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ORIGINAL RESEARCH

Sleep Disturbances Before Pregnancy and Subsequent Risk of Gestational Diabetes Mellitus

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Purpose: To investigate the relationship between sleep disturbances before pregnancy and the subsequent risk for gestational diabetes mellitus (GDM).

Patients and Methods: Pregnant women who attended antenatal clinic before the 12th gestational week between September 2019 and June 2020 were enrolled. The sleep status at the month before the last menstrual period was collected by filling the Pittsburgh Sleep Quality Index (PSQI) and Berlin Questionnaire (BQ) to evaluate the sleep duration, quality and the risk of obstructive sleep apnea (OSA). With monthly antenatal care, the oral glucose tolerance test (OGTT) was performed during 24–28 gestational weeks. According to the results, GDM and non-GDM group were classified. The sleep status and baseline characters were compared between the two groups.

Results: A total of 355 pregnant women were enrolled in this study, and 63 of them (17.7%) were diagnosed with GDM. Univariate analysis showed that maternal age, body mass index (BMI), family history of diabetes, PSQI score and positive BQ were associated with GDM ($p < 0.05$). Maternal age (aOR 1.10, 95% CI, 1.01–1.17), BMI before pregnancy (aOR 1.12, 95% CI, 1.02–1.23), family history of diabetes (aOR 2.35, 95% CI, 1.33–4.17), positive BQ (aOR 4.03, 95% CI, 1.04–15.63) were independent risk factors for GDM in multivariate analysis. The decision tree indicated that among the pregnant women with BMI >20.6 kg/m^2 and age >28.5, the risk for GDM with positive BQ increased from 27.5% to 66.7%.

Conclusion: The high risk of OSA before pregnancy may increase the risk for GDM during pregnancy.

Keywords: sleep, gestational diabetes mellitus, obstructive sleep apnea, women

Introduction

Gestational diabetes mellitus (GDM) refers to any degree of hyperglycaemia with onset or first detection during pregnancy, which is the most common pregnancy-related disease.[1,2] The documented prevalence of GDM varies substantially worldwide, ranging from 1% to >30%.[1] And the incidence of GDM in mainland China is 14.8%.[2] Advanced age, obesity, and family history of diabetes and other factors have been identified as high-risk factors for GDM.[2,3] Complications of GDM include obesity and cardiovascular disease for both mothers and their offspring.[4–7] Sleep is an important part of a human's life; its functions are very complicated and different sleep disturbances have mutual influences. The sleep deficiency problems are more common with modern lifestyle, such as longer work hours, increased dependence on technology, and increased incidence of depression.[8–10] The prevalence of sleep disturbances in women is 17.7% to 25.1%.[11] Sleep disturbances mainly include insomnia, sleep-related breathing disorders, hypersomnia etc.[12]

The relationship between the sleep disturbances and GDM has been attracting growing attention. Most of the studies focus on the effect of sleep status in the first and second trimester during pregnancy on GDM, and the conclusion is still

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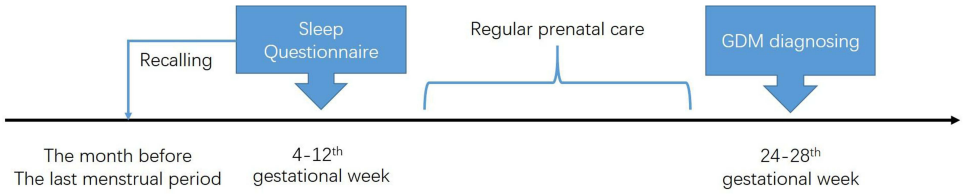
Graphical Abstract



The high risk of OSA before preganancy may increase the risk for GDM during pregnancy

controversial.[13–16] Studies have found that improving life behaviors before pregnancy,[17–19] including regular exercise and folic acid supplementation, can reduce the occurrence of GDM. As an important part of life behavior, there is limited recognition on the relationship between the pre-pregnancy sleep status and GDM.[20,21] Intervention for sleep disturbances require a certain process. For pregnant women, no matter sleep disturbances are related to GDM in which stage, the time for reducing the occurrence of GDM by providing sleep improvement is very limited. Furthermore, most researches on the relationship between sleep distributions and GDM only focus on one or two dimensions, such as sleep duration, sleep quality, or OSA. Therefore, the aim of this study was to explore whether sleep disturbances before pregnancy such as short sleep duration, poor sleep quality, and high risk for OSA are risk factors for the subsequent occurrence of GDM during pregnancy.

