

Complications of Obesity

Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis

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Summary

The objective of this study is to assess and quantify the risk for gestational diabetes mellitus (GDM) according to prepregnancy maternal body mass index (BMI). The design is a systematic review of observational studies published in the last 30 years. Four electronic databases were searched for publications (1977–2007). BMI was elected as the only measure of obesity, and all diagnostic criteria for GDM were accepted. Studies with selective screening for GDM were excluded. There were no language restrictions. The methodological quality of primary studies was assessed. Some 1745 citations were screened, and 70 studies (two unpublished) involving 671 945 women were included (59 cohorts and 11 case–controls). Most studies were of high or medium quality. Compared with women with a normal BMI, the unadjusted pooled odds ratio (OR) of an underweight woman developing GDM was 0.75 (95% confidence interval [CI] 0.69 to 0.82). The OR for overweight, moderately obese and morbidly obese women were 1.97 (95% CI 1.77 to 2.19), 3.01 (95% CI 2.34 to 3.87) and 5.55 (95% CI 4.27 to 7.21) respectively. For every 1 kg m⁻² increase in BMI, the prevalence of GDM increased by 0.92% (95% CI 0.73 to 1.10). The risk of GDM is positively associated with prepregnancy BMI. This information is important when counselling women planning a pregnancy.

Keywords: Body mass index, gestational diabetes, obesity, pregnancy.

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Introduction

Obesity is a serious public health problem that currently affects a large part of the world population, including many developing nations. In the USA, the average body mass index (BMI) is increasing among all age categories, and women are entering pregnancy at higher weights (1). In Europe, the prevalence of obesity in adults (BMI \geq 30) has risen from 10% to 40% in the last decades (2).

Gestational diabetes mellitus (GDM) represents a failure to maintain normal glucose tolerance during the extreme metabolic stress of pregnancy. This disease, defined as any degree of glucose intolerance with onset or first recognition

during pregnancy, is potentially hazardous to both mother and foetus (3). Women with GDM experience increased risk for prenatal morbidity and for impaired glucose tolerance and type 2 diabetes in the years following pregnancy (4). Similarly, their offspring face higher risk for perinatal morbidity as well as childhood obesity, retarded psychomotor development and early onset of type 2 diabetes mellitus (5).

It is estimated that GDM affects 1–14% of all pregnancies (3,6–8). This wide variation may be due to the lack of standardization of screening tests and diagnostic criteria for GDM, and may also reflect differences in the distribution of genetic and environmental risk factors. While genetic predisposition, ethnicity and age all play a significant role in the development of GDM, maternal obesity is consistently pointed out as a major and modifiable risk factor (8–11).

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Although various studies indicate an increased risk for GDM in women with higher BMI compared with those in the normal range (9,10,12,13), this increase in risk varies widely across publications, and the effect of prepregnancy maternal underweight on GDM is less clear. To our knowledge, there has been no systematic review of the literature quantifying the impact of all prepregnancy BMI categories on the risk of developing GDM. This information could be useful for prepregnancy counselling, for better prediction of a woman's risk of developing GDM according to her specific prepregnancy BMI and to target clinical surveillance in a more effective manner.

We conducted a systematic review of the literature to examine the association between prepregnancy BMI and the risk of GDM and to quantify the change in this risk according to increasing BMI.

Methods

This systematic review followed the Cochrane methodology and the recommendations for reporting proposed by the meta-analysis of observational studies in epidemiology (MOOSE) group (14).

Selection criteria for studies

Types of studies

Observational studies (cohort, case-control and cross-sectional) were considered for inclusion in this systematic review if they provided the following information: GDM as an outcome variable (for cohort studies) or to define cases (in case-control studies) and prepregnancy BMI as an exposure variable (for cohort studies) or one of the risk factors (in case-control studies).

Types of participants

Women with information on prepregnancy or first trimester BMI (either self-reported or measured) and having been submitted to investigation for GDM during their index pregnancy were eligible for inclusion. We accepted participants of any age, parity, education, socioeconomic status, race or ethnic group fulfilling the previous criteria. Women with previously diagnosed diabetes (type 1 or 2) were excluded.

