

Maternal Obesity and Risk of Gestational Diabetes Mellitus

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OBJECTIVE — Numerous studies in the U.S. and elsewhere have reported an increased risk of gestational diabetes mellitus (GDM) among women who are overweight or obese compared with lean or normal-weight women. Despite the number and overall consistency of studies reporting a higher risk of GDM with increasing weight or BMI, the magnitude of the association remains uncertain. This meta-analysis was conducted to better estimate this risk and to explore differences across studies.

RESEARCH DESIGN AND METHODS — We identified studies from three sources: 1) a PubMed search of relevant articles published between January 1980 and January 2006, 2) reference lists of publications selected from the PubMed search, and 3) reference lists of review articles on obesity and maternal outcomes published between January 2000 and January 2006. We used a Bayesian model to perform the meta-analysis and meta-regression. We included cohort-designed studies that reported obesity measures reflecting pregnancy body mass, that had a normal-weight comparison group, and that presented data allowing a quantitative measurement of risk.

RESULTS — Twenty studies were included in the meta-analysis. The unadjusted ORs of developing GDM were 2.14 (95% CI 1.82–2.53), 3.56 (3.05–4.21), and 8.56 (5.07–16.04) among overweight, obese, and severely obese compared with normal-weight pregnant women, respectively. The meta-regression analysis found no evidence that these estimates were affected by selected study characteristics (publication date, study location, parity, type of data collection [retrospective vs. prospective], and prevalence of GDM among normal-weight women).

CONCLUSIONS — Our findings indicate that high maternal weight is associated with a substantially higher risk of GDM.

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Gestational diabetes mellitus (GDM), or glucose intolerance that begins or is first recognized during pregnancy, affects ~7% of pregnancies, representing >200,000 cases annually in the U.S. (1). The risk of GDM is higher among women who are obese, and the recent dramatic increase in obesity prevalence in the U.S. mirrors a worrisome rise in the prevalence of GDM (2–4). Future individual health and societal medical costs

could be substantial as obesity and GDM not only increase the risk of adverse pregnancy and infant outcomes (5–7) but also are associated with a higher risk of developing type 2 diabetes later in life in both the mother and child (8–10).

Despite the number and consistency of studies reporting a higher risk of GDM with increasing body weight or BMI, the magnitude of this association remains uncertain. This is due in part to the wide

variation in reported GDM prevalence among different populations, as well as the lack of consistency in diagnostic methods and definitions for GDM (11). To provide a quantitative summary of the evidence, we conducted a meta-analysis of systematically identified studies that examined the association between maternal obesity and risk of GDM.

RESEARCH DESIGN AND METHODS

Search process

Using recommendations from the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (12), we identified studies for possible inclusion in this analysis using three sources. First, we searched PubMed from January 1980 to January 2006 using the following criteria: (overweight or obesity or BMI or body mass index or weight gain) AND (pregnancy or prepregnancy) AND (risks or effects or complications).

From this search, the full text was retrieved for abstracts that mentioned a relationship between maternal obesity and pregnancy complications from a case-control or cohort study. Studies that reported GDM as an outcome were included for consideration. Studies that did not have the full text in English were translated for review.

Second, we manually reviewed the reference lists of the publications previously retrieved and obtained the entire text of studies that potentially could be included in the meta-analysis. Finally, we obtained review articles on obesity and maternal outcomes published between January 2000 and January 2006 and searched their reference lists for additional potential studies. If there were multiple papers on GDM from the same study population, we only included the most current publication. We did not attempt to locate any unpublished studies.

Studies that were considered potentially eligible were then screened for inclusion in the pooled analysis if they met the following criteria: 1) obesity measures (maternal weight, percent over ideal weight, and BMI) reflected status preceding any significant pregnancy weight gain (i.e., was measured or reported prepreg-

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Abbreviations: GDM, gestational diabetes mellitus.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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nancy or during the first trimester or first prenatal visit), 2) there was a comparison group of normal-weight women, and 3) data were presented in tables, figures, or the text that allowed for a quantitative measurement of obesity and risk of GDM.

