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SYSTEMATIC REVIEW

Effects of Maternal Exercise During Pregnancy on Perinatal Growth and Childhood Obesity Outcomes: A Meta-analysis and Meta-regression

Yanting Chen[1,3] · Guiling Ma[2] · Yun Hu[2] · Qiyuan Yang[4] · Jeanene M. Deavila[1,3] · Mei-Jun Zhu[5] · Min Du[1,3]

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Abstract

Background Perinatal growth abnormalities program susceptibility to childhood obesity, which is further exaggerated by maternal overweight and obesity (MO) during pregnancy. Exercise is highly accessible, but reports about the benefits of maternal exercise on fetal growth and childhood obesity outcomes are inconsistent, reducing the incentives for pregnant women to participate in exercise to improve children's perinatal growth.

Objective This systematic review and meta-analysis aims to establish evidence-based efficacy of exercise in mothers with normal weight (MNW) and MO during pregnancy in reducing the risks of perinatal growth abnormalities and childhood obesity. In addition, the impacts of exercise volume are also assessed.

Methods The PubMed, ScienceDirect, Web of Science, and Cochrane Library databases were searched from inception to February 15, 2020. We included randomized controlled trials with exercise-only intervention or exercise with other confounders in pregnant MNW (body mass index, BMI 18.5–24.9 kg/m^2) and MO (BMI ≥ 25 kg/m^2), which were further subgrouped in the meta-analysis. Primary outcomes included birth weight, preterm birth, small for gestational age (SGA), large for gestational age (LGA), infant and childhood weight, and childhood obesity. A linear meta-regression analysis was also used to explore the effects of exercise volume on outcomes.

Results 99 studies were included in the meta-analysis (n = 596,876), and individual study quality ranged from fair to good according to the Newcastle–Ottawa scale assessment. Exercise only interventions in MNW reduced preterm birth by 15% (26 studies, n = 76,132; odds ratio [OR] 0.85; 95% CI 0.72, 1.01; I^2 = 83.3%), SGA by 17% (33 studies, n = 92,351; OR 0.83; 95% CI 0.71, 0.98; I^2 = 74.5%) and LGA by 17% (29 studies, n = 84,310; OR 0.83; 95% CI 0.74, 0.95; I^2 = 60.4%). Exercise only interventions in MO reduced preterm birth by 33% (2 studies, n = 3,050; OR 0.67; 95% CI 0.70, 0.96; I^2 = 0%), SGA by 27% (8 studies, n = 3,909; OR 0.73; 95% CI 0.50, 1.05; I^2 = 40.4%) and LGA by 55% (9 studies, n = 81,581; OR 0.45; 95% CI 0.18, 1.11; I^2 = 98.3%). Exercise only interventions in MNW reduced childhood obesity by 53% (3 studies, n = 6,920; OR 0.47; 95% CI 0.36, 0.63; I^2 = 77.0%). However, no significant effect was observed in outcomes from exercise confounders in either MNW or MO. In the meta-regression, the volume of exercise-only intervention in MNW was negatively associated with birth weight, greatly driven by volumes more than 810 metabolic equivalents (MET)-min per week. Other outcomes were not associated with exercise volume.

Conclusions This systematic review and meta-analysis suggests that exercise during pregnancy in both MNW and MO safely and effectively reduce the risks of preterm birth, SGA, and LGA. Furthermore, MNW exercise also reduces the risk of childhood obesity. Overall, regardless of prepregnancy BMI, maternal exercise during pregnancy provides an excellent opportunity to mitigate the high prevalence of adverse birth outcomes and childhood obesity.

Yanting Chen and Guiling Ma contributed equally to this research.

✉ Min Du
min.du@wsu.edu

Extended author information available on the last page of the article

Key Points

Maternal exercise during pregnancy effectively reduces the risks of preterm birth, SGA, LGA, and childhood obesity.

Exercise volume over 810 metabolic equivalents per min per week contributes to lower birth weight but is not associated with preterm birth or SGA.

Maternal exercise interventions can be used to reduce adverse birth outcomes and childhood obesity across different maternal body mass indices.

1 Introduction

Globally, over 41 million children under age 5 are obese, and over 340 million children aged 5–19 years are either overweight or obese [1, 2]. The prevalence of child obesity has tripled since 1975 and is currently up to 18% [1, 2]. Childhood obesity is likely sustained into adolescence and adulthood, which predisposes children to the development of serious health complications at an early age, including type 2 diabetes mellitus, hypertension, and cardiovascular diseases [3]. The increase in childhood obesity is associated with multiple factors, including high energy food intake, a lack of physical activity, and imbalanced nutrition [4]. However, growing evidence suggests that early intrauterine life also plays a critical role in shaping the trajectory of child weight gain and fatness [5].

Gestational age and birth weight are critical variables in fetal development [6–8]. Abnormal early development programs long-term child health, including predisposition to obesity and type 2 diabetes mellitus. Adverse fetal development and birth outcomes, including preterm birth (defined as < 37 completed weeks of gestation), small birth weight for gestational age (SGA; birth weight < 10th percentile for age and sex), and large birth weight for gestational age (LGA; birth weight > 90th percentile for age and sex), account for 11.1, 15.5, and 13% of the world's live births, respectively, and substantially increase the risks of child obesity by 59, 19, and 100%, respectively [6–8]. While abnormal prenatal growth is associated with multiple etiologies, prepregnancy maternal overweight and obesity (MO; body mass index BMI ≥ 25 kg/m^2) is one of the main drivers of fetal growth restriction, preterm birth, and excessive growth [9]. Previous meta-analyses have revealed that prepregnancy MO increases the risk of preterm birth by 50%, SGA by 70%, and LGA by 57%, contributing to a more than twofold increase in childhood obesity risk [10–14]. Currently, approximately one-third of women of childbearing age are obese in the United States, perpetuating "a vicious mother–child obesity cycle" [15–17].

During the last few decades, a large volume of studies have shown that exercise during pregnancy benefits maternal health and postpartum recovery, and these studies have been systematically reviewed in previous meta-analyses [18–23]. A 2017 meta-analysis showed that exercise during pregnancy can effectively improve psychological well-being and reduce postpartum depressive symptoms [18]. A 2018 meta-analysis showed that exercise during pregnancy can also reduce the risk of cesarean section by 12% [19]. Similar beneficial effects have also been reported in other meta-analyses [20, 21, 24]. In addition, the role of exercise during pregnancy in controlling gestational weight gain and diabetes has also been evaluated in meta-analyses [19, 20, 22, 23]. Without considering maternal body weight as a subgroup factor, previous meta-analyses reported that exercise reduces gestational weight gain by 1.1 kg [20] and the risk of gestational diabetes by 41% [22]. After taking into account maternal body weight, exercise during pregnancy reduces the risk of gestational diabetes by 42% in normal-weight women [19], and the diabetic risk by 24% in overweight and obese women [23], showing that body weight during pregnancy is a critical factor in altering pathophysiological responses to exercise interventions.

In addition to improving maternal health, systematic reviews and meta-analyses also reveal that maternal exercise may benefit the intrauterine environment, which improves fetal development and birth outcomes, though data are limited and inconsistent [20, 25–28]. Several meta-analyses have shown that maternal exercise during pregnancy can reduce the risks of LGA [20] and preterm birth [25], and has no negative impact on SGA risk [20, 25, 26] or gestational length [20], showing that exercise during pregnancy is safe and beneficial for fetal development. However, other meta-analyses showed that maternal exercise is associated with SGA [27] and has no effect on reducing LGA risk [26] and preterm birth [28], leading to substantial confusion and reducing incentives to exercise during pregnancy [29–31]. Accordingly, the American College of Obstetricians and Gynecologists (ACOG) and the US Department of Health and Human Services (DHHS) recommended pregnant women without contraindications to perform moderate-intensity aerobic exercise for at least 20–30 min per day or 150 min per week [32, 33]. Despite that, only 9–15% of pregnant women meet the current exercise recommendations, and the number is much less for overweight and obese pregnant women [29–31].

