Physical Activity Before and During Pregnancy and Risk of Gestational Diabetes Mellitus: A Meta-Analysis

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Accessibility
Physical Activity Before and During Pregnancy and Risk of Gestational Diabetes Mellitus

A meta-analysis

Deirdre K. Tobias, SM1
Cui Ling Zhang, MD, PhD2
Rob M. van Dam, MD, PhD1,3

Katherine Bowers, PhD2
Frank B. Hu, MD, PhD1,4

OBJECTIVE — Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy and is associated with a substantially elevated risk of adverse health outcomes for both mothers and offspring. Physical activity may contribute to the prevention of GDM and is crucial for dissecting the vicious circle involving GDM, childhood obesity, and adulthood obesity, and diabetes. Therefore, we aimed to systematically review and synthesize the current evidence on the relation between physical activity and the development of GDM.

RESEARCH DESIGN AND METHODS — Medline, EMBASE, and Cochrane Reviews were searched from inception to 31 March 2010. Studies assessing the relationship between physical activity and subsequent development of GDM were included. Characteristics including study design, country, GDM diagnostic criteria, ascertainment of physical activity, timing of exposure (prepregnancy or early pregnancy), adjusted relative risks, CIs, and statistical methods were extracted independently by two reviewers.

RESULTS — Our search identified seven prepregnancy and five early pregnancy studies, including five prospective cohorts, two retrospective case-control studies, and two cross-sectional study designs. Prepregnancy physical activity was assessed in 34,929 total participants, which included 2,813 cases of GDM, giving a pooled odds ratio (OR) of 0.45 (95% CI 0.28–0.75) when the highest versus lowest categories were compared. Exercise in early pregnancy was assessed in 4,401 total participants, which included 361 cases of GDM, and was also significantly protective (0.76 [95% CI 0.70–0.83]).

CONCLUSIONS — Higher levels of physical activity before pregnancy or in early pregnancy are associated with a significantly lower risk of developing GDM.

Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy, affecting ~7% of all pregnancies in the U.S. (i.e., >200,000 cases annually) (1), and this number is increasing as the prevalence of obesity among women at reproductive age escalates (2–4). GDM is associated with a significantly elevated risk for short-term and long-term complications for both mothers and offspring. Women with GDM have an increased risk for perinatal morbidity and impaired glucose tolerance and type 2 diabetes in the years after pregnancy (5,6). Children of women with GDM are more likely to be obese and have impaired glucose tolerance and diabetes in childhood and early adulthood (1). In a recent meta-analysis of randomized trials on the effect of treatment for GDM, various interventions for blood glucose control, including diet, glucose monitoring, insulin use, and pharmaceutical interventions, did not significantly reduce the risk for adverse perinatal and neonatal end points, including cesarean section and perinatal or neonatal death (7). Collectively, these data indicate that prevention of GDM altogether could be crucial for avoiding its associated adverse health outcomes.

Physical activity has long been known for its role in improving glucose homeostasis through its direct or indirect impact on insulin sensitivity via several mechanisms. For instance, physical activity has independent effects on glucose disposal by increasing both insulin-mediated and non–insulin-mediated glucose disposal (8,9). Physical activity can also exert long-term effects on improvement in insulin sensitivity through increased fat-free mass (10). Furthermore, the benefits of preventing or delaying the onset of type 2 diabetes among non-pregnant individuals have been reported repeatedly (11,12). Therefore, physical activity may have the potential for preventing GDM and related adverse health outcomes. However, evidence for its impact on GDM has not been systematically synthesized. The aim of this systematic review and meta-analysis was to assemble the current evidence for the relationship between physical activity and the development of GDM.

