

Impact of prenatal exercise on neonatal and childhood outcomes: a systematic review and meta-analysis

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ABSTRACT

Objective We aimed to identify the relationship between maternal prenatal exercise and birth complications, and neonatal and childhood morphometric, metabolic and developmental outcomes.

Design Systematic review with random-effects meta-analysis and meta-regression.

Data sources Online databases were searched up to 6 January 2017.

Study eligibility criteria Studies of all designs were eligible (except case studies and reviews) if published in English, Spanish or French, and contained information on the relevant population (pregnant women without contraindication to exercise), intervention (subjective/objective measures of frequency, intensity, duration, volume or type of exercise, alone ('exercise-only') or in combination with other intervention components (eg, dietary; 'exercise+cointervention')), comparator (no exercise or different frequency, intensity, duration, volume, type or trimester of exercise) and outcomes (preterm birth, gestational age at delivery, birth weight, low birth weight (<2500 g), high birth weight (>4000 g), small for gestational age, large for gestational age, intrauterine growth restriction, neonatal hypoglycaemia, metabolic acidosis (cord blood pH, base excess), hyperbilirubinaemia, Apgar scores, neonatal intensive care unit admittance, shoulder dystocia, brachial plexus injury, neonatal body composition (per cent body fat, body weight, body mass index (BMI), ponderal index), childhood obesity (per cent body fat, body weight, BMI) and developmental milestones (including cognitive, psychosocial, motor skills)).

Results A total of 135 studies (n=166 094) were included. There was 'high' quality evidence from exercise-only randomised controlled trials (RCTs) showing a 39% reduction in the odds of having a baby >4000 g (macrosomia: 15 RCTs, n=3670; OR 0.61, 95% CI 0.41 to 0.92) in women who exercised compared with women who did not exercise, without affecting the odds of growth-restricted, preterm or low birth weight babies. Prenatal exercise was not associated with the other neonatal or infant outcomes that were examined.

Conclusions Prenatal exercise is safe and beneficial for the fetus. Maternal exercise was associated with reduced odds of macrosomia (abnormally large babies) and was not associated with neonatal complications or adverse childhood outcomes.

INTRODUCTION

Neonatal outcomes, such as premature birth, small-for-gestational age (SGA) or large-for-gestational age (LGA) birth weight, and intrauterine growth restriction (IUGR), are associated with increased risk of infant morbidity and mortality.^{1 2} Neonates born prematurely and/or growth-restricted (SGA or IUGR) are more likely to require admission to the neonatal intensive care unit (NICU) after delivery, have greater risk of infection, and suffer from respiratory and metabolic disorders in infancy.^{3 4} Babies born LGA are more likely to be delivered by caesarean section, experience shoulder dystocia during delivery, and have hypoglycaemia or jaundice.^{5 6} Such neonatal complications are increased in pregnant women who are overweight or obese,⁷ have excessive gestational weight gain,⁸ and/or develop cardiovascular and metabolic disorders during pregnancy.^{9–11} Other reviews in this special issue^{12 13} have shown the positive effects of prenatal physical activity on each of these maternal risk factors for neonatal complications.

In addition to the short-term impact of neonatal complications, there is increasing evidence that neonatal complications are associated with negative long-term effects on childhood development (eg, neurodevelopment scores)¹⁴ and health across the lifespan (eg, obesity, diabetes, cardiovascular disease).^{15–18} Whether maternal physical activity impacts the incidence of neonatal complications^{17–23} is not known.

Since the first guidelines for prenatal exercise were developed by the American College of Obstetricians and Gynecologists in 1985,²⁴ a growing body of literature has overwhelmingly demonstrated the safety and benefits of exercise for the mother.^{12 13 25–32} Despite this, only 9%–15% of pregnant women^{33 34} meet the current physical activity recommendations of moderate-intensity activity for 150 min per week,^{35 36} with some women concerned that prenatal exercise may harm the fetus.³⁷ Although such risks of activity have not been substantiated within the literature,^{38–42} the associations between maternal physical activity and short-term neonatal outcomes are yet to be fully elucidated.^{38–46}

The present systematic review and meta-analysis was conducted as part of a series of reviews that



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form the evidence base for the development of the 2019 *Canadian guideline for physical activity throughout pregnancy* (herein referred to as the *Guideline*).⁴⁷ The purpose of this review was to evaluate the effect of prenatal exercise on neonatal and childhood health outcomes, and to establish whether a dose–response relationship existed between frequency, intensity and volume of maternal exercise, and the outcomes of interest, specifically (1) birth complications, and (2) neonatal and childhood morphometric, metabolic and developmental outcomes.

METHODS

In October 2015, the Guidelines Consensus Panel assembled to identify priority outcomes for the *Guideline* development. The Guidelines Consensus Panel included researchers, methodological experts, a fitness professional, and representatives from the Canadian Society for Exercise Physiology (CSEP), the Society of Obstetricians and Gynaecologists of Canada (SOGC), the College of Family Physicians of Canada, the Canadian Association of Midwives, the Canadian Academy of Sport and Exercise Medicine, Exercise is Medicine Canada, and a representative health unit (the Middlesex-London Health Unit). The Guidelines Consensus Panel selected 20 ‘critical’ and 17 ‘important’ outcomes related to prenatal exercise and maternal/fetal health. Six of the ‘critical’ outcomes and six of the ‘important’ outcomes were examined in this review. This systematic review and meta-analysis was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the checklist was completed.⁴⁸

Protocol and registration

Two systematic reviews examining the impact of prenatal exercise on fetal and maternal health outcomes were registered a priori with PROSPERO, the International Prospective Register of Systematic Reviews (*fetal health*: trial registration number CRD42016029869; *maternal health*: trial registration number CRD42016032376). Since the relationships between prenatal exercise and neonatal outcomes were examined in studies related to both fetal and maternal health, records retrieved from both of these reviews were evaluated for inclusion in the present study.

Eligibility criteria

The PICOS (population, intervention, comparison, outcome and study design) framework⁴⁹ was used to guide this review.

Population

The population of interest was pregnant women without absolute or relative contraindication to exercise (according to the SOGC/CSEP and the American College of Obstetricians and Gynecologists guidelines; see online supplementary materials for more details).^{35 50} Absolute contraindications to exercise were defined as high-order pregnancy, gestational hypertension, pre-eclampsia, uncontrolled type 1 diabetes, hypertension or thyroid disease, or other serious cardiovascular, respiratory or systemic disorders, persistent second or third trimester bleeding, placenta previa, incompetent cervix, IUGR, ruptured membranes, and premature labour. Relative contraindications were defined as a history of spontaneous abortion or premature labour, mild/moderate cardiovascular or respiratory disease, anaemia, iron deficiency, malnutrition, eating disorder, twin pregnancy after 28 weeks or other significant medical conditions.^{35 50}

Intervention (exposure)

The intervention/exposure of interest was subjective or objective measures of frequency, intensity, duration, volume or type of exercise. Although exercise is a subtype of physical activity, for the purpose of this review the terms are used interchangeably. Exercise and physical activity were defined as any bodily movement generated by the skeletal muscles that resulted in energy expenditure above the resting levels.⁵¹ Acute (ie, a single exercise session) or habitual (ie, usual activity) prenatal exercise, as well as interventions including exercise alone (termed ‘exercise-only’ interventions, which could include standard care) or in combination with other interventions (such as diet; termed ‘exercise+cointerventions’), were considered. Studies were not eligible if exercise was performed after the beginning of labour.

