Exercise during pregnancy and risk of preterm birth in overweight and obese women: a systematic review and meta-analysis of

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Exercise during pregnancy and risk of preterm birth in overweight and obese women: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: The incidence of overweight and obesity in pregnancy has risen significantly in the last decades. Overweight and obesity have been shown to increase the risk for some adverse obstetric outcome. Lifestyle interventions, such as diet, physical activity and behavior changes, may reduce these risks promoting weight loss and/or preventing excessive weight gain. The possible impact of exercise on the risk of preterm birth (PTB) in overweight or obese women is controversial. Therefore, the aim of our study was to evaluate the effect of exercise on the risk of PTB in overweight or obese pregnant women. *Material and methods:* MEDLINE, EMBASE, Web of Sciences, Scopus, ClinicalTrial.gov, OVID and Cochrane Library were searched from their inception to November 2016. This meta-analysis included only randomized controlled trials (RCTs) of pregnant women assigned before 25 weeks to an aerobic exercise regimen or not. Types of participants included overweight or obese (mean body mass index ≥25 kg/m^2) women with singleton pregnancies without any contraindication to physical activity. The summary measures were reported as relative risk (RR) or as mean difference (MD) with 95% confidence intervals (CI). The primary outcome was the incidence of PTB <37weeks. *Results:* Nine trials, including 1,502 overweight or obese singleton gestations, were analyzed. Overweight and obese women who were randomized in early pregnancy to aerobic exercise for about 30-60 minutes 3-7 times per week had a lower percentage of PTB <37weeks (RR 0.62, 95% CI 0.41 to 0.95) compared to controls. The incidence of gestational age at delivery (MD 0.09 week, 95% CI -0.18

to 0.24) and cesarean delivery (RR 0.93, 95% CI 0.77 to 1.10) were similar in both groups. Women in the exercise group had a lower incidence of gestational diabetes mellitus (RR 0.61, 95% CI 0.41-0.90) compared to controls. No differences in birth weight (MD 16.91 grams, 95% CI -89.33 to 123.19), low birth weight (RR 0.58, 95% CI 0.25 to 1.34), macrosomia (RR 0.92, 95% CI 0.72 to 1.18) and stillbirth (RR 2.13, 95% CI 0.22 to 20.4) between exercise group and controls were found. *Conclusions:* Overweight and obese women with singleton pregnancy can be counseled that, compared to being more sedentary, aerobic exercise for about 30-60 minutes 3-7 times per week during pregnancy is associated with a reduction in the incidence of PTB. Aerobic exercise in overweight and obese pregnant women is also associated with a significant prevention of gestational diabetes mellitus, and should be therefore encouraged.

Key words

physical activity, exercise in pregnancy, preterm birth, preterm delivery, obesity

Abbreviations:

body mass index (BMI);

preterm birth (PTB);

randomized clinical trials (RCTs);

relative risk (RR);

mean difference (MD);

confidence interval (CI);

Key message

Exercise during pregnancy in obese women is safe and reduces preterm birth rate

INTRODUCTION

The incidence of overweight and obesity has risen significantly in the last decades. Approximately one in four women are overweight after childbirth and one in five is obese before pregnancy.[1] Overweight and obesity have been shown to increase the risk for adverse obstetric outcome. Maternal complications correlated with high body mass index (BMI) values are gestational hypertension, pre-eclampsia, gestational diabetes and cesarean delivery.[2] Weight status, before and during pregnancy, also has consequences for fetal outcomes, such as, macrosomia, shoulder dystocia, congenital anomalies and stillbirth.[3,4] Lifestyle interventions, including diet, exercise and behavior changes, may reduce these risks promoting weight loss or prevent weight gain. Being overweight or obese has been associated with preterm birth (PTB) in some studies.[3] while other studies do not support this fact.[5] An even more controversial association is between exercise and risk of PTB in overweight and obese pregnant women.

The aim of this systematic review and meta-analysis was to evaluate the effect of exercise on the risk of PTB in overweight and obese pregnant women.

MATERIAL AND METHODS

Eligibility criteria

This meta-analysis was performed according to a protocol recommended for systematic review.[6] The review protocol was designed a priori defining methods for collecting, extracting and analyzing data. The research was conducted using MEDLINE, EMBASE, Web of Sciences, Scopus, ClinicalTrial.gov, OVID and Cochrane Library as electronic databases. The trials were identified with the use of a combination of the following text words: “exercise” or “physical activity” and “high risk pregnancy” and “overweight” and “obese” and “preterm birth” or “preterm delivery” and “randomized trial” as publication type, from the inception of each database to November 2016. Review of articles also included the abstracts of all references retrieved from the search.

