control arms for either cost or clinical effectiveness for all outcome measures (for more details see *Appendix 11*). The CEAC (*Figure 16*) shows if the maximum willingness to pay for a major outcome averted for obese pregnant women was £120,000, then the probability that the intervention was cost-effective would be 0.52.

TABLE 31 Results of PSA: average costs (£) for intervention group compared with care as usual for obese women[a]

	Cost (95% CI)	
Group allocation	Mean	Difference
Intervention	3675 (1794 to 6321)	191 (–247 to 809)
No intervention[b]	3484 (1608 to 6129)	

a Note that the mean results in the PSA are not the same as the point estimates used in the base-case analysis because of the use of log-normal distributions which create a non-linearity in the model.
b As it was assumed that routine antenatal care was received by all women this was not included in the total costs, as there would be no difference in these costs between model arms.

TABLE 32 Results of PSA: analysis for a cohort of 10,000 obese women[a]

	Number of women experiencing complications, mean (95% CI)		
Outcome	Intervention	No intervention	Number of complications avoided per 10,000 women (95% CI)
Any major outcome	7252 (6992 to 7524)	7268 (7108 to 7444)	16 (–194 to 197)
PE	553 (396 to 750)	529 (437 to 630)	–24 (–189 to 108)
GDM	1517 (1164 to 1940)	1636 (1482 to 1786)	119 (–262 to 445)
PIH	564 (403 to 778)	513 (420 to 615)	–51 (–223 to 95)
Preterm delivery	1021 (912 to 1130)	1018 (911 to 1125)	–3 (–17 to 10)
Caesarean section	3518 (3329 to 3700)	3518 (3336 to 3699)	1 (–19 to 21)
IUD	25 (10 to 50)	25 (10 to 49)	0 (–1 to 1)
LGA	1587 (1463 to 1716)	1590 (1463 to 1720)	3 (–17 to 25)
SGA	906 (820 to 993)	903 (822 to 985)	–4 (–27 to 16)
NICU admission	1192 (1070 to 1316)	1193 (1076 to 1319)	1 (–15 to 16)

a Note that the mean results in the PSA are not the same as the point estimates used in the base-case analysis because of the use of log-normal distributions which create a non-linearity in the model.

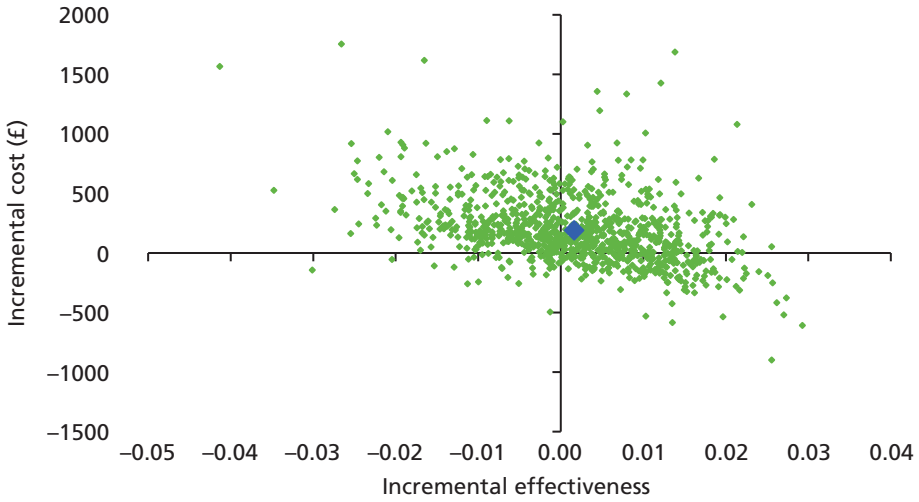

FIGURE 15 Incremental cost-effectiveness scatterplot of intervention compared with care as usual for obese pregnant women: major outcome averted. The mean of the distribution is highlighted.

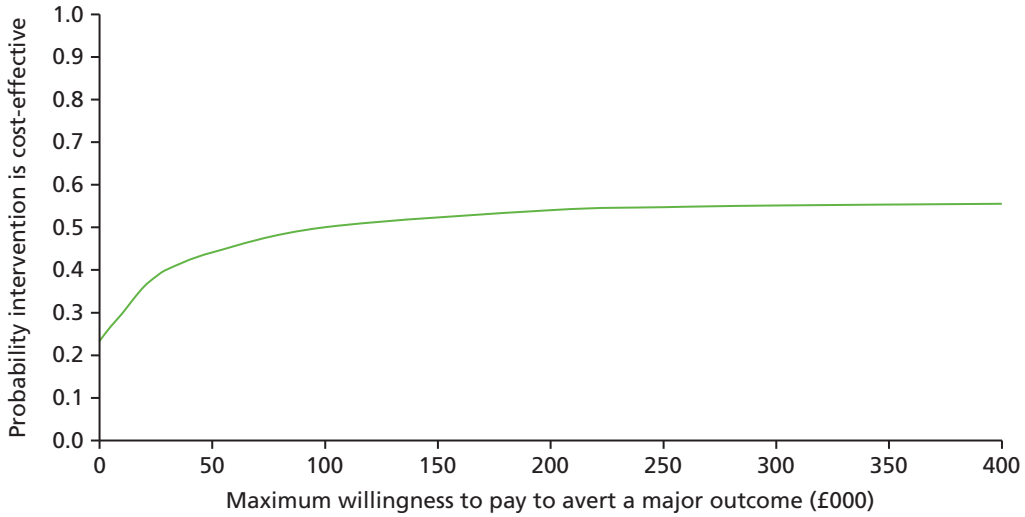

FIGURE 16 Incremental CEAC of intervention for obese pregnant women: major outcome averted.

Overweight women

The results of the secondary analysis for overweight women are reported in *Tables 33* and *34*. As for obese women, care as usual had the lowest cost, with the average cost estimated at £3114 (excluding routine antenatal care). The intervention arm was slightly more expensive, with average costs estimated at £3326 (excluding routine antenatal care). In the base-case model (using point estimates) there were 115 fewer overweight women who developed PIH (see *Table 34*). However, for all other clinical outcomes,

TABLE 33 Average costs (£) for intervention group compared with care as usual: overweight women

	Cost	
Group allocation	Total (point estimate)	Difference
Intervention	3326	211
No intervention[a]	3114	

a As it was assumed that routine antenatal care was received by all women this was not included in the total costs, as there would be no difference in these costs between model arms.

TABLE 34 Results for analysis for a cohort of 10,000 overweight women

Outcome	Number of women experiencing complications (point estimate)		Number of complications avoided per 10,000 women (point estimate)	Cost (£) per complication avoided
	Intervention	No intervention		
Any major outcome	6915	6903	–11	[a]
PE	459	439	–21	[a]
GDM	996	871	–126	[a]
PIH	293	407	115	18,000
Preterm delivery	1039	1034	–5	[a]
Caesarean section	3531	3521	–10	[a]
IUD	25	25	0	[a]
LGA	1618	1614	–4	[a]
SGA	879	881	1	1,621,000
NICU admission	1206	1198	–8	[a]

a Intervention is less clinically effective than care as usual/no difference in clinical effectiveness.

the intervention did not lead to a reduction in adverse outcomes. The PSA results allow an assessment of the uncertainty in the estimates of cost and clinical effectiveness between the intervention arm and the care-as-usual arm (*Tables 35* and *36*). It is evident that it is uncertain whether the intervention is more or less effective than usual care and whether the costs associated with the intervention arm are greater or lower than the alternative. Hence, there is no significant difference between the intervention and control arm results for either cost or effectiveness for overweight women. This is further illustrated by *Figure 17*, which plots the result of each simulation on the cost-effectiveness plane and shows that no significant differences were found between the intervention arm and control arm for either cost or effectiveness (for more details see *Appendix 11*). The CEAC (*Figure 18*) shows that, even if the maximum willingness to pay for a major outcome averted for overweight pregnant women was £500,000, then the probability that the intervention is cost-effective would be < 0.5.

Normal weight women

The results of the secondary analysis for normal weight women are reported in *Tables 37* and *38*. The intervention arm had the lowest costs, with an average cost estimated at £3056 (excluding routine antenatal care). This was because the additional costs associated with delivering the intervention were outweighed by savings associated with reduced health-care use overall. However, the care-as-usual arm was only slightly more expensive, with average costs estimated at £3063 (excluding routine antenatal care).

TABLE 35 Results of PSA: average costs (£) for intervention group compared with care as usual for overweight women[a]

Group allocation	Cost (95% CI)	
	Mean	Difference
Intervention	3399 (1546 to 6419)	231 (–279 to 980)
No intervention[b]	3169 (1334 to 6002)	

a Note that the mean results in the PSA are not the same as the point estimates used in the base-case analysis because of the use of log-normal distributions which create a non-linearity in the model.
b As it was assumed that routine antenatal care was received by all women this was not included in the total costs, as there would be no difference in these costs between model arms.

TABLE 36 Results of PSA: analysis for a cohort of 10,000 overweight women[a]

Outcome	Number of women experiencing complications, mean (95% CI)		Number of complications avoided per 10,000 women (95% CI)
	Intervention	No intervention	
Any major outcome	6930 (6613 to 7318)	6902 (6720 to 7095)	–28 (–351 to 206)
PE	472 (248 to 800)	438 (324 to 569)	–34 (–325 to 158)
GDM	1019 (581 to 1624)	871 (712 to 1031)	–148 (–703 to 257)
PIH	299 (159 to 530)	405 (299 to 530)	107 (–72 to 265)
Preterm delivery	1039 (921 to 1159)	1033 (915 to 1150)	–6 (–31 to 12)
Caesarean section	3535 (3328 to 3729)	3525 (3328 to 3714)	–10 (–43 to 14)
IUD	25 (9 to 52)	26 (9 to 53)	0 (–2 to 2)
LGA	1616 (1482 to 1759)	1614 (1475 to 1754)	–2 (–25 to 32)
SGA	882 (785 to 974)	882 (796 to 970)	0 (–40 to 27)
NICU admission	1206 (1073 to 1341)	1197 (1068 to 1332)	–9 (–33 to 9)

a Note that the mean results in the PSA are not the same as the point estimates used in the base-case analysis because of the use of log-normal distributions which create a non-linearity in the model.

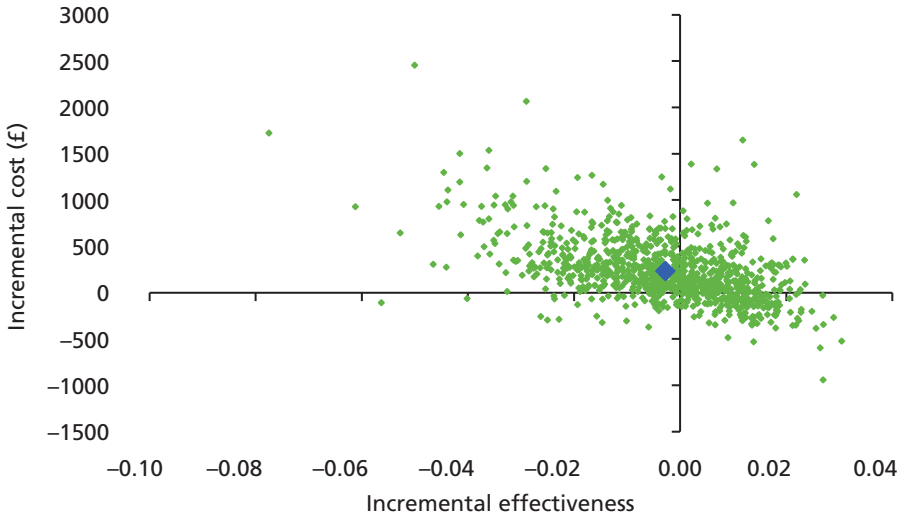

FIGURE 17 Incremental cost-effectiveness scatterplot of intervention compared with care as usual for overweight pregnant women: major outcome averted. The mean of the distribution is highlighted.

In the base-case model (using point estimates) there were 108 fewer women who experienced any major outcome in the intervention arm, 231 fewer cases of PE and 53 fewer women who developed GDM. There were also reductions in the rate of preterm delivery, Caesarean section, IUD, SGA, and NICU admission.

The results suggested that, for most clinical outcome measures reported, the intervention was less costly and more effective than care as usual. These results need to be considered alongside the results of the PSA (*Tables 39* and *40*). The PSA results show the modelled uncertainty in terms of the cost and the effectiveness for the intervention arm and the care-as-usual arms. The findings suggest that it is uncertain whether the intervention is more or less effective than usual care and whether the intervention costs are higher or lower than the costs associated with usual care. Hence, there is no significant difference between the intervention and the control arm results for either cost or effectiveness for women of normal weight. This is further illustrated by *Figure 19*, which plots the result of each simulation on the

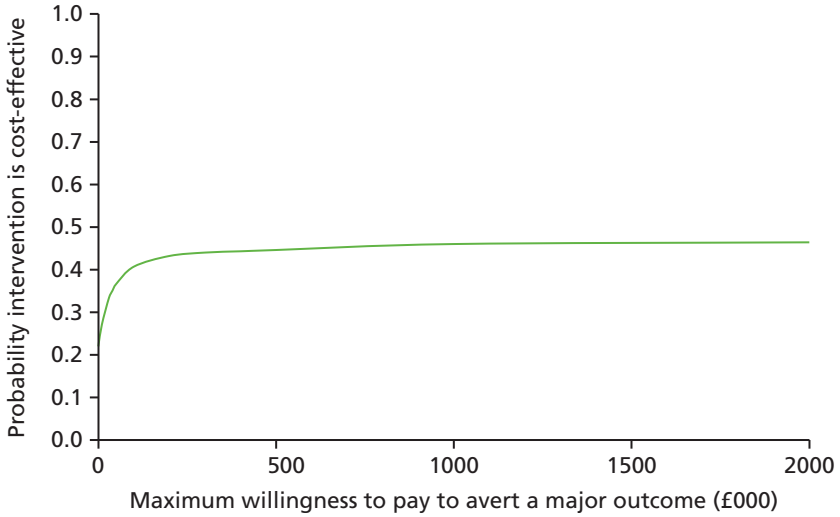

FIGURE 18 Incremental CEAC of intervention for overweight pregnant women: major outcome averted.

TABLE 37 Average costs (£) for intervention group compared with care as usual: women of normal weight

	Cost	
Group allocation	Mean (point estimate)	Difference
Intervention	3056	–7
No intervention[a]	3063	

a As it was assumed that routine antenatal care was received by all women this was not included in the total costs, as there would be no difference in these costs between intervention arms.

TABLE 38 Results of analysis for a cohort of 10,000 normal weight women

	Number of women experiencing complications (point estimate)		Number of complications avoided per 10,000 women (point estimate)	Cost (£) per complication avoided
Outcome	Intervention	No intervention[a]		
Any major outcome	6677	6785	108	[b]
PE	275	506	231	[b]
GDM	573	626	53	[b]
PIH	274	274	0	[b]
Preterm delivery	1029	1056	28	[b]
Caesarean section	3518	3541	24	[b]
IUD	25	25	0	[b]
LGA	1639	1621	–18	[c]
SGA	854	880	26	[b]
NICU admission	1197	1213	17	[b]

a As it was assumed that routine antenatal care was received by all women this was not included in the total costs, as there would be no difference in costs between intervention arms.
b Intervention dominates usual care.
c Intervention is less clinically effective than care as usual/no clinical difference in effectiveness.

TABLE 39 Results of PSA: average costs (£) for intervention group compared with care as usual for normal weight women[a]

Outcome	Cost (95% CI)	
	Mean	Difference
Intervention	3140 (1244 to 6264)	22 (–563 to 741)
No intervention[b]	3118 (1265 to 6041)	

a Note that the mean results in the PSA are not the same as the point estimates used in the base-case analysis because of the use of log-normal distributions which create a non-linearity in the model.
b As it was assumed that routine antenatal care was received by all women this was not included in the total costs, as there would be no difference in costs between intervention arms.

TABLE 40 Results of PSA: analysis for a cohort of 10,000 normal weight women[a]

Outcome	Number of women experiencing complications, mean (95% CI)		Number of complications avoided per 10,000 women (95% CI)
	Intervention	No intervention	
Any major outcome	6704 (6403 to 7068)	6784 (6599 to 6972)	80 (–240 to 286)
PE	290 (121 to 580)	505 (376 to 662)	214 (–44 to 394)
GDM	603 (275 to 1125)	627 (504 to 757)	24 (–466 to 340)
PIH	299 (96 to 725)	272 (186 to 379)	–27 (–421 to 195)
Preterm delivery	1028 (908 to 1155)	1056 (933 to 1179)	28 (4 to 59)
Caesarean section	3520 (3302 to 3722)	3545 (3345 to 3736)	24 (–5 to 62)
IUD	26 (8 to 54)	26 (9 to 53)	0 (–2 to 2)
LGA	1636 (1493 to 1780)	1621 (1481 to 1760)	–15 (–43 to 24)
SGA	858 (761 to 954)	882 (793 to 972)	23 (–13 to 54)
NICU admission	1195 (1055 to 1337)	1212 (1080 to 1352)	17 (–6 to 50)

a Note that the mean results in the PSA are not the same as the point estimates used in the base-case analysis because of the use of log-normal distributions which create a non-linearity in the model.

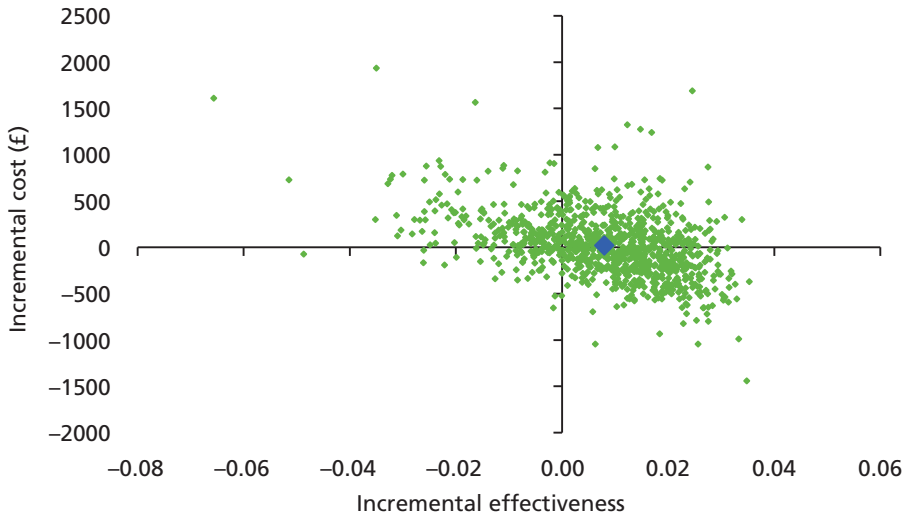

FIGURE 19 Incremental cost-effectiveness scatterplot of intervention compared with care as usual for normal weight pregnant women: major outcome averted. The mean of the distribution is highlighted.

cost-effectiveness plane and shows that, although there is a trend towards lower cost and increased effectiveness for the intervention arm, there is no statistically significant difference between the intervention and the control arms for either cost or effectiveness (see more details in *Appendix 11*). The CEAC (*Figure 20*) shows that as the willingness to pay for a major outcome averted for normal weight women increases, the probability that the intervention is cost-effective also increases. Thus, if the threshold for cost-effectiveness was £30,000 to avert a major outcome for normal weight women, then the probability that the intervention was cost-effective would be 0.67.

Deterministic sensitivity analysis

As demonstrated in *Table 41*, the results of the deterministic sensitivity analysis were as follows: (1) varying the cost of the intervention affected the average cost of the intervention arm and the cost per major outcome avoided, with this rising to £170,000 per major outcome avoided for the highest intervention cost; (2) improving the effect of the intervention meant that the intervention arm was more cost-effective than the control arm, the model was particularly sensitive to the estimate of the effect of the intervention on the odds of developing of PE; (3) varying the timing and mode of delivery did not change the overall result for the development of pregnancy-related conditions; (4) increasing and decreasing the costs for each condition had some impact on the overall results; (5) varying the costs associated with various types of delivery had a negligible effect on the overall results; and (6) increasing the costs of IUD had a negligible impact on overall results. As expected, the multivariate analyses demonstrated that using the highest estimates of effectiveness meant that the intervention arm dominated the control arm (it was less costly and more effective), as the additional costs of the intervention were outweighed by lower health-care resource use.

Discussion

Principal findings

The results of this analysis suggest that there is no evidence that mixed interventions in pregnancy are cost-effective compared with care as usual. Although the primary base-case analysis indicated a small reduction in pregnancy-related complications, the PSA demonstrated that there is no evidence of a significant difference between the intervention and the control arms for either cost or clinical effectiveness. Similarly, the results of the secondary analysis suggested that for obese, overweight and normal weight women it is uncertain whether or not the intervention is more clinically effective than usual care (with respect to all the outcome measures) and whether or not the intervention is more costly than the

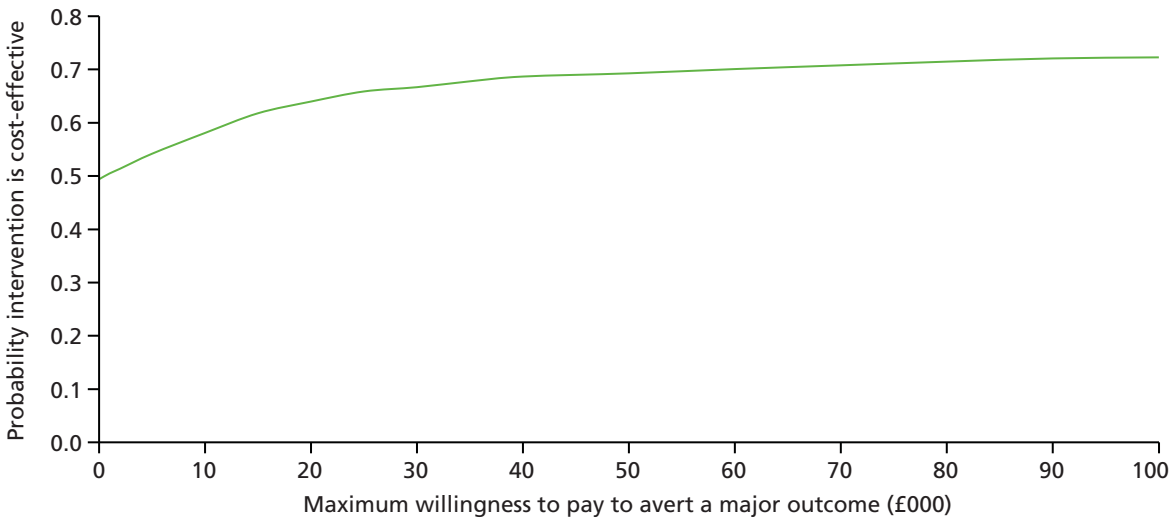

FIGURE 20 Incremental CEAC of intervention for normal weight pregnant women: major outcome averted.

TABLE 41 Deterministic sensitivity analysis: selected results

	Value		Result	
Scenarios	Original	Revised	Original	Revised
Univariate analyses				
(1) Varying the costs of the intervention	£217	£136–1023	Cost of intervention arm: £3390	Cost of intervention arm: £3309–4187
			Cost per major outcome avoided: £26,000	Cost per major outcome avoided: £12,000–170,000
(2) Changing the intervention effect [development of pregnancy-related conditions (OR)]	PE: 0.99	PE: 0.79–1.24	Cases of PE avoided: 5	Cases of PE avoided: 101 to –112
	GDM: 0.89	GDM: 0.72–1.10	Cost per case of PE avoided: £306,000	Cost per case of PE avoided: £7000[a]
	PIH: 0.93	PIH: 0.37–2.73	Cases of GDM avoided: 113	Cases of GDM avoided: 293 to –100
			Cost per case of GDM avoided: £13,000	Cost per case of GDM avoided: £3000[a]
			Cases of PIH avoided: 29	Cases of PIH avoided: 128 to –101
			Cost per case of PIH avoided: £51,000	Cost per case of PIH avoided: £9000[a]
(3) Varying the timing and mode of delivery	Preterm delivery: • PE: 0.234 • GDM: 0.076 • PIH: 0.049	Preterm delivery: • PE: 0.193–0.278 • GDM: 0.061–0.093 • PIH: 0.03–0.076	Cost per case of PE avoided: £306,000 Cost per case of GDM avoided: £13,000	Unchanged
	Caesarean section: • PE: 0.46 • GDM: 0.279 • PIH: 0.355	Caesarean section: • PE: 0.410–0.511 • GDM: 0.316–0.373 • PIH: 0.235–0.327	Cost per case of PIH avoided £51,000	
(4) Increasing and decreasing the costs for each condition	Varies according to pathway	PE: £4476–12,052	Cost per case of PE avoided: £306,000	Cost per case of PE avoided: £312,000–305,000
		GDM: £3105–8753	Cost per case of GDM avoided: £13,000	Cost per case of GDM avoided: £15,000–10,000
		PIH: £2988–5530	Cost per case of PIH avoided £51,000	Cost per case of PIH avoided £53,000–51,000
(5) Varying the costs associated with various types of delivery	Caesarean section (CC score of 0 or 1): £3363	Caesarean section (CC score of 0–1): £1818–4289	Cost per major outcome avoided: £27,000	Cost per major outcome avoided: £26,000–27,000
	Caesarean section (CC score of 2 or 3): £4059	Caesarean section (CC score of 2–3): £2085–4289		
	Normal delivery (CC score of 0): 1461	Normal delivery (CC score of 0): 854–2688		
	Normal delivery (CC score of 1): 1623	Normal delivery (CC score of 1): 898–2968		

continued

TABLE 41 Deterministic sensitivity analysis: selected results (*continued*)

Scenarios	Value		Result	
	Original	Revised	Original	Revised
	Normal delivery (CC score of 2): 1892	Normal delivery (CC score of 2): 957–3349		
(6) Increasing the costs of IUD	IUD cost: £1242	IUD cost: £1804	Cost per major outcome avoided: £27,000	Unchanged
Multivariate analyses				
(1) Varying estimates of effect simultaneously	PE: 0.99	PE: 0.79–1.24	Cost per case of PE avoided: £306,000	Intervention is cost saving with highest estimates of effect and dominated using lowest estimates of effect
	GDM: 0.89	GDM: 0.72–1.10	Cost per case of GDM avoided: £13,000	
	PIH: 0.93	PIH: 0.37–2.73	Cost per case of PIH avoided: £51,000	
(2) Varying estimates of cost simultaneously	Varies according to pathway	PE: £4476–12,052	Cost per case of PE avoided: £306,000	Cost per case of PE avoided: £219,000–374,000
		GDM: £3105–8753	Cost per case of GDM avoided: £13,000	Cost per case of GDM avoided: £9000–16,000
		PIH: £2988–5530	Cost per case of PIH avoided: £51,000	Cost per case of PIH avoided: £37,000–63,000

CC, complications and comorbidity.
a Intervention less effective than care as usual.

alternative. The results of the deterministic sensitivity analyses demonstrated that the results were particularly sensitive to the estimates of the treatment effect in terms of the odds of developing PE.

Strengths and limitations of the economic study

The strength of this model-based economic evaluation is that the effect of interventions to manage weight gain in pregnancy was estimated via an IPD meta-analysis, involving data relating to 17,727 women and 30 studies. Furthermore, the resource use data were collected via a series of systematic reviews to identify studies that collected primary cost data. These reviews involved wide and detailed search and inclusion strategies. In addition, the study benefited from significant clinical input throughout its design and development. This study contributes to an area in which there is a paucity of economic studies.[101] The current public health emphasis on obesity and healthy lifestyles[139] highlights the importance of contributions to understanding the costs and benefits of interventions in this area.

