

The role of sleep duration and sleep disordered breathing in gestational diabetes mellitus

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Abstract

Many women experience sleep problems during pregnancy. This includes difficulty initiating and maintaining sleep due to physiologic changes that occur as pregnancy progresses, as well as increased symptoms of sleep-disordered breathing (SDB). Growing evidence indicates that sleep deficiency alters glucose metabolism and increases risk of diabetes. Poor sleep may exacerbate the progressive increase in insulin resistance that normally occurs during pregnancy, thus contributing to the development of maternal hyperglycemia. Here, we critically review evidence that exposure to short sleep duration or SDB during pregnancy is associated with gestational diabetes mellitus (GDM). Several studies have found that the frequency of GDM is higher in women exposed to short sleep compared with longer sleep durations. Despite mixed evidence regarding whether symptoms of SDB (e.g., frequent snoring) are associated with GDM after adjusting for BMI or obesity, it has been shown that clinically-diagnosed SDB is prospectively associated with GDM. There are multiple mechanisms that may link sleep deprivation and SDB with insulin resistance, including increased levels of oxidative stress, inflammation, sympathetic activity, and cortisol. Despite emerging evidence that sleep deficiency and SDB are associated with increased risk of GDM, it has yet to be demonstrated that improving sleep in pregnant women (e.g., by extending sleep duration or treating SDB) protects against the development of hyperglycemia. If a causal relationship can be established, behavioral therapies for improving sleep can potentially be used to reduce the risk and burden of GDM.

Keywords: pregnancy; sleep duration; sleep disordered breathing; gestational diabetes; women; metabolism

1. Introduction

Sleep problems are common during pregnancy. Sleep disturbances during gestation can arise from psychological distress, physical discomfort, and disordered sleep arising from hormonal and anatomical changes. Healthy sleep is thought to be important for normal glucose homeostasis. Studies in non-pregnant populations indicate that exposure to short sleep duration [1-3] or sleep-disordered breathing (SDB) [4, 5] is associated with increased risk for developing type 2 diabetes. Experimentally-induced sleep restriction also results in decreased glucose tolerance and reduced insulin sensitivity [6]. In gravid women, adaptations in glucose metabolism and pancreatic β -cell function result in a progressive increase in insulin resistance beginning near mid-pregnancy [7]. Pregnant women may therefore be especially vulnerable to effects of short sleep and disordered sleep on glucose metabolism.

In the past few years, growing evidence suggests that poor sleep may contribute to the development of gestational diabetes mellitus (GDM) [8], which is defined as glucose intolerance with onset or first recognition in pregnancy. Higher maternal glucose levels are associated with adverse perinatal health outcomes in both mother and child [9, 10]. Additionally, women with GDM are more likely to develop type 2 diabetes and atherosclerosis later in life [11, 12], and their offspring are at increased risk of becoming obese and developing type 2 diabetes [13, 14]. With the increasing global health burden of GDM [15-17], it is critical to identify modifiable behavioral risk factors. Toward this goal, it is important to assess the impact of inadequate sleep on glucose metabolism during pregnancy. The goals of this article are (1) to discuss factors that contribute to sleep problems during pregnancy, (2) to critically review evidence that exposure to short sleep duration or SDB may increase risk for GDM, and (3) to review mechanisms by which poor sleep may contribute to changes in glucose metabolism.

2. Sleep duration and gestational diabetes

2.1 Changes in sleep during pregnancy

Pregnancy is associated with changes in sleep duration and sleep quality relative to the nongravid state. Based on retrospective reporting of sleep behavior [18, 19] and longitudinal assessments of sleep using polysomnography [20], total sleep time at night increases in the first trimester relative to pre-conception, but then decreases by the third trimester. Prospective and cross-sectional surveys of sleep behavior have found nocturnal sleep duration decreases by 25-40 minutes from early to late pregnancy [21, 22], with little or no change in the duration of daytime naps across trimesters [22]. Hence, naps make up a larger percentage of total daily sleep in the later part of pregnancy but may not compensate fully for reduced nocturnal sleep duration. In a large survey-based study ($n = 2,427$), the frequency of women who reported ≤ 6 hours of total daily sleep (naps plus nocturnal sleep) increased from about 17% in the first trimester to 33% near term (**Fig. 1**), suggesting that the proportion of women with insufficient sleep increases across pregnancy.

Sleep quality often worsens across pregnancy, characterized by reduced total sleep time and nonrestorative sleep [23, 24]. In the first trimester, symptoms of morning sickness are commonly reported including nausea, vomiting, and diarrhea [19]. In the second trimester, fetal movements and esophageal reflux (heartburn) are commonly experienced for the first time, and in the third trimester there are numerous causes of sleep problems (**Fig. 1**) including nocturia (frequent urination), difficulty finding a comfortable position, pain in the back and pelvic region, heartburn, symptoms of restless legs syndrome, and SDB (discussed below in greater detail) [19, 22]. Additionally, many women experience sleep difficulties caused by worrying about their

baby, labor, and delivery [22]. In summary, a combination of psychosocial, biological, and physical factors can give rise to insufficient sleep during pregnancy.

2.2 Sleep duration and risk of gestational diabetes

During pregnancy, shorter nighttime sleep duration has been shown to associate with higher plasma glucose concentrations in response to a non-fasting glucose challenge test [25-27], suggesting that sleep duration may influence glucose tolerance. In the past decade, several studies have examined the relationship between sleep duration and GDM (**Table 1, Fig. 2**). The first 3 studies included women who were predominantly Caucasian and African-American, attending clinics in individual American cities (either Chicago or Seattle). In a study that recruited 189 nulliparous women with a singleton pregnancy from Chicago-area clinics [28], self-reported sleep behavior was assessed during the first or third trimester, and GDM status was determined from medical records. Exposure to short sleep (<7 hours per night) was associated with increased risk of GDM, adjusting for age, ethnicity, pre-pregnancy BMI, and frequent snoring (**Table 1**). However, only 10 women in the sample were diagnosed with GDM, and the estimated adjusted odds ratio (aOR) was imprecise with large confidence intervals (aOR = 11.7, 95% CI 1.2 to 114.5). In another study that included 1,290 pregnant women recruited from clinics in Seattle [29], self-reported sleep duration was assessed near the end of the first trimester and results of a fasting oral glucose tolerance test (OGTT) performed at 24-28 weeks of gestation were compared across different sleep duration groups (≤ 4 hours, 5-8 hours, 9 hours, and ≥ 10 hours). Women who reported ≤ 4 hours of sleep ($n = 21$, 3 GDM cases) per night exhibited a significant increase in relative risk (aRR) of GDM compared with women who reported 9 hours of sleep ($n = 257$, 7 GDM cases), adjusting for maternal age and ethnicity (aRR = 5.56, 95% CI

1.31 to 23.69) (**Table 1**). However, this result is based on an extreme definition of short sleep that occurred rarely (1.6% of the sample) and may have included women with severe insomnia or other sleep disorders. Additionally, in the model that adjusted for pre-pregnancy BMI, exposure to ≤ 4 hours of sleep per night was not associated with GDM (aRR = 4.18, 95% CI 0.94 to 18.60). Similar to these results, a Chicago-area study that included 169 women with a singleton pregnancy (26 GDM cases) found that exposure to < 7 hours of sleep per night was not associated with greater odds of GDM compared with women who reported longer sleep durations (unadjusted OR = 2.4, 95% CI 1.0 to 5.9; $P = 0.06$) [26].