Types of exposures and outcomes

In order to reduce heterogeneity, we elected BMI as the only measure of obesity to define exposure. Studies were considered eligible if they registered BMI before significant pregnancy weight gain (i.e. before pregnancy or at first prenatal visit). We used the BMI categories as defined by the authors of each article. Although the cut-offs vary slightly, underweight is defined by most as BMI < 20, normal weight as 20–24.9, overweight as 25–29.9 and obese as BMI > 29.9. Studies that only reported maternal

weight or percentage over ideal weight or other measures of obesity were excluded. The measured outcome was GDM, and any criterion used for this diagnosis was accepted.

Studies were excluded if any of the following applied: (i) no odds ratio (OR) or relative risk or insufficient data available for their calculation; (ii) no definition of BMI categories; (iii) BMI was registered after significant pregnancy weight gain (i.e. later than first prenatal visit); and (iv) explicit statement indicating that screening or diagnostic tests for GDM had been performed exclusively on high-risk women, i.e. those with specific personal characteristics (higher maternal age, parity, obesity), family history of diabetes or obstetric history. Studies that performed a GDM screening or diagnostic test for all women (unselected) were included. The decision to exclude studies with selective screening for GDM was taken to avoid overestimating the potential effect of maternal BMI on the development of GDM, because of the use of a preselected high-risk population. We excluded studies that reported BMI measurement late in pregnancy in order to avoid the possible effect of maternal pregnancy weight gain on this measure, as our aim was to evaluate pregravid maternal BMI (and not weight gain) as a risk factor for GDM. Studies that reported no data for crude OR estimates but provided adjusted OR for the risk of GDM according to various BMI categories were included.

Search strategy for identification of studies

The search strategy, developed with the assistance of a librarian experienced in systematic reviews based in the World Health Organization (WHO), used the following terms, adapted for each database searched: 'body mass index' or 'Quetelet Index' or 'BMI' or 'body size' or 'body weight' or 'body mass' or 'body weight changes' or 'obesity' or 'overweight' or 'adiposity' or 'overnutrition' or 'morbid obesity' and 'gestational diabetes' or 'gestational diabetes mellitus' or 'pregnancy induced diabetes' or 'diabetes mellitus gravidarum' or 'pregnancy diabetes mellitus'. (Appendix S1).

Four electronic databases (MEDLINE, EMBASE, CINAHL and LILACS) were searched for articles published between January 1977 and March 2007. There were no language or country restrictions. Classic review articles, textbooks and published letters were also examined for potentially eligible studies. We checked the references of all articles chosen for full manuscript review. Experts were contacted, and emails were sent to the authors of all potentially eligible studies, inquiring about details of their studies, unpublished material and their knowledge of other relevant studies on the topic. The search for unpublished studies also included reviewing the abstract books of international congresses of obstetrics and gynaecology, endocrinology and obesity (1997–2006). The authors of

potentially relevant abstracts were contacted for additional data and information.

Screening and data-extraction form

All citations identified by electronic databases were downloaded into Reference Manager® software version 10 (The Thompson Corporation, NY, USA). The citations were organized, duplicates deleted, and each citation was assigned a unique identification number. Initially, two investigators (MRT and APB) independently screened the results of the electronic searches to select potentially relevant citations based on title and abstracts. The studies were screened using predefined exclusion criteria (see above). Discrepancies were resolved through consensus. When the citation was relevant or when title/abstract was not sufficient for decision on inclusion/exclusion, the full texts were retrieved and evaluated.

All articles selected at first screening were read and abstracted by the two reviewers using a structured data extraction form specifically created for this systematic review on the basis of a form developed for the WHO systematic review on maternal mortality and morbidity (15). Differences between the two reviewers were resolved by consensus. Information extracted from each article included: (i) general characteristics of the study, such as design, population, setting, source of data; (ii) inclusion/exclusion criteria for women entering study, method of recruitment, number of participants, lost of follow-up or completeness of the records; (iii) information on BMI (exposure) assessment and categorization; (iv) information on GDM (outcome) screening and diagnosis methods used; (v) data to calculate unadjusted estimates of the risk (relative risk or OR); if given by the authors, (vi) confounder-adjusted estimates and the confidence interval (CI); and (vii) variables included in the multivariate analysis. When data in the original publication were not sufficiently detailed, the authors were contacted for additional information.