There were also some weaknesses. First, limited evidence was available about the resource use associated with some conditions in pregnancy. Although resource use data from high-quality RCTs were used to inform the model, the paucity of studies available limited the comparisons that could be undertaken to examine variations in costs for different groups of patients. A second limitation was that the study included a wide range of studies with different kinds of intervention models. This meant that it was difficult to estimate the costs associated with the intervention precisely; instead a median value was used, based on the findings of a systematic review. The cost of the intervention varied widely in the sensitivity analysis to account for the diversity of intervention types included in the IPD meta-analysis. In addition, for some outcomes, such as admission to the NICU of an infant whose mother did not have a pregnancy-related complication, it was difficult to obtain robust estimates of resource use. To address this limitation, the sensitivity analysis explored a

wide range of plausible values for the costs associated with pregnancy-related conditions. A further limitation of the study is that outcomes were expressed in terms of clinical effectiveness rather than in terms that would allow comparison across programme areas, such as quality-adjusted life-years (QALYs). The absence of robust QALY data for women who are experiencing pregnancy-related conditions[101,136] meant that a full cost–utility analysis incorporating QALYs was not possible. This means that some of the results are difficult to interpret as no willingness-to-pay threshold exists for individual clinical outcomes. As the results of the sensitivity analysis demonstrated that there was no significant difference between the intervention and the control arms results for either costs or clinical effectiveness, longer-term economic modelling was not undertaken. Finally, the economic evaluation was based on the results of the IPD meta-analysis. The findings may have been different if the evaluation had been based on the results of the meta-analysis using aggregated data (as these showed a statistically significant reduction for some outcomes). Further work could be undertaken to explore the cost-effectiveness of diet- and physical activity-based interventions using data from the aggregate meta-analyses, as this was beyond the scope of the current project.

Comparison with other studies

A limited number of studies were identified that were concerned with the costs and benefits of interventions to promote weight management during pregnancy. Only one study was identified that concluded that such an intervention was cost-effective. Dodd *et al.*[128] concluded that an intervention involving a lifestyle advice service was likely to be cost-effective using a monetary value of AUD 20,000 as a threshold for avoiding additional infants with a birthweight above 4 kg. However, several other studies have found no evidence of statistically significant differences in outcome measures and concluded that the intervention to manage weight gain in pregnancy was not cost-effective. For example, Oostdam *et al.*[132] examined the cost-effectiveness of an exercise intervention and concluded that the intervention was not cost-effective based on a range of outcome measures including infant birthweight and QALYs. Similarly, Kolu *et al.* found that a mixed intervention to prevent GDM was not cost-effective based on improvements in birthweight or 15D instrument scores.[129] A large-scale study concluded that a health training intervention was not cost-effective compared with usual care, based on comparison of QALY gains and costs for women.[68] Finally, a cost-comparison study for a weight-gain restriction programme for obese women found that that the weight-gain restriction programme was effective but had higher costs.[127]

Meaning of the study

The results of the economic evaluation suggest that there is no evidence of cost-effectiveness for mixed interventions to manage weight gain in pregnancy. However, the lack of robust data on the quality of life of women and infants in the perinatal period means that further research is needed to fully understand the benefits of such programmes.

Unanswered questions and future research

The results of this economic evaluation highlight the need for accurate data on the quality of life of mothers and infants in the perinatal period, particularly around the impacts on quality of life for women with pregnancy-related conditions. This would enable a fuller analysis of the impact of interventions to manage weight gain in pregnancy on women's health and that of their children. There is also a need for further work exploring the longer-term costs of weight gain in pregnancy for the mother and infant. This would need to include consideration of the wider societal costs of weight gain during pregnancy, as these are likely to be broader than health alone.

Chapter 9 Discussion

Summary of findings

Diet- and lifestyle-based interventions have a similar effect in all pregnant women for GWG, composite maternal and fetal/neonatal outcomes, irrespective of the woman's characteristics such as BMI at booking, age, parity, Caucasian ethnicity and underlying medical condition(s). The interventions are effective in achieving a modest reduction in GWG, but there are no effects on composite maternal and fetal outcomes. There is no evidence of additional harm to the fetus. Adherence to the IOM-recommended GWG targets does not significantly reduce the risk of composite maternal or fetal/neonatal outcomes.

Strengths and limitations

Our IPD meta-analysis is the largest to date, and has greater power to detect any differential treatment effect across groups than single trials or aggregate meta-analysis. We modelled individual risk status (prognostic factor values) across participants within trials, to assess for variability in patient outcome. This is in contrast to aggregate data meta-analysis, which can model only average risk status values across studies, and thus only explain between-study variation. Our findings are more homogeneous, and are less likely to be affected by selective and biased reporting observed in aggregate meta-analysis. We have included more participants, and more outcomes than those that are currently available in the published literature by including available but unpublished data, particularly for outcomes such as preterm birth and SGA fetuses.

Although individual trials identified in our systematic review were powered to detect an overall treatment effect, the individual trial sample sizes were not sufficient to evaluate an effect in relevant subgroups of women. The sample size needed to be increased fourfold to have sufficient power to detect an interaction with the same magnitude as the overall treatment effect, and a 20-fold increase for an interaction term that is half the size of the overall treatment effect.[140] The costs and time to undertake a new trial for this purpose would be immense. By obtaining IPD from the multiple trials that have already been conducted, we have increased the sample size beyond a single trial, with substantially increased power to detect genuine interactions.

We focused on assessing the effect of the intervention on women across the BMI spectrum, including traditional categories of normal weight, overweight and obese. Ours is the first work to assess the effects of prognostic factors such as parity, ethnicity and underlying medical condition on the effectiveness of the intervention. The information about the components of the intervention was obtained in detail, including the adherence to the intervention by directly contacting the primary researchers. As experiencing more than one outcome out of GDM, preterm birth and PE was considered to be equally important for clinical management, we used composite outcome measures. We identified the components of the composite through a robust and transparent Delphi process.[19] The effects of the intervention on the individual components of the composite showed very similar effect sizes, confirming the valid use of the composite. We assessed the risk of bias in studies that contributed IPD and compared this with the risk of bias overall in all published studies. The relationship between GWG and pregnancy outcomes was evaluated using good-quality randomised data.

We were not able to explore the effects of ethnicity in detailed subcategories because of the wide variation in the definitions of race and ethnicity in individual studies. Furthermore, our assessment of differential effects for various individual characteristics was limited to those studies that only included women from all the subgroups. The trials varied in the type of intervention, duration, intensity, setting, provider and compliance. We were unable to fully disentangle the components of the intervention, and

thus to identify those features that are effective in improving outcomes. The variation in criteria for the diagnosis or definition of GDM and PE may also have influenced the results. All studies that contributed to IPD were included in the analysis of the composite outcome, as the individual components of the outcome were not reported in all studies.

Very few studies that evaluated diet provided IPD, affecting the precision of the estimates for diet-based intervention. We approached all relevant authors within the time frame of the IPD meta-analysis. Although we identified more studies in the updated search, it was too late within the project to obtain data from these groups. However, the proportion of individual data not shared was lower than the proportion of studies not included in the IPD. Availability of additional non-IPD studies to our work may have improved the precision in our estimates. For validation of weight change as an outcome, we used the data only from control women, which reduced the available sample size for analysis. Inclusion of both intervention and control groups may help to improve the precision of the estimates, although precision may also be affected by the effects of intervention.

Comparison to existing evidence

Current national and international recommendations provide advice on diet and physical activity to manage weight in pregnancy.[10,141,142] These do not quantify the expected benefit to the woman or her infant from lifestyle-based interventions. They vary in their advice on compliance with weight-gain targets in pregnancy. Our findings are consistent with the previous systematic review that found a reduction in GWG.[24] Based on the findings of IPD meta-analysis, we were able to provide robust estimates for composite and individual maternal and fetal/neonatal outcomes, with minimal heterogeneity that limited previously published reviews.

Our findings on the effect of interventions for fetal/neonatal outcomes are similar to those of the recently published large studies that found no significant benefit.[68,72] Meta-analysis of published aggregate data showed significant benefit for GDM, preterm birth and Caesarean section compared with the observed trend in reduction of maternal composite and individual outcomes in our IPD meta-analysis. This is probably because of the inclusion of additional participants, although there were no large differences in sample sizes for individual maternal outcomes in both meta-analyses. However, unlike IPD, aggregate meta-analysis did not account for baseline prognostic factors in assessing the effects of intervention.

In the USA, the IOM guidance recommends weight-gain ranges in pregnancy for normal weight, overweight and obese women based on observational data.[143] In the absence of validation of these data in large interventional trials, the benefits of adhering to these targets in pregnancy are unclear. We have not found an association between GWG, including adherence to IOM targets and improvement in pregnancy outcomes.

Relevance to clinical practice

Currently, only obese pregnant women are offered diet and lifestyle interventions, which are often delivered by dietitians in many hospitals in the UK. Our work has shown that the effects of the interventions do not vary according to the maternal BMI for reduction in GWG. Existing strategy needs to be broadened to include normal weight and overweight women, as reduced GWG has the potential to minimise postpartum weight retention,[144] thereby preventing these women from entering subsequent pregnancies as overweight or obese, respectively. Women should be encouraged to follow any intervention that is convenient and available, as the effects on GWG were similar for diet, physical activity and mixed-approach interventions. Similarly, it is not essential to configure services to target pregnant women based on age, ethnicity or underlying medical risk factors to deliver the intervention.

Health-care professionals should reassure women that lifestyle interventions do not increase the risk of adverse outcomes in their unborn child. The potential for benefit in improving maternal outcomes needs discussion. Pregnant women should be informed of the absence of relationship between prespecified weight-gain targets and composite adverse outcomes.

Research recommendations

The i-WIP Collaborative Network has provided a platform for lead researchers in this field to prioritise outcomes, standardise variables, plan future studies and influence public policies.[19,20] Further evaluation is needed to assess the differential effects of the interventions for individual maternal and fetal/neonatal outcomes. Addition of data from non-IPD studies to IPD meta-analysis for individual outcomes would be more informative than the comparison of IPD with only published aggregate data. Compliance with the IOM-recommended weight-gain targets and individual outcomes would add to the current evidence base.

Although interventions in pregnancy have been widely studied, very few have focused on the optimisation of the health of the mother in early pregnancy. Future studies will need to focus on interventions that optimise the health of women in the pre-pregnancy period. Such a strategy should also target women in the postpartum period, to ensure that their health status is optimal on entering a subsequent pregnancy. Long-term follow-up of women and their children exposed to the interventions should be prioritised as a research topic by funders and researchers. Health service delivery research is required to identify the ideal way to effectively deliver diet- and lifestyle-based interventions.

Acknowledgements

We acknowledge all researchers, research nurses and staff of the participating centres in the trials contributing to this IPD meta-analysis.

Contributions of authors

Anneloes E Ruifrok, **Christianne JM de Groot**, **Sally Kerry**, **Richard D Riley** and **Shakila Thangaratinam** developed the protocol.

Louise Jackson, **Pelham Barton** and **Tracy Roberts** wrote the health economic part of the protocol.

Julie Dodds oversaw the project and drafted the manuscript.

Ewelina Rogozińska, **Nadine Marlin** and **Shakila Thangaratinam** conducted the review, drafted the manuscript and led the project.

Ben Willem Mol and **Khalid S Khan** provided input into the protocol development and the drafting of the initial manuscript.

Ewelina Rogozińska and **Emma Molyneaux** undertook the literature searches and study selection.

Ewelina Rogozińska, **Girish Rayanagoudar**, **Anneloes E Ruifrok**, **Emma Molyneaux** and **Shakila Thangaratinam** acquired IPD.

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Ewelina Rogozińska, **Nadine Marlin** and **Girish Rayanagoudar** mapped the variables in the available data sets.

Ewelina Rogozińska and **Nadine Marlin** cleaned and quality-checked data.

Nadine Marlin harmonised the data.

Nadine Marlin, **Sally Kerry** and **Richard D Riley** conducted the data analysis.

Louise Jackson, **Pelham Barton** and **Tracy Roberts** performed the health economic simulations, with input from **Shakila Thangaratinam**, and wrote the health economic part of the report.

Arri Coomarasamy, **Ben Willem Mol** and **Khalid S Khan** were involved in project development and provided input at all stages.

All authors critically appraised the final draft of the report.

Publication

The International Weight Management in Pregnancy (i-WIP) Collaborative Group. Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials. *BMJ* 2017;**358**:j3119.

Data sharing statement

Requests for access to data should be addressed to the corresponding author.

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Appendix 1 Outcomes prioritised in Delphi survey

TABLE 42 List of maternal and neonatal outcomes considered to be relevant to patient care when evaluating dietary and lifestyle interventions in pregnancy

Outcomes	
Maternal	**Fetal**
Weight gain in pregnancy	SGA
Postpartum weight retention	LGA
Interpregnancy weight gain	Skinfold thickness
GDM	Fetal fat mass (%)
PE/PIH	Abdominal circumference
Postpartum haemorrhage	Head circumference
Prolonged labour	Ponderal index (g/cm^3 × 100)
Preterm delivery	Neonate length/crown–heel length
Induction of labour	Head-to-abdomen ratio
Prelabour rupture of membranes	Birthweight-related outcomes, such as BMI
Caesarean section	Hypoglycaemia
Instrumental delivery	Hyperbilirubinaemia
Perineal trauma	IUD
Puerperal pyrexia (≥ 38 °C)	Respiratory distress syndrome
Miscarriage	Admission to the NICU
Need for resuscitation at delivery	Shoulder dystocia
Antepartum haemorrhage	≥ 1 perinatal complication
Thromboembolism	Birth trauma number
Admission to high-dependency unit/intensive therapy unit	Neural tube defect
Anaemia	Cleft lip or palate or both
Infections	Other congenital abnormalities
Postnatal infections	Apgar score
Postnatal depression	Cardiotocograph abnormalities
Anxiety	Abnormal cord pH
Quality of life	Long-term neurological sequelae
Physical activity	Cord abnormalities
Dietary behaviour	Long-term metabolic sequelae
Body fat (%)	
Back pain	
Breastfeeding	
Threatened abortion	
Failed instrumental delivery	
Coronary artery disease	
Non-infective respiratory distress	

TABLE 43 Maternal, and fetal and neonatal outcomes ranked by the Delphi panel

Items	Round			
	First		Second	
	Median	Interquartile range	Median	Interquartile range
Maternal outcomes				
PE[a]	8.5	1	9	0
PIH[a]	8.5	1	9	1
GDM	8.5	1	9	0
Preterm delivery	7.5	1	8	2
Caesarean section: elective[a]	8	2	8	1
Caesarean section: emergency[a]	8	2	8	0
Fetal outcome				
IUD	9	1.25	9	0
SGA	8	1	8	1
LGA	8	1	8	1
Admission to the NICU	8	1	8	0

a Combined into one outcome.

Appendix 2 Search strategies

TABLE 44 Search strategy for MEDLINE (via Ovid)

Item	Term
1	Pregnancy/
2	pregnan*.tw.
3	Gravidity/
4	gravid*.tw.
5	gestation*.tw.
6	Pregnant Women/
7	pregnant wom#n.tw.
8	(child adj3 bearing).tw.
9	childbearing.tw.
10	matern*.tw.
11	or/1-10
12	Weight Gain/ph [Physiology]
13	weight gain*.tw.
14	Weight Loss/ph [Physiology]
15	weight loss*.tw.
16	weight change*.tw.
17	Obesity/dh, me, ph, pc, px, th [Diet Therapy, Metabolism, Physiology, Prevention & Control, Psychology, Therapy]
18	obes*.tw.
19	Adiposity/ph [Physiology]
20	adipos*.tw.
21	Overweight/dh, me, ph, pc, px, th [Diet Therapy, Metabolism, Physiology, Prevention & Control, Psychology, Therapy]
22	overweight*.tw.
23	Body Mass Index/
24	bmi.tw.
25	or/12-24
26	exp Randomized Controlled Trial/
27	"randomized controlled trial".pt.
28	"controlled clinical trial".pt.
29	(random$ or placebo$).tw,sh.
30	((singl$ or double$ or triple$ or treble$) and (blind$ or mask$)).tw,sh.
31	single-blind method/
32	double-blind method/
33	or/26-32

continued

TABLE 44 Search strategy for MEDLINE (via Ovid) (*continued*)

Item	Term
34	11 and 25 and 33
35	exp Animals/
36	(rat$ or mouse or mice or hamster$ or animal$ or dog$ or cat$ or bovine or sheep or lamb$).af.
37	35 or 36
38	Humans/
39	human$.tw,ot,kf.
40	37 or 38
41	37 not (37 and 40)
42	34 not 41

TABLE 45 Search strategy for The Cochrane Library

Item	Terms
#1	(Pregnancy):ti,ab,kw
#2	pregnan*
#3	Gravidity
#4	gravid*
#5	gestation*
#6	"Pregnant Women"
#7	childbearing
#8	matern*
#9	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10	(Weight Gain):ti,ab,kw
#11	(Weight Loss):ti,ab,kw
#12	weight loss*
#13	weight change*
#14	(Obesity):ti,ab,kw
#15	obes*
#16	Adiposity:ti,ab,kw
#17	adipos*
#18	Overweight:ti,ab,kw
#19	overweight*
#20	"Body Mass Index"
#21	BMI
#22	(#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21)
#23	(#9 AND #22)

Appendix 3 International Weight Management in Pregnancy individual participant data meta-analysis project variables

TABLE 46 Variables

Variable label	Variable type	Variable format	Variable range
Height (cm)	Numeric	999	999 = missing
Pre-pregnancy weight (kg)	Numeric	999.9	999 = missing
Pre-pregnancy BMI (kg/m^2)	Numeric	99.99	99 = missing
Early pregnancy weight (kg)	Numeric	999.9	999 = missing
Early pregnancy BMI (kg/m^2)	Numeric	99.99	99 = missing
Gestational age at baseline (weeks)	Numeric	99	0–50, 99 = missing
Gestational age at baseline (days)	Numeric	9	0–6, 9 = missing
Gestational age at follow-up (weeks)	Numeric	99	0–50, 99 = missing
Gestational age at follow-up (days)	Numeric	9	0–6, 9 = missing
Follow-up weight (kg)	Numeric	999.9	999 = missing
Follow-up BMI (kg/m^2)	Numeric	99.99	99 = missing
Total weight gain (kg)	Numeric	999.9	999 = missing
Weight post delivery (kg)	Numeric	999.9	999 = missing
Babies birthweight (g)	Numeric	9999	9999 = missing
Age (years)	Numeric	99.9	99 = missing
Land of birth	String		
Race/ethnicity	Numeric categorical	9	1 = Caucasian, 2 = Asian, 3 = Afro-Caribbean, 4 = Central/ South American, 5 = Middle Eastern, 6 = other, 9 = nk
Education mother, detail	String		
Education mother, low/medium/high	Numeric categorical	9	1 = low, 2 = middle, 3 = high, 9 = nk
Current smoker	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
Ex-smoker (pre pregnancy)	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
Allocation	Numeric categorical	9	0 = control, 1 = intervention1, 2 = intervention2, 9 = nk
Unit of randomisation	String		For example participantid, centre id . . .
Adherence	Numeric categorical	9	2 = control group, 1 = yes, 0 = no, 9 = nk
Number of fetuses	Numeric categorical	9	1 = singleton, 2 = twin or more, 9 = missing

continued

TABLE 46 Variables (*continued*)

Variable label	Variable type	Variable format	Variable range
Gestational age at delivery (weeks)	Numeric	99	99 = missing
Mode of delivery	Numeric categorical	9	1 = nvd, 2 = instrumental/vacuum/forceps, 3 = cs, 9 = nk
Number of times giving birth before this pregnancy	Numeric	99	99 = missing
Previous miscarriages	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
Gravidity (number of times pregnant)	Numeric	99	99 = missing
Obesity (BMI of $\geq$ 30 kg/m^2)	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
Previous large baby ($\geq$ 4.5 kg)	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
Previous GDM	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
Family history of DM	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
Baseline GDM	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
Baseline DM	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
Baseline PIH	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
Baseline hypertension	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
Exercise detail	String		
GDM test value	Numeric	999.9	999 = missing
GDM test unit	Text		
Type of GDM test	Text		
GDM	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
PIH	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
PE	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
Preterm delivery	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
Caesarean section	Numeric categorical	9	0 = no, 1 = cs unspecified, 2 = elective, 3 = emergency, 9 = nk
IUD	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
SGA	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
LGA	Numeric categorical	9	0 = no, 1 = yes, 9 = nk
Admission to the NICU	Numeric categorical	9	0 = no, 1 = yes, 9 = nk

cs, Caesarean section; ID, identification; nk, not known; nvd, normal vaginal delivery.

Appendix 4 Variables recoding

TABLE 47 Standardisation of IPD ethnicity data

Caucasian (including Russia and Australia)	Asian	Afro-Caribbean	Central/South American	Middle Eastern (including Iran and Turkey)	Other
Afro-Caribbean	Malaysia	Tunisia	Argentina	Iran	Aboriginal
Australia	Nepal	Uganda	Brazil	Iraq	Australia/ Aboriginal
Australian – Aboriginal	Pakistan	*Unclassified (other)*	Brazil Black	Israel	Fiji
Austria	Pakistani	Zimbabwe	Brazil Pardo	Lebanon	New Zealand
Belgian/Dutch	Philippines	Maghreb	Brazil White	Middle Eastern	Non-Caucasian
Belgium	South East Asian		Chile	Turkey	Other
Bosnia	Sri Lanka		Colombia	Turkish	
Bosnia-Herzegovina	Sri-Lanka		Columbia		
Bulgaria	Taiwan		El Salvador		
Caucasian	Thailand		Mexico		
Caucasian, excluding Turkey and Morocco	*Unclassified (other)*				
Croatia	Uzbekistan				
Czech	Vietnam				
Denmark	Japan				
East European					
England					
European					
Finland/England/ Sweden/Russia					
France					
Germany					
Greece					
Hungary					
Iceland					
Iraq					
Italian					
Italy					
Kosovo					
Latvia					
Lebanon					
North American White					
Norway					

continued

TABLE 47 Standardisation of IPD ethnicity data (*continued*)

Caucasian (including Russia and Australia)	Asian	Afro-Caribbean	Central/South American	Middle Eastern (including Iran and Turkey)	Other
Other White					
Pakistan					
Poland					
Romania					
Russia					
Serbia					
Slovakia					
Spain					
Sweden					
The Faroes					
Turkey					
Ukraine					
Unclassified (other)					
White Irish					
Yugoslavia					
Caucasian					

We assumed IPD data to be clean and, therefore, individual items (in italic) may seem to be in the wrong category.

We assumed IPD data to be clean and, therefore, individual items may seem to be in the wrong category. However, if the study already had categories that matched our structure, then we used those rather than the additional details provided.

TABLE 48 Standardisation of IPD education data

Low	Medium	High
< 12 years (preparatory school or occupational school)	12 years (high school)	Vocational training school
< 4 years of study	4–8 years of study	< 4 years additional education
First degree	A-level (or equivalent)	> 12 years (university or equivalent to it)
Grammar school ≤ 10 years	GCE (or equivalent)	> 8 years of study
LBO	General secondary school	≥ 4 years additional education
Less than high school	General upper secondary education	College/university < 4 years
Low	HAVO/VWO	Further education 1–2 years
Low (basic or secondary education)	High school	Graduate degree
None	High school/grammar school	Graduated, 14 years
Preliminary, 5 years	High school diploma	Graduated, 16 years

TABLE 48 Standardisation of IPD education data (*continued*)

Low	Medium	High
Preliminary, 9 years	High school, 12 years	HBO
Primary	Intermediate secondary school	High (university degree)
Primary and secondary school	MBO	Higher degree
Primary education	Medium (polytechnic education)	Postgraduate education
Primary or less	Secondary	Postgraduate
Primary school	Secondary school 12 years	Tertiary
VMBO	Upper secondary school	Tertiary education 3–4 years (Bachelor level)
Year 10 or below	Vocational upper secondary education	Undergraduate
Year 11 or equivalent	Year 12 or equivalent	University
Elementary school	Complete secondary	University degree
Grade school (< 6 years)	High school	University/university college < 4 years
Junior high school (7–9 years)	High school (13 years)	University/university college > 4 years
Less than primary school	High school (10–12 years)	Vocational qualification
Less than primary school	Medium-length education	WO
Middle	School maximum 10 years, additional education	Year 12 or equivalent
Middle school (8 years)	Technical, additional education	Bachelors level
Primary school	Until 18 year, possible a speciality of 1/2 year	College (university)
School maximum 10 years, education unfinished	Vocational training	College/university degree
Some secondary		College/university 4+ years
Technical/high school, education unfinished		Complete third level
		Graduate or professional education
		Graduated
		High school, additional education
		Masters level or higher
		Post graduation level
		Same college (< 4 years)
		Some third-level university

GCE, General Certificate of Education; HAVO/VWO, hoger algemeen voortgezet onderwijs & voorbereidend wetenschappelijk onderwijs; HBO, hoger beroepsonderwijs; LBO, laag beroepsonderwijs; MBO, middelbaar beroepsonderwijs; VMBO, voorbereidend middelbaar beroepsonderwijs; WO, wetenschappelijk onderwijs.

TABLE 49 Standardisation of IPD baseline activity data

Level of activity	
No exercise/sedentary	**At least some activity**
< 600 MET minutes/week	≥ 10,000 steps/day
< 600 MET hours/week	≥ 600 MET minutes/week
Accelerometer < 2.5 hours/week	≥ 600 MET hours/week
Does not attend gym	Accelerometer ≥ 2.5 hours/week
Does not exercise regularly at inclusion	Does attend gym
Fewer than 10,000 steps/day	Exercise regularly at inclusion
Low	Handiwork
PPAQ < 1000 cal	Hard
Sedentary	High
Sedentary work	Light–moderate
Work mainly sedentary	Moderate
Completely inactive	Moderate–hard
Completely sedentary	PPAQ ≥ 1000 cal
Lying	Physically active
Sedentary	Work in movement
Sedentary work	Work standing
Sitting	Work standing and in movement
Some activity occasionally	Active
	Active (PPAQ)
	Active (exercise two or three times a week)
	Active work
	High-performance athlete
	Housewife
	Professional athlete
	Something active
	Standing
	Very active
	Very active (regular exercise four or five times a week)
	Walking

MET, metabolic equivalent of task; PPAQ, Paffenbarger Physical Activity Questionnaire.

