Physical activity before and during pregnancy and risk of gestational diabetes mellitus: a meta-analysis

Running Title: Physical activity and GDM: a meta-analysis

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http://care.diabetesjournals.org

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Objective: Gestational diabetes mellitus (GDM) is one of the most common pregnancy complications 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 thus is crucial for dissecting the vicious circle involving GDM, childhood obesity, and adulthood obesity and diabetes. Therefore, we aim 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 March 31, 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 (pre-pregnancy, early pregnancy), adjusted relative risks, confidence intervals, and statistical methods were extracted independently by 2 reviewers.

Results: Our search identified 7 pre-pregnancy and 5 early pregnancy studies, including 5 prospective cohorts, 2 retrospective case-controls, and 2 cross-sectional study designs. Pre-pregnancy physical activity was assessed in 34,929 total participants including 2,813 GDM cases, giving a pooled odds ratio of 0.45 (95% CI: 0.28-0.75) when comparing the highest vs. lowest categories. Exercise in early pregnancy was assessed in 4,401 total participants including 361 GDM cases, and was also significantly protective (OR=0.76, 95%CI: 0.70, 0.83).

Conclusions: Higher levels of physical activity prior to pregnancy or in early pregnancy are associated with a significantly lower risk of developing GDM.
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). Further, benefits in preventing or delaying the onset of type 2 diabetes among non-pregnant individuals have been repeatedly reported (11; 12). Therefore, physical activity may have 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 is 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, Bethesda, MD), EMBASE, and Cochrane Reviews (The Cochrane Collaboration) through March 2010, and a manual bibliography check. The Medline search is 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 insure a complete study listing. For relevant abstracts, full publications were retrieved for evaluation based on criteria that were established a priori. All original research articles were considered except case reports. We sought to include studies which assessed the relationship between physical activity and the risk of developing of GDM. Studies only reporting impaired glucose tolerance (IGT) or an IGT+GDM combined endpoint were not included. Our criteria did not restrict on the measurement of physical activity (frequency, intensity, type, etc), or the exposure period (pre-pregnancy, 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 diagnosed with 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. Papers were independently screened for meeting the eligibility criteria by 2 reviewers (DT, KB). For each accepted article, study characteristics were extracted independently by 2 researchers (DT, KB), including authors, publication year, study design, country, and GDM screening and diagnostic criteria. Details of the exposure included the specific time period under investigation, and the method of ascertainment. The unadjusted and adjusted relative risks and 95% confidence intervals were extracted as reported by authors. Statistical methods were noted, including which covariables 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 pre-pregnancy 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 and 95% confidence interval to convert the direction of the effect estimate. Cochrane’s 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 I^2 statistic and 95% confidence intervals to evaluate the percent 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 versus frequency only; number of quantiles), and country of study (19). This was 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’s and Begg’s test, 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 (non-symmetric) distribution of standard errors around the study-level effect estimates.

Analyses were conducted in STATA Version 10.0 (STATA Corp, College Station, Texas). We used the METAN command to calculate the pooled effect estimates and the tests for heterogeneity. The METAREG and HETERO GI 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 (Figure 1). Ten studies were excluded for reasons listed in Figure 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 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 pre-pregnancy 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 pre-pregnancy 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 pre-pregnancy results.

Ultimately, the 8 studies in our analysis (pre-pregnancy k=7, early pregnancy k=5) represented a total of 34,929 subjects (pre-pregnancy n=34,929, early pregnancy n=4,401), with 2,855 total cases of GDM (pre-pregnancy n=2,813, early pregnancy n=361) (22-29). This included 5 prospective cohort studies (22; 24-26; 28), 2 retrospective case-control studies (26; 27), and 2 cross-sectional surveys (23; 29). (The total number of study designs is greater than the total number of publications because Rudra et al (26) presents results for 2 distinct studies in the same paper.) All but 1 study was conducted among US women, which was published by Harizopoulou et al among Greek participants (23). In the prospective cohort studies (22; 24-26; 28), physical activity interviews or questionnaires for both pre-pregnancy and early pregnancy habits were
administered prior to participants receiving 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 post-partum hospital stay, with the exception of the study by Redden et al, which collected exposure data 2-7 months post-partum (29). The pre-pregnancy time period was defined in 6 studies as 1 year prior to the index pregnancy (23-28), in 1 study as 3 months prior to the index pregnancy (29), and in 1 study as the average exposure over several years of follow-up prior to the index pregnancy (22). All but 1 study (29) reported use of a validated physical activity questionnaire to assess exposure, although only 1 of these questionnaires has been specifically validated in pregnant women, with satisfactory results (24). GDM was physician-diagnosed in all but 1 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/week), energy expenditure (MET-hours/week), and level of exertion or intensity. Physical activity types included total physical activity as well as specific activities (walking, stairs, etc). In the meta-analyses of total physical activity, 5 of the 8 studies analyzed physical activity in units of energy expenditure (22; 23; 26-28), which incorporates both frequency and intensity, while 3 of the 8 studies analyzed physical activity in units of frequency only (24; 25; 29). All but the 2 cross-sectional studies reported relative risks for across quantiles of exposure (23; 29).

