

Sleep-Disordered Breathing and Gestational Diabetes Mellitus

A meta-analysis of 9,795 participants enrolled in epidemiological observational studies

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OBJECTIVE—Recently, sleep-disordered breathing (SDB) has been reported to be associated with the development of gestational diabetes mellitus (GDM). Accordingly, as this is emergent area of research that has significant clinical relevance, the objective of this meta-analysis is to examine the relationship between SDB with GDM.

RESEARCH DESIGN AND METHODS—We searched several electronic databases for all of the studies published before January 2013 and reviewed references of published articles. Meta-analytic procedures were used to estimate the unadjusted and BMI-adjusted odds ratios (ORs) using a random effects model. Significant values, weighted effect sizes, and 95% CIs were calculated, and tests of homogeneity of variance were performed.

RESULTS—Results from nine independent studies with a total of 9,795 pregnant women showed that SDB was significantly associated with an increased risk of GDM. Women with SDB had a more than threefold increased risk of GDM, with a pooled BMI-adjusted OR 3.06 (95% CI 1.89–4.96).

CONCLUSIONS—These findings demonstrate a significant association between SDB and GDM that is evident even after considered confounding by obesity. This meta-analysis indicates a need to evaluate the role of early recognition and treatment of SDB early during pregnancy.

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Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy and often diagnosed at 24–28 weeks of gestation (1–3). GDM is a major concern for public health, as the number of affected women is expected to rise as a result of increased sedentary habits and hypercaloric diets (4).

The impact of GDM on maternal and fetal health is well established. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study showed that globally, GDM is associated with adverse perinatal and

maternal outcomes such as fetal macrosomia, preeclampsia, primary cesarean section, neonatal hypoglycemia, premature delivery, intensive neonatal care, and hyperbilirubinemia, as well as with increased levels of cord blood serum C-peptide (5–8). The HAPO study also demonstrated that associations between maternal glycemia and adverse outcomes are continuous across the range of glucose concentrations and are observable even below diagnostic levels of diabetes (9). This broad range of morbidity indicates a need to identify modifiable risk factors for impaired glucose tolerance in pregnancy.

Sleep-disordered breathing (SDB) has emerged as an important risk factor for the development of high blood pressure, heart failure, stroke, diabetes, atrial fibrillation, and premature mortality (10–12). The risk is particularly elevated among racial/ethnic minority groups and individuals from disadvantaged neighborhoods. Mounting evidence, from observational and experimental intervention studies, indicates that sleep disturbances, such as SDB (defined as habitual snoring or sleep study–documented obstructive sleep apnea), are associated with poor glucose control and possibly GDM (13,14).

Experimental studies have shown that short sleep duration decreases insulin sensitivity compared with longer sleep (15,16). Experimental overnight intermittent hypoxemia, an essential feature of SDB, also alters glucose metabolism in animal and human studies (17,18). Epidemiological studies have shown that SDB is a risk factor for prevalent and incident diabetes, and recent clinical trials indicate that metabolic abnormalities improve with treatment of SDB (19,20).

Recently, SDB has been reported to be associated with the development of GDM (21). This finding, if confirmed across populations, has a potential large public health impact related to the increasing prevalence of obesity, a major risk factor for SDB. The objective of this meta-analysis is to examine whether SDB is associated with the occurrence of GDM and to assess the extent to which such an association is influenced by control for prepregnancy or early pregnancy BMI.

RESEARCH DESIGN AND METHODS

This meta-analysis was conducted according to internationally accepted reporting guidelines (22).

Data sources and study selection

Studies were identified by searching the National Center for Biotechnology’s PubMed/MEDLINE database, Embase (Elsevier), the Web of Science (Thomson), BIOSIS (Thomson), CINAHL (EBSCO), Cochrane Central (Wiley), and the reviews

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and registry of the Cochrane Pregnancy and Childbirth group. Controlled vocabulary terms (e.g., MeSH or Emtree terms) were used when available and appropriate. No language or date limits were applied. Additionally, we reviewed the bibliographies of relevant articles and consulted with experts in the field to identify studies not otherwise indexed or discoverable. The terms used to interrogate each databases are presented in the Supplementary Table 1.

