Review article

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

Joshua J. Gooley⁎, Litali Mohapatra, Derek Chao Kuan Twan

Center for Cognitive Neuroscience, Program in Neuroscience and Behavioral Disorders, Duke-NUS Medical School, 8 College Road, Singapore 169857, Singapore

ARTICLE INFO

Keywords:
• Pregnancy
• Sleep duration
• Sleep disordered breathing
• Gestational diabetes
• Women
• Metabolism

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.

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 (Cappuccio et al., 2010; Holliday et al., 2013; Shan et al., 2015) or sleep-disordered breathing (SDB) (Marshall et al., 2009; Muraki et al., 2010) is associated with increased risk for developing type 2 diabetes. Experimentally-induced sleep restriction also results in decreased glucose tolerance and reduced insulin sensitivity (Killick et al., 2012). In gravid women, adaptations in glucose metabolism and pancreatic β-cell function result in a progressive increase in insulin resistance beginning near mid-pregnancy (Buchanan and Xiang, 2005). 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) (Reutrakul and Van Cauter, 2014), 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 (Catalano, 2010; Metzger et al., 2008). Additionally, women with GDM are more likely to develop type 2 diabetes and atherosclerosis later in life (Kim et al., 2002; Gunderson et al., 2014), and their offspring are at increased risk of becoming obese and developing type 2 diabetes (Clausen et al., 2008; Kim et al., 2012). With the increasing global health burden of GDM (Dabelea et al., 2005; Ferrara, 2007; Zhu and Zhang, 2016), 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.

⁎ Correspondence to: Duke-NUS Medical School, 8 College Road, Singapore 169857, Singapore. E-mail address: joshua.gooley@duke-nus.edu.sg (J.J. Gooley).

https://doi.org/10.1016/j.nbscr.2017.11.001
Received 3 August 2017; Received in revised form 17 November 2017; Accepted 17 November 2017
Available online 28 November 2017
2451-9944/ © 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).
Sleep duration and risk of GDM.

Table 1

| Study                     | No GDM (n) | GDM (n) | Comparison | Unadjusted OR/RR (95% CI) | Adjusted OR/RR (95% CI) |
|---------------------------|------------|---------|------------|---------------------------|------------------------|
| (Facco et al., 2010)      | 172        | 10      | < 7 h vs ≥ 7 h | OR = 10.6 (1.3 to 85.5)   | OR = 11.7 (1.2 to 114.5) |
| (Qiu et al., 2010)        | 258        | 10      | < 4 h vs 9 h  | RR = 5.24 (1.46 to 18.81) | RR = 5.56 (1.31 to 23.69) |
| (Rawal et al., 2017)      | 1569       | 63      | 5 to 6 h vs 8 to 9 h | RR = 5.56 (2.85 to 10.88) | RR = 5.46 (2.70 to 10.94) |
| (Cai et al., 2017)        | 11359      | 897     | ≥ 7 h vs ≤ 7 h | OR = 1.00 (0.98 to 1.02)  | OR = 1.00 (0.97 to 1.03)  |
| (Reutrakul et al., 2011)  | 555        | 131     | < 6 h vs ≥ 6 h | OR = 1.00 (0.99 to 1.02)  | OR = 1.00 (0.97 to 1.03)  |
| (Facco et al., 2010)      | 1698       | 70      | 7 h vs 8 to 9 h | RR = 2.01 (1.00 to 4.03)  | RR = 2.01 (1.00 to 4.03)  |
| (Rawal et al., 2017)      | 1554       | 60      | ≥ 10 h vs 8 to 9 h | RR = 1.63 (1.03 to 2.57)  | RR = 1.63 (1.03 to 2.57)  |

1 OR or RR was calculated based on data presented in the original article.
2 Adjusted for maternal age, race/ethnicity, pre-pregnancy BMI, and frequent snoring.
3 Adjusted for maternal age and race/ethnicity.
4 Adjusted for maternal age, pre-pregnancy BMI, gestational weight gain, education, parity, gravidity, family history of diabetes, smoking, drinking, exercise, and employment status.
5 Adjusted 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.
6 Adjusted 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.
7 Adjusted for early pregnancy BMI.
8 Adjusted for frequent snoring.
The non-fasting glucose challenge test (Herring et al., 2014; Reutrakul et al., 2011; Twedt et al., 2015), 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 (Facco et al., 2010), 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 h 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 1.2–114.5). In another study, that included 1,290 pregnant women recruited from clinics in Seattle (Qiu et al., 2010), 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 h, 5–8 h, 9 h, and ≥ 10 h). Women who reported ≤ 4 h 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 h 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 h of sleep per night was not associated with GDM (aRR = 4.18, 95% CI 0.94–18.60). Similar to these results, a Chicago-area study that included 169 women with a singleton pregnancy (26 GDM cases) found that exposure to < 7 h 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 1.0–5.9; P = 0.06) (Reutrakul et al., 2011).