Study selection

Selection criteria included only randomized clinical trials (RCTs) of overweight or obese pregnant women randomized to an exercise regimen or not. We included only RCTs reporting PTB as an outcome in overweight and/or obese pregnant women. Types of participants included women with a mean BMI ≥25 kg/m^2, singleton pregnancies without any obstetric contraindication to physical activity. In all the trials, the intervention group participated in planned aerobic exercise. In the control group, women did not participate in exercise sessions and only attended regular scheduled obstetric visits. RCTs including women with a mean BMI ≤24.9 kg/m^2 were excluded. Only data on women with BMI ≥25 kg/m^2 were analyzed. RCTs including only diet, counseling and/or weight monitoring and those only in at-risk populations (e.g. all women were smokers) were excluded. Quasi-randomized trials (i.e. trials in which allocation was done on the basis of a pseudo-random sequence, e.g. odd/even hospital number or date of birth, alternation) were also excluded.

Risk of bias

The risk of bias in each included study was assessed by using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*.[6] Seven domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting; and 7) other bias. Review authors' judgments were categorized as "low risk," "high risk" or "unclear risk" of bias.[6]

Data extraction and outcomes

All analyses were done using an intention-to-treat approach, evaluating women according to the treatment group to which they were randomly allocated in the original trials. The primary outcome was the incidence of PTB <37weeks. Secondary outcomes were gestational age at delivery, incidence of cesarean delivery, gestational diabetes and neonatal outcomes including birth weight, low birth weight (i.e. birth weight <2500 grams), macrosomia (i.e. birth weight >4,000 grams), and stillbirth. We assessed the primary outcome also in subgroup analysis according to intervention protocol.

Data analysis

Data analysis was completed using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Center, Cochrane Collaboration, 2014).[6] Statistical heterogeneity between studies was assessed using the Higgins I^2 statistics. In case of statistical significant heterogeneity ($I^2 \geq 50\%$), the random effects model of DerSimonian and Laird was used to obtain the pooled risk ratio estimate; otherwise ($I^2 < 50\%$), a fixed effect models was used.[6] The summary measures were reported as relative risk (RR) or as mean difference (MD) with 95% confidence intervals (CI).

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement.[7] Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42016039065).

Two authors (EMM, GS) independently assessed inclusion criteria, risk of bias, data extraction and data analysis. Disagreements were resolved by discussion with a third reviewer (VB). Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. Differences were reviewed, and further resolved by common review of the entire process. Data not presented in the original publications were requested from the principal investigators.

RESULTS

Study selection and study characteristics

Figure 1 shows the flow diagram (PRISMA template) of information derived from review of potentially relevant articles.[8-17] Nine RCTs, including 1,502 overweight end obese women with singleton pregnancy were included in the meta-analysis.[8-10,12-17] One study[11] was excluded since was a follow-up study, of an another included trials.[10]

For all trials, only data for overweight or obese women were able to be included.

The quality of RCTs included in our meta-analysis was assessed by the Cochrane Collaboration's tool.[7]

All the included studies used had low risk of bias in "random sequence generation" and "incomplete outcome data." High risk of reporting bias was not found in any of the included trials. No method of blinding as to the group allocation was reported (Figure 2).

Table 1 shows the characteristics of the nine included trials. Two studies[8,12] included only overweight women, two studies[10,16] included only obese women, three studies[9,14,15] included both overweight to obese while in two studies[13,17] women were stratified by BMI categories. Gestational age at randomization was for all studies in the first trimester except in three RCT[8,9,16] in which women were randomized only or also during the second trimester. The intervention program included aerobic exercise and dietary counseling in five RCTs,[9,10,12,13,16] aerobic exercise and dietary intervention by a dietitian in one study[15] and only aerobic exercise in three studies.[8,14,17] One trial,[16] randomized obese women in 3 groups: physical activity and dietary intervention (group 1); physical activity intervention (group 2); standard care (group 3). We included both physical activity groups, with and without dietary intervention, in the exercise group. Two studies[13,17] included all BMI categories; all data of underweight and normal weight women were excluded in our meta-analysis.

Table 2 shows inclusion and exclusion criteria in these trials. Characteristics of the women included in the trials (maternal age, parity, job, smoking habits, pre-pregnancy BMI as mean and standard deviation for both overweight and obese categories included, number and rate of overweight women, number and rate of obese women, prior PTB) are reported in Table 3. All nine studies randomized overweight and/or obese women with singleton gestations. Women were excluded in case of any obstetric contraindications to exercise, mostly as recommended by ACOG.[18] The intervention group participated in aerobic exercise consisting of a protocol of exclusive walking session in three trial,[14-16] of an exclusive light-intensity to moderate-intensity exercise in two trials[10,13] and of the two associated components in four trials.[8,9,12,17] The mean time of every session was around 40 minutes (30-60 minutes), three times a week in four trials,[8,13,15,17] four times a week in one trials,[12] five times a week in two trials[9,14] while in two trials[10,16] physical activity was recommended daily. In the control group, women did not participate in exercise sessions and only attended regular scheduled obstetric visits and prenatal care advises.