Appendix 5 Details of trials with unavailable individual participant data

TABLE 50 Eligible trials for without access to IPD

Study (first author and reference number)	Reason	Intervention group	Country	Sample size
Asbee *et al.*[28]	No response	Mixed	USA	100
Barakat *et al.*[42]	Conflict of interest	Exercise	Spain	100
Barakat *et al.*[43]	Conflict of interest	Exercise	Spain	510
Bechtel-Blackwell[30]	No response	Diet	USA	46
Briley *et al.*[31]	No response	Diet	USA	20
[a]Callaway *et al.*[145]	Not approached	Exercise	Australia	50
Clapp *et al.*[44]	Data loss	Exercise	USA	51
Deveer *et al.*[32]	No response	Diet	Turkey	100
Garshasbi *et al.*[33]	No response	Exercise	Iran	212
Gomez-Tabarez *et al.*[34]	No response	Diet	Colombia	60
Hopkins *et al.*[146]	Contact loss	Exercise	New Zealand	81
Huang *et al.*[35]	No response	Mixed	Taiwan	125
Jackson *et al.*[147]	Contact loss	Mixed	USA	321
Korpi-Hyövälti *et al.*[39]	Lack of time	Diet	Finland	54
Lee *et al.*[45]	Data loss	Exercise	UK	370
Marquez-Sterling *et al.*[148]	Contact loss	Exercise	USA	15
Polley *et al.*[36]	No response	Mixed	USA	110
Quinlivan *et al.*[41]	Data sharing issues	Diet	Australia	132
Santos *et al.*[37]	No response	Exercise	Australia	72
Sedaghati *et al.*[38]	No response	Exercise	Iran	90
Thornton *et al.*[40]	Lack of time	Diet	USA	232
Vesco *et al.*[149]	Contact loss	Mixed	USA	114
Ramírez-Vélez *et al.*[59]	Not approached	Exercise	Colombia	64
Ramírez-Vélez[60]	Not approached	Exercise	Colombia	20
Badrawi *et al.*[29]	No response	Diet	Egypt	100
Cordero *et al.*[47]	Not approached	Exercise	Spain	342
de Oliveria Melo *et al.*[47]	Not approached	Exercise	Brazil	187
Di Carlo *et al.*[50]	Not approached	Diet	Italy	154
Hawkins *et al.*[51]	Not approached	Mixed	USA	68
Hui *et al.*[52]	Not approached	Mixed	Canada	113
Jing *et al.*[53]	Not approached	Mixed	China	262
Kong *et al.*[54]	Not approached	Exercise	USA	42

continued

TABLE 50 Eligible trials for without access to IPD (*continued*)

Study (first author and reference number)	Reason	Intervention group	Country	Sample size
Murtezani *et al.*[57]	Not approached	Exercise	Republic of Kosovo	72
Price *et al.*[58]	Not approached	Exercise	USA	91
Li *et al.*[57]	Not approached	Mixed	China	239
Ronnberg *et al.*[61]	Not approached	Exercise	Sweden	445
Bisson *et al.*[46]	Not approached	Exercise	Canada	37
Mujsindi *et al.*[47]	Not approached	Mixed	USA	79

a Data from secondary publication Dekker Nitert *et al.*[49]

Appendix 6 Clinical characteristics of the randomised controlled trials

TABLE 51 Characteristics of studies in the repository

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
Althuizen *et al.*,[90] 2013; English	Method of randomisation: computerised random number generator Allocation concealment: prestratified allocation schedule for each practice with group allocation at random Blinding: examiners who assessed anthropometric outcome measures were unaware of group allocation. Participants could not be blinded but were requested not to reveal information about their treatment to the examiners. The coding key for group assignment was only known to the central database programmer	Inclusion criteria • First pregnancy • Ability to read, write and speak Dutch • Gestational age < 14 weeks Number of participants: • Intervention, $n = 123$ • Control, $n = 123$	Two personal counsellors with a background in physical activity or remedial education provided five counselling sessions at 18, 22, 30 and 36 weeks of gestation and at 8 weeks post partum. Principles of a psychological intervention method called 'problem-solving treatment for primary care' were used. Sessions lasted for 15 minutes, except the first that lasted 30 minutes. A general information brochure was provided after the first session. The sessions were aimed at making the participants aware of issues related to weight gain in pregnancy, including IOM guidelines. Weight gain charts specific to BMI categories with markings to show recommended weight gain (IOM guidelines) were provided. Dietary advice was provided as per Dutch nutrition centre guidelines, with emphasis on healthy eating, adjusting energy intake to activity levels and decreasing intake of high-fat food. Physical activity was assessed by questionnaires and general information provided. Specific individualised activities were discussed in those not meeting physical activity guidelines. The American Centre for Disease Control and Prevention guidelines formed the basis for physical activity counselling. The last counselling session (via telephone) focused on delivery, breastfeeding, care of the newborn infant along with physical activity and diet	Standard care	Primary: • change in bodyweight and BMI (measured at 15, 25 and 35 weeks of pregnancy and at 7, 25 and 51 weeks post partum) • skin fold thickness and body fat percentage Secondary: • physical activity by Short Questionnaire to Assess Health (SQUASH) enhancing physical activity and accelerometer data • questionnaire for nutrition and related behaviours (Dutch Eating Behavior Questionnaire) • leptin, ghrelin, fasting glucose, insulin, cortisol insulin growth factor-1, insulin growth factor binding proteins-1 and three from a subgroup of participants and cord blood

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
			The counsellors were trained for the study by recording conversations with 10 pregnant women, followed by feedback on performance by other members of the research team		
Baciuk *et al.*,[79] 2008; English	Method of randomisation: computer-generated randomisation list of numbers. Volunteers were enrolled sequentially and randomised to one of the two study groups Allocation concealment: each sequential number corresponded to a sealed opaque envelope containing the information on the randomisation group Blinding: outcomes assessors	Pregnant women < 20 weeks of gestation, carrying single fetus, with no gestational risk factors Inclusion criteria: • pregnant women of < 20 weeks of pregnancy • singleton pregnancy • no gestational risk factors • received prenatal care at the research institution and intended to give birth there Exclusion criteria: • practising regular physical exercise • two or more Caesarean sections • clinical and/or laboratory diagnoses of neurological, cardiovascular, pulmonary, musculoskeletal or endocrine disorders • any disorder that could represent a risk to the woman's health, such as morbid obesity, severe anaemia or vaginal bleeding during pregnancy Number of participants: • Intervention, $n = 34$ • Control, $n = 37$	Physical activity (water aerobics): the intervention was the regular, moderate practice of water aerobics for 50 minutes three times a week in an indoor swimming pool with water warmed at 28–30 °C. Water aerobics was initiated following the first physical evaluation and continued up to delivery. The moderate intensity of exercises during the sessions was assured by monitoring patients' heart rate using a heart rate monitor and kept around 70% of one's predicted maximum heart rate	No intervention	• Request for analgesia • Caesarean section • Apgar score at 1 minute of ≥ 7 • Vaginal delivery • Preterm birth (< 37 weeks) • Low birthweight (< 2500 g), adequacy of neonatal weight to gestational age, length of labour (minutes) • Birthweight • Gestational age • Weight gain • Body fat (%) • Fat-free mass (%) • BMI

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
Barakat *et al.*,[80] 2008; English	Method of randomisation: not reported Allocation concealment: the investigator responsible for randomly assigning participants did not know in advance which group the next person would be allocated to, and was not part of assessment Blinding: outcomes assessors	Inclusion criteria: • singleton and uncomplicated pregnancy • not at high risk for preterm delivery (no history of recurrent spontaneous preterm birth, i.e. number of previous preterm deliveries ≤ 1) • aged 25–35 years • sedentary before gestation (not exercising > 20 minutes on > 3 days/week) Exclusion criteria: • not being under medical follow-up throughout the entire pregnancy period • women not planning to give birth in the same obstetrics hospital associated with the study • women with any serious medical condition preventing them from exercising safely Number of participants: • Intervention, $n = 80$ • Control, $n = 80$	The programme consisted of 35- to 40-minute sessions thrice weekly from 12–13 weeks of gestation to end of pregnancy (38–39 weeks), with an estimated average of 80 sessions per participant. They were supervised by a trained fitness specialist with each group consisting of 10–12 women. The venue was spacious and well lit with favourable conditions (altitude 600 m, temperature 19–21 °C and humidity 50–60%). The sessions were accompanied by music. The exercise activity was of light to moderate intensity with a target heart rate of ≤ 80% of maximum predicted heart rate for age (220 – age). All participants were provided with heart rate monitors. Each session included a warm-up (8 minutes), a core session (20 minutes) and a cool-down period (8 minutes). Warm-up and cool-down components involved light stretching exercises for limbs, neck and trunk. In addition, the cool-down period included relaxation exercises The core portion involved toning and very mild resistance exercises. Toning included shoulder shrugs and rotations, arm elevations and leg lateral elevations, pelvic rocks and tilts. The resistance exercises included one set of 10–12 repetitions of each of (1) abdominal curls and (2) the below exercises using barbells (3 kg/exercise) or low to medium resistance bands: bicep curls, arm side lifts and extensions, shoulder elevations, bench press, seated	The women were asked to maintain their level of activity	• GWG (weight before delivery minus weight before pregnancy) • Preterm deliveries • Birthweight • Macrosomia • Birth length • Head circumference • Ponderal index • Apgar score at 1 minute • Apgar score at 5 minutes

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
			lateral row, leg circles and lateral leg elevations, knee (hamstring) curls and extensions, ankle flexions and extensions Exercises such as jumping, ballistics, extreme stretching and joint overextension were avoided		
Barakat *et al.*,[81] 2011; English	Method of randomisation: use of a random number table Allocation concealment: not reported Blinding: not reported	Inclusion criteria: • pregnant women in first trimester attending the hospital associated with the study Exclusion criteria: • not planning to deliver in the same department • not receiving medical follow-up throughout the pregnancy • absolute contraindication to aerobic activity in pregnancy • haemodynamically significant heart disease • restrictive lung disease • recent pulmonary embolism (previous 5 years) • cervical incompetence/cerclage • multiple pregnancy • risk of premature labour • PIH/PE • thrombophlebitis • acquired infectious disease	The programme consisted of 35- to 45-minute sessions thrice weekly from 6–9 weeks of gestation to the end of pregnancy (38–39 weeks), with an estimated average of 85 sessions per participant. The participants were supervised by a trained fitness specialist with each group consisting of 10–12 women. The venue was spacious and well lit with favourable conditions (altitude 600 m, temperature 19–21 °C and humidity 50–60%). High room temperatures and humid environment were avoided. The sessions were accompanied by music. The exercise activity was of light to moderate intensity with a target heart rate of ≤ 70% of maximum predicted heart rate for age (220 – age). All participants were provided with heart rate monitors Each session included a warm-up (7–8 minutes), a core session (25 minutes) and a cool-down period (7–8 minutes). Warm-up and cool-down components	Usual care	• Maternal perception of health status (Short Form questionnaire-36 items King's Health questionnaire) • Frequency of urine incontinence (CIQ-SF incontinence classification • GWG • Gestational age at delivery • Type of delivery (normal, instrumental, Caesarean) • Delivery lacerations type • Systolic and diastolic blood pressure • 1-hour glucose level • Birthweight • Macrosomia • Apgar score at 1 minute • Apgar score at 5 minutes

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
		• intrauterine growth restriction • major blood disorders • absence of prenatal control Number of participants: • Intervention, $n = 40$ • Control, $n = 40$	involved light stretching exercises for limbs, neck and trunk. In addition, the cool-down period included relaxation and pelvic floor exercises The core portion involved toning and very mild resistance exercises. Toning included shoulder shrugs and rotations, arm elevations and leg lateral elevations, pelvic rocks and tilts. The resistance exercises included one set of 10–12 repetitions of each of (1) abdominal curls and (2) the below exercises using barbells (3 kg/exercise) or low- to medium-resistance bands: bicep curls, arm side lifts and extensions, shoulder elevations, bench press, seated lateral row, leg circles and lateral leg elevations, knee (hamstring) curls and extensions, ankle flexions and extensions Exercises such as jumping, ballistics, extreme stretching and joint overextension were avoided. Supine exercises were limited to 2 minutes and exercises involving the Valsalva manoeuvre were avoided. Care was taken to ensure adequate nutrition prior to exercise sessions		

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
Barakat *et al.*,[42] 2012; English	Method of randomisation: computer-generated list of random numbers Allocation concealment: not reported Blinding: randomisation procedure including sequence generation, allocation concealment, and implementation was made for three different authors to facilitate blinding	Inclusion criteria • healthy uncomplicated singleton pregnancy Exclusion criteria: • absolute obstetrical contraindication to exercise [as per ACOG (2002)] • plans to deliver baby elsewhere • not receiving antenatal care throughout the pregnancy • participating in another physical activity programme • regular exercise before pregnancy (four or more times per week) Number of participants: • Intervention, $n = 160$ • Control, $n = 160$	The programme consisted of 40- to 45-minute sessions thrice weekly from 6 to 9 weeks of gestation to end of pregnancy (38–39 weeks), with an estimated average of 85 sessions per participant. The participants were supervised by a trained fitness specialist with each group consisting of 10–12 women. The venue was spacious and well lit with favourable conditions (altitude 600 m, temperature 19–21 °C and humidity 50–60%). The sessions were accompanied by music The exercise activity was of light to moderate intensity with a target heart rate of ≤ 70% of maximum predicted heart rate for age (220 – age). All participants were provided with heart rate monitors. Each session included a warm-up (7–8 minutes), a core session (25 minutes) and a cool-down period (7–8 minutes). Warm-up and cool-down components involved light stretching exercises for limbs, neck and trunk The core portion included exercises for arms and abdomen, and aerobic dance to improve posture, strengthen muscles of labour and pelvic floor and prevent lower back pain	Usual care	• Type of delivery (normal, instrumental, Caesarean) • Gestational age at delivery • Preterm delivery (< 37 weeks) • Maternal weight gain • Blood pressure • 1-hour glucose tolerance test • Gestational diabetes • Birthweight/length • pH of the umbilical cord blood • Apgar score

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
			Exercises such as jumping, ballistics, extreme stretching and joint overextension were avoided. Supine exercises were limited to a maximum of 2 minutes and exercises involving the Valsalva manoeuvre were avoided. Care was taken to ensure adequate nutrition prior to exercise sessions		
Bogaerts *et al.*,[64] 2013; English	Method of randomisation: not reported Allocation concealment: opaque envelopes Blinding: not reported	Inclusion criteria: • BMI of ≥ 29 kg/m^2 (classified as obese) Exclusion criteria: • gestational age of > 15 weeks • pre-existing type 1 DM • multiple pregnancy • primary need for nutritional advice • incomplete knowledge of Dutch language Number of participants: • Intervention 1 (brochure group), $n = 58$ • Intervention 2 (lifestyle group), $n = 76$ • Control, $n = 63$	Brochure group: a study-specific brochure containing information on diet and physical activity during pregnancy including tips to limit excessive GWG was provided Lifestyle intervention group: this group received the same brochure but additionally had four antenatal lifestyle intervention sessions. The sessions included a group of up to three women led by a midwife trained in motivational intervention techniques. Each session lasted 1.5 to 2 hours and occurred: • before 15 weeks of pregnancy • between 18 and 22 weeks • between 24 and 28 weeks • between 30 and 34 weeks The sessions focused on energy balance and energy expenditure, physical activity and other issues and queries related to pregnancy. The suggested dietary composition was based on national recommendations and included 50–55% carbohydrates, 30–35% fat and 9–11% protein intake. The lifestyle and dietary habits in relation to the participants' 7-day food	Routine antenatal care as per national guideline 'prenatal care'	• Total GWG (weight at delivery minus self-reported pre-pregnancy weight) • GWG at first trimester (weight at 14 weeks minus pre-pregnancy weight) • GWG at second trimester (weight at 22 weeks minus pre-pregnancy weight) • GWG at third trimester (weight at 34 weeks minus pre-pregnancy weight) • Anxiety (State and Trait Anxiety Inventory) • Depression (10-item Edinburgh Postnatal Depression Scale) • PIH • PE • GDM • Induction of labour • Method of delivery (vaginal, vacuum/forceps, elective Caesarean section and emergency Caesarean section) • Birthweight • Apgar score at 1 minute • Apgar score at 5 minutes

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
			diaries were discussed, including topics such as reading food labels and shopping methods. The intervention was based on the concept of motivational interviewing and the behaviour change model of Prochaska and others.[150] The communication was directive and focused on intrinsic motivation to resolve discrepancies and conflicts about making changes without undue pressure. After each session the women were asked to set personal goals and identify behaviours that need changing. Positive reinforcement was provided to increase self-confidence by identifying and dealing with barriers to behavioural change		
Dodd *et al.*,[72] (LIMIT) 2011; English	Method of randomisation: central telephone randomisation with computer-generated schedule, balanced variable blocks prepared by an independent investigator not involved in recruitment and clinical care, with stratification for BMI category (overweight vs. obese) parity (parity zero vs. one or more) and participating centre	Inclusion criteria: • singleton, live gestation between 10 and 20 weeks' gestation • obese or overweight at their first antenatal visit Exclusion criteria: • multiple pregnancy • pre-existing type 1 or 2 DM Number of participants: • Intervention, $n = 1108$ • Control, $n = 1104$	Intervention: a combination of dietary, exercise and behavioural strategies, delivered by a research dietitian and trained research assistants. Balanced diet containing carbohydrates, fat and protein was encouraged. They were asked to reduce refined carbohydrates and saturated fats, increase intake of fibre, and consume two servings of fruit and five servings of vegetables each day. Women were encouraged to adopt a more active lifestyle, mainly by increasing the amount of walking. Interventions were tailored by stage theories of health decision-making that suggests individuals' progress through a series of cognitive phases when undertaking behavioural change. Initially, as part of a planning session	Usual hospital guidelines, with no routine provision of dietary, lifestyle and behavioural recommendations	Primary: • LGA infant (birthweight ≥ 90th centile for gestational age) Secondary: • preterm birth (< 37 weeks' gestation) • mortality (stillbirth or infant death) • death of a live-born infant prior to hospital discharge, and excluding lethal congenital anomalies • congenital anomalies • infant birthweight ≥ 4000 g

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
	Allocation concealment: central randomisation service Blinding: only assessor blinded to outcomes		with a research dietitian, women were given written dietary and activity information, a tailored diet and physical activity plan, a diary and recipe book. Women were encouraged to set their own goals for lifestyle changes and monitor their progress with support from the research team They were also asked to identify the barriers to achieving their goals. They were supported at regular intervals throughout their pregnancy, by the research dietitian (at 28 weeks' gestation) and trained research assistants (telephone calls at 22, 24 and 32 weeks' gestation and a face-to-face interview at 36 weeks' gestation)		• hypoglycaemia requiring intravenous treatment • admission to the NICU or special care baby unit • hyperbilirubinaemia requiring phototherapy • nerve palsy • fracture • birth trauma • shoulder dystocia • maternal hypertension and PE • maternal GDM • antenatal hospital stay • antepartum haemorrhage requiring hospitalisation • preterm prelabour ruptured membranes • chorioamnionitis requiring antibiotic use during labour • need and reason for induction of labour • any antibiotic use during labour • Caesarean section • postpartum haemorrhage (defined as blood loss ≥ 600 ml) • perineal trauma • wound infection • endometritis • use of postnatal antibiotics • length of postnatal hospital stay • thromboembolic disease • maternal death

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
El Beltagy *et al.*,[65] 2013; abstract, English	Method of randomisation: information not available Allocation concealment: not reported Blinding: not reported	Inclusion criteria: • 'obese women at risk of gestational diabetes' Exclusion criteria: • not reported Number of participants: • Intervention, $n = 48$ • Control, $n = 48$	Mild physical activity programme and diet modification for 12 weeks	No details	• GDM • GWG • Neonatal outcomes
Guelinckx *et al.*,[66] 2010; English	Method of randomisation: random allocation through block randomisation Allocation concealment: not reported Blinding: none	Inclusion criteria: • obese (BMI of > 29.0 kg/m^2, IOM criteria) • white women with gestational age < 15 weeks consecutively attending the antenatal clinic Exclusion criteria: • pre-existing DM or developing GDM • multiple pregnancy • gestational age of > 15 weeks • premature labour (< 37 weeks) • special nutritional needs such as metabolic disorder, allergic conditions kidney problems and Crohn's disease • suboptimal knowledge of Dutch language	Lifestyle intervention based on a brochure or on active education Passive group: provided with a brochure containing information on diet, physical activity and tips to limit GWG at the first antenatal consultation Active group: received same brochure and also actively counselled by a trained nutritionist in three group sessions at 15, 20 and 32 weeks of gestation. The sessions had up to five women and lasted 1 hour each. Counselling on balanced diet was based on the official national dietary recommendations (energy intake: 9–11%, proteins; 30–35%, fat; 50–55%, carbohydrates). Aim was to limit intake of energy-dense foods, replacing with healthier alternatives such as fruits, increasing wholewheat grains and low-fat dairy products, and reducing saturated fatty acids. General topics such as energy balance, body composition, food labels, and physical activity were discussed. Tips for behavioural	No intervention	• PIH, PE, chronic hypertension • GWG in accordance with IOM • GWG > 11.2 kg (weight gain from pre-pregnancy to 38 weeks) • Gestational age at delivery • Induction of labour • Caesarean section • Birthweight/length • Macrosomia (birthweight > 4000 g) • Total physical activity score

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
		Number of participants: • Intervention (active), $n = 65$ • Intervention (passive), $n = 65$ • Control, $n = 65$	modification to reduce emotional eating and binge eating were provided. Total energy intake was not restricted in any group but aimed to do so indirectly by limiting the intake of energy-dense foods. Nutritional data were obtained from 7-day dietary records. A physical activity score was calculated for each trimester of the pregnancy by using the Baecke questionnaire		
Haakstad and Bo,[82] 2011; English	Method of randomisation: simple computerised randomisation without stratification by a secretary not involved in exercise classes or assessment Allocation concealment: not reported Blinding: assessor blind. Participants were asked not to reveal their allocation to the principal investigator involved in outcomes assessment	Inclusion criteria: • nulliparous women ≤ 24 weeks of gestation • not involved before pregnancy in structured exercise programme (> 60 minutes/week) including brisk walking (> 120 minutes/week) in past 6 months • ability to understand, read and speak Norwegian Exclusion criteria: • more than two miscarriages • severe heart disease (including symptoms suggesting angina, myocardial infarction or arrhythmias) • persistent bleeding after 12 weeks of gestation • multiple pregnancy • poorly controlled thyroid disease • PIH/PE	Physical activity: the exercise programme followed the ACOG exercise prescription. Participants were encouraged to participate in at least two out of three possible 1-hour classes per week, for a minimum of 12 weeks. Each session had a maximum of 25 participants and was supervised by certified aerobic instructor. Each session included 5 minutes of warm up, 35 minutes of aerobic dance, 15 minutes of strength training focusing on deep abdominal, pelvic floor and back muscles and 5 minutes stretching and relaxation The aerobic activities were low-impact and of moderate intensity with ratings of perceived exertion at 12–14 (somewhat hard) on the 6–20 Borg's rating scale. Sudden movements were avoided and activities such as jumping, running and rotations were restricted	Participants were neither encouraged nor discouraged from exercising	• GWG (weight after completion of intervention at around 37 weeks minus self-reported pre-pregnancy weight) • Weight gain as per IOM categories • Postpartum weight retention • Skin fold thickness

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
		• DM/GDM • any other diseases potentially affecting participation • inability to attend weekly exercise classes Number of participants: • Intervention, $n = 52$ • Control, $n = 53$	Women were also asked to include 30 minutes of self-imposed moderate exercise at home on no-exercise days		
Harrison *et al.*,[73] 2013; English	Method of randomisation: computer-generated randomisation Allocation concealment: sealed opaque envelopes Blinding: care providers, researchers and outcome assessors were blinded to group allocation	Inclusion criteria: • gestational age of 12–15 weeks • overweight [BMI of ≥ 25 or ≥ 23 kg/m^2 if high-risk ethnicity (Polynesian, Asian and African populations) or obese (BMI of ≥ 30 kg/m^2)] • increased risk of GDM as per a validated risk prediction tool. • willing to complete an oral glucose tolerance test at 28 weeks of gestation instead of the standard glucose challenge test at GDM screening Exclusion criteria: • multiple pregnancies • type 1 or 2 DM • BMI of ≥ 45 kg/m^2 • pre-existing chronic medical conditions • non-English-speaking Number of participants: • Intervention, $n = 121$ • Control, $n = 107$	Individual four sessions behaviour change lifestyle intervention in antenatal clinic setting at 14–16, 20, 24 and 28 weeks of gestation. The intervention was based on the social cognitive theory, adapted from the study group's earlier lifestyle intervention programme (HeLP-her) The sessions were delivered by a health coach (exercise physiologist). Healthy eating and physical activity were encouraged along with specific dietary advice in pregnancy. Behavioural change strategies were aimed at identifying short-term goals and promoting self-efficacy and self-monitoring Goals included lifestyle changes such as reducing high-fat or convenience foods, increasing fruit/vegetable intake and increasing frequency of physical activity. Participants themselves set goals	A single brief education session based on Australian Dietary and Physical Activity Guidelines was provided along with written versions of guidelines. GWG was not discussed	Primary: • GWG (weight was measured at baseline; 12, 16 and 28 weeks of gestation) Secondary: • diagnosis of GDM as per Australasian Diabetes in Pregnancy Society criteria. International Association of the Diabetes and Pregnancy Study Groups criteria were also evaluated • physical activity using pedometer and International Physical Activity Questionnaire • risk perception for GDM development and excess GWG (four-point Likert scale adapted from the theory of health stage of change was used)

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
			Pedometers and weight-gain charts based on IOM recommendations were provided to monitor the progress. Written Australian dietary and physical activity guidelines and other resources to encourage optimal health, GWG and lifestyle were provided		
Hui *et al.*,[91] 2012; English	Method of randomisation: computer-generated randomisation allocation table performed by a staff member without involvement in the study design Allocation concealment: sealed, labelled envelope Blinding: participants and study staff were not blinded	Inclusion criteria: • no pre-existing DM Exclusion criteria: • medical, obstetric, skeletal or muscular disorders that could contraindicate physical exercise during pregnancy Number of participants: • Intervention, $n = 112$ • Control, $n = 12$	Exercise component: a community-based exercise programme – recommended exercise included walking, mild to moderate aerobic, stretching and strength exercises (3–5 times per week for 30–45 minutes/session). The programme started around 20–26 weeks of gestation and finished at 36 weeks. The group exercise sessions were held in air-conditioned gymnasia in community centres. Group floor aerobic, stretching and strength exercises were led by licensed fitness trainers. Participants were instructed to record daily physical activities in activity logs Dietary component: interviews and counselling were provided twice in pregnancy by registered dietitians (at enrolment and 2 months after enrolment). Dietitians provided personalised dietary counselling to participants based on their food choice map interview results, pregnancy week, weight gain and the Health Canada guidelines for food intake in pregnancy[151,152]	Standard care: standard prenatal care recommended according to the Society of Obstetricians and Gynaecologists of Canada. Exercise instruction and dietary intervention were not provided to participants in the control group	• Excessive weight gain • Intake • Physical activity • LGA • GDM • Weight-related obstetric procedures • GWG • Birthweight

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
Jeffries *et al.*,[92] 2009; English	Method of randomisation: computer random number generator Allocation concealment: number cards allocating women to the two groups were placed in opaque, sequentially numbered envelopes Blinding: patients	Inclusion criteria: • pregnant women with gestational age of ≤ 14 weeks Exclusion criteria: • aged < 18 or > 45 years • non-English speaking • multiple pregnancy • type 1 or 2 DM Number of participants: • Intervention, $n = 148$ • Control, $n = 138$	Women allocated to the intervention group were given personalised weight measurement card including information on optimal GWG (based on their BMI at the time of recruitment and the US IOM guidelines) and were asked to record their weight at 16, 20, 24, 28, 30, 32 and 34 weeks of gestation The patient was allowed to choose to measure weight at hospital or at home	No intervention	• GWG: weekly and total from 11 weeks to delivery (and compliance with IOM recommendation) • Birthweight • SGA and LGA (weight < 10 centile and > 90 centile) • Preterm delivery • Instrumental delivery • Caesarean delivery • PE • PIH • GDM • Apgar score at 5 minutes of < 7 • Hypoglycaemia • Shoulder dystocia • Gestational age at delivery
Khaledan *et al.*,[83] 2010; Persian/ English	Method of randomisation: not reported Allocation concealment: not reported Blinding: none	Inclusion criteria: • singleton pregnancy • intact amniotic membrane Exclusion criteria: • heart disease associated with significant haemodynamic changes • chronic lung disease/airway inflammation • cervical incompetence or its correction • multiple pregnancy • permanent vaginal bleeding at second and third trimester of pregnancy • placenta praevia after 20^{+6} weeks of pregnancy	Three exercise sessions per week of 30–45 minutes each for 8 weeks. The first 15 minutes included stretching exercises. The aerobic component started as 5-minute session and progressively increased by 1 minute per session. The intensity was maintained by heart rate within 60% of maximum heart rate. This was followed by cooling down in sitting position for 10 to 15 minutes. Maximal heart rate was calculated through the formula 220 – age × 60/100	No intervention	• Gestational age at delivery • Caesarean section • Neonatal weight • Mothers' weight after 1 and 2 months of intervention between 28 to 36 weeks of pregnancy

