

Physical Activity Interventions in Pregnancy and Risk of Gestational Diabetes Mellitus

A Systematic Review and Meta-analysis

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OBJECTIVE: Gestational diabetes mellitus (GDM) is a common complication of pregnancy associated with an increased incidence of pregnancy complications, adverse pregnancy outcomes, and maternal and fetal risks of chronic health conditions later in life. Physical activity has been proposed to reduce the risk of GDM and is supported by observational studies, but experimental research assessing its effectiveness is limited and conflicting. We aimed to use meta-analysis to synthesize existing randomized controlled studies of physical activity and GDM.

DATA SOURCES: We searched MEDLINE, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov for eligible studies.

METHODS OF STUDY SELECTION: The following combination of keywords was used: (pregnant or pregnancy or gestation or gestate or gestational or maternity or maternal or prenatal) AND (exercise or locomotion or activity or training or sports) AND (diabetes or insulin sensitivity or glucose tolerance) AND (random* or trial). Eligibility was restricted to studies that randomized participants to an exercise-only-based intervention (ie, separate from dietary interventions) and presented data regarding GDM risk. Two authors performed the database search, assessment of eligibility, and abstraction of data from included studies, and a third resolved any discrepancies. A total of 469 studies was retrieved, of which 10 met inclusion criteria and could be used for analysis (3,401 participants).

TABULATION, INTEGRATION, AND RESULTS: Fixed-effects models were used to estimate summary relative risk (RR) and 95% confidence interval (CI) and I^2 to assess heterogeneity. There was a 28% reduced risk (95% CI 9–42%) in the intervention group compared with the control group (RR 0.72, $P=.005$). Heterogeneity was low ($I^2=12%$) and nonsignificant ($P=.33$).

CONCLUSION: The results from this meta-analysis suggest that physical activity in pregnancy provides a slight protective effect against the development of GDM. Studies evaluating type, timing, duration, and compliance of physical activity regimens are warranted to best inform obstetric guidelines.

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Gestational diabetes mellitus (GDM), defined as carbohydrate intolerance with the onset or first recognition during pregnancy,¹ affects an estimated 2–10% of pregnancies in the United States² with rates varying by population subgroup and diagnostic test utilized. Prevalence of GDM varies by race–ethnicity, ranging from a low of 6.8% among non-Hispanic whites to 16.3% among Asians and Pacific Islanders.³ Data have suggested that the incidence of GDM is increasing in all race–ethnicities in the United States, a trend paralleling the increase in prevalence of type 2 diabetes.² Gestational diabetes mellitus is associated with increased risk of fetal macrosomia, large-for-gestational-age neonates, preeclampsia, perinatal mortality, and cesarean delivery^{4–6} as well as long-term hazards, including a higher risk of maternal type 2 diabetes and obesity,⁷ glucose intolerance, and metabolic syndrome in the offspring of women born to mothers diagnosed with GDM.⁸

Established risk factors for GDM include a history of GDM in a prior pregnancy,⁹ history of delivering a macrosomic neonate,¹⁰ advanced maternal age,⁹

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nonwhite race-ethnicity,¹¹ and high parity.¹⁰ Additional nonmodifiable factors that are suggested to be related to GDM risk include family history of diabetes mellitus¹² and maternal high or low birth weight.⁹ Potentially modifiable factors that may increase the risk of GDM include being overweight or obese (having a body mass index [calculated as weight (kg)/[height (m)]²] of at least 25),¹³ being sedentary lifestyle,¹⁴ and consuming a low-fiber and high-glycemic-load diet.¹⁵

Low levels of physical activity have been described as a potentially modifiable risk factor for GDM.^{16,17} Observational studies have observed that higher levels of physical activity before the onset of pregnancy and during early pregnancy are associated with a lower prevalence of GDM.¹⁷ Results from randomized controlled trials (RCTs) have been inconsistent regarding the association between physical activity and GDM,^{6,18} and a meta-analysis from 2013 that included data from four trials of an exercise intervention and one of a yoga intervention yielded a nonsignificant summary effect.¹⁸

The purpose of this meta-analysis is to summarize all available data from RCTs reported to date looking at the effect of physical activity-only interventions on the risk of GDM.