Recently, 3 studies examined the relationship between sleep duration and risk of GDM in samples of Asian women that included a larger number of GDM cases [30-32]. In a study that included 542 pregnant women (136 GDM cases) recruited from clinics in Sichuan Province, China [30], exposure to < 7 hours of sleep per night in early pregnancy was associated with increased odds of GDM compared with women who reported 7 to < 9 hours of sleep (aOR = 7.38, 95% CI 2.25 to 24.17), adjusting for several covariates including pre-pregnancy BMI, maternal age, gestational weight gain, and history of diabetes (**Table 1**). By comparison, exposure to longer sleep durations (≥ 9 hours per night) was not associated with GDM (aOR = 1.13, 95% CI 0.73 to 1.74). Opposite findings were reported in a study of 12,506 pregnant women (919 GDM cases) who took part in a universal GDM screening program in Tianjin, China [31]. In that study, self-reported exposure to < 7 hours of sleep per day was not associated with GDM (aOR = 1.36, 95% CI 0.87 to 2.14), whereas exposure to ≥ 9 hours of sleep per day was associated with increased odds of GDM compared with women who reported 7 to < 9 hours of sleep (aOR = 1.29, 95% CI 1.09 to 1.52), adjusting for covariates including BMI at the first antenatal visit, maternal age, gestational weight gain, and family history of GDM (**Table 1**). The third study to examine

sleep duration and GDM risk in Asian women recruited 686 participants (131 GDM cases) taking part in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) mother-offspring cohort study [32]. In this multi-ethnic cohort (Chinese, Malay, Indian), exposure to <6 hours of sleep per night at 26-28 weeks of gestation was associated with significantly greater odds of GDM compared with women who reported longer sleep durations (aOR = 1.96, 95% CI 1.05 to 3.66), adjusting for BMI in the first trimester, maternal age, ethnicity, maternal education, previous history of GDM, and anxiety.

A limitation of the studies discussed thus far is that subjects were recruited from a single region or city, hence limiting the generalizability of the findings. This issue was addressed in a pair of recent studies that recruited pregnant women from multiple clinical sites across the United States [33, 34]. As part of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Developmental Fetal Growth Studies-Singleton Cohort study, 2,581 women (107 GDM cases) from 12 participating sites reported their typical sleep duration in the first and second trimesters [33]. Nocturnal sleep duration was reported across 4 different categories (5-6 hours, 7 hours, 8-9 hours, and ≥ 10 hours), and GDM status was extracted from medical records. In analyses that included all women (both non-obese and obese), exposure to short or long sleep durations was not associated with increased risk for GDM, compared with the reference group that reported 8-9 hours of sleep per night (**Table 1**). In a secondary analysis of non-obese women ($n = 2,081$; 70 GDM cases), sleep duration in the second trimester, but not the first trimester, associated with GDM, adjusting for pre-pregnancy BMI, maternal age, ethnicity, gestational age at the time of interview, family history of diabetes, parity, and marital status. Relative to the reference group that reported 8-9 hours of sleep per night in the second trimester, exposure to 5-6 hours of sleep or 7 hours of sleep was associated with about a 2-fold increase in risk of GDM (5-

6 hours, aRR = 2.52, 95% CI 1.27 to 4.99; 7 hours, aRR = 2.01, 95% CI 1.09 to 3.68). Similarly, exposure to ≥ 10 hours of sleep per night in non-obese women was associated with increased risk of GDM (aRR = 2.17, 95% CI 1.01 to 4.67).

The only study to use objectively-assessed sleep parameters to examine the relationship between sleep duration and GDM was the Sleep Duration and Continuity Study, which enrolled pregnant women across 8 clinical sites [34]. This sub-study of the Nulliparous Pregnancy Outcomes: Monitoring Mothers-to-Be (nuMoM2b) study included a subset of 782 women (33 GDM cases) with 5-7 days of valid actigraphy data that was used to derive estimates of sleep duration, midpoint of nocturnal sleep, and indices of sleep fragmentation [35]. Exposure to < 7 hours of sleep per night was associated with increased odds of GDM compared with longer nocturnal sleep, adjusting separately for several covariates including BMI (aOR = 2.12, 95% CI 1.04 to 4.30), maternal age (aOR = 2.26, 95% CI 1.12 to 4.58), and ethnicity (aOR = 2.31, 95% CI 1.13 to 4.73). Exposure to short sleep did not associate with GDM after controlling for snoring (aOR = 2.29, 95% CI 0.97 to 5.39; $P = 0.59$), however, and multiple covariate adjustment was not performed. In other analyses, a later midpoint of sleep (after 5:00am) was associated with increased odds of GDM, adjusting separately for BMI, maternal age, ethnicity, and snoring. In contrast, wake after sleep onset (WASO) and sleep fragmentation did not associate with GDM.

2.3 Summary and limitations

Several studies have found that the frequency of GDM is higher in women with shorter sleep durations (**Fig. 2**). Of the 7 studies that either adjusted for BMI or stratified their subject pool into obese and non-obese groups, 5 studies provided evidence that shorter sleep was

associated with increased odds of GDM [28, 30, 32-34] (**Table 1**). Studies have included participants from diverse geographical regions and different ethnic groups, and applied different criteria for short sleep (≤ 4 hours, < 6 hours, or < 7 hours) and for diagnosing GDM (National Diabetes Data Group, 1979; World Health Organization, 1999; American Diabetes Association, 2003; International Association of Diabetes and Pregnancy Study Group, 2010) [36]. Despite differences in study populations and methodology, the results thus far point toward a potential role for sleep duration in modulating glucose metabolism in gravid women. To date, only 2 studies have provided evidence that exposure to long sleep durations (≥ 9 hours or ≥ 10 hours) is associated with GDM [31, 33]. Additional studies are needed to establish whether there is a U-shape relationship between sleep duration and relative risk of GDM, similar to what has been reported for type 2 diabetes in which both short and long sleep durations are associated with greater risk [3].