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
		• risk of preterm delivery in the current pregnancy • rupture of fetal membranes • hypertension during pregnancy • severe anaemia • untreated arrhythmias in mother • poorly controlled type 1 DM • extreme morbid obesity • very low maternal weight • very sedentary lifestyle • fetal growth restriction in current pregnancy • uncontrolled hypertension • skeletal and structural limitations • seizure disorders • uncontrolled hyperthyroidism • heavy smoking All participants received diet based on food pyramid guidelines recommended by the American Agricultural Department and iron and folic tablets Number of participants • Intervention, $n = 20$ • Control, $n = 24$		

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
Khoury *et al.*,[76] 2005; English	Method of randomisation: the randomisation list was generated from a table of random numbers drawn up by the investigator who had no contact with the participants Allocation concealment: consecutively numbered, sealed, opaque envelopes provided to dietitian delivering intervention Blinding: investigators/ clinicians and outcomes assessors	Inclusion criteria: • aged 21–38 years • BMI of 19 to 32 kg/m^2 • non-smokers or ex-smokers (quit ≥ 5 years ago) • not immigrants to Norway from non-Western countries • single healthy fetus at 17–20 weeks' gestation on ultrasound • no previous pregnancy complications • first, second or third pregnancy • not vegetarian or following a Mediterranean-type diet Exclusion criteria: • high-risk pregnancies caused by DM, endocrine disease, hypertension, drug abuse, thromboembolic disease or significant cardiac, gastrointestinal, pulmonary or haematological disease • history of neonatal death, stillbirth, preterm delivery or recurrent abortion (more than three previous spontaneous abortions) • ongoing hyperemesis gravidarum or bleeding after gestational age of 12 weeks in the current pregnancy Number of participants: • Intervention, $n = 141$ • Control, $n = 149$	Diet/dietary advice: cholesterol-lowering diet from gestational week 17–20 to birth Dietitian visits were arranged at inclusion, and at 24, 30 and 36 weeks of gestation Aims of dietary intervention were to: • limit dietary cholesterol to 150 mg/day • reduce the intake of saturated fat to 8% of dietary energy • target total fat 32% of total energy intake (including 8–9% of energy from polyunsaturated fat and 16–17% from monounsaturated fat), protein 16–17% of energy, and carbohydrates 50–51% of energy • tailor energy intake for target at a weight gain of 8 to 14 kg from pre-pregnancy levels • encourage the intake of fatty fish, vegetable oils, mainly olive oil and rapeseed oil, nuts, nut butters, margarine based on olive oil or rapeseed oil • at least six-a-day of fresh fruits and vegetables was advised • prefer low-fat dairy products Subjects were advised to have meat for a main meal twice a week and use legumes, fatty fish, poultry, etc. on other days	Control group was advised to consume their usual diet, not to introduce more oils, low-fat meat and dairy products than usual. Target weight gain was 8–14 kg and energy intake breakdown of fats, carbohydrate and proteins was same as intervention group	• Gestational age at delivery • Preterm delivery • Maternal weight gain between inclusion and week 30 • Preterm stillbirth • Intrauterine growth restriction • Hypertensive complications (PIH/PE) • Fetal distress • Birthweight • Maternal and neonatal lipid profile

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
			Cooking lessons were arranged for special foods. Coffee was limited to two cups/day		

Luoto *et al.*,[62] 2011; English	Method of randomisation: cluster randomisation of municipalities that were paired on the basis of number of births, population size, socioeconomic status and type (rural/urban). The municipalities, not participants, were randomised into intervention and study groups
	
	Allocation concealment: not reported
	
	Blinding: not reported
		Inclusion criteria:
		
		• at least one of the following risk factors:
		  ○ BMI of ≥ 25 kg/m^2
		  ○ GDM or any signs of glucose intolerance or macrosomic baby (≥ 4500 g) in any prior pregnancy
		  ○ family history of type 1 or 2 DM in first- or second-degree relatives
		• aged ≥ 40 years
		
		Exclusion criteria:
		
		• at least one of the following:
		  ○ abnormal baseline oral glucose tolerance test at 8–12 weeks' gestation (fasting glucose > 5.3 mmol/l, 1-hour glucose > 10.0 mmol/l or 2-hour > 8.6 mmol/l
		  ○ pre-existing type 1 or 2 DM
		• could not speak Finnish
		• aged < 18 years
		• twin pregnancy
		• contraindications to physical activity
		• substance abuse, treatment
		• psychiatric illness
			Five counselling sessions at 8–12 weeks, 16–18 weeks, 22–24 weeks, 32–34 weeks and 36–37 weeks. One primary session each for physical activity and diet followed by booster sessions. The primary session was 20- to 30-minutes long, but the booster sessions lasted for 10–15 minutes. The interventions were based on PRECEDE–PROCEED and stages of change models. GWG: IOM recommendations were discussed. A BMI-specific weight-gain chart was included
			
			Physical activity: the aim was to increase leisure time physical activity to meet recommendations or maintain it if they had already reached it. The weekly action plan was agreed with each participant and the recommended minimum weekly leisure time physical activity dose was 800 MET minutes. Monthly 2-hour thematic meetings including group exercises were offered and these were led by physiotherapists
			
			Diet: advised as per Finnish dietary recommendations – saturated fat ≤ 10%, polyunsaturated fat 5–10% and total fat 25–30% (includes saturated, monounsaturated, polyunsaturated and trans-fatty acids) of total energy intake and fibre 25 to 35 g/day. They were encouraged to include high-fibre bread, five portions of fruits/vegetables, low-fat dairy products, fish twice weekly, only
				Routine care including usual dietary and physical activity counselling	Primary:
					
					• Proportion of women developing GDM assessed by glucose tolerance and weight of the newborn infant adjusted for gestational age

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
		Number of participants: • Intervention, seven municipalities, $n = 196$ • Control, seven municipalities, $n = 246$	moderate amounts of spread/oil and restrict sugar containing snacks/drink. The nurse checked if the written objectives were met at each booster visit		
Nascimento *et al.*,[84] 2011; English	Method of randomisation: list of random numbers generated by SAS version 9.1 statistical program (SAS Institute Inc., Cary, NC, USA) Allocation concealment: sealed sequentially numbered opaque envelopes Blinding: not blinded	Inclusion criteria: • pregnancy • pre-pregnancy overweight (BMI of 26.0–29.9 kg/m^2) or obesity (BMI of $\geq$ 30.0 kg/m^2) • aged $\geq$ 18 years • gestational age of 14 to 24 weeks Exclusion criteria: • multiple pregnancy • exercising regularly • contraindications for exercise, such as cervical incompetence, severe hypertension, DM with vascular complications and risk of abortion Number of participants: • Intervention, $n = 39$ • Control, $n = 41$	Exercise protocol: women performed exercise weekly under the guidance of a trained physical therapist. The exercises were light to moderate intensity exercises, with heart rates not exceeding 140 beats per minute. (ACOG recommendations). Standardised research protocol consisting of a 22-exercise sequence was followed. Group or individual exercises lasted 40 minutes with 10 minutes of general stretching, 22 minutes of exercises to strengthen the limb muscles, and 10 minutes of guided relaxation. Home exercise counselling. Women were counselled on home exercise to be done five times/week, with exercises from the protocol or walking. They were required to note the details of daily exercise in a monthly exercise book	Routine antenatal advice and standard nutritional counselling. They were not provided physical activity counselling	Primary: • GWG • excessive maternal weight gain Secondary: • increased blood pressure • perinatal outcomes: Caesarean section, newborn infant weight, gestational age at delivery, preterm birth, Apgar scores at 1 and 5 minutes, LGA, SGA • quality of life (World Health Organization Quality of Life – BREF questionnaire)

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
Ong *et al.*,[67] 2009; English	Method of randomisation: none reported Allocation concealment: none reported Blinding: not reported	Inclusion criteria: • singleton pregnancy • normal 18-week anatomy scan • no evidence of cardiovascular disease • no pre-existing DM Number of participants: • Intervention, $n = 6$ • Control, $n = 6$	Physical activity: home-based exercise programme beginning at week 18 of gestation; three sessions per week of stationary cycling (home-based) supervised exercise. Exercise training was performed at home on an upright stationary cycle ergometer provided to each participant for the study period. Each session consisted of a 10-minute warm-up followed by one or two 15-minute bouts of cycling (with rest periods if necessary). Exercise intensity was controlled by heart rate initially aimed at 50–60% of maximum heart rate and later increased to 60–70% of maximum heart rate. The duration was later increased to 40–45 minutes. Sessions ended with a 10-minute cool-down period of slow pedalling	No intervention	• Weight gain from 18 to 28 weeks' gestation • Postintervention glucose and insulin levels on oral glucose tolerance test

Oostdam *et al.*,[75] 2012; English	Method of randomisation: computer generated randomised allocation schedule prestratified to the centre where participant will be followed up. Within each centre, participants randomly allocated to study or control group. Block randomisation in blocks of four performed
	
	Allocation concealment: only the programmer of central database knew key of coding related to group assignment
		Inclusion criteria:
		
		• obese (BMI of ≥ 30 kg/m^2) or overweight (BMI of ≥ 25 kg/m^2) with at least one of the following:
		  ○ history of macrosomia (birthweight > 97th percentile of gestational age)
		  ○ history of abnormal glucose tolerance during previous pregnancy
		  ○ family history of type 2 DM in first-degree relative
			Exercise programme of aerobic and strength training twice weekly under supervision of a trained physiotherapist from recruitment through to remainder of pregnancy. Each session lasted for 60 minutes. Aerobic training provided using cycle ergometers, treadmills, cross-trainers and rowing machines. Strength and aerobic training tailored to individual participants, taking into consideration predicted maximum muscle strength, aerobic capacity and target heart rate. ACOG recommendations were used as a guidance	Usual care by midwives and obstetricians	Primary:
					
					• fasting plasma glucose and relative increase in insulin resistance in mother
					• neonatal birthweight
					
					Secondary:
					
					• maternal serum triglycerides, high-density lipoprotein, cholesterol and HbA_{1c}
					• GWG
					• maternal physical activity level
					• fetal growth
					• changes in health-care and non-health-care costs

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
	Blinding: independent examiners assessing outcomes blinded but participants and researchers could not be blinded	• gestational age of 14–20 weeks • aged > 18 years • sufficiently fluent in Dutch • capable of moderately physical activity • willing to give consent Exclusion criteria: • GDM diagnosis before randomisation • hypertension (systolic > 160 mmHg and/or diastolic > 100 mmHg) • alcohol abuse (i.e. two glasses of alcohol or more per day) • drug abuse (except for incidental analgesic agents) • use of medication affecting insulin secretion/sensitivity (antiviral, corticosteroids, antihypertensive drugs) • serious pulmonary (chronic obstructive pulmonary disease, exercise-induced asthma), cardiac, hepatic or renal (serum creatinine level of < 150 µmol/l) impairment • malignant disease • serious mental or physical impairment impacting on ability to participate in the study Number of participants: • Intervention, $n = 62$ • Control, $n = 59$			

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
Perales *et al.*,[85] 2015; English	Method of randomisation: computer-generated list of random numbers was used Allocation concealment: not reported Blinding: researchers and outcome assessors were blinded. Randomisation procedure including sequence generation, allocation concealment, and implementation was made for three different authors to facilitate blinding. Blinding of participants was not possible	Inclusion criteria: • pregnant women living in Madrid, Spain, who underwent ultrasound examination within 12 weeks of gestation Exclusion criteria: • absolute obstetrical contraindication to exercise [as per ACOG (2002)] • plans to deliver baby elsewhere • not receiving antenatal care throughout the pregnancy • participating in another physical activity programme • regular exercise before pregnancy (four or more times per week) Number of participants: • Intervention, $n = 101$ • Control, $n = 83$	The programme consisted of three 55- to 60-minute sessions thrice weekly from 9–12 weeks of gestation to the end of pregnancy (39–40 weeks of gestation). Each session consisted of warm-up (5–8 minutes), aerobic dance and resistance exercises for muscle groups of legs, buttocks and abdomen to stabilise the lower back (25 minutes), balancing exercises (10 minutes), pelvic floor muscle training (10 minutes) and a cool-down period (5–8 minutes). Exercises in supine position were limited to 2 minutes and extreme stretching, jumping, ballistic movements, overextension of joints and exercises involving Valsalva manoeuvre were specifically avoided The exercise intensity was light to moderate and was guided by the target heart rate (55–60% of maximum heart rate) for each participant displayed on a poster. All participants wore heart rate monitors during exercise sessions. Karvonen's formula based on trimester, physical condition and age was used to calculate maximum heart rate. Borg scale ratings were also used to adjust the intensity of exercise. Sessions had groups of 10–12 women and were supervised by a qualified fitness specialist and assisted by an obstetrician. The venue was a spacious well-lit room in a hospital (altitude 600 m, temperature 19–21 °C, and humidity 50–60%) and sessions were accompanied by music. Care was taken to ensure adequate nutrition prior to exercise sessions	Usual care	• Center for Epidemiologic Studies Depression Scale questionnaire for depression at 9–12 weeks of gestation and end of pregnancy • GWG • Percentage of women with excessive weight gain (as per IOM guidelines) • Percentage of women with adequate weight gain (as per IOM guidelines) • Gestation age at delivery • Mode of delivery (normal, instrumental, Caesarean section) • Birthweight • Length of the baby at birth • Head circumference • Apgar score at 1 minute • Apgar score at 5 minutes

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
Perales *et al.*,[85] 2015; English	Method of randomisation: computer-generated list of random numbers Allocation concealment: not reported Blinding: not reported	Inclusion criteria: • pregnant women living in Madrid, Spain, who underwent ultrasound examination at 9–11 weeks of gestation Exclusion criteria: • absolute obstetrical contraindication to exercise [as per ACOG (2002)] • plans to deliver baby elsewhere • not receiving antenatal care throughout the pregnancy • participating in another physical activity programme • additional exercises ≥ 2 times per week lasting ≥ 20 minutes • regular exercise before pregnancy (≥ 4 times per week) • prior Caesarean section Number of participants: • Intervention, $n = 122$ • Control, $n = 117$	The programme consisted of three 55- to 60-minute sessions thrice weekly from 9–12 weeks of gestation to end of pregnancy (39–40 weeks' gestation). Each session consisted of warm-up (5–8 minutes), aerobic dance and resistance exercises for muscle groups of legs, buttocks and abdomen to stabilise the lower back (25 minutes), balancing exercises (10 minutes), pelvic floor muscle training (10 minutes) and a cool-down (5–8 minutes). Exercises in supine position were limited to 2 minutes and extreme stretching, jumping, ballistic movements, overextension of joints and exercises involving Valsalva manoeuvre were specifically avoided The exercise intensity was light to moderate and was guided by the target heart rate (55–60% of maximum heart rate) for each participant displayed on a poster. All participants wore heart rate monitors during exercise sessions. Karvonen's formula based on trimester, physical condition and age was used to calculate maximum heart rate. Borg scale ratings were also used to adjust the intensity of exercise. Sessions had groups of 10–12 women and were supervised by a qualified fitness specialist and assisted by an obstetrician. The venue was a spacious well-lit room in a hospital (altitude 600 m, temperature 19–21 °C, and humidity 50–60%) and sessions were accompanied by music. Care was taken to ensure adequate nutrition prior to exercise sessions	Usual care	• Duration of stages of labour • GWG • Percentage of women with excessive weight gain (as per IOM guidelines) • Percentage of women with adequate weight gain (as per IOM guidelines) • Gestation age at delivery • Mode of delivery (normal, instrumental) • Birthweight • Birth length • Head circumference • Apgar score at 1 minute • Apgar score at 5 minutes • pH of umbilical cord

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
Petrella *et al.*,[74] 2014; English	Method of randomisation: computer program that generated random allocation in blocks of three Allocation concealment: sealed numbered white envelopes Blinding: both gynaecologist and dietitian delivering the interventions knew allocation of the patient	Inclusion criteria: • women with singleton pregnancies • pre-pregnancy BMI of ≥ 25 kg/m^2 and aged > 18 years were recruited during 12th week of gestation from antenatal clinics Exclusion criteria: • twin pregnancy • chronic conditions such as DM, hypertension and untreated thyroid diseases • other medical conditions known to affect bodyweight • previous GDM • smoking during pregnancy • previous bariatric surgery • women who just started regular physical activity, or used herbal products or dietary supplements known to affect bodyweight • not intending to deliver at the study centre Number of participants: • Intervention, $n = 33$ • Control, $n = 30$	Diet: the intervention group diet was initiated at randomisation by a gynaecologist and a dietitian who provided a further 1-hour counselling on recommended weight gain in pregnancy for each BMI category. The calorie allowance was 1500 kcal/day with an extra 200 kcal/day for obese women and 300 kcal/day for overweight women to account for physical activity programme. The target diet composition was 55% carbohydrate (80% complex low glycaemic index), 20% protein (50% animal and 50% vegetable) and 25% fat (12% monounsaturated, 7% polyunsaturated and 6% saturated fat) given as three main meals and three snacks. The last snack was 2 hours after dinner to prevent overnight hypoglycaemia The minimum recommended intake of carbohydrates was 225 g/day. Urine was examined for ketonuria thrice during pregnancy Exercise: the exercise intervention was in line with recommendations for the general population. Women were advised 30 minutes of moderate intensity activity for a minimum of 3 days a week. Adherence was checked by a pedometer. Women were advised that the exercise intensity should allow them to maintain a conversation ('talk test')	The control group received a simple nutritional booklet based on Italian guidelines for a healthy diet during pregnancy	Primary: • rate of women with weight gain exceeding the ranges recommended by IOM for each BMI category Secondary: • diagnoses of GDM • gestational hypertension • rate of preterm delivery

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
Phelan *et al.*,[93] 2011; English	Method of randomisation: computerised, randomly changing block sizes, stratified as per clinic and BMI category Allocation concealment: opaque envelopes Blinding: no blinding	Inclusion criteria: • aged > 18 years • singleton pregnancy • gestational age of between 10 and 16 weeks • BMI of between 19.8 and 40 kg/m^2 • non-smoker • fluent in English • access to a telephone Exclusion criteria: • self-reported major health or psychiatric diseases • weight loss during pregnancy • ≥ three miscarriages Number of participants: • Intervention, $n = 201$ • Control, $n = 200$	Standard care plus a behavioural lifestyle intervention ('Fit for Delivery') to avoid excessive weight gain during pregnancy. The intervention was based on the 1990 IOM guidelines for weight and nutrition during pregnancy and used established principles of learning theory to encourage changes in eating and physical activity. The intervention included a face-to-face interview with an interventionist at the start of treatment. Discussion focused on appropriate GWG targets, physical activity (30 minutes of walking, most days), and calorie intake (20 kcal/kg). Daily self-monitoring of weight, diet and physical activity was recommended along with emphasis on limiting high-fat foods Weight scales, food diaries and pedometers were given to facilitate self-monitoring Postcards promoting healthy lifestyle were mailed weekly. Personalised weight gain graphs with feedback were provided following each visit Telephone support of dietitian was offered thrice during intervention to all women in intervention group. Women failing to meet targets received up to two additional telephone calls/month with personalised advice including structured meal plans until targets were met	Standard scheduled visits, monthly until 28 weeks of gestation, fortnightly between 28 and 36 weeks of gestation, weekly until delivery and at 6 weeks after delivery. Participants were provided standard nutrition counselling by physicians, nutritionists, nurses, and counsellors A brief (15-minute) face-to-face visit with the study interventionist was arranged at recruitment. Women were provided with study newsletters containing general information related to pregnancy such as vitamins, at 2-monthly intervals and post partum. Women were weighed regularly but were not given weight graphs	Primary: • proportion of women with an excessive GWG on the basis of the 1990 IOM guidelines • proportion of women at (± 9 kg) or below their pre-pregnancy weights at 6 months post partum Secondary: • GDM • maternal hypertension • PE • gestational age at delivery • preterm delivery • Caesarean section • infant birthweight • low birthweight • macrosomia

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
Poston *et al.*,[68] (UPBEAT trial) 2015; English	Method of randomisation: online, computer-generated program. The randomisation schedule was minimised according to ethnicity, parity, age, BMI and centre Allocation concealment: sequential study numbers allocated, irrespective of allocation to the intervention or control group Blinding: not reported	Inclusion criteria: • women with singleton pregnancy between 15 and 18^{+6} weeks' gestation and BMI of ≥ 30 kg/m^2 at first antenatal appointment Exclusion criteria: • no informed consent • outside 15 to 18^{+6} weeks' gestation • multiple pregnancy • medical disorders including essential hypertension requiring treatment, pre-existing renal disease, systemic lupus erythematosus, sickle cell disease, antiphospholipid syndrome, thalassaemia, coeliac disease and thyroid disease • current psychosis • on metformin Number of participants: • Intervention, $n = 783$ • Control, $n = 772$	One-to-one interview at baseline with a health trainer specifically trained for the study, followed by eight weekly sessions of 1 to 1.5 hours each. Women are encouraged to attend all and strongly recommended to attend a minimum of five sessions with other sessions covered by telephone or e-mail. Health trainers cover specific goal-setting, self-monitoring and feedback on performance, problem-solving and use of social support. Women were provided with handbook, DVD of recommended exercise regime, pedometer, logbook for recording weekly goals and steps achieved through pedometer	Routine antenatal care, explaining the risks of obesity, advising on healthy diet and safe levels of physical activity	Primary: • diagnosis of GDM according to International Association of the Diabetes and Pregnancy Study Groups criteria • LGA baby (> 90th weight centile) Secondary: • PE • mode of delivery • induction of labour • blood loss at delivery • inpatient nights • GWG • fasting glucose, insulin, insulin resistance at 28 weeks' gestation • referral to antenatal clinic after oral glucose tolerance test • fetal growth at 28 weeks' gestation • insulin or metformin treatment in pregnancy • quality of life • anthropometry including mid-arm, hip, thigh circumference and skin fold thickness • fructosamine, lipid profile • epigenetic, urinary and metabolomic biomarkers • diet and physical activity • depression • smoking • birthweight of baby

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
			Exercise advice: to increase pedometer steps and daily activity incrementally; moderate activity in the form of walking encouraged in line with UK RCOG recommendations, with more options depending on baseline activity Diet: to promote healthier eating with no restriction of calories, substitute low glycaemic index for medium/high glycaemic index food, restrict sugar-sweetened beverages but not fruits and reduce saturated fatty acid intake		• gestational age at delivery • neonatal death • neonatal complications • baby's anthropometry including head/abdominal circumference and skin fold thickness • epigenetic and other markers • infant feeding habits and anthropometry at 6 months
Prevedel *et al.*,[86] 2003; Portuguese (Brazilian)	Method of randomisation: women were randomly selected (model randomised) Allocation concealment: not reported Blinding: no blinding used	Inclusion criteria: • primiparous or adolescents, with singleton pregnancy • absence of disease (medical or obstetric) • gestational age of 16–20 weeks Exclusion criteria: • more than three absences/ month at hydrotherapy sessions or withdrawal • prenatal care and childbirth out of service • development of medical or obstetric complications Number of participants: • Intervention, $n = 29$ • Control, $n = 31$	Physical activity (moderate intensity hydrotherapy): the hydrotherapy programme was delivered by the physiotherapist accompanied by the obstetrician in subgroups of up to 10 pregnant women. The exercises were of moderate intensity and carried out at a heated and covered swimming pool (temperature between 28 °C and 32 °C) thrice a week and duration of 1 hour. The sessions were based on ACOG recommendations and comprised stretching, heating, resistance, localised exercises and relaxation with breathing exercises Exercise intensity was controlled by heart rate monitoring by frequency–grip	No intervention	• Bodyweight at baseline (16–20 weeks) and at delivery (36–40 weeks) • Preterm birth • Birthweight (g) • LGA • Lean mass • Total fat, relative fat (%)

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
Rauh *et al.*,[63] 2013; English	Method of randomisation: computer-generated cluster randomisation of gynaecological practices into intervention or control groups Allocation concealment: randomisation performed by a researcher not involved in study design Blinding: study design did not permit blinding	Inclusion criteria: • aged > 18 years • singleton pregnancy • gestational age of < 18 weeks • BMI of ≥ 18.5 kg/m^2 • language skills: 'sufficient' German Exclusion criteria: • contraindication to physical activity, such as cervical incompetence, placenta praevia, or persistent bleeding • pre-pregnancy DM • uncontrolled chronic diseases affecting weight such as thyroid dysfunction or psychiatric diseases Number of participants: • Intervention, four practices, $n = 167$ • Control, four practices, $n = 83$	The intervention group received two individual counselling modules at 20 and 30 weeks of gestation, the first session lasting 60 minutes and the second 30 minutes. General lifestyle advice including nutrition, physical activity and appropriate GWG was provided. Healthy nutrition and energy balance as per German Nutrition Society were explained. The dietary goals were to reduce the intake of high-fat and energy-dense foods and increase the intake of low-fat foods and fruits, wholegrain foods and vegetables. Women were encouraged to consume more fish and advised regarding appropriate fat/cooking oil/spreads Physical activity equivalent to 30 minutes of moderate-intensity exercises on most days was recommended. Non-weight bearing endurance exercises such as walking, swimming, aquatic exercises and cycling were suggested. Women were also provided with information on local antenatal exercise programmes and encouraged to join them. The exercise recommendations were based on the guidelines of ACOG and Society of Obstetricians and Gynecologists of Canada Women were provided with personalised weight charts as per BMI category including IOM recommendations for that category. They were asked to monitor their weights on a weekly basis	Routine antenatal care including an information leaflet consisting of 10 general statements on a healthy lifestyle during pregnancy not including advice on diet or gaining weight	Primary: • proportion of pregnant women exceeding IOM recommendations for weight gain Secondary: • postpartum weight retention (self-reported weight at 4 months postpartum minus pre-pregnancy weight) • birthweight • length of the baby at birth • GDM/impaired glucose tolerance • mode of delivery (spontaneous, Caesarean, vacuum) • induction of labour • preterm delivery • infant sex • LGA • SGA

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
			The individual counselling sessions also provided personalised feedback on diet and physical activity based on the 7-day records of diet and physical activity questionnaires		
Renault *et al.*,[69] 2014; English	Method of randomisation: randomisation was stratified by parity to ensure equal distribution of primiparous women in all groups Allocation concealment: a web allocation by an independent agency allowed allocation concealment Blinding: not reported	Inclusion criteria • BMI of ≥ 30 kg/m^2 • aged > 18 years • singleton pregnancy • normal scan at 11–14 weeks' gestation • gestational age of < 16 weeks at inclusion • ability to read and speak Danish Exclusion criteria • multiple pregnancy • pre-pregnancy DM • conditions limiting level of physical activity • history of bariatric surgery • alcohol or drug abuse Number of participants: • Intervention 1 (exercise), $n = 142$ • Intervention 2 (diet and exercise), $n = 142$ • Control, $n = 141$	All participants (before enrolment) received one consultation with a dietitian after the initial ultrasound scan at 11–14 weeks of gestation. A low-fat low-calorie (1200–1675 kcal/day) Mediterranean-style diet, with preference to fish and oils was recommended. Dietary advice was as per Danish national guidelines for healthy eating. Only oral advice was given and women were asked to aim for a GWG of < 5 kg Physical activity: a dietitian advised to increase physical activity aiming for a daily step count of 11,000/day, a validated pedometer was provided to the participants. Pedometer data were recorded for a consecutive 7-day period every 4 weeks. Women were reminded through text messages when a recording period started and encouraged to achieve the target. If 11,000 steps were not achievable, they were asked to set their own targets. They were asked to enter the pedometer data and weight into a chart and return it Diet: the women in the physical activity plus diet group also had alternate face-to-face or telephone consultations with an experienced dietitian every 2 weeks (11–13 consultations) during pregnancy. They received feedback,	Standard care including one consultation with a dietitian after the initial ultrasound scan at 11–14 weeks' gestation. Dietary advice was as per Danish national guidelines for healthy eating. Only oral advice was given and women were asked to aim for a GWG of < 5 kg	Primary: • GWG (weight at 36–37 weeks minus self-reported pregestational weight) Secondary: • GDM (oral glucose tolerance test at 17–20 weeks and 27–30 weeks) • gestational hypertension • PE • induction of labour • Caesarean section (emergency/planned) • gestational age at delivery • preterm delivery (28–34 weeks and 34–37 weeks) • fetal birthweight • relative birthweight • SGA • LGA • macrosomia • pH of umbilical cord blood • placental weight

