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## Exercise for pregnant women with pre-existing diabetes for improving maternal and fetal outcomes (Protocol)

Brown J, Ceysens G, Boulvain M, West HM

Brown J, Ceysens G, Boulvain M, West HM.

Exercise for pregnant women with pre-existing diabetes for improving maternal and fetal outcomes.

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[Intervention Protocol]

# Exercise for pregnant women with pre-existing diabetes for improving maternal and fetal outcomes

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## ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the effects of exercise interventions for improving maternal and fetal outcomes in women with pre-existing diabetes.

## BACKGROUND

The original review, Exercise for diabetic pregnant women (Ceysens 2006), has been split into two new review titles, to reflect the role of exercise for pregnant women with gestational diabetes and for pregnant women with pre-existing diabetes.

- Exercise for pregnant women with gestational diabetes for improving maternal and fetal outcomes (Ceysens 2016)
- Exercise for pregnant women with pre-existing diabetes for improving maternal and fetal outcomes (this review)

There will be similarities in the background, methods and outcomes between these two systematic reviews. Portions of the methods section of this protocol are based on a standard template used by the Cochrane Pregnancy and Childbirth Review Group.

## Description of the condition

### Diabetes and pregnancy

It is estimated that 2% to 5% of pregnant women have pre-existing or gestational diabetes (CEMACH 2007). Up to 0.4% of women in the UK and 0.9% of pregnant women in the USA and have pre-existing diabetes (type 1 or type 2; CEMACH 2007; Correa 2015). The prevalence of type 1 and type 2 diabetes is increasing. The number of pregnant women with pre-existing type 2 diabetes more than quadrupled in the USA between 1994 and 2004, overtaking the rates of pre-existing type 1 diabetes (0.42% versus 0.33%; Albrecht 2010). This increase in type 2 diabetes in pregnant women has been partly attributed to increasing obesity and older mothers (ACOG 2005; Zhu 2016). Type 2 diabetes has particularly increased in certain minority ethnic groups (including people of African, black Caribbean, South Asian, Middle East-

ern, and Chinese family origin; [CEMACH 2007](#)). An association between type 2 diabetes and socioeconomic status has also been noted ([Correa 2015](#); [Murphy 2009](#)).

Type 1 diabetes tends to begin in childhood, while type 2 diabetes mellitus usually occurs later in adulthood. In type 1 diabetes, sudden onset of insulin deficiency is believed to be caused by an autoimmune attack of the insulin-producing pancreatic beta-cells (cells that store and release insulin; [Galerneau 2004](#); [Griffith 2004](#)). In type 2 diabetes, tissues become resistant to the action of insulin and insulin secretion is disrupted, leading to increasing levels of glucose in the blood ([Dunne 2005](#)).

Gestational diabetes is characterised by glucose intolerance that begins or is first detected during pregnancy. The incidence of gestational diabetes is also increasing as a result of higher rates of obesity in the general population, and more pregnancies in older women. After a pregnancy with gestational diabetes, women have an increased risk of progression to 'pre-existing' diabetes (i.e. type 2 diabetes) in the next pregnancy ([Khambalia 2013](#)).

### Adverse outcomes for women and infants associated with pre-existing diabetes

Pregnancies with pre-existing diabetes are high risk, with increased risk of poorer fetal, neonatal, and maternal outcomes ([Owens 2015](#)). Women with type 1 diabetes have an elevated risk of pregnancy loss, perinatal mortality, fetal macrosomia (a fetus that is large-for-gestational age), and congenital malformations ([NICE 2015](#); [Platt 2002](#)). This is also the case for women with pre-existing type 2 diabetes ([CEMACH 2007](#); [Inkster 2006](#)), although neonatal outcomes may be poorer when the mother has type 1 diabetes ([Owens 2015](#)). However, a systematic review found perinatal mortality to be higher for women with type 2 compared with type 1 diabetes (odds ratio 1.50, 95% confidence interval 1.15 to 1.96; [Balsells 2009](#)).