Synthesis of results

Of the 1,502 women included in the meta-analysis, 824 (55%) were randomized to the exercise group and 678 (45%) to the control group. The statistical heterogeneity within the studies was low. Table 4 shows the pooled data of primary and secondary outcomes of the meta-analysis. Pregnant overweight or obese who were randomized in early pregnancy to approximately 30-60 minutes of aerobic exercise 3-7 times per week until at least week 35 or up to delivery had a lower percentage of PTB <37 weeks (RR 0.62, 95% CI 0.41 to 0.95; Figure 3) compared to controls. The incidence of gestational age at delivery (MD 0.09 week, 95% CI -0.18 to 0.24) and cesarean delivery (RR 0.93, 95% CI 0.77 to 1.10) were similar in both groups. Women in the exercise group had a lower incidence of gestational diabetes mellitus (RR 0.61, 95% CI 0.41-0.90) compared to controls. No differences in birth weight (MD 16.91 grams, 95% CI -89.33 to 123.19), low birth weight (RR 0.58, 95% CI 0.25 to 1.34), macrosomia (RR 0.92, 95% CI 0.72 to 1.18) and stillbirth (RR 2.13, 95% CI 0.22 to 20.4) between exercise group and controls were found.

Table 5 shows the primary outcome in subgroup analysis according to and intervention protocols.

DISCUSSION

This meta-analysis of nine RCTs, including 1,502 women, showed that aerobic exercise in overweight or obese singleton pregnancies is associated with a reduced risk of PTB. The mean gestational age at delivery and the incidence of cesarean delivery are similar in women who exercised regularly versus controls. Women in the exercise group have a significantly lower incidence of gestational diabetes mellitus. There is no difference in birth weight, low birth weight, macrosomia and stillbirth.

A recent Cochrane Review[19] evaluated the effect of exercise during pregnancy, with or without diet intervention, on the risk of PTB, and it included all BMI categories. The authors found no statistically significant difference between intervention group and control group with regard to PTB outcome. This Cochrane Review[19] supports our findings of no effect of exercise during

pregnancy on mode of delivery. In another meta-analysis, a slight increase in the probability of vaginal delivery was found in only healthy normal weight women performing regular exercise during pregnancy.[20] In our meta-analysis the results suggest a protective effect of aerobic exercise in developing gestational diabetes. Another prior meta-analysis, which also included all BMI categories without looking only at overweight or obese women, also found that exercise in pregnancy is associated with a significant decrease in gestational diabetes mellitus.[21] Recently, Di Mascio et al. in a meta-analysis including 2,059 women showed that aerobic exercise can be safely performed by normal-weight singletons with uncomplicated gestations because this was not associated with an increased risk of preterm delivery but was associated with higher rate of vaginal delivery and lower caesarean section, gestational diabetes mellitus and hypertensive disorders.[22] Magro-Malosso et al. in a meta-analysis of seventeen trials, including 4,815 uncomplicated low risk singleton pregnancies, found that aerobic exercise for about 30-60 minutes 2-7 times per week during pregnancy, as compared to being more sedentary, was associated with a significantly reduced risk of gestational hypertensive disorders.[23]

Our study has several strengths. This meta-analysis included all RCTs - nine- published so far on the topic. To our knowledge, there are no other meta-analyses on the issue of exercise in overweight or obese pregnant women and risk of PTB. The studies in general were at low risk of bias according to the Cochrane risk of bias tools. The number of the included women - 1,502 - was high. The statistical heterogeneity within the studies was low. These are key elements needed to evaluate the reliability of a meta-analysis.

The main limitation of our study was that dietary counseling or interventions were provided in addition to exercise in some trials (Table 1). Another limitation of this study is that individual trials differ in how they define aerobic exercise, intensity of exercise and time of exercise. Therefore, even if the statistically heterogeneity within the trial was judged as low, the clinical heterogeneity was high. The most important confounding variables were the dietary interventions, which were not described in details in the included studies, and which could have profound effects on the outcomes and conclusions. The different definition of aerobic exercise and the different dietary interventions used are the major shortcoming of our meta-analysis. Calculation of calories utilized with the exercise regimen were not described by the original trials. Moreover, one trial, while the mean BMI was >25 kg/m^2, might have included a small

number of women with BMI <25 kg/m^2. Finally, data on PTB refer to both spontaneous and indicated preterm delivery.