SOURCES

Two separate searches were performed using PubMed (1966–2014) and Cochrane Central Register of Controlled Trials: Issue 7 of 12, July 2014, to review studies on physical activity and GDM with publication dates through August 15, 2014. An additional search was performed in the ClinicalTrials.gov database, reviewing all registered trials with published results, results uploaded to the database, or both. Although prior reviews have restricted attention to individuals without a history of GDM in an earlier pregnancy, we did not place similar restrictions regarding study participants to evaluate physical activity interventions in a more general clinical population.¹⁸ The following combination of keywords was used: (pregnant or pregnancy or gestation or gestate or gestational or maternity or maternal or prenatal) AND (exercise or locomotion or activity or training or sports) AND (diabetes or insulin sensitivity or glucose tolerance) AND (random* or trial).

The following inclusion criteria were used: 1) RCT, 2) pregnant women without GDM at baseline, 3) increased physical activity was the only intervention and comparison arms were assigned to usual care, and 4) incidence of GDM was documented separately for the control and intervention groups with diagnosis

criteria as defined in individual trials. Two authors independently performed the literature search and excluded any articles that did not meet the established inclusion criteria. A third author was consulted to resolve any disagreements or uncertainty regarding inclusion. Information regarding authorship, publication dates, and journals was recorded for included papers. Data regarding number of participants and events by group were retrieved for analysis. Method of randomization and patient management were evaluated as part of assessment of the risk of bias.

Data from each study were analyzed using Cochrane Review Manager 5.2 to calculate relative risks (RRs) and 95% confidence intervals (CIs). A summary estimate of the association between physical activity and GDM found in the RCTs was calculated using both fixed and random-effects models. Heterogeneity between studies was assessed by calculation of Cochran's Q statistic and corresponding χ^2 as well as the I^2 statistic,¹⁹ and publication bias was assessed by visual inspection from a funnel plot.²⁰

STUDY SELECTION

A total of 469 unique trials was identified, from which 55 abstracts were reviewed after eliminating studies that clearly did not meet inclusion criteria. After further exclusions based on review of abstracts, full text for 20 published papers was screened. From these, 10 were determined to meet the inclusion criteria and contributed data for analysis (Fig. 1).^{21–30} One study otherwise met criteria, but no cases of GDM were observed rendering it uninformative for this statistical analysis.³¹ In addition, although used in a previous meta-analysis,¹⁸ we excluded a study that compared a yoga intervention with a daily walking group,³² because both the intervention and comparison groups were assigned to physical activity. Details of the included studies are described in Table 1. In total, there were 3,401 participants and 275 events (diagnosis of GDM) accounted for in our analysis. Trials were conducted in various countries: three in Spain,^{21–23} two in the United States,^{25,27} and one each in Australia²⁴ Croatia,³⁰ Denmark,²⁸ The Netherlands,²⁶ and Norway.²⁹ All studies included a single physical activity-only intervention arm and a usual-care comparison arm, except for a study by Renault et al,²⁸ which included three distinct groups: 1) a combined physical activity and dietary intervention arm, 2) a physical activity-only intervention arm, and 3) a usual-care comparison arm. Only the results from the physical activity-only arm and comparison arm were included in this analysis, whereas the results from the combined physical activity and dietary arm were excluded.