Most studies that have examined the relationship between sleep duration and GDM have collected data on sleep behavior using questionnaires. Self-reported sleep duration captures information about a typical night, but other characteristics of sleep may also be important for glucose metabolism, including sleep continuity, sleep timing, and variability in sleep duration. Objective measures of sleep behavior are required to assess these aspects of sleep reliably. To date, however, only one study has used actigraphy to examine associations between sleep behavior and GDM [34]. In addition, most studies have not examined the relationship between short sleep duration and GDM prospectively. In one study that collected sleep behavior data at more than one time point [33], sleep duration in the second trimester (i.e., closest to the OGTT), but not in the first trimester, associated with GDM. Such findings raise the possibility that recent sleep history may be most relevant for results of glucose tolerance testing. However, the

relationship between sleep duration and insulin sensitivity has not been examined longitudinally during pregnancy. Additionally, it has not been tested whether increasing total sleep time, either by extending nocturnal sleep or napping, benefits glucose tolerance in pregnant women with or without GDM.

3. Sleep disordered breathing and gestational diabetes

3.1 Factors contributing to sleep disordered breathing during pregnancy

Physiologic and hormonal changes during pregnancy contribute to sleep disordered breathing (SDB), which refers to conditions in which abnormal respiratory patterns and gas exchange occur during sleep. Obstructive sleep apnea (OSA) is the most common type of SDB, characterized by repetitive complete or partial obstruction of the upper airway. During pregnancy, changes in chest diameter and elevation of the diaphragm occur to compensate for the enlarging uterus. These changes result in tracheal shortening and a progressive reduction in the volume of air in the lungs at the end of passive expiration (functional residual capacity), and in the maximum volume of air expelled after normal expiration (expiratory reserve volume) [37]. The progressive increase in estrogen levels during pregnancy is thought to contribute to vasomotor rhinitis, leading to narrowing of the airway and increased airflow resistance that can cause or exacerbate SDB [38]. Body mass index (BMI) and change in neck circumference are also significant predictors of apnea symptoms and PSG-diagnosed OSA [39, 40], suggesting that the amount of gestational weight gain modulates risk of developing SDB.

Respiratory events in SDB can result in loud snoring, frequent arousals, sleep fragmentation, and reduced slow-wave sleep [8, 41]. Although snoring is not specific to OSA, it is the most commonly reported symptom of SDB and has been studied most extensively in

gravid women. Most longitudinal studies have shown that habitual snoring increases from about 7-11% in the first trimester to about 16-25% in the third trimester [21, 42, 43]. Symptoms of OSA, including loud snoring, snorting, gasping, and witnessed apneas, worsen significantly by 28-29 weeks of pregnancy and continue to increase in the third trimester [39]. The severity of OSA can be assessed polysomnographically by the sum of the number of apneas (cessation of airflow) and hypopneas (reduced airflow with pathophysiologic changes) per hour of sleep, defined as the apnea-hypopnea index (AHI). In a prospective study of 105 pregnant women, the percentage of participants with OSA ($AHI \geq 5$) increased from about 11% to 27% across pregnancy [40]. Using the same AHI criterion for diagnosing OSA, a prospective study of pregnant women at high risk of SDB (e.g., obese, hypertensive, or diabetic) found that the incidence of OSA increased from 29% in the first trimester to 47% in the third trimester [44]. More recently, a large prospective study of more than 3,000 women found that the incidence of OSA ($AHI \geq 5$) increased from 3.6% in early pregnancy to 8.3% in midpregnancy [45]. Although the prevalence of OSA in the general pregnant population has not been firmly established, these studies suggest that SDB is common, especially in the later part of pregnancy.

3.2 Sleep-disordered breathing and risk of GDM

Longitudinal cohort studies have shown that OSA is associated with increased incidence of type 2 diabetes [46, 47]. In addition, experimentally-induced sleep fragmentation [48-50] or intermittent hypoxia during wakefulness results in reduced insulin sensitivity [51] and/or elevated plasma glucose levels [52]. Consistent with these findings, 3 meta-analyses have found that exposure to SDB during pregnancy is associated with increased risk of GDM, with SDB defined by self-reported symptoms (e.g., habitual snoring or a positive score on the Berlin

Questionnaire) or PSG-diagnosed OSA [53-55]. In a meta-analysis that included 6 studies with prospective or retrospective study designs [53], gravid women with SDB had a more than 3-fold increase in the pooled adjusted odds of GDM (pooled aOR = 3.06, 95% CI 1.89 to 4.96). A subsequent meta-analysis that included 5 studies found that exposure to SDB was associated with an approximately 2-fold increase in the pooled adjusted odds of GDM (pooled aOR = 1.86, 95% CI 1.30 to 2.42) [55], and nearly the same result was obtained in another meta-analysis that included 7 studies with prospective or retrospective study designs (pooled aOR = 1.98, 95% CI 1.32 to 2.96) [54]. In a secondary analysis that included only prospective studies, however, exposure to SDB was not associated with GDM (pooled OR = 1.20, 95% CI 0.93 to 1.53), and another meta-analysis that included 4 cohort studies did not find an association between OSA and GDM (pooled RR = 1.40, 95% CI 0.62 to 3.19) [56]. In the following sections, we will critically evaluate studies that were included in these meta-analyses, while also highlighting recently published research on the relationship between SDB and GDM.

3.2.1 Habitual snoring and self-reported symptoms of OSA

Several studies have examined the association between habitual snoring during pregnancy and GDM (**Table 2**). In unadjusted models, most studies have found that loud or frequent snoring is associated with increased odds of GDM (OR range, 1.67 to 4.9) [26, 28, 29, 42, 57-59]. Of the 5 studies that adjusted for BMI (with ≥ 10 GDM cases), 3 studies found that exposure to loud/frequent snoring associated with GDM [26, 28, 57]. The first of these studies [57] used a cross-sectional study design in which 996 women (52 GDM cases) completed the Multivariable Apnea Prediction Index [60] immediately postpartum. About a third of women (35%) reported loud snoring frequently/always during pregnancy, and this was associated with a

2-fold increase in the odds of being diagnosed with GDM, adjusting for maternal age, BMI at delivery, smoking, and multifetal pregnancy (aOR = 2.1, 95% CI 1.3 to 3.4). In a smaller, prospective study that included 170 nulliparous women (10 GDM cases), 18.5% of participants reported frequent snoring during pregnancy, defined as ≥ 3 times per week [28]. Frequent snoring was associated with increased odds of GDM, adjusting for maternal age, race/ethnicity, pre-pregnancy BMI, and short sleep duration (aOR = 6.9, 95% CI 1.4 to 33.9). Similarly, in a study that included 116 women with normal glucose tolerance and 26 women with GDM [26], frequent snoring was associated with increased odds of GDM when adjusting for BMI (aOR = 3.4, 95% CI 1.3 to 8.8).