There are various reasons for a lack of exercise during pregnancy, such as knowledge gaps, lack of time, energy, motivation, social support, accessibility of exercise options,

and poor physical health [34]. In addition, studies have also reported that fear regarding baby health during and after exercise is one of the main reasons women are sedentary during pregnancy [34]. Although mounting evidence suggests that maternal exercise is safe and beneficial for fetal and child health, some inconsistent reports, showing negative impacts on fetal growth [35, 36], could potentially reduce the incentive to exercise during pregnancy. To alleviate public concerns and fully uncover the benefits of gestational exercise in child health, it is necessary to perform a systematic review and meta-analysis with better consideration of factors affecting exercise outcomes. Because maternal normal weight (MNW) and MO women differ in physiological and metabolic status during pregnancy [37], maternal body weight is a critical factor in how fetal development is altered due to maternal exercise [20, 25, 26, 38], which was not fully considered in previous meta-analyses [20, 25–28], potentially contributing to the inconsistent association between exercise and outcomes. In addition, maternal exercise is often intermingled with other lifestyle factors, including diet, smoking, alcohol drinking, and stress, which were also not well considered in previous studies [20, 25–28]. Failure to differentiate exercise impacts from confounders not only substantially introduces study variations, but also prevents revealing the full impacts of maternal exercise on child health [20, 25, 26, 38]. Furthermore, altering the intrauterine environment and fetal development may exert long-term impacts on child growth and health, which were not covered in previous meta-analyses [20, 25–28]. Considering the limitations of previous studies, the objective of this systematic review and meta-analysis was to synthesize existing evidence of the effects of exercise-only and exercise with confounders during pregnancy, in both MNW and MO, on child growth trajectory and obesity risks. In addition, the impacts of exercise volume (dose) were also assessed.

2 Methods

2.1 Search Strategy and Selection Criteria

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement, and the checklist was completed (Electronic Supplementary Material Table S1) [39]. This meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020205031). Eligibility criteria followed the PICOS guideline (Population; Intervention; Comparison; Outcome; Study design) [33].

2.1.1 Population

Women who did not receive exercise interventions (control or usual care arms) versus those who received exercise interventions during pregnancy (> 16 years) were the population of interest in this meta-analysis. The included pregnant women had uncomplicated singleton pregnancies and no health issues (2 weeks before and during pregnancy) including (a) type 1 and 2 diabetes mellitus, (b) hypertension or heart issues, (c) chronic renal disease, (d) multiple pregnancy, (e) Rh sensitization, (f) corticosteroid medication, (g) cervical incompetence or cerclage history, (h) antibiotics or tocolytics, (i) sickle cell disease, (j) thalassemia, (k) hemoglobin C, (l) lung diseases, (m) hyperthyroidism, (n) polycystic ovarian syndrome with medication, (o) anemia, (p) eating disorder, and (q) psychosis. The included population also did not have exercise contraindications during or immediately following exercise, including uterine contraction, hypoxia, and other fetal distress, which were defined by the American College of Obstetricians and Gynecologists Committee Opinion and Society of Obstetricians and Gynecologists of Canada [33, 40]. Included studies included pregnant women with prepregnancy normal weight (MNW; BMI 18.5–24.9 kg/m^2) and prepregnancy maternal overweight or obesity (MO; BMI ≥ 25 kg/m^2). Data from maternal overweight (25 ≤ BMI < 30 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) exercisers were analyzed together in the meta-analysis due to limited data and no separation in randomized trials.

2.1.2 Interventions

Exercise interventions included both quantified physical activity (skeletal muscle movement with energy expenditure above sedentary conditions, such as recreational, household, and occupational activity) and exercise (planned, structured, and repetitive with the objectives of improving or maintaining physical fitness) [41]. All maternal subjects received interventions during the period of pregnancy and before labor (e.g., labor contraction or water breaking). Because confounders (e.g., dietary nutrition, alcohol drinking, tobacco, food borne infections) were often associated with maternal exercise, to discern "the main effect of exercise", we performed subgroup analysis if confounders were used, including 'maternal exercise-only interventions' and 'maternal exercise + confounders' in both MNW and MO groups.

2.1.3 Comparison

Quantified outcomes from maternal exercise and physical activity during pregnancy were compared with control group outcomes from no or less exercise with various types, frequencies, durations, and enrolled time [e.g., treadmill (type);

three times per week (frequency); 60 min per session (duration); 13 gestational weeks (enrolled time)].

2.1.4 Outcomes

Maternal exercise outcomes included child obesity indicators in early life [neonates (birth) and infants (0 < age < 2 years)] and childhood (2–15 years)], including birth weight; preterm (< 37 gestational weeks); SGA (birth weight < 10th percentile for age and sex, or < 2,500 g, or > 2 standard deviations below the mean); LGA (birth weight > 90th percentile for age and sex, or > 4000*g*, or > 2 standard deviations above the mean); childhood weight and obesity (body mass index ≥ 95th percentile for age and sex); the circumference of the head, chest and waist; body length; fat mass (arm, thigh, abdominal) and fat volume (visceral, subcutaneous, and abdominal).

2.1.5 Study design

All randomized controlled trials were included. Other types of studies (e.g., reviews and abstracts) were not included in the current meta-analysis.

2.2 Data Extraction and Quality Assessment

Data search was done by two authors (YT, GL) independently through the NCBI PubMed MeSH, Web of Science, ScienceDirect, and Cochrane Library database. The search was limited to randomized human studies with English language restrictions. Keywords were constructed including primary items of exercise, pregnancy, BMI, obesity and offspring with detailed search keys (Electronic Supplementary Material Table S2). Searching was from inception date to Feb 15, 2020. Library and author contacts were necessarily made for information completeness.

Two authors (YH, QY) independently screened the titles and abstracts and then checked the full texts. PICOS guidelines were used to extract the necessary information. If decisions regarding study quality were not consistent between the reviewers, the article was further sent to the Article Decision Committee (MD, MJ) for a final decision. Before rapid title screening, duplicates were removed by DistillerSR (Evidence Partners, Ottawa, Ontario, Canada). Criteria for study inclusion were data completeness and sufficient sample size ($n \geq 2$). The extracted content included the first author, year, title, study design, country, population, selection criteria, participant number, age, prepregnancy BMI, prepregnancy weight, parity, height, tobacco use, alcohol use, labor hours, gestational age, physical treatment details (e.g., exercise type, frequency, intensity, and duration), preterm birth, 1 min Apgar score, cesarean section percentage, stillbirth rate, birth weight, LGA, SGA, fat mass, fat volume, muscle mass, infant weight, infant obesity, childhood weight, child obesity, head and waist circumference, and other child obesity related data. When data were not fully reported in the articles, the authors contacted librarians for data requests. In total, 42 articles were requested from librarians; full manuscripts were received for all requests. Selection, information and confounding biases were determined according to the Newcastle–Ottawa Quality Assessment for cohort studies (Electronic Supplementary Material Table S3) [42].

The quality of each study and publication bias were assessed by two individuals (GL, YT) according to the Cochrane Handbook and Newcastle–Ottawa scale method [42]. The following criteria were used for quality assessment: (a) research hypothesis related to the impacts of exercise-only interventions or exercise + other interventions in MNW and MO during pregnancy on obesity indicators in fetuses, neonates, infants, and children; (b) randomized controlled design; (c) blinded subjects assignment; (d) the similarity of the control group; (e) the similarity of the treatment group; (f) result standardization; (g) bias risks. Microsoft Excel (Excel, Microsoft Corp., Redmond, WA, USA) was used for data collection.

2.3 Statistical Analysis

All analyses were conducted using R v.3.4.3 software [43] and the *metafor* package [44]. Data were pooled using a random effects model. Dichotomous variable comparison was performed with the effect size (ES) of two group comparison—log odds ratio (OR) and transferred back to an OR with the '*transf*' method [45]. The effects of prenatal exercise on continuous variables (e.g., child weight) were analyzed by the ES of the standardized mean difference (SMD) [44, 46, 47].

A random model was chosen for meta-analysis according to the DerSimonian and Laird method [48]. The Knapp and Hartung methods were used to adjust the confidence interval [49]. Q test of χ^2 and I^2 was used to analyze heterogeneity [49]. Values of I^2 in the range of 0–50%, 50–75%, and 75–100% indicate low, medium, and high data heterogeneity, respectively [50]. Publication bias was assessed by a funnel plot with Egger's regression [51, 52]. Sensitivity was analyzed by the trim-and-fill method, which trimmed publication bias, added missing values and checked the study stability [53]. Subgroup analysis was prioritized as follows: (a) normal-weight subjects with normal prepregnancy BMI 18.5–24.9 kg/m^2; and (b) MO subjects with prepregnancy BMI ≥ 25 kg/m^2. In meta-regression, logOR and SMD variables were analyzed by the random model [54]. Linear regression of the explanatory variables was conducted to examine the existence of the dose–response relationship between maternal exercise volumes and child obesity outcomes [55,

56]. The exercise volume was quantified using metabolic equivalent (MET)-min per week, which is the product of exercise intensity and the minutes of exercise per week [57]. A permutation test was used to analyze the robustness of the meta-regression model [58]. Only studies with complete data (mean, replicates, standard deviation or standard error of both control and treatment groups) were included in the meta-analysis.