Organogenesis (development of organs) in early pregnancy can be affected by metabolic disruptions when there are high concentrations of maternal blood glucose. Cardiovascular malformations are the most common birth defects in infants born to diabetic mothers ([Inkster 2006](#)). Apart from macrosomia (high birthweight, often defined as more than 4000 g), other adverse outcomes for infants may include large-for-gestational age, shoulder dystocia (difficulty in delivering shoulders of baby), neonatal hypoglycaemia (blood sugar that is lower than normal), preterm birth, hyperbilirubinaemia (excess bilirubin), hypocalcaemia (lower than normal calcium), and neonatal intensive care admission ([Jensen 2004](#); [Macintosh 2006](#); [Ray 2001](#); [Walkinshaw 2005](#); [Weintrob 1996](#)). Long-term follow-up of the infants of diabetic mothers suggests that they may also have an increased risk of obesity and type 2 diabetes when older ([Dabelea 2000](#)).

In pregnant women with type 1 (insulin-dependent) diabetes, insulin is used to control fluctuations in blood glucose concentrations throughout the day ([Galerneau 2004](#)). In type 2 diabetes,

lifestyle changes (including diet and exercise) are the first line of treatment, with the option of using oral hypoglycaemic agents or insulin to lower blood glucose if necessary. Therefore, management of diabetes in pregnancy aims for control of glucose concentrations using careful combinations of diet, exercise, and insulin or other anti-diabetogenic drugs, if required ([ACOG 2005](#); [NICE 2015](#)).

### Description of the intervention

The American College of Sports Medicine defines physical activity as any bodily movement that is produced as a result of the contraction of skeletal muscle, and defines exercise as physical activity comprising planned, structured, and repetitive body movements, which are undertaken to improve one or more components of physical fitness ([ACSM 2014](#)).

Physical activity in non-diabetic pregnant women has been shown to be beneficial. It was not shown to be harmful to the fetus and can potentially lead to long-term health benefits for the mother. Benefits observed include cardio-respiratory fitness, prevention of stress urinary incontinence, prevention of lumbar pain, decreased depression, and control of weight gain during pregnancy ([Nascimento 2012](#)).

In women with type 2 diabetes who were not pregnant, physical activity, combined with diet and hypoglycaemic medication has been shown to be effective in maintaining glycaemic control ([Tuomilehto 2001](#)).

This evidence may not be generalisable to pregnant women with pre-existing diabetes, but it does suggest that mild exercise during pregnancy may have the potential to reduce the risk of complications associated with pre-existing diabetes.

The American College of Obstetricians and Gynecologists notes that physical activity during pregnancy appears to have benefits for most women and has few risks associated with it, although some adaptation may be required, due to anatomical and physiological changes in pregnancy ([ACOG 2015](#)). They recommend that pregnant women have a clinical evaluation prior to starting an exercise programme, to ensure that there are no medical contraindications, and that women be encouraged to participate in aerobic and strength-conditioning exercises before, during, and after uncomplicated pregnancies.

[ACOG 2015](#) recommends that aerobic exercise during pregnancy is contraindicated in a number of medical conditions, including:

1. cardiac disease;
2. restrictive lung disease;
3. incompetent cervix or cerclage;
4. multiple gestation at risk of preterm birth;
5. persistent second or third trimester bleeding;
6. placenta praevia after 26 weeks' gestation;
7. preterm labour (current pregnancy);
8. ruptured membranes;
9. pre-eclampsia or pregnancy-induced hypertension;

10. severe anaemia.

ACOG 2015 considers these activities are safe to continue with, or initiate during an uncomplicated pregnancy, following medical advice:

1. walking;
2. swimming;
3. stationary cycling;
4. low-impact aerobics;
5. modified yoga (avoiding positions that result in decreased venous return);
6. modified Pilates;
7. racquet sports;
8. running or jogging;
9. strength training.

However, running, jogging, or strength training should only be undertaken after consultation with an obstetrical care provider (ACOG 2015). During pregnancy, the duration, frequency, and intensity of physical activity may have to be modified (Nascimento 2012).