Materials and Methods

This study was a case-control analysis. We invited the pregnant women during the first trimester who visited the prenatal clinic to participate in our cohort between September 1, 2019, and June 10, 2020 in Peking University Third Hospital, Beijing, China. The pre-pregnancy sleep status was collected at the same time, which was recalled by participants for the sleep status during the month before the first day of the last menstrual period. After the first clinic visited, all pregnant women undergo regular prenatal care for each month. During the second trimester, based on whether GDM was diagnosed, women were divided into two groups, GDM group and non-GDM group. The sleep disturbances before pregnancy were compared between the two groups. Inclusion criteria were as following: (1) age ≥18 years; (2) women did not complicate with one of the following diseases: diabetes, hyperadrenocorticism, functional pituitary adenoma, or pheochromocytoma. (3) women without history of anxiety or depression. Exclusion criteria were as following: (1) incomplete sleep questionnaire; (2) spontaneous abortion before 24 weeks of gestation; (3) lack of oral glucose tolerance test (OGTT) results. (4) Blood glucose results within first antenatal care meet the diagnostic criteria of IGT or pGDM.[22] All investigated participants took an electronic questionnaire in Chinese at the beginning of the study by scanning the Quick Response code, which took approximately 10–15 min to complete the questionnaire by themselves. On the first page of the electronic questionnaire, pregnant women would sign the informed consent forms if they agree to participate in this study. Then, they were asked to fill in the sleep status for the month before the first day of the last menstrual period and the baseline information, as shown in Supplementary Material A. The 75-g OGTT was performed at 24–28 gestational weeks for diagnosing GDM, which was defined by any one of the following abnormal levels of blood glucose: fasting ≥5.1 mmol/L, 1-hour ≥10.0 mmol/L, or 2-hour ≥8.5 mmol/L.[23] Women with normal OGTT results were defined as non-GDM group. This study was proved by the Ethics Review Committee of Peking University Third Hospital (No.2019-319-01), which is also in accordance with The Code of Ethics of the World Medical Association for experiments involving humans. All participants signed the informed consent forms.

Baseline characteristics including maternal age, gestational weeks at enrollment, height, weight before pregnancy, medical history of parity, hyperthyroidism, repeated vulvovaginal candidiasis,[24] oligomenorrhea,[24] spontaneous abortion, family history of diabetes and hypertension, income, and frequent overtime work were collected through the

questionnaire. Body mass index (BMI) = weight/squared body height (kg/m2). Frequent overtime work was identified as average overtime work ≥3 times per week.

The status of sleep included sleep duration, sleep quality and the risk of OSA as follows. "The month before pregnancy" refers to "the month before the last menstruation", which is indicated in each question in the questionnaire. (1) Sleep duration: Assessment of sleep duration contained nighttime sleep and daytime nap. The nighttime sleep duration was obtained through the fourth question in the Pittsburgh Sleep Quality Index (PSQI) scale,[25] which was "One month before pregnancy, how many hours of actual sleep did you get at night?" Nighttime sleep duration was divided into <7 h, 7–9 h, and ≥9 h. In order to explore the situation of daytime nap, according to previous literature reports,[26] we set up two questions in addition to the PSQI scale[25] and Berlin questionnaire (BQ).[27]. The first question is about the frequency of daytime nap, "how many times do you take naps during the day before pregnancy?" with the answer options included "no nap," "1–2 days per week," and "≥3 days per week." Another question is about daytime nap duration, "how many minutes do you usually nap during the day in the month before pregnancy?", and the answer was classified into "no nap," "≤60 min," and ">60 min." (2) Sleep quality was evaluated by PSQI scale.[25] PSQI with a maximum score of 21 points was used to measure the sleep quality. The score represents the sum of the scores of all the aspects including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, the use of sleep medications, and daytime dysfunction. According to previous studies, pregnancy women with PSQI score ≤5 points indicated good sleep quality and >5 points indicated poor sleep quality. Compared with objective research, PSQI has a diagnostic sensitivity of 89.6% and a specificity of 86.5% in differentiating between good and poor sleepers.[25] (3) The risk for OSA was assessed by BQ.[27] BQ was used to screen for risk of OSA. The BQ consists of ten questions in three categories. The first category consists of four questions about snoring. The second category consists of three questions on waketime sleepiness or fatigue. The third category has two questions on history of obesity or hypertension. Patients with significant symptoms in any two of these three categories were defined as positive BQ. The sensitivity and specificity of positive BQ for diagnosing OSA were 86.0% and 77.0%, respectively.[27] Both PSQI scale and BQ were from the Chinese versions of the original literature.[28,29]