3 Results

3.1 Search Results and Study Characteristics

Initial searching with no language restriction yielded a total of 37,418 records (Fig. 1). After screening for English language, title, abstract, and removing duplicates, 315 eligible full texts remained. After excluding reviews and original studies lacking interventions, outcomes, and replicates (Electronic Supplementary Material Table S4), 99 studies were eligible for this meta-analysis, representing 250,028 pregnancies (births) associated with exercise interventions during pregnancy and 346,848 control pregnancies (births) not associated with exercise interventions (Electronic Supplementary Material Table S5) [35, 36, 59–155].

All studies included in the analysis had a randomized controlled design, and were conducted in Asia, Australia, America, Europe, Ireland, Netherlands, New Zealand or West Africa (Electronic Supplementary Material Table S5) [35, 36, 59–155]. Studies included varied exercise types, including leisure activity (walking, standing, and household) and training (yoga, bicycling, treadmill exercise, running, jogging, and other ACOG-recommended exercise) [156]. Exercise duration also varied, with a range from 8 weeks to full pregnancy, and exercise volume ranged from 80 to 6000 MET-min per week. Various exercise outcomes were described in different studies, with birth weight as the most commonly reported (81 studies). Because of considerable clinical variations and heterogeneity within and between studies, we used the Newcastle–Ottawa scale to assess study quality [42], a funnel plot-Egger's test to assess publication bias [52], and a trim-and-fill analysis to assess result sensitivity [53].

3.2 Study Quality, Bias, and Result Sensitivity

All studies included in this meta-analysis were of fair to good quality as indicated by ≥ 5 scores on the Newcastle–Ottawa scale tests (Electronic Supplementary Material Table S6) [35, 36, 59–155]. Funnel plot analysis further assessed the risk of publication bias if data were available, including exercise-only interventions in MNW, exercise + confounders in MNW, exercise-only intervention in MO, and exercise + confounders in MO (Electronic

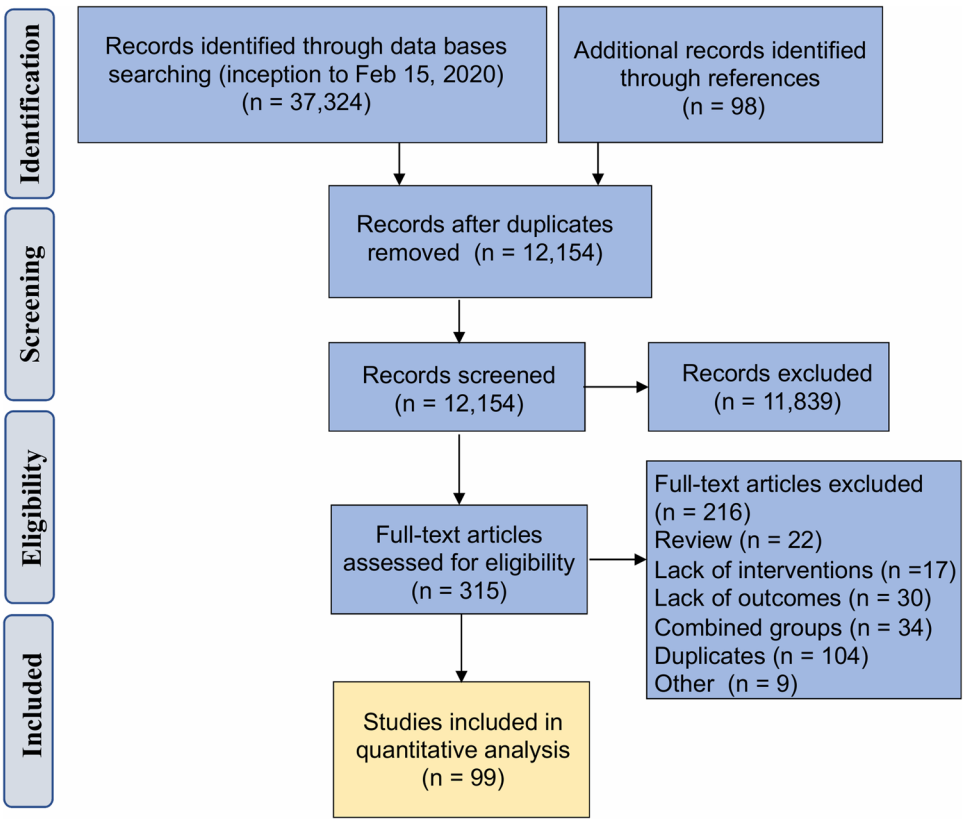
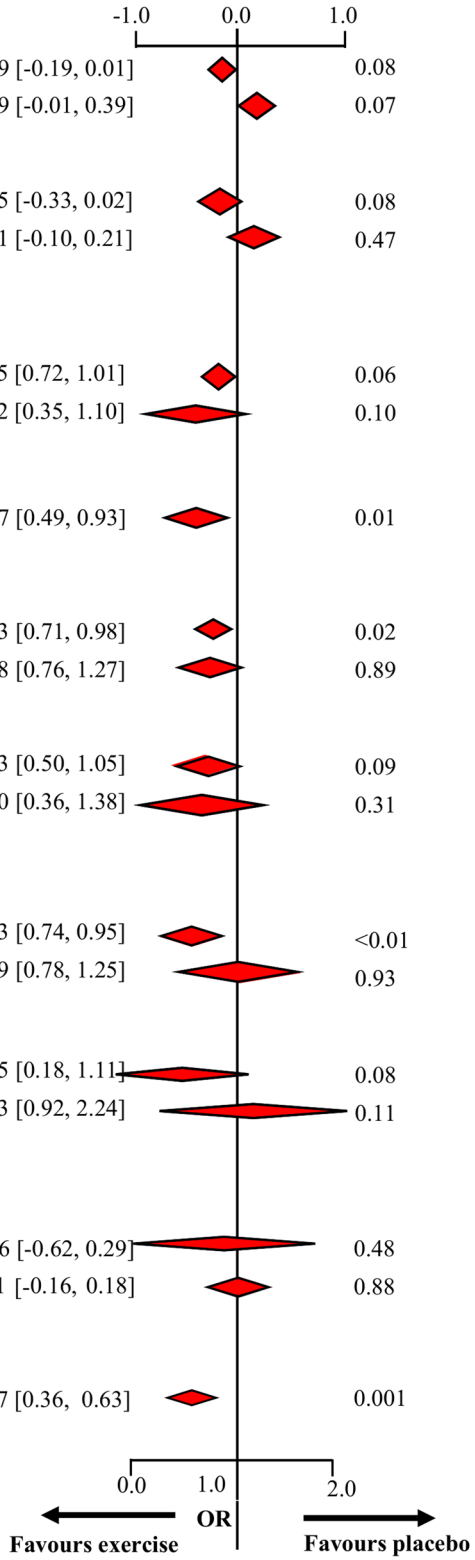