Assessing methodological quality of primary studies

To assess the quality of included studies, we created a specific checklist (Appendix S2), based on the criteria proposed by Strengthening the Reporting of Observational Studies in Epidemiology and Tooth *et al.* for the assessment of observational studies (16,17). Briefly, we assessed the quality of all included studies in accordance with the following items: type of study, loss of follow-up, sample size, participant selection, comparability of groups, BMI categorization and assessment, GDM diagnosis and source of information. According to the score achieved (from 0 to 18), studies were classified as high (>14), medium (11–14) or low (<11) quality. All studies were graded for quality

after receiving eventual answers from the authors. Therefore, the final quality assessment reflected the quality of the study and not necessarily the reporting quality.

Statistical analysis

For each study we calculated the unadjusted OR and 95% CI for GDM comparing each BMI category (underweight [BMI < 20], overweight [~25–29.9], obese general [~≥30], moderately obese [~30–34.9] and morbidly obese [≥35]) with the normal weight group (BMI ~20–24.9). The exact cut-offs for these categories varied slightly, according to the criteria used by the various authors as there is no consensus on this. For instance, while many studies used the criteria proposed specifically for pregnant women by the Institute of Medicine (18), others used the criteria proposed for the general population (2). We also compared the OR for GDM in two broader categories, overweight in general (BMI > 25) vs. non-overweight in general (BMI < 25) and obese in general (BMI > 30) vs. non-obese in general (BMI < 30). Studies that presented OR adjusted for potential confounders were analysed separately, and the covariates and method used for multivariate analysis were recorded.

The meta-analyses combining the OR across studies were performed using the RevMan 4.2 software (Review Manager (Revman), The Nordic Cochrane Centre, Copenhagen, Denmark) (Copenhagen: the Nordic Cochrane Centre, the Cochrane Collaboration, 2003). Heterogeneity of OR was assessed graphically using forest plots and statistically using the *Q*-test and the *I*² test. If the *Q*-test (19) was significant, the between-studies variability was higher than expected by chance, and this required the use of a random-effects model (20). The *I*² value estimates the proportion of total variation that is due to heterogeneity (21,22). An *I*² value greater than 50% was considered an indication of heterogeneity between studies.

Random-effects meta-regression (23) was used to explore the contribution of several covariates to variations in individual OR. Meta-regression, with a permutation test (using 1000 Monte Carlo simulations, StataCorp, TX, USA) to calculate *P*-values and to reduce the chance of spurious false-positive findings, was used to assess the role of several covariates in the heterogeneity among studies. Covariates were defined a priori and included: (i) publication year; (ii) study setting (USA and Canada, Latin America, Eastern Europe, Western Europe, Asia, Middle East or Oceania); (iii) study design (prospective cohort, retrospective cohort, nested case-control or retrospective case-control); (iv) criteria for the diagnosis of GDM (glucose load of 75 g, of 100 g or other criteria); (v) adjustment for possible confounders (demographic and behavioural variables or previous GDM or no adjustment); (vi) criteria used to define the reference and exposed groups; (vii) source of information on BMI; (viii) sample size; and (ix)

study quality (high, medium or low). All covariates associated with a P -value ≤ 0.20 (24) in univariate analyses were included in the final multivariate meta regression model.

To assess the mean change in the risk of GDM for each unit change (kg m^{-2}) in BMI, we used a weighted mixed effects linear regression. Data on the prevalence of GDM in each BMI category from all studies were plotted in a single scattergraph. The x -axis represented the midpoint of each BMI category and the y -axis, the prevalence of GDM. When the BMI category was defined as less or greater than a certain value, a value one decimal place lower or higher than the value was used.