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
			encouragement and specific dietary advice if diet was incorrect or if weight targets were not being achieved		
Ruiz *et al.*,[87] 2013; English	Method of randomisation: computer generated Allocation concealment: not reported Blinding: not reported	Inclusion criteria • sedentary (not exercising > 20 minutes on > 3 days a week • singleton pregnancy • uncomplicated pregnancy • not at high risk of preterm delivery (≤ 1 previous preterm delivery) • no participation in any other trial Exclusion criteria • contraindication to exercise Number of participants: • Intervention, $n = 481$ • Control, $n = 481$	The programme consisted of supervised 50- to 55-minute physical activity sessions thrice weekly from week 9 to weeks 38–39, with an estimated average of 85 sessions per participant. Each group consisted of 10–12 women. The exercise activity was of light to moderate intensity with a target heart rate of ≤ 60% of maximum predicted heart rate for age [208 – (0.7 × age in years)]. All participants were provided with heart rate monitors. Intensity was also guided by Borg's conventional (6–20 point) scale, with the rate of perceived exertion ranging from 10 to 12 ('fairly light' to 'somewhat hard') Each session included a warm-up period (10 minutes), a core session (25–30 minutes) and a cool-down period (10 minutes). Warm-up and cool-down components involved walking and light stretching exercises for limbs, neck and trunk. In addition, the cool-down period included relaxation and pelvic floor exercises The core portion involved moderate-intensity aerobic exercises once weekly and resistance exercises twice a week. Aerobic dance took place for periods of 3–4 minutes with 1-minute breaks and included stretching and relaxation. Resistance exercises for pectoral muscles, back, shoulder, upper and lower limb muscles aimed to improve posture,	Usual care with regular scheduled visits to obstetricians and midwives. Information health-care professionals provided nutrition and physical activity counselling and they were not discouraged from exercising	Primary: • GWG (weight at last clinic visit before delivery minus weight at first antenatal weight) Secondary: • GDM • hypertension • gestational age at delivery • type of delivery (natural, instrumental or Caesarean) • time of dilatation, expulsion and childbirth • birthweight • low birthweight • macrosomia

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
			strengthen muscles of labour and pelvic floor and prevent lower back pain. They involved exercises using barbells (3 kg/exercise) or low to medium resistance elastic and included biceps curls, arm side lifts and extensions, shoulder elevations, bench press, seated lateral row, leg circles and lateral leg elevations, knee (hamstring) curls and extensions and ankle flexions and extensions Exercises such as jumping, ballistics, extreme stretching and joint overextension were avoided. Supine exercises were limited to a maximum of 2 minutes		
Sagedal *et al.*,[153] 2016; English	Method of randomisation: computer-generated randomisation list with groups of 20 women. Consecutive randomisation based on the time of completion of consent form, questionnaires and blood tests required prior to enrolment Allocation concealment: staff providing intervention and checking outcomes were not involved in randomisation Blinding: not reported	Inclusion criteria: • aged ≥ 18 years • BMI of ≥ 19 kg/m^2 • singleton pregnancy • gestational age of < 20 weeks • fluency in Norwegian or English Exclusion criteria: • pre-existing DM • physical disabilities preventing participation in a physical activity programme (as per recommendations of the ACOG) • current substance abuse • no plans to deliver in the study centres (planned relocation) Number of participants: data unpublished	Diet: an initial telephone consultation with a physician, nutritionist or graduate student of public health, followed by another follow-up session 4–6 weeks later. Recommendations based on Norwegian directorate of health guidance. Focus on 10 key recommendations including intake of fruits and vegetables, drinking water instead of energy drinks, having regular meals and reducing intake of drinks and snacks containing added sugar. Pamphlets containing the key recommendations provided to the intervention group along with password-protected access to an interactive website containing information on healthy eating and exercise in pregnancy. They were also invited to two evening meetings where further information on the trial was provided along with a hands-on cooking class to reinforce their dietary recommendations	Standard prenatal care	• Maternal weight gain and postpartum weight retention • Body composition at 36 weeks of gestation • Infant birthweight and the per cent of LGA (> 90th percentile) infants • Maternal glucose values and hormones related to glucose metabolism • Incidence of operative deliveries and delivery complications

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
			Physical activity: two exercise sessions each week lasting 1 hour at local fitness centres where attendance was registered. The sessions were supervised by physiotherapists or graduates of sports science. Uniform exercise plan for all the women in intervention group, consisting of 40 minutes of strength training and moderate cardiovascular exercises, and 20 minutes warm-up and stretching. Pelvic floor exercises were included in each session. The women were also encouraged to have at least one additional unsupervised exercise session weekly with the eventual goal of achieving a total of 30 minutes of moderate activity 5 days a week. Information on safe physical activity in pregnancy provided in pamphlets and on the website		
Stafne *et al.*,[88] 2012; English	Method of randomisation: concealed randomisation in blocks of 30 by web-based computerised procedure Allocation concealment: staff involved with training/assessment not involved in randomisation Blinding: unblinded except glucose and insulin measurements blinded to group allocation	Inclusion criteria: • white women aged ≥ 18 years • singleton live fetus Exclusion criteria: • high-risk pregnancies • diseases that could interfere with participation • women who lived too far (more than 30-minute drive) from the hospitals Number of participants: • Intervention, $n = 375$ • Control, $n = 327$	Standardised exercise programme including aerobic activity, strength training and balance exercises supervised by a physiotherapist. Training sessions in groups of 8–15 women offered once weekly for 12 weeks (between 20 and 36 weeks of gestation). Each session lasted 60 minutes A written 45-minute home exercise programme (30 minutes of endurance training and 15 minutes of strength/balance exercises) was recommended twice weekly and women were asked to record the exercise activities in personal training diaries. Physical activity was also assessed by questionnaires	Usual care, not discouraged from exercising. Written recommendations on diet, pelvic floor exercises and pregnancy-related lumbopelvic pain	Primary: • prevalence of GDM at 32–36 weeks' gestation • insulin resistance estimated by the homeostasis model assessment method Secondary: • maternal weight at follow-up • weight gain at follow-up • BMI at follow-up • PE • gestational hypertension • Caesarean delivery • operative vaginal delivery • gestational age at delivery

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
					• birthweight • birthweight ≥ 4000 g • Apgar score • admission to the NICU
Vinter *et al.*,[70] 2011; English	Method of randomisation: computerised 1 : 1 randomisation with stratification by smoking status Allocation concealment: closed envelopes were used Blinding: not reported	Inclusion criteria: • aged 18–40 years • gestational age of 10–14 weeks • BMI of 30–45 kg/m^2 (pregestational or first measured weight in pregnancy) Exclusion criteria: • prior major obstetric complications • chronic diseases (e.g. DM and hypertension) • positive oral glucose tolerance test in pregnancy • alcohol/drug abuse • unable to speak Danish • multiple pregnancy Number of participants: • Intervention, $n = 180$ • Control, $n = 180$	Intervention type: dietary counselling and exercise Diet: trained dietitians provided counselling based on official Danish recommendations at 15, 20, 28 and 35 weeks' gestation. The goal was to limit GWG in pregnancy to 5 kg. Individualised calorie goals based on weight and activity level were provided Physical activity: moderate physical activity lasting 30–60 minutes was encouraged and a pedometer was provided to motivate and improve physical activity. A free full-time membership to local fitness centre was provided for 6 months. This included a 1-hour weekly closed training session with a physiotherapist. The exercises included aerobic activities with elastic bands and light weights, and balance exercises. The women were grouped 4–6 times with the physiotherapist after physical training	Information on purpose and content of the study. Access to a website with advice on diet and physical activity in pregnancy	Primary: • GWG (weight at 35 weeks minus weight at inclusion) • PE • PIH • GDM • Caesarean section • macrosomia/LGA • admission to the NICU
Vítolo *et al.*,[77] 2011; Portuguese	Method of randomisation: not reported Allocation concealment: not reported Blinding: not reported	Inclusion criteria • pregnant women between 10 and 29 weeks' gestation Exclusion criteria: • positive human immunodeficiency virus test • previous diagnosis of DM	Dietary counselling according to nutritional status. For pregnant women with low birthweight, this was adopted as a priority to increase the energy density of the diet with the addition of a tablespoon of oil in the main meals, eat two snacks per day of high energy (with sample portions) 100 g once a week and fruit daily. Well-nourished pregnant women received vegetables,	The control group did not receive the dietary guidelines but were informed about their nutritional status and were asked to carry on with their prenatal care	• GWG • DM • PE • Infant birthweight • Prematurity

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
		• hypertension • anaemia • any conditions preventing women from undertaking exercise in pregnancy • aged > 35 years Number of participants: • Intervention, *n* = 159 • Control, *n* = 162	legumes, fruits and water six times per day and restricted the consumption of foods rich in fat and cooking oils. For pregnant women with excess weight, between meals (3–4 hours) were prioritised; not repeat the food portions of meals and snacks; restrict daily consumption of soft drinks and sweets, processed foods high in fat and also oil preparations. They were determined daily servings of vegetables, vegetables and fruit. All guidance provided values and portion sizes		
Walsh *et al.*,[78] (ROLO trial) 2012; English	Method of randomisation: not reported Allocation concealment: not reported Blinding: not reported	Inclusion criteria: • secundigravid women with previous macrosomic infant (birthweight > 4 kg) were recruited at first antenatal consultation Exclusion criteria: • women with medical disorders including history of gestational DM • those on any drugs, and those unable to give full informed consent were excluded • aged < 18 years • gestational age > 18 weeks • multiple pregnancy Number of participants: • Intervention, *n* = 394 • Control, *n* = 406	One 2-hour dietary education session with the research dietitian in groups of two to six women. The diet was in line with current recommendations for pregnant women. General advice on healthy eating in pregnancy and following the food pyramid was provided. Women were taught about the rationale for having low glycaemic index food and encouraged to replace high glycaemic index carbohydrates with low glycaemic index alternatives. Written resources were provided after the education session. Women were not advised to reduce their total caloric intake. The research dietitian met women again at 28 and 34 weeks of gestation to reinforce the advice and clarify any doubts	Routine antenatal care with no specific dietary recommendation or advice about GWG	Primary: • mean birthweight centiles and ponderal indices at 14, 28 and 34 weeks' gestation, at birth and 3 months post partum Secondary: • maternal weight gain at 14, 28 and 34 weeks' gestation, at birth and 3 months post partum • adherence to IOM recommendations for GWG • maternal glucose intolerance

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
			All women completed three food diaries of 3 days each: before dietary intervention and in the second and third trimesters of pregnancy A questionnaire was provided at 34 weeks visit to assess adherence to the diet. It was based on a five-point Likert-type scale (1 = 'I followed the recommended diet all of the time', 5 = 'I followed the recommended diet none of the time')		
Wolff *et al.*,[71] 2008; English	Method of randomisation: computerised randomisation Allocation concealment: not reported Blinding: investigators/ clinicians	Inclusion criteria: • Caucasian • BMI of ≥ 30 kg/m^2 • early pregnancy (15 ± 3 weeks of gestation) • non-diabetic at inclusion Exclusion criteria: • smoking • aged < 18 or > 45 years • multiple pregnancy • medical complications known to affect fetal growth adversely • contraindication for limiting weight gain Number of participants: • Intervention, $n = 28$ • Control, $n = 38$	Ten 1-hour dietary consultations (healthy diet, restriction of energy intake): the intervention group received 10 consultations of 1 hour each with a trained dietitian during the pregnancy. Women were asked to eat a healthy diet according to the official Danish dietary recommendations (fat intake, maximum 30 energy per cent; protein intake, 15–20 energy per cent; carbohydrate intake, 50–55 energy per cent). Energy intake was restricted on the basis of individually estimated energy requirements and estimated energy requirements of fetal growth [energy requirement = basal metabolic rate × 1.4 (physical activity level factor of 1.2 + 0.2 added to cover energetic cost of fetal growth)]	No intervention	• GDM • Gestational age at delivery • PIH • PE • Prolonged pregnancy • Caesarean delivery, • Total GWG (weight at delivery minus self-reported pre-pregnancy weight) • Weight gain from 15 weeks to 36 week • Birthweight • Placental weight • Infant length • Head circumference • Abdominal circumference

continued

TABLE 51 Characteristics of studies in the repository (*continued*)

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
Yeo *et al.*,[89] 2000; English	Method of randomisation: not reported Allocation concealment: not reported Blinding: not reported	Inclusion criteria: • aged ≥ 18 years • high risk of gestational hypertensive disorders (mild hypertension, history of gestational hypertensive disorders or family history of hypertensive disorders) Exclusion criteria: • DM • renal disease • multiple pregnancies • extremely vigorous exercisers (more than three times per week at a level > RPE 14 for longer than 30 minutes per session) Number of participants: • Intervention, $n = 8$ • Control, $n = 8$	Exercise of moderate intensity Exercise sessions of 30 minutes each were held in a laboratory three times a week A motorised treadmill and bicycle ergometer were alternated. Exercise consisted of a 5-minute warm-up using the Branching protocol, followed by a 30-minute steady state, and ended with a 10-minute cool down. Steady state was defined as RPE 13, which was considered a moderate level of exercise	No intervention	• Resting blood pressure before and after 10 weeks of exercise • Mean percentage body fat of mother • Percentage of time/energy spent on light/moderate/ heavy exercise

Yeo,[27] 2013; protocol, English	Method of randomisation: predetermined block randomisation
	
	Allocation concealment: information not available
	
	Blinding: not reported
		Inclusion criteria
		
		• gestational age less than 12 weeks' gestation plus one or more of the following:
		  ○ history of PE
		  ○ type 2 DM
		  ○ chronic hypertension
		  ○ BMI of ≥ 30 kg/m^2 either pre-pregnancy or at first visit in the first trimester for primiparous women
		  ○ Diastolic blood pressure of ≥ 90 mmHg before 12 weeks' gestation
			There are two intervention groups, walking exercise and stretching and the intervention runs for 10 weeks and involves 30-minute activity three times a week. The participants are free to choose the days of exercise provided they have a rest day between two exercise days. Research staff will train both groups for the first 2 weeks. Subsequently, one session per week will be supervised and the remaining two unsupervised. Childcare facilities are arranged either onsite or by arranging exercise venues with child care arrangements	Research nurse visits for 30 minutes every other week to take measurements and is allowed to answer any queries related to healthy pregnancy and lifestyle	• Recruitment rate: 15 subjects in 3 months
					• Feasibility of walking and stretching exercise: 85% of frequency and drop-out rate within 5 weeks < 10% due to social and behavioural reasons (excluding obstetrical reasons)
					• Feasibility of collecting scheduled blood samples and establishing a protocol for measuring superoxide dismutase
					• Sample size estimation for a larger study

Study, year and language	Methods	Participants	Interventions	Control	Outcomes
		Exclusion criteria: any of the following conditions: • multiple pregnancy • vaginal bleeding • diagnosed placenta praevia • antenatal care provider or primary care provider's objection to participation in the study • any condition prohibiting regular exercise (walking exercise and stretching) between 12 and 22 weeks of gestation • inability to complete questionnaires or communicate with research staff • already exercising > thrice weekly during the first 11 weeks of pregnancy The women are divided into three groups: walking, stretching and standard care Number of participants: data unpublished	The walking group: walking exercise consists of 30 minutes of moderate intensity walking in an environment (home, gym, workplace and neighbourhood) agreed with the research staff. The exercise intensity is guided by a heart rate monitor and the RPE. Women are advised to maintain the heart rate to 55–69% of age determined maximum heart rate and are guided by the digital screen on their wrists that senses information from the chest belts they wear. The suggested RPE is 12 or 13. If there is a discrepancy between heart rate and RPE, they are advised to keep both within/below the recommended limits Stretching group: this consists of 30 minutes of stretching exercise thrice weekly without increasing the heart rate by more than 10% of the resting heart rate. The exercise involves slow muscle movements without aerobic or muscle resistance components, and participants are guided by a videotape showing recommended movements		

ACOG, American College of Obstetricians and Gynecologists; CIQ-SF, Consultation on Incontinence Questionnaire-Short Form; DVD, digital versatile disc; PRECEDE–PROCEED, Predisposing, Reinforcing and Enabling Constructs in Educational Diagnosis and Evaluation – Policy, Regulatory, and Organizational Constructs in Educational and Environmental Development; RPE, rate of perceived exertion; UPBEAT, UK Pregnancies: Better Eating and Activity Trial.

Appendix 7 Risk-of-bias assessment

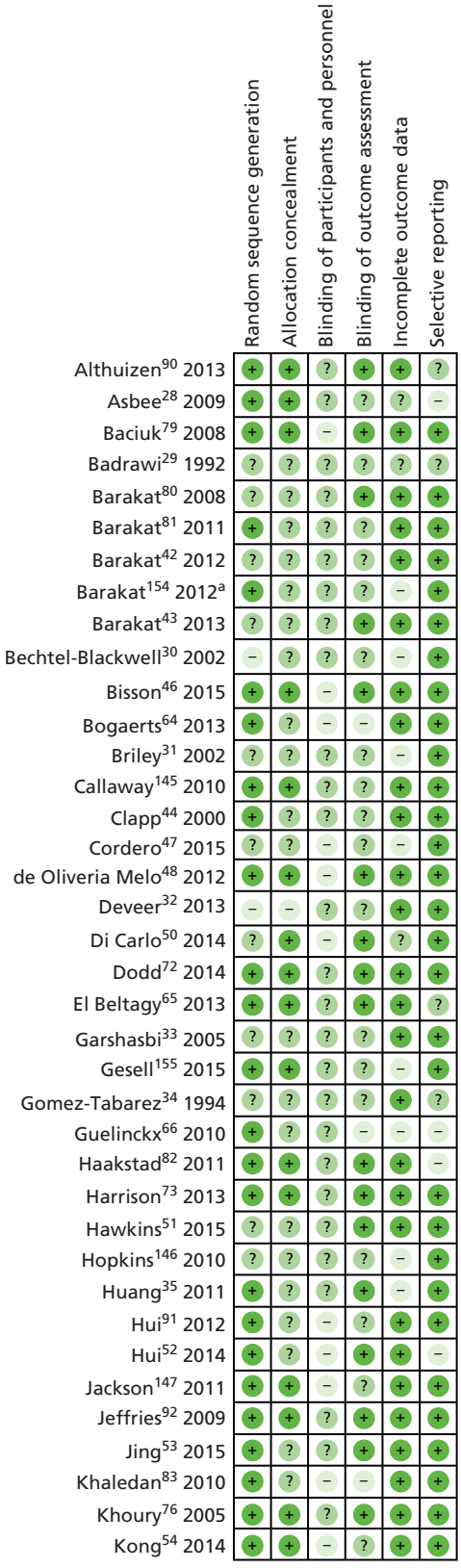

FIGURE 21 Detailed assessment of risk of bias: all eligible trials ($n = 74$). a, Data from the secondary publication of Dekker Nitert *et al.*[49]

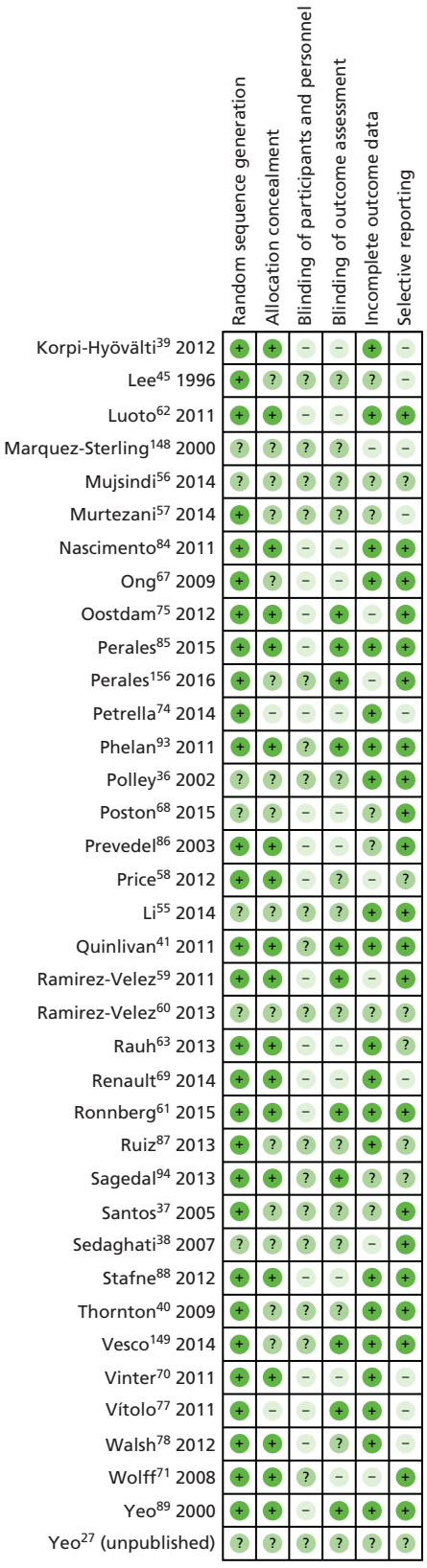

FIGURE 22 Detailed assessment of risk of bias: all eligible trials ($n = 74$) (continuation).

TABLE 52 Global classification of risk of bias on study level: trials contributing IPD ($n = 35$)

Study (first author and reference number)	Item						
	1: randomisation	2: allocation concealment	3: blinding of participants	4: blinding of outcome assessment	5: incomplete outcome data	6: selective reporting	Global risk of bias
Baciuk *et al.*[79]	Low	Low	High	Low	Low	Low	Low/medium
Barakat *et al.*[80]	Unclear	Unclear	Unclear	Low	Low	Low	Low/medium
Barakat *et al.*[81]	Low	Unclear	Unclear	Unclear	Low	Low	Low/medium
Barakat *et al.*[42]	Low	Unclear	Unclear	Unclear	High	Low	High
Bogaerts *et al.*[64]	Low	Unclear	High	High	Low	Low	High
Dodd *et al.*[72]	Low	Low	Unclear	Low	Low	Low	Low/medium
El Beltagy *et al.*[65]	Low	Low	Unclear	Low	Low	Unclear	Low/medium
Guelinckx *et al.*[66]	Low	Unclear	Unclear	High	High	High	High
Haakstad and Bo[82]	Low	Low	Unclear	Low	Low	High	Low/medium
Harrison *et al.*[73]	Low	Low	Unclear	Low	Low	Low	Low/medium
Hui *et al.*[91]	Low	Unclear	High	Unclear	Low	Low	Low/medium
Jeffries *et al.*[92]	Low	Low	Unclear	Low	Low	Low	Low/medium
Khaledan *et al.*[83]	Low	Unclear	High	High	Low	Low	High
Khoury *et al.*[76]	Low	Low	Unclear	Low	Low	Low	Low/medium
Luoto *et al.*[62]	Low	Low	High	High	Low	Low	High
Nascimento *et al.*[84]	Low	Low	High	High	Low	Low	High
Ong *et al.*[67]	Low	Unclear	High	High	Low	Low	High
Oostdam *et al.*[75]	Low	Low	High	Low	High	Low	High

continued

TABLE 52 Global classification of risk of bias on study level: trials contributing IPD ($n = 35$) (*continued*)

Study (first author and reference number)	Item						Global risk of bias
	1: randomisation	2: allocation concealment	3: blinding of participants	4: blinding of outcome assessment	5: incomplete outcome data	6: selective reporting	
Perales *et al.*[85]	Low	Low	High	Low	Low	Low	Low/medium
Perales *et al.*[156]	Low	Unclear	Unclear	Low	High	Low	High
Petrella *et al.*[74]	Low	High	High	High	Low	High	High
Phelan *et al.*[93]	Low	Low	Unclear	Low	Low	Low	Low/medium
Poston *et al.*[68]	Unclear	Unclear	High	High	Unclear	Unclear	High
Prevedel *et al.*[86]	Low	Low	High	High	Unclear	Low	High
Rauh *et al.*[63]	Low	Low	High	High	Low	Unclear	High
Renault *et al.*[69]	Low	Low	High	High	Low	High	High
Ruiz *et al.*[87]	Low	Unclear	Unclear	Unclear	Low	Unclear	Low/medium
Sagedal *et al.*[153]	Low	Low	Unclear	Low	Unclear	Unclear	Low/medium
Stafne *et al.*[88]	Low	Low	High	High	Low	Low	High
Vinter *et al.*[70]	Low	Low	High	High	Low	High	High
Vítolo *et al.*[77]	Low	High	High	Low	Low	High	Low/medium
Walsh *et al.*[78]	Low	Low	High	Unclear	Low	High	Low/medium
Wolff *et al.*[71]	Low	Low	Unclear	High	High	Low	High
Yeo *et al.*[89]	Low	Low	High	Low	Low	Low	Low/medium
Yeo (unpublished)[27]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High

Appendix 8 Sensitivity analysis for the main outcomes

TABLE 53 Summary of sensitivity analyses for GWG as an outcome

Sample size (number of studies)	Group, mean GWG (SD)		Adjusted difference[a] (95% CI)	95% PI
	Control	Intervention		
Primary analysis for GWG				
9320 (33)	10.8 (5.4)	10.1 (5.4)	–0.70 (–0.92 to –0.48)	–1.24 to –0.16
Analysis including aggregate data				
12,895 (60)	11.5[b]	10.5[b]	–1.13 (–1.58 to –0.68)	–4.10 to 1.83
Analysis excluding studies rated as being at a high risk of bias				
5585 (15)	11.5 (5.3)	10.9 (5.2)	–0.67 (–0.95 to –0.38)	–1.14 to –0.19
Analysis excluding participants with gestational age at follow-up < 37 weeks				
5324 (28)	12.2 (5.3)	11.4 (5.4)	–0.91 (–1.17 to –0.66)	–1.17 to –0.66
Analysis excluding women not adherent to intervention				
8565 (33)	10.8 (5.4)	10.3 (5.4)	–0.76 (–1.00 to –0.52)	–1.31 to –0.21
Analysis using change in BMI (kg/m²)				
9238 (31)	3.9 (2.0)	3.6 (2.0)	–0.3 (–0.39 to –0.21)	–0.60 to 0.00
Intervention groups *Analysis including only studies with diet-based interventions*				
1168 (4)	11.0 (4.8)	10.2 (4.4)	–0.72 (–1.48 to 0.04)	–1.75 to 0.30
Analysis including only studies with physical activity-based interventions				
2915 (15)	10.8 (5.3)	9.8 (4.4)	–0.73 (–1.11 to –0.34)	–1.50 to 0.05
Analysis including only studies with mixed approach				
5369 (15)	10.6 (5.9)	10.2 (6.0)	–0.71 (–1.10 to –0.31)	–1.42 to 0.01

a Model accounting for baseline weight and clustering effect.
b Not estimable.