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 (Zhou et al., 2016; Wang et al., 2017; Cai et al., 2017). In a study that included 542 pregnant women (136 GDM cases) recruited from clinics in Sichuan Province, China (Zhou et al., 2016), exposure to < 7 h of sleep per night in early pregnancy was associated with increased odds of GDM compared with women who reported 7 to < 9 h 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 h 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 (Wang et al., 2017). In that study, self-reported exposure to <7 h of sleep per day was not associated with GDM (aOR = 1.36, 95% CI 0.87–2.14), whereas exposure to ≥9 h of sleep per day was associated with increased odds of GDM compared with women who reported 7 to <9 h 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 (Cai et al., 2017). In this multi-ethnic cohort (Chinese, Malay, Indian), exposure to <6 h 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 (Rawal et al., 2017; Facco et al., 2017). As part of the Eunice Kennedy Shriver National Institute of Child Health and Human Development 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 (Rawal et al., 2017). Nocturnal sleep duration was reported across 4 different categories (5–6 h, 7 h, 8–9 h, and ≥10 h), 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 h 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 h of sleep per night in the second trimester, exposure to 5–6 h of sleep or 7 h of sleep was associated with about a 2-fold increase in risk of GDM (5–6 h, aRR = 2.52, 95% CI 1.27 to 4.99; 7 h, aRR = 2.01, 95% CI 1.09 to 3.68). Similarly, exposure to ≥10 h of sleep per night in non-obese women was associated with increased risk of GDM (aRR = 2.17, 95% CI 1.01–4.67).

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 (Facco et al., 2017). 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 (Reid et al., 2017). Exposure to <7 h 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 (Facco et al., 2010; Zhou et al., 2016; Cai et al., 2017; Rawal et al., 2017; Facco et al., 2017) (Table 1). Studies have included participants from diverse geographical regions and different ethnic groups, and applied different criteria for short sleep (≤4 h, <6 h, or <7 h) 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) (Agarwal, 2015). 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 h or ≥10 h) is associated with GDM (Wang et al., 2017; Rawal et al., 2017). 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 (Shan et al., 2015).

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 (Facco et al., 2017). 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 (Rawal et al., 2017), 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) (Izci Balsrak, 2015). 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 (Bourjeily et al., 2012). Body mass index (BMI) and change in neck...
circuitous are also significant predictors of apnea symptoms and PSG-diagnosed OSA (Pien et al., 2005; Pien et al., 2014), 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 (Reuterkul and Van Cauter, 2014; Reuterkul and Mokhlesi, 2017). 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 the frequency of habitual snoring increases from about 7–11% in the first trimester to about 16–25% in the third trimester (Facco et al., 2010; O’Brien et al., 2012; Sarberg et al., 2014). Symptoms of OSA, including loud snoring, snoring, gasping, and witnessed apneas, worsen significantly by 28–29 weeks of pregnancy and continue to increase in the third trimester (Pien et al., 2005). 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 ≥ 5) increased from about 11% to 27% across pregnancy (Pien et al., 2014). 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 (Facco et al., 2014). More recently, a large prospective study of more than 3,000 women found that the incidence of OSA (AHI ≥ 5) increased from 3.6% in early pregnancy to 8.3% in midpregnancy (Facco et al., 2017). 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 (Anothaisintawee et al., 2016; Nagayoshi et al., 2016). In addition, experimentally-induced sleep fragmentation (Stamatakis and Punjabi, 2010; Tasali et al., 2008; Herzog et al., 2013) or intermittent hypoxia during wakefulness results in reduced insulin sensitivity (Louis and Punjabi, 1985) and/or elevated plasma glucose levels (Newhouse et al., 2017). 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 (Luque-Fernandez et al., 2013; Ding et al., 2014; Pamidi et al., 2014). In a meta-analysis that included 6 studies with prospective or retrospective study designs (Luque-Fernandez et al., 2013), gravid women with SDB had a more than 3-fold increase in the pooled adjusted odds of GDM (pooled aOR = 3.06, 95% CI 1.89–4.96). 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 1.30–2.42) (Pamidi et al., 2014), 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 1.32–2.96) (Ding et al., 2014). In a secondary analysis that included only prospective studies, however, exposure to SDB was not associated with GDM (pooled OR = 1.20, 95% CI 0.93–1.53), and another meta-analysis that included 4 cohort studies did not find an association between OSA and GDM (pooled RR = 1.40, 95% CI 0.62–3.19) (Xu et al., 2014). 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