RESEARCH DESIGN AND METHODS

Data collection

Relevant published English-language articles were identified by searching the Medline database (National Library of Medicine) and the Cochrane Database of Systematic Reviews. Hand searching of reference lists of included studies was conducted as appropriate. The search was updated until April 2010. All studies assessing the relationship between physical activity and GDM were included. Characteristics including study design, country, GDM diagnostic criteria, ascertainment of physical activity, timing of exposure (prepregnancy or early pregnancy), adjusted relative risks, CIs, and statistical methods were extracted independently by two reviewers.
Physical activity and GDM: a meta-analysis

Medicine, Bethesda, MD), EMBASE, and Cochrane Reviews (The Cochrane Collaboration) through March 2010 and by a manual bibliography check. The Medline search was as follows, with similar terms for other databases: (diabetes, gestational [MeSH] AND (lifestyle OR “risk factor” OR physical activity [MeSH] OR exercise), where MeSH stands for “Medical Subject Headings.” Bibliographies of accepted studies as well as recent reviews were screened to ensure a complete study listing.

For relevant abstracts, full publications were retrieved for evaluation on the basis of criteria that were established a priori. All original research articles were considered except case reports. We sought to include studies that assessed the relationship between physical activity and the risk of developing GDM. Studies reporting only impaired glucose tolerance or an impaired glucose tolerance and GDM combined end point were not included. Our criteria did not restrict on the measurement of physical activity (frequency, intensity, type, and others) or the exposure period (prepregnancy or early pregnancy). One exception to this was the exclusion of studies evaluating physical activity during the total pregnancy period, such as retrospective questionnaires that did not specifically probe a pre-GDM gestational age time period. The rationale behind this exclusion is that women with the diagnosis of GDM may undergo therapy for glucose control that includes physical activity recommendations; thus, there is a potential for reverse causation (13,14). Our criteria did not restrict to particular populations or countries. Articles were independently screened for meeting the eligibility criteria by two reviewers (D.K.T. and K.B.).

For each accepted article, study characteristics, including authors, publication year, study design, country, and GDM screening and diagnostic criteria, were extracted independently by two researchers (D.K.T. and K.B.). Details of the exposure included the specific time period under investigation and the method of ascertainment. The unadjusted and adjusted relative risks and 95% CIs were extracted as reported by authors. Statistical methods were noted, including which covariates were considered and adjusted for. Authors were contacted for clarification of any of the above extracted data points if needed.

Statistical analysis
A random-effects meta-analysis was conducted to combine the relative risks reported for the original studies (15). Separate analyses were done for the prepregnancy and early pregnancy time periods. We chose to use a random-effects meta-analysis, which takes into account between-study heterogeneity, because the study design and exposure dose and intensity were not uniform across studies; therefore, similar effect sizes were not assumed. To facilitate a comparable exposure across studies, we analyzed the relative risks for the highest physical activity category versus the lowest (reference) category. When studies used the highest amount of activity as their reference group, we exponentiated the negative of the log odds ratio (OR) and 95% CI to convert the direction of the effect estimate.

The Cochrane Q test was used to evaluate the presence of heterogeneity, with a null hypothesis that the treatment effect is equal across all studies (16). We considered heterogeneity to be significant at $P < 0.1$, a conservative standard for meta-analyses (17). In addition, we calculated the I² statistic and 95% CIs to evaluate the percentage of heterogeneity that was due to between-study variation (18). In the presence of heterogeneity, sensitivity analyses were performed to evaluate effect modification by study-level characteristics including study design, GDM diagnostic criteria, physical activity measures (METs vs. frequency only; number of quantiles), and country of study (19). These were done by performing a random-effects meta-regression for each study-level variable. Stratified pooled effect estimates were calculated and reported if there was evidence of effect measure modification by a given characteristic. The influence of outliers was also assessed to evaluate the impact of their removal and the robustness of the meta-analysis.

Publication bias was assessed through Egger and Begg tests, using a significance level of $P < 0.05$ to indicate significant asymmetry (20,21). We also performed a visual inspection of the funnel plot for publication bias, looking for a skewed (nonsymmetric) distribution of standard errors around the study-level effect estimates.

Analyses were conducted in Stata (version 10.0; StataCorp, College Station, TX). We used the METAREG command to calculate the pooled effect estimates and the tests for heterogeneity. The METAREG and HETEROI commands were used to conduct analyses for heterogeneity.