TABLE 54 Sensitivity analyses for primary outcome composite maternal events

Sample size (number of studies)	Group, *n* (%)		Summary OR[a] (95% CI)	95% PI
	Control	Intervention group		
Primary analysis for composite maternal outcome				
8852 (24)	1837/4227 (43.5)	1896/4624 (41.0)	0.90 (0.79 to 1.03)	0.68 to 1.20
Analysis excluding studies rated as being at a high risk of bias				
4873 (10)	1009/2421 (41.7)	979/2452 (39.9)	0.91 (0.77 to 1.08)	0.70 to 1.19
Analysis excluding women not adherent to intervention				
7949 (24)	1837/4227 (43.5)	1527/3722 (41.0)	0.92 (0.80 to 1.06)	0.66 to 1.30
Analysis of the intervention effects on the individual components of composite maternal outcome				
PE or PIH				
9618 (22)	423/4600 (9.2)	432/5018 (8.6)	0.95 (0.78 to 1.16)	0.69 to 1.31
Pooled-effect GDM				
9427 (27)	571/4510 (12.7)	584/4917 (11.9)	0.89 (0.72 to 1.10)	0.49 to 1.60
Preterm delivery				
11,676 (32)	345/5631 (6.1)	332/6045 (5.5)	0.94 (0.78 to 1.13)	0.78 to 1.13
Caesarean section				
11,410 (32)	1506/5500 (27.4)	1527/5910 (25.8)	0.91 (0.83 to 0.99)	0.83 to 1.99
Intervention groups				
Analysis including only studies with diet-based interventions				
397 (3)	84/218 (38.5)	42/179 (23.5)	0.60 (0.20 to 1.75)	0.02 to 14.27
Analysis including only studies with physical activity-based interventions				
2311 (9)	367/1115 (32.9)	346/1196 (28.9)	0.81 (0.61 to 1.09)	0.48 to 1.37
Analysis including only studies with mixed approach				
6259 (13)	1438/3009 (47.8)	1508/3250 (46.4)	0.97 (0.84 to 1.12)	0.82 to 1.13

a Model accounting for clustering effect.

TABLE 55 Sensitivity analyses for primary outcome composite fetal events

Sample size (number of studies)	Group, *n* (%)		Summary OR[a] (95% CI)	95% PI
	Control	Intervention group		
Primary analysis for fetal and neonatal composite outcome				
7981 (18)	951/3802 (25.0)	1007/4179 (24.1)	0.94 (0.83 to 1.08)	0.74 to 1.21
Two-stage meta-analysis fetal composite excluding studies rated as being at a high risk of bias				
3708 (6)	467/1855 (25.2)	417/1853 (22.5)	0.86 (0.71 to 1.06)	0.69 to 1.07
Two-stage meta-analysis fetal composite excluding non-adherent participants				
6875 (18)	951/3802 (25.0)	720/3073 (23.4)	0.94 (0.83 to 1.06)	0.83 to 1.06
Analysis of the intervention effects on the individual components of fetal and neonatal composite outcome				
IUD				
Insufficient data	–	–	–	–
SGA				
11,666 (33)	632/5633 (11.2)	709/6033 (11.8)	1.06 (0.94 to 1.20)	0.94 to 1.20
LGA				
12,047 (34)	759/5811 (13.1)	744/6236 (11.9)	0.90 (0.76 to 1.07)	0.63 to 1.30
Admissions to the NICU				
8140 (16)	279/3865 (7.2)	302/4275 (7.1)	1.01 (0.84 to 1.23)	0.84 to 1.23
Intervention groups				
Analysis including only studies with diet-based interventions				
346 (2)	48/180 (26.7)	34/166 (20.5)	0.71 (0.03 to 18.23)	–
Analysis including only studies with physical activity-based interventions				
1274 (5)	143/641 (22.3)	138/633 (21.8)	0.99 (0.67 to 1.46)	0.64 to 1.54
Analysis including only studies with mixed approach				
6494 (12)	797/3114 (25.6)	835/3380 (24.7)	0.95 (0.81 to 1.11)	0.71 to 1.27

a Model accounting for clustering effect.

Appendix 9 Results of aggregate meta-analyses

Maternal outcomes

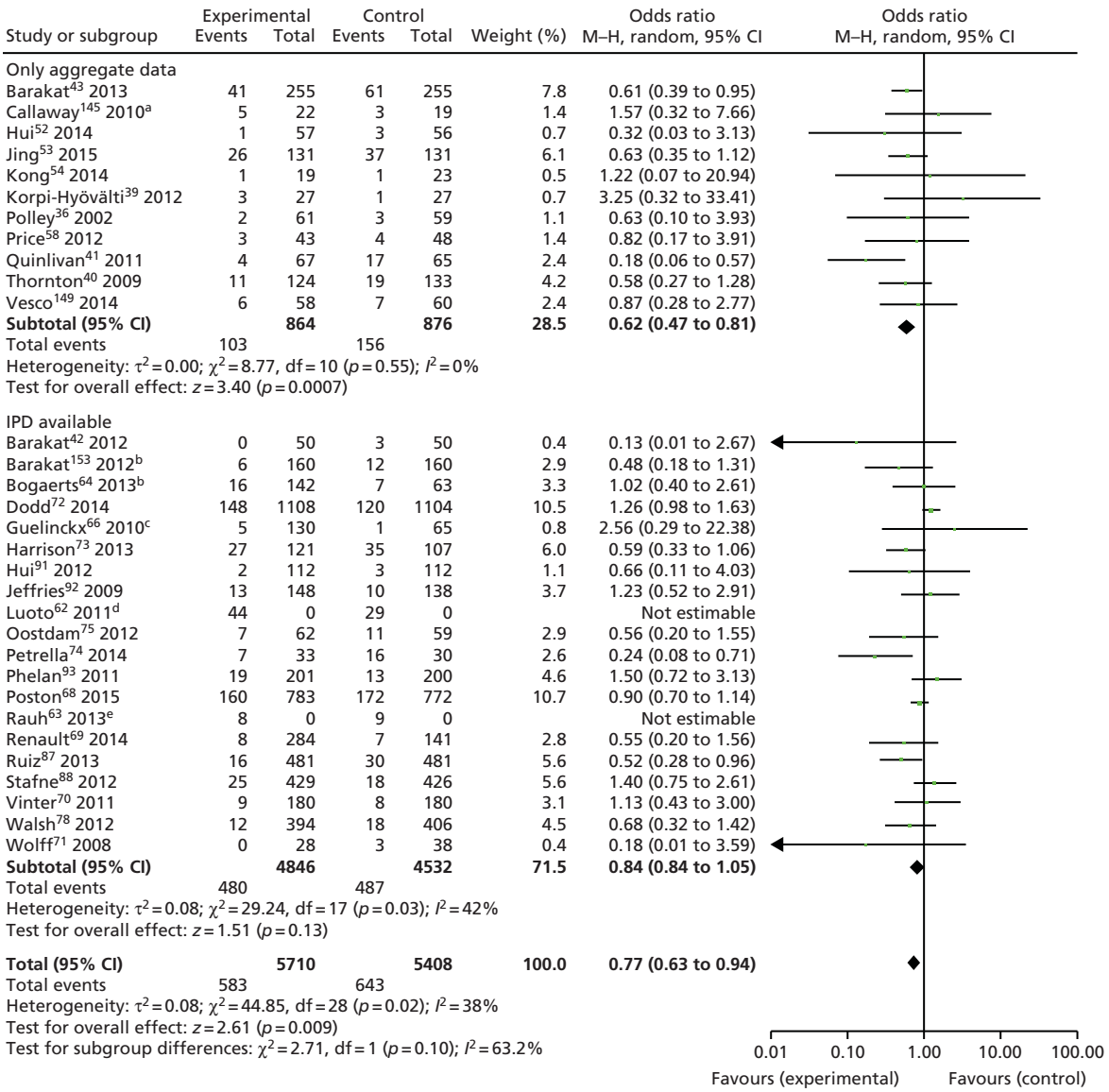

FIGURE 23 Outcome: GDM. a, Data from the secondary publication Dekker Nitert *et al.*;[49] b, combined active and passive; c, combined active and passive; d, cluster RCT; e, cluster RCT. df, degrees of freedom; M–H, Mantel–Haenszel.

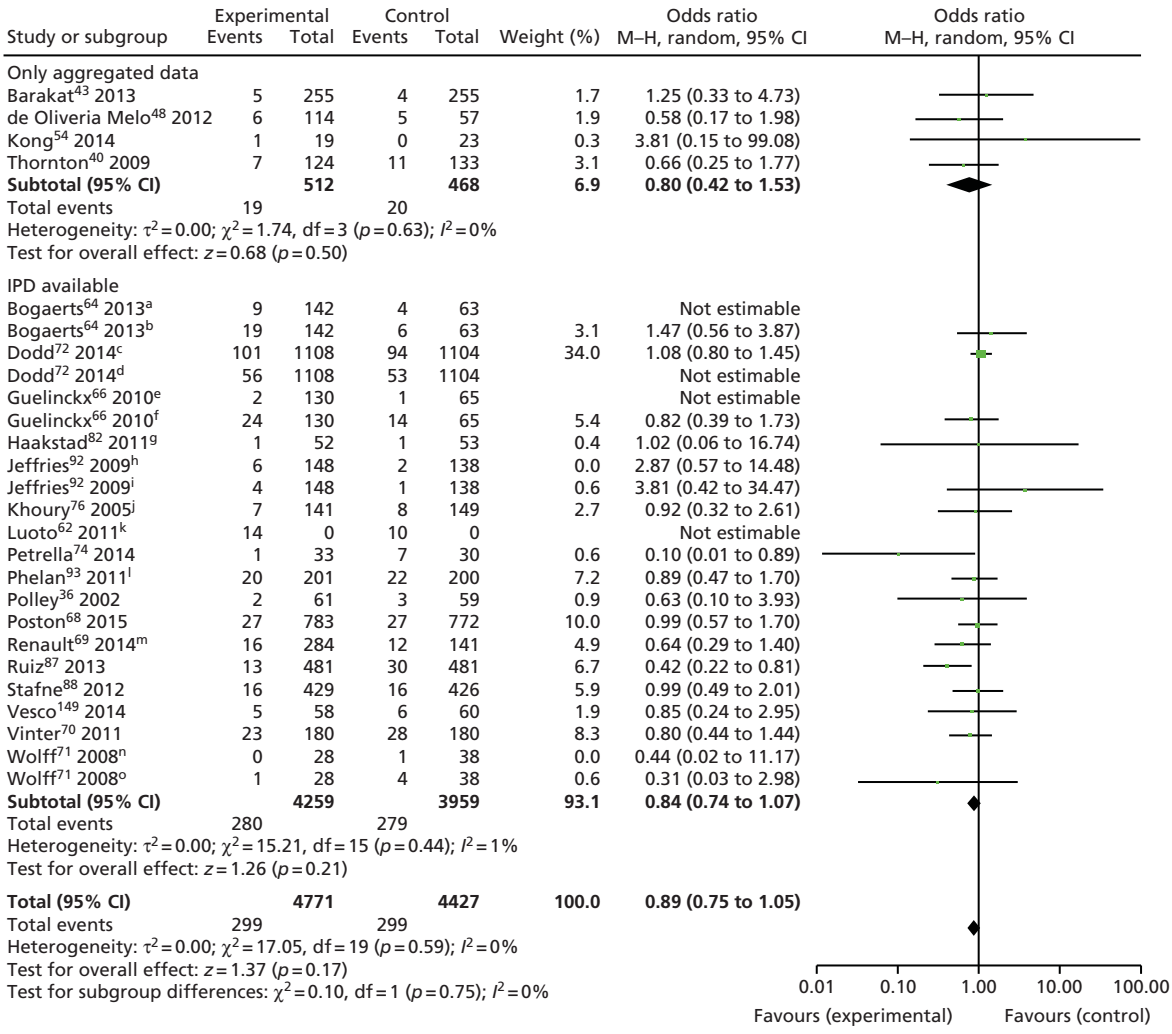

FIGURE 24 Outcome: PE or PIH. a, PE: combined active and passive; b, PIH: combined active and passive; c, PIH; d, PE; e, PE; f, PIH: combined active and passive; g, hypertension in exercise group, PE in control; h, PE; i, PIH; j, PE; k, cluster RCT; l, maternal hypertension; m, two intervention arms combined; n, PE; o, PIH. df, degrees of freedom; M–H, Mantel–Haenszel.

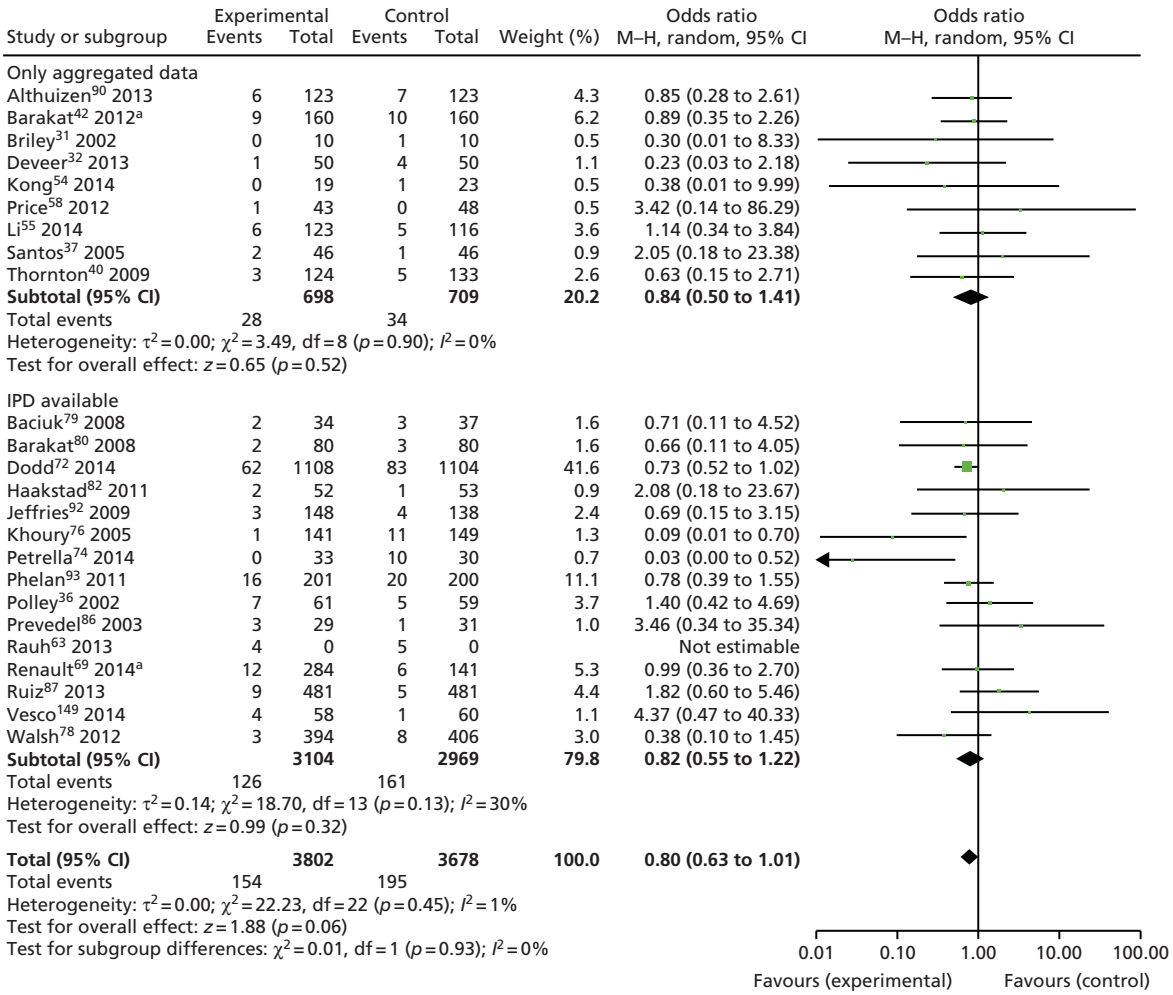

FIGURE 25 Outcome: preterm birth. a, Two intervention arms combined. df, degrees of freedom; M–H, Mantel–Haenszel.

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight (%)	Odds ratio M–H, random, 95% CI
Only aggregate available						
Althuizen[90] 2013	16	123	22	123	1.9	0.69 (0.34 to 1.38)
Asbee[28] 2009	8	57	12	43	0.9	0.42 (0.15 to 1.15)
Barakat[42] 2012[a]	22	160	35	160	2.7	0.57 (0.32 to 1.02)
Barakat[43] 2013	33	255	42	255	3.7	0.75 (0.46 to 1.23)
Callaway[145] 2010[b]	9	19	4	16	0.4	2.70 (0.64 to 11.47)
Deveer[32] 2013	16	50	20	50	1.4	0.71 (0.31 to 1.60)
Gomez-Tabarez[34] 1994	14	30	12	30	0.9	1.31 (0.47 to 3.65)
Hui[52] 2014	0	57	2	56	0.1	0.19 (0.01 to 4.04)
Khaledan[83] 2010	11	20	16	24	0.6	0.61 (0.18 to 2.08)
Kong[54] 2014	5	19	9	23	0.5	0.56 (0.15 to 2.08)
Lee[45] 1996	26	182	25	177	2.6	1.01 (0.56 to 1.83)
Marquez-Sterling[148] 2000	3	9	2	6	0.2	1.00 (0.11 to 8.95)
Polley[36] 2002	4	61	10	59	0.6	0.34 (0.10 to 1.17)
Price[58] 2012	2	43	10	48	0.4	0.19 (0.04 to 0.90)
Ramírez-Vélez[59] 2011	7	33	3	31	0.4	2.51 (0.59 to 10.76)
Thornton[40] 2009	91	124	83	133	3.2	1.66 (0.98 to 2.82)
Vesco[149] 2014	21	58	26	60	1.7	0.74 (0.35 to 1.56)
Subtotal (95% CI)		**1300**		**1294**	**22.4**	**0.80 (0.61 to 1.04)**
Total events	288		333			
Heterogeneity: $\tau^2 = 0.09$; $\chi^2 = 23.54$, df = 16 ($p = 0.10$); $I^2 = 32\%$						
Test for overall effect: $z = 1.65$ ($p = 0.10$)						
IPD available						
Baciuk[79] 2008	12	34	17	37	1.0	0.64 (0.25 to 1.67)
Barakat[81] 2011	7	40	10	40	0.8	0.64 (0.22 to 1.88)
Barakat[42] 2012	12	50	6	50	0.8	2.32 (0.79 to 6.76)
Bogaerts[64] 2013[a]	34	142	19	63	2.1	0.73 (0.38 to 1.41)
Dodd[72] 2014	197	1108	214	1104	17.3	0.90 (0.73 to 1.11)
Guelinckx[66] 2010[c]	20	130	7	65	1.1	1.51 (0.60 to 3.77)
Hui[91] 2012	2	112	3	112	0.3	0.66 (0.11 to 4.03)
Jeffries[92] 2009	41	148	30	138	3.1	1.38 (0.80 to 2.37)
Nascimento[84] 2011	25	40	29	42	1.1	0.75 (0.30 to 1.87)
Oostdam[75] 2012	7	62	8	59	0.8	0.81 (0.27 to 2.40)
Perales[85] 2015	14	101	19	83	1.6	0.54 (0.25 to 1.16)
Perales[85] 2015[a]	11	122	14	177	1.4	1.15 (0.51 to 2.63)
Petrella[74] 2014	11	33	9	30	0.8	1.17 (0.40 to 3.38)
Phelan[93] 2011	57	201	67	200	5.0	0.79 (0.51 to 1.20)
Poston[68] 2015	271	783	274	772	18.1	0.96 (0.78 to 1.18)
Rauh[63] 2013[d]	47	0	33	0	0.0	0.60 (0.34 to 1.06)
Renault[69] 2014[e]	83	284	50	141	4.9	0.75 (0.49 to 1.15)
Ruiz[87] 2013	93	481	93	481	8.5	1.00 (0.73 to 1.38)
Stafne[88] 2012	45	429	50	426	4.9	0.88 (0.57 to 1.35)
Vinter[70] 2011	40	180	39	180	3.7	1.03 (0.63 to 1.70)
Wolff[71] 2008	2	28	3	38	0.3	0.90 (0.14 to 5.76)
Subtotal (95% CI)		**4508**		**4238**	**77.6**	**0.92 (0.83 to 1.02)**
Total events	984		961			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 12.39$, df = 19 ($p = 0.87$); $I^2 = 0\%$						
Test for overall effect: $z = 1.50$ ($p = 0.13$)						
Total (95% CI)		**5808**		**5532**	**100.0**	**0.90 (0.82 to 0.99)**
Total events	1272		1294			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 36.89$, df = 36 ($p = 0.43$); $I^2 = 2\%$						
Test for overall effect: $z = 2.15$ ($p = 0.03$)						
Test for subgroup differences: $\chi^2 = 0.99$, df = 1 ($p = 0.32$); $I^2 = 0\%$						

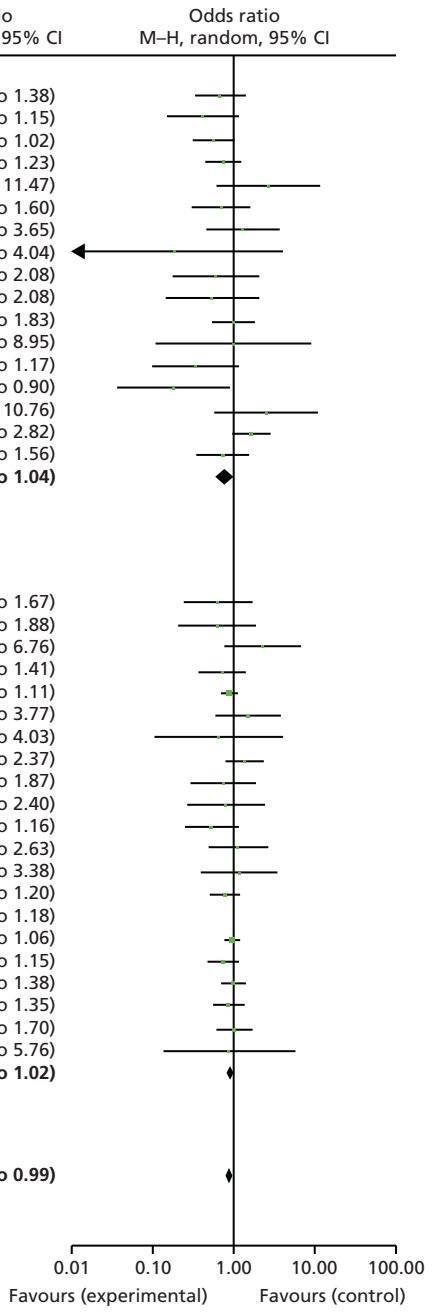

FIGURE 26 Outcome: any Caesarean section. a, Combined active and passive; b, data from the secondary publication Dekker Nitert *et al.*;[49] c, combined active and passive; d, cluster RCT; and e, combined two intervention arms. df, degrees of freedom; M–H, Mantel–Haenszel.

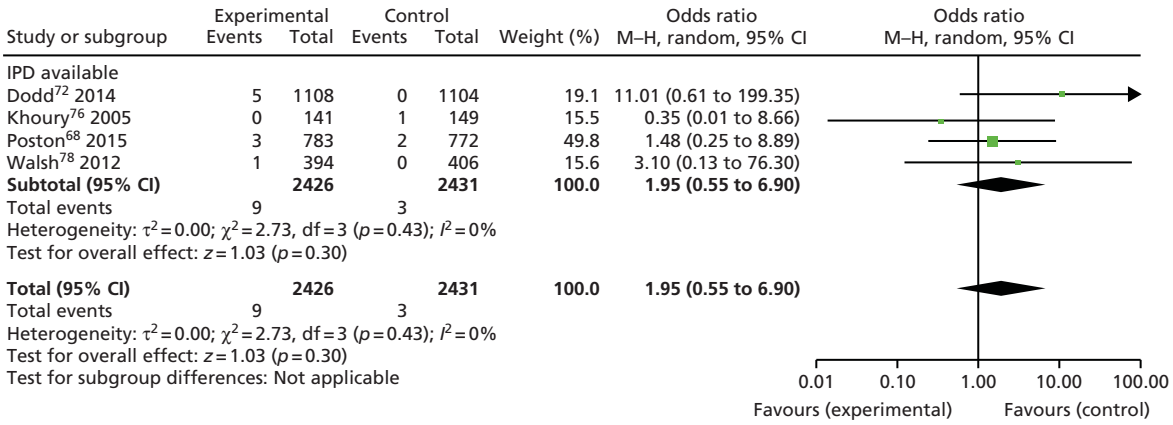

FIGURE 27 Outcome: IUD. df, degrees of freedom; M–H, Mantel–Haenszel.

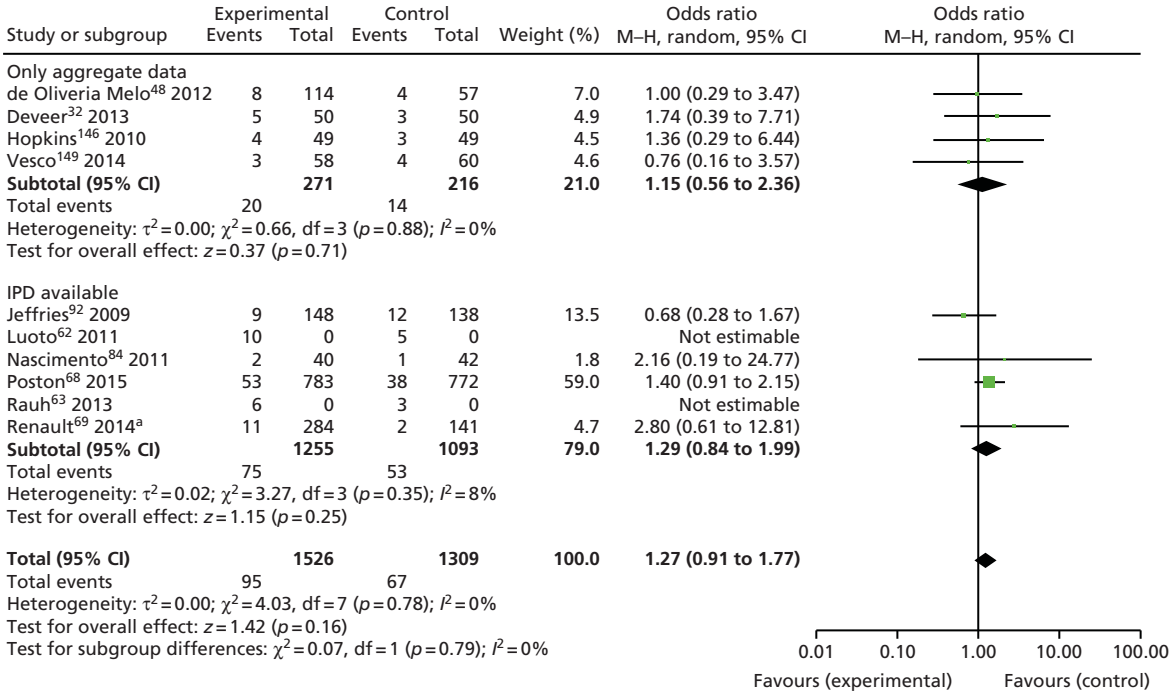

FIGURE 28 Outcome: SGA infant. a, Combined two intervention arms. df, degrees of freedom; M–H, Mantel–Haenszel.