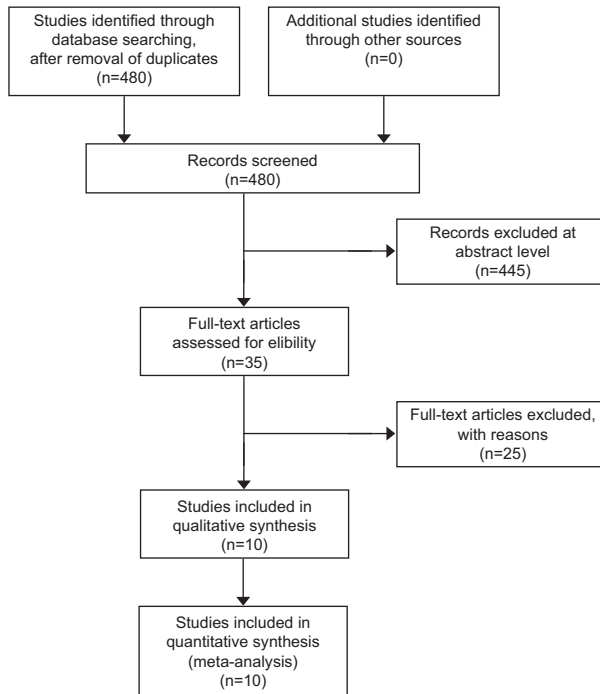


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of search results, study screening, and study inclusion.

Russo. *Exercise and Gestational Diabetes Meta-analysis. Obstet Gynecol* 2015.

Interventions varied with regard to exercise type along with the frequency and intensity at which they were performed (Table 1). Gestational age at baseline ranged from 6–8 weeks³⁰ to 18–22 weeks²⁹ with the majority of studies enrolling participants at less than 16 weeks of gestation. Timing of the intervention varied among studies. Participants in all 10 studies received the exercise intervention until they were screened for GDM. Six of the trials used only group exercise interventions^{21–23,26,27,30} two used only individual exercise interventions,^{24,28} and two used combined group and individual exercise interventions.^{25,29} All of the interventions included an aerobic component (walking, land or water aerobics or both, cycling), and four included an anaerobic component (strength training and balance exercises).^{22,26,27,29} Duration of exercise ranged from 105 to 240 minutes per week. Diagnostic criteria for GDM varied among included studies, four studies reported using a 75-g oral glucose tolerance test,^{22,24,28,29} four studies used a two-step 50-g oral glucose challenge test and 100-g oral glucose tolerance test,^{21,26,27,30} and criteria for GDM were not available for two studies.^{23,25} Six studies reported the timing of the GDM screen, which ranged from 17 to 36 weeks of gestation.

Study size ranged from 50²⁴ to 1,196^{24,25} with five studies enrolling 200 or fewer participants.^{21,23,24,26,27} Loss to follow-up ranged from 6%²⁵ to 33%.²⁷ Of the six group exercise interventions, five reported a measure of adherence in the intervention arm,^{21–23,26,27} ranging from 16.3%²⁶ to greater than 95%.^{22,23} Stafne et al²⁹ combined group exercise and home-based intervention and reported 55% meeting the goal of three or more exercise sessions per week. Both home-based interventions reported participant adherence to exercise volume per week goals with Renault et al reporting mean step counts of 8,828±2,798 steps per week at 13 weeks of gestation, 8,829±2,980 at 21 weeks of gestation and 5,972±2,133 at 37 weeks of gestation (goal of 10,000 steps per week),²⁸ and Callaway et al²⁴ reporting that 73% in the intervention arm and 42% in the comparison arm met the intervention goal of 900 kcal per week as assessed by questionnaire at 36 weeks of gestation.

The results from a fixed-effects model used for this meta-analysis indicate a significant 28% lower risk of GDM (95% CI 9–42%) among women randomized to exercise during pregnancy (RR 0.72, 95% CI 0.58–0.91, $P=.005$; Fig. 2). Similar results were observed in a random-effects model (RR 0.74, 95% CI 0.57–0.97). Heterogeneity as reflected by Cochran's Q was non-significant ($P=.33$) and, similarly, low heterogeneity was indicated by the I^2 statistic ($I^2=12%$). A funnel plot did not suggest obvious publication bias on study findings (Fig. 3).