We suggest overweight and obese women with singleton pregnancy can safely perform aerobic exercise for about 30-60 minutes 3-7 times per week during pregnancy. Women can be counseled that, compared to a more sedentary pregnancy, exercise during pregnancy is associated with a reduced risk of PTB and is not associated with an effect on mean gestational age at delivery or on incidence of cesarean delivery. Aerobic exercise in overweight and obese pregnant women is also associated with a significant prevention in gestational diabetes mellitus. During pregnancy, aerobic exercise is safe and beneficial, and should therefore be encouraged.

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Table 1. Characteristics of the included trials

	Santos, 2005 (8)	**Nascimento , 2011 (9)**	**Vinter, 2011 (10,11)**	**Price, 2012 (12)**	**Ruiz, 2013 (13)**	**Kong, 2014 (14)**	**Petrella, 2014 (15)**	**Renault, 2014 (16)**	**Barakat, 2016 (17)**
Study location	Brazil	Brazil	Denmark	USA	Spain	USA	Italy	Denmark	Spain
Sample size*	72 (37 vs 35)	80 (39 vs 41)	304 (150 vs 154)	62 (31 vs 31)	275 (146 vs 129)**	37 (18 vs 19)	61 (33vs 28)	389 (130 vs 125 vs 134) ***	222 (115 vs 107)**
Type of exercise	Warm up, aerobic (walking, pedaling a bicycle ergometer, gymnastic) and resistance exercise, stretching	Exercise protocol (stretching, exercises to strengthen the lower and upper limb muscles, relaxation) or walking	Aerobic (low-step), training with light weights, elastic bands and balance exercise	1st day: aerobics 2nd day: walking 3rd day: circuit training 4th day: brisk walk (individually	Aerobic, resistance and flexibility exercises	Walking session	Walking session	Walking session	Aerobic exercise, aerobic dance, muscular strength and flexibility preceded by walking and light stretching

	and relaxation			)					and followed by relaxation and pelvic floor exercise
Diet intervention in exercise group	-	Dietary counseling	Dietary counseling	Dietary counseling	Dietary counseling	-	Dietary interventio n	Dietary interventio n or dietary counseling	-
GA (weeks) at randomization	≤20	14 to 24	10 to 14	12 to 14	5 to 6	12 to 14	12	<16	9 to 11
End of exercise program (weeks)	Until delivery	Until at least week 36	Until delivery	36	38-39	until at least week 35	Until at least week 36	36-37	38-39
Duration of a single session (min)	60	40	30-60	1st to 3rd: 45-60 4th: 30-60	50-55	30	30	-	50-55
Times per weeks (days)	3	5	7	4	3	5	3	7	3

Intensity of exercise (HR)	50-60% of the maximum predicted HR, never exceeding 140 bpm	HR did not exceed 140 bpm	NR	NR	<60% of their age-predicted max HR	NR	NR	NR	<70% of their age-predicted max HR
Self-reported intensity of exercise (Borg scale)†	NR	NR	NR	12-14	10-12	NR	NR	NR	12-14
Control group	Weekly relaxation session and focus group discussion concerning maternity. Women were neither encouraged	No PA counseling; only routine prenatal care advice	Access to a website with advice about dietary habits and PA in pregnancy, but no	No exercise sessions; only activity needed for work or house-hold chores	Regular scheduled visits until the 35th week of GA then weekly until delivery; general nutrition and PA	No restriction from PA participation during pregnancy	Regular scheduled visit until delivery. Delivery of a nutritional booklet	Standard care for obese pregnant women	General advice from their health care provider about positive effects of PA; regular scheduled visits;

	to exercise nor discouraged from exercising		additional intervention		counseling				women were not discouraged from PA, women who performed aerobic exercise 3 d/wk (≥20 min/session) were excluded from the study
Primary outcome	Submaximal exercise capacity	GWG, and excessive maternal weight gain.	GWG, preeclampsia, PIH, GDM, CD, macrosomia/LGA, admission	Cardiorespiratory fitness	GWG	Amount of moderate-intensity PA, GWG	Excessive weight gain over the IOM recommended ranges for each BMI	GWG	Gestational hypertension

			to NICU				category		
Other comments	-	-	PA was monitored by a pedometer	-	Women underweight or normal weight were excluded from our analysis	PA was monitored by a pedometer	PA was monitored by a pedometer	PA was monitored by a pedometer, aiming at a daily step count of 11,000	-

HR, hearth rate; bpm, beats per minute; GA, gestational age; BMI, body mass Index; GDM, gestational diabetes mellitus; ACOG, American College of Obstetricians and Gynecologists; NR, not reported, IOM, Institute of Medicine; GWG, gestational weight gain; PA, physical activity; PIH, pregnancy-induced hypertension; GDM, gestational diabetes mellitus; CD, cesarean delivery; LGA; large for gestational age; NICU, neonatal intensive care unit.

