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

A meta-analysis

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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 thus 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.

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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 preg-

nancy (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

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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 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 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 I^2 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 METAN command to calculate the pooled effect estimates and

the tests for heterogeneity. The METAREG and HETEROGI 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 (pregnancy $k = 7$; early pregnancy $k = 5$) represented a total of 34,929 subjects (pregnancy $N = 34,929$; early pregnancy $N = 4,401$), with 2,855 total cases of GDM (pregnancy $n = 2,813$; 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

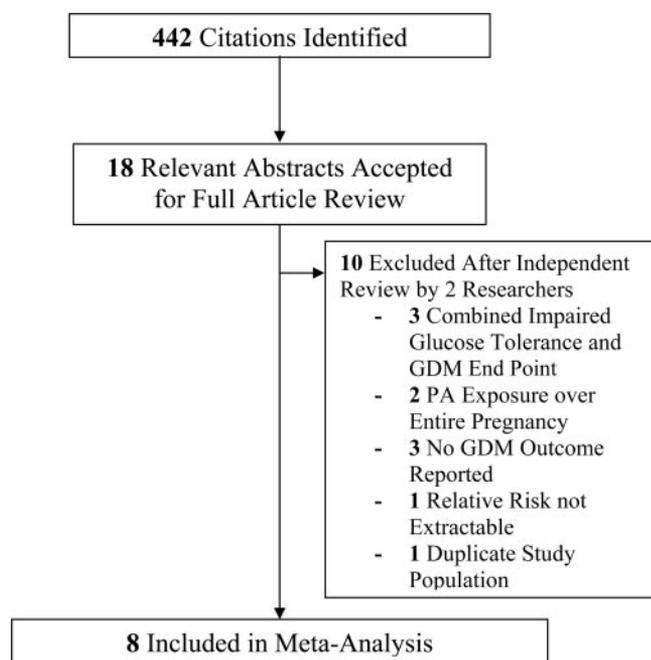


Figure 1—Study attrition diagram. PA, physical activity.

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 the 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 I^2 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 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 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 I^2 statistic suggested that heterogeneity was possible, given the wide CI (95% CI 0–79%). 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 (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 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.: >2 h/day vs. ≤ 2 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 (pregnancy: 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

Table 1—Study characteristics

Study design	Chasan-Taber et al., 2008 (24)	Dempsey et al., 2004 (28)	Dempsey et al., 2004 (27)	Harizopoulou et al., 2009 (23)	Oken et al., 2006 (25)	Redden et al., 2010 (29)	Rudra et al., 2006 (26)	Zhang et al., 2006 (22)
Total subjects (N)	1,006	909	155	40	91	808	42	1,428
Cases of GDM (n)	33	42	U.S.	Greece	U.S.	U.S.	U.S.	U.S.
Country of study	U.S.	U.S.	U.S.	Hospital-based participants	Project Viva	PRAMS	OMEGA Study	Nurses' Health Study II
Study population	Latina Pregnancy Study	OMEGA Study	Alpha Study				Alpha Study	
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)	Frequency (h/week)	Frequency (days/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	None (Ref), 0.1–14.9, 15.0–29.9, ≥30
GDM diagnostic criteria	Not reported	NDDG	NDDG	NDDG	ADA	Self-report	NDDG	Validated self-report (various)
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	Standardized questionnaire	Stanford Seven-Day PA Recall; Minnesota Leisure-Time PAQ; Borg rating scale	Stanford Seven-Day PA Recall; Minnesota Leisure-Time PAQ; Borg rating scale
Model covariables	Age, prepregnancy BMI	Age, race/ethnicity, prepregnancy BMI, parity	Age, race/ethnicity, prepregnancy BMI, nulliparity, smoking during pregnancy	Age, prepregnancy BMI, prepregnancy weight gain, income, education, occupation, residence, family history of diabetes, prior glucose intolerance, previous infant with macrosomia, current glycosuria	Age, race/ethnicity, prepregnancy BMI, history of GDM, maternal history of diabetes	Age, race/ethnicity, prepregnancy BMI, parity, no., prenatal care visits, income, alcohol consumption during pregnancy	Age, race/ethnicity, prepregnancy BMI, nulliparity, prepregnancy hypertension	Age, race/ethnicity, prepregnancy 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.