Fig. 1 PRISMA flow diagram of studies selected for present meta-analysis

Outcome	Studies (N)	Exercise (N)	Placebo (N)	Summary Effect Estimates of Forest Plots: SMD or OR [95% CI]	P value	Heterogeneity: I^2 (%)	P
Birth weight (SMD)							
MNW							
Exercise only	59	98,919	136,806	-0.09 [-0.19, 0.01]	0.08	98.7	<0.01
Exercise + confounders	8	2,238	3,223	0.19 [-0.01, 0.39]	0.07	88.3	<0.01
MO							
Exercise only	10	2,269	2,210	-0.15 [-0.33, 0.02]	0.08	81.7	<0.01
Exercise + confounders	4	290	475	0.01 [-0.10, 0.21]	0.47	0.0	<0.01
Preterm birth (OR)							
MNW							
Exercise only	23	40,417	35,715	0.85 [0.72, 1.01]	0.06	83.3	<0.01
Exercise + confounders	4	1,411	1,304	0.62 [0.35, 1.10]	0.10	15.8	0.31
MO							
Exercise only	2	2,211	839	0.67 [0.49, 0.93]	0.01	0.0	0.77
SGA (OR)							
MNW							
Exercise only	29	45,593	46,758	0.83 [0.71, 0.98]	0.02	74.5	<0.01
Exercise + confounders	5	1,837	1,728	0.98 [0.76, 1.27]	0.89	0.0	0.85
MO							
Exercise only	6	2,765	1,144	0.73 [0.50, 1.05]	0.09	40.4	0.11
Exercise + confounders	3	239	524	0.70 [0.36, 1.38]	0.31	0.0	0.56
LGA (OR)							
MNW							
Exercise only	25	50,331	33,999	0.83 [0.74, 0.95]	<0.01	60.4	<0.01
Exercise + confounders	6	2,054	3,026	0.99 [0.78, 1.25]	0.93	0.0	0.82
MO							
Exercise only	9	33,328	48,253	0.45 [0.18, 1.11]	0.08	98.3	<0.01
Exercise + confounders	4	372	550	1.43 [0.92, 2.24]	0.11	0.0	0.78
Child body weight (SMD)							
MNW (Exercise only)							
Infant (< 2 years)	3	133	91	-0.16 [-0.62, 0.29]	0.48	57.6	<0.001
Child (2-15 years)	2	16,952	25,650	0.01 [-0.16, 0.18]	0.88	88.9	<0.001
Child obesity (OR)							
MNW (Exercise only)							
Childhood	1	5,452	1,468	0.47 [0.36, 0.63]	0.001	77.0	<0.01



◂**Fig. 2** Summary of forest plot displaying efficacies of exercise-only interventions and exercise + confounders during pregnancy in mothers with maternal normal weight (MNW; prepregnancy BMI 18.5–24.9 kg/m^2) or maternal overweight and obesity (MO; prepregnancy BMI ≥ 25 kg/m^2) in altering birth weight (standard mean difference, SMD), odds ratio (OR) of preterm birth (< 37 gestational week), OR of small for gestational age (SGA; birth weight < 10th percentile, or < 2500 g, or > 2 standard deviation below the mean), OR of large for gestational age (LGA; birth weight > 90th percentile, or > 4000 g, or > 2 standard deviation above the mean), infant (SMD; age ≤ 2 years) and childhood weight (SMD; age 2–15 years), and OR of childhood obesity (BMI ≥ 95th percentile; age 2–15 years). Error bars indicate 95% confidence interval

Supplementary Material Fig S1) [52]. Primary outcomes included birth weight, the OR of preterm birth, the OR of SGA, the OR of LGA, infant and child body weight, and the OR of child obesity. Egger's test did not find significant publication bias and asymmetry ($P > 0.05$) in funnel plots, indicating a low publication bias and high quality of the included studies (Electronic Supplementary Material Fig S1) [35, 36, 59–155]. To assess result sensitivity, after excluding asymmetric outlying studies in the funnel plot using the trim-and-fill method, the results were also highly consistent with the meta-results (Electronic Supplementary Material Table S7), demonstrating the high repeatability and sensitivity of the meta-results.

3.3 Birth Weight

Eighty-one studies ($n = 246{,}340$ births) showed no overall effect (including both MNW and MO; SMD, 0.01; 95% CI −0.10, 0.12; $I^2 = 98.3\%$; $P = 0.25$) of exercise in pregnancy on birth weight (Electronic Supplementary Material Fig S2) [35, 36, 59–75, 78, 81, 82, 84, 87–94, 96–99, 101–104, 108–111, 116–118, 120–134, 136–143, 145–147, 149, 151–153]. In subgroups, exercise-only interventions in MNW ($n = 235{,}725$ births; Fig. 2 and Electronic Supplementary Material Fig S2) tended to reduce birth weight (SMD, −0.09; 95% CI −0.19, 0.01; $I^2 = 98.7\%$; $P = 0.08$;) [35, 36, 59–75, 78, 81, 82, 84, 87–89, 91, 92, 94, 96, 97, 99, 101, 103, 104, 108–110, 116, 118, 120–122, 125, 126, 128, 131–133, 136–138, 140, 141, 143, 146, 151, 152], which was also observed in exercise-only interventions in MO ($n = 4389$ births; SMD, −0.15; 95% CI −0.33, 0.02; $I^2 = 81.7\%$; $P = 0.08$) [90, 93, 98, 117, 123, 124, 127, 130, 139, 153]. However, exercise + confounders in MNW tended to increase the birth weight ($n = 5{,}461$ births; SMD, 0.19; 95% CI −0.01, 0.39; $I^2 = 88.3\%$; $P = 0.07$; Fig. 2 and Electronic Supplementary Material Fig S2) [102, 111, 125, 129, 142, 145, 147, 149]. No significance was observed in exercise + confounders in MO ($n = 765$ births; SMD, 0.06; 95% CI −0.10, 0.21; $I^2 = 0.0\%$; $P = 0.47$; Fig. 2 and Electronic Supplementary Material Fig S2) [90, 111, 134, 153].

3.4 Preterm Birth

Preterm birth and fetal growth restriction contributed to the reduced birth weight, which increased the risks of later life obesity and other metabolic dysfunctions [157]. Thirty-two studies (overall) reported an OR of preterm birth in pregnancies with exercise interventions ($n = 81{,}897$ births), showing a reduced overall risk of preterm birth by 18% (OR 0.82; 95% CI 0.70, 0.96; $I^2 = 80.7\%$; $P = 0.01$; Fig. 3) [65, 66, 76, 81, 84, 86, 88, 96, 102–106, 108, 111, 114, 115, 118, 121, 130, 140–142, 146–149, 152]. In subgroup analyses, a decrease in preterm birth risk was also observed in exercise-only interventions in both MNW ($n = 76{,}132$ births; OR 0.85; 95% CI 0.72, 1.01; $I^2 = 83.3\%$; $P = 0.06$; Figs. 2 and 3) and MO ($n = 3{,}050$ births; OR 0.67; 95% CI 0.49, 0.93; $P = 0.01$; Figs. 2 and 3) [65, 66, 76, 81, 84, 86, 88, 96, 103–106, 108, 114, 115, 118, 121, 130, 140, 141, 146–148, 152], showing the benefits of exercise-only interventions in reducing the risk of preterm birth. However, exercise + confounders in MNW did not affect preterm birth risk ($n = 2715$ births; OR 0.62; 95% CI 0.35, 1.10; $I^2 = 15.8\%$; $P = 0.10$; Figs. 2 and 3) [102, 111, 142, 149]. No eligible studies reported the OR of preterm birth in the exercise + confounders in MO subgroup.

3.5 SGA

Fifty-three studies (overall) included an OR of SGA following maternal exercise intervention in pregnancy ($n = 100{,}588$ births), showing a reduced risk of SGA by 18% (OR 0.82; 95% CI 0.72, 0.93; $I^2 = 65.7\%$; $P = 0.003$; Fig. 4) [35, 65, 76–80, 87, 90, 91, 93, 97, 102, 105, 114–116, 119, 121–123, 126, 129–132, 134, 136, 138, 139, 141, 142, 145, 146, 148, 149, 153]. A notable decrease in SGA risk was also observed in exercise-only interventions in both MNW ($n = 92{,}351$ births; OR 0.83, 95% CI 0.71, 0.98; $I^2 = 74.5\%$; $P = 0.02$; Figs. 2 and 4) and MO ($n = 3{,}909$ births; OR 0.73, 95% CI 0.50, 1.05; $I^2 = 40.4\%$; $P = 0.09$; Figs. 2 and 4) [35, 65, 76–80, 87, 91, 93, 97, 105, 114–116, 119, 121–123, 126, 130–132, 136, 138, 139, 141, 146, 148, 153], showing that exercise-only interventions in pregnancy effectively reduced the risk of low birth weight. For maternal exercise with confounders, the OR of SGA was not significantly affected in either MNW ($n = 3565$ births; OR 0.98; 95% CI 0.76, 1.27; $I^2 = 0.0\%$; $P = 0.89$; Figs. 2 and 4) or MO exercise ($n = 763$ births; OR 0.70; 95% CI 0.36, 1.38; $I^2 = 0.0\%$; $P = 0.31$; Figs. 2 and 4) [90, 102, 129, 134, 142, 145, 149, 153].