| Study | No GDM (n) | GDM (n) | Measure | Unadjusted OR/RR (95% CI) | Adjusted OR/RR (95% CI) |
|-------|------------|---------|---------|--------------------------|------------------------|
| (Bourjely et al., 2010) | 944 | 52 | Loud snoring | OR = 2.7 (1.7 to 4.3) | OR = 2.1 (1.3 to 3.4)* |
| (Facco et al., 2010) | 160 | 10 | Frequent snoring | OR = 4.9 (1.3 to 18.1) | OR = 6.9 (1.4 to 33.9)† |
| (Qi et al., 2010) | 1192 | 66 | Frequent snoring | RR = 2.03 (1.07 to 3.86) | RR = 1.86 (0.88 to 3.94)* |
| (Reuterkul et al., 2011) | 116 | 26 | Frequent snoring | OR = 3.6 (1.5 to 8.8) | OR = 3.4 (1.3 to 8.8)‡ |
| (Micheli et al., 2011) | 862 | 78 | Frequent snoring | OR = 1.97 (0.85 to 4.56) | Not reported |
| (Ugur et al., 2012) | 444 | 21 | Frequent snoring | OR = 3.86 (1.54 to 9.71) | Not reported |
| (O’Brien et al., 2012) | 1075 | 203 | Frequent snoring | OR = 1.67 (1.10 to 2.52) | OR = 0.91 (0.55 to 1.49)* |
| (Oliveirez et al., 2011) | 165 | 55 | Berlin positive or ESS score ≥ 10 | OR = 1.00 (0.50 to 2.01) | Not reported |
| (Io et al., 2013) | 276 | 10 | Berlin positive | OR = 0.51 (0.11 to 2.47) | Not reported |
| (Chen et al., 2011) | 4746 | 167 | OSA in patient database | OR = 1.45 (0.99 to 2.11) | OR = 1.63 (1.07 to 2.48)‡ |
| (Louis et al., 2014) | Not reported | Not reported | OSA in patient database | OR = 5.03 (4.50 to 5.62) | OR = 1.89 (1.67 to 2.14)‡ |
| (Bin et al., 2016) | 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)* |
| (Spence et al., 2017) | 276,325 | 28,676 | OSA in patient database | OR = 1.40 (0.93 to 2.10) | OR = 1.04 (0.65 to 1.65) |
| (Louis et al., 2012) | 144 | 17 | AHl ≥ 5 | OR = 1.70 (0.51 to 5.72) | Not reported |
| (Facco et al., 2014) | 39 | 18 | AHl ≥ 15 | OR = 4.6 (1.0 to 22.1) | OR = 3.6 (0.6 to 21.8)* |
| (Facco et al., 2017) | 2,947 | 128 | AHl ≥ 5 | OR = 6.30 (3.77 to 10.53) | OR = 3.47 (1.95 to 6.19)* |