Results

Included studies

The electronic database search identified 1745 citations (Fig. 1). In the first screening (abstracts/titles), 1510 citations were excluded, and 229 underwent full-text evaluation. Another 171 were excluded at this point (reasons listed in Appendix S3), resulting in 58 included studies from the electronic search (9,11,25–80). An additional 12 articles

were included in the systematic review: 10 identified in the reference lists of other articles (81–90) and two unpublished studies that were sent to us by authors we contacted (91, Murakami 2007, unpublished). No unpublished studies that met our inclusion criteria were identified from congress proceedings. A total of 70 studies involving 671 945 women were included in the systematic review. The descriptive information of each included study is presented on Table S1.

Table S2 shows selected characteristics of the 70 studies included. There were 11 case–control and 59 cohort studies. Most of the studies (81.4%) were of medium (43) or high (14) quality (Appendix S4). A total of 53 studies were from developed and 17 from developing countries, 11 (15.7%) of which were not in English (three French, three Spanish, three Polish, three Chinese and one Italian). A total of 22 studies reported that BMI had been measured in pregnancy, in 33 studies BMI was self-reported and 15 studies did not give details on how BMI was assessed. The diagnosis of GDM was made using the 100 g in 50% (35) of the studies while 26% used the 75 g curve and 24% offered no details or reported that more than one diagnostic criterion had been used.

Risk of GDM according to maternal BMI

Table S3 (and meta-analysis graphs provided in Appendix S6) summarizes the association (crude and adjusted OR) between BMI and the risk of developing GDM in women of various BMI categories. For crude OR, we pooled the results from individual studies using both fixed and random-effects models. A fixed-effects model was associated with higher estimates of association in most cases. Therefore, we chose to focus on the results of the random-effects model for providing a more conservative interpretation of the results.

Women with a low BMI (<20) had a risk of developing GDM 25% lower than women with normal BMI (OR = 0.75, 95% CI = 0.69–0.82), based on 16 cohort studies totaling 356 403 participants. Whereas, compared with the normal weight category, the OR for GDM in overweight women (BMI ~ 25 –29) was 1.97 (95% CI = 1.77–2.19), according to 17 cohort studies totaling 395 338 participants.

The OR for GDM in obese (BMI > 30), compared with normal weight women, was 3.76 (95% CI = 3.31–4.28), based on 31 cohort studies totaling 364 668 subjects. For the moderately (BMI ~ 30 –35) and severely (BMI > 35) obese women, compared with women with normal BMI, the OR were 3.01 (95% CI = 2.34–3.87) and 5.55, (95% CI = 4.27–7.21) respectively. These last two pooled OR were derived from six to seven cohort studies and included 23 988 and 22 742 participants respectively.

Compared with the non-overweight in general (BMI < 25), women with a BMI of at least 25 had an OR

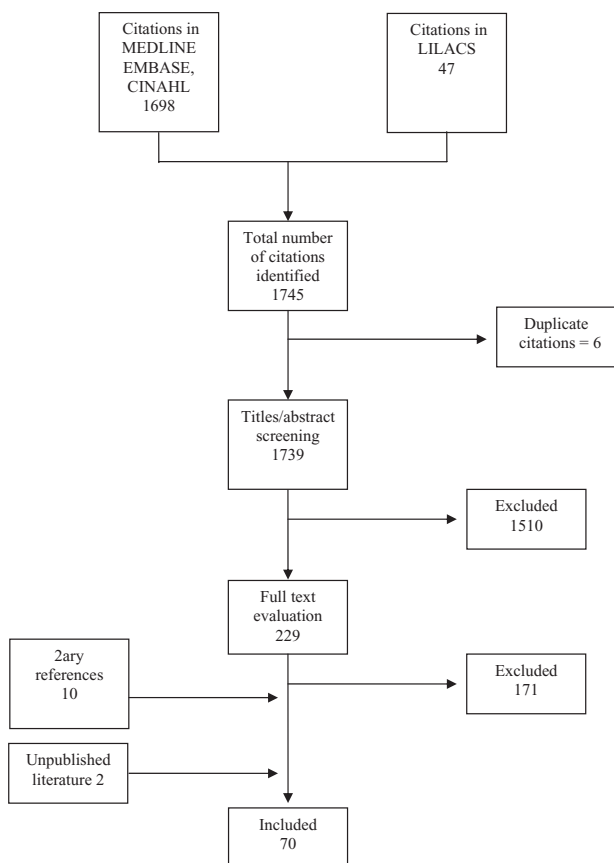


Figure 1 Flow diagram of the process of identifying and including references for the systematic review.