Comparison

Eligible comparators were no exercise; different frequency, intensity, duration, volume or type of exercise; different intervention duration; or exercise in a different trimester.

Outcome

Relevant ‘critical’ outcomes were preterm birth, low birth weight (<2500 g), high birth weight (>4000 g), SGA, LGA, IUGR, neonatal hypoglycaemia and childhood obesity (up to 18 years; per cent body fat, body weight, body mass index (BMI)). Relevant ‘important’ outcomes included gestational age, birth weight, metabolic acidosis (cord blood pH, base excess), hyperbilirubinaemia, Apgar scores, NICU admittance, shoulder dystocia, brachial plexus injury, neonatal body composition (per cent body fat, fat mass, body weight, BMI, ponderal index) and developmental milestones (ie, cognitive, psychosocial, motor skills).

Study design

Primary studies of any design were eligible, except for case studies (n=1) or reviews. A staged approach was used to determine inclusion of study designs other than randomised controlled trials (RCTs), as follows. For each outcome, evidence from RCTs was initially examined. If fewer than 2000 women were included in the meta-analysis of RCTs for a given outcome, the impact of prenatal exercise on the specific outcome was explored further using evidence from observational studies (non-randomised interventions, cohort, cross-sectional and case–control studies).

Information sources

A comprehensive search was created and run by a research librarian (LGS) in the following databases: MEDLINE, EMBASE, PsycINFO, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Scopus and Web of Science Core Collection, CINAHL Plus with Full Text, Child Development & Adolescent Studies, Education Resources Information Center, SPORTDiscus, ClinicalTrials.gov and the Trip Database up to 6 January 2017 (see online supplementary materials for complete search strategies).

Study selection and data extraction

Two independent reviewers screened the titles and abstracts of all retrieved articles. Abstracts that were judged to have met the initial screening criteria by at least one reviewer were retrieved as full-text articles. Full-text articles were reviewed for relevant PICO information by two independent reviewers. If there was a difference of opinion regarding inclusion, the characteristics of the study were presented to the Guidelines Steering Committee who oversaw the systematic reviews (MHD, MFM, S-MR, CEG,

VJP, AJG and NB), and a final decision was made by consensus. All included studies were imported into DistillerSR (Evidence Partners, Ottawa, Ontario, Canada) for data extraction. At this point, studies from the maternal and fetal reviews that were included were de-duplicated against one another in DistillerSR and were considered as one review from this point forward.

Data extraction tables were created in DistillerSR in consultation with methodological experts and the Guidelines Steering Committee. Data were extracted by one person; a content expert (MHD, MFM or S-MR) then independently verified the extracted data. Reviewers were not blinded to study authors. For each single study, the most recent or complete version (publication) was selected as the 'parent' paper; however, relevant data from all publications related to each unique study were extracted. Information on study characteristics (ie, year, study design, country) and population characteristics (eg, number of participants, age, prepregnancy BMI, parity and pregnancy complications), intervention/exposure (measured and/or prescribed exercise frequency, intensity, duration and type, duration of the intervention, measure of physical activity) and outcomes was extracted (online supplementary table 1). If data were not available for extraction, attempts were made to contact the corresponding authors for additional information.

Quality of evidence assessment

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to assess the quality of evidence across studies for each study design and health outcome.

Accordingly, evidence from RCTs was considered 'high' quality and evidence from non-randomised studies was considered 'low' quality unless it was graded down based on concerns with risk of bias, indirectness, inconsistency or imprecision because the presence of these factors reduce the level of confidence in the observed effects. The risk of bias in RCTs and non-randomised intervention studies was assessed following the Cochrane Handbook,⁵² and the risk of bias in observational studies was assessed using the characteristics recommended by Guyatt *et al.*⁵³ All studies were assessed for potential sources of selection bias, reporting bias, performance bias, detection bias, attrition bias and 'other' sources of bias. Risk of bias across studies was rated as 'serious' when studies with the greatest influence on the pooled result (assessed using weight (%) given in forest plots or sample size in studies that were narratively synthesised) presented 'high' risk of bias. The greatest influence on the pooled result was determined as follows: the studies that had the greatest individual % contribution in the meta-analyses, when taken together, contribute to >50% of the weight of the pooled estimate. Additionally, studies were considered to reflect a serious risk of bias when the sample size of narratively synthesised studies was similar to the total sample size of studies contributing to >50% of the weight of the pooled estimate in the meta-analyses. Given the nature of exercise interventions, it is not possible to blind participants to group allocation, and the risk of selection bias was rated as 'low' if this was the only source of bias identified. Performance bias was rated as 'high' when <60% of participants performed 100% of prescribed exercise sessions or attended 100% of counselling sessions (defined as low compliance), or when compliance to the intervention was not reported. Attrition bias was rated as 'high' when >10% of data were missing at the end of the study and intention-to-treat analysis was not used.

Inconsistency across studies was considered serious when heterogeneity was high ($I^2 \geq 50\%$) or when only one study was assessed (I^2 unavailable). Indirectness was considered serious

when the effect of exercise+cointervention on an outcome was assessed. Imprecision was considered serious when the 95% CI crossed the line of no effect, and was wide, such that interpretation of the data would be different if the true effect were at one end of the CI or the other. When only one study was assessed, imprecision was not considered serious because inconsistency was already considered serious for this reason. For birth weight the 95% CI was considered wide if it was >500 g (as determined by the Guidelines Consensus Panel). Finally, publication bias was assessed if possible (ie, at least 10 studies were included in the forest plot) via funnel plots (see online supplementary materials). If there were fewer than 10 studies, publication bias was deemed non-estimable and not rated down. If there were no important threats to validity, the quality of the evidence was eligible to be upgraded if there was a large magnitude of effect and there was evidence of a dose-response gradient in the findings.⁵⁴

Due to time constraints and feasibility, one reviewer evaluated the quality of evidence across each health outcome using the protocol, and a second person reviewed the GRADE tables as a quality control measure. Quality of evidence assessment is presented in online supplementary tables 2–17.