* 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).
* Adjusted for maternal age, BMI, chronic hypertension; based on sleep screening in early pregnancy.
‡ Adjusted for maternal age, race/ethnicity, BMI, and short sleep duration.
‡‡ Adjusted for maternal age and race/ethnicity.
§ Adjusted for BMI.
## Adjusted for maternal age, race/ethnicity, pre-pregnancy BMI, weight gain, gravidity, smoking, education level, individual or family history of gestational hypertension or pre-eclampsia.
# Adjusted for maternal education, marital status, gestational hypertension, anemia, coronary heart disease, hyperlipidemia, obesity, geographic region, paternal age, infant’s sex, and parity.
* Adjusted for maternal age, race/ethnicity, household income, multiple birth, tobacco, alcohol, and drug use, primary payer insurance, rural/urban status, obesity, coronary heart disease, anemia, hyperlipidemia, hypothyroidism, disorders of the adrenal gland, pre-pregnancy hypertension (women with pre-pregnancy diabetes excluded).
** Adjusted for maternal age, country of birth, smoking, obesity, parity, socioeconomic disadvantage.
†† Adjusted for maternal age, race/ethnicity, multiple birth, hospital size, smoking, obesity.
‡‡‡ Adjusted for maternal age, pre-pregnancy BMI, race/ethnicity, chronic hypertension, twin gestation.
‡‡‡‡ Adjusted for maternal age, BMI, chronic hypertension; based on sleep screening in early pregnancy.
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) (Reutrakul et al., 2011; Facco et al., 2010; Qiu et al., 2010; O’Brien et al., 2012; Bourjeily et al., 2010; Micheli et al., 2011; Ugur et al., 2012). Of the 5 studies that adjusted for BMI (with ≥10 GDM cases), 3 studies found that exposure to loud/frequent snoring associated with GDM (Reutrakul et al., 2011; Facco et al., 2010; Bourjeily et al., 2010). The first of these studies (Bourjeily et al., 2010) used a cross-sectional study design in which 996 women (52 GDM cases) completed the Multivariable Apnea Prediction Index (Maislin et al., 1995) 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 (Facco et al., 2010). 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 (Reutrakul et al., 2011), 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 (Qiu et al., 2010; O’Brien et al., 2012). In a study that included 1,290 women (68 GDM cases) (Qiu et al., 2010), 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 (O’Brien et al., 2012). 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 0.72–1.39).

Associations between SDB and GDM have also been examined using the Berlin Questionnaire (Netzer et al., 1999), 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%) (Reutrakul et al., 2011). 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) (Olivarez et al., 2011), 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) (Ko et al., 2013). 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 (Chen et al., 2012). 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 (Louis et al., 2014), 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 (Binn et al., 2016). 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 0.82-1.46). 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 (Spence et al., 2017). 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 mid-pregnancy) (Facco et al., 2017), 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 (Louis et al., 2012), 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 (Facco et al., 2014), 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 (Izci Balserak et al., 2013), 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 0.83–1.28).

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 (Facco et al., 2017), 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 1.95–6.19). 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 1.64–7.44), 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 1.63–4.77), 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 (Luque-Fernandez et al., 2013; Ding et al., 2014; Pamidi et al., 2014; Xu et al., 2014), 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 (Facco et al., 2017). In this study, it was found that AHI in either early pregnancy 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 (O’Brien et al., 2012). 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 (Neutrausk and Van Cauter, 2014; Okun et al., 2009; O’Keeffe and St-Onge, 2013). 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 (Izci Balserak, 2015; Okun and Coussons-Read, 2007). 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 (Wieser et al., 2013). In non-pregnant adults, exposure to sleep restriction results in increased expression of genes in blood associated with oxidative stress (Moller-Levet et al., 2013). Similarly, OSA is
associated with increased markers of oxidative stress and reduced anti-oxidant activity (Christou et al., 2003). 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 (Fialova et al., 2006). However, the concentration of advanced oxidation protein products is higher in women with GDM compared with women with normal glucose tolerance (Karacay et al., 2010), 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) (Espósito et al., 2002). 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 (Mullington et al., 2010), as evidenced by elevated levels of IL-6, TNF-α, and C-reactive protein (CRP) (Meier-Ewert et al., 2004; Vgontzas et al., 2004; Haack et al., 2007; Irwin et al., 2006). By comparison, sleep deprivation results in reduced levels of leptin, an adipokine critical in appetite regulation and energy balance, that is associated with pro-inflammatory immune responses (Spiegel et al., 2004). Normal pregnancy is associated with increased levels of TNF-α, CRP, and leptin (Okun and Coussons-Read, 2007; Kirwan et al., 2002), and levels of TNF-α and leptin correlate inversely with insulin sensitivity (Kirwan et al., 2002; McLachlan et al., 2006). In women with GDM, 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 (Xu et al., 2014). Additionally, levels of adinoinpectin, 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 (Okun et al., 2007). 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 (Retnakaran et al., 2003; Winkler et al., 2002).