Statistical analysis was performed by Statistical Product and Service Solutions for Windows (SPSS V22.0). Normally distributed data were reported as mean ± standard deviation, and a *t*-test was used for comparison between the GDM and non-GDM groups. In contrast, the variables that were not normally distributed were expressed as median (25% and 75% percentiles) and the Wilcoxon test was used for comparison. Categorical variables were expressed by frequency (n) and percentage (%), and the Chi-square test or Fisher exact test was used for comparison as deemed appropriate. Multivariate analysis was performed by binary logistic regression to assess the relationship between sleep disturbances and GDM. All variables with p-value <0.1, as covariates variables, were included in the logistic regression model. Multicollinearity diagnosis was conducted to detect multicollinearity among the independent variables. Values of variance inflation factors (VIF) exceeding 10 were regarded as indicating multicollinearity, and it can be included in the multivariate regression model only when there is no multicollinearity. The backward elimination method was used when fitting the logistic regression model. Interaction between age, BMI, sleep duration, and sleep quality, respectively, and BQ outcome were also tested by the logistic regression analysis. Two-sided p-value <0.05 was considered as statistically significant. Additionally, we built a decision tree to assess GDM incidence in different subgroups and to find out relevant risk factors and cut-points. The Classification and Regression Trees (CART) algorithm was used to build the decision tree for GDM, which divided the data into homogeneous segments with respect to the dependent variable (GDM) until we reached a "terminal" node in which all cases have the same value for the dependent variable. Nevertheless, variables might be selected repeatedly on different levels of the tree. Gini index was used to split nodes and the decision tree stopped when its improvement was <0.005, whereas pruning was used to avoid over fitting the model.

Results

Among the 407 pregnant women in total, 52 (12.8%) were excluded: 25 cases did not complete the sleep items in the questionnaire, whereas 13 cases were spontaneous abortion, and 11 cases were lack of OGTT results caused by intolerance of the test. One case was diagnosed as IGT based on the blood glucose results at first antenatal care, and 2 cases were diagnosed as pGDM. Thus, a total of 355 pregnant women were included in this study (Figure 1). The