Data abstraction

All articles were read and abstracted by two reviewers using the same structured data form. A final abstraction was compiled from the two forms after correction or resolution of any differences between the reviewers. Abstracted information included study design, setting, location, time period, number and characteristics of study subjects, the source and categorization of obesity measures, the diagnostic criteria and the source(s) for GDM (e.g., medical records, clinical databases), and statistical methods, including adjustment factors.

Statistical analysis

For each study, we constructed separate two-by-two tables to calculate the odds ratios (ORs) and 95% CIs of GDM for each BMI/weight category analyzed (i.e., overweight, obese, and severely obese versus normal BMI/weight, respectively). Because about two-thirds of the studies did not present adjusted ORs, only crude ORs were used in the primary meta-analysis. However, we also performed sensitivity analyses, combining adjusted ORs when available. The BMI/weight categories used varied somewhat among the studies. In general, we used the BMI/weight categories for normal, overweight, obese, and severely obese as defined by each study (Table 1); in two studies, narrow intervals were collapsed into grouping that more appropriately fit overweight, obese, and severely obese categories (e.g., 19.8–22.0 and 22.1–24.9 were combined into one 19.8–24.9 normal-weight category).

Sources for information on prepregnancy BMI/weight, GDM, and other variables varied among studies but most frequently were medical records or clinical databases (Table 1). Diagnostic criteria for GDM varied among the studies and were based on the following: Fourth International Workshop Conference on GDM ($n = 3$) (11), National Diabetes Data Group ($n = 4$) (13), Carpenter and Coustan ($n = 2$) (14), and other published criteria ($n = 4$) (15–17); seven studies did not specify criteria used for GDM diagnosis.

Meta-analyses combining ORs

across studies were conducted using both DerSimonian-Laird and Bayesian random-effects models (18,19), both of which incorporate within- and between-study variances. In addition, the Bayesian model incorporates uncertainty in the between-study variance, which gives slightly wider CIs. Because the point estimates of the two models were similar, we chose to use the more conservative Bayesian estimates.

The Bayesian model assumes that the counts in the exposed and unexposed groups follow binomial distributions with different mean probabilities. These means are modeled on the logit scale so that their difference represents the logOR and thus is a hierarchical logistic regression model. The mean and variance of the logOR are random variables in the Bayesian model. To represent our lack of prior knowledge about the value of these hyperparameters, we used diffuse priors that encompassed a wide range of possible values. For means and regression coefficient parameters, these were normal distributions with mean 0 and extremely large variance 10^7 ; for the variance parameters, we used inverse γ (1.0, 0.1) distributions. To compute the Bayesian estimates, we used a Markov chain Monte Carlo algorithm running three parallel chains and monitoring convergence with the Gelman-Rubin diagnostic (20). On convergence, which generally occurred within 1,000 runs, we saved 15,000 samples from each chain to estimate posterior distributions of model parameters. The Markov chain Monte Carlo algorithm used is described in greater detail by Schmid et al. (19).

We also conducted a Bayesian meta-regression analysis to assess whether the relationship between obesity and GDM varied by certain study characteristics. In these models, the logORs are related to the study characteristics by a linear regression model. These included date of publication (1985–1999, 2000–2003, or 2004–2006), study location (U.S. versus all others), type of data collection (prospective versus retrospective), and GDM prevalence (as a percentage) in the study population.

RESULTS— The PubMed search identified 7,327 studies; 142 abstracts reported a finding on the relationship between maternal obesity and pregnancy complications from a case-control or cohort study, and the full text of these articles were retrieved for detailed examination. Of the retrieved ar-

ticles, 40 studies mentioned GDM as an outcome. Because only three case-control studies (GDM case versus no-GDM control) were identified, we excluded those studies and only included those with a cohort design, leaving a total of 37 studies from the PubMed search to be screened for inclusion. After reviewing the reference lists of the 142 studies retrieved, we identified another 16 studies for possible inclusion. Three additional studies were identified from our examination of recent review article reference lists. Of the total 56 studies screened for final inclusion in the meta-analysis, 36 studies were excluded because the BMI or weight measure did not reflect prepregnancy status ($n = 12$), there was no normal-weight comparison group or overweight and obese groups were combined ($n = 15$), or data were not presented in a way to allow the construction of appropriate two-by-two tables ($n = 9$).