Criteria for study inclusion into the review

First, the titles were reviewed to exclude any studies not related to the objective of this meta-analysis. A priori articles were considered for full reading if authors reported data from an original peer-reviewed study (i.e., not case reports, comments, letters, meeting abstracts, or review articles), and study designs were prospective or retrospective cohort or case-control study.

Full texts of the selected studies were then retrieved and read in full in an unblinded and independent manner by two authors (M.A.L.-F. and B.G.). Studies were considered eligible for full manuscript data extraction if the study met all the following criteria: 1) study participants were pregnant women without a diagnosis of diabetes requiring treatment prior to pregnancy, 2) the study considered SDB as an exposure and defined and evaluated SDB as habitual snoring or an apnea hypopnea index ≥ 5 using overnight sleep monitoring (23,24), 3) the study considered GDM as an outcome and diagnosed participants with fasting glucose or the oral glucose tolerance test (OGTT) following international validated medical criteria (3,25,26), and 4) the study included an assessment of obesity, measured during the prepregnancy period or during early pregnancy. Disagreement was resolved by a third author (M.A.W.) who independently examined the studies.

Data extraction

We developed a modified data extraction sheet based on the Cochrane Consumers and Communication Review Group's data extraction template and pilot tested it on two randomly selected included studies (27). Two authors (M.A.L.-F. and B.G.) extracted the data from the included studies, and the other authors reviewed the extracted data.

We extracted and recorded specific data from studies: authors, year of publication, country of origin, study design, total

sample size, measure used to assess SDB, the recall period between the assessment of the exposure and the diagnosis of GDM, diagnosis criteria to evaluate GDM, whether the study restricted the sample to singleton pregnancies, adjustment or stratification by BMI in multivariate analysis, and type of BMI measurement (prepregnancy or during early pregnancy).

Quality assessment

We assessed the methodological quality and risk of bias for each study based on the Newcastle-Ottawa quality criteria for observational studies (28) (Supplementary Table 2). In addition, a study was considered to be of high quality based on 1) the observational design being considered a case-control, prospective, or retrospective cohort; 2) case and control subjects being well defined; 3) the recall period specified; 4) the exposure being measured using standardized SDB screening questionnaires (24) or by an objective measurement (29); and 5) in multivariate analysis the measure of association being adjusted or stratified by BMI in multivariate analysis, as SDB and GDM both are associated with increased adiposity (30,31). One author was contacted to clarify whether the association between SDB and GDM was adjusted by BMI in multivariate analysis.

After the quality assessment and prior to conducting the pooled analysis, we assumed that effect size of the association between SDB and GDM may differ according to the methodological quality of the studies. Therefore, we decided a priori to use a random effects meta-analysis approach. In addition, we assessed the overall risk of bias by conducting sensitivity analyses to explore possible sources of heterogeneity across studies.

Data synthesis and statistical analysis

First, we described the characteristics of each included study summarizing the information of the extracted data and the quality assessment (Table 1 and Supplementary Table 2). Afterward, we used the Stata (Stata, College Station, TX) program "metan" (32) to generate summary and pooled odds ratios (ORs) using an inverse variance-weighted random effects analysis based on the DerSimonian and Laird method to account for within- and between-study variation (33).

Summary and pooled ORs were represented as a point estimate and 95% CIs on a forest plot (34). The assumption of

homogeneity of true effect sizes was assessed by the Cochran Q test, and the degree of heterogeneity across studies was calculated presenting the I^2 statistic and 95% CI (35,36).

In order to explain the source of heterogeneity, we conducted a subgroup analysis based on whether the effect of BMI during the study design or analysis was conceptualized as a confounder or as an effect modifier. When assessing any source of variability between studies that could explain the presence of heterogeneity, subgroup analysis is considered the best approach, as it is easily done and is preferred when the number of studies is short rather than a meta-regression (35). We evaluated publication bias using a Funnel plot (37).

Finally, as planned a priori, we conducted sensitivity analyses based on the knowledge of individual studies rather than applying weights to studies in the meta-analysis based simply on quality scoring criteria (38). We assessed whether the type of SDB measurement (questionnaire or polysomnography), the type of study (case-control or cohort), and BMI used as a confounder or effect modifier in multivariate analysis explained the variability across studies.