There are 2 studies with large samples that did not find an association between frequent snoring and GDM in models that adjusted for covariates [29, 42]. In a study that included 1,290 women (68 GDM cases) [29], participants were categorized as snorers if they reported snoring most or all of the time (6.9% of women) in early pregnancy. Exposure to frequent snoring was associated with increased risk of GDM in the unadjusted analysis, but not after adjustment for maternal age and race/ethnicity (aRR = 1.86, 95% CI 0.88 to 3.94). Similar results were obtained in a study that included 1,719 women (203 GDM cases) with a singleton pregnancy who were recruited in the third trimester [42]. Habitual snoring was defined as snoring at least 3-4 times per week, and separate analyses were performed for chronic snorers (self-reported snoring before and during pregnancy) and pregnancy-onset snorers. Chronic snoring or pregnancy-onset snoring was not associated with increased odds of GDM compared with absence of snoring, adjusting for maternal age, pre-pregnancy BMI, ethnicity/race, and other covariates (chronic snoring, aOR = 0.91, 95% CI 0.55 to 1.49; pregnancy-onset snoring, aOR = 1.00, 95% CI 0.72 to 1.39).

Associations between SDB and GDM have also been examined using the Berlin

Questionnaire [61], which is used to identify individuals at higher risk of OSA based on their answers across 3 categories, including snoring and witnessed apneas, daytime sleepiness, and obesity/hypertension. Positive symptoms across at least 2 categories indicate increased likelihood of SDB. Using the Berlin Questionnaire, it was found that gravid women with GDM (n = 26) were more likely to report symptoms of SDB compared with women with normal glucose tolerance (n = 116; 52% versus 31%) [26]. Exposure to SDB symptoms was associated with increased odds of GDM (unadjusted OR = 3.0, 95% CI 1.2 to 7.4), but results were not adjusted for BMI, which was higher in women with GDM. By comparison, in another study that included 220 women (55 GDM cases) [62], participants were defined as having symptoms of SDB if they had a positive score on the Berlin Questionnaire or if they reported excessive daytime sleepiness on the Epworth Sleepiness Scale (score ≥ 10). Using these criteria, SDB symptoms were not associated with GDM (unadjusted OR = 1.00, 95% CI 0.50 to 2.01). Similarly, another study that included 276 women (10 GDM cases) found that a positive score on the Berlin Questionnaire was not associated with GDM (unadjusted OR = 0.51, 95% CI 0.11 to 2.47) [63]. An important limitation of these studies is that frequent snoring or a positive score on the Berlin Questionnaire cannot be used to accurately infer the presence of OSA. It is therefore important to consider the relationship between PSG-diagnosed OSA and GDM, which shall be reviewed in the following sections.

3.2.2 Population studies of OSA based on patient databases

The relationship between OSA and GDM has been examined in retrospective studies with large samples derived from patient databases. A study that used the Taiwan National Health Insurance database included 791 women with PSG-diagnosed OSA within 1 year before delivery

and 3,955 randomly selected women without OSA (5 controls for every OSA case) matched by age [64]. Exposure to OSA was associated with increased odds of GDM, adjusting for obesity and other covariates (aOR = 1.63, 95% CI 1.07 to 2.48). Comparable results were obtained using data from the Nationwide Inpatient Sample database in the United States [65], which included 55,781,965 pregnancy-related hospital discharges over a 10-year period. Exposure to OSA was associated with a 2-fold increase in the odds of GDM compared with women who were not diagnosed with OSA (aOR = 1.89, 95% CI 1.67 to 2.14), adjusting for maternal age, obesity, ethnicity/race, and other covariates including clinical comorbidities.

Recently, two retrospective studies with large samples did not find an association between OSA and GDM. Using data derived from the New South Wales Admitted Patient Data Collection database in Australia, hospital records were obtained from 636,227 women who gave birth over a 10-year period [66]. There were 519 women who were diagnosed with sleep apnea in the year before pregnancy or during pregnancy. Exposure to OSA was not associated with GDM, adjusting for maternal age, obesity, and other covariates (aRR = 1.09, 95% CI 0.82 to 1.46). In another study, hospital records from 305,001 women who gave birth at military treatment facilities in the United States were examined over a 6-year period, including 266 OSA cases [67]. Although pregnant women with OSA had a higher rate of GDM compared with women without OSA (22.9% versus 9.4%), exposure to OSA was not associated with increased odds of GDM when adjusting for maternal age, obesity, race/ethnicity, multiple birth, and hospital size (aOR = 1.04, 95% CI 0.65 to 1.65). While studies based on patient databases have produced mixed results on the relationship between OSA and GDM, it is important to note that the percentage of gravid women diagnosed with OSA in all of these studies (<0.3%) is much lower than the expected rate based on prospective studies of PSG-diagnosed SDB (i.e., about 8% by

midpregnancy) [45], suggesting that many gravid women in these retrospective studies may have had undiagnosed OSA.

3.2.3 Prospective studies with PSG-diagnosed OSA

Few studies have prospectively examined the relationship between PSG-diagnosed OSA and GDM. In a study that included 175 obese pregnant women (pre-pregnancy BMI >30 kg/m²) who underwent in-home PSG monitoring to screen for SDB [68], exposure to OSA (AHI ≥ 5) was not associated with GDM (unadjusted OR = 1.70, 95% CI 0.51 to 5.72). Similar results were obtained in a prospective study of 182 high-risk patients [69], defined as women with BMI ≥ 30 kg/m², chronic hypertension, diabetes prior to pregnancy, prior preeclampsia, and/or a twin gestation. Based on AHI estimated using a Watch-PAT device, the rate of GDM increased with AHI severity, but exposure to either mild SDB (AHI ≥ 5 to <15) or moderate-to-severe SDB (AHI ≥ 15) was not associated with increased odds of GDM relative to women without SDB (AHI <5), adjusting for maternal age, pre-pregnancy BMI, race/ethnicity and other covariates (mild SDB, aOR = 1.5, 95% CI 0.4 to 6.0; moderate-to-severe SDB, aOR = 3.6, 95% CI 0.6 to 21.8). In another prospective study that included 104 pregnant women [70], participants underwent PSG in the first trimester to assess OSA (AHI ≥ 5), and a glucose challenge test (50-g glucose, non-fasting) was performed in the late second trimester. Exposure to OSA was not associated with hyperglycemia, defined as a 1-hour glucose concentration ≥ 135 mg/dL (unadjusted OR = 1.03, 95% CI 0.83 to 1.28).