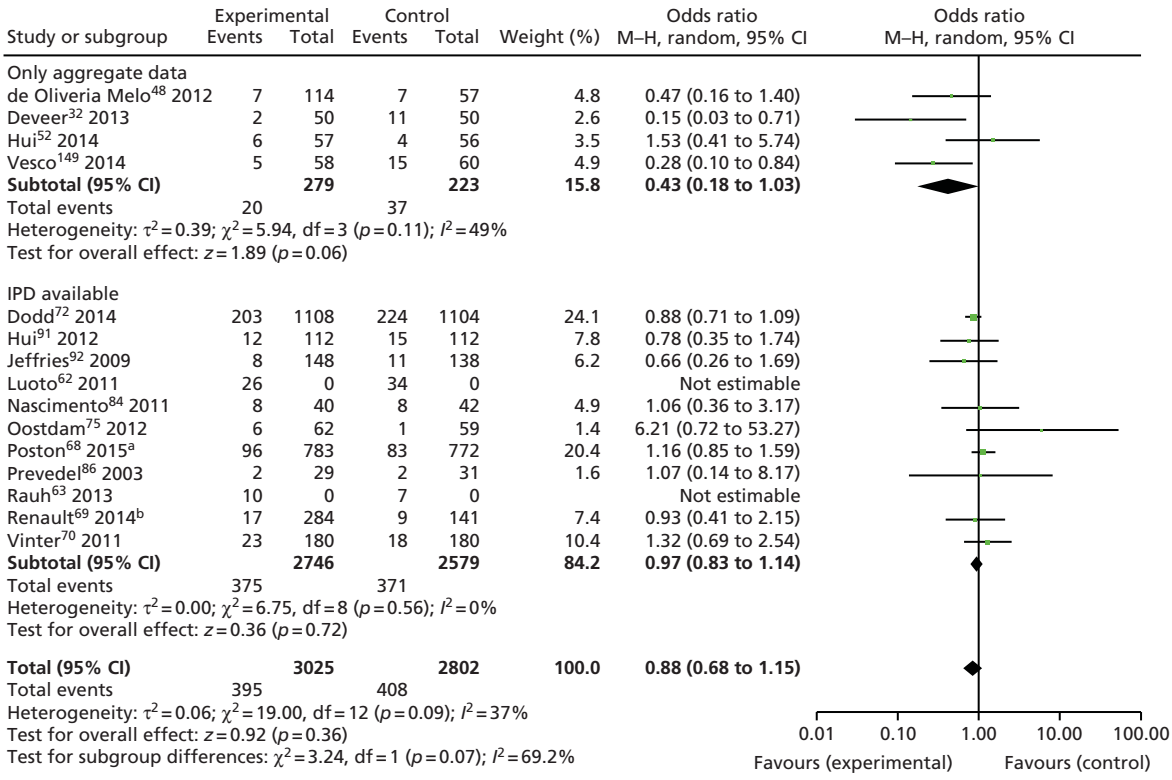

FIGURE 29 Outcome: LGA infant. a, > 90th centile population birthweight; and b, combined two intervention arms. df, degrees of freedom; M–H, Mantel–Haenszel.

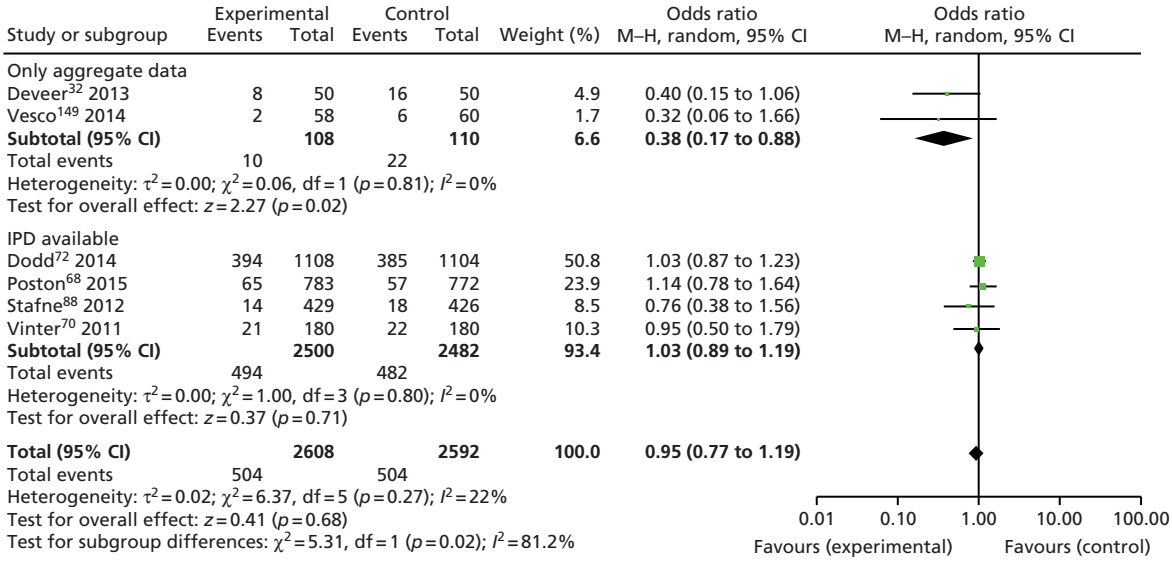

FIGURE 30 Outcome: admissions to the NICU. df, degrees of freedom; M–H, Mantel–Haenszel.

Appendix 10 Search strategies for systematic reviews undertaken to inform economic modelling

TABLE 56 Example of a search strategy for the systematic review of studies considering the costs associated with hypertensive disorders in pregnancy: MEDLINE

#	Term
1	Pre-Eclampsia/ or preeclamp*.mp.
2	pre-eclamp*.mp.
3	(pre and eclamp*).mp.
4	(pregnan* and hypertens*).mp.
5	Eclampsia/ or eclampsia.mp.
6	(EPH-gestosis or gestosis).mp.
7	(hypertension and pregnancy).mp.
8	Hypertension, Pregnancy-Induced/
9	Hypertension/
10	Pregnancy/
11	9 and 10
12	cost benefit analysis.mp. or exp Cost-Benefit Analysis/
13	(cost$ adj2 (effective$ or utili$ or benefit$ or consequence$ or minimi$)).ti,ab,kw.
14	(decision adj (analy$ or model$ or tree$)).ti,ab,kw.
15	(cost$ or economic$ or pharmacoeconomic$).ti.
16	quality-adjusted life year$.ti,ab,kw. or exp Quality-adjusted Life Years/
17	exp "costs and cost analysis"/ or exp Health Care Costs/
18	exp Economics, Pharmaceutical/ or exp Economics, Medical/ or Economics/ or exp Economics, hospital/
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 11
20	12 or 13 or 14 or 15 or 16 or 17 or 18
21	19 and 20

TABLE 57 Example of a search strategy for the systematic review of studies considering the costs associated with GDM in pregnancy: MEDLINE

#	Term
1	Diabetes, Gestational/
2	(diabet$ adj3 ("pregnancy induced" or gestat$ or gravid$)).ti,ab.
3	GDM.ti,ab.
4	exp DIABETES MELLITUS/
5	diabet$.ti.
6	PREDIABETIC STATE/
7	prediabet$.ti,ab.
8	impaired glucose tolerance.ti,ab.
9	IGT.ti,ab.
10	Impaired fasting glucose.ti,ab.
11	IFG.ti,ab.
12	Impaired glucose regulation.ti,ab.
13	IGR.ti,ab.
14	GLUCOSE INTOLERANCE/
15	PREGNANCY/
16	(pregnan$ or gestation$).ti,ab.
17	PREGNANT WOMEN/
18	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
19	15 or 16 or 17
20	18 and 19
21	1 or 2 or 3 or 20
22	cost benefit analysis.mp. or exp Cost-Benefit Analysis/
23	(cost$ adj2 (effective$ or utili$ or benefit$ or consequence$ or minimi$)).ti,ab,kw.
24	(decision adj (analy$ or model$ or tree$)).ti,ab,kw.
25	(cost$ or economic$ or pharmacoeconomic$).ti.
26	quality-adjusted life year$.ti,ab,kw. or exp Quality-adjusted Life Years/
27	exp "costs and cost analysis"/ or exp Health Care Costs/
28	exp Economics, Pharmaceutical/ or exp Economics, Medical/ or Economics/ or exp Economics, hospital/
29	22 or 23 or 24 or 25 or 26 or 27 or 28
30	21 and 29

TABLE 58 Example of a search strategy for the systematic review of studies considering the costs and benefits of interventions to manage weight gain in pregnancy: MEDLINE

#	Term
1	Pregnant Women/
2	Gravidity/
3	gravid*.tw.
4	pregnan*.tw.
5	childbearing.tw.
6	matern*.tw.
7	1 or 2 or 3 or 4 or 5 or 6 or 7
8	Weight Gain/ph [Physiology]
9	obes*.tw.
10	overweight*.tw.
11	bmi.tw.
12	Body Mass Index/
13	weight los*.tw.
14	Weight Loss/ph [Physiology]
15	weight change*.tw.
16	weight control.mp.
17	weight management.mp.
18	weight reduction.mp.
19	diet*.tw.
20	exp Diet/
21	nutritional therapy.mp.
22	food restriction.mp. or Caloric Restriction/
23	fast$.mp.
24	Energy Intake/ph [Physiology]
25	Exercise/ or Exercise Therapy/ or exercise$.mp.
26	exercis*.tw.
27	aerobics.mp.
28	physical activit*.tw.
29	calisthenics.mp. or Gymnastics/
30	Diabetes, Gestational/
31	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	economic evaluation$.tw.
33	Cost-Benefit Analysis/ec, mt, og, sn, ut [Economics, Methods, Organization & Administration, Statistics & Numerical Data, Utilization]
34	cost effectiv*.tw.
35	cost utility.tw.

continued

TABLE 58 Example of a search strategy for the systematic review of studies considering the costs and benefits of interventions to manage weight gain in pregnancy: MEDLINE (*continued*)

#	Term
36	cost consequence*.tw.
37	health care cost*.tw.
38	cost*.tw.
39	Economics, Medical/ec, sn [Economics, Statistics & Numerical Data]
40	economic$.mp.
41	decision model*.tw.
42	markov model*.tw.
43	Decision Trees/
44	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
45	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46	8 and 32 and 45
47	limit 46 to humans
48	limit 47 to English language
49	limit 48 to last 15 years

Appendix 11 Probabilistic sensitivity analysis additional results

Figures 31–54 show additional results for the PSAs that were conducted. Details of the methods and discussion of results are available in *Chapter 8*.

Additional results of probabilistic sensitivity analysis: primary analysis for a cohort of 10,000 pregnant women

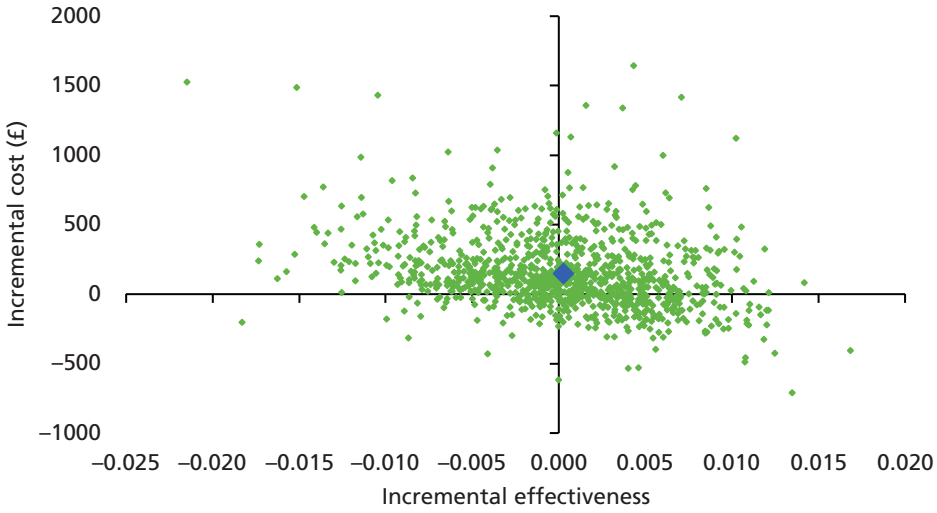

FIGURE 31 Incremental cost-effectiveness scatterplot of the intervention compared with care as usual for all women: cases of PE averted. The mean of the distribution is shown by the blue diamond.

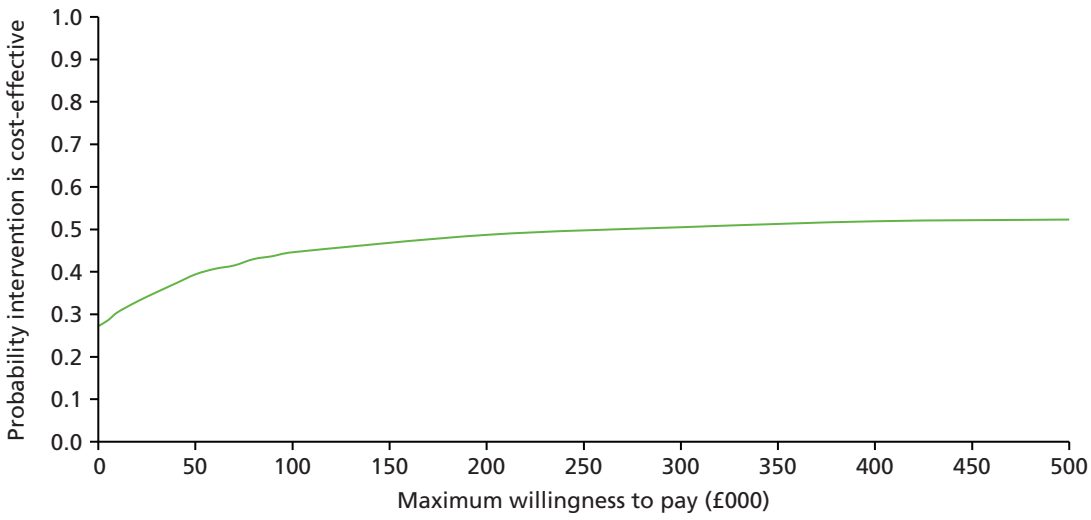

FIGURE 32 Incremental CEAC of the intervention for all pregnant women: cases of PE averted.

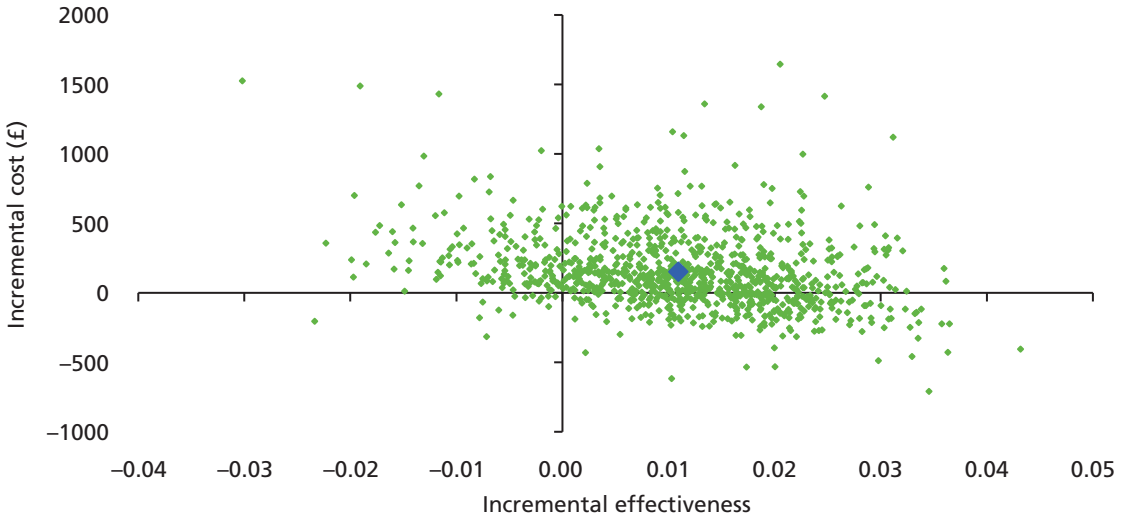

FIGURE 33 Incremental cost-effectiveness scatterplot of the intervention compared with care as usual for all pregnant women: cases of GDM averted. The mean of the distribution is shown by the blue diamond.

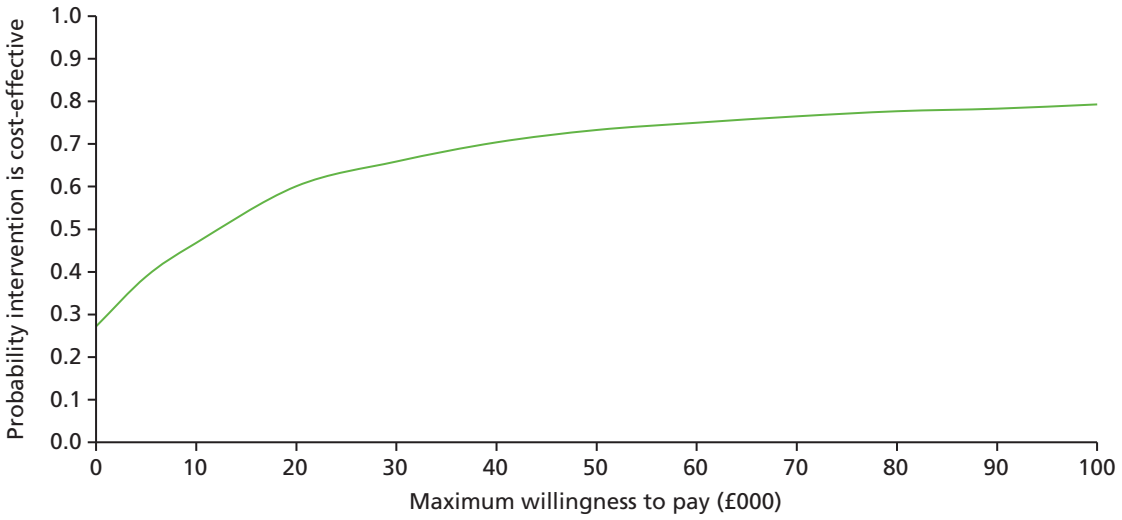

FIGURE 34 Incremental CEAC of the intervention for all pregnant women: cases of GDM averted.

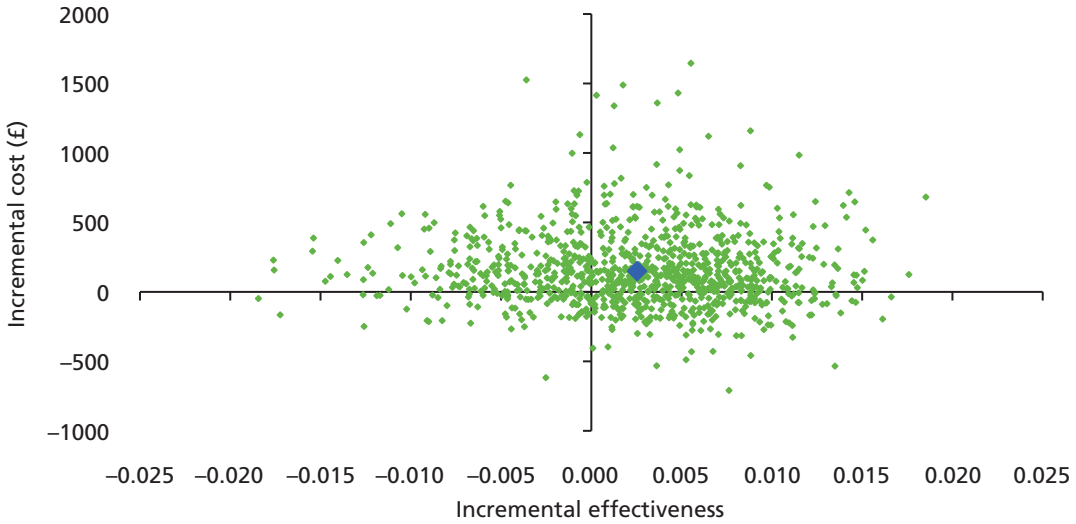

FIGURE 35 Incremental cost-effectiveness scatterplot of the intervention compared with care as usual for all pregnant women: cases of PIH averted. The mean of the distribution is shown by the blue diamond.

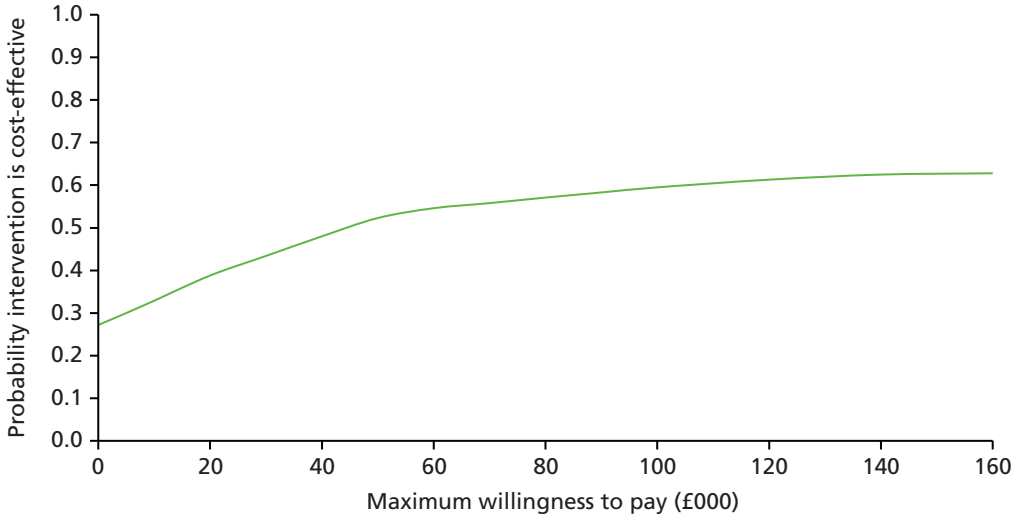

FIGURE 36 Incremental CEAC of the intervention for all pregnant women: cases of PIH averted.

Additional results of probabilistic sensitivity analysis: secondary analysis for a cohort of 10,000 obese pregnant women

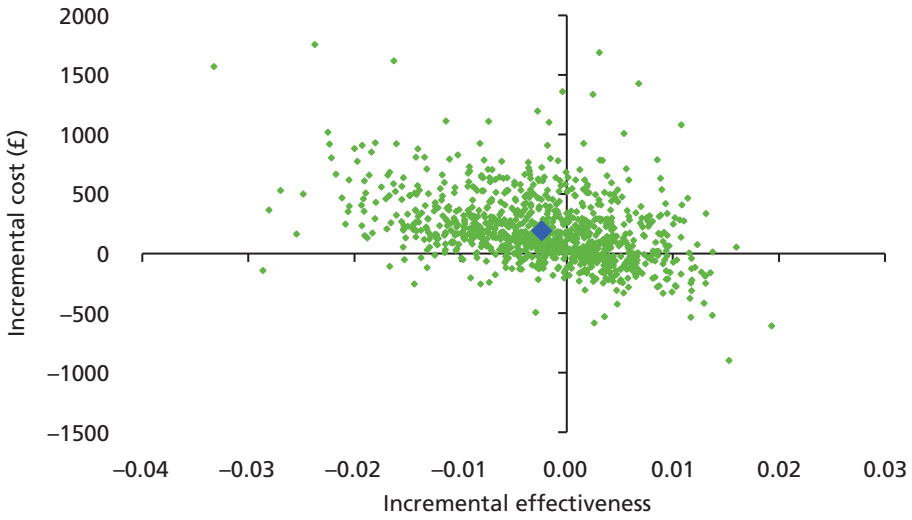

FIGURE 37 Incremental cost-effectiveness scatterplot of the intervention compared with care as usual for obese pregnant women: cases of PE averted. The mean of the distribution is shown by the blue diamond.

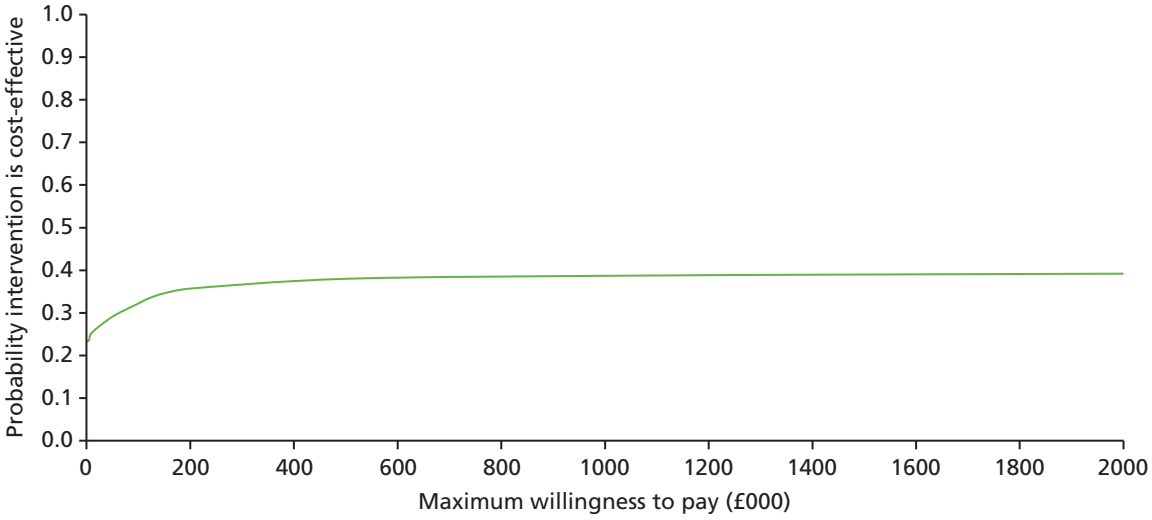

FIGURE 38 Incremental CEAC of the intervention for obese pregnant women: cases of PE averted.

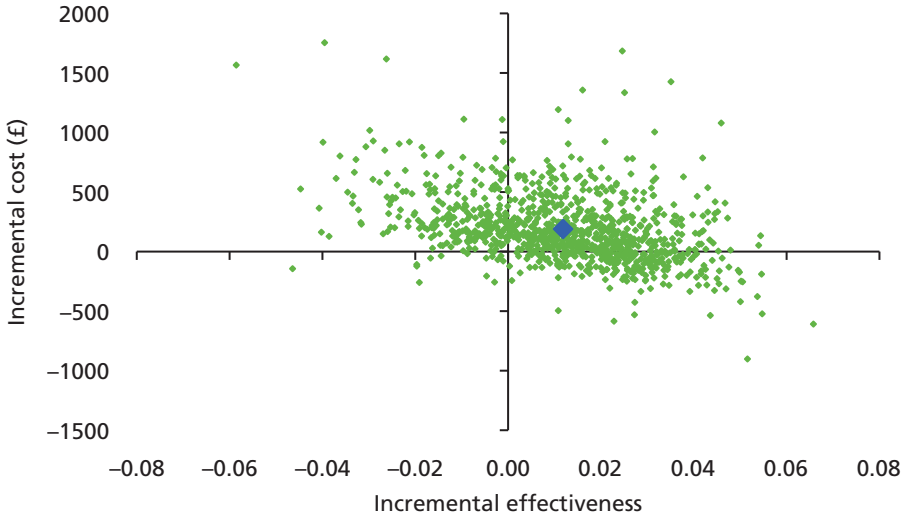

FIGURE 39 Incremental cost-effectiveness scatterplot of the intervention compared with care as usual for obese women: cases of GDM averted. The mean of the distribution is shown by the blue diamond.