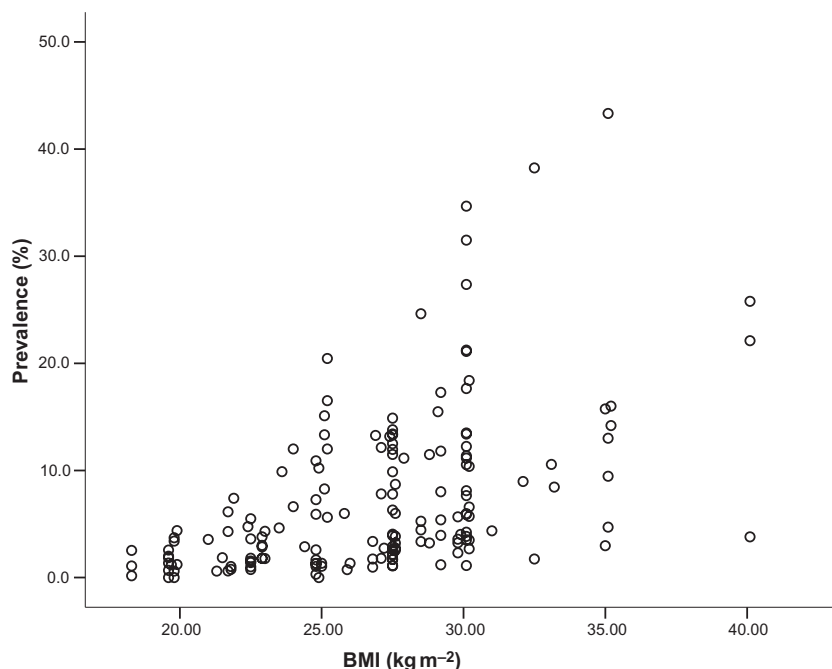


Figure 2 Prevalence of gestational diabetes mellitus according to initial maternal body mass index (BMI).

for GDM of 2.95 (95% CI = 2.68–3.24), based on 34 cohort studies, totalizing 566 224 participants. Based on 40 cohort studies that involved 563 111 participants, women with a BMI > 30 had an OR for GDM of 3.36 (95% CI = 3.01–3.74) when compared with those with a BMI < 30. The pooled OR obtained from the case–control studies were consistently higher for all comparisons.

A total of 21 studies provided adjusted OR for GDM (Table S3, details provided in Appendix S5). Even after adjusting for various potential confounders, there was a consistent increase in the risk for GDM associated with increased maternal BMI.

Heterogeneity ($I^2 > 50\%$) was high for the pooled OR of the cohort studies comparing BMI > 30 vs. women with normal weight. Sensitivity analyses were performed (Table S4), and sample size was clearly associated with the pooled effect, with small studies (<500 participants) presenting a higher pooled effect. On the other hand, the pooled effect was statistically significant among the largest studies (>1000 participants). In the random-effects meta-regression, the sample size explained 12.5% of the between-studies heterogeneity. The other variables were not able to further explain the heterogeneity.

Figure 2 presents the estimate of the degree of change in the risk of GDM according to increasing BMI. This graph was constructed using the 56 cohort studies that provided raw data for unadjusted OR calculations (165 comparisons between various BMI categories) totalizing 631 763 women. For each one point increase in BMI, the risk for GDM increased 0.92% (95% CI 0.73–1.10). This means that in every change in BMI category (which corresponds to

five BMI points), there is an increase of approximately 4.6% in the prevalence of GDM.

Discussion

The results of this study indicate that maternal prepregnancy BMI is directly associated with the risk of developing GDM. Compared with women of normal weight, the unadjusted OR of an underweight woman developing GDM was 0.75, while the OR for overweight, moderately obese and morbidly obese women were 1.97, 3.01 and 5.55 respectively. We calculated that for each 1 kg m⁻² increase in BMI the prevalence of GDM increased 0.92%.