**Data are presented as total number (number in the exercise group vs number in the control group)*

*** Data of underweight and normal weight women were excluded. Original trial included all BMI categories.*

****Group1/group2/group3. Group 1 = physical activity and dietary intervention; group 2 = physical activity intervention; group 3 = standard care*

†Borg Scale is a 15 category scale (from 6 to 20) to measure the level of perceived exertion. Light exercise is about 6-11; 13 somewhat hard; 15 hard; 19 extremely hard.

Table 2. Inclusion and exclusion criteria of the women included in the trials.

	Inclusion criteria	**Exclusion criteria**
Santos, 2005[8]	Healthy, nonsmoking pregnant women, aged 20 years or more, GA≤20 weeks, BMI of 26-31 kg/m^2, compliance to the run in period protocol	Hypertension, diabetes mellitus, conditions considered to contraindicate exercise such as preterm labor, an incompetent cervix, multiple gestation, uncontrolled thyroid disease
Nascimento, 2011[9]	Pregestational BMI categorized as overweight (26-29.9 kg/m^2) or obese (≥30 kg/m^2), age ≥18 years, GA between 14 and 24 weeks	Multiple gestations, exercising regularly, conditions that contraindicate exercise, such us cervical incompetence, severe arterial hypertension, diabetes with vascular disease and risk of abortion
Vinter, 2011[10,11]	Maternal age between 18 and 45 yr, BMI of 30-45 kg/m^2	Prior serious obstetric complications; chronic diseases (e.g. hypertension and diabetes); positive OGTT in early pregnancy; alcohol or drug abuse; non Danish speaking, multiple pregnancy
Price, 2012[12]	No aerobic exercise more than once per week for at least the past 6 months, singleton pregnancy, BMI<39 kg/m^2	Chronic heart or lung disease, poorly controlled diabetes, hypertension, epilepsy, hyperthyroidism, severe anemia (hematocrit level <27%), orthopedic limitations, history of premature delivery, infant delivered for small for gestational age, unexplained fetal death

Ruiz, 2013[13]	Sedentary women with singleton, uncomplicated gestations	High risk of preterm delivery, participating in any other trial, any obstetric contraindication to exercise
Kong, 2014[14]	Maternal age between 18 and 45 yr, singleton pregnancy, non-smoker, self-reported overweight (BMI ≥25 kg/m^2) or obese (BMI ≥25 kg/m^2) before pregnancy, sedentary women	Prior history of chronic diseases, prior history of gestational diabetes
Petrella, 2014[15]	Pre-pregnancy BMI ≥25 kg/m^2, age >18 years, singleton pregnancy	Twin pregnancy, chronic diseases, gestational diabetes mellitus in previous pregnancy, smoking during pregnancy, previous bariatric surgery, women who just engaged in regular physical activity, dietary supplements or herbal products known to affect body weight, other medical conditions that might affect body weight, plans to deliver in another Birth Center
Renault, 2014[16]	Pre-pregnancy BMI >30 kg/m^2, age >18 years, singleton pregnancy, normal scan in weeks 11-14, GA at inclusion <16 weeks, ability to read and speak Danish	Multiple pregnancy, pregestational diabetes, other serious diseases limiting their level of physical activity, previous bariatric surgery, alcohol or drug abuse
Barakat, 2016[17]	Singleton pregnancies	Pregestational diabetes (type 1, type 2) GDM, history or risk of preterm delivery; not planning to give birth in the obstetrics department of the study; not receiving medical

		follow-up throughout pregnancy; obstetric contraindication to exercise.

BMI, Body Mass Index; GDM, gestational diabetes mellitus; OGTT, Oral Glucose Tolerance Test; GA, gestational age.

Table 3. Characteristics of the women included in the trials.

	Santos, 2005[8]	**Nascimento, 2011[9]**	**Vinter, 2011[10,11]**	**Price, 2012[12]**	**Ruiz, 2013[13]**	**Kong, 2014[14]**	**Petrella, 2014[15]**	**Renault, 2014[16]**	**Barakat, 2016[17]**
Maternal age (y)	26.0±3.4 vs 28.6±5.9	29.7±6.8 vs 30.9±5.9*	29 (27-32) vs 29 (26-31)	30.5±5 vs 27.6±7.3	31.6±4 vs 31.9±4**	27.4±3.9 vs 26.5±3.8	31.5±4.2 vs 32.4±5.9	31.1±4.7 vs 31.3±4.2	31.6±4.2 vs 31.8±4.5**
Nulliparous	NR	12/40 (30.0%) vs 10/42 (23.8%)*	NR	NR	NR	6/18 (33.3%) vs 8/19 (42.1%)	13/33 (39.4%) vs 13/30 (43.3%)	NR	259/382 (67.8%) vs 229/383 (59.8%)**
Housewife			NR	NR	126/841 (26.2%)	NR	7/33 (21.2%) vs	NR	72/382 (18.8%)