RESULTS — Our literature search produced 442 citations, of which we selected 18 for further review of the full text (Fig. 1). Ten studies were excluded for reasons listed in Fig. 1. Therefore, eight publications met our criteria for inclusion in this meta-analysis and review (22–29) (Table 1). Findings for the OMEGA Study prospective cohort and Alpha Study case-control population were presented in three different publications (26–28). We assessed which outcomes were reported more than once to avoid inclusion of duplicate effect estimates in our meta-analyses. Two publications by Dempsey et al. (27,28) reported results for the OMEGA Study and Alpha Study populations, including both prepregnancy and early pregnancy exercise exposures. In a more recent, single publication, Rudra et al. (26) updated the results for both study populations, but for the prepregnancy exposure only. Therefore, the publications by Dempsey et al. (27,28) were included in our meta-analysis for their early pregnancy results only, and the relative risks from Rudra et al. (26) were included for its prepregnancy results.

Ultimately, the eight studies in our analysis (prepregnancy $k = 7$; early pregnancy $k = 5$) represented a total of 34,929 subjects (prepregnancy $N = 34,929$; early pregnancy $N = 4,401$), with 2,855 total cases of GDM (prepregnancy $n = 2,813$; early pregnancy $n = 361$) (22–29). These included five prospective cohort studies (22,24–26,28), two retrospective case-control studies (26,27), and two cross-sectional surveys (23,29). The total number of study designs is greater than the total number of publications because Rudra et al. (26) presented results for two distinct studies in the same study.) All studies were conducted among U.S. women except one, which was conducted by Harizopoulou et al. (23) among Greek participants. In the prospective cohort studies (22,24–26,28), physical activity interviews or questionnaires for both prepregnancy and early pregnancy habits were administered before participants received their diagnosis of GDM. For the retrospective case-control and cross-sectional studies (23,26,27,29), participants were asked about their physical activity during their postpartum hospital stay, with the exception of the study by
Redden et al. (29), which collected exposure data 2–7 months postpartum. The prepregnancy time period was defined in six studies as 1 year before the index pregnancy (23–28), in one study as 3 months before the index pregnancy (29), and in one study as the average exposure over several years of follow-up before the index pregnancy (22). All but one study (29) reported use of a validated physical activity questionnaire to assess exposure, although only one of these questionnaires was specifically validated in pregnant women, with satisfactory results (24). GDM was physician-diagnosed in all but one study, which used validated self-report of having received a physician's diagnosis (22). Other relevant study characteristics are tabulated in Table 1.

Units of physical activity varied and included frequency (hours per week), energy expenditure (MET-hours per week), and level of exertion or intensity. Physical activity types included total physical activity as well as specific activities (walking, climbing stairs, and others). In the meta-analyses of total physical activity, five of the eight studies analyzed physical activity in units of energy expenditure (22,23,26–28), which incorporates both frequency and intensity, whereas three of the eight studies analyzed physical activity in units of frequency only (24,25,29). All but two cross-sectional studies reported relative risks across quantiles of exposure (23,29).

**Total physical activity**

**Prepregnancy.** Seven studies reported the association between total prepregnancy physical activity and GDM (22–26,29). A meta-analysis of relative risks indicated a 55% lower risk of GDM for women in the highest physical activity quantiles compared with those in the lowest (pooled OR 0.45 [95% CI 0.28–0.75]; P = 0.002) (Fig. 2). The Cochrane Q statistic indicated significant heterogeneity in study results (Q = 32.6, P < 0.001), with an I² value estimating that 82% (63–91%) of the variance is due to between-study differences.

We conducted additional sensitivity analyses to evaluate potential sources of heterogeneity in the results. Meta-regression did not show a significant difference in effect estimates among studies with a prospective versus retrospective study design (meta-regression P = 0.54) (supplementary Fig. 1, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc10-1368/DC1). Likewise, meta-regression results indicated a lack of effect measure modification by GDM diagnosis criteria (P = 0.58), physical activity analysis by energy expenditure versus frequency (P = 0.40), study size being >100 cases (P = 0.15), and country of study (P = 0.078). When we ran the meta-regression on the total number of exposure categories, there was a borderline significant association (P = 0.053); however, the number of studies in each strata was few. When we stratified by whether studies adjusted for specific confounders, we did not find a statistically significant difference among effect estimates that controlled for family history of diabetes (P = 0.97), smoking status (P = 0.23), race or ethnicity (P = 0.33), parity (P = 0.67), or socioeconomic status co-variables (P = 0.47). Finally, to evaluate the robustness of the main pooled effect estimate, we removed the largest study by Zhang et al. (22), which accounted for 62% of the total study participants. This did not substantially alter the pooled OR or significance level (pooled OR 0.39 [0.20–0.73]; P = 0.004).