Evidence synthesis: statistical analysis and narrative synthesis

Statistical analyses were conducted using Review Manager V.5.3 (Cochrane Collaboration, Copenhagen, Denmark). Statistical significance was set at $p < 0.05$. Odds ratios (ORs) were calculated for all dichotomous outcomes. Inverse-variance weighting was applied to obtain ORs using a random-effects model. For continuous outcomes, mean differences (MD) between the exercise and control groups were calculated. Separate meta-analyses were performed according to study design (in cases where multiple study designs were included, as per the staged approach described earlier). For RCTs and non-randomised interventions, sensitivity analyses were performed to evaluate whether the effects were different when examining relationships between exercise-only interventions versus exercise+cointerventions and the outcomes of interest. In studies where there were no observed events in the intervention or control group, data were entered into forest plots, but were considered 'not estimable' and excluded from the pooled analysis as per the recommendation in the Cochrane Handbook.⁵⁵

When possible, the following a priori determined subgroup analyses were conducted for exercise-only interventions and observational studies: (1) women diagnosed with diabetes (gestational, type 1 or type 2) compared with women without diabetes; (2) samples of women with overweight or obesity (mean BMI >25.0 kg/m²) prior to pregnancy compared with samples of women who were of various BMI (mean BMI <25 kg/m² but possibly with some individuals with BMI >25.0 kg/m²); (3) women >35 years of age compared with women <35 years of age; and (4) women who were previously inactive compared with those who were previously active (as defined by individual study authors). If a study did not provide sufficient detail to allow for inclusion in subanalyses, then a third group called 'unspecified' was created. Tests for subgroup differences were conducted with statistical significance set at $p < 0.05$. Effects within subgroups were only interpreted when statistically significant differences between subgroups were found. Subgroup analyses were conducted for exercise-only RCTs reporting on 'critical' outcomes to identify whether a specific type of exercise was associated with greater benefit. I^2 was calculated for subgroup analyses to indicate the per cent of total variability that was attributable to between-study heterogeneity.

Dose–response meta-regression^{56–58} was carried out by weighted no-intercept regression of log ORs with a random-effects for study, using the metafor⁵⁹ package in R⁶⁰ V.3.4.1. Models did not include an intercept term since the log OR is assumed to be zero when the exercise dose is zero. Restricted cubic splines with knots at the 10th, 50th and 90th percentiles of the explanatory variable⁶¹ were used to investigate whether there was evidence for a non-linear relationship. Fitting was performed by maximum likelihood, and non-linearity was assessed using a likelihood ratio test. Although both linear and spline regressions were performed, only the model with the best fit was reported. It was determined that an accepted cut-off point for a clinically meaningful decrease does not exist in the literature. Therefore, a 25% reduction in the odds of the outcomes of interest was selected by expert opinion of the Guidelines Steering Committee.

For outcomes or for subsets of studies where a meta-analysis was not possible, a narrative synthesis of the results was presented, organised around each outcome. Unless otherwise

specified, studies were not included in meta-analyses if data were reported incompletely (SD, SE or number of cases/controls not provided), if data were adjusted for confounding factors or if the study did not include a non-exercising control group. In studies where data were included in the meta-analysis but additional information was available, the studies were included in both the meta-analysis and narrative synthesis. Within each outcome, the results were presented by study design.

RESULTS

Study selection

The initial search was not limited by language. However, the Guidelines Steering Committee decided to exclude studies published in languages other than English, Spanish or French for feasibility reasons. A PRISMA diagram of the search results, including reasons for exclusion, is shown in figure 1. A comprehensive list of excluded studies is presented in the online

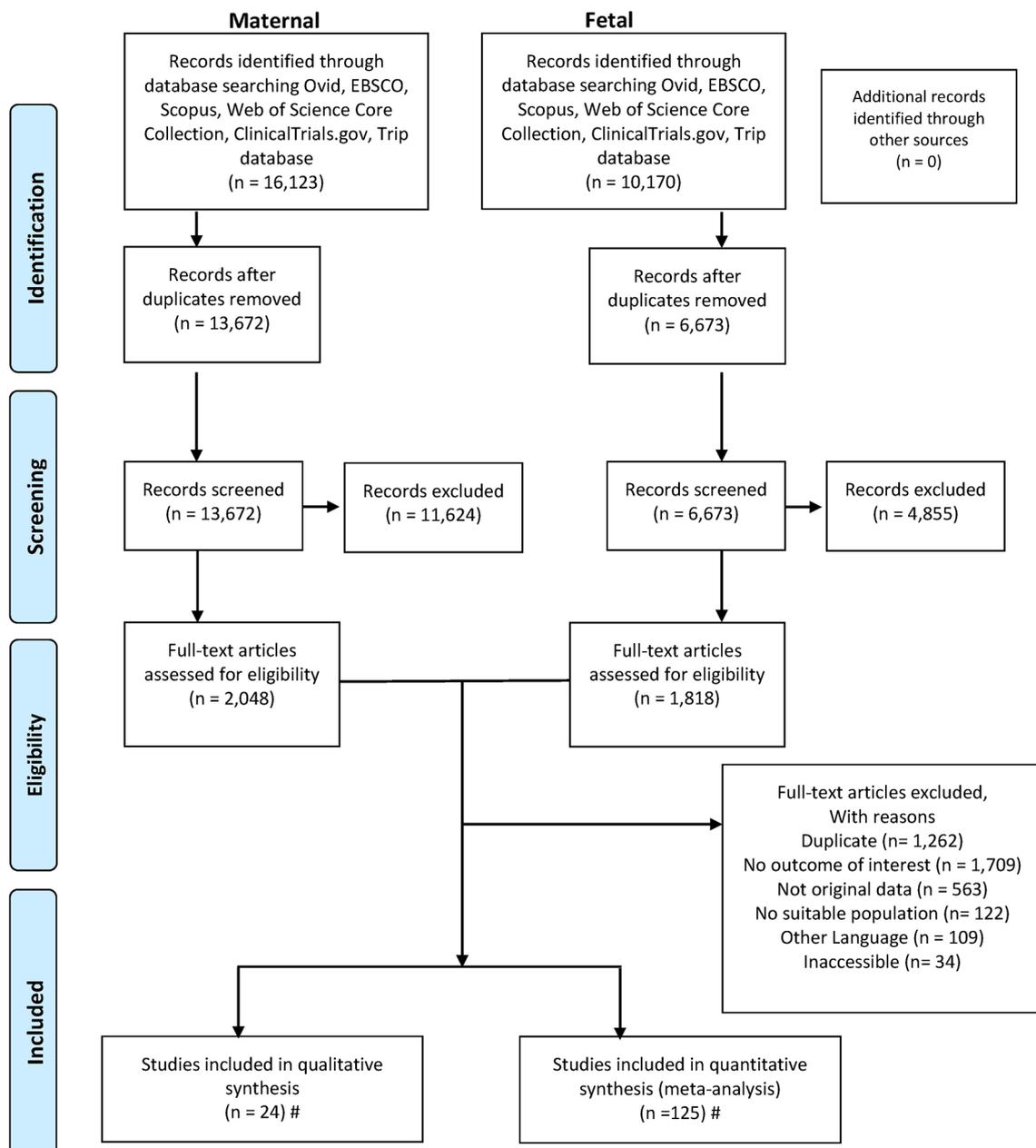


Figure 1 Flow diagram of studies selected for the present study. #14 studies were included in both the qualitative and quantitative analyses.

supplementary materials. Consistent with the planned staged approach, if fewer than 2000 participants were included in RCTs, data from other study designs were included.