The studies discussed thus far are limited by their relatively small sample sizes and number of women diagnosed with GDM or hyperglycemia (≤ 18 cases in each study). To date, only one large-scale prospective study has examined the relationship between objectively-

determined SDB and GDM. In the Sleep Disordered Breathing Substudy of the nuMoM2b Study [45], in-home SDB assessments were performed in nulliparous women with a singleton pregnancy during early pregnancy (n = 3,132) and mid-pregnancy (n = 2,474). Women were recruited from 8 clinical sites across the United States, and AHI results were blinded to care providers, researchers, and participants. In early pregnancy, the odds of GDM were more than 3-fold higher in women with an AHI ≥ 5 compared with women without SDB, adjusting for maternal age, BMI, and chronic hypertension (aOR = 3.47, 95% CI 1.95 to 6.19). The frequency and odds of GDM also increased with SDB severity, demonstrating an exposure-response relationship between AHI and GDM (**Fig. 3**). Compared with the reference group with no apneas or hypopneas, exposure to mild sleep apnea (AHI 5 to <15) in early pregnancy was associated with a 3.5-fold increase in odds of GDM (aOR = 3.50, 95% CI 1.64 to 7.44), and exposure to moderate-to-severe apnea (AHI ≥ 15) was associated with a more than 8-fold increase in odds of GDM (aOR = 8.44, 95% CI 1.90 to 37.60). Comparable results were obtained for PSG-based SDB screening in mid-pregnancy (**Fig. 3**), in which the odds of GDM in women with sleep apnea (AHI ≥ 5) was about 3-fold greater than in women without SDB (aOR = 2.79, 95% CI 1.63 to 4.77), and the frequency and odds of GDM increased with AHI severity. These findings, which are based on a rigorous prospective study design, provide strong evidence that exposure to SDB during pregnancy is associated with GDM.

3.3 Summary and limitations

About half of studies that have controlled for BMI or obesity have found an association between SDB and GDM (**Table 2**). Results for frequent snoring, the Berlin Questionnaire, and AHI have been pooled in meta-analyses [53-56], but these exposure variables carry different types of

information. The best approach for evaluating SDB and its relationship with glucose metabolism is to perform large-scale prospective studies that include PSG-derived measures of SDB. To date, only one study fits this description, namely the Sleep Disordered Breathing Substudy of the nuMoM2b study [45]. In this study, it was found that AHI in either early or midpregnancy associated with GDM, and the frequency of SDB increased substantially between time points. However, it has not been determined whether changes in AHI during pregnancy associate linearly with changes in plasma glucose when adjusting for changes in adiposity and weight gain. Additionally, few studies have collected longitudinal data to assess whether pre-existing SDB and pregnancy-onset SDB differentially predict maternal health outcomes. Previously, it was found that women with pregnancy-onset snoring had increased odds of gestational hypertension and preeclampsia compared with women who snored prior to pregnancy, but these subgroups did not differ in their risk of GDM [42]. Additional research using PSG to diagnose OSA is needed to determine whether women with pre-existing versus pregnancy-onset SDB differ in their risk of developing maternal hyperglycemia.

4. Mechanisms linking sleep and glucose metabolism

There are multiple pathways by which insufficient sleep and disordered sleep can lead to increased insulin resistance [8, 71, 72]. It is likely that sleep-related mechanisms that contribute to altered glucose homeostasis in non-pregnant populations are operative during pregnancy. However, adaptive changes during normal pregnancy give rise to increased maternal adiposity, inflammation, and insulin resistance [37, 73]. Therefore, effects of sleep deficiency and SDB must be considered on the background of metabolic changes that occur during pregnancy. In the following sections, we will discuss potential mechanisms linking short sleep and SDB with

impaired glucose metabolism.

4.1 Oxidative stress and inflammation

Exposure to sleep deprivation or SDB is associated with elevated markers of oxidative stress and proinflammatory cytokines. This is thought to promote endothelial damage and alterations in metabolism that can contribute to the development of hypertension and diabetes [74]. In non-pregnant adults, exposure to sleep restriction results in increased expression of genes in blood associated with oxidative stress [75]. Similarly, OSA is associated with increased markers of oxidative stress and reduced antioxidant activity [76]. This is likely driven by effects of repetitive hypoxia and reoxygenation, as well as sleep fragmentation. Even in healthy pregnancies, markers of oxidative stress increase during the first and second trimesters relative to non-pregnant women [77]. However, the concentration of advanced oxidation protein products is higher in women with GDM compared with women with normal glucose tolerance [78], hence raising the possibility that exposure to risk factors that increase oxidative stress (e.g., sleep deficiency or SDB) may contribute to the development of maternal hyperglycemia.

In non-pregnant adults, experimentally-induced hyperglycemia results in an increase in pro-inflammatory markers including interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) [79]. This effect is reversed with infusion of the antioxidant glutathione, suggesting that oxidative stress contributes to hyperglycemia-mediated inflammation. Exposure to partial sleep deprivation induces an inflammatory response [80], as evidenced by elevated levels of IL-6, TNF- α , and C-reactive protein (CRP) [81-84]. By comparison, sleep deprivation results in reduced levels of leptin, an adipokine critical in appetite regulation and energy balance, that is made in adipose cells and associated with pro-inflammatory immune responses [85]. Normal

pregnancy is associated with increased levels of TNF- α , CRP, and leptin [73, 86], and levels of TNF- α and leptin correlate inversely with insulin sensitivity [86, 87]. In women with GDM, however, pro-inflammatory responses are greater than in women with normal glucose levels who are matched by BMI, as evidenced by higher levels of TNF- α and leptin [88]. Additionally, levels of adiponectin, an anti-inflammatory adipokine, are lower in women with GDM compared with pregnant controls. While a direct link between poor sleep during pregnancy, increased inflammation, and GDM has yet to be established, self-reported sleep problems in late pregnancy have been shown to associate with increased plasma IL-6 [89]. Such findings suggest that exposure to poor sleep or insufficient sleep during pregnancy may contribute to increased circulating levels of pro-inflammatory cytokines observed in GDM [90, 91].