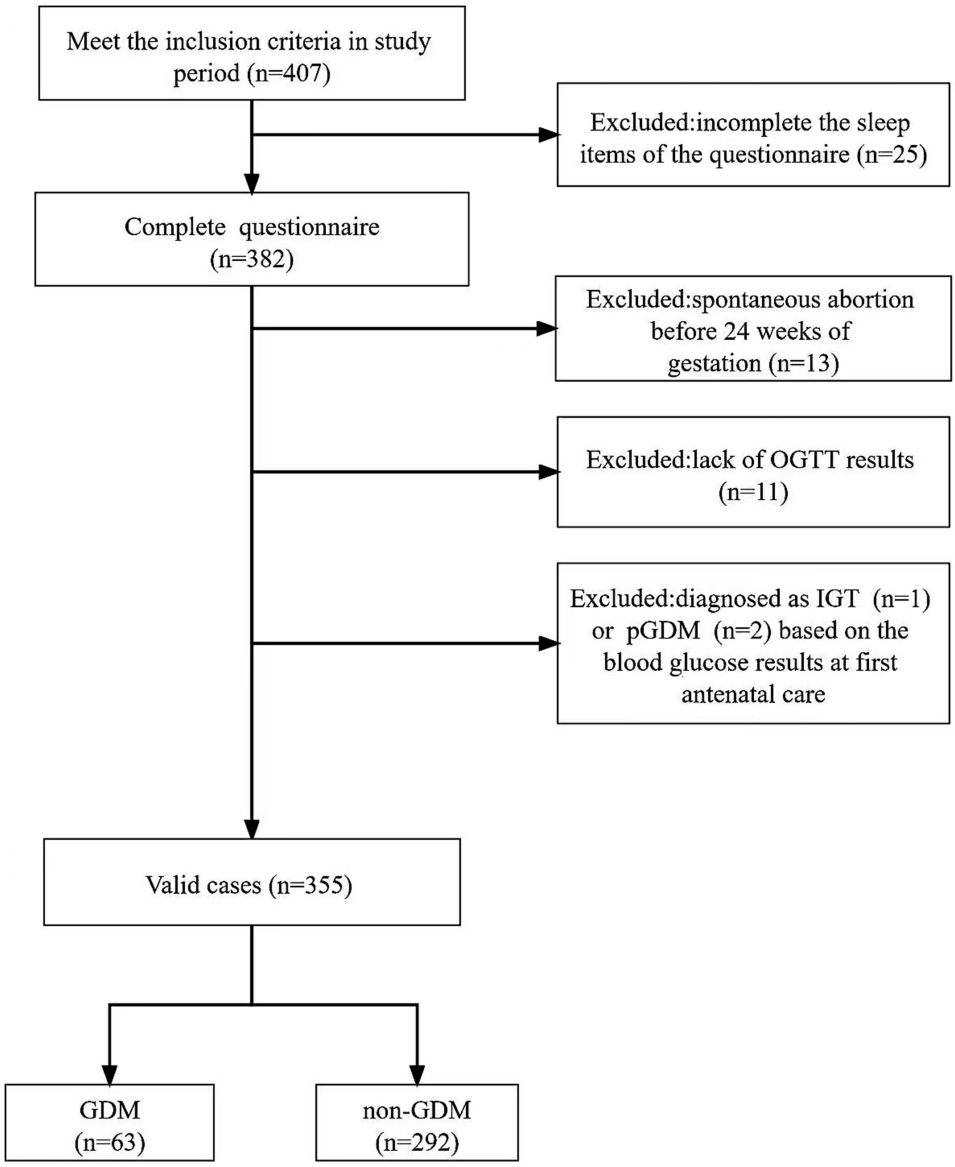


Figure 1 Flow chart of study and analysis inclusion. Among the 407 pregnant women in total, 52 were excluded, 25 cases did not complete the sleep items in the questionnaire, whereas 13 cases were spontaneous abortion, and 11 cases were lack of OGTT results caused by intolerance of the test. One case was diagnosed as IGT based on the blood glucose results at first antenatal care, and 2 cases were diagnosed as pGDM. Thus, a total of 355 pregnant women were included in this study, 63 were diagnosed with GDM, while the other 292 were a part of the non-GDM group.
Abbreviations: GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test.

baseline characteristics were similar in both included (n = 355) and excluded (n = 52) subjects, as shown in Supplementary Material B (Table B.1).

Univariate Analysis of Baseline Characteristics in GDM Population

Out of 355 pregnant women, 63 (17.7%) were diagnosed with GDM, while the other 292 (82.3%) were a part of the non-GDM group. As compared with the non-GDM group, the maternal age (32.7±3.4 vs 31.3±3.9, $p = 0.011$), BMI (22.8 ±3.2 kg/m^2 vs 21.4±2.7 kg/m^2, $p = 0.001$), and the proportion of family history of diabetes (54.0% vs 32.5%, $p = 0.001$) in GDM group were significantly higher. There were no significant differences in the other clinical characteristics between the two groups (Table 1).