**Early pregnancy.** Five studies reported effect estimates for the association between early pregnancy physical activity and development of GDM (23–25,27,28). Results for activity during this time period indicated a significant 24% lower risk of GDM associated with the highest activity group compared with the lowest activity group, as shown in Fig. 2 (OR 0.76 [0.70–0.83]; P < 0.0001). The Q test was not significant for heterogeneity but was possibly underpowered because of few studies (Q = 1.83; P = 0.77). Despite a point estimate of 0%, the I² statistic suggested that heterogeneity was possible, given the wide CI (95% CI 0.79–79%). In a sensitivity analysis we removed the study by Harizopoulou et al. (23) because it contributed to 96% of the weight in the pooled OR. The pooled OR remained statistically significant with a similar magnitude of effect (0.65 [0.43–0.98]; P = 0.04).

Finally, the Egger and Begg tests for the primary analyses did not indicate the presence of publication bias in the analysis of total physical activity (prepregnancy P = 0.30; early pregnancy P = 0.81). Visual inspection of the funnel plot was in agreement with the statistical test, with no apparent asymmetry.

**Walking**

The association between walking and GDM risk was evaluated in three studies (22,25,27). Two studies analyzed the association between walking duration and GDM risk (Oken et al.: 3 miles/day vs. 0.23 h/day; Dempsey et al.: 3 miles/day vs. <1 mile/day) (25, 27). Overall there did not seem to be an association between walking duration and GDM risk (prepregnancy: pooled OR 0.95 [95% CI 0.50–1.83]; early pregnancy: 0.77 [0.51–1.16]). However, when the joint effect of walking duration and usual walking pace was analyzed, there was
| Study design            | Prospective cohort | Retrospective case-control | Cross-sectional survey | Prospective cohort | Cross-sectional survey | Prospective cohort | Retrospective case-control | Prospective cohort |
|-------------------------|--------------------|-----------------------------|------------------------|--------------------|------------------------|--------------------|--------------------------|---------------------|
| Total subjects (N)      | 1,006              | 909                         | 155                    | 40                 | 91                     | 808                | 42                       | 216                 |
| Cases of GDM (n)        | 33                 | 42                          | 195                    | 40                 | 91                     | 808                | 42                       | 216                 |
| Country of study        | U.S.               | U.S.                        | Greece                 | U.S.               | U.S.                   | U.S.               | U.S.                     | U.S.                |
| Study population        | Latina Pregnancy Study | OMEGA Study             | Alpha Study            | Project Viva        | PRAMS                  | OMEGA Study         | Alpha Study             | Study II          |
| Prepregnancy meta-analysis | ✓                  | ✓                           | ✓                      | ✓                  | ✓                      | ✓                  | ✓                        | ✓                   |
| Early pregnancy meta-analysis | ✓                  | ✓                           | ✓                      | ✓                  | ✓                      | ✓                  | ✓                        | ✓                   |
| Total activity measure  | Energy expenditure (KPAS score 4–20) | Energy expenditure (MET-h/week) | Energy expenditure (MET-h/week) | Energy expenditure (MET-h/week) | Energy expenditure (MET-h/week) | Energy expenditure (MET-h/week) | Energy expenditure (MET-h/week) | Energy expenditure (MET-h/week) |
| Exposure groups         | Prepregnancy: 7.9, 9.5, 10.8, 12.3; early pregnancy: 6.8, 8.1, 9.2, 10.7 (quartile medians) | None (Ref), <28, ≥28 | None (Ref), 0.1–9.9, 10–19.9, 29.9, ≥30 | 0–10 (Ref), ≥10 | 0–2 (Ref), 3–6, 7–13, ≥14 | 0–1 (Ref), 1–4, ≥5 | None (Ref), 0.1–14.9, 15.0–29.9, ≥30 | None (Ref), 0.1–14.9, 15.0–29.9, ≥30 |
| GDM diagnostic criteria | NDDG                | NDDG                        | NDDG                   | ADA                | Self-report            | NDDG               | Carpenter and Coustan    | NDDG               |
| Exposure assessment method(s) | KPAS               | Stanford Seven-Day PA Recall; Minnesota Leisure-Time PAQ; Borg rating scale | Stanford Seven-Day PA Recall; Minnesota Leisure-Time PAQ; Borg rating scale | IPAQ               | PASE                   | Stanford Seven-Day PA Recall; Minnesota Leisure-Time PAQ; Borg rating scale | Validated self-report (various) | Standardized questionnaire |
| Model covariables        | Age, pre-pregnancy BMI | Age, race/ethnicity, pre-pregnancy BMI, nulliparity, smoking during pregnancy | Age, race/ethnicity, pre-pregnancy BMI, pregnancy weight gain, income, education, occupation, residence, family history of diabetes, prior glucose intolerance, previous infant with macrosomia, current glycosuria | Age, race/ethnicity, pre-pregnancy BMI, parity, no. prenatal care visits, income, alcohol consumption during pregnancy | Age, race/ethnicity, pre-pregnancy BMI, nulliparity, pre-pregnancy hypertension | Age, race/ethnicity, pre-pregnancy BMI, nulliparity, pre-pregnancy hypertension | Age, race/ethnicity, pre-pregnancy BMI, parity, smoking status, family history of diabetes, alcohol intake, total caloric energy intake, cereal fiber, glycemic load, total grams of fat |