ACOG 2015 recommends avoiding these activities during pregnancy:

1. contact sports (e.g. ice hockey, soccer, boxing);
2. activities with a high risk of falling (e.g. skiing, surfing, off-road cycling);
3. scuba diving;
4. sky diving;
5. 'hot yoga' or 'hot Pilates'.

## How the intervention might work

Physical activity may improve glycaemic control in those with types 1 and 2 diabetes because of the interaction between insulin sensitivity and the uptake of glucose by skeletal muscles (Asano 2014). Skeletal muscle takes glucose from the blood using a membrane transporter; improved insulin sensitivity following regular physical activity can increase the efficiency of this transport mechanism (Chibalin 2000; Dela 1993; Hjeltnes 1998).

## Why it is important to do this review

Pre-existing diabetes during pregnancy is associated with short- and long-term adverse effects for the woman and her infant. Identifying interventions to improving health outcomes for women with diabetes and their infants is a priority, as rates of diabetes continue to increase. Exercise has been shown to have benefits for non-pregnant individuals with pre-existing type 2 diabetes, such as improving glycaemic control, and reducing visceral adipose tissue and plasma triglycerides (Thomas 2006). The benefits and safety for a woman during pregnancy and for her baby remains unclear.

## OBJECTIVES

To evaluate the effects of exercise interventions for improving maternal and fetal outcomes in women with pre-existing diabetes.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include published or unpublished randomised controlled trials or cluster-randomised trials in full text or abstract format. Quasi-randomised and cross-over trials will be excluded. Conference abstracts will be handled in the same way as full-text publications.

#### Types of participants

Pregnant women diagnosed with pre-gestational diabetes (type 1 or type 2 diabetes), as defined by the trialists. Women with gestational diabetes mellitus (GDM) will be excluded, as this will be covered in a separate Cochrane review (Ceysens 2016).

#### Types of interventions

We will include any type of exercise programme, added to standard care, targeted at women with known pre-gestational diabetes (type 1 or type 2 diabetes), at any stage of pregnancy compared with 1) standard care alone or 2) standard care plus another intervention.

#### Types of outcome measures

##### Primary outcomes

##### Mother

1. Hypertensive disorders of pregnancy (as reported by the trialists, and including pre-eclampsia, pregnancy-induced hypertension, eclampsia);
2. Caesarean section.

### Neonate and infant

1. Large-for-gestational age (more than 4 kg);
2. Perinatal mortality (stillbirth and neonatal mortality);
3. Mortality or morbidity composite (variously defined by trials, e.g. perinatal or infant death, shoulder dystocia, bone fracture or nerve palsy);
4. Neurosensory disability (defined as any of the following: legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, developmental delay or impairment (defined as developmental quotient less than two standard deviations (SDs) below the mean).

### Secondary outcomes

#### Short-term maternal outcomes

1. Induction of labour;
2. Perineal trauma;
3. Placental abruption;
4. Postpartum haemorrhage (more than 500 mL blood loss, or otherwise defined by trialists);
5. Postpartum infection (as defined by trialists);
6. Weight gain during pregnancy;
7. Adherence to the intervention;
8. Behaviour changes associated with the intervention;
9. Relevant biomarker changes associated with the intervention (e.g. adiponectin, free fatty acids, triglycerides, high density lipoproteins, low density lipoproteins, insulin);
10. Sense of well-being and quality of life (as defined by trialists);
11. Views of the intervention;
12. Breastfeeding (e.g. at discharge, six weeks postpartum);
13. Use of additional pharmacotherapy;
14. Glycaemic control during and at the end of treatment (as defined by trialists);
15. Maternal hypoglycaemia;
16. Maternal mortality.

#### Long-term maternal outcomes

1. Postnatal depression (as defined by trialists);
2. Postnatal weight retention or return to pre-pregnancy weight;
3. Body mass index (BMI);
4. Cardiovascular health (as defined by trialists, including blood pressure (BP), hypertension, cardiovascular disease, metabolic syndrome).