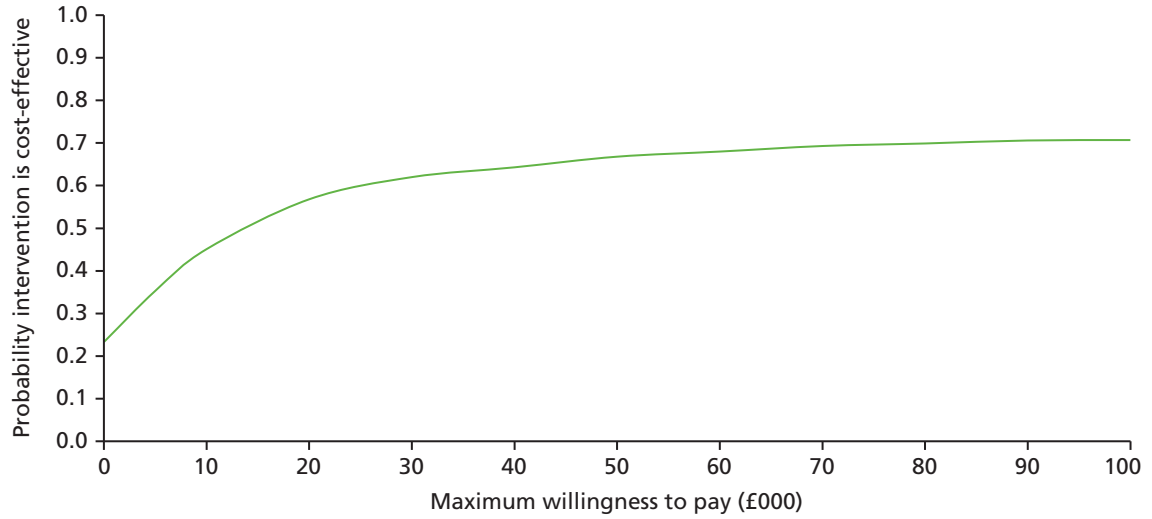

FIGURE 40 Incremental CEAC of the intervention for obese pregnant women: cases of GDM averted.

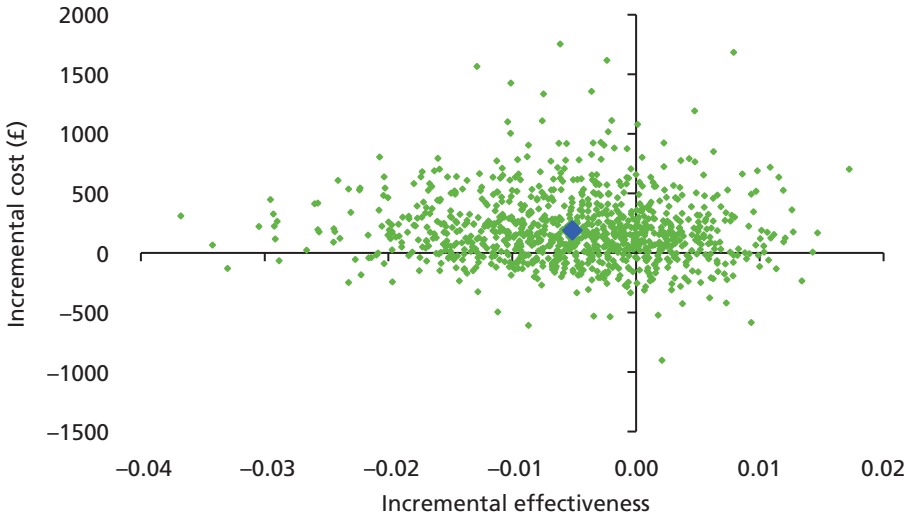

FIGURE 41 Incremental cost-effectiveness scatterplot of the intervention compared with care as usual for obese women: cases of PIH averted. The mean of the distribution is shown by the blue diamond.

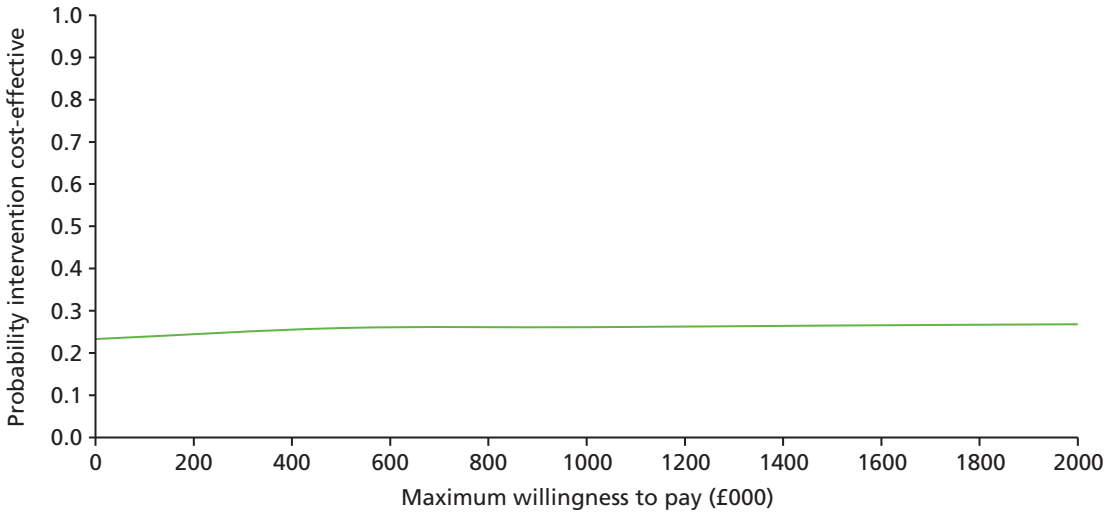

FIGURE 42 Incremental CEAC of the intervention for obese pregnant women: cases of PIH averted.

Additional results of probabilistic sensitivity analysis: secondary analysis for a cohort of 10,000 overweight pregnant women

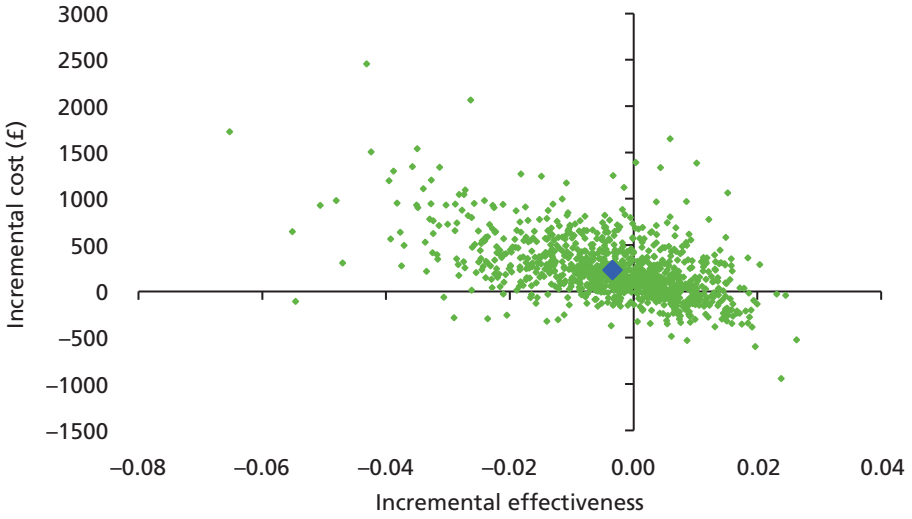

FIGURE 43 Incremental cost-effectiveness scatterplot of the intervention compared with care as usual for overweight women: cases of PE averted. The mean of the distribution is shown by the blue diamond.

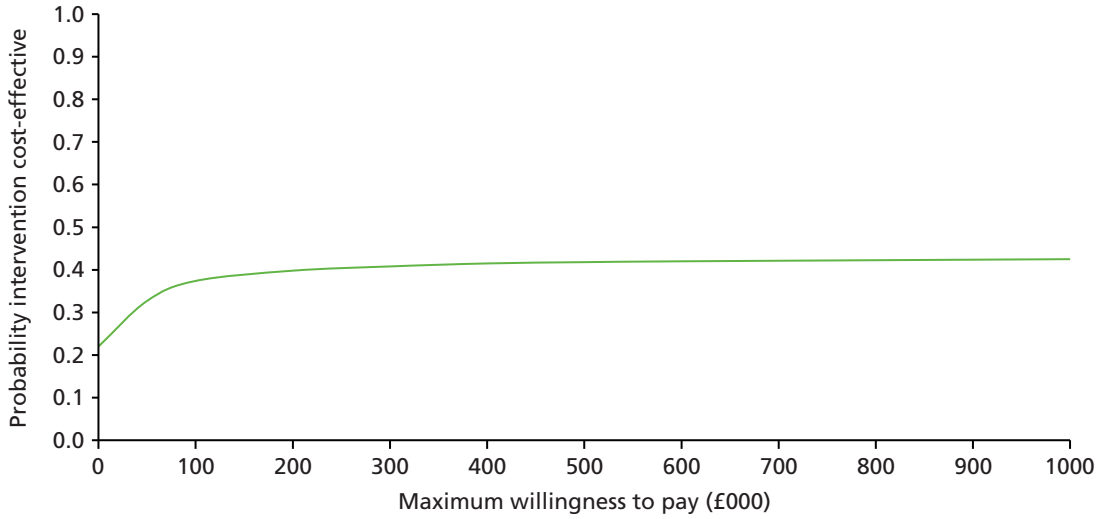

FIGURE 44 Incremental CEAC of the intervention for overweight pregnant women: cases of PE averted.

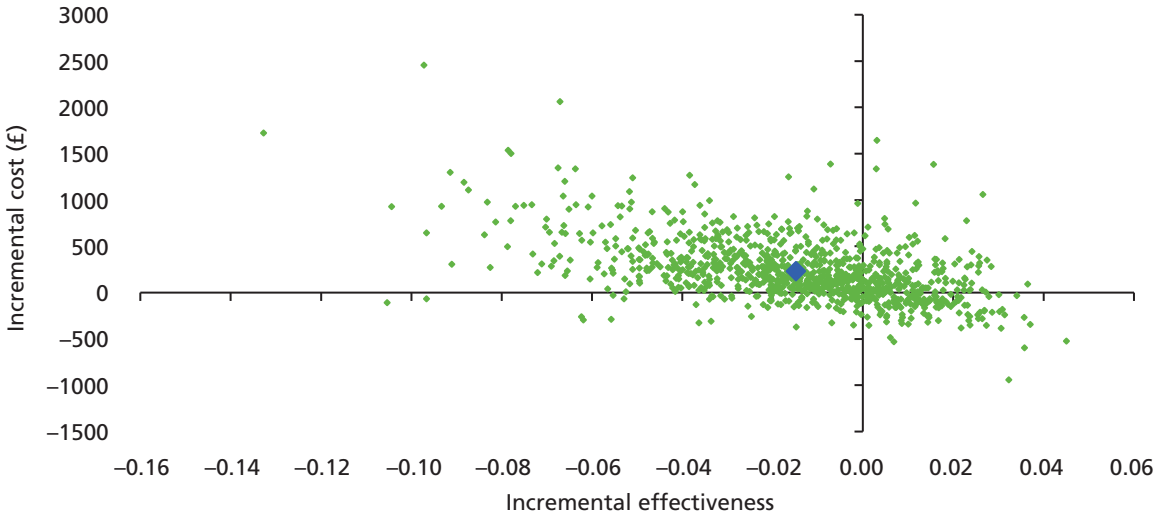

FIGURE 45 Incremental cost-effectiveness scatterplot of intervention compared with care as usual for overweight women: case of GDM averted. The mean of the distribution is shown by the blue diamond.

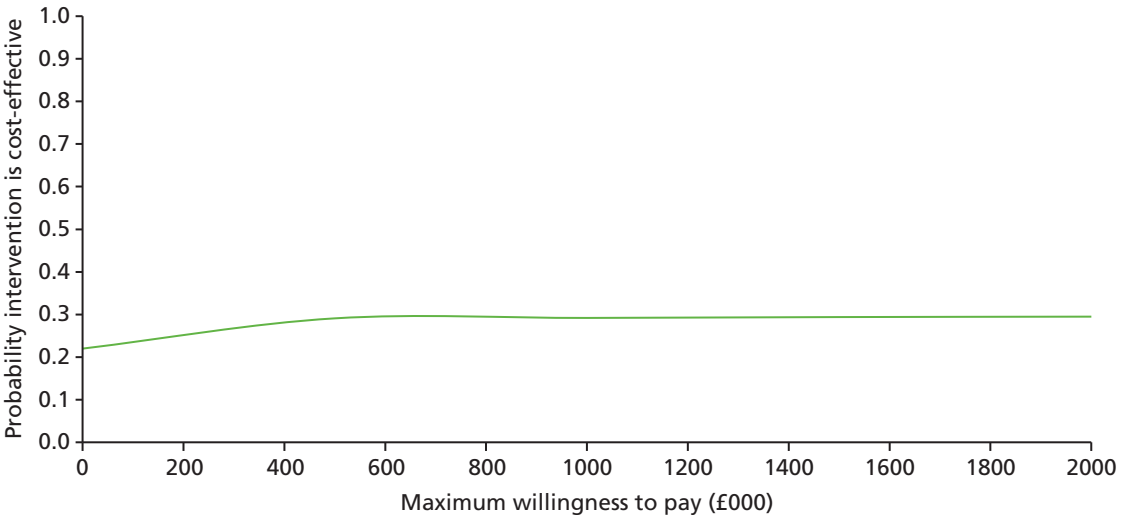

FIGURE 46 Incremental CEAC of intervention for overweight pregnant women: case of GDM averted.

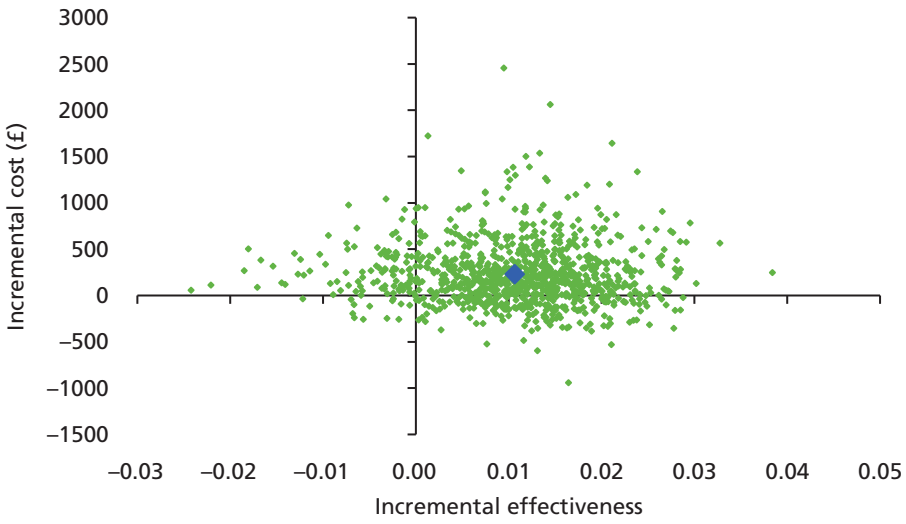

FIGURE 47 Incremental cost-effectiveness scatterplot of intervention compared with care as usual for overweight pregnant women: case of PIH averted. The mean of the distribution is shown by the blue diamond.

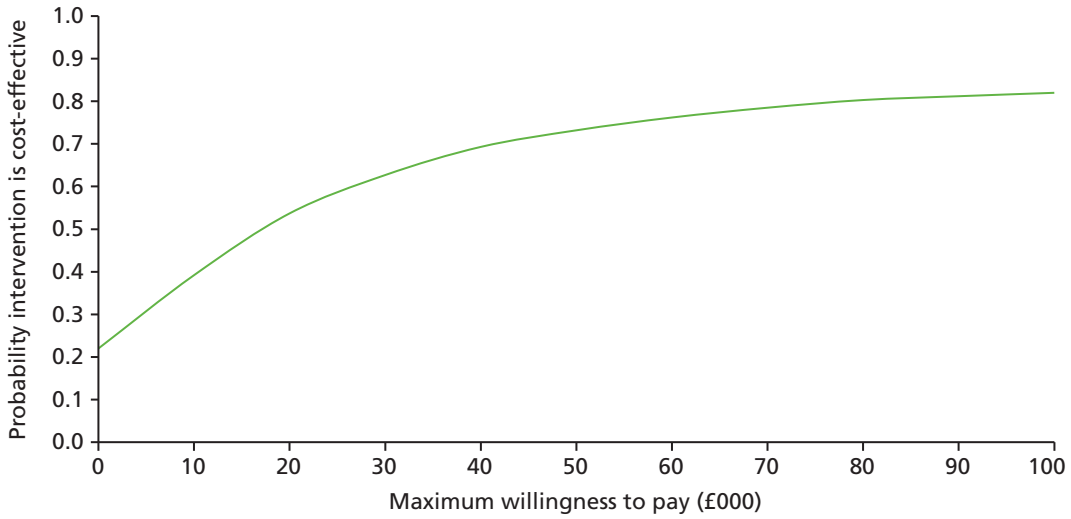

FIGURE 48 Incremental CEAC of intervention for overweight pregnant women: case of PIH averted.

Additional results of probabilistic sensitivity analysis: secondary analysis for a cohort of 10,000 normal weight pregnant women

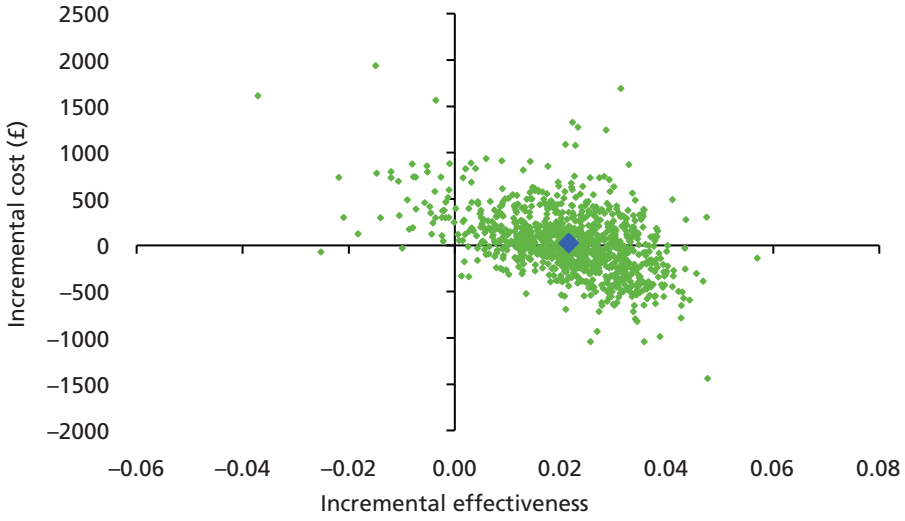

FIGURE 49 Incremental cost-effectiveness scatterplot of intervention compared with care as usual for normal weight pregnant women: case of PE averted. The mean of the distribution is shown by the blue diamond.

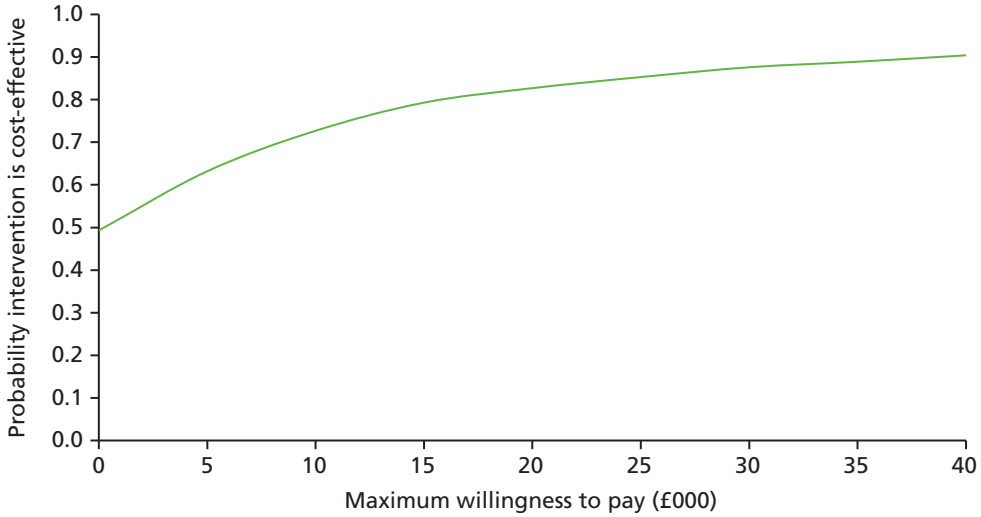

FIGURE 50 Incremental CEAC of intervention for normal weight pregnant women: case of PE averted.

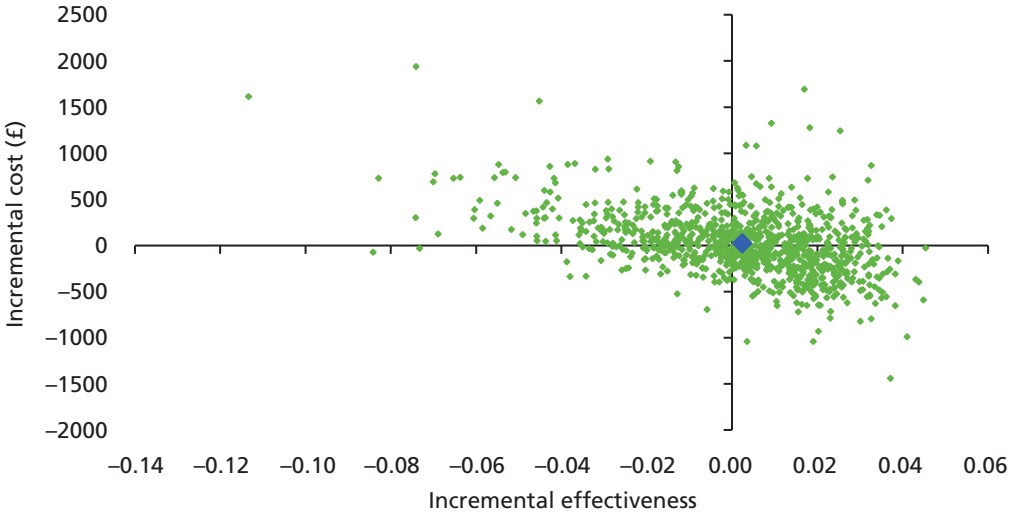

FIGURE 51 Incremental cost-effectiveness scatterplot of intervention compared with care as usual for normal weight pregnant women: case of GDM averted. The mean of the distribution is shown by the blue diamond.

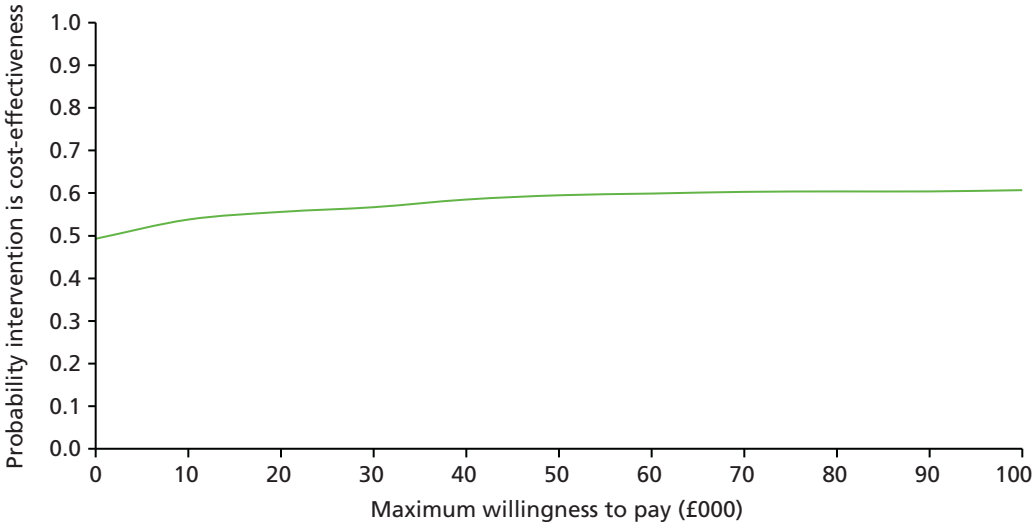

FIGURE 52 Incremental CEAC of intervention for normal weight pregnant women: case of GDM averted.

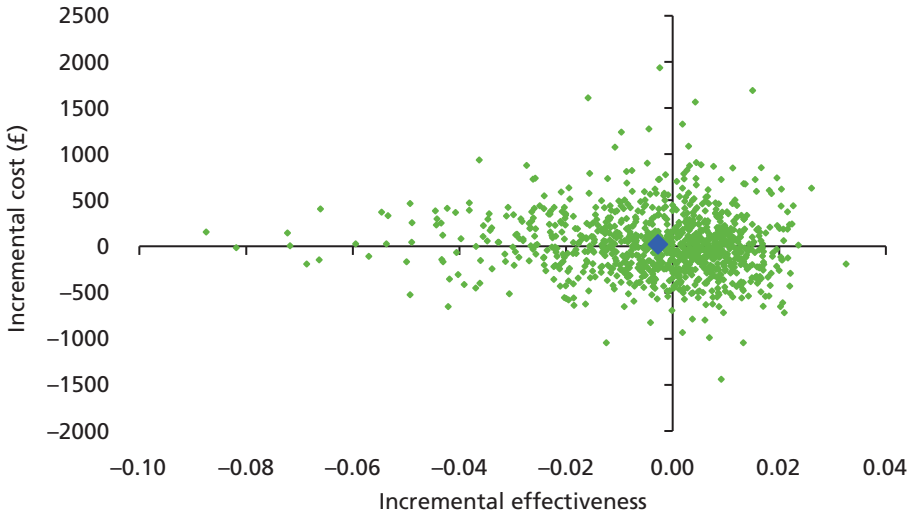

FIGURE 53 Incremental cost-effectiveness scatterplot of intervention compared with care as usual for normal weight pregnant women: case of PIH averted. The mean of the distribution is shown by the blue diamond.

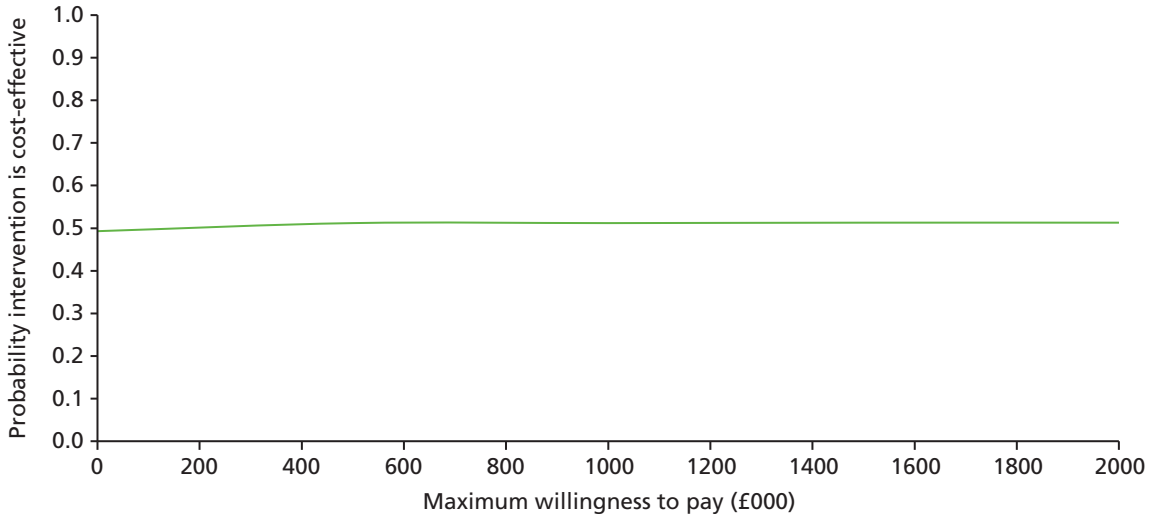

FIGURE 54 Incremental CEAC of intervention for normal weight pregnant women: case of PIH averted.

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