Table 1 Baseline Data of Women with GDM Group and Non GDM Group (n = 355)

Clinical Characteristics[a]	GDM (n = 63)	Non GDM (n = 292)	*p*-value
Age (y)	32.7±3.4	31.3±3.9	0.011
Gestational age at enrollment (weeks)	8.7±2.0	8.2±1.8	0.117
BMI (kg/m^2)	22.8±3.2	21.4±2.7	0.001
Primipara	43 (68.3)	226 (77.4)	0.124
History of Hyperthyroidism	2 (3.2)	4 (1.4)	0.289
History of repeated vaginal candidiasis	8 (12.7)	42 (14.4)	0.727
History of oligomenorrhea	3 (4.8)	7 (2.4)	0.392
History of spontaneous abortion	13 (20.6)	50 (17.1)	0.585
Family history of diabetes	34 (54.0)	95 (32.5)	0.001
Family history of hypertension	41 (65.1)	167 (57.2)	0.249
Yearly household income (CNY)			
80,000–140,000	14 (22.2)	57 (19.5)	0.418
150,000–290,000	22 (34.9)	110 (37.7)	
300,000–490,000	21 (33.3)	77 (26.4)	
≥500,000	6 (9.5)	48 (16.4)	
History of frequent overtime work	13 (20.6)	56 (19.2)	0.861

Notes: [a]Data are mean ± SD or n (%); Statistical significance was accepted when p < 0.05.
Abbreviations: BMI, body mass index; CNY, Chinese Yuan; GDM, gestational diabetes mellitus.

Univariate Analysis of Sleep Status Before Pregnancy in GDM Group

The average nighttime sleep duration was 7.3 h in the GDM group and 7.5 h in the non-GDM group during prepregnancy (p = 0.117). There was no difference in the proportion of normal (7–9 h), short (<7 h), and long (≥9 h) sleep duration between the two groups. There were one case and 0 case for nighttime sleep duration ≤5h in GDM group and non-GDM group, respectively. The pregnant women diagnosed with GDM had a higher proportion for daytime nap duration >60 min before pregnancy compared with those without GDM (12.7% vs 6.2%, p = 0.188). In the GDM group, the score of PSQI was significantly higher than the non-GDM group (4.0 (3.0, 5.0) vs 3.0 (2.0, 5.0), p = 0.026). The proportion of positive BQ significantly increased in the GDM group than the non-GDM group (9.5% vs 1.7%, p = 0.001) (Table 2). We performed a univariate analysis of the relationship between different component of the BQ and GDM. The results showed that the first category (p=0.003) and second category (p=0.008) were associated with GDM, and the third category was not statistically different between GDM group and non-GDM group (p=0.449). (Supplementary Material B, Table B.2).

Multivariate Analysis for Sleep Status Before Pregnancy and Subsequent GDM

Multicollinearity and Variance inflation factors (VIF) of sleep duration, sleep quality, and BQ outcome were assessed before building the logistic regression model. The results were that all VIF values less than 10, which considered to indicate the absence of multicollinearity, as shown in Supplementary Material B, Table B.3. Then, multivariate logistic regression model was established with GDM as the dependent variable. Factors with p < 0.1, such as maternal age, BMI, family history of diabetes, PSQI score, and BQ outcome were included in the multivariate analysis. The results indicated that maternal age (*a*OR 1.10, 95% *CI*, 1.01–1.17), BMI (*a*OR 1.12, 95% *CI*, 1.02–1.23), family history of diabetes (*a*OR 2.35, 95% *CI*, 1.33–4.17), positive BQ (*a*OR 4.03, 95% *CI*, 1.04–15.63) were the independent risk factors for GDM. According to the analysis, there is no effect of PSQI on GDM (Table 3). In addition, Interaction between age, BMI, nighttime sleep duration, and sleep quality, respectively, and BQ outcome were also tested by the logistic regression analysis, and the results were negative (p>0.05), as shown in Supplementary Material B, Table B.4.