A recent meta-analysis (92) including 20 studies reported that the unadjusted OR of developing GDM were 2.14 (95% CI = 1.82–2.53), 3.56 (95% CI = 3.05–4.21) and 8.5 (95% CI = 5.07–16.04) among overweight, moderately obese and morbidly obese respectively, compared with normal weight women. However, the pooled OR of that meta-analysis could be imprecise as over one-third of the included participants were from studies that used absolute body weight, instead of BMI, to define maternal obesity. Combining the results of studies that used different measures of obesity in a single pooled OR, as was done in that study, may increase heterogeneity and thus affect the interpretation of the results. Unfortunately, the authors provide no information on heterogeneity for their meta-analyses. Furthermore, they did not exclude studies that used selective screening for GDM, which could explain their consistently higher pooled OR.

Strengths of the systematic review

A robust search strategy was developed for the review, and four electronic databases were included. Furthermore, we strived to get information on unpublished results, following the MOOSE recommendations and managed to retrieve two studies.

A second strong point is that a single measure of obesity (BMI) was used to define exposure. Self-reported prepregnancy BMI is a reliable indicator of obesity and has been validated in previous publications (93). Although it is not a perfect indicator of body composition, BMI appears to be superior to maternal weight for identifying risk for GDM (10).

Another strength of this systematic review is that it excluded studies that used selective instead of universal screening for GDM thus avoiding selection bias. This decision was based on the concept that selective screening, although justifiable in some settings because of economic or organizational reasons, is inadequate for the objective of this systematic review. Previous studies have indicated that 23% (81) to 72% (94) of all women diagnosed with GDM have no risk factors. Therefore, the OR derived from studies that used selective screening for GDM could be misleading.

Finally, this is the first meta-analysis to compare the risk of GDM in underweight vs. normal weight women, showing the protective effect of lower BMI. This finding should be put in perspective in the context of the potential maternal and perinatal risks associated with being underweight, such as low birth weight (73,95), preterm birth (73,96), foetal growth restriction (25,73) and maternal anaemia (73).

Limitations of the systematic review

Sources of bias in any meta-analysis are the selection of the included studies, publication bias, use of different statistical methods and assumptions of study homogeneity. Regarding this last point, a specific limitation of our meta-analysis is related to the difficulty of combining studies that used different methods to assess and classify the exposure (BMI categories) and outcome (GDM diagnosis) status of the participants. This is directly related to the lack of consensus about the categorization of BMI and the diagnostic criteria for GDM. As for any meta-analysis, there is no alternative but to use the data as defined and classified by the authors of each study. In order to evaluate the effect of different diagnostic criteria on the risk of developing GDM in obese women, we performed subgroup analyses (Table S4). Compared with average weight women (BMI 20–24.9), obese women (BMI > 30) had a pooled OR for GDM of 4.19 when the 100 g curve was used, while the pooled OR was 2.86 when the 75 g curve was used. Because of these

inherent differences between studies, we decided to create a graph depicting the association between increasing BMI and the risk for GDM. Although this graph might be useful in clinical practice and as a research tool, the result should be interpreted with caution. The use of the midpoint value for each BMI category may have led to imprecision about the true mean BMI within that category. For the lowest and highest categories, the use of values closest to the respective category cut-off values may have led to an overestimate of the true relation between BMI and GDM.

An issue often criticized in studies involving obesity in pregnancy is the reliance on patient-reported information on prepregnancy height and weight. Although self-reported weight and height data are generally considered valid even in epidemiologic studies (97), underestimation of weight is especially common among overweight women (98). This would lead to underestimation of the OR presented here.

Publication bias must also be considered, as this meta-analysis included mostly published studies. Although an effort was made to review unpublished material, only two studies that met the inclusion criteria were located. The omission of unpublished studies with possibly negative results might have led to an overestimate of the relation between maternal BMI and GDM.

Finally, various other risk factors may also have contributed to the risk of developing GDM. Ethnicity, age, parity, smoking, weight gain and several other variables besides pregravid BMI may increase the risk of developing GDM. However, all the 21 studies that used multivariate analysis to adjust for these potential confounders and effect modifiers observed a consistent increase in the OR for GDM with increasing maternal BMI.