DISCUSSION

Estimates from this meta-analysis suggest a 28% lower risk of GDM among those assigned to a physical activity intervention compared with those in a control group (RR 0.72, 95% CI 0.58–0.91). These results are consistent with findings from observational research. A 2011 meta-analysis of observational studies of GDM and physical activity found a significant protective effect for exercise in early pregnancy (odds ratio 0.76, 95% CI 0.70–0.83, respectively).¹⁷ Observational studies comparing risks among those who are physically active in pregnancy with those who are not face the challenge of confounding by factors related to health behaviors, which affects the assessment of causal effects of physical activity. A 2013 meta-analysis of experimental studies found a nonsignificant summary RR of 0.91 ($P=.7$) based on analysis of data from five studies with a total of 947 participants. Results of this meta-analysis, which included data from 10 trials and a total of 3,401 study participants, suggest that physical activity in pregnancy reduces the risk of GDM independent of other health behaviors



Table 1. Summary of Studies Included in This Meta-analysis

Author (y)	Inclusion Criteria		Intervention Frequency and Description	Gestational Age (wk) at Initiation	GDM RR (95% CI)	GDM Diagnostic Criteria
	BMI (kg/m ²)	Exercise				
Barakat (2012) ²¹	No restrictions	Not reported	3 times/wk 35–45 min: 2 land aerobic sessions and 1 aquatic session	6–9	0.15 (0.01–2.88)	American Diabetes Association
Barakat (2013a) ²²	No restrictions	Sedentary	3 times/wk 50–55 min: resistance training plus walking and stretching	10–12	0.70 (0.49–0.99)	World Health Organization, International Association for Diabetes in Pregnancy Study Group*
Barakat (2013b) ²³	No restrictions	4 times/wk or less	3 times/wk 55–60 min: walking, aerobic dance, balancing exercises	9–13	0.85 (0.25–2.84)	Not reported
Callaway (2010) ²⁴	Obese	N/R	Individualized program with an energy expenditure goal of 900 k/cal	12	1.44 (0.40, 5.24)	Australasian Diabetes in Pregnancy Society
Ko (2014) ²⁵	No restrictions	Not reported	2 times/wk 30 min, with ultimate goal of 45 min 4–5 times/wk: aerobic exercise	Varied	0.78 (0.47–1.29)	Not reported
Oostdam (2012) ²⁶	25 or greater	Not reported	2 times/wk 60 min: aerobic and strength exercises	15	0.66 (0.28–1.57)	Not reported
Price (2012) ²⁷	No restrictions	Sedentary	4 times/wk 45–60 min: walking, cycling, and weight training	12–14	0.75 (0.18–3.08)	American Diabetes Association
Renault (2014) ²⁸	30 or greater	Not reported	Daily goal of 11,000 steps	11–14	0.31 (0.06–1.45)	Danish Society of Obstetrics and Gynecology
Stafne (2012) ²⁹	No restrictions	Not reported	1 time/wk 60 min class, 2 times/week+, 45-min home exercise program, aerobic, resistance, and balancing exercises	18–22	1.21 (0.67–2.18)	World Health Organization
Tomić (2013) ³⁰	No restrictions	Not reported	3 times/wk 50 min: aerobic exercise and stretching	6–8	0.22 (0.06–0.74)	2-step OGCT and 100 g OGTT

BMI, body mass index; GDM, gestational diabetes mellitus; RR, relative risk; CI, confidence interval; OGCT, oral glucose challenge test; OGTT, oral glucose tolerance test.

* See the Appendix, available online at <http://links.lww.com/AOG/A610>.

such as diet. Notably, only two of the 10 included studies reported statistically significant protective effects of physical activity; however, sample size calculations suggest a required sample size of approximately 3,225 total to achieve 80% power with $\alpha=0.05$ for the observed meta-analytic RR estimate of 0.72 given a GDM incidence of 10%.