CART Decision Tree

Figure 2 shows a CART decision tree with 5 levels, 9 nodes, and 5 terminal nodes. When looking at the overall results of the decision tree, BMI > 20.6 kg/m^2 was the most important factor for higher risk of GDM than BMI ≤ 20.6 kg/m^2

Table 2 Sleep Status Before Pregnancy and Subsequent GDM (n = 355)

Clinical Characteristics[a]	GDM (n = 63)	Non GDM (n = 292)	*p*-value
Nighttime sleep duration (h)	7.3±0.8	7.5±0.9	0.117
Nighttime sleep group			
<7h	9 (14.3)	39 (13.4)	0.421
≥7 to <9h	53 (84.1)	237 (81.2)	
≥9h	1 (1.6)	16 (5.5)	
Days nap per week			
No	13 (20.6)	70 (24.0)	0.746
1 or 2 days	21 (33.3)	102 (34.9)	
≥ 3 days	29 (46.0)	120 (41.1)	
Daytime nap duration (min)			
No	13 (20.6)	70 (24.0)	0.188
≤60	42 (66.7)	204 (69.9)	
>60	8 (12.7)	18 (6.2)	
PSQI score	4.0 (3.0, 5.0)	3.0 (2.0, 5.0)	0.026
Sleep quality (PSQI)			
Poor sleep quality (PSQI>5)	13 (20.6)	50 (17.1)	0.508
Good sleep quality (PSQI≤5)	50 (79.4)	242 (82.9)	
BQ outcome			
Positive BQ	6 (9.5)	5 (1.7)	0.001
Negative BQ	57 (90.5)	287 (98.3)	

Notes: [a]Data are mean ± SD or n (%) or median (P25, P75); Statistical significance was accepted when p < 0.05.
Abbreviations: BQ, Berlin Questionnaire; GDM, gestational diabetes mellitus; PSQI, Pittsburgh Sleep Quality Index.

Table 3 Multivariate Analysis of the Relationship Between Sleep Status and GDM (n = 355)

Clinical Characteristics	*Adjusted* OR[a]	95% *CI*[a]
Age (y)	1.10	(1.01, 1.17)
BMI (kg/m^2)	1.12	(1.02, 1.23)
Family history of diabetes	2.35	(1.33, 4.17)
Positive BQ	4.03	(1.04, 15.63)
PSQI score	1.06	(0.92, 1.22)

Note: [a]OR and 95% *CI* estimated with multivariable logistic regression adjusted for maternal age, BMI, family history of diabetes.
Abbreviations: BMI, body mass index; BQ, Berlin Questionnaire; CI, confidence interval; OR, odds ratio; PSQI, Pittsburgh Sleep Quality Index.

(23.2% vs 8.9%), whereas age >28.5 years was in the second place. Among the pregnant women with BMI > 20.6 kg/m^2 and age >28.5, the risk of GDM with positive BQ increased from 27.5% to 66.7% (Figure 2).

Discussion

Knowledge about the effects of non-pregnancy sleep disorders on GDM is still lacking.[18,19] This case-control study set out to assess the relationships between sleep disturbances before pregnancy and subsequent GDM. The most important finding was that even considering the other characteristics of sleep, BQ positive before pregnancy was an independent risk factor for GDM. The result of decision tree showed that for women with BMI > 20.6 kg/m^2 and age >28.5, the prevalence of GDM was increased from 27.5% to 66.7% with pre-pregnancy positive BQ, which was consistent with that of multivariate analysis. This finding suggested that women with the high risk of OSA may increase the occurrence of GDM during pregnancy.

Risk factors for GDM included overweight or obesity, advanced age, family history of diabetes mellitus and non-white ancestry.[2,3] In this study, multivariate analysis showed that higher BMI, advanced age, and family history of