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 (Chun et al., 2012), sleep restriction (Spiegel et al., 2004; Spiegel et al., 1999), or experimentally-induced suppression of slow-wave sleep (Tasali et al., 2008). In non-pregnant adults, exposure to sleep restriction has also been shown to result in increased levels of norepinephrine and epinephrine (Nedeltcheva et al., 2009; Irwin et al., 1999). SDB is likewise associated with increased sympathetic activity and catecholamine levels (Reutrakul and Mokhlesi, 2017). 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 (Poyhonen-Alho et al., 2010). 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 (O’Keefe and St-Onge, 2013). In contrast, it is well established that cortisol secretion increases markedly in gravid women (Kirwan et al., 2002). 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 (Rizza et al., 1982). Sleep disturbances during pregnancy could also act as a stressor and contribute to increased sympathetic activity and cortisol secretion (Palagini et al., 2014). 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

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 (Leproul et al., 2015; Killick et al., 2015). 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 (Ferraro et al., 2014), 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 (van Straten et al., 2017; Seyffert et al., 2016), or mindfulness-based training, which has been implemented to improve sleep and reduce psychological stress (Garland et al., 2016). 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.

6. 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 postprandial glucose responses and minimizing risk of GDM.

Conflict of Interest

The authors have no conflicts of interest or financial relationships to disclose.

Funding

This work was supported by the Ministry of Education, Singapore (MOE2015-T2-2-077); and the Far East Organization. The study sponsors were not involved in the study design; data collection, analyses, and interpretation; the writing of the report; or in the decision to submit the article for publication.

References

Agarwal, M.M., 2015. Gestational diabetes mellitus: an update on the current interna- tional diagnostic criteria. World J. Diabetes 6, 782-791.
Anothaisintawee, T., Reutrakul, S., Van Caster, E., Thakkinstian, A., 2016. Sleep dis- turbances compared to traditional risk factors for diabetes development: systematic
review and meta-analysis. Sleep Med. Rev. 30, 11–24.

Bin, Y.S., Cistulli, P.A., Ford, J.B., 2016. Population-Based Study of Sleep Apnea in Pregnancy and Maternal and Infant Outcomes. J. Clin. Med. 2012, 871–877.

Bourjey, G., Raker, C., Chahlouh, M., Miller, M., 2010. Pregnancy and fetal outcomes of sleep apnea syndrome: a meta-analysis of observational studies. J. Obstet. Gynaecol. 30, 449–455.

Bourjey, G., Barbara, N., Larson, L., He, M., 2012. Clinical manifestations of obstructive sleep apnoea in pregnancy: more than snoring and witnessed apnoeas. J. Obstet. Gynaecol. J. Inst. Obstet. Gynaecol. 32, 434–438.

Buchanan, T.A., Xiang, A.H., 2005. Gestational diabetes mellitus. J. Clin. Invest. 115, 485–491.

Cai, S., Tan, S., Gluckman, P.D., Godfrey, K.M., Saw, S.M., Teoh, O.H., et al., 2017. Sleep quality and nocturnal sleep duration in pregnancy and risk of gestational diabetes mellitus. Sleep 40.

Cappuccio, F.P., D’Elia, L., Strazzullo, P., Miller, M.A., 2010. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care 33, 414–20.

Catalano, P.M., 2010. The impact of gestational diabetes and maternal obesity on the mother and her offspring. Dev. Orig. Health Dis. 1, 208–215.

Chen, Y.H., Kang, J.H., Lin, C.C., Wang, I.T., Keller, J.J., Lin, H.C., 2012. Obstructive sleep apnea and the risk of adverse pregnancy outcomes. Am. J. Obstet. Gynecol. 206 (136), e1–e5.

Christou, K., Moulas, A.N., Pastaka, C., Gourgoulianis, K.I., 2006. Sleep hygiene for a healthy pregnancy: a brief review. ISRN Fam. Med. 928293.

Chua, E.C., Tan, W.Q., Yeo, S.C., Lau, P., Lee, I., Mien, I.H., et al., 2012. Heart rate variability can be used to estimate sleepiness-related decrements in psychomotor vigilance during total sleep deprivation. Sleep 35, 325–334.

Catalano, P.M., 2010. The impact of gestational diabetes and maternal obesity on the mother and her offspring. Dev. Orig. Health Dis. 1, 208–215.

Chen, Y.H., Kang, J.H., Lin, C.C., Wang, I.T., Keller, J.J., Lin, H.C., 2012. Obstructive sleep apnea and the risk of adverse pregnancy outcomes. Am. J. Obstet. Gynecol. 206 (136), e1–e5.

Chua, E.C., Tan, W.Q., Yeo, S.C., Lau, P., Lee, I., Mien, I.H., et al., 2012. Heart rate variability can be used to estimate sleepiness-related decrements in psychomotor vigilance during total sleep deprivation. Sleep 35, 325–334.