4.2 Sympathetic activity and cortisol

Insufficient sleep results in a shift in sympathovagal balance toward increased sympathetic nervous system activity. This is reflected by changes in heart rate variability in individuals exposed to total sleep deprivation [92], sleep restriction [85, 93], or experimentally-induced suppression of slow-wave sleep [49]. In non-pregnant adults, exposure to sleep restriction has also been shown to result in increased levels of norepinephrine and epinephrine [94, 95]. SDB is likewise associated with increased sympathetic activity and catecholamine levels [41]. During pregnancy, plasma noradrenaline levels during the late part of the night are higher compared with levels in non-pregnant women, with a shift toward increased sympathetic tone based on changes in heart rate variability [96]. These changes that occur during pregnancy, when combined with effects of insufficient sleep or SDB, can potentially promote insulin resistance and gluconeogenesis.

Some but not all studies have found that exposure to sleep deprivation results in elevated cortisol levels [72]. In contrast, it is well established that cortisol secretion increases markedly in gravid women [86]. Chronically-elevated cortisol can alter glucose metabolism by suppressing insulin secretion by pancreatic β -cells, impairing glucose uptake and downstream insulin signaling, and enhancing gluconeogenesis [97]. Sleep disturbances during pregnancy could also act as a stressor and contribute to increased sympathetic activity and cortisol secretion [98]. It has yet to be demonstrated, however, whether changes in insulin sensitivity during pregnancy are influenced by effects of sleep disturbances on cortisol levels.

5. Future directions and conclusions

5.1 Future research directions

The most important gap in knowledge regarding the role of sleep in glucose metabolism during pregnancy is whether improving sleep can reduce maternal hyperglycemia and improve insulin sensitivity. In healthy individuals who are habitually exposed to short sleep as part of their usual lifestyle, interventions that involve spending more time in bed for sleep have been shown to improve some indices of insulin sensitivity [99, 100]. In pregnant women, however, it has not been tested whether improving sleep duration or sleep quality can reduce the risk of GDM. Similarly, it has not been evaluated whether improving sleep during pregnancy can protect against excessive gestational weight gain (e.g., by reducing energy intake and sedentary activity), which may contribute to SDB and GDM. Women who voluntarily curtail their sleep before and during pregnancy may benefit by more time in bed for sleep and better sleep hygiene [101], but these approaches may not work in women who experience pregnancy-onset sleep disturbances that include difficulty initiating and maintaining sleep. Strategies for improving

sleep could include cognitive behavioral therapy, which is an effective non-pharmacologic intervention for treating insomnia in non-pregnant populations [102, 103], or mindfulness-based training, which has been implemented to improve sleep and reduce psychological stress [104]. Future studies should examine whether improving sleep quality using these behavioral interventions has a positive impact on glucose metabolism. Similarly, there is a need to assess whether treatment of SDB during pregnancy reduces hyperglycemia and adverse pregnancy outcomes.

5.2 Conclusions

Many gravid women experience reduced nocturnal sleep and pregnancy-onset sleep disturbances. A growing body of evidence suggests that short sleep and SDB are risk factors for GDM, but more prospective studies are needed to assess whether sleep problems during pregnancy predict changes in glucose metabolism. Exposure to poor sleep during pregnancy may contribute to increased insulin resistance through effects on oxidative stress, inflammation, sympathetic activity, and cortisol levels. Therefore, healthy sleep during pregnancy may be important for normal glucose responses and minimizing risk of GDM.

6. References

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Table 1

Sleep duration and risk of GDM

Study	No GDM (n)	GDM (n)	Comparison	Unadjusted OR/RR (95% CI)	Adjusted OR/RR (95% CI)
Facco et al., 2010 [28]	172	10	<7 h vs ≥7 h	OR = 10.6 (1.3 to 85.5)	OR = 11.7 (1.2 to 114.5) ^a
Qiu et al., 2010 [29]	258	10	≤4 h vs 9 h	RR = 5.24 (1.46 to 18.81) [†]	RR = 5.56 (1.31 to 23.69) ^b
	1009	59	5 to 8 h vs 9 h	RR = 2.19 (1.01 to 4.77) [†]	RR = 1.99 (0.89 to 4.4) ^b
	366	13	≥10 h vs 9 h	RR = 1.63 (0.56 to 4.76) [†]	RR = 1.82 (0.60 to 5.57) ^b
Reutrakul et al., 2011 [26]	116	26	<7 h vs ≥7 h	OR = 2.4 (1.0 to 5.9)	Not reported
Zhou et al., 2016 [30]	205	79	<7 h vs 7 to <9 h	OR = 6.21 (2.70 to 14.30) [†]	OR = 7.38 (2.25 to 24.17) ^c
	400	126	≥9 h vs 7 to <9 h	OR = 0.86 (0.58 to 1.27) [†]	OR = 1.13 (0.73 to 1.74) ^c
Wang et al., 2017 [31]	5248	377	<7 h vs 7 to <9 h	OR = 1.36 (0.87 to 2.14)	OR = 1.12 (0.69 to 1.81) ^d
	11359	897	≥9 h vs 7 to <9 h	OR = 1.21 (1.03 to 1.42)	OR = 1.29 (1.09 to 1.52) ^d
Cai et al., 2017 [32]	555	131	<6 h vs ≥6 h	OR = 1.70 (0.99 to 2.93)	OR = 1.96 (1.05 to 3.66) ^e
Rawal et al., 2017 [33]	1569	63	5 to 6 h vs 8 to 9 h	RR = 1.38 (0.81 to 2.33)	RR = 1.51 (0.89 to 2.60) ^f
	1698	70	7 h vs 8 to 9 h	RR = 1.40 (0.87 to 2.24)	RR = 1.38 (0.85 to 2.23) ^f
	1554	60	≥10 h vs 8 to 9 h	RR = 1.21 (0.69 to 2.13)	RR = 1.49 (0.82 to 2.68) ^f
Facco et al., 2017 [34]	749	33	<7 h vs ≥7 h	OR = 2.24 (1.11 to 4.53)	OR = 2.12 (1.04 to 4.30) ^g
					OR = 2.29 (0.97 to 5.39) ^h

^aAdjusted for maternal age, race/ethnicity, pre-pregnancy BMI, and frequent snoring.