ADA, American Diabetes Association; IPAQ, International Physical Activity Questionnaire; KPAS, Kaiser Physical Activity Survey; NDDG, National Diabetes Data Group; PA, Physical Activity; PAQ, Physical Activity Questionnaire; PASE, Pregnancy Risk Assessment and Monitoring System; PRAMS, Pregnancy Risk Assessment and Monitoring System; Ref, referent.
an inverse association in the prepregnancy time period. In the studies by Dempsey et al. (27) and Zhang et al. (22), women who reported a brisk usual walking pace and walked for a longer duration (Dempsey et al.: >2 miles/day; Zhang et al.: >30 min/day) were associated with a lower risk of GDM, compared with women reporting a casual usual walking pace and shorter duration (pooled OR 0.59 [95% CI 0.30–0.87]). This association was slightly attenuated in early pregnancy, as reported by Dempsey et al. but did not reach statistical significance (OR 0.83 [95% CI 0.48–1.45]). Although only three studies reported associations between walking and GDM risk, findings were consistent for an inverse association with intensity of walking pace, although it is unclear whether walking duration (distance or time) has similar benefits.

Stair climbing
Two studies assessed the association between stair climbing and GDM risk as the number of flights of stairs climbed per day during the prepregnancy period (22,27). They each found a significant inverse association between GDM and the highest category of stair climbing (Dempsey et al.: ≥10 flights/day; Zhang et al.: ≥15 flights/day) compared with women who did not climb stairs, after adjustment for several potential confounders, including prepregnancy BMI (Dempsey et al.: OR 0.47 [95% CI 0.26–0.93]; Zhang et al.: 0.50 [0.27–0.90]; pooled OR 0.49 [95% CI 0.26–0.72]). Dempsey et al. (27) also assessed stair climbing in early pregnancy and found a similar inverse association (OR 0.26 [95% CI 0.13–0.52]).

Vigorous activity
Four studies evaluated physical activity of vigorous intensity (22,25–27). Overall, there was an inverse association between participation in vigorous activity compared with no vigorous activity in prepregnancy (pooled OR 0.47 [95% CI 0.19–0.75]). Two studies also reported an association of GDM and vigorous activity intensity in early pregnancy (25,27). The pooled effect estimate suggests an inverse association with vigorous physical activity (0.55 [0.21–1.43]), although this did not reach statistical significance.