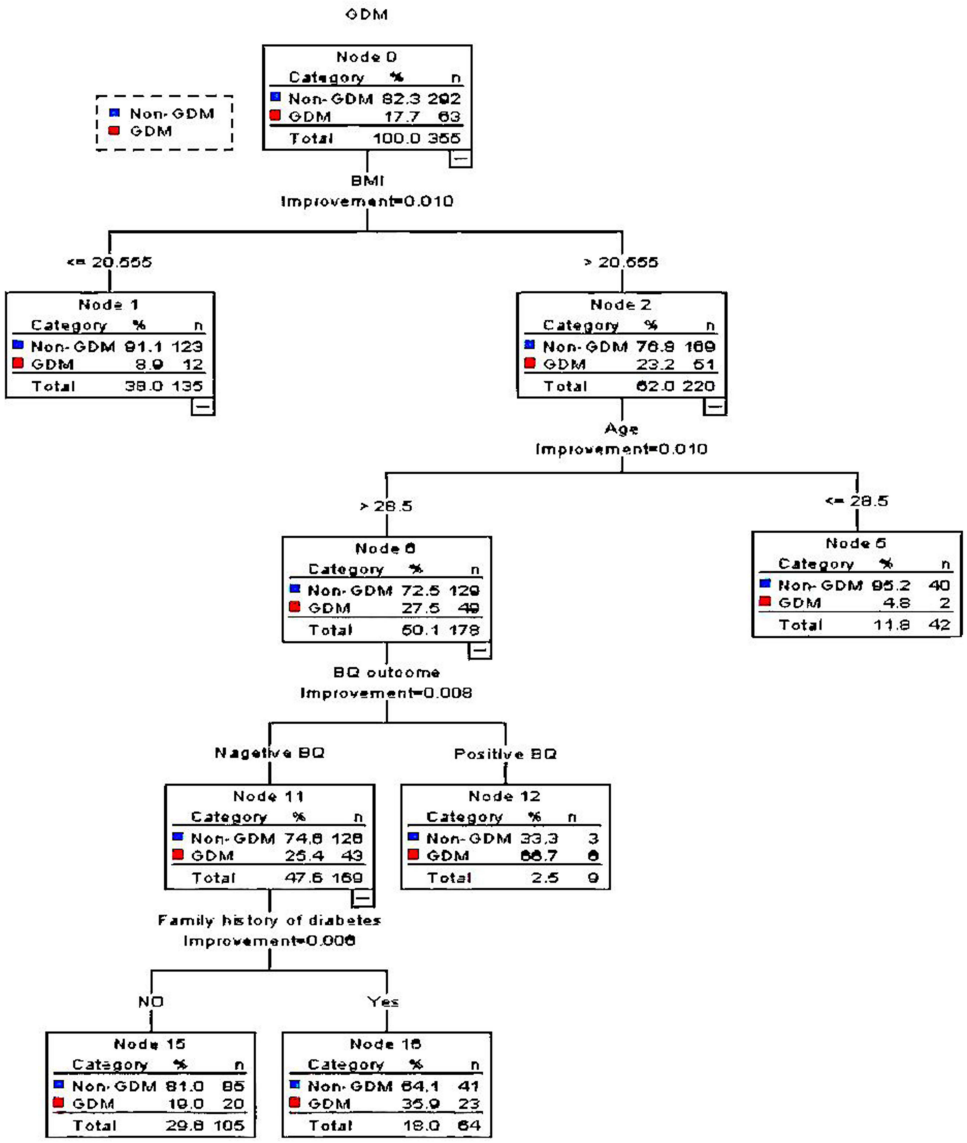


Figure 2 The decision tree for GDM. Among the pregnant women with BMI >20.6 kg/m^2 and age >28.5, the risk for GDM with positive BQ increased from 27.5% to 66.7%.
Abbreviations: BMI, body mass index; BQ, Berlin Questionnaire; GDM, gestational diabetes mellitus.

diabetes were independent risk factors for GDM. The results of CART analysis are similar to those of multivariate analysis. The results are consistent with previous studies.[30–32]

In present study, BQ was used to assess the risk of OSA, and the results showed that the proportion of BQ positive in the GDM group was 9.5%, which was significantly higher than that in the non-GDM group of 1.7%. In multivariate analysis, by adjusting BMI, age, family history of diabetes and the other sleep factors, women with the positive BQ before pregnancy had a four times risk for GDM compared with the negative BQ. We further explored the relation between the different component of the BQ and the occurrence of GDM, and found that the first category (p=0.003) and second category (p=0.008) were associated with GDM, which means that the effect of pre-pregnancy OSA on GDM is mainly reflected in snoring and waketime sleepiness. OSA is the most common type of sleep-disordered breathing, with the main clinical manifestation of snoring.[33,34] A prospective cohort study found that chronic snoring (habitual snoring before and during pregnancy) rather than pregnancy onset snoring can increase the odds of GDM,[20] which is consistent with this study. A common and acceptable BQ was used to evaluate the OSA risk in this study, which is widely