Study characteristics

Overall, 135 unique studies (n=166 094 women) from 32 countries were included in the analysis of both neonatal and childhood outcomes. There were 91 RCTs, 8 non-randomised interventions, 30 cohort, 2 cross-sectional and 4 case-control studies. Among the included exercise interventions, the frequency of exercise ranged from 1 to 7 days per week, the intensity of exercise ranged from low to vigorous, the duration of exercise ranged from 10 to 90 min per session, and the types of exercise were walking, swimming, cycling, water gymnastics, resistance training, stretching, yoga and pelvic floor muscle training. RCTs were initiated in the first (n=23), second (n=52) and third (n=15) trimester, while one RCT was unspecified. Non-randomised interventions were initiated in the second trimester (one was unspecified). Sixty-one RCTs and three non-randomised interventions were exercise-only interventions. The cointerventions included diet, insulin, education about healthy pregnancy and behaviour change, and relaxation techniques. Additional details about the studies can be found in the online supplementary materials (Study characteristics and online supplementary table 1).

Quality of evidence

Overall, the quality of evidence ranged from 'very low' to 'high' (online supplementary tables 2–17). The most common reasons for downgrading the quality of evidence were (1) serious risk of bias, (2) indirectness of the interventions and (3) imprecision. Common sources of bias included poor or unreported compliance with the intervention and inappropriate treatment of missing data when attrition rate was high. Publication bias was not identified among the analyses where it was possible to systematically assess this using funnel plots.

Meta-regression

The results of the meta-regression analysis are presented in the online supplementary materials (Meta-regressions and online supplementary figures 94–121). For the meta-regression analyses, linear regression was a better fit than spline for all outcomes. However, there was no significant dose-response relationship between prenatal exercise (frequency, intensity, duration or volume) and any outcome.

Birth weight

There was 'low' quality evidence from 73 RCTs (n=14 978; downgraded for serious risk of bias and indirectness) regarding the association between prenatal exercise and birth weight. Overall, prenatal exercise was not associated with birth weight (MD -0.02 kg, 95% CI -0.04 to 0.00, $I^2=38\%$; online supplementary figure 1).⁶²⁻¹³⁴ Three RCTs included in the pooled estimates reported additional data showing no association between prenatal exercise and birth weight.^{94 112 135}

Sensitivity analysis

The pooled estimate for the exercise-only interventions was not significantly different from the pooled estimate for the exercise+cointerventions (p=0.38). Both exercise-only interventions ('moderate' quality evidence; downgraded for serious risk of bias) and exercise+cointerventions ('low' quality evidence; downgraded for serious risk of bias and indirectness) did not

affect birth weight compared with no exercise (online supplementary figure 1).

Subgroup analyses

The tests for subgroup differences performed for exercise-only interventions were significant subgroups based on previous physical activity levels (p=0.0003) and gestational diabetes status (p=0.01). Specifically, among women who were previously inactive, those who participated in exercise-only interventions had babies with a significantly lower birth weight than those who did not exercise ('moderate' quality evidence; downgraded for serious risk of bias; p=0.002).^{63 64 66 71 72 76-78 80 81 84 86-88 91 93 100 101 104 110} Among women who were previously active, those who participated in exercise-only interventions had babies with a higher birth weight than those who did not exercise ('low' quality evidence; downgraded for serious risk of bias and inconsistency; p=0.003)⁹² (online supplementary figure 5). Additionally, among women who exercised during pregnancy, there was 'moderate' quality evidence (downgraded for serious risk of bias) that women with gestational diabetes mellitus (GDM) had babies with lower birth weight^{80 85 101} compared with babies of women without GDM (p=0.005; online supplementary figure 3). The remaining test for subgroup differences (ie, for women of various BMI vs women with overweight/obesity) was not statistically significant (see online supplementary figure 4). Subgroup analysis by maternal age ≥ 35 years could not be conducted.

Birth weight <2500 g

There was 'very low' quality evidence (downgraded for serious risk of bias, inconsistency, indirectness and imprecision) from 22 RCTs (n=6351) indicating no effect of prenatal exercise on the odds of birth weight <2500 g (pooled estimated based on 20 RCTs, n=6094; OR 0.91, 95% CI 0.73 to 1.14, $I^2=0\%$; figure 2).^{64-66 72 83 86-88 93 97 98 100 109 114 130 131 136-141} Two RCTs that could not be included in the analysis reported no association between prenatal exercise and birth weight <2500 g.^{65 72} Three RCTs included in the pooled estimates reported additional data showing no association between prenatal exercise and birth weight <2500 g.^{65 72}

Sensitivity analysis

The pooled estimate for the exercise-only interventions was not significantly different from the pooled estimate for the exercise+cointervention subgroups (p=0.96). Both exercise-only interventions ('low' quality evidence; downgraded for serious risk of bias, inconsistency and imprecision) and exercise+cointerventions ('very low' quality evidence; downgraded for serious risk of bias, indirectness and imprecision) did not affect birth weight <2500 g compared with no exercise (figure 2).

Subgroup analysis

The tests for subgroup differences performed for exercise-only interventions were not statistically significant (see online supplementary figures 6–9).

Birth weight <10th percentile

There was 'very low' quality evidence (downgraded for serious risk of bias, indirectness and imprecision) from 15 RCTs indicating no effect of prenatal exercise on the odds of birth weight <10th percentile (n=5178; OR 1.20, 95% CI 0.96 to 1.49, $I^2=0\%$; online supplementary figure 10).^{72 75 76 78 82 88 97 111 112 128 131-134 142} Two RCTs included in the pooled estimates reported