3.6 LGA

Forty-four studies (overall) reported an OR of LGA following maternal exercise interventions during pregnancy

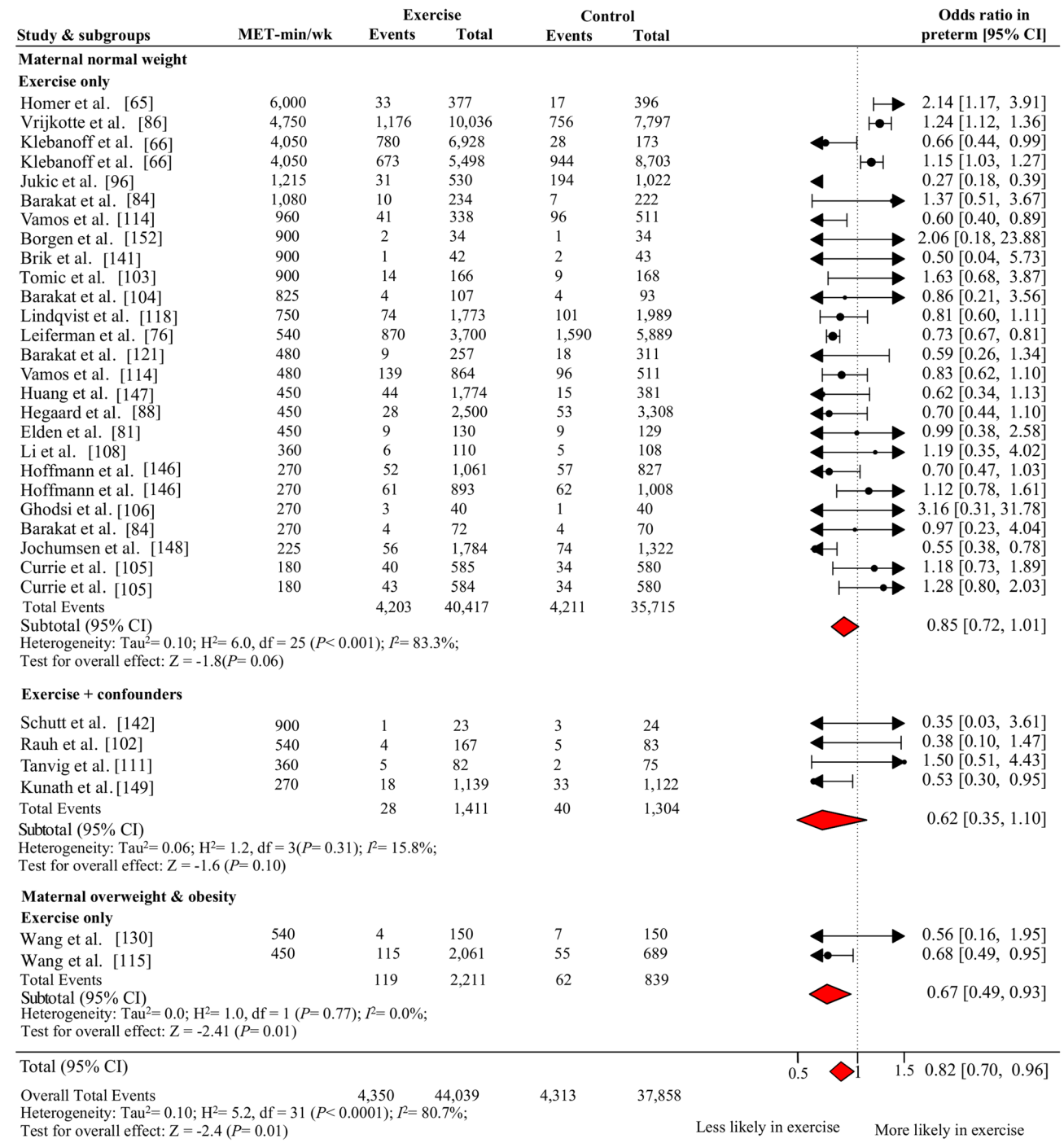


Fig. 3 Forest plot displaying effects of exercise-only interventions and exercise + confounders of pregnant women with prepregnancy normal weight (MNW; BMI 18.5–24.9 kg/m^2) and overweight and obesity (MO; BMI ≥ 25 kg/m^2) on odds ratio (OR) of preterm birth. Error bars indicate 95% CI. MET means metabolic equivalent

($n = 171{,}893$ births), showing a 28% decrease in LGA (OR 0.72; 95% CI 0.55, 0.95; $I^2 = 95.8\%$; $P = 0.02$; Fig. 5) [83–85, 87, 88, 90, 91, 93, 97, 98, 101–103, 105, 108, 111, 112, 115–117, 120–122, 124–127, 129–132, 134, 137, 138, 140, 142, 145, 146, 148, 149, 153]. In subgroup analyses, exercise-only interventions in MNW also reduced the risk of LGA by 17% ($n = 84{,}310$ births; OR 0.83; 95% CI 0.74, 0.95; $I^2 = 60.4\%$; $P = 0.005$; Figs. 2 and 5) [84, 85, 87, 88, 91, 97, 98, 101, 103, 105, 108, 112, 116, 120–122, 125, 126, 131, 132, 137, 138, 140, 146, 148], and exercise-only

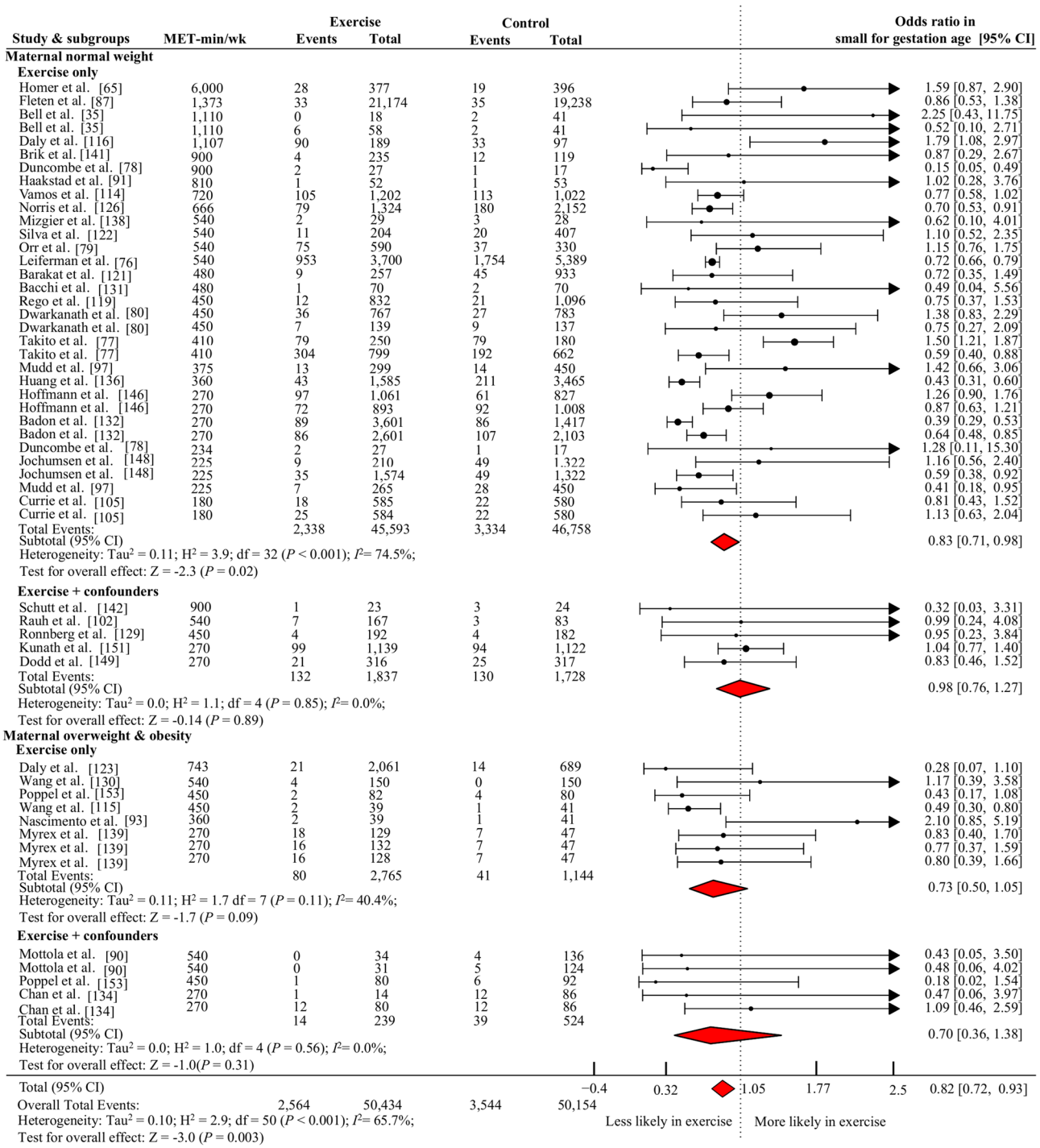


Fig. 4 Forest plot displaying effects of exercise-only interventions and exercise + confounders of pregnant women with prepregnancy normal weight (MNW; BMI 18.5–24.9 kg/m^2) and overweight and obesity (MO; BMI ≥ 25 kg/m^2) on odds ratio (OR) of small for gestational age (SGA). Error bars indicate 95% CI. MET means metabolic equivalent