RESULTS—The systematic search yielded 873 total references, of which 579 were unique. With use of prespecified inclusion criteria, a title review rejected 514 references, yielding 65 candidate abstracts. A subsequent abstract review rejected 56 of these references, yielding nine candidate studies. Each of these studies was reviewed and selected for data extraction; however, based on quality criteria we decided to differentiate two groups for further subgroup analysis. One group was constituted of six studies (39–44) that included BMI in multivariate analysis, whereas the other was constituted of three studies that only presented unadjusted measures of association without adjustment by BMI (45–47). Among the BMI-adjusted studies, four used BMI in multivariate analysis as a classic confounder (39–42), while two stratified the analysis by BMI (Fig. 1) (43,44).

A total of 9,795 pregnant women were included in the analysis. Study populations included were primarily located in the U.S. (seven studies), whereas the other two study populations were from Turkey and Taiwan (42,47). All included studies were observational; seven were designed as prospective or retrospective cohorts,

Table 1—Description of the principal characteristics of the primary studies included in the systematic review and meta-analysis (n = 9)

First author and year	Type of study	Journal	Sample size	Country	Measure	Exposure: SDB measurement		Questionnaire	Recall period	Outcome: GDM diagnosis		Multivariate analysis adjusted by BMI	Restricted to singleton	Multivariate analysis stratified by BMI	Time of BMI measurement
						During pregnancy	OGTT###			Yes	No				
Boutley G, 2010	Cohort retrospective	European Respiratory Journal	938	U.S.	Snoring frequently ≥ 3 nights per week	During pregnancy	OGTT##	Multivariate Apnea Prediction Index (MAPI)*	During pregnancy	OGTT##	Yes	No	No	No	At delivery
Facco F, 2010	Cohort prospective	American Journal of Obstetrics and Gynecology	180	U.S.	Snoring frequently ≥ 3 nights per week	During pregnancy	OGTT###	Modification of the Berlin sleep questionnaire†	During pregnancy	OGTT###	Yes	Yes	No	No	Prepregnancy
Qiu C, 2010	Cohort retrospective	BMC Women's Health	1,290	U.S.	Snoring most of the time	During pregnancy	OGTT##	Adaption of Berlin sleep questionnaire: snoring frequency	During pregnancy	OGTT##	No	No	No	Yes	Prepregnancy
Reutrakul S, 2011	Cohort retrospective	Diabetes Care	180	U.S.	Snoring frequently ≥ 3 nights per week	During pregnancy	OGTT##	Berlin sleep questionnaire‡	During pregnancy	OGTT##	Yes	No	No	No	Prepregnancy
Louis J, 2012	Cohort prospective	Obstetrics and Gynecology	178	U.S.	OSA (hypopnea index ≥ 5)	During pregnancy	OGTT####	Objective measurement: polysomnography	During pregnancy	OGTT####	No	No	No	No	Prepregnancy
Ugur M, 2012	Cohort retrospective	Clinical and Experimental Obstetrics and Gynecology	465	Turkey	Snoring frequently ≥ 3 nights per week	During pregnancy	Not specified	Berlin sleep questionnaire‡	During pregnancy	Not specified	No	No	No	No	Prepregnancy
Facco F, 2012	Hospital-based case-control	American Journal of Perinatology	145	U.S.	OSA prior to the index pregnancy (hypopnea index ≥ 5)	Before pregnancy	Not specified	Objective measurement: polysomnography	Before pregnancy	Not specified	No	Yes	No	No	Prepregnancy
Chen Y-H, 2012	Population-based case-control	American Journal of Obstetrics and Gynecology	4,746	Taiwan	OSA 1 year prior to delivery (ICD-9-CM index ≥ 5)	Before and during pregnancy	Not specified	Objective measurement: polysomnography	Before and during pregnancy	Not specified	Yes	Yes	No	No	Prepregnancy
O'Brien L, 2012	Cohort prospective	American Journal of Obstetrics and Gynecology	1,673	U.S.	Habitual snoring during pregnancy	During pregnancy	Not specified	Chronic and pregnancy-onset snoring	During pregnancy	Not specified	No	Yes	Yes	Yes	Prepregnancy

OSA, obstructive sleep apnea. *Matslin G, Pack AI, Kribbs NB, et al. A survey screen for prediction of apnea. *Sleep* 1995;18:158–166. †Facco FL, Kramer J, Ho KH, Zee PC, Grobman WA. Sleep disturbances in pregnancy. *Obstet Gynecol* 2010;115:77–83. ‡Ref. 24. ††Ref. 3. †††Ref. 25. ††††Ref. 26.