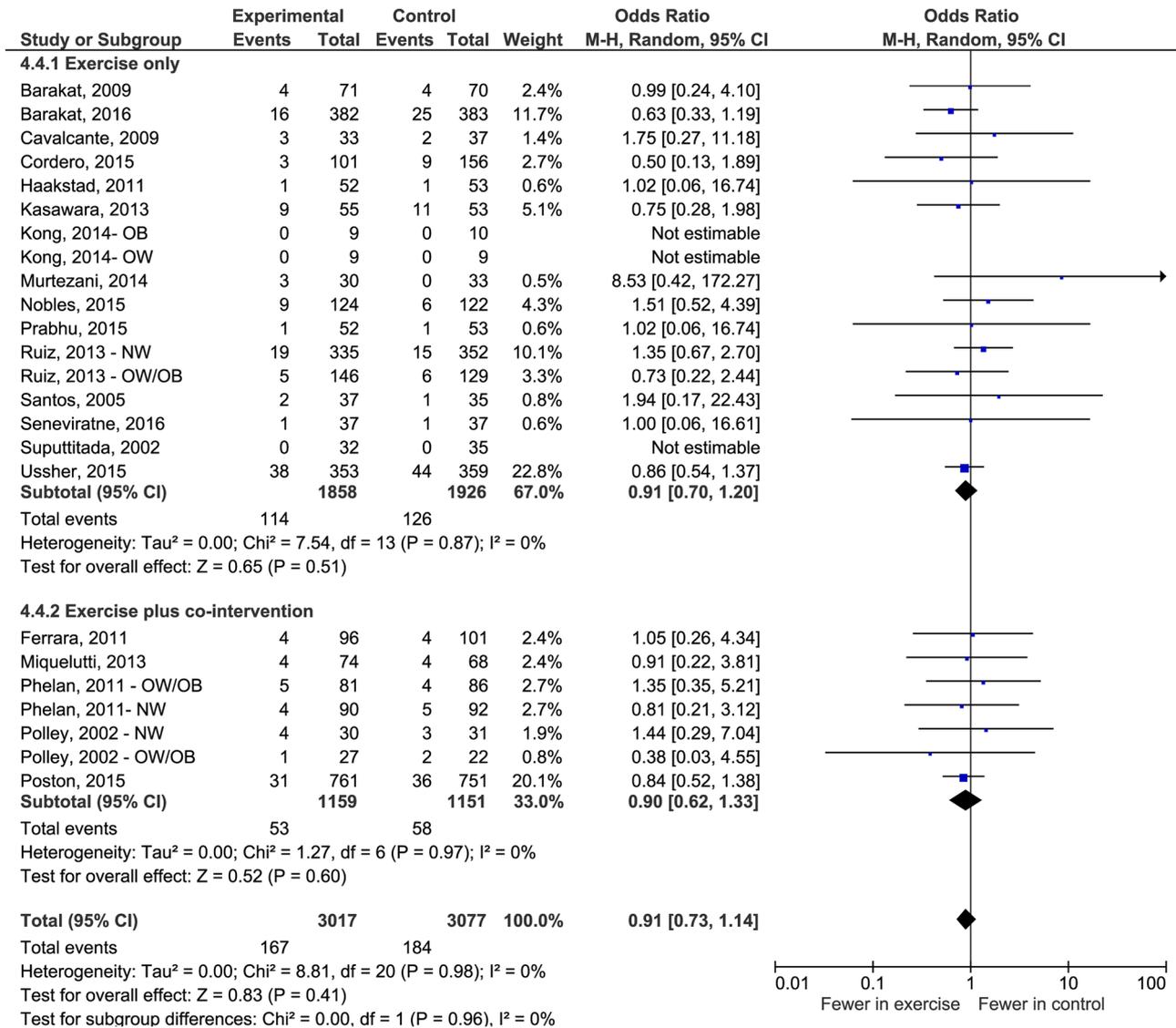


Figure 2 Effects of prenatal exercise compared with control on the odds of birth weight <2500 g (randomised controlled trials). Sensitivity analyses were conducted with studies including exercise-only interventions and those including exercise+cointerventions. Analyses conducted with a random-effects model. *Note: Studies with zero events in both arms are included in the forest plot but are 'not estimable' and not included in the pooled analysis.* M-H, Mantel-Haenszel method; NW, normal weight; OB, obese; OW, overweight.

additional data showing no association between prenatal exercise and birth weight <10th percentile.^{112 128}

Sensitivity analysis

The pooled estimate for the exercise-only interventions was not significantly different from the pooled estimate for the exercise+cointervention subgroups ($p=0.35$). Both exercise-only interventions and exercise+cointerventions did not affect the odds of birth weight <10th percentile compared with no exercise (online supplementary figure 10).

Subgroup analyses

The test for subgroup differences performed for exercise-only interventions were not statistically significant (online supplementary figures 12–14).

Intrauterine growth restriction

Overall, there was 'moderate' quality evidence (downgraded due to inconsistency) from one RCT ($n=334$) indicating no

association between prenatal exercise and IUGR compared with no exercise (OR 1.11, 95% CI 0.48 to 2.60; online supplementary figure 15).⁹⁴

Findings from other study designs (non-randomised interventions, cohort and case-control studies) were not in accordance with findings from RCTs and suggested a reduction in the odds of having IUGR (see online supplementary materials).

Macrosomia (birth weight >4000 g)

There was 'low' quality evidence from 33 RCTs ($n=9444$ women; downgraded for serious risk of bias and indirectness) indicating no association between prenatal exercise and macrosomia. The pooled estimate was based on 31 RCTs ($n=8937$; OR 0.85, 95% CI 0.71 to 1.02, $I^2=21\%$; figure 3).^{66 71 80 83 86 87 93 94 97 100 101 109 115–118 121 124 126 128 130 131 133 134 136 137 140–143}

The two RCTs^{72 95} that could not be included in the analysis also found no relationship between prenatal exercise and macrosomia. Five RCTs included in the pooled estimates reported additional data; four of them indicated no association between prenatal exercise