interventions in MO reduced the risk of LGA by 55% (n = 81,581 births; OR 0.45; 95% CI 0.18, 1.11; I^2 = 98.3%; P = 0.08; Figs. 2 and 5) [83, 90, 93, 115, 117, 124, 127, 130, 153], showing a substantial decrease in risk of large birth weight. For exercise with confounders, the OR of LGA was not affected in either MNW (n = 5080 births; OR 0.99; 95%

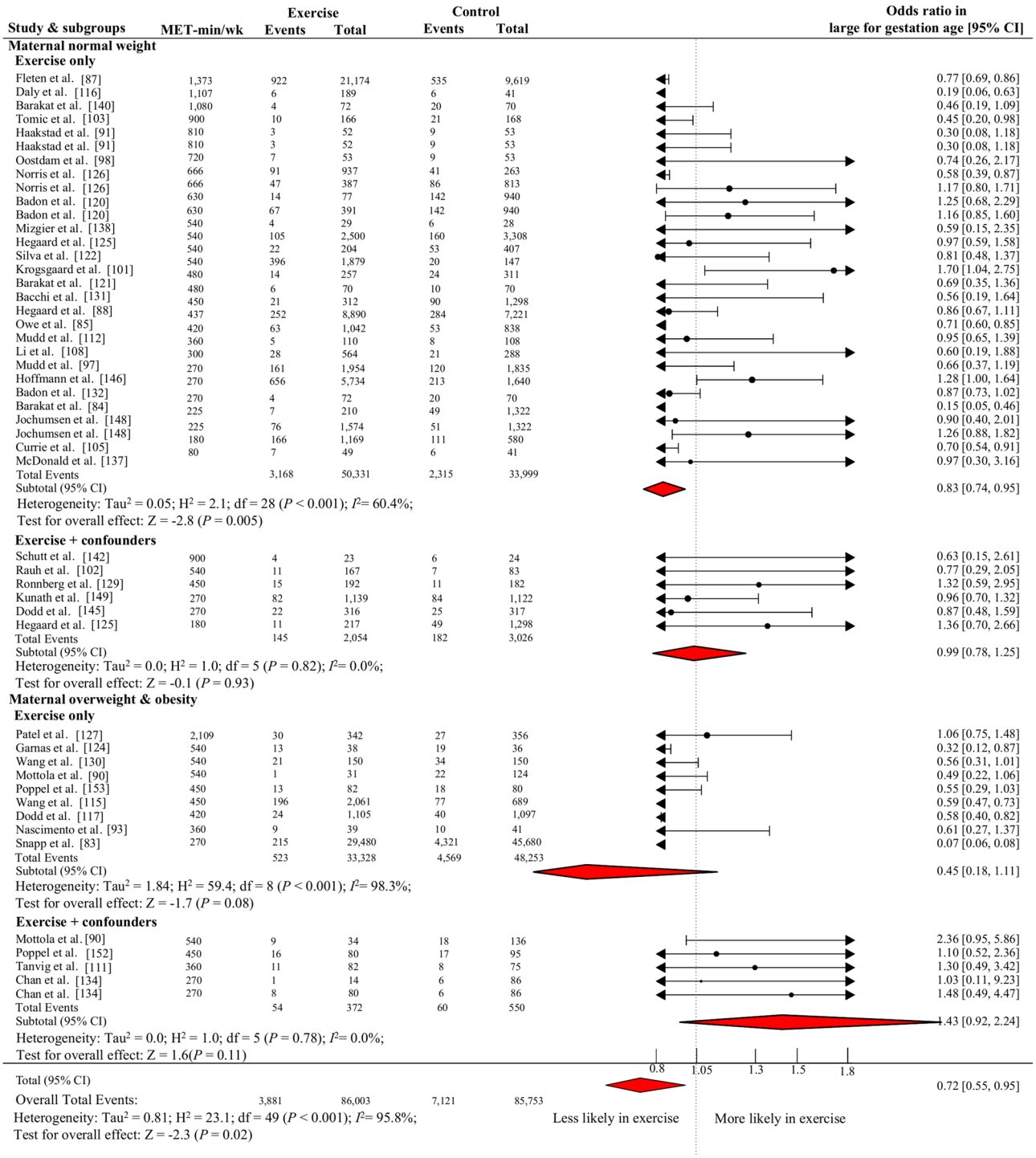


Fig. 5 Forest plot displaying effects of exercise-only interventions and exercise + confounders of pregnant women with prepregnancy normal weight (MNW; BMI 18.5–24.9 kg/m^2) and overweight and obesity (MO; BMI ≥ 25 kg/m^2) on odds ratio (OR) of large for gestational age. Error bars indicate 95% CI. MET means metabolic equivalent

CI 0.78, 1.25; $I^2 = 0.0\%$; $P = 0.93$; Figs. 2 and 5) or MO exercise ($n = 922$ births; OR 1.43; 95% CI 0.92, 2.24; $I^2 = 0.0\%$; $P = 0.11$; Figs. 2 and 5) [90, 102, 111, 125, 129, 134, 142, 145, 149, 153].

3.7 Childhood Weight and Obesity Risk

Seven studies (overall) reported infant and child body weight following maternal exercise interventions during

pregnancy ($n = 43{,}040$) and showed no significant change in body weight (SMD, −0.05; 95% CI −0.23, 0.14; $I^2 = 90.5\%$; $P = 0.63$) [89, 94, 100, 107, 111, 150, 154]. In subgroup analysis, three studies reported infant body weight (age < 2 years, $n = 224$ infants; Fig. 2 and Electronic Supplementary Material Fig S3) [89, 107, 150], and two studies reported child body weight (2–15 years; $n = 42{,}602$ children) following exercise-only interventions in MNW [94, 100]. No significant effect was observed in either infant (SMD, −0.16; 95% CI −0.62, 0.29; $I^2 = 57.6\%$; $P = 0.48$) or child body weight (SMD, 0.01; 95% CI −0.16, 0.18; $I^2 = 88.9\%$; $P = 0.88$) following exercise-only interventions in MNW (Fig. 2 and Electronic Supplementary Material Fig S3). Only one study reported infant [111] or child body weight [114] from exercise + confounders in MNW, which was insufficient for subgroup analysis. Furthermore, no eligible studies reported infant and child body weight from exercise-only intervention or exercise + confounders in MO.

Two studies (overall) reported an OR of childhood obesity (2–15 years) following maternal exercise during pregnancy ($n = 27{,}410$ children; Fig. 2 and Electronic Supplementary Material Fig S4) [111, 135], and showed significant decrease in child obesity risk by 35% (OR 0.65; 95% CI 0.45, 0.94; $I^2 = 80\%$; P = 0.02; Fig. 2 and Electronic Supplementary Material Fig S4), disclosing a long-term effect of maternal exercise in reducing the risk of child obesity. Furthermore, exercise-only interventions in MNW also reduced childhood obesity risk by 53% ($n = 6920$ children; OR 0.47; 95% CI 0.36, 0.63; $I^2 = 77\%$; $P < 0.001$) [111]. Insufficient studies were available for assessing the OR of childhood obesity from exercise-only interventions or exercise + confounders in MO.