	NR	NR			vs 118/481 (24.5%)**		11/30 (36.7%)		vs 93/383 (24.3%)**
Active job	NR	NR	NR	NR	155/481 (32.2%) vs 175/481 (36.4%)**	NR	12/33 (36.4%) vs 9/30 (30.0%)	NR	139/382 (36.4%) vs 142/383 (37.1%)**
Sedentary work	NR	NR	NR	NR	195/481 (40.5%) vs 184/481 (38.3%)**	NR	14/33 (42.4%) vs 1/30 (33.3%)	NR	171/382 (44.8%) vs 148/383 (38.6%)**
Smoking	0/37 vs 0/35	NR	11/150 (7.3%) vs 18/154 (11.7%)	0/31 vs 0/31	NR	0/18 vs 0/19	0/33 vs 0/30	19/251 (7.6%) vs 11/134 (8.2%)	40/382 (10%) vs 54/383 (14.1%)**
BMI	28.0±2.1 vs 27.5±2.1	34.8±6.6 vs 36.4±6.9*	33.4 (31.7-36.5) vs	26.6±3.1 vs 28.7±5.4	23.7±3.9 vs	30.6±2.9 vs	32.1±5 vs	34.3±4.3 vs 33.7±3.5	23.6±3.8 vs

			33.3 (31.7-36.9)		23.5±4.2**	30.8±2.5	32.9±6.2		23.4±4.2**
BMI 25-29.9	NR	9/39 (23.1%) vs 5/41 (12.2%)*	0/150 vs 0/154	NR	111/146 (76.0%) vs 92/129 (71.3%)	9/18 (50.0%) vs 9/19 (47.4%)	15/33 (45.5%) vs 10/30 (33.3%)	NR	90/115 (78.3%) vs 78/107 (72.9%)
BMI ≥ 30	NR	30/39 (76.9%) vs 36/41 (87.8%)*	150/150 (100%) vs 154/154 (100%)	NR	35/146 (24.0%) vs 37/129 (28.7%)	9/18 (50.0%) vs 10/19 (52.6%)	18/33 (54.5%) vs 20/30 (66.7%)	NR	25/115 (21.7%) vs 29/107 (27.1%)
Prior PTB	0/37 vs 0/35	NR	NR	0/31 vs 0/31	0/146 vs 0/129	NR	NR	NR	0/115 vs 0/107

Data are presented as number (percentage), or as mean ± standard deviation, or as median (interquartile range). Data are presented as number in the exercise group vs number in the control group.

BMI, Body Mass Index; NR, Not Reported.

**Data calculated on 82 randomized women (study group= 40; control group= 42): two women, one for each group, were subsequently excluded because of discontinued participation.*

*** Data shown here include all BMI categories: underweight, normal weight, overweight, obese. Only data on overweight and obese women from this trial were otherwise used in all other analyses.*

Table 4. Primary and secondary outcomes in the overall analysis

	Santos, 2005[8]	**Nascimento, 2011[9]**	**Vinter,* 2011[10,11]**	**Price, 2012[12]**	**Ruiz, 2013[13]**	**Kong, 2014[14]**	**Petrella, 2014[15]**	**Renault, 2014[16]**	**Barakat, 2016[17]**	**Total**	**RR or MD (95% CI)**
PTB <37 weeks	2/37 (5.4%) vs 1/35 (2.8%)	0/39 vs 0/41	6/150 (4%) vs 3/154 (1.9%)	1/31 (3.2%) vs 0/31 (0%)	4/146 (2.7%) vs 2/129 (1.5%)	0/18 vs 1/19 (5.3%)	0/33 vs 10/28 (35.7%)	12/255 (4.7%) vs 6/134 (4.5%)	10/115 (8.7%) vs 15/107 (14.0%)	35/824 (4.2%) vs 38/678 (5.6%)	**0.62 (0.41 to 0.95)**
GA at delivery (weeks)	NR	38.5±2.6 vs 38.5±1.5	40.4 (39-41) vs 40.4. (39-41)	39.2±1.4 vs 39.3±1.1	39.6±2.1 vs 39.6±1.4	39.3± 1.9 vs 39.4 ±0.9	39.8±1 vs 37.3±3	39.7±1.8 vs 39.7±1.7	NR	-	0.09 week (-0.18 to 0.24)
CD	NR	25/39 (64.1%)	40/150 (26.7%)	4/31 (12.9%)	38/146 (26.0%)	5/18 (27.8	11/33 (33.3%)	83/255 (32.5%)	NR	206/672 (30.6%)	0.93 (0.77 to 1.10)