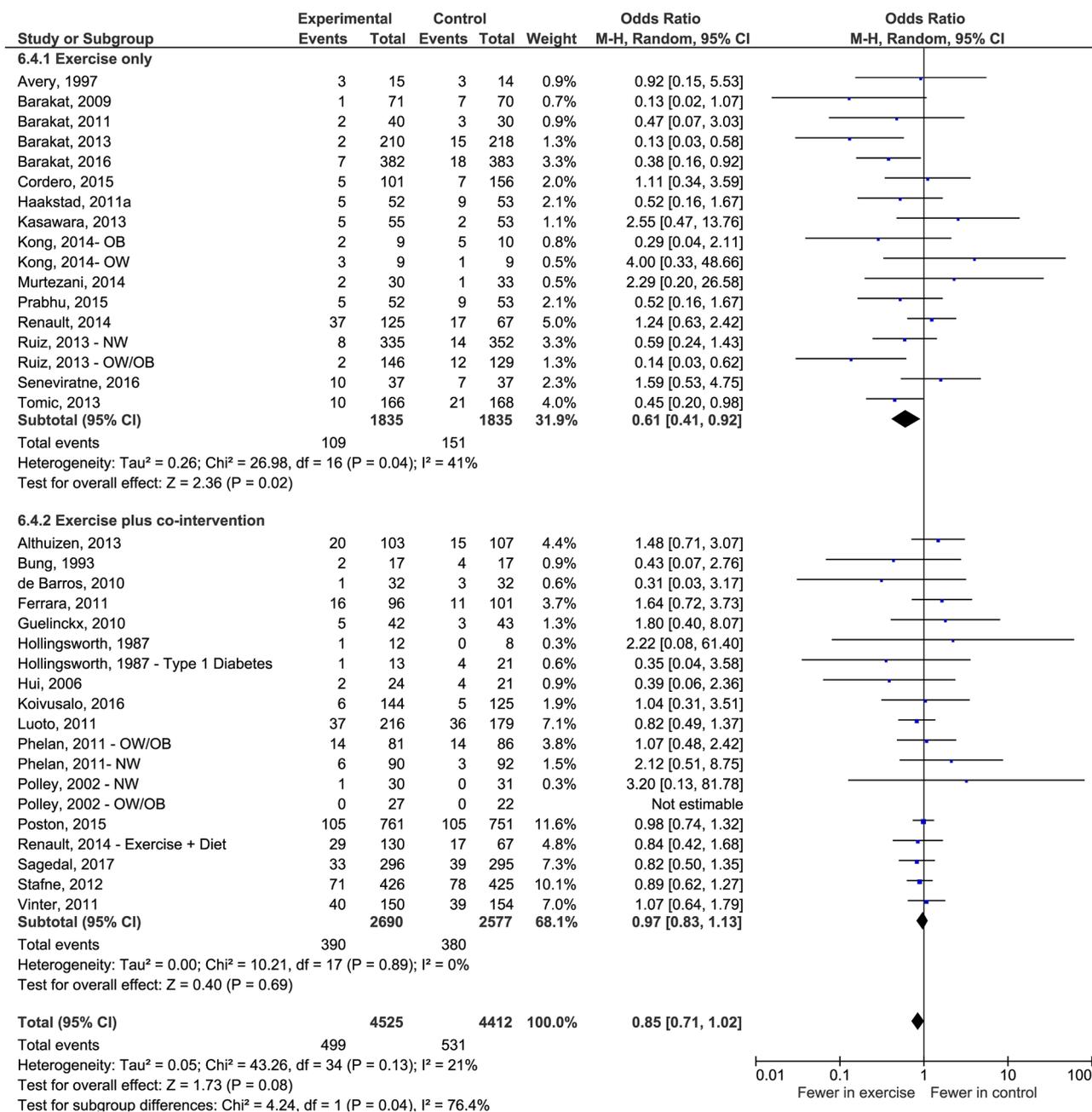


Figure 3 Effects of prenatal exercise compared with control on the odds of birth weight >4000 g (randomised controlled trials). Sensitivity analyses were conducted with studies including exercise-only interventions and those including exercise+cointerventions. Analyses conducted with a random-effects model. Note: Studies with zero events in both arms are included in the forest plot but are 'not estimable' and not included in the pooled analysis. M-H, Mantel-Haenszel method; NW, normal weight; OB, obese; OW, overweight; type 1 diabetes, women with type 1 diabetes.

and birth weight >4000 g,^{80 94 128 136} while one showed that women who were inactive during pregnancy had an increased odds of having a baby >4000 g.¹⁰⁹

Sensitivity analysis

The pooled estimate for the exercise-only interventions was significantly different from the pooled estimate for the exercise+cointervention subgroups ($p=0.04$). There was 'high' quality evidence from 15 exercise-only RCTs showing a 39% decrease in the odds of macrosomia with exercise compared with no exercise ($n=3670$ women; OR 0.61, 95%CI 0.41 to 0.92, $I^2=41%$; figure 3).^{66 71 80 83 86 87 93 94 97 100 101 109 136 137 142} The two RCTs^{72 95} that could not be included in the analysis also found no relationship between prenatal exercise and

macrosomia. However, there was no significant effect of exercise+cointerventions on the odds of macrosomia with exercise compared with no exercise ($n=5267$ women; OR 0.97, 95%CI 0.83 to 1.13, $I^2=0%$; figure 3).

Subgroup analysis

The tests for subgroup differences performed for exercise-only intervention were not statistically significant for prepregnancy BMI, previous activity level or GDM (see online supplementary figures 19–21). The test for subgroup differences by type of exercise was statistically significant ($p=0.04$). There was 'high' quality evidence that interventions combining more than one type of exercise reduced the odds of having a baby with a birth weight >4000 g ($n=2755$ women; OR 0.46, 95%CI 0.29 to

0.73, $I^2=18\%$; online supplementary figure 22).^{71 80 83 87 93 100 109 137} Interventions including aerobic exercise and resistance training were not significant.

Birth weight >90th percentile

Overall, there was 'very low' quality evidence (downgraded for serious risk of bias, indirectness and imprecision) from 19 RCTs ($n=5268$) indicating no association between prenatal exercise and birth weight >90th percentile (OR 0.91, 95%CI 0.74 to 1.11, $I^2=8\%$; online supplementary figure 23).^{72 76 78 82 88 95 97 111 112 122 123 128 131-133 136 142-144} Two RCTs included in the pooled estimates reported additional data; one RCT¹¹² did not identify a relationship between exercise and birth weight >90th percentile; however, a cluster RCT¹²⁸ identified a reduction in the odds of having an LGA baby in women who were active during pregnancy (OR 0.55, 95%CI 0.30 to 0.98; Online Supplementary Table 6).

Sensitivity analysis

The pooled estimate for the exercise-only interventions was not significantly different from the exercise+cointervention subgroups ($p=0.49$). Both exercise-only interventions and exercise+cointerventions did not affect birth weight >90th percentile (online supplementary figure 23).

Subgroup analysis

The tests for subgroup differences (previous level of physical activity, women with overweight/obesity and women with GDM) among exercise-only interventions were not statistically significant (see online supplementary figures 25–27). Subgroup analysis by maternal age or women with GDM could not be conducted.

Gestational age at delivery

Overall, there was 'low' quality evidence (downgraded for serious risk of bias and indirectness) from 61 RCTs ($n=13\,989$ women) regarding the association between prenatal exercise and gestational age at delivery.^{63 65 66 68-71 73-77 79-83 85-89 92-97 99-103 106 108-114 116-124 126 128-131 133 134 136 142 145 146} (online supplementary figure 28). The pooled estimate based on 61 studies ($n=13\,989$) indicated no significant effect of exercise on gestational age compared with no exercise ($p=0.58$, MD 0.02, 95%CI -0.06 to 0.10 , $I^2=40\%$; online supplementary figure 28). Additional data from one RCT⁹⁴ that could not be included in the meta-analysis did not identify a significant relationship between prenatal exercise and gestational age.

Sensitivity analysis

The pooled estimate for the comparison of exercise versus control groups was not significantly different from the pooled estimate for the comparison of exercise+cointerventions versus control groups ($p=0.62$). Both exercise-only interventions and exercise+cointerventions did not affect gestational age at delivery compared with no exercise (online supplementary figure 28).