**Total Physical Activity.** *Pre-pregnancy*—Seven studies reported the association between total pre-pregnancy 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 to those in the lowest (pooled OR=0.45, 95% CI: 0.28-0.75; p=0.002) (Figure 2). Cochrane’s 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 between studies with a prospective versus retrospective study design (meta-regression p=0.54) (Supplemental Figure 1 in the online appendix available at [http://care.diabetesjournals.org](http://care.diabetesjournals.org)). Similarly, 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 greater than 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 were few. When we stratified by whether studies adjusted for specific confounders, we did not find a statistically significant difference between 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 socio-economic status covariables (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 odds ratio or significance level (pooled OR=0.39, 95% CI: 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 to the lowest activity group, as shown in Figure 2 (OR=0.76, 95% CI: 0.70, 0.83; p<0.0001). The Q-test was not significant for heterogeneity but was possibly under-powered due to few studies (Q=1.83, p=0.77). Despite a point estimate of 0%, the I² statistic suggested heterogeneity was possible, given the wide confidence interval (95%CI: 0-79%). In a sensitivity analysis we removed the study by Harizopoulou et al (23) since it contributed to 96% of the weight in the pooled OR. The pooled OR remained statistically significant with a similar magnitude of effect (OR=0.65, 95% CI: 0.43, 0.98; p=0.04).

Finally, the Egger’s and Begg’s test for the primary analyses did not indicate the presence of publication bias in the analysis of total physical activity (pre-pregnancy: 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 of walking and GDM risk was evaluated in 3 studies (22; 25; 27). Two studies analyzed the association of walking duration and GDM risk (Oken: >2 hour/day vs. ≤2 hour/day; Dempsey: >3 miles/day vs. ≤1 mile/day) (25; 27). Overall there did not appear to be an association between walking duration and GDM risk (pre-pregnancy: pooled OR=0.95, 95%CI: 0.50, 1.83; early pregnancy: pooled OR=0.77, 95%CI: 0.51, 1.16). However, when the joint effect of walking duration and usual walking pace was analyzed, there was an inverse association in the pre-pregnancy 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: >2 miles/day; Zhang: >30 minutes/day) were associated with a lower risk of GDM, compared to 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 report associations between walking and GDM risk, findings are 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 of stair climbing on GDM risk as the number of flights of stairs climbed per day during the pre-pregnancy period (22; 27). They each found a significant inverse association between GDM and women in the highest category of stair climbing (Dempsey ≥10 flights/day; Zhang ≥15 flights/day) compared to women who did not climb stairs, after adjustment for several potential confounders, including pre-pregnancy BMI (Dempsey: OR=0.47, 95%CI: 0.26, 0.93; Zhang: OR=0.50, 95%CI: 0.27, 0.90; pooled OR=0.49, 95%CI: 0.26, 0.72). Dempsey et al also assessed stair climbing in early pregnancy and found a similar inverse association (OR=0.26, 95%CI: 0.13, 0.52) (27).

**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 to no vigorous activity in pre-pregnancy (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 (pooled OR=0.55, 95%CI: 0.21, 1.43), although this did not reach statistical significance.

**Physical Inactivity.** Few studies addressed sedentary or inactive lifestyle in pre-pregnancy or early pregnancy on the risk of GDM. In the prospective cohort by Oken et
al, those who reported being sedentary (≤2 hours/week total physical activity) has a non-significantly higher risk of GDM for both time periods (pre-pregnancy: OR=1.4, 95%CI:0.7-3.0; early-pregnancy: OR=1.4, 95%CI: 0.8-2.6) (25). Hours spent watching television was not associated with GDM risk in two prospective cohort studies (Oken: RR=1.03, 95%CI: 0.6, 1.8; Zhang: not reported) (22; 25).

CONCLUSIONS
The results from our systematic review and meta-analyses indicate that greater total physical activity before pregnancy or during early pregnancy was significantly associated with a lower risk of GDM. The magnitude of this association was greatest for pre-pregnancy physical activity with women in the highest quantiles of activity experiencing a 55% reduction in risk, compared to women with the lowest activity. Heterogeneity in study results were substantial, suggesting differences between study populations or methodology may have affected the results. Our analyses to detect sources of heterogeneity were likely underpowered since few studies were in each strata. However, removal of individual influential studies did not dramatically alter our findings, supporting the robustness of the pooled estimate. Early pregnancy physical activity was also associated with a statistically significant 25% lower risk for women participating in high levels of physical activity.