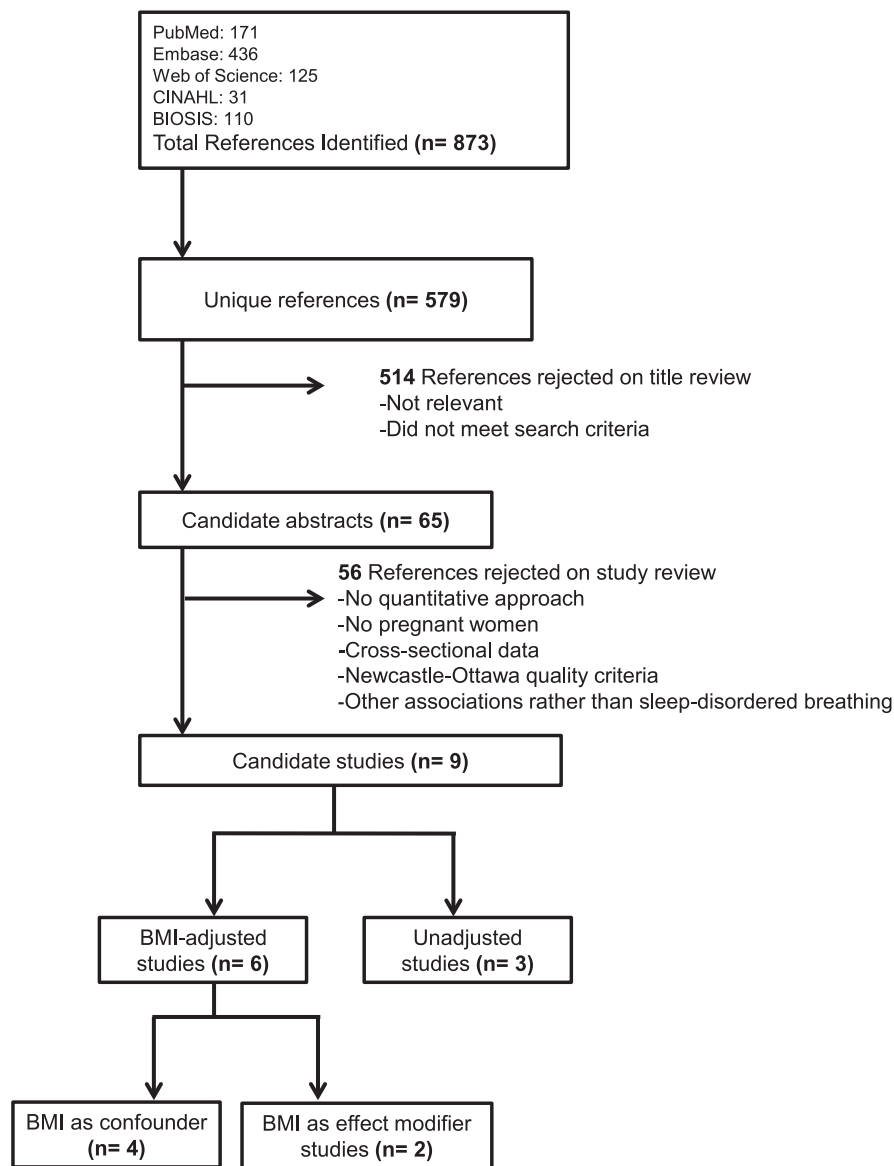


Figure 1—Flowchart of the systematic literature review.

while two were hospital- or population-based case-control studies (42,46). Four studies restricted the sample to singleton pregnancies (40,42,44,46).

Only three studies used an objective measurement of SDB (obstructive sleep apnea defined as an elevated apnea hypopnea index on polysomnography), while the others identified habitual snoring during pregnancy using standardized questions (24). Four studies did not specify the criteria used to diagnose GDM (42,44,46,47), and three studies did not present an adjusted measure of association (45–47) (Table 1).