Physical inactivity
Few studies addressed the association of sedentary or inactive lifestyle in prepregnancy or early pregnancy with the risk of GDM. In the prospective cohort by Oken et al. (25), those who reported being sedentary (≤2 h/week total physical activity) has a nonsignificantly higher risk of GDM for both time periods (prepregnancy: OR 1.4 [95% CI 0.7–3.0]; early pregnancy:

Figure 2—Results of meta-analyses. A: Prepregnancy physical activity. B: Early pregnancy physical activity.
more long-term role in glucose tolerance may also have an indirect and potentially dothelial function (11,12). Researchers direct effects on oxidative stress and en-
crease in GLUT4, a glucose transport protein (34,35). Physical activity also has shown that exercise-induced improve-
tions in muscle mass have been shown to have positive effects on glycemic control (37). In our literature search we did not identify results of any randomized clinical trials evaluating the effect of physical activity on prevention of GDM risk. However, it is reasonable to infer that physical activity might prevent GDM through similar pathways.

Although the findings in this meta-
alysis give support for physical activity in the prevention of GDM, there are some limitations. Assessment of physical activity was done via self-report in questionnaires; thus, misclassification is plausible. For the prospective studies in our analy-

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References
1. American Diabetes Association. Gestational diabetes mellitus. Diabetes Care 2004;27(Suppl. 1):S88–S90
2. Albrecht SS, Kuklina EV, Bansl P, Jamie-
sent DJ, Whitteman MK, Kouriis AP, Pos-
er SF, Callaghan WM. Diabetes trends among delivery hospitalizations in the U.S., 1994–2004. Diabetes Care 2010; 33:768–773
3. Dabelea D, Snell-Begeon JK, Hartsfield