		vs 29/41 (70.7%)	vs 39/154 (25.3%)	vs 12/31 (38.7%)	vs 29/129 (22.5%)	%) vs 9/19 (47.4 %)	vs 9/28 (32.1%)	vs 50/134 (37.3%)		vs 177/536 (33%)	
GDM	NR	NR	9/150 (6.0%) vs 8/154 (5.2%)	3/31(9.7 %) vs 4/31(12. 9%)	9/146 (6.2%) vs 12/129 (9.3%)	1/18 (5.5%) vs 1/19 (5.3%)	7/33 (23.3%) vs 16/28 (57.1%)	8/255 (3.1%) vs 7/134 (5.2%)	3/115 (2.6%) vs 5/107 (4.7%)	40/748 (5.3%) vs 53/602 (8.8%)	**0.61 (0.41 to 0.90)**
Birth weight (g)	3363±504 vs 3368±518	3367±70 0 vs 3228±59 1	3742 (3464-4070) vs 3593 (3335-3930)	3329±51 9 vs 3308±10 3	3269±49 6 vs 3305±46 5	3650 ±475 vs 3765± 470	3498±3 42 vs 3010±7 15	NR	NR	-	16.91 grams (-89.33 to 123.19)

LBW	2/37 (5.4%) vs 1/35 (2.8%)	0/39 (0.0%) vs 0/41 (0.0%)	NR	NR	5/146 (3.4%) vs 6/129 (4.6%)	0/18 (0.0%) vs 0/19 (0.0%)	NR	NR	3/115 (2.6%) vs 9/107 (8.4%)	10/355 (3.0%) vs 16/331 (4.8%)	0.58 (0.25 to 1.34**)**
Macrosomia	NR	NR	40/150 (26.7%) vs 39/154 (25.3%)	NR	2/146 (1.4%) vs 12/129 (9.3%)	5/18 (27.8 %) vs 6/19 (31.6 %)	NR	66/255 (25.9%) vs 33/134 (24.6%)	1/115 (0.9%) vs 8/107 (7.5%)	114/684 (16.7%) vs 98/543 (18.0%)	0.92 (0.72 to 1.18)
Stillbirth	NR	NR	2/150 (1.3%) vs 1/154 (0.6%)	NR	NR	NR	NR	1/255 (0.4%) vs 0/134 (0.0%)	NR	3/405 (0.74%) vs 1/288 (0.34%)	2.13 (0.22 to 20.4)

Data are presented as number (percentage), or as mean ± standard deviation, or as median (interquartile range). Data are presented as number in the exercise group vs number in the control group. Boldface data, statistically significant

PTB, preterm birth, GA, gestational age; GDM, gestational diabetes mellitus; LBW, low birth weight; RR, relative risk; MD, mean difference; CI, confidence interval; NR, not reported; CD, cesarean delivery

Table 5. Incidence of preterm birth in subgroup analysis according to intervention protocol

Aerobic exercise + dietary counseling[9,10,12,13,15,16]			
	Intervention group	**Control Group**	**RR (95% CI)**
PTB <37 weeks	23/654 (3.5%)	21/517 (4.1%)	1.07 (0.36 to 3.16)
Aerobic exercise only[8,14,17]			
	Intervention group	**Control Group**	**RR (95% CI)**
PTB <37 weeks	12/170 (7.1%)	17/161 (10.6%)	0.67 (0.33 to 1.34)