Overall, SDB (determined by habitual snoring or polysomnography-documented obstructive sleep apnea) during the index

pregnancy were statistically significantly associated with the diagnosis of GDM. The unadjusted OR for the risk of developing GDM in women with SDB for each of the nine individual studies included in the meta-analysis ranged from 1.44 (95% CI 1.00–2.10) to 7.63 (95% CI 1.21–48.25), with a summary pooled unadjusted OR of 2.18 (95% CI 1.59–2.99). Approximately 53% of the variability between studies' measures of association was due to the presence of a moderate heterogeneity, assessed through the statistic I^2 (53% [95% CI 0–78]), Cochran Q test P value = 0.031 (Fig. 2).

The pooled BMI-adjusted OR of the six studies analyzing the effect of SDB on GDM (37–42) was 3.06 (95% CI

1.89–4.96), and the studies' specific measures of association ranged from 1.63 (95% CI 1.07–2.48) to 6.90 (95% CI 1.40–33.95). Approximately 62% of the variability between studies was due to moderate heterogeneity, with an I^2 61% (95% CI 5–84), Cochran Q test P value = 0.024 (Supplementary Fig. 1). We found BMI as an important factor that explains heterogeneity across studies. Hence, we presented our final results based on a stratified analysis, consisting of four studies using BMI as a confounder in multivariate analysis (39–42) and two other studies that considered BMI as an effect modifier (as inferred by the presentation of BMI-stratified results) (43,44) (Fig. 3).

Figure 3 shows that the summary pooled adjusted OR of the subgroup of studies that adjusted for BMI was 2.17 (95% CI 1.45–3.25), with individual study-adjusted ORs ranging from 1.63 (95% CI 1.07–2.48) to 6.90 (95% CI 1.40–33.95). The BMI-adjusted subgroup showed low evidence of heterogeneity among studies, with an I^2 33% (95% CI 0–76), Cochran Q test P value = 0.217. The summary pooled OR of the second subgroup of studies that stratify results by BMI was 5.27 (95% CI 2.87–9.66), and the specific studies' measures of association ranged from 4.12 (95% CI 1.78–9.53) to 6.90 (95% CI 2.87–16.59). This subgroup showed no evidence of heterogeneity, with a P value = 0.405 (Cochran Q test).

Sensitivity analyses based on the stratification of SDB defined as habitual snoring (subjective measurement) or documented obstructive sleep apnea (objective measurement) shows that the pooled OR of the studies that used habitual snoring as the exposure measure was 2.46 (95% CI 1.63–3.71), while the OR was 1.79 (95% CI 0.91–3.53) for the studies that modeled objectively measured SDB. Furthermore, stratified analysis by type of study (case-control or cohort) also shows no evidence of variation, with a pooled OR 2.34 (95% CI 1.61–3.41) for the cohort studies and 2.20 (95% CI 1.99–2.94) for the case-control studies.

Finally, there was no evidence of a significant publication bias (Supplementary Fig. 2), confirmed by the Egger test for publication bias (H_0 : intercept = 0; P value = 0.724).