^bAdjusted for maternal age and race/ethnicity.

^cAdjusted for maternal age, pre-pregnancy BMI, gestational weight gain, education, parity, gravidity, family history of diabetes, smoking, drinking, exercise, and employment status.

^dAdjusted for maternal age, height, family history of diabetes, parity, Han ethnicity, education, pre-pregnancy BMI, systolic blood pressure at first antenatal visit, multiple pregnancies, weight gain from pre-pregnancy to glucose challenge test, habitual smoking and alcohol consumption before/during pregnancy, and sleep quality.

^eAdjusted for maternal age, race/ethnicity, education, BMI at <14 weeks of gestation, history of GDM, and State-Trait Anxiety Inventory total score.

^fAdjusted for maternal age, gestational age, race/ethnicity, parity, education, pre-pregnancy BMI, marital status, family history of diabetes, and napping frequency in the second trimester.

^gAdjusted for early pregnancy BMI.

^hAdjusted for frequent snoring.

[†]OR or RR was calculated based on data presented in the original article.

Table 2

Sleep disordered breathing and risk of GDM

Study	No GDM (n)	GDM (n)	Measure	Unadjusted OR/RR (95% CI)	Adjusted OR/RR (95% CI)
Bourjeily et al., 2010 [57]	944	52	Loud snoring	OR = 2.7 (1.7 to 4.3)	OR = 2.1 (1.3 to 3.4) ^a
Facco et al., 2010 [28]	160	10	Frequent snoring	OR = 4.9 (1.3 to 18.1)	OR = 6.9 (1.4 to 33.9) ^b
Qiu et al., 2010 [29]	1192	66	Frequent snoring	RR = 2.03 (1.07 to 3.86) [†]	RR = 1.86 (0.88 to 3.94) ^c
Reutrakul et al., 2011 [26]	116	26	Frequent snoring Berlin positive	OR = 3.6 (1.5 to 8.8) [†] OR = 3.0 (1.2 to 7.4)	OR = 3.4 (1.3 to 8.8) ^d Not reported
Micheli et al., 2011 [58]	862	78	Frequent snoring [*]	OR = 1.97 (0.85 to 4.56) [†]	Not reported
Ugur et al., 2012 [59]	444	21	Frequent snoring	OR = 3.86 (1.54 to 9.71) [†]	Not reported
O'Brien et al., 2012 [42]	1075	203	Frequent snoring [*]	OR = 1.67 (1.10 to 2.52)	OR = 0.91 (0.55 to 1.49) ^e
Olivarez et al., 2011 [62]	165	55	Berlin positive or ESS score ≥ 10	OR = 1.00 (0.50 to 2.01) [†]	Not reported
Ko et al., 2013 [63]	276	10	Berlin positive	OR = 0.51 (0.11 to 2.47) [†]	Not reported
Chen et al., 2012 [64]	4746	167	OSA in patient database	OR = 1.45 (0.99 to 2.11)	OR = 1.63 (1.07 to 2.48) ^f
Louis et al., 2014 [65]	Not reported [*]	Not reported [*]	OSA in patient database	OR = 5.03 (4.50 to 5.62)	OR = 1.89 (1.67 to 2.14) ^g
Bin et al., 2016 [66]	596,626	39,601	Sleep apnea in patient database	RR = 1.30 (0.97 to 1.74)	RR = 1.09 (0.82 to 1.46) ^h
Spence et al., 2017 [67]	276,325	28,676	OSA in patient database	OR = 1.40 (0.93 to 2.10)	OR = 1.04 (0.65 to 1.65) ⁱ
Louis et al., 2012 [68]	144	17	AHI ≥ 5	OR = 1.70 (0.51 to 5.72) [†]	Not reported
Facco et al., 2014 [69]	39	18	AHI ≥ 15	OR = 4.6 (1.0 to 22.1)	OR = 3.6 (0.6 to 21.8) ^j
Facco et al., 2017 [45]	2,947	128	AHI ≥ 5	OR = 6.30 (3.77 to 10.53)	OR = 3.47 (1.95 to 6.19) ^k

^aAdjusted for maternal age, BMI at delivery, smoking, multifetal pregnancy

^bAdjusted for maternal age, race/ethnicity, BMI, and short sleep duration

^cAdjusted for maternal age and race/ethnicity

^dAdjusted for BMI

^eAdjusted for maternal age, race/ethnicity, pre-pregnancy BMI, weight gain, gravidity, smoking, education level, individual or family history of gestational hypertension or preeclampsia

^fAdjusted for maternal education, marital status, gestational hypertension, anemia, coronary heart disease, hyperlipidemia, obesity, geographic region, paternal age, infant's sex, and parity

^gAdjusted for maternal age, race/ethnicity, household income, multiple birth, tobacco, alcohol, and drug use, primary payer, rural/urban status, obesity, coronary heart disease, anemia, hyperlipidemia, hypothyroidism, disorders of the adrenal gland, pre-pregnancy hypertension (women with pre-pregnancy diabetes excluded)

^hAdjusted for maternal age, country of birth, smoking, obesity, parity, socioeconomic disadvantage

ⁱAdjusted for maternal age, race/ethnicity, multiple birth, hospital size, obesity

^jAdjusted for maternal age, pre-pregnancy BMI, race/ethnicity, chronic hypertension, twin gestation

^kAdjusted for maternal age, BMI, chronic hypertension; based on sleep screening in early pregnancy

[†]OR or RR was calculated based on data presented in the original article

^{*}OR is indicated for frequent snoring versus no snoring

*Data in the original article are reported as rates (GDM in 19.13% of patients with OSA; GDM in 4.51% of patients without OSA; based on 55,781,965 hospital discharges)

Figures and Legends

Fig. 1

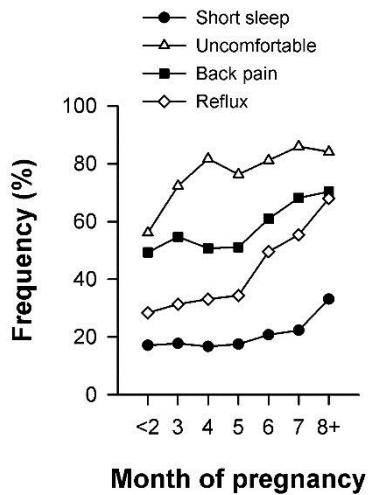


Fig. 1. Changes in the frequency of short sleep and sleep disturbances during pregnancy. The frequency of women who reported short total sleep (≤ 6 hours per day) increased during late pregnancy. Additionally, the frequency of women who reported disturbed sleep sometimes/often as a consequence of uncomfortable position, back pain, and reflux increased progressively across month of pregnancy. Data are plotted from results of an online survey published by Mindell et al., *Sleep Medicine*, 2014 [22].