Catalano, P.M., 2010. The impact of gestational diabetes and maternal obesity on the mother and her offspring. Dev. Orig. Health Dis. 1, 208–215.

Chen, Y.H., Kang, J.H., Lin, C.C., Wang, I.T., Keller, J.J., Lin, H.C., 2012. Obstructive sleep apnea and the risk of adverse pregnancy outcomes. Am. J. Obstet. Gynecol. 206 (136), e1–e5.

Christou, K., Moulas, A.N., Pastaka, C., Gourgoulianis, K.I., 2006. Sleep hygiene for a healthy pregnancy: a brief review. ISRN Fam. Med. 928293.

Chua, E.C., Tan, W.Q., Yeo, S.C., Lau, P., Lee, I., Mien, I.H., et al., 2012. Heart rate variability can be used to estimate sleepiness-related decrements in psychomotor vigilance during total sleep deprivation. Sleep 35, 325–334.

Catalano, P.M., 2010. The impact of gestational diabetes and maternal obesity on the mother and her offspring. Dev. Orig. Health Dis. 1, 208–215.

Chen, Y.H., Kang, J.H., Lin, C.C., Wang, I.T., Keller, J.J., Lin, H.C., 2012. Obstructive sleep apnea and the risk of adverse pregnancy outcomes. Am. J. Obstet. Gynecol. 206 (136), e1–e5.

Chua, E.C., Tan, W.Q., Yeo, S.C., Lau, P., Lee, I., Mien, I.H., et al., 2012. Heart rate variability can be used to estimate sleepiness-related decrements in psychomotor vigilance during total sleep deprivation. Sleep 35, 325–334.

Catalano, P.M., 2010. The impact of gestational diabetes and maternal obesity on the mother and her offspring. Dev. Orig. Health Dis. 1, 208–215.

Chen, Y.H., Kang, J.H., Lin, C.C., Wang, I.T., Keller, J.J., Lin, H.C., 2012. Obstructive sleep apnea and the risk of adverse pregnancy outcomes. Am. J. Obstet. Gynecol. 206 (136), e1–e5.

Chua, E.C., Tan, W.Q., Yeo, S.C., Lau, P., Lee, I., Mien, I.H., et al., 2012. Heart rate variability can be used to estimate sleepiness-related decrements in psychomotor vigilance during total sleep deprivation. Sleep 35, 325–334.

Catalano, P.M., 2010. The impact of gestational diabetes and maternal obesity on the mother and her offspring. Dev. Orig. Health Dis. 1, 208–215.

Chen, Y.H., Kang, J.H., Lin, C.C., Wang, I.T., Keller, J.J., Lin, H.C., 2012. Obstructive sleep apnea and the risk of adverse pregnancy outcomes. Am. J. Obstet. Gynecol. 206 (136), e1–e5.

Chua, E.C., Tan, W.Q., Yeo, S.C., Lau, P., Lee, I., Mien, I.H., et al., 2012. Heart rate variability can be used to estimate sleepiness-related decrements in psychomotor vigilance during total sleep deprivation. Sleep 35, 325–334.

Catalano, P.M., 2010. The impact of gestational diabetes and maternal obesity on the mother and her offspring. Dev. Orig. Health Dis. 1, 208–215.

Chen, Y.H., Kang, J.H., Lin, C.C., Wang, I.T., Keller, J.J., Lin, H.C., 2012. Obstructive sleep apnea and the risk of adverse pregnancy outcomes. Am. J. Obstet. Gynecol. 206 (136), e1–e5.

Chua, E.C., Tan, W.Q., Yeo, S.C., Lau, P., Lee, I., Mien, I.H., et al., 2012. Heart rate variability can be used to estimate sleepiness-related decrements in psychomotor vigilance during total sleep deprivation. Sleep 35, 325–334.
Netzer, N.C., Strohs, R.A., Netzer, C.M., Clark, K., Strohl, K.P., 1999. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann. Intern. Med. 131, 485–491.

Newhouse, L.P., Joyner, M.J., Carr, T.R., Laurenti, M.C., Man, C.D., Cobelli, C., et al., 2017. Three hours of intermittent hypoxia increases circulating glucose levels in healthy adults. Physiol. Rep. 5.