A total of 20 studies were included in the meta-analysis; of these, 15, 18, and 7 presented data for overweight, obese, and severely obese pregnant women, respectively, compared with normal-weight pregnant women (21–40). Eight studies were conducted in the U.S.; the remainder were from Canada, Australia, Italy, France, United Arab Emirates, Israel, Finland, Nova Scotia, and the U.K. (Table 1). Five of the studies were prospectively designed. GDM prevalence varied among the studies, ranging from 1.3 to 19.9%; the higher rates were among studies that included high-risk populations (e.g., Cree Native Indians) or were not population based.

Based on our meta-analysis, the unadjusted ORs of developing GDM were 2.14 (95% CI 1.82–2.53), 3.56 (3.05–4.21), and 8.56 (5.07–16.04) among overweight, obese, and severely obese women, respectively, compared with normal-weight pregnant women. None of the covariates in the meta-regression analysis (study year [<2000 , 2000–2003, or 2004–2005], study design [prospective or retrospective], geographic location [U.S., non-U.S.], or rate of GDM in the study population) were significant.

CONCLUSIONS— Based on meta-analysis of the literature, we estimate that the risk of developing GDM is about two, four, and eight times higher among overweight, obese, and severely obese women, respectively, compared with normal-weight pregnant women.

Table 1—Characteristics of cohort studies examining the relation between BMI and GDM

Citation	Country	Type and source of cohort, study period	GDM prevalence (%)	Cohort size	BMI/weight categories (kg/m ²)			Severely obese
					Normal	Overweight	Obese	
Baeten, 2001	U.S.	Prospective cohort from birth certificate records, 1992–1996	2.1	96,801	20–24.9	25–29.9	≥30	NA
Berkowitz, 1992	U.S.	Prospective cohort from medical center database, 1987–1989	3.2	10,187	<27.3	27.3–32.2	≥32.3	NA
Bianco, 1998	U.S.	Retrospective cohort from medical center perinatal database, 1988–1995	4.8	11,926	19–27	NA	>35	NA
Brennand, 2005	Canada	Retrospective cohort from medical records of Cree women, 1994–2000	18.6	603	18.5–24.9	25–29.9	≥30	NA
Callaway, 2006	Australia	Retrospective cohort from hospital obstetric database, 1998–2002	2.0	11,252	20.01–25	25.01–30	30.01–40	>40
Di Gianni, 2003	Italy	Retrospective cohort from university department medical records, 1995–2001	8.7	3,950	<25	25–29	≥30	NA
Dyck, 2002	Canada	Prospective cohort from survey and hospital records of aboriginal and nonaboriginal women, 1998	3.9	1,612	20–24.9	25–29.9	≥30	NA
Dye, 1997	U.S.	Retrospective population-based birth registry, 1995–1996	2.9	12,538	19.8–26.0	26.1–29.0	29.1–33.0	>33.0
Galtier-Dereure, 1995	France	Retrospective cohort from obstetrics department medical records, 1990–1993	19.9	166	18–24.9	25–29.9	30–34.9	≥35
Grossetti, 2004	France	Retrospective cohort from maternity ward medical records, 2002–2003	2.0	2,496	20–25	NA	NA	>40
Harris, 1997	Canada	Retrospective cohort from hospital medical records of Ojibwa-Cree women, 1990–1993	9.5	719	19.8–24.9	25–29.9	≥30	NA
Kumari, 2001	United Arab Emirates	Retrospective cohort from maternity unit medical records, 1996–1998	9.8	488	22–28	NA	NA	≥40
Michlin, 2000	Israel	Retrospective cohort from hospital medical records, August 1995–November 1995	3.6	334	19.8–26	NA	>29	NA
Ogunyemi, 1998	U.S.	Retrospective cohort of low-income African-American women from hospital medical records, 1990–1995	2.6	582	19.8–26	26.1–29	>29	NA
Raatikainen, 2006	Finland	Retrospective cohort from a university hospital, 1989–2001	2.6	25,601	≤25	26–29	≥30	NA
Ramos, 2005	U.S.	Retrospective cohort from medical center medical records, 1981–2001	3.5	22,685	19.8–26	26.1–29	>29	NA
Robinson, 2005	Nova Scotia	Prospective cohort from population-based perinatal database, 1988–2002	2.6	89,139	55–75 kg	NA	90–120 kg	>12 kg
Rosenberg, 2003	U.S.	Retrospective cohort from state birth certificate file, 1998–1999	3.5	213,208	100–149 lb	150–199 lb	200–299 lb	≥300 lb
Sebire, 2001	U.K.	Retrospective cohort from a maternity ward database, 1989–1997	1.3	325,395	20–24.9	25–29.9	≥30	NA
Solomon, 1997	U.S.	Prospective cohort from self-reported questionnaires of nurses, 1992–1994	4.9	14,613	20–24.9	25–29.9	≥30	NA