Research in the general adult population has consistently found that physical activity of various types, frequencies, and durations is linked to a lower

risk and improved management of type 2 diabetes.^{33,34} The mechanisms underlying the association between exercise and improvements in glucose intolerance and insulin resistance may be responsible for the lowered risk of GDM in pregnant women randomized to physical activity. Exercise is associated with improved insulin sensitivity and glucose uptake in cells,³⁵ improvements in beta-cell and epithelial function in insulin production,³⁶ and a lowering of excess adipose tissue, which influences the hormonal



and inflammatory environment.³⁷ Increased blood glucose and an associated increase in insulin production are a natural part of late pregnancy. Pregnant women with underlying insulin resistance may have difficulty producing enough insulin to lower blood glucose to safe levels,¹ and exercise-induced improvements in cellular glucose uptake and insulin production thereby help prevent the excessive blood glucose levels associated with GDM.

Inferences that may be drawn from meta-analysis are affected by the quality of the available data from existing studies as well as the methodologic variation among those studies. The majority of the studies were of moderate to high quality. One study did not use random number generation to determine treatment assignment for participants, but instead alternating assignment between intervention and control in a one-to-one ratio. Several studies did not report whether outcome assignment was blinded. One study noted missing data for GDM, although the proportion missing data were small and did not differ between study groups (2.8% in the intervention group compared with 3.8% in the comparison group).²⁹ One study excluded eight of 48 participants in the comparison group who chose to exercise, which may have introduced a differential bias if those participants differed from the rest of the comparison group in the risk of GDM (eg, were more health conscious).²⁷ The GDM status of participants at baseline was unclear in another study, as noted by the authors. If participants had GDM at baseline, the estimate obtained in the study would be a combined measurement of both the random assignment of those with GDM to study group (for those with GDM at baseline) as well as the effect of the intervention on GDM risk (for those without GDM at baseline), which limits inferences regarding GDM risk as used for our analysis.²⁴

Study 1 st author, year	Physical activity		Control		Weight	Risk ratio [95%CI]
	Events	Total	Events	Total		
Barakat, 2012 (22)	0	40	3	43	2.1%	0.15 [0.01, 2.88]
Barakat, 2013a (23)	41	210	61	218	37.6%	0.70 [0.49, 0.99]
Barakat, 2013b (24)	5	106	5	90	3.4%	0.85 [0.25, 2.84]
Callaway, 2010 (25)	5	22	3	19	2.0%	1.44 [0.40, 5.24]
Ko, 2014 (26)	25	591	33	605	20.5%	0.78 [0.47, 1.29]
Oostdam, 2012 (27)	7	49	11	51	6.8%	0.66 [0.28, 1.57]
Price, 2011 (28)	3	31	4	31	2.5%	0.75 [0.18, 3.08]
Renault, 2014 (29)	2	125	7	134	4.2%	0.31 [0.06, 1.45]
Stafne, 2012 (30)	25	375	18	327	12.1%	1.21 [0.67, 2.18]
Tomic, 2013 (31)	3	166	14	168	8.7%	0.22 [0.06, 0.74]
Total	116	1715	159	1686	100%	
Fixed effect						0.72 [0.58, 0.91] (P=0.005)
Random effect						0.74 [0.57, 0.97] (P=0.027)

Heterogeneity: $\chi^2=10.21$ (df=9), P=0.33; I²=12%

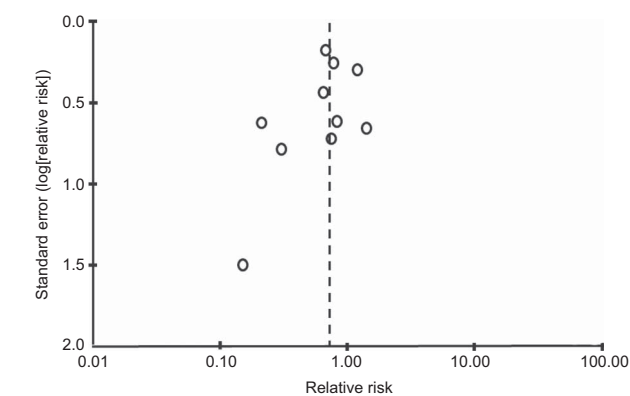


Fig. 3. Funnel plot of included randomized controlled trials assessing physical activity interventions and risk of gestational diabetes mellitus.