CONCLUSIONS—To our knowledge, this is the first meta-analysis examining

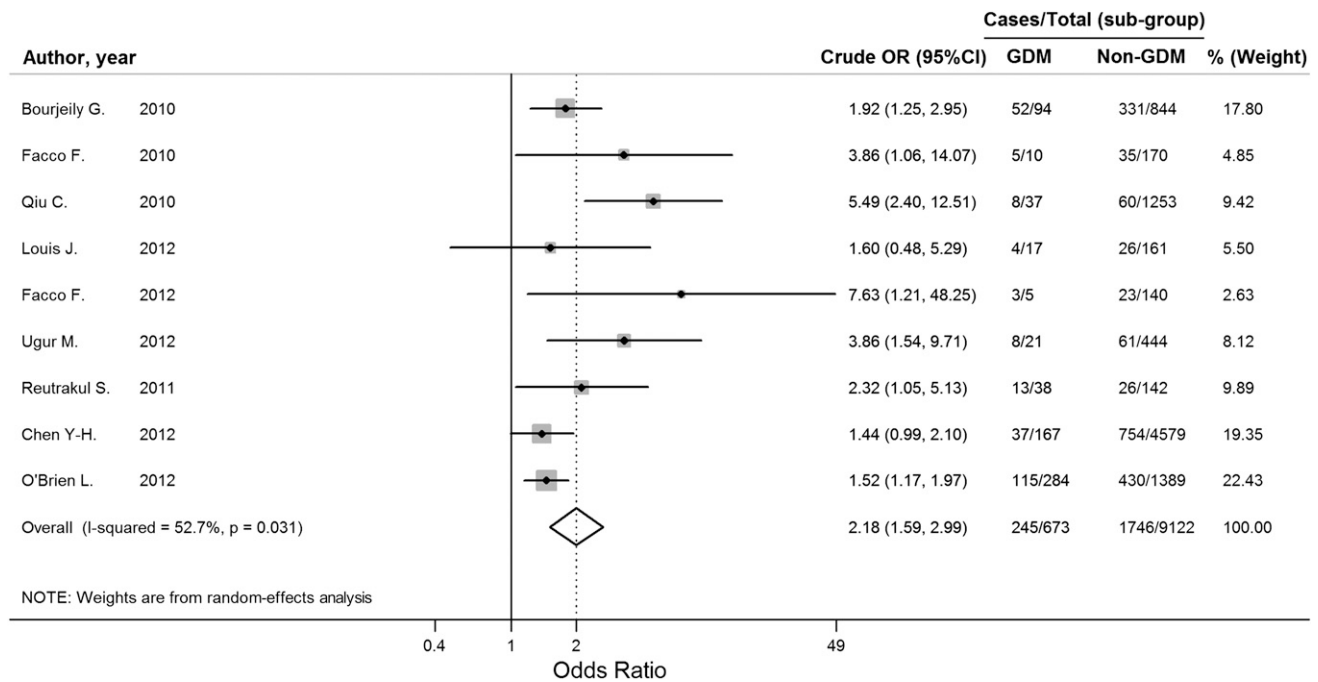


Figure 2—Forest plots showing studies' unadjusted ORs of the association between SDB and GDM and the pooled summary OR (n = 9).

the evidence for an association between SDB and GDM. Overall, in a pooled analysis we observed a significant association between SDB (defined as habitual snoring or an increase in the measured apnea hypopnea index) and risk of GDM. Women with SDB during pregnancy had more than a threefold increased risk of GDM. Furthermore, a significant association was demonstrated in analyses that considered confounding or effect modification by BMI.

Strengths and limitations

The primary strengths of this meta-analysis include the expansive literature search and inclusion of ~10,000 pregnant women, pooled from nine peer-reviewed published articles. Our findings, consistent with prior hypotheses in the literature, suggest SDB as a novel risk factor for GDM. In addition, we examined the influence of BMI (prepregnancy or early pregnancy BMI) on the association between SDB and GDM. We also explored potential heterogeneity associated with use of alternative metrics to assess SDB (habitual snoring or measured obstructive sleep apnea).

Results from this meta-analysis must be interpreted in light of the following limitations. First, the nature of the evidence of this meta-analysis is based on observational studies. Meta-analyses are not designed to address problems with residual confounding that may be inherent

in the original studies and does not address causality. Following international guidelines, we have used the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement and the Newcastle-Ottawa criteria to assess the quality of the selected studies.

Therefore, based on quality criteria for observational studies, we have some confidence that the selected studies are not biased and our pooled measure of association has sufficient power to avoid a systematic statistical type II error. In addition, we have presented stratified analyses by BMI, type of SDB measurement (polysomnography or questionnaire), and type of study (case-control or cohort) in order to explore sources of variability across studies.

Second, while the majority of studies to date have been conducted in U.S., two studies were conducted in Taiwan and Turkey, respectively. Thus, given the growing problem of SDB and GDM globally, more variability in terms of geographical representation of the populations of pregnant women is needed.

Third, although we found no statistically significant evidence for publication bias, we cannot exclude the possibility that publication bias may have affected the results.