GDM prevalence (%) is the rate for total study population. NA, not available.

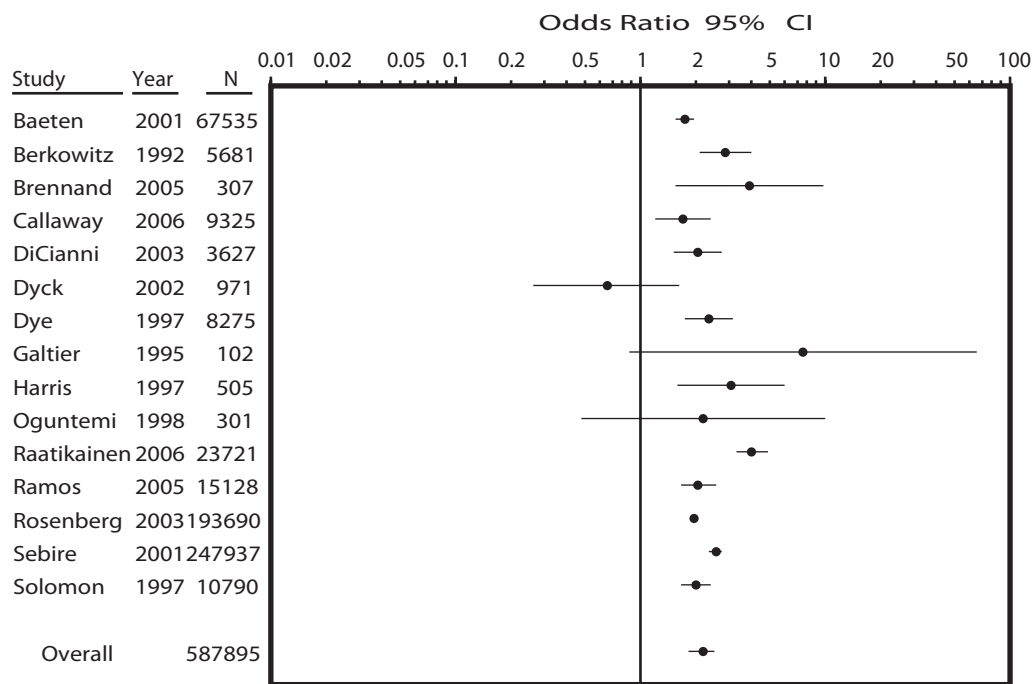


Figure 1—Association of GDM with overweight versus normal maternal BMI.

The public health implications for the U.S. are significant because of the high prevalence of obesity, increasing prevalence of GDM, and the potential adverse consequences associated with obesity and GDM, including higher risk of adverse infant outcomes, higher risk of diabetes for the mother later in life, and a higher risk of diabetes and overweight for the offspring.

Fetal macrosomia is a common adverse infant outcome related to GDM, especially if GDM is unrecognized and untreated (5,7,41–43). For the infant, macrosomia increases the risks of shoulder dystocia, clavical fractures, and brachial plexus injury and is also associated with depressed 5-min Apgar scores and increased rates of admission to neonatal intensive care unit (44). For the mother, the primary risk associated with macrosomia is an increased risk of cesarean delivery; these mothers also have an increased risk of postpartum hemorrhage and vaginal lacerations (42).