Subgroup analysis

The tests for subgroup differences (previous level of physical activity, women with overweight/obesity and women with GDM) among exercise-only interventions were not statistically significant (see online supplementary figures 30–32).

Preterm birth

Overall, there was 'very low' quality evidence (downgraded for serious risk of bias, inconsistency, indirectness and imprecision) from 41 RCTs ($n=10\,232$) indicating no association between prenatal exercise and preterm birth. The pooled estimate was based on 40 RCTs.^{46 63-66 68 73 78 80 81 84-86 88 93 94 97 98 100 101 109 110 114 115 117 121 129-134 136 137 139 142-144 147 148} ($n=10\,303$; OR 1.00, 95%CI 0.85 to 1.18, $I^2=0\%$; figure 4). The one study that could not be included in the pooled estimate indicated no association between prenatal exercise and preterm birth.¹³⁸

Sensitivity analysis

The pooled estimate for the comparison of exercise versus control groups was not significantly different from the pooled estimate for the comparison of exercise+cointerventions versus control groups ($p=0.20$). Both exercise-only interventions and exercise+cointerventions did not affect birth weight compared with control (figure 4).

Subgroup analysis

The tests for subgroup differences (previous level of physical activity, women with overweight/obesity, women with GDM and type of exercise) among exercise-only interventions were not statistically significant (see online supplementary figures 33–36).

Additional outcomes

There were no significant associations between prenatal exercise and any remaining outcomes (ie, IUGR, Apgar scores, neonatal per cent body fat, neonatal fat mass, ponderal index, neonatal BMI, cord blood pH, hyperbilirubinaemia, neonatal hypoglycaemia, childhood developmental outcomes (ie, cognitive, psychosocial, motor skills), childhood per cent body fat, childhood body weight and childhood BMI) compared with no exercise, for either the complete sample or examined subgroups (see the online supplementary materials for detailed results). Data for the relationships between prenatal exercise and NICU admittance, shoulder dystocia, brachial plexus injury and base excess were not identified.

DISCUSSION

In this comprehensive systematic review and meta-analysis of 135 studies, there was 'very low' to 'high' quality evidence from exercise-only RCTs indicating that prenatal exercise was associated with a 39% decreased odds of macrosomia (birth weight >4000g) without any increase in the odds of preterm birth, low birth weight (<2500g), SGA (<10th percentile) or IUGR. Moreover, there was 'very low' to 'high' quality evidence from exercise-only RCTs indicating that prenatal exercise did not affect gestational age, birth weight, LGA, neonatal hypoglycaemia, metabolic acidosis (cord blood pH), hyperbilirubinaemia, Apgar scores, neonatal body composition (per cent body fat, body weight, BMI), childhood obesity (per cent body fat, body weight, fat mass) and developmental milestones (ie, cognitive, psychosocial, motor skills). No information was found regarding the associations between prenatal exercise and NICU admittance, shoulder dystocia, brachial plexus injury and base excess. Findings from the meta-regressions identified no dose-response relationship between maternal exercise and neonatal or childhood outcomes. Overall, these results confirm that prenatal exercise in women without contraindication does not adversely affect neonatal or childhood outcomes, and is beneficial in reducing the odds of macrosomia.

The incidence of adverse neonatal outcomes is rising,¹ possibly as a result of increased rates of maternal obesity,¹⁴⁹ excessive

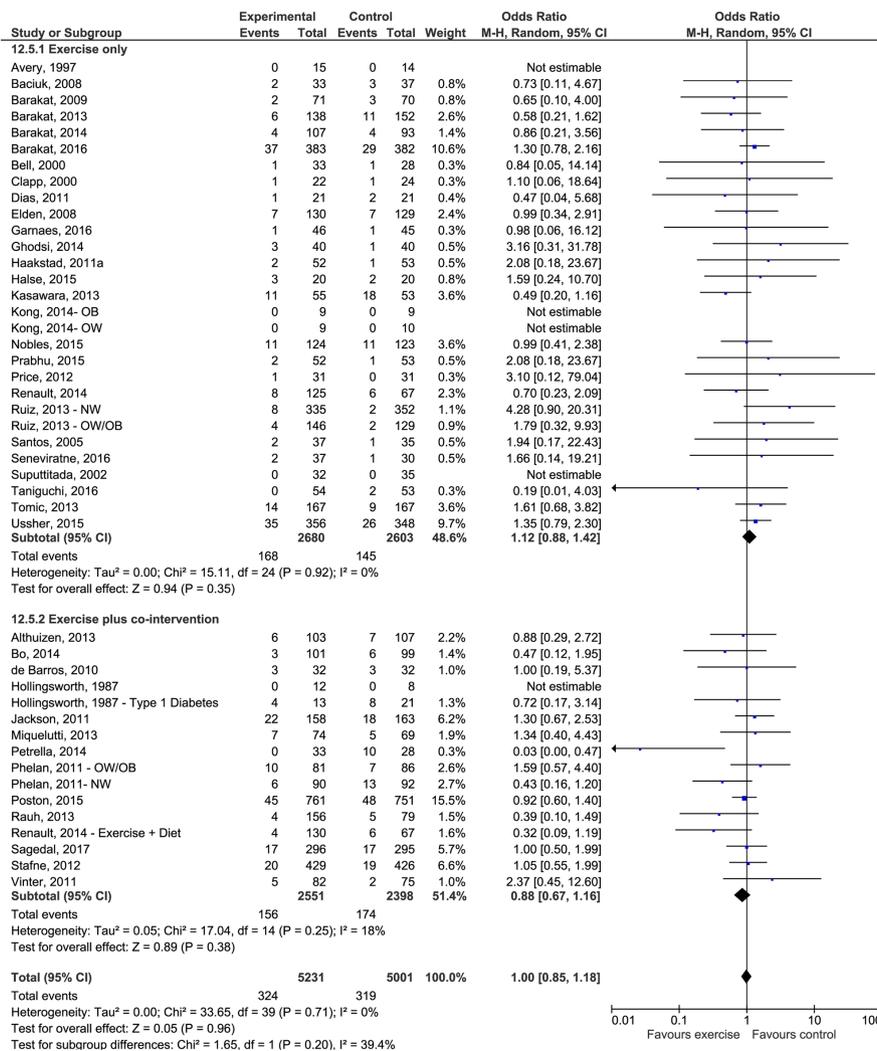


Figure 4 Effects of prenatal compared with control on the odds of preterm birth (randomised controlled trials). Analyses conducted with a random-effects model. *Note: Studies with zero events in both arms are included in the forest plot but are 'not estimable' and not included in the pooled analysis.* M-H, Mantel-Haenszel method; NW, normal weight; OB, obese; OW, overweight; type 1 diabetes, women with type 1 diabetes.

gestational weight gain,¹⁵⁰ complications such as GDM²³ and pregnancy-related hypertensive disorders.^{151–152} Women who develop GDM are more likely to give birth to LGA babies, with increased risks of complicated deliveries, whereas women who develop pregnancy-related hypertensive disorders are more likely to deliver SGA or IUGR babies prematurely.^{9–11, 152} In other papers in the current issue of the *British Journal of Sports Medicine*, it was identified that prenatal exercise reduced the odds of maternal metabolic and hypertensive disorders¹² and also played a role in managing gestational weight gain.¹³ These positive maternal benefits likely also transfer to reducing the risks of unfavourable neonatal outcomes.