#### Neonatal and infant outcomes

1. Stillbirth;

2. Neonatal mortality;
3. Gestational age at birth;
4. Preterm birth (less than 37 weeks' gestation, and less than 32 weeks' gestation);
5. Apgar score (less than seven at five minutes);
6. Macrosomia (higher than 90<sup>th</sup> percentile);
7. Small-for-gestational age (lower than 10<sup>th</sup> percentile);
8. Birthweight and z-score;
9. Head circumference and z-score;
10. Length and z-score;
11. Ponderal index;
12. Adiposity (including skin fold thickness, neonatal fat mass);
13. Shoulder dystocia;
14. Bone fracture;
15. Nerve palsy;
16. Respiratory distress syndrome;
17. Hypoglycaemia requiring treatment (as defined by trialists);
18. Hyperbilirubinaemia (as defined by trialists);
19. Neonatal hypocalcaemia (as defined by trialists);
20. Polycythaemia (as defined by trialists);
21. Relevant biomarker changes associated with the intervention (e.g. cord C-peptide, cord insulin).

#### Later infant and childhood outcomes

1. Weight and z-scores;
2. Height and z-scores;
3. Head circumference and z-scores;
4. Adiposity (e.g. as measured by BMI, skinfold thickness);
5. BP;
6. Type 1 diabetes;
7. Type 2 diabetes;
8. Impaired glucose tolerance;
9. Dyslipidaemia or metabolic syndrome;
10. Educational achievement.

#### Child and adult outcomes

1. Weight;
2. Height;
3. Adiposity (e.g. as measured by BMI, skinfold thickness);
4. Cardiovascular health (as defined by trialists, including BP, hypertension, cardiovascular disease, metabolic syndrome);
5. Type 1 diabetes;
6. Type 2 diabetes;
7. Impaired glucose tolerance (as defined by trialists);
8. Dyslipidaemia or metabolic syndrome (as defined by trialists);
9. Employment, education, social status and achievement.

#### Health service use

1. Number of hospital or health professional visits (e.g. midwife, obstetrician, physician, dietitian, diabetic nurse);
2. Number of antenatal visits or admissions;
3. Length of antenatal stay;
4. Neonatal intensive care unit admission;
5. Length of postnatal stay (mother);
6. Length of postnatal stay (baby);
7. Costs to families associated with the management provided;
8. Costs associated with the intervention;
9. Cost of maternal care;
10. Cost of offspring care.

## Search methods for identification of studies

The following methods sections of this protocol are based on a standard template used by Cochrane Pregnancy and Childbirth.

### Electronic searches

We will search Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist.

The Register is a database containing over 22,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate Pregnancy and Childbirth's Trials Register, including the detailed search strategies for CENTRAL, MEDLINE, Embase, and CINAHL, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about [Cochrane Pregnancy and Childbirth](#) in the Cochrane Library, and select the 'Specialized Register' section from the options on the left side of the screen.

Briefly, the Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals, plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that will be fully

accounted for in the relevant review sections (Included, Excluded, Awaiting Classification, or Ongoing).

In addition, we will search [ClinicalTrials.gov](#) and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned, and ongoing trial reports. The search terms we will use are given in [Appendix 1](#).

### Searching other resources

We will search the reference lists of retrieved studies. We will not apply any language or date restrictions.

## Data collection and analysis

### Selection of studies

Two review authors will independently assess for inclusion, all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion, or if required, we will consult a third person.

We will create a study flow diagram to map out the number of records identified, included, and excluded.

### Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will independently extract the data using the agreed form. We will resolve discrepancies through discussion, or if required, we will consult a third person. We will enter data into Review Manager 5 software and check for accuracy ([RevMan 2014](#)). When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

### Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We will resolve any disagreement by discussion, or by involving a third assessor.

#### (I) Random sequence generation (checking for possible selection bias)

For each included study, we will describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);



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

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

For each included study, we will describe the method used to conceal allocation to interventions prior to assignment, and will assess whether intervention allocation could have been foreseen in advance of, during recruitment, or changed after assignment.