O’Brien, L.M., Bullough, A.S., Owusu, J.T., Tremblay, K.A., Brincat, C.A., Chemes, M.C., et al., 2012. Pregnancy-onset habitual snoring, gestational hypertension, and pre-eclampsia: prospective cohort study. Am. J Obstet. Gynecol. 207 (487), e1–e9.

O’Keefe, M., St-Onge, M.P., 2013. Sleep duration and disorders in pregnancy: implications for glucose metabolism and pregnancy outcomes. Int. J. Obes. 37, 765–770.

Okun, M.L., Coussons-Read, M.E., 2007. Sleep disruption during pregnancy: how does it influence serum cytokines? J. Reprod. Immunol. 73, 158–165.

Okun, M.L., Hall, M., Coussons-Read, M.E., 2007. Sleep disturbances increase interleukin-6 production during pregnancy: implications for pregnancy complications. Reprod. Sci. 14, 560–567.

Okun, M.L., Roberts, J.M., Marsland, A.L., Hall, M., 2009. How disturbed sleep may be a risk factor for adverse pregnancy outcomes. Obstet. Gynecol. Surv. 64, 273–280.

Olivarez, S.A., Ferres, M., Antony, K., Matteval, A., Maheshwari, B., Sangi-Haghpeykar, H., et al., 2011. Obstructive sleep apnea screening in pregnancy, perinatal outcomes, and impact of maternal obesity. Am. J. Perinatol. 28, 651–658.

Palagini, L., Gemignani, A., Banti, S., Manconi, M., Mauri, M., Riemann, D., 2014. Chronic sleep loss during pregnancy as a determinant of stress: impact on pregnancy outcome. Sleep Med. 15, 853–859.

Pamidi, S., Pinto, L.M., Marc, I., Benedetti, A., Schwartzman, K., Kimoff, R.J., 2014. Maternal sleep-disordered breathing and adverse pregnancy outcomes: a systematic review and metaanalysis. Am. J. Obstet. Gynecol. 210 (52), e1–e14.

Pien, G.W., Fie, D., Pack, A.J., Nikwou, J.E., Schwab, R.J., 2005. Changes in symptoms of sleep-disordered breathing during pregnancy. Sleep 28, 1299–1305.

Pien, G.W., Pack, A.J., Jackson, N., Maislin, G., Macones, G.A., Schwab, R.J., 2014. Risk factors for sleep-disordered breathing in pregnancy. Thorax. 69, 371–377.

Poyhonen-Alho, M., Viitasalo, M., Nicholls, M.G., Lindstrom, R.M., Vaananen, H., Kaaja, R., 2010. Imbalance of the autonomic nervous system at night in women with gestational diabetes. Diabet. Med. 27, 988–994.

Qiu, C., Enquobahrie, D., Frederick, I.O., Abetew, D., Williams, M.A., 2010. Glucose intolerance and gestational diabetes risk in relation to sleep duration and snoring during pregnancy: a pilot study. BMC Women’s Health 10, 17.

Rawal, S., Hinkle, S.N., Zhu, Y., Albert, P.S., Zhang, C., 2017. A longitudinal study of sleep duration in pregnancy and subsequent risk of gestational diabetes: findings from a prospective, multiracial cohort. Am. J. Obstet. Gynecol. 216 (399), e1–e8.

Reid, K.J., Facco, F.L., Grobman, W.A., Parker, C.B., Herbas, M., Hunter, S., et al., 2017. Sleep during pregnancy: the mUMoM2b pregnancy and sleep duration and continuity study. Sleep 40 zsx045.

Retnakaran, R., Hanley, A.J., Raif, N., Connelly, P.W., Sermer, M., Zinman, B., 2003. C-Reactive protein and gestational diabetes mellitus in pregnant Chinese women. Diabet. Med. 20, 968–973.

Rizza, R.A., Mandarino, L.J., Gerich, J.E., 1982. Cortisol-induced insulin resistance in man: impaired suppression of glucose production and stimulation of glucose utilization due to a postreceptor defect of insulin action. J. Clin. Endocrinol. Metab. 54, 131–138.

Sarberg, M., Svanborg, E., Wirhuhn, A.B., Josefsson, A., 2014. Snoring during pregnancy and its relation to sleepiness and pregnancy outcome - a prospective study. BMC Pregnancy Childbirth 14, 15.

Schweiger, M.S., 1972. Sleep disturbance in pregnancy. A subjective survey. Am. J Obstet. Gynecol. 114, 879–882.