Finally, given that some studies used habitual snoring rather than objective recordings of obstructive sleep apnea, it

is possible that there may be some misclassification in SDB status, although sensitivity analysis stratified by the objective and subjective measurement of SDB did not show significant differences. Snoring, an indicator of airflow limitation, is in general a fairly sensitive but not specific symptom of obstructive sleep apnea, which characteristically causes overnight intermittent hypoxemia. Self-reported snoring also does not provide quantitative data on the severity of overnight hypoxemia, which may be a critical driver of metabolic disturbances (48). Thus, if the relevant exposure increasing risk of GDM is related to intermittent hypoxemia rather than due to less severe airflow limitation, there may have been an underestimation of the associations. Future research using quantitative metrics of overnight hypoxemia may elucidate whether there are "exposure-response" associations or thresholds of SDB severity that are associated with increased risk of GDM. Nonetheless, snoring history is a readily accessible measure that can be identified in routine clinical obstetrical care and thus is directly relevant for clinicians as an initial step in assessing risk.

Interpretation

The results from subgroup analysis comparing effect estimates for analyses that adjusted for BMI compared with those two that stratified by obesity suggest that the association between SDB and GDM

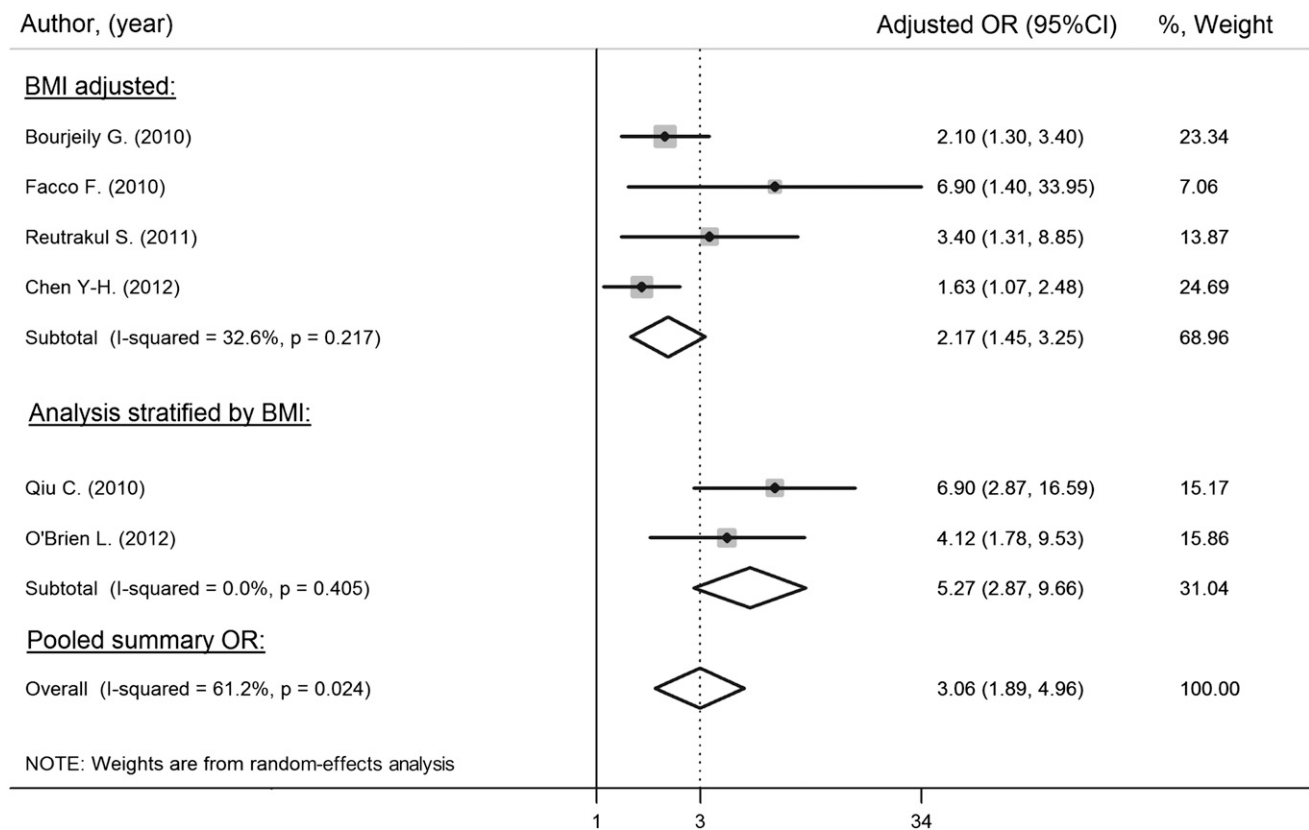


Figure 3—Subgroup analysis: Forest plots showing studies' adjusted ORs of the association between SDB and GDM and the pooled summary OR (n = 6).