Also of concern is the finding from several longitudinal studies that infants of women with GDM are at increased risk of becoming overweight or obese as young children and adolescents (45–47) and are more likely to develop type 2 diabetes later in life (48–50). It has been suggested that the relationship between decreased insulin sensitivity and excessive fetal growth in obese women and women with

GDM may explain some of the increased incidence of obesity and glucose intolerance in their offspring (51). Some of this association is likely explained by other factors associated with maternal obesity, such as shared genetic factors or similar dietary and physical activity behaviors in families (9); however, if this association does prove causal, an increasing GDM prevalence could further elevate type 2 diabetes rates in future generations.

An increase in GDM prevalence also has implications for prevention of type 2 diabetes in women who have had GDM. Because ~50% of women with a history of GDM develop diabetes within 5–10 years after delivery (10), the postpartum period offers an opportunity to both screen women at an early stage for preexisting diabetes and to counsel women about type 2 diabetes prevention. Both the American College of Obstetricians and Gynecologists and the American Diabetes Association have recommended follow-up glucose testing of women with a history of GDM (52,53). However, current postpartum GDM screening rates are low (54–56), resulting in many missed opportunities for counseling and treatment of women who are at high risk for type 2 diabetes. Improving postpartum follow-up rates will require a better understanding of patient, provider, and health care system barriers to postpartum screening (56).

There are several possible biases to consider in our analysis. First, the studies included in this meta-analysis used varying weight and BMI categories for normal, overweight, obese, and severely obese women; thus, the pooled estimate does not exactly reflect the same comparison for all studies. In addition, because of the different BMI/weight categories and different diagnostic criteria used for GDM, there is likely some misclassification of the exposure and the outcome; if significant, the findings would be biased toward a null result or cause significant heterogeneity in the meta-analysis model. The ORs for the comparisons between normal-weight and overweight and obese women, respectively, were fairly consistent among the studies, suggesting that the varied definitions of exposure and outcome did not have major effects on these findings (Figs. 1 and 2). Results were more disparate in the comparison between normal-weight and severely obese women (Fig. 3). Although there is clearly a positive association between severe obesity and GDM, the magnitude of the association varied widely among studies. Hence, there is less confidence in this summary measure than for the other comparisons; however, the two outlying ORs were from studies with the smallest sample sizes.

A second limitation is that studies did not or could not (e.g., birth registries) specify whether all pregnant women were