The course of a normal pregnancy includes increased metabolic stress and disturbances in lipid and glucose homeostasis in the third trimester (30; 31). There is marked insulin resistance in maternal muscle with the intent to increase glucose supply for the developing fetus. The development of GDM might reflect an impaired capacity to handle such metabolic challenges, such as underlying β-cell dysfunction (32). Therefore, women more equipped to handle metabolic stress might be more likely to maintain normal glucose levels (33). The inverse association we observed between physical activity and development of GDM is biologically plausible. Research among non-pregnant individuals has shown exercise-induced improvements in glycemic control may be due to increases in GLUT-4, a glucose transport protein (34; 35). Physical activity also has direct effects on oxidative stress and endothelial function (11; 12). Researchers have demonstrated physical activity may also have an indirect and potentially more long-term role in glucose tolerance through changes in body composition (36; 37). Decreases in fat mass and increases 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 GDM risk. However, it is reasonable to infer that physical activity might prevent GDM through similar pathways.

Although the findings in this meta-analysis 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 analysis, misclassification of pre-pregnancy physical activity in the prospective studies is likely to be random with respect to exposure, since women were unaware of their GDM diagnosis at the time of assessment; however, attenuation of the effect estimates may lead to an underestimation of the true association. Additionally, the inverse association between physical activity and GDM risk did not differ by study design (i.e. prospective vs. retrospective) in our meta-regression, alleviating the concern for recall bias among the retrospective studies. Adjustment for major confounders was consistent across studies, although unknown or residual
Physical activity and GDM: a meta-analysis

confounding is possible. The small number of published studies makes it difficult to assess heterogeneity in the pooled odds ratios. There is also the chance for publication bias, when researchers are less likely to publish null or uninteresting findings. The methods used in this review did not suggest publication bias. Finally, although we were able to analyze the pre-pregnancy and early pregnancy physical activity periods separately, our analysis is unable to determine the independent biological relevance of the two exposure periods. Pre-pregnancy physical activity is one of the strongest predictors of physical activity in early pregnancy, thus it is difficult to know which, or if both, could be contributing to the inverse associations seen in our analyses, due to their high correlation (38). Much of the benefit that we observed for pregravid physical activity could also reflect continued activity during pregnancy, and vice versa.

In conclusion, results from this systematic review and meta-analyses demonstrate that greater total physical activity before or during early pregnancy is significantly associated with lower risk of GDM, with the magnitude of the association being stronger for pre-pregnancy physical activity. Given the consistent evidence across several studies, promoting physical activity among women of reproductive 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 determine the joint and independent effect of physical activity before and during early pregnancy.

Author contributions: DT – Literature search, independent review of articles and extraction of data, data analysis, manuscript preparation; CZ – Critical revision of the article for important intellectual content; RvD – Critical revision of the article for important intellectual content; KB – Independent review of articles and extraction of data; FH – Critical revision of the article for important intellectual content.

ACKNOWLEDGMENTS

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Disclosures: None.