Fig. 2

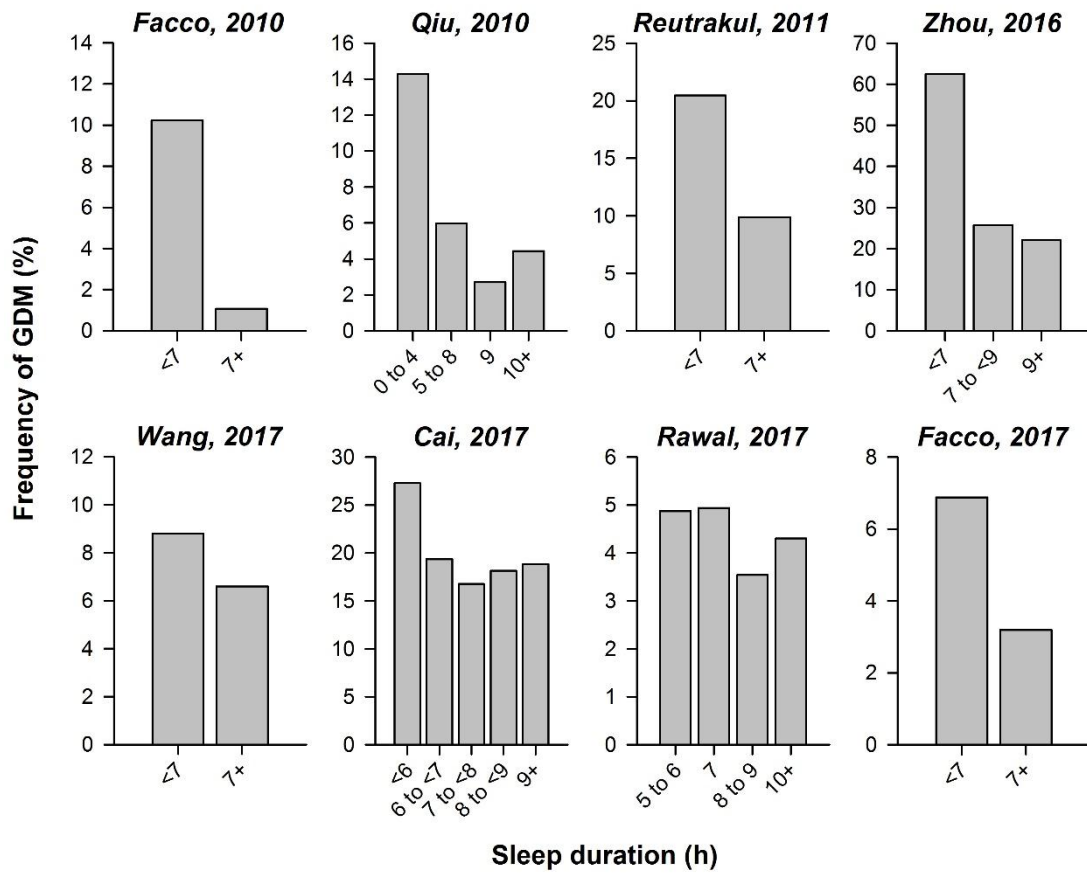


Fig. 2. Frequency of gestational diabetes mellitus (GDM) for women with different sleep durations. Data are plotted from several studies in which the frequency of GDM was reported for women grouped by different sleep durations [26, 28-34]. Across studies, the frequency of GDM was highest in women with shorter sleep durations. The lead author and year of publication are indicated above each plot.

Fig. 3

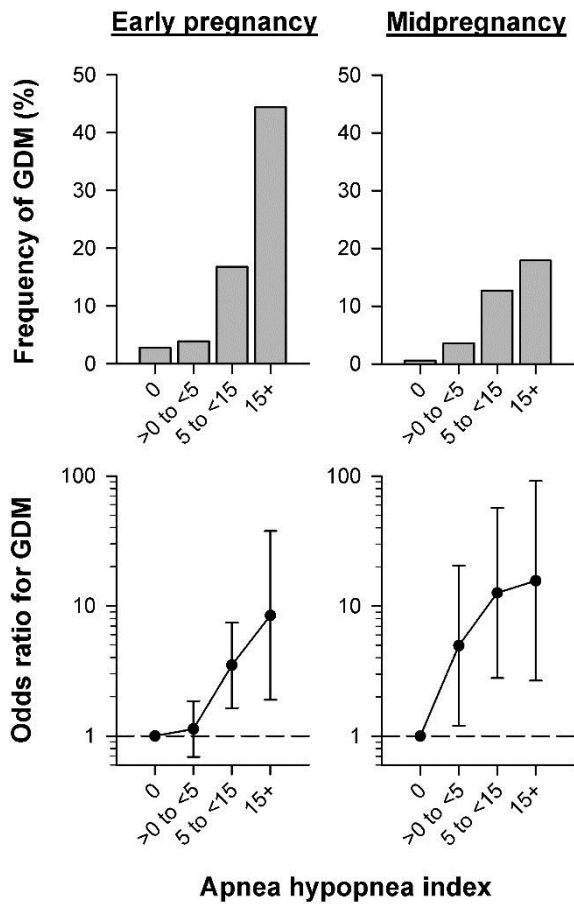


Fig. 3. Frequency and odds ratios for gestational diabetes mellitus (GDM) in women with different apnea hypopnea index (AHI) values. In a prospective cohort study, pregnant women underwent sleep-disordered breathing (SDB) assessments in early pregnancy and midpregnancy. The frequency of GDM increased with SDB severity at both time points. The adjusted odds ratio for GDM also increased with SDB severity, demonstrating an exposure-response relationship between AHI and GDM. Error bars indicate 95% confidence intervals. Data are plotted from results published by Facco et al., *Obstetrics & Gynecology*, 2017 [45].

Highlights

- Many pregnant women experience reduced sleep or sleep-disordered breathing.
- Growing evidence suggests that short sleep is associated with gestational diabetes.
- Sleep-disordered breathing may increase risk of gestational diabetes.
- Poor sleep during pregnancy may promote mechanisms linked with insulin resistance.
- Future studies should test if improving sleep reduces risk of gestational diabetes.

Accepted manuscript