We will assess the methods as:

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

**(3.1) Blinding of participants and personnel (checking for possible performance bias)**

For each included study, we will describe the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high, or unclear risk of bias for participants;
- low, high, or unclear risk of bias for personnel.

**(3.2) Blinding of outcome assessment (checking for possible detection bias)**

For each included study, we will describe the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high, or unclear risk of bias.

**(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data)**

For each included study, and for each outcome or class of outcomes, we will describe the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported, and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related

to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses that we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

**(5) Selective reporting (checking for reporting bias)**

For each included study, we will describe how we investigated the possibility of selective outcome reporting bias and what we found.

We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

**(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)**

For each included study, we will describe any important concerns we have about other possible sources of bias.

We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

**(7) Overall risk of bias**

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - see [Sensitivity analysis](#).

## Assessment of the quality of the evidence using the GRADE approach

The quality of the evidence will be assessed for outcomes relating to the mother and for the infant, child, or adult for the main comparisons, using the GRADE approach, outlined in the [GRADE handbook](#) and Chapters 11 and 12 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011).

### Maternal

1. Hypertensive disorders of pregnancy (as reported by trialists, including pre-eclampsia, pregnancy-induced hypertension, eclampsia)
2. Caesarean section
3. Perineal trauma
4. Postnatal weight retention or return to pre-pregnancy weight
5. Postnatal depression (as defined by trialists)
6. Induction of labour

### Child (as a fetus, neonate, child, adult)

1. Large-for-gestational age (more than 4 kg)
2. Perinatal mortality (stillbirth and neonatal mortality)
3. Mortality and morbidity composite (variously defined by trials, e.g. perinatal or infant death, shoulder dystocia, bone fracture or nerve palsy)
4. Hypoglycaemia requiring treatment (as defined by trialists)
5. Adiposity (including skin fold thickness, neonatal fat mass)\*
6. Diabetes (type 1, type 2)\*
7. Neurosensory disability (defined as any of the following: legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, developmental delay or impairment (defined as developmental quotient less than two standard deviations (SDs) below the mean)

[GRADEpro](#) Guideline Development Tool will be used to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes will be produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

\*These outcomes will be reported for each stage of life where data are reported.

## Measures of treatment effect

### Dichotomous data

For dichotomous data, we will present results as a summary risk ratio (RR) with 95% confidence intervals (CI).

### Continuous data

For continuous data, we will use the mean difference (MD) with 95% CI if outcomes are measured in the same way between trials. We will use the standardised mean difference (SMD) with 95% CI to combine trials that measure the same outcome, but use different methods.

### Unit of analysis issues

#### Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. If any included studies are cluster-randomised trials, we will make adjustments using the methods described in the *Cochrane Handbook of Systematic Reviews for Interventions* (Section 16.3.4 or 16.3.6), using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial, or from a study of a similar population (Higgins 2011). If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. We will consider it reasonable to combine the results from both cluster-randomised trials and individually-randomised trials if there is little heterogeneity between the study designs, and is unlikely there will be an interaction between the effect of intervention and the choice of randomisation unit. If cluster-randomised trials are included, we will seek statistical advice on the appropriate analysis to enable us to include the data in the meta-analyses.

#### Other unit of analysis issues

#### Multiple pregnancy

There may be unit of analysis issues that arise when the women randomised have a multiple pregnancy. We will present maternal data as per woman randomised, and neonatal data per infant.

### Multiple-arm studies

Where a trial has multiple intervention arms, we will avoid 'double counting' participants by combining groups to create a single pairwise comparison, if possible. Where this is not possible, we will split the 'shared' group into two or more groups with smaller sample sizes, and include two or more (reasonably independent) comparisons.

### Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by performing a sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

### Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the  $Tau^2$ ,  $I^2$ , and  $Chi^2$  statistics. We will regard heterogeneity as substantial, if  $I^2$  is greater than 30%, and either  $Tau^2$  is greater than zero, or there is a low P value (less than 0.10) in the  $Chi^2$  test for heterogeneity.

### Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

### Data synthesis

We will carry out statistical analysis using the Review Manager 5 software (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary

will be treated as the average of the range of possible treatment effects, and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of  $Tau^2$  and  $I^2$ .

### Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses.

1. Group exercise versus individual exercise;
2. Low-intensity exercise (cumulative duration of exercise at 50%  $VO_2$  max (maximal oxygen consumption) for shorter than 180 minutes) versus high-intensity exercise (cumulative duration of exercise at 50%  $VO_2$  max) for longer than 180 minutes.

We will test the following primary outcomes in subgroup analysis.

#### Maternal outcomes

1. Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia);
2. Caesarean section

#### Neonatal outcomes

1. Large-for-gestational age;
2. Perinatal mortality (stillbirth and neonatal mortality);
3. Mortality or morbidity composite (variously defined by trials, e.g. perinatal or infant death, shoulder dystocia, bone fracture, or nerve palsy);
4. Neurosensory disability.

We will assess subgroup differences with the interaction tests available within RevMan 5 (RevMan 2014). We will report the results of subgroup analyses quoting the  $Chi^2$  statistic and P value, and the  $I^2$  value.

### Sensitivity analysis

If there is evidence of substantial heterogeneity, we will explore this by assessing the impact of the risks of bias of the included trials for the primary outcomes.

#### Maternal outcomes

1. Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia);
2. Caesarean section

#### Neonatal outcomes

1. Large-for-gestational age;
2. Perinatal mortality (stillbirth and neonatal mortality);
3. Mortality or morbidity composite (variously defined by trials, e.g. perinatal or infant death, shoulder dystocia, bone fracture, or nerve palsy);

#### 4. Neurosensory disability.

We will compare trials that have low risk of bias for allocation concealment with those judged to be of unclear or high risk of bias; conference abstracts will be excluded from the meta-analysis. We will also investigate the effect of the randomisation unit (i.e. where we include cluster-randomised trials along with individually-randomised trials).

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As part of the pre-publication editorial process, this protocol has been commented on by two peers (an editor and referee who is external to the editorial team), members of Cochrane Pregnancy and Childbirth's international panel of consumers, and the Group's Statistical Adviser.

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\* Indicates the major publication for the study

## APPENDICES

### Appendix I. Search terms for ICTRP and ClinicalTrials.gov

exercise AND diabetes AND pregnancy

## CONTRIBUTIONS OF AUTHORS

Dr Gilles Ceysens and Dr Michel Boulvain prepared the original 2006 protocol and review upon which this review is based ([Ceysens 2006](#)). The development of the protocol has been supported by Dr Julie Brown and Dr Helen West, who provided methodological support. Dr Brown is the guarantor for this review.

## DECLARATIONS OF INTEREST

Dr Gilles Ceysens - none known.

Dr Julie Brown - none known.

Dr Michel Boulvain received research funding from Centre de Recherche Clinique (Advanced researcher grant scheme (2007-2010)) to study exercise in pregnancy. One of the studies was a randomised controlled trial evaluating the effects of exercise in women with gestational diabetes. This study will not be eligible for inclusion in this review, but may be eligible for inclusion in the review on exercise for pregnant women with gestational diabetes - Michel Boulvain will not be involved in any decisions relating to the inclusion of his own study in this review. All tasks relating to that study (assessment for inclusion, risk of bias, data extraction) will be carried out by the other members of the review team who were not directly involved in the trial. In 2012, he was invited to speak at the DIP 2012 Congress on gestational diabetes and was reimbursed for travel and accommodation.

Dr Helen West was paid to work on Cochrane reviews by a grant to Cochrane Pregnancy and Childbirth. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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### **Internal sources**

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### **External sources**

- (HW) NIHR Cochrane Programme Grant Project: 13/89/05 - Pregnancy and childbirth systematic reviews to support clinical guidelines, UK.