Seifert, M., Lagatsky, P., Landgraf, J., Chopra, V., Pfeifer, P.N., Conte, M.L., et al., 2016. Internet-Delivered Cognitive Behavioral Therapy to Treat Insomnia: a Systematic Review and Meta-Analysis. PLoS One 11, e0149139.

Shan, Z., Ma, H., Xie, M., Yan, P., Guo, Y., Yao, B., et al., 2015. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. Diabetes Care 38, 529–537.

Spence, D.L., Allen, R.C., Lustigendorf, M.A., Gary, V.R., Richard, J.D., Gonzalez, S.C., et al., 2017. Association of obstructive sleep apnea with adverse pregnancy-related outcomes in military hospitals. Eur. J. Obstet. Gynecol. Reprod. Biol. 210, 166–172.

Spiegel, K., Leproult, R., Van Cauter, E., 1999. Impact of sleep debt on metabolic and endocrine function. Lancet 354, 1435–1439.

Spiegel, K., Leproult, R., L’Hermitte-Baleriaux, M., Copinschi, G., Penev, P.D., Van Cauter, E., 2004. Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. J. Clin. Endocrinol. Metab. 89, 5762–5771.

Stamatakis, K.A., Punjabi, N.M., 2010. Effects of sleep fragmentation on glucose metabolism in normal subjects. Chest 137, 95–101.

Taslasi, E., Leproult, R., Ehrmann, D.A., Van Cauter, E., 2008. Slow-wave sleep and the risk of type 2 diabetes in humans. Proc. Natl. Acad. Sci. USA 105, 1044–1049.

Todri, R., Bradley, M., Deuseroth, D., Althouse, A., Facco, F., 2015. Sleep Duration and Blood Glucose Control in Women With Gestational Diabetes Mellitus. Obstet. Gynecol. 126, 326–331.

Ugur, M.G., Boyukalin, K., Atak, Z., Ustuner, I., Atakan, R., Baykal, C., 2012. Sleep disturbances in pregnant patients and the relation to obstetric outcome. Clin. Exp. Obstet. Gynecol. 39, 214–217.

van Straten, A., van der Zoe, T., Kleiboer, A., Cuijpers, P., Morin, C.M., Lancee, J., 2017. Cognitive and behavioral therapies in the treatment of insomnia: a meta-analysis. Sleep. Med. Rev Epub ahead of print.

Vgontzas, A.N., Zoumakis, E., Bixler, E.O., Lin, H.M., Follett, H., Kales, A., et al., 2004. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. J. Clin. Endocrinol. Metab. 89, 2119–2126.

Wang, H., Leng, J., Li, W., Wang, L., Zhang, C., Li, W., et al., 2017. Sleep duration and quality, and risk of gestational diabetes mellitus in pregnant Chinese women. Diabet. Med. 34, 44–50.

Wiester, V., Moschen, A.R., Tilg, H., 2013. Inflammation, cytokines and insulin resistance: a clinical perspective. Arch. Immunol. Ther. Exp. 61, 119–125.

Winkler, G., Caeb, K., Baranyi, E., Melczer, Z., Speer, G., Hajos, P., et al., 2002. Tumor necrosis factor-alpha, leptin and adiponectin in gestational diabetes mellitus: a systematic review and meta-analysis. PLoS One 11, e0149139.

Xu, J., Zhao, Y.H., Chen, Y.P., Yuan, X.L., Wang, J., Zhu, H., et al., 2014. Maternal circulating concentrations of tumor necrosis factor-alpha, leptin, and adiponectin in gestational diabetes mellitus: a systematic review and meta-analysis. Sci. World J. 2014 926932.

Xu, T., Feng, Y., Peng, H., Guo, D., Li, T., 2014. Obstructive sleep apnea and the risk of perinatal outcomes: a meta-analysis of cohort studies. Sci. Rep. 4, 6982.

Zhou, F.M., Yang, L.Q., Zhao, R.P., Liu, D., Li, R., Wang, Y., et al., 2016. [Effect of Sleep in Early Pregnancy on Gestational Diabetes: a Prospective Study]. J. Sichuan Da Xue Xue Bao Yi Xue Ban 47, 964–968.

Zhu, Y., Zhang, C., 2016. Prevalence of Gestational Diabetes and Risk of Progression to Type 2 Diabetes: a Global Perspective. Curr. Diabetes Rep. 16, 7.