The current findings demonstrated lower odds of delivering a macrosomic baby with exercise-only interventions. In another systematic review in this issue, we showed that prenatal exercise was beneficial in the control of maternal blood glucose,³⁰ a key determinant of fetal growth.¹⁵³ Pregnancy is associated with mild insulin resistance, an adaptation that ensures adequate fetal nutrition; however, instances of greater maternal insulin resistance lead to increased fetal size.^{153–155} Acute and regular exercise in pregnant women improves glycaemic control.^{156–161} In combination with reduced excessive gestational weight gain associated with prenatal exercise, physical activity during pregnancy may

prevent excessive fetal weight gain and therefore macrosomia. Additionally, prenatal exercise promotes placental growth and vascular development,^{162–163} which may also enable appropriate growth for gestational age. Macrosomia has been associated with significant short-term neonatal complications,^{5–6} and as such reducing the odds would improve clinical infant outcomes.¹⁶⁴

The present analyses did not show any significant association between prenatal exercise and LGA (>90th percentile). This discrepancy between two seemingly similar neonatal outcome parameters (birth weight >4000 g and >90th percentile) may be due to differences in the number of women included in exercise-only RCTs, as well as the quality of evidence. The analysis of macrosomia included a greater number of women, had higher quality evidence and likely had more power than the analysis of birth weight >90th percentile to detect a difference between the intervention and control group (n=3670, 'high' quality vs n=1407, 'low' quality, respectively). Additionally, our subgroup analyses showed that exercise-only interventions were more beneficial in reducing the odds of macrosomia than exercise+cointerventions. The majority of studies included in the analysis of birth weight >90th percentile were exercise+cointerventions, where there were other factors that confounded potential relationships. Importantly, the majority of these studies included

unsupervised exercise or counselling-based interventions that are typically associated with lower intervention adherence¹⁶⁵ and tended to have lower compliance (defined as <60% of participants performing 100% of prescribed exercise).

For decades, women have avoided prenatal exercise for fear of raising the risk of adverse pregnancy outcomes, including growth restriction and preterm birth.¹⁶⁶ Early research in this area raised concerns of growth restriction or preterm birth as a result of exercise-induced redirection of blood flow and nutrients away from the growing baby and towards the working maternal muscle.^{43–46} However, the present analyses did not show any increased odds of SGA, IUGR or preterm birth with prenatal exercise, in agreement with other findings.^{38–42} We also showed no association of prenatal exercise with gestational age at delivery or birth weight. Our analyses did not identify a dose–response relationship between increasing frequency, intensity, duration or volume of prenatal exercise with these neonatal outcomes. Furthermore, there were no associations between prenatal exercise and neonatal morphometric outcomes, metabolic birth outcomes or Apgar scores. These data strongly support the safety of prenatal exercise.

The ‘Developmental Origins of Health and Disease’ hypothesis states that the in utero environment and the neonatal period have critical implications for long-term health.¹⁶⁷ This hypothesis has been largely supported by examining neonatal outcomes and their association with long-term effects on health.¹⁶⁷ As such, all factors that reduce these potential complications should be encouraged to promote lifelong health.¹⁶⁸ For example, it has been shown that infants born LGA are at an increased risk of overweight and obesity later in life.¹⁶⁹ Although the present findings demonstrate reduced odds of macrosomia in neonates of mothers who exercised compared with those who did not, no long-term impacts of maternal exercise on childhood morphometrics (ie, infant BMI, fat mass, body weight) or developmental outcomes (ie, cognitive, psychosocial, motor skills) were found. Only nine observational studies assessed the impact of maternal exercise on morphometric and developmental outcomes in children (details in the online supplementary materials). More RCTs examining the effect of prenatal exercise on long-term child health are needed to fill this critical gap in the literature.

This systematic review and meta-analysis was conducted using rigorous methodological standards (GRADE) to guide the systematic review process. A variety of study designs and articles in different languages (English, French and Spanish) were included. The analyses of birth outcomes such as LGA, SGA and preterm birth demonstrated the safety of exercise. However, analyses of IUGR, metabolic birth outcomes (cord blood pH), childhood developmental and both neonatal and childhood morphometric outcomes included small sample sizes (the majority of outcomes were <100 women) and were likely not adequately powered to detect an effect of prenatal exercise. More studies are needed to establish the effect of prenatal exercise on these parameters. In the majority of analyses, the level of quality evidence from RCTs was downgraded due to serious risk of bias, including high risk of performance and attrition bias. Authors of future studies should therefore monitor compliance to the exercise intervention more rigorously and consider factors that may influence compliance and retention of study participants. Additionally, researchers should consider confounding variables, such as maternal nutritional intake¹⁷⁰ and socioeconomic status, which also influence fetal growth.¹⁷¹ Finally, quality evidence from the majority of observational studies was rated down due to risk of bias related to performance bias, specifically due to potentially flawed measurement of the physical activity.

In conclusion, the current systematic review and meta-analysis identified that prenatal exercise-only interventions were associated with a 39% reduction in the odds of macrosomia (birth weight >4000 g), and were not significantly associated with preterm birth, gestational age at delivery, birth weight, low birth weight (<2500 g), SGA (<10th percentile), LGA (>90th percentile), IUGR, neonatal hypoglycaemia, metabolic acidosis (cord blood pH), hyperbilirubinaemia, Apgar scores, neonatal body composition (per cent body fat, body weight, BMI), childhood obesity (per cent body fat, body weight, fat mass) and developmental milestones (including cognitive, psychosocial, motor skills). These results reinforce the positive effects of prenatal exercise for newborns in addition to the more established benefits for mothers.

What is already known

- ▶ Fetal and neonatal complications, such as intrauterine growth restriction, preterm birth, and low birth weight or high birth weight, are associated with long-term health issues.
- ▶ Such neonatal complications can increase the risk of childhood obesity and the development of cardiovascular and metabolic diseases in later life.
- ▶ Despite having many known benefits for the mother, prenatal exercise has previously been suggested to potentially increase the odds of neonatal complications such as preterm birth and intrauterine growth restriction.

What are the new findings

- ▶ Interventions that comprised exercise alone reduced the odds of high birth weight babies (>4000 g) by 39%.
- ▶ There were no associations between prenatal exercise and birth weight, gestational age at delivery, preterm birth or low birth weight.

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