may be stronger in obese women. However, these results have to be interpreted cautiously owing to the relatively small number of studies and their observational design that precludes delineation of the temporal relation between SDB and GDM. These associations may result from bidirectional relationships or they may be the outcome of a third factor affecting both glucose metabolism and breathing during sleep, such as weight gain during pregnancy or psychosocial stress—both areas that warrant further investigation using observational causal inference methodological tools (49). Nonetheless, we consider the fact that all crude estimates of the analyzed studies showed higher odds of GDM for women with SDB to be a consistent finding that strengthens the evidence of the observed association.

There are several possible pathophysiological mechanisms that may explain the observed relationship of SDB and GDM. SDB causes recurrent arousals from sleep (50); sleep fragmentation with a resultant decrease in slow-wave sleep (stage N3) has been shown to alter the effectiveness of both glucose tolerance and insulin sensitivity (21). Reduced stage N3 has been linked to increased

risk of impaired glucose tolerance and insulin sensitivity (51), presumably as a result of the disruption of the hypothalamic-pituitary-adrenal axis or through increased activity of the sympathetic nervous system. Alterations in cortisol synthesis and release may also represent a mechanism through which altered sleep disrupts glucose metabolism (21). And finally, intermittent hypoxemia occurring in association with recurrent apneas and hypopneas facilitates the generation of reactive oxidative species resulting in increased oxidative stress and proinflammatory cascade, dyslipidemia, and insulin resistance (21). Intermittent hypoxemia also may negatively influence pancreatic β -cell function (52). Since the majority of normal pregnancies are accompanied with some degree of insulin resistance and a reduction in the duration or quality of sleep, which independently of SDB may impair glucose metabolism (13), pregnancy may be a time of particular vulnerability to SDB-related stresses and adverse metabolic outcomes.

Implications

The prevalence of GDM in the U.S. continues to be a major concern for public

health, as the number of affected women is expected to rise as a result of the high prevalence of obesity in women as they enter pregnancy. Results of this study suggest that even after considering the effects of prepregnancy obesity, SDB is a factor risk of GDM. In addition, the association between SDB and GDM may be stronger in obese or overweight women. The recognition and treatment of SDB early during pregnancy may lead to improved outcomes.

Currently, there are no specific guidelines for screening pregnant women for SDB. The results of this meta-analysis indicate the potential importance of considering screening for SDB in high-risk pregnancies, especially among obese women or women who gain excessive weight during pregnancy. The usefulness of current pregnancy guidelines for reducing SDB in pregnancy—such as sleeping in a lateral sleeping position or with head elevation, treatment of nasal congestion, and avoidance of sedatives, alcohol, excessive gestational weight gain, and sleep deprivation—as well as the utility of formal sleep apnea testing and treatment, needs evaluation (48).

Some studies of the general population with SDB that have shown clear

improvement in insulin resistance and glycemic control after nasal continuous positive airway pressure (CPAP) treatment, while others have not (53). Nasal CPAP therapy has been used and tolerated during pregnancy (54), and no adverse events were reported among pregnant women with obstructive sleep apnea who were treated with nasal CPAP (55,56). Our analysis also indicates the need for research to evaluate the role of CPAP in modifying risk of GDM (53).

In summary, this systematic review and meta-analysis contributes to the growing evidence of the increased risk of GDM in women with preexisting or pregnancy-associated SDB.

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M.A.L.-F. designed the protocol, extracted data, wrote the manuscript, developed the statistical analysis, and reviewed and edited the manuscript. P.A.B., S.R., and M.A.W. contributed to the design of the protocol and reviewed and edited the manuscript. B.G. extracted data, contributed to the design of the protocol, and reviewed and edited the manuscript.

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