Russo. Exercise and Gestational Diabetes Meta-analysis. *Obstet Gynecol* 2015.

Like with many behavioral health interventions, adherence to an intervention protocol was a major limitation of the individual studies. Reported adherence to the interventions varied widely and were as low as 16%. Additionally, loss to follow-up was as high as 33%, reducing power and potentially introducing differential bias, although the majority of studies saw little differences in rates of and reasons for loss to follow-up between the exercise and comparison groups. Future intervention studies looking at this association would benefit from careful consideration of factors that influence retention of study participants, including feasibility and acceptability of intervention content for participants and ensuring adequate power to account for a reasonable estimate of nonadherence.

To assess potential heterogeneity of effect size by study characteristics, both fixed and random-effects models were used to estimate summary effects. The similarity in estimates from fixed and random-effects

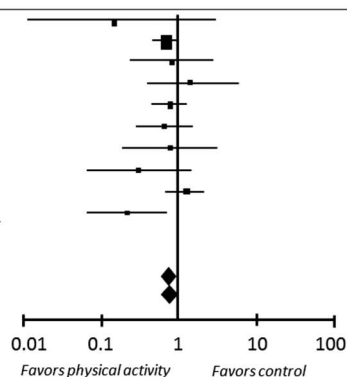


Fig. 2. Forest plot and results of fixed effects meta-analytic regression of risk of gestational diabetes mellitus in randomized controlled trials of physical activity interventions compared with a control group.

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models (RR 0.72, 95% CI 0.58–0.91 and RR 0.74, 95% CI 0.57–0.97, respectively) suggest that heterogeneity was not a major limitation in calculating the summary estimate. Consideration was given to the potential influence of publication bias; studies assessing GDM as a secondary outcome may be less likely to report results related to GDM if they were null or conflicting. Publication bias was assessed by use of a funnel plot, and the association between individual estimates of standard error and logarithm of RR fell within the expected distribution pattern, suggesting that publication bias may not be a major concern in this analysis.

As a result of the differences in study design and intervention content, the limited number of studies, and general null findings in individual studies, the effectiveness of specific interventions cannot be estimated, limiting the application of the findings from this study to practice. Additionally, eight of the 10 studies utilized group exercise models, intervention models that may represent a high burden for both participants and those implementing the intervention. Future research is needed to identify effective interventions that are translatable to practice. Because not all women in the exercise intervention will adhere to guidelines (and not all in the comparison will abstain from engaging in adequate physical activity), adherence is an important consideration for future research. Use of objective measures like accelerometers may be useful to determine effects of activity on risk of GDM. Diagnostic criteria also varied between studies; inconsistent classification, misclassification of GDM, or both may have occurred and would be expected to lead to an underestimation the association between participation in an exercise intervention and risk of GDM. Clear and consistent diagnostic criteria for GDM are important to best draw inference from future research in the area.

Despite a large overall sample size of more than 3,000 women, the relatively small number of studies included in this meta-analysis limited ability to perform subanalyses by numerous factors of potential interest. Race–ethnicity was fairly homogeneous among studies with most studies being conducted among predominantly white study groups, limiting the potential to assess differential effects of exercise on GDM by race–ethnicity. Additionally, only three studies restricted participation to women who were overweight or obese and results were not reported stratified by weight status in other studies. Evaluation of the proposed interventions among diverse populations and among overweight and obese women who are at a higher risk for GDM is warranted in future studies.

This study adds to the evidence base supporting an association between exercise during pregnancy and lower risk of GDM. Because the benefit of exercise identified in this study occurred with physical activity that began after recognition of pregnancy and enrollment in prenatal care, these findings suggest clear future clinical and public health applications. To advance our ability to promote optimum health in pregnancy, more research is needed to evaluate which types, durations, and intensities of physical activity are associated with a reduction in risk of GDM and the effectiveness of various intervention models.

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