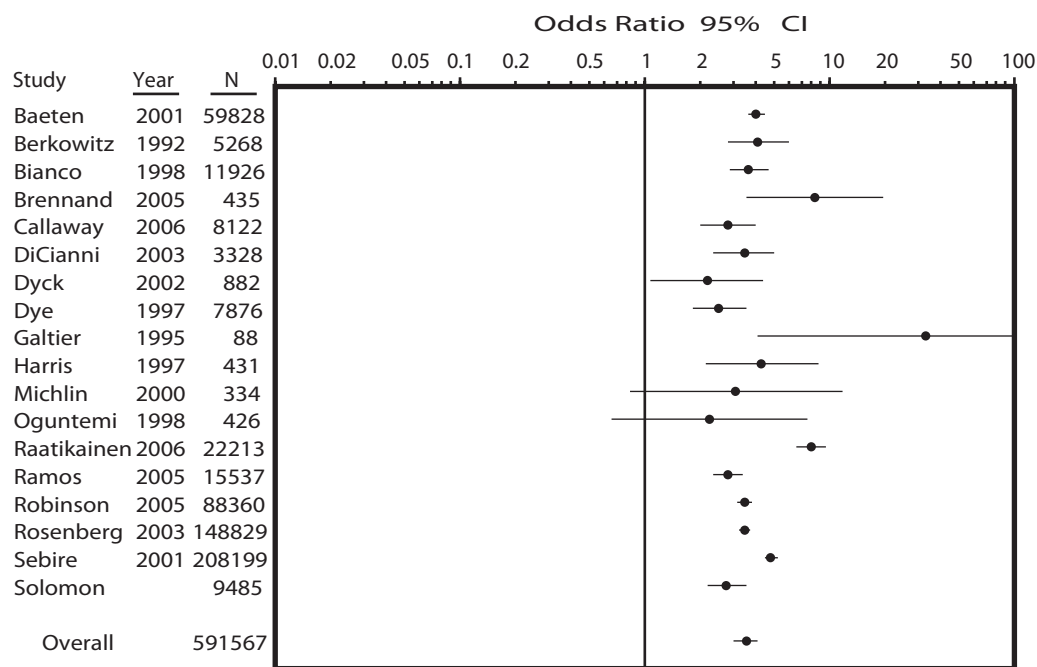


Figure 2—Association of GDM with obese versus normal maternal BMI.

screened for GDM or if screening was done based on a risk profile (e.g., previous adverse pregnancy outcome). Risk-based screening could bias our findings if screening was done preferentially on overweight or obese women compared with normal-weight women. However, because recommended risk-based screening for GDM excludes relatively few women, as a practical matter, clinicians routinely screen all pregnant women for GDM (52). However, we were not able to account for differences in screening practices, if they exist.

Third, because not all studies presented adjusted odds and adjustment factors varied among those that did, we only used crude study estimates in our meta-

analysis. If there were strong effects from confounding factors (e.g., maternal age is associated with both increased body weight and risk of GDM), the estimates included in the meta-analysis might be biased. When we did a separate meta-analysis pooling studies that provided adjusted ORs, the summary adjusted ORs were lower than the unadjusted estimates, although they were still of substantial magnitude (overweight vs. normal adjusted OR 1.86 [95% CI 1.22–2.78], obese vs. normal adjusted 3.34 [2.43–4.55], and severely obese vs. normal adjusted 5.77 [3.60–9.39]). Finally, our findings may be biased because published studies do not represent all studies ever done on a particular subject and because

statistically significant results are more likely to be submitted and published than nonsignificant and null results (57). If study publication bias were strong, we would overestimate the risk of GDM with increasing BMI.

In summary, our findings suggest that GDM risk increases substantially with increasing maternal BMI. The increasing prevalence of obesity and related conditions such as GDM and type 2 diabetes in the U.S. are already changing predictions of the cost of medical care in the future (58,59). Preventing GDM depends on preventing obesity in young women; preventing type 2 diabetes in obese women who have GDM depends on effective nutrition and physical activity interventions

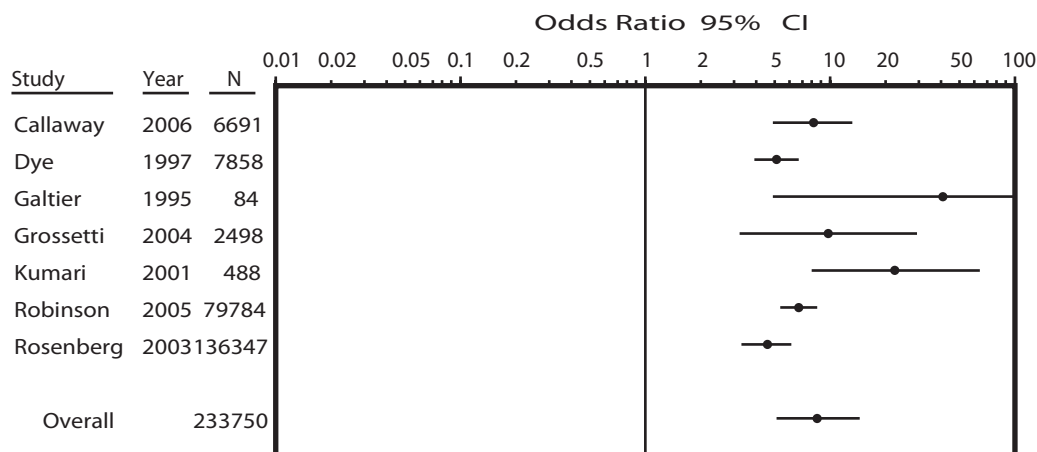


Figure 3—Association of GDM with severely obese versus normal maternal BMI.

that produce weight loss. These and other prevention strategies, aimed at both individual and societal levels, are needed to control the growing epidemic of diabetes.

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