3.8 Meta-regression of Exercise Volume on Outcomes and Sensitivity Analysis

We also conducted meta-regression to investigate the dose (volume) effects of exercise on fetal growth and childhood obesity outcomes (Table 1). Birth weight was negatively and dose-dependently associated with the volume of exercise-only interventions in MNW ($P = 0.01$; $n = 235{,}725$ births; Table 1) [35, 36, 59–75, 78, 81, 82, 84, 87–89, 91, 92, 94, 96, 97, 99, 101, 103, 104, 108–110, 116, 118, 120–122, 125, 126, 128, 131–133, 136–138, 140, 141, 143, 146, 151, 152]. The reduced birth weight was particularly driven by exercise volume over 810 MET-min per week (Electronic Supplementary Material Fig S5). The volume of exercise + confounders in MNW was positively and linearly associated with birth weight ($P = 0.01$; $n = 5461$ births; Table 1), ranging from 180 to 945 MET-min per week (Electronic Supplementary Material Fig S5) [102, 111, 125, 129, 142, 145, 147, 149]. Except for the birth weight, no significant exercise dose effect was observed for other outcomes (Table 1). To test the meta-regression sensitivity, we conducted a permutation test [58] and the results observed were consistent with the meta-regression, showing a high sensitivity of the meta-regression results (Table 1).

4 Discussion

4.1 Summary of Evidence

The prevalence of child obesity has dramatically increased in recent decades, becoming a serious public health concern [158]. The "developmental origins of health and disease" suggest that the intrauterine environment programs fetal organ/tissue development, projecting a trajectory of metabolic diseases in the later life of offspring [159–161]. Previous systematic reviews have summarized that exercise during pregnancy benefits maternal health, including reduced occurrence of gestational and postpartum weight gain, gestational diabetes, hypertension, pre-eclampsia, depression, and anxiety [18, 19, 22, 162]. Exercise in women with normal pregnancies or with gestational diabetes also has no adverse effect on fetal heart rate, hyperthermia, neonatal morbidity or mortality [163, 164]. Notably, a recent meta-analysis showed that maternal exercise during pregnancy reduces the risk of macrosomia [165], which may exert preventive effects against childhood obesity [166, 167], but the programming impacts of exercise in MNW and MO during pregnancy on fetal growth and childhood obesity are largely unknown. The current meta-analysis of 99 randomized controlled trials, including exercise interventions in MNW and MO (250,028) and controls (346,848) during pregnancy, showed that maternal exercise-only interventions reduced the risks of adverse fetal growth and birth outcomes, including the OR of preterm birth, SGA, and LGA (Fig. 2). In addition, exercise interventions in MNW substantially reduced risk of childhood obesity. The beneficial outcomes were more evident in maternal exercise-only interventions relative to exercise with confounders. In meta-regression, exercise-only volume in MNW dose-dependently reduced birth weight, particularly for exercise volumes greater than 810 MET-min per week (ACOG and DHHS recommendation: 500 MET-min per week equals approximately 150 min/week moderate aerobic exercise) [32, 33], but no significant dose effect was observed in other maternal exercise-only outcomes. Overall, this analysis suggests that exercise in pregnant women improves fetal growth, effectively reducing susceptibility to childhood obesity.

SGA is a leading cause of neonatal mortality and morbidity that primarily results from preterm birth and fetal growth restriction [157]. SGA babies have a greater risk for complications from immature fetal development, including in the brain, pancreas, skeletal muscle, and adipose tissue,

Table 1 Meta-regression assessing association between maternal exercise volume (MET-min per week) and perinatal growth abnormality and childhood obesity outcomes, and permutation test evaluating result sensitivity

Item	Intercept	SE	*t*	*P*	CI	Coefficient	SE	*t*	*P*	95% CI	Tau	I^2 (%)	R^2 (%)	*P* (H)	*P* (PT-intercept)	*P* (PT–coefficient)
Birth weight																
Maternal normal weight																
Exercise only	0.12	0.11	1.08	0.29	−0.10, 0.34	−0.0002	0.0001	−2.64	0.01	−0.0004, −0.0001	0.37	99.5	9.5	<0.001	0.24	0.03
Exercise + confounders	−0.33	0.16	−2.2	0.07	−0.7, 0.03	0.001	0.0003	3.66	0.01	0.0004, 0.002	0.03	72.4	81.4	0.008	0.07	0.01
Maternal overweight and obesity																
Exercise only	−0.33	0.16	−2.06	0.07	−0.67, 0.03	0.0003	0.0002	1.44	0.17	−0.0002, 0.0007	0.09	81.9	14.0	<0.001	0.11	0.16
Exercise + confounders	−0.07	0.15	−0.46	0.68	−0.55, 0.41	0.0003	0.0004	0.86	0.45	−0.0009, 0.002	0.00	0.00	NA	0.0008	0.65	0.45
Preterm birth odds ratio																
Maternal normal weight																
Exercise only	−0.29	0.11	−2.59	0.02	−0.52, −0.06	0.0001	0.0001	1.84	0.08	0.0, 0.0002	0.12	81.7	15.6	<0.001	0.03	0.08
Exercise + confounders	0.01	0.85	0.02	0.99	−3.65, 3.69	−0.001	0.002	−0.61	0.60	−0.009, 0.007	0.25	43.6	0	0.18	0.96	0.67
SGA odds ratio																
Maternal normal weight																
Exercise only	−0.27	0.10	−2.79	0.01	−0.47, −0.07	0.0001	0.0001	1.63	0.11	0.0, 0.0003	0.13	76.5	7.4	<0.001	0.04	0.13
Exercise + confounders	0.31	0.23	1.33	0.28	−0.43, 1.04	−0.001	0.0008	−1.47	0.24	−0.004 0.001	0.00	0.00	NA	0.86	0.28	0.22
Maternal overweight and obesity																
Exercise only	0.39	0.59	0.67	0.53	−1.0, 1.82	−0.002	0.002	−1.29	0.24	−0.005, 0.002	0.06	26.1	39.4	0.17	0.52	0.23
Exercise + confounders	0.94	0.76	1.4	0.30	−1.47, 3.35	−0.004	0.002	−1.79	0.17	−0.01, 0.003	0.00	0.00	100	0.70	0.60	0.47
LGA odds ratio																
Maternal normal weight																
Exercise only	−0.02	0.16	−0.16	0.87	−0.34, 0.29	−0.0003	0.0003	−1.27	0.21	−0.0008, 0.0002	0.07	63.0	0.0	<0.001	0.97	0.15
Exercise + confounders	0.18	0.20	0.9	0.42	−0.37, 0.74	−0.0006	0.0006	−1.0	0.36	−0.002, 0.001	0.00	0.00	NA	0.78	0.34	0.33
Maternal overweight and obesity																
Exercise only	−1.27	0.38	−3.36	0.01	−2.16, −0.38	0.0007	0.0004	1.59	0.16	−0.0003, 0.0018	0.53	93.9	14.8	<0.001	0.01	0.15
Exercise + confounders	−0.29	0.67	−0.43	0.70	−2.43, 1.86	0.002	0.002	0.99	0.36	−0.004, 0.007	0.00	0.00	NA	0.73	0.83	0.53
Infant and child body weight																
Maternal normal weight																
Infant age (0–2 years)	0.08	0.09	0.85	0.44	−0.16,0.31	−0.0001	0.0001	−1.31	0.25	−0.0003, 0.0001	0.03	74.6	14.9	0.002	0.29	0.29
Child age (2–15 years)	0.11	0.40	0.28	0.80	−1.61,1.83	−0.0005	0.0005	−0.83	0.49	−0.002, 0.002	0.12	53.3	0.0	0.11	0.67	0.50
Child obesity odds ratio																
Maternal normal weight																
Child age (2–15 years)	−0.53	0.34	−1.55	0.36	−4.85, 3.80	−0.0003	0.0005	−0.72	0.60	−0.007, 0.006	0.24	80.6	0.0	0.60	0.83	0.67