Mechanism of disease

Obesity causes major changes in maternal intermediary metabolism, and insulin resistance appears to play a central role. Insulin receptors and post-receptor defects associated with obesity may be further exacerbated by pregnancy (5). Inflammation is another possible explanation for the link between obesity and GDM. Although the exact mechanisms involved in the development of GDM are not completely understood, a systemic inflammation seems to be involved as indicated by higher levels of serum C-reactive protein, interleukin-6 (99,100) and ferritin (101). As adipocytes secrete proinflammatory cytokines (102), inflammation is usually associated with obesity. Therefore, the abundance of adipocytes in obese women could produce excess inflammatory markers that in turn would lead to the development of GDM.

Implications for practice

The results of this systematic review could be used for a better prediction of a woman's specific risk of developing

GDM according to her prepregnancy BMI category. It could also be useful in counselling young non-pregnant women about their risk for GDM because of high BMI and could encourage them to reduce their weight, through nutritional advice.

Out of the five classic risk factors for GDM, family history of diabetes, ethnicity, parity, maternal age and obesity (8), only the last is possibly modifiable. Therefore, just as a smoker who plans to get pregnant is counselled about the risks of this habit and encouraged to quit, an obese woman should also be informed about her risks and encouraged to reduce weight before conception. Data from the present study suggest that a reduction of 1 kg m^{-2} is associated with a reduction of almost 1% in the prevalence of GDM. Therefore, even a modest decrease in maternal prepregnancy BMI could potentially result in a significant reduction in the incidence of GDM and its adverse maternal and perinatal outcomes. The cost savings of this intervention might also be significant for national healthcare systems.

Implications for research

More epidemiological studies on obesity and GDM are needed to explore the interaction between prepregnancy BMI and maternal weight gain on the development of GDM. And because GDM is a multifactorial disease, it would be interesting to clarify how other risk factors, such as family history of diabetes, ethnicity, parity and age, interact with obesity to increase the risk of GDM. Better knowledge of the risk profile could optimize the early and adequate management of women at higher risk for GDM. New studies focusing on the best screening and diagnostic strategies for GDM in overweight and obese women are also needed. Specifically, it would be interesting to discover what would be the most cost-effective strategy in terms of timing (ideal gestational age for testing), type of exam (screening test first, universal diagnostic test) and number of repetitions of these tests (first, second and third trimester) needed to yield the highest sensitivity and specificity in the diagnosis of GDM for these high-risk women.

Finally, as obesity is a modifiable risk factor clearly associated with GDM, there is a need for more research on the effectiveness of various interventions aimed at reducing weight among reproductive age women and their impact on pregnancy complications. It is worthy to remember that the prepregnancy period and pregnancy represent unique opportunities for the initiation of intervention programmes, and evidence suggests that targeting obesity in pregravid women may be particularly beneficial (67). There have been studies suggesting that physical activity during pregnancy may prevent GDM in high-risk women (40,41), and this is another area of interest for future research.

Conclusion

There is convincing evidence for the association between increasing prepregnancy BMI and the risk for GDM, starting in the lowest weight categories. There is a linear increase in the risk for GDM with increasing maternal BMI.

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Conflicts of Interest

All authors declare that they have no conflicts of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1. Characteristics of 70 observational studies examining the relationship between maternal BMI and GDM

Table S2. Selected characteristics of the included studies by study design

Table S3. Pooled crude and adjusted odds ratios (OR) of the relationship between prepregnancy body mass index (BMI) and gestational diabetes (see Appendix S6 for corresponding meta-analysis graphs of crude OR)

Table S4. Sensitivity and subgroup analysis of meta-analysis of the relationship between prepregnancy maternal BMI > 30 vs. normal and gestational diabetes (cohort studies only)

Appendix S1. Search strategy used for CINAHL, EMBASE and MEDLINE

Appendix S2. Quality assessment extraction form

Appendix S3. Reasons for Exclusion of 171 studies selected for full text reading

Appendix S4. Quality assessment (grade) of the 70 included studies

Appendix S5. Adjusted odds ratio for gestational diabetes according to initial maternal BMI (N = 21 studies)

Appendix S6. Meta-analyses of maternal BMI vs risk of GDM (5 Figures)

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