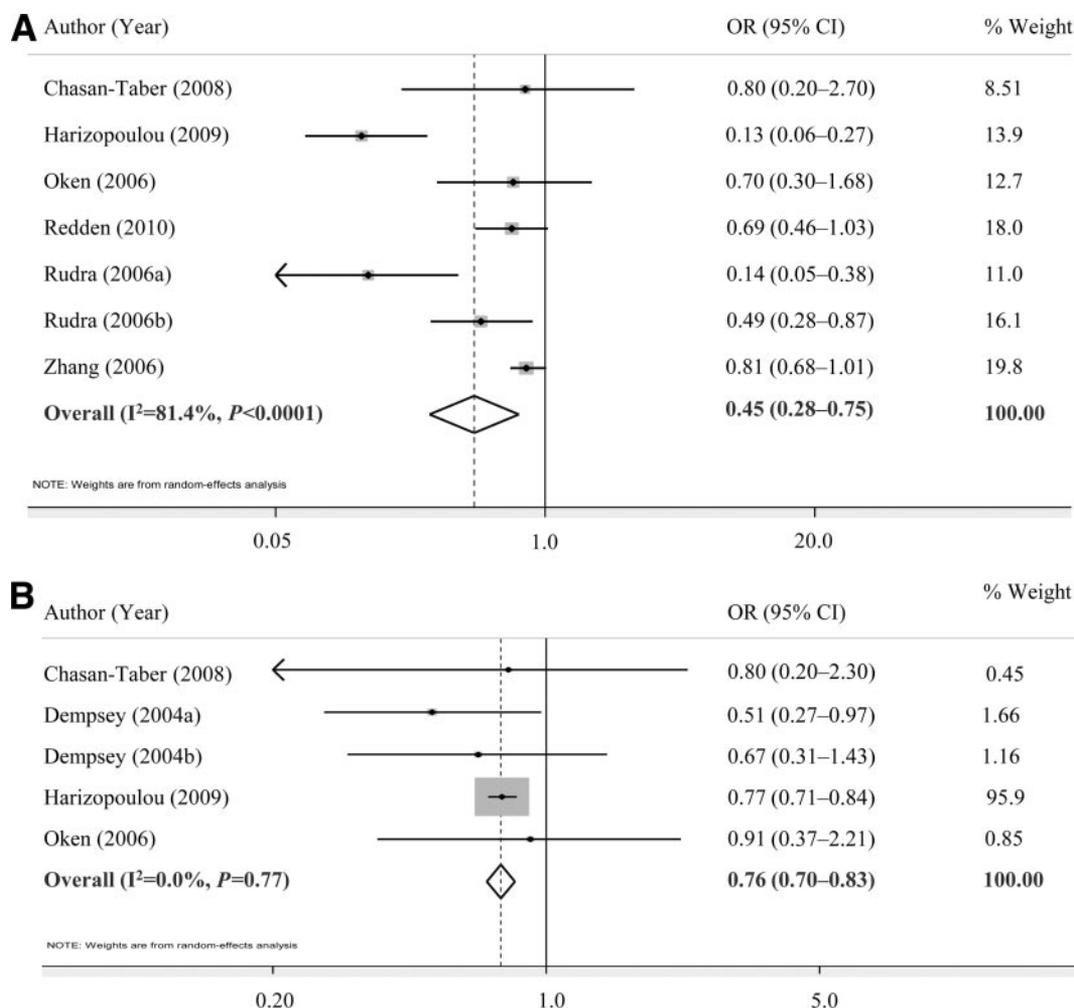


Figure 2—Results of meta-analyses. A: Prepregnancy physical activity. B: Early pregnancy physical activity.

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 (pregnancy: OR 1.4 [95% CI 0.7–3.0]; early pregnancy:

1.4 [0.8–2.6]). Hours spent watching television was not associated with GDM risk in two prospective cohort studies (Oken et al.: relative risk 1.03 [95% CI 0.6–1.8]; Zhang et al.: 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 prepregnancy physical activity with women in the highest quantiles of activity experiencing a 55% reduction in risk, compared with that for women with the lowest activity. Heterogeneity in study results were substantial, suggesting that differences among study populations or methodology may have affected the results. Our analyses to detect sources of heterogeneity were probably underpowered because few studies were in each stratum. 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 nonpregnant individuals has shown that exercise-induced improvements in glycemic control may be due to increases in GLUT4, a glucose transport protein (34,35). Physical activity also has direct effects on oxidative stress and endothelial function (11,12). Researchers have demonstrated that 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 in-

creases 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-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 prepregnancy physical activity in the prospective studies is likely to be random with respect to exposure, because 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. In addition, 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 confounding is possible. The small number of published studies makes it difficult to assess heterogeneity in the pooled ORs. 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 prepregnancy and early pregnancy physical activity periods separately, our analysis is unable to determine the independent biological relevance of the two exposure periods. Prepregnancy physical activity is one of the strongest predictors of physical activity in early pregnancy; thus, it is difficult to know which one, or whether both, could be contributing to the inverse associations seen in our analyses, because of 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 summary, 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 associa-

tion being stronger for prepregnancy 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 effects of physical activity before and during early pregnancy.

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D.K.T. performed a literature search, independent review of articles, and extraction of data, analyzed data, and wrote the manuscript. C.Z., R.M.v.D., and F.B.H. reviewed/edited the manuscript. K.B. performed independent review of articles and extraction of data.

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