SE = standard error, CI = confidence interval, Tau determining variance between studies, I^2 determining the heterogeneity of studies, *P*(H) determining significance of study heterogeneity, *P*(PT-Intercept) determining significance of permutation test in estimating the significance of intercept, *P*(PT-Coefficient) determining significance of permutation test in estimating the significance of coefficient, SGA small for gestation age, LGA large for gestation age, MET metabolic equivalent, NA = non-available

contributing to an increased risk of childhood obesity and type 2 diabetes [168]. Exercise during pregnancy significantly increases oxygen and nutrient consumption in maternal skeletal muscle, which potentially reduces their availability to growing fetuses during and shortly after exercise [169, 170]. In addition, exercise may stimulate the release of oxytocin and uterine contraction [171], which may increase the risks of preterm birth [36, 63, 89] and fetal growth restriction [36, 65, 66]. Although these negative impacts are not assured, they discourage participation in active physical activity during pregnancy, especially in the last trimester [34]. By synthesizing a large body of available data, our meta-analysis showed that exercise-only interventions in both MNW and MO have a tendency to reduce birth weight, but the decrease in birth weight is not associated with an increased risk of preterm birth and SGA; indeed, maternal exercise-only interventions significantly reduced the risks of preterm birth (MNW, 15% decrease; MO, 33% decrease) and SGA (MNW, 17% decrease; MO, 27% decrease), revealing that maternal exercise has no adverse effects but rather improves birth outcomes by reducing the risks of preterm birth and restricted fetal growth. Notably, the exercise volume from exercise-only interventions in MNW dose-dependently reduced birth weight, and the association was dominantly driven by exercise volumes over 810 MET-min per week. Because this dose is much greater than the 500 MET-min per week recommended by ACOG and DHHS [32, 33], moderate aerobic exercise in pregnancy is safe and has a minimal impact on fetal growth. An impairment of placental vascular branching and nutrient perfusion is mainly responsible for the fetal growth restriction observed in obese pregnant women [172]. Recent studies have showed that maternal exercise promotes placental angiogenesis, branching, and blood flow in healthy and obese pregnant mice [173], which enhances placental nutrient exchange, likely contributing to the reduced risks of fetal growth restriction in exercise interventions in both MNW and MO.

Gestation is coupled with an increased maternal insulin resistance, which favors glucose partitioning to growing fetuses [174]. However, aggravated insulin resistance causes excessive movements of glucose and nutrients across the placenta, leading to fetal overgrowth and resulting in LGA or macrosomia. In addition to the risks of shoulder dystocia, brachial plexus trauma, and hypoglycemia in delivery, macrosomic babies likely have excessive body fat deposition [175] and accelerated pancreatic β-cell maturation [176], contributing to childhood obesity and type 2 diabetes [7]. MO and gestational diabetes increase the risk of macrosomia [7, 11]. Exercise counteracts hyperglycemia and hyperlipidemia by increasing insulin sensitivity and glucose and lipid consumption in skeletal muscle, reducing the risk of fetal overgrowth and associated childhood obesity [166, 173]. Consistently, a recent meta-analysis showed that exercise in women with gestational diabetes can reduce the risk of babies born LGA and neonatal adiposity [177]. In this meta-analysis, exercise-only interventions in both MNW and MO reduced the risk of LGA (> 90th percentile) by 17% and 55%, respectively, clearly showing that maternal exercise during pregnancy effectively reduces the risk of fetal excessive growth regardless of prepregnancy BMI.

Childhood obesity is prevalent worldwide, and its prevention has become a public health priority [1, 2]. Though genetic variance and living environment play substantial roles in the development of childhood obesity, evidence in recent decades also shows that childhood obesity can be traced back to intrauterine life, which is affected by maternal lifestyle, including overweight and obesity, alcohol consumption and smoking [159, 160]. Our systematic review and meta-analysis showed that maternal exercise-only interventions during pregnancy reduce the risks of fetal premature birth and excessive growth, which are important indicators of later life obesity [10–14]. Consistently, exercise-only interventions in MNW significantly reduced the risk of childhood obesity by 53%, exerting a persistent anti-obesity effect. However, due to limited data in the current literature, we cannot evaluate the impacts of exercise interventions in MO on the OR of childhood obesity, and call for more studies in this area. Supportively, recent studies in mice show that MO exercise reduced macrosomia, and exerted anti-obesity effects in childhood and adults [166, 173]. In this meta-analysis, although maternal exercise alone showed significant benefits on fetal and child healthy growth, these effects were not observed in maternal exercise with confounders. The number of published studies involved in exercise with confounders was much lower than that for exercise-only interventions, which potentially reduced the robustness of the analyses measuring interactive effects between exercise and other confounders. Furthermore, confounders were involved in multiple lifestyle alterations, including alcohol drinking, diet, stress, and smoking [102, 111, 125, 129, 142, 145, 147, 149], which increased study variations and confounding of treatment effects. Nonetheless, developing healthy lifestyles in pregnant women, such as consuming high-quality food and limiting stress, smoking and alcohol drinking, has been demonstrated to robustly improve fetal growth and child health [161, 178, 179]; more studies are required to better understand the interactive and optimal effects of maternal exercise along with those confounders on fetal development and childhood obesity.

4.2 Strengths and Limitations

To our knowledge, there is no meta-analysis covering the effects of exercise interventions (exercise-only intervention, exercise + confounders) in MNW and MO during pregnancy on prenatal growth and childhood obesity. This systematic

review and meta-analysis synthesized data from available randomized trials, which significantly increases the power of the conclusion. Publication bias risk was also assessed by funnel plots, and sensitivity was assessed by the trim-and-fill method. In this meta-analysis, sensitivity analysis was conducted along with meta-regression, showing the high repeatability of the data. In relation to dose effects, the meta-regression also revealed that high doses of maternal exercise during pregnancy were associated with reduced birth weight but were not related to the OR of preterm birth and SGA. The permutation test also showed the high sensitivity of meta-regression. A limitation of the current systematic review and meta-analysis is the existence of exercise intervention heterogeneity (varied type, intensity, duration, participating age and trimester stage), which may confound data interpretation. In addition, data on the programming impacts of exercise in MO during pregnancy on childhood weight and obesity risk are scarce, limiting the quality of assessment. Other confounding factors, such as maternal and child lifestyle behaviors (dietary nutrition, smoking, alcohol drinking, and socioeconomic status), may also increase data variations.

4.3 Future Directions

Due to limited data assessing the long-term impacts of exercise in MNW and MO on child growth and health, more follow-up studies are urgently required. In addition, metabolic, genetic, and epigenetic data of fetal and postnatal offspring affected by maternal exercise during pregnancy are also very limited in the current literature; thus, fundamental studies are needed to deepen our understanding of the beneficial impacts of maternal exercise on child health. Greater mechanistic understanding could lead to pharmaceutical intervention targets to mimic exercise, which could benefit the fetal growth and child health of pregnant women with exercise contraindications.

5 Conclusions

Overall, our findings revealed that maternal exercise-only intervention during pregnancy effectively reduced the risks of abnormal fetal growth and childhood obesity, including the risk of preterm birth (18% overall decrease), SGA (18% overall decrease), LGA (28% overall decrease), and childhood obesity (53% decrease from exercise-only interventions in MNW). Birth weight, infant, and childhood weight were not altered by exercise in either MNW or MO. Increased exercise volume in MNW was associated with reduced birth weight, particularly with exercise volume over 810 MET-min per week, but was not associated with the risk of preterm birth and SGA. Overall, maternal exercise during pregnancy, regardless of prepregnancy BMI, is a safe and beneficial nonpharmaceutical intervention for reducing the risk of adverse fetal growth and childhood obesity, providing an opportunity to prevent prevalent type 2 diabetes and cardiovascular diseases later in life.

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Declarations

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Conflict of interest Yanting Chen, Guiling Ma, Qiyuan Yang, Yun Hu, Jeanene Deavila, Meijun Zhu, and Min Du declare that they have no conflicts of interest relevant to the content of this review.

Data availability statement All data are available in the submitted manuscript or as electronic supplementary material.

Code availability Not applicable.

Author contributions All authors contributed to the design, data interpretation, and revising of the article. YC, GM, YH, QY, and JD screened the studies and extracted and analyzed data. YC, GM, YH, QY, JD, MZ, and MD contributed to the literature search, data extraction, and analysis. YT and GM led the quantitative analysis. MZ and MD were expert advisers. All authors read and approved the final manuscript.

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Authors and Affiliations

Yanting Chen[1,3] · Guiling Ma[2] · Yun Hu[2] · Qiyuan Yang[4] · Jeanene M. Deavila[1,3] · Mei-Jun Zhu[5] · Min Du[1,3]

[1] Center for Reproductive Biology, School of Molecular Biosciences, Washington State University, Pullman, WA 99164, USA

[2] College of Animal Science and Technology, Yangzhou University, Yangzhou 225009, People's Republic of China

[3] Nutrigenoimics and Growth Biology Laboratory, Department of Animal Sciences, Washington State University, Pullman, WA 99164, USA

[4] Department of Molecular, Cell and Cancer Biology, University of Massachusetts Medical School, Worcester, MA 01655, USA

[5] School of Food Science, Washington State University, Pullman, WA 99164, USA