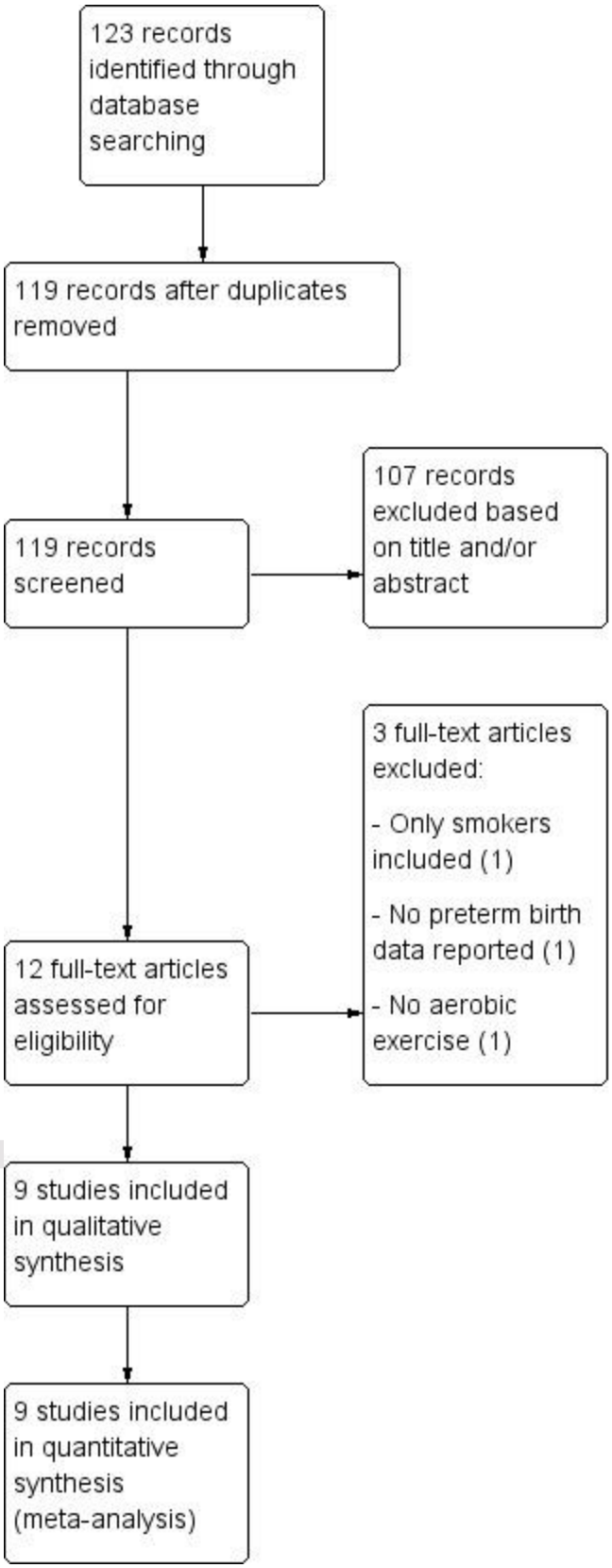
BMI, body mass index; RR, relative risk; CI, confidence interval; PTB, preterm birth

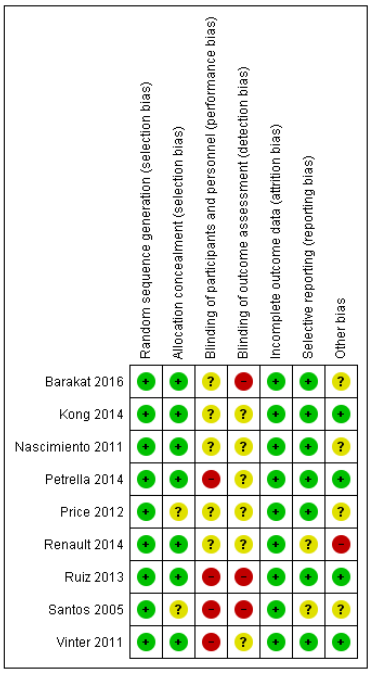
FIGURE legends

Figure 1. Flow diagram of studies identified in the systematic review. (Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses])

Figure 2. Assessment of risk of bias. (A) Summary of risk of bias for each trial; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

Figure 3. Forest plot for the risk of the preterm birth. CI, confidence interval; M-H, Mantel-Haenszel; df, degrees of freedom.





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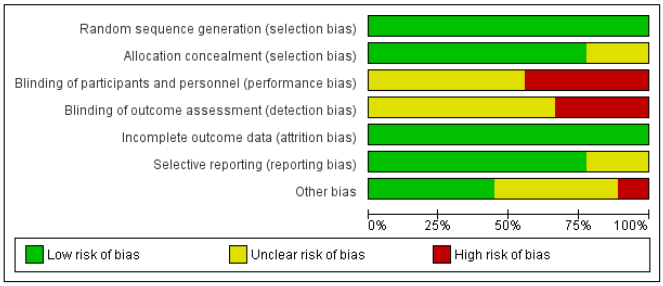

B

Study or Subgroup	Exercise Events	Exercise Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Santos 2005	2	37	1	35	2.4%	1.89 [0.18, 19.95]	2005
Vinter 2011	6	150	3	154	6.9%	2.05 [0.52, 8.06]	2011
Nascimiento 2011	0	39	0	41		Not estimable	2011
Price 2012	1	31	0	31	1.2%	3.00 [0.13, 70.92]	2012
Ruiz 2013	4	146	2	129	5.0%	1.77 [0.33, 9.49]	2013
Kong 2014	0	18	1	19	3.4%	0.35 [0.02, 8.09]	2014
Renault 2014	12	255	6	134	18.4%	1.05 [0.40, 2.74]	2014
Petrella 2014	0	33	10	28	26.5%	0.04 [0.00, 0.66]	2014
Barakat 2016	10	115	15	107	36.3%	0.62 [0.29, 1.32]	2016
Total (95% CI)		**824**		**678**	**100.0%**	**0.62 [0.41, 0.95]**	
Total events	35		38				

Heterogeneity: Chi² = 9.54, df = 7 (P = 0.22); I² = 27%

Test for overall effect: Z = 2.18 (P = 0.03)