REFERENCES


**Figure Legend**

Figure 1. Study attrition diagram

Figure 2. Results of meta-analyses
   a. Pre-pregnancy physical activity
   b. Early pregnancy physical activity
<table>
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<tr>
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<tr>
<td><strong>Study Design</strong></td>
<td>Prospective Cohort</td>
<td>Prospective Cohort</td>
<td>Retrospective Case-Control</td>
<td>Cross-Sectional Survey</td>
<td>Prospective Cohort</td>
<td>Cross-Sectional Survey</td>
<td>Prospective Cohort</td>
<td>Retrospective Case-Control</td>
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<td>Total Subjects (N)</td>
<td>1,006</td>
<td>909</td>
<td>521</td>
<td>160</td>
<td>1,805</td>
<td>8,608</td>
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<td>Cases of GDM (n)</td>
<td>33</td>
<td>42</td>
<td>155</td>
<td>40</td>
<td>91</td>
<td>808</td>
<td>42</td>
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<td><strong>Study Population</strong></td>
<td>Latina Pregnancy Study</td>
<td>OMEGA Study</td>
<td>The Alpha Study</td>
<td>Hospital-based participants</td>
<td>Project Viva</td>
<td>Pregnancy Risk Assessment and Monitoring System (PRAMS)</td>
<td>OMEGA Study</td>
<td>Alpha Study</td>
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<tr>
<td>Early Pregnancy Meta-Analysis</td>
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<td><strong>Total Activity Measure</strong></td>
<td>Energy Expenditure (KPAS Score 4-20)</td>
<td>Energy Expenditure (MET-Hours/Week)</td>
<td>Energy Expenditure (MET-Hours/Week)</td>
<td>Energy Expenditure (MET-Hours/Week)</td>
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<td><strong>Exposure Groups</strong></td>
<td>Pre-Pregnancy: 7.9, 9.5, 10.8, 12.3; Early Pregnancy: 6.8, 8.1, 9.2, 10.7 (Quartile Medians)</td>
<td>None (Ref), &lt;28, ≥28</td>
<td>None (Ref), 0.1-9.9, 10-19.9, 29.9, ≥30</td>
<td>0-10 (Ref), ≥10</td>
<td>0-2 (Ref), 3-6, 7-13, ≥14</td>
<td>0-1 (Ref), 1-4, ≥5</td>
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<td>None (Ref), 0.1-14.9, 15.0-29.9, ≥30</td>
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<td>NDDG</td>
<td>NDDG</td>
<td>ADA</td>
<td>Self-Report</td>
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<td>Carpenter and Coustan</td>
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<td>Exposure Assessment Method(s)</td>
<td>Kaiser Physical Activity Survey (KPAS)</td>
<td>Stanford Seven-Day PA Recall; Minnesota Leisure-Time PAQ; BORG rating scale</td>
<td>Stanford Seven-Day PA Recall; Minnesota Leisure-Time PAQ; BORG rating scale</td>
<td>International Physical Activity Questionnaire (IPAQ)</td>
<td>Modified Physical Activity Scale for the Elderly (PASE)</td>
<td>Standardized questionnaire</td>
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<tr>
<td>Model Covariates</td>
<td>age, pre-pregnancy BMI</td>
<td>age, race/ethnicity, pre-pregnancy BMI, parity</td>
<td>age, pre-pregnancy BMI,妊 pregnancy weight gain, income, education, occupation, residence, family history of diabetes, prior glucose intolerance, previous infant w/ macrosomia, current glycosuria</td>
<td>age, race/ethnicity, pre-pregnancy BMI, preg pregnancy BMI, history of GDM, maternal history of diabetes</td>
<td>age, race/ethnicity, pre-pregnancy BMI, parity, # prenatal care visits, income, alcohol consumption during pregnancy</td>
<td>age, race/ethnicity, pre-pregnancy BMI, nulliparity, pre-pregnancy hypertension</td>
<td>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</td>
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Figure 1

442 Citations Identified

18 Relevant Abstracts Accepted for Full Article Review

10 Excluded After Independent Review by 2 Researchers
  - 3 Combined Impaired Glucose Tolerance and GDM Endpoint
  - 2 PA Exposure over Entire Pregnancy
  - 3 No GDM Outcome Reported
  - 1 Relative Risk not Extractable
  - 1 Duplicate Study Population

8 Included in Meta-Analysis
Figure 2

a.

<table>
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<tr>
<th>Author (Year)</th>
<th>OR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
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<tr>
<td>Chasan-Taber (2008)</td>
<td>0.80 (0.20, 2.70)</td>
<td>8.51</td>
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<tr>
<td>Harizopoulou (2009)</td>
<td>0.13 (0.06, 0.27)</td>
<td>13.9</td>
</tr>
<tr>
<td>Oken (2006)</td>
<td>0.70 (0.30, 1.68)</td>
<td>12.7</td>
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<tr>
<td>Redden (2010)</td>
<td>0.69 (0.46, 1.03)</td>
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<tr>
<td>Rudra (2006a)</td>
<td>0.14 (0.05, 0.38)</td>
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<td>Rudra (2006b)</td>
<td>0.49 (0.28, 0.87)</td>
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<tr>
<td>Zhang (2006)</td>
<td>0.81 (0.68, 1.01)</td>
<td>19.8</td>
</tr>
<tr>
<td>Overall (I²=81.4%, p&lt;0.0001)</td>
<td>0.45 (0.28, 0.75)</td>
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NOTE: Weights are from random effects analysis.

b.

<table>
<thead>
<tr>
<th>Author (Year)</th>
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<tr>
<td>Chasan-Taber (2008)</td>
<td>0.80 (0.20, 2.30)</td>
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<td>Dempsey (2004a)</td>
<td>0.51 (0.27, 0.97)</td>
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<td>Dempsey (2004b)</td>
<td>0.67 (0.31, 1.43)</td>
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<td>Harizopoulou (2009)</td>
<td>0.77 (0.71, 0.84)</td>
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<td>Oken (2006)</td>
<td>0.91 (0.37, 2.21)</td>
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<tr>
<td>Overall (I²=0.0%, p=0.77)</td>
<td>0.76 (0.70, 0.83)</td>
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NOTE: Weights are from random effects analysis.