used in different populations and more accurate than the question for snoring in previous study.[35–38] Intermittent hypoxia and sleep interruption due to OSA were both implicated as a cause of increased levels of oxidative stress, inflammation, sympathetic activity, and cortisol, which lead to insulin resistance.[39,40] The CART analysis can show the weight of different risk factors affecting GDM and showed that BMI was the most important factor for higher risk of GDM, whereas maternal age and a positive BQ were in the second and third place, respectively. According to the decision tree, women with positive BQ can reach a higher incidence of GDM incidence, even considering with traditional risk factors. Similarly, a meta analysis in 2021, two sub-groups of age (<30 y vs.≥30 y) (n = 10) and BMI (<24 kg/m^{2}vs.≥24kg/m^2) (n = 15) were analyzed, finding that the positive BQ was also associated with GDM for the groups of age ≥30 and BMI ≥24kg/m^2.[41] It is also important to note that a family history of diabetes can increase the risk of GDM from 19% to 36% in high-risk BMI and age population with a negative BQ by CART analysis. Further studies need to diagnose OSA through respiratory sleep monitoring before pregnancy and observe the relationship with subsequent GDM during pregnancy, to clarify its role and make it possible for early intervention.

In terms of sleep quality, the median score of PSQI before pregnancy was 4.0 for the GDM group, which was significantly higher than that of the non-GDM group (3.0). The results of the multivariate analysis did not reveal that the PSQI score was independent factor for GDM. For sleep duration, we observed that the women with GDM have similar average nighttime sleep duration (7.3h Vs 7.5h). Furthermore, the daytime naps for more than 60 minutes were higher in the GDM group (12.7% and 6.3%), which is consistent with the results of second category in BQ. There are currently no reports on the impact of sleep quality or sleep duration before pregnancy on the subsequent occurrence of GDM. However, most previous studies have confirmed that both the short sleep duration (≤5h) and poor sleep quality were related to the risk of incident diabetes.[42–44] Guo et al[26] found that the risk of type 2 diabetes with the habit of taking a daytime nap >60 min increased by 31% compared with those without naps. This may be related to the fact that long daytime nap may cause sleep-wake cycle disturbance and disrupt the sympathetic parasympathetic balance, which subsequently impairs glucose tolerance,[45] and the obesity caused by the daytime nap.[46] The impact of sleep quality and sleep duration before pregnancy on GDM needs to be confirmed by more large sample researches in the future.

The merits of our study could be summarized as following: Firstly, the present study investigated the relationship between sleep disturbances 1 month before pregnancy and the subsequent risk for GDM, which would assist health-care providers to identify women's sleep behaviors related to GDM before pregnancy. Secondly, instead of the questions for snoring or sleep quality, the sleep disturbances were collected by completing authoritative scales in this study, which can comprehensively assess sleep quality and risk of OSA. In addition, various dimensions of sleep disturbances were considered in the multivariate analysis to balance their effect for each other. Nevertheless, the present study still has some limitations. The sleep disturbances before pregnancy were evaluated by recalling the sleep state one month before the last menstruation in early pregnant women. There may be recall bias when filling out the sleep scale with an average recall interval of about 2 months, rather than the most recent month as is usual, that may lead to over- or under-estimation of the severity of sleep disturbances. For pregnant women, the first day of their last menstruation marks the beginning of pregnancy – usually easy to remember, which may help to reduce the recall bias to some extent. Pregnant women were not diagnosed with GDM until several months after the questionnaire was collected in early pregnancy, so there was no difference in recall bias between the GDM group and the non-GDM group. In addition, the different situations of the pregnancy (ie, planned or accidental pregnancy, natural pregnancy or assisted reproduction, etc.) were not involved, which may also be related to the sleep disturbances. Prospective studies in the future and applying objective methods and interventions in the diagnosis of OSA will provide more favorable evidence for the prevention of GDM.

Conclusion

Sleep disturbances before pregnancy were assessed by two scales to evaluate the relationships with the subsequent occurrences of GDM. High risk for OSA during prepregnancy increased the odds of GDM. Health-care professionals should assess the sleep disturbances of pregnant women with the aim of improving pregnancy outcomes.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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