In summary, results from this system-
atic review and meta-analyses demon-
strate that greater total physical activity before or during early pregnancy is signifi-
cantly associated with lower risk of GDM, with the magnitude of the associa-
tion being stronger for prepregnancy physical activity. Given the consistent evi-
dence across several studies, promoting physical activity among women of repro-
ductive age may represent a promising approach for the prevention of GDM and subsequent complications of children born from pregnancies affected by GDM. It is still unknown whether beginning an exercise routine in early pregnancy among previously sedentary or minimally active women incurs GDM prevention, and further research is warranted to de-
termine the joint and independent effects of physical activity before and during early pregnancy.
Bender R, Bastian H, Lange S, Siebenhofer A. Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis. BMJ 2010;340:c1395
8. Annuzzi G, Riccardi G, Capaldo B, Kaisjer L. Increased insulin-stimulated glucose uptake by exercised human muscles one day after prolonged physical exercise. Eur J Clin Invest 1991;21:6–12
9. Devlin JT. Effects of exercise on insulin sensitivity in humans. Diabetes Care 1992;15:1690–1693
10. Shulman GI, Rothman DL, Jue T, Stein P, DeFronzo RA, Shulman RG. Quantitation of muscle glycogen synthesis in normal subjects and subjects with non-insulin-dependent diabetes by 13C nuclear magnetic resonance spectroscopy. N Engl J Med 1990;322:223–228
11. Boule NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. JAMA 2001;286:1218–1227
12. Jeon CY, Lokken RP, Hu FB, van Dam RM. Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. Diabetes Care 2007;30:744–752
13. American Diabetes Association. Gestational diabetes mellitus. Diabetes Care 2003;26(Suppl. 1):S103–S105
14. Guideline Development Group. Management of diabetes from preconception to the postnatal period: summary of NICE guidance. BMJ 2008;336:714–717
15. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997;127:820–826
16. Cochrane W. The combination of estimates from different experiments. Biometrics 1954;10:101–129
17. Pettiti DB. Approaches to heterogeneity in meta-analysis. Stat Med 2001;20:3625–3633
18. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–1558
19. Berlin JA, Antman EM. Advantages and limitations of metaanalytic regressions of clinical trials data. Online J Curr Clin Trials 1994;Doc No 134
20. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–1101
21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634
22. Zhang C, Solomon CG, Manson JE, Hu FB. A prospective study of pregravid physical activity and sedentary behaviors in relation to the risk for gestational diabetes mellitus. Arch Intern Med 2006;166:543–548
23. Harzopoulou VC, Kritikos A, Papanikolaou Z, Sarantzi E, Vavilis D, Klotos E, Papadimas I, Goulis DG. Maternal physical activity before and during early pregnancy as a risk factor for gestational diabetes mellitus. Acta Diabetol. 18 July 2009 [Epub ahead of print]
24. Chasan-Taber L, Schmidt MD, Pekow P, Sternfeld B, Manson JE, Solomon CG, Braun B, Markenson G. Physical activity and gestational diabetes mellitus among Hispanic women. J Womens Health (Larchmt) 2008;17:999–1008
25. Oken E, Ning Y, Rifas-Shiman SL, Radesky JS, Rich-Edwards JW, Gillman MW. Associations of physical activity and inactivity before and during pregnancy with glucose tolerance. Obstet Gynecol 2006;108:1200–1207
26. Rudra CB, Williams MA, Lee IM, Miller RS, Sorensen TK. Perceived exertion in physical activity and risk of gestational diabetes mellitus. Epidemiology 2006;17:31–37
27. Dempsey JC, Butler CL, Sorensen TK, Lee IM, Thompson ML, Miller RS, Frederick IO, Williams MA. A case-control study of maternal recreational physical activity and risk of gestational diabetes mellitus. Diabetes Res Clin Pract 2004;66:203–215
28. Dempsey JC, Sorensen TK, Williams MA, Lee IM, Miller RS, Dashow EE, Luthy DA. Prospective study of gestational diabetes mellitus risk in relation to maternal recreational physical activity before and during pregnancy. Am J Epidemiol 2004;159:663–670
29. Redden SL, Lamonte MJ, Freudenheim JL, Rudra CB. The association between gestational diabetes mellitus and recreational physical activity. Matern Child Health J. 6 March 2010 [Epub ahead of print]
30. Knopp RH, Bergelin RO, Wahl PW, Walden CE, Chapman M, Irvine S. Population-based lipoprotein lipid reference values for pregnant women compared to nonpregnant women classified by sex hormone usage. Am J Obstet Gynecol 1982;143:626–637
31. Knopp RH, Warth MR, Charles D, Childs M, Li JR, Mabuchi H, Van Allen MI. Lipoprotein metabolism in pregnancy, fat transport to the fetus, and the effects of diabetes. Biol Neonate 1986;50:297–317
32. Metzger BE, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR, Hod M, Kitzmiller JL, Kjos SL, Oats JN, Pettitt DJ, Sacks DA, Zouzas C. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. Diabetes Care 2007;30(Suppl. 2):S251–S260
33. Mottola MF. The role of exercise in the prevention and treatment of gestational diabetes mellitus. Curr Diab Rep 2008;8:290–304
34. Yung LM, Laher I, Yao X, Chen ZY, Huang Y, Leung FP. Exercise, vascular wall and cardiovascular diseases: an update (part 2). Sports Med 2009;39:45–63
35. Ryder JW, Chibalin AV, Zierath JR. Intracellular mechanisms underlying increases in glucose uptake in response to insulin or exercise in skeletal muscle. Acta Physiol Scand 2001;171:249–257
36. Ivy JL. Role of exercise training in the prevention and treatment of insulin resistance and non-insulin-dependent diabetes mellitus. Sports Med 1997;24:321–336
37. Marwick TH, Horder MD, Miller T, Chyun DA, Berti AG, Blumenthal RS, Philippides G, Rocchini A, Council on Clinical Cardiology, American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, Council on Nutrition, Physical Activity, and Metabolism, Interdisciplinary Council on Quality of Care and Outcomes Research. Exercise training for type 2 diabetes mellitus: impact on cardiovascular risk: a scientific statement from the American Heart Association. Circulation 2009;119:3244–3262
38. Ning Y, Williams MA, Dempsey JC, Sorensen TK, Frederick IO, Luthy DA. Correlates of recreational physical activity in early pregnancy. J Matern Fetal Neonatal Med 2003;13:385–393

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