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Obstructive Sleep Apnea and Risk of Miscarriage

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Abstract: The purpose of this project was to evaluate whether screening positive on obstructive sleep apnea questionnaires in the first trimester of pregnancy was associated with miscarriage. This was a secondary analysis of a prospective observational cohort study of participants who were screened for sleep apnea during pregnancy with the Epworth Sleepiness Scale, Berlin Questionnaire, and novel items related to sleep and napping. This secondary analysis was IRB exempt. Our primary outcome was miscarriage in the index pregnancy. An association between responses to the sleep apnea screening questions with miscarriage of the index pregnancy was queried via Poisson regression. We found that gravidae who had elevated scores on both the Epworth Sleepiness Scale and the Berlin Questionnaire were more likely to experience miscarriage than those who had elevated scores on only one questionnaire or neither ($p = 0.018$). Gravidae who reported snoring ($p = 0.042$) or hypertension ($p = 0.013$) in the first trimester were more likely to experience miscarriage than gravidae who did not. Gravidae who reported napping in the first trimester were less likely to experience miscarriage ($p = 0.045$), even after adjusting for confounding variables ($p = 0.007$). In conclusion, we found that screening positive on both the Berlin Questionnaire and Epworth Sleepiness Scale was statistically significantly associated with miscarriage prior to adjustment for confounding variables, as did snoring and hypertension. After adjusting for confounding variables, only not napping was associated with miscarriage. Given the small sample size, further investigation into this topic is warranted.

Keywords: miscarriage; obesity; pregnancy; snoring; sleep-disordered breathing; obstructive sleep apnea

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1. Introduction

Miscarriage is a common, and yet potentially personally devastating pregnancy outcome that occurs in 11% to 22% of recognized pregnancies [1]. The etiology of miscarriages is complex and often multifactorial with the most common identifiable cause linked to chromosomal aneuploidies and cytogenetic rearrangements. Recent hypotheses have also associated miscarriage with immunological and vascular phenomena, although causality remains poorly ascribed [2–4]. Miscarriage carries an appreciable cost to pregnant people and their families, healthcare systems, and society, resulting from both direct healthcare costs and indirect costs such as short-term loss of work and societal productivity [5]. Miscarriage is also associated with a risk for psychological morbidity, such as anxiety, depression, post-traumatic stress disorder, and suicide [5].

Obstructive sleep apnea is associated with increased body-mass index (BMI) and older age, both of which are risk factors for miscarriage. Obstructive sleep apnea itself has also been recognized as a potential risk factor for miscarriage itself due to sleep fragmentation

and intermittent hypoxia [6]. The prevalence of obstructive sleep apnea within the reproductive age population has been estimated at 9% for women and between 3.6 and 32% during pregnancy [7–10]. Obstructive sleep apnea can result in upregulation of sympathetic nervous system activity, renin-angiotensin, aldosterone system activity, endothelial dysfunction, inflammation, oxidative stress, and metabolic dysregulation, which can result in serious morbidity, including hypertension and cardiovascular diseases in the general population [11,12]. Obstructive sleep apnea has also been associated with adverse outcomes, including hypertensive disorders of pregnancy, in the obstetric population [13,14]. Given the known effects of obstructive sleep apnea on vasculature and recent hypotheses associating miscarriage with immunologic and vascular phenomena, it is plausible that obstructive sleep apnea could be a potentially reversible or treatable cause of miscarriage.

We sought to examine the relationship between elevated scores on questionnaires used to screen for obstructive sleep apnea and excessive sleepiness, and miscarriage. Our hypothesis was that elevated Epworth Sleepiness Scale and Berlin Questionnaire scores, suggestive of higher pretest probability for obstructive sleep apnea, would be independently associated with miscarriage. We adjusted our analyses for age, smoking status, and history of miscarriage, given the known associations between these factors and risk of miscarriage.

2. Materials and Methods

The data for the parent prospective observational cohort study enabling the current analyses were collected from the Harris County Hospital District (now Harris Health System) between May 2010 and September 2012. The parent study was approved by the Institutional Review Board at Baylor College of Medicine (IRB H-19183, initial approval date 4 April 2006) and was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) [15,16]. Informed consent was obtained from all participants at the time of the parent study. This current secondary analysis was determined to be exempt from approval by the Minimal Risk Health Sciences Institutional Review Board at the University of Wisconsin–Madison. All unique identifiers were removed from the dataset prior to use in this current study.

In the parent study, gravidae presenting to two community clinics and one tertiary clinic were approached for enrollment, and gravidae who screened positive for sleep apnea in the parent study were referred for diagnostic sleep testing [15,16]. Gravidae of all gestational ages were recruited for the parent study which evaluated the association between screening measures of obstructive sleep apnea and adverse perinatal outcomes. Exclusion criteria were known sleep-disordered breathing, multifetal gestation, fatal fetal anomalies (if known), underlying pulmonary or cardiac conditions, and age < 18 or >50. For the current study, only gravidae completing the questionnaire in the first trimester were included for analysis.

Consenting participants were administered a questionnaire (in English or Spanish), which comprised the Berlin Questionnaire (BQ) and the Epworth Sleepiness Scale (ESS), in addition to other sleep-related questions. The BQ is a 10-item questionnaire used to assess risk of obstructive sleep apnea (OSA) [17]. A higher score indicates higher risk of OSA. In studies performed in non-pregnant male populations, it has a high positive predictive value for OSA (0.866), but it performs less well in pregnancy [15,18,19]. The ESS is an 8-item questionnaire used to assess daytime sleepiness [20]. A higher score indicates a higher-than-average sleep propensity, and its intended use is to assess sleepiness rather than sleep apnea. While it has a low sensitivity and specificity as a screening tool for sleep apnea, it has been used both clinically and in research in the non-pregnant and pregnant population [21–23]. While it should not be used alone to screen for sleep apnea, it may be used to assess sleepiness in tandem with other tools [24]. A separate study was performed to evaluate the association between other adverse perinatal outcomes and these screening measures of obstructive sleep apnea [16]. Individual items related to snoring, snoring volumes, and hypertension reported here were taken from questions on the BQ. Additional

question items related to napping and napping frequency were added to the ESS and BQ for this study. Gravidae who screened positive for sleep apnea were referred for diagnostic polysomnography; very few diagnostic tests were completed, therefore for this analysis only the screening data were used [15,16]. If participants completed a questionnaire more than once, duplicate questionnaires were excluded. Questionnaires with incomplete items were excluded from each respective analysis. Participants who subsequently terminated their pregnancy, who were screened in the second or third trimester, or who delivered or transferred care to a non-study site (who had no outcomes available for analysis) were excluded (Figure 1). The remaining 213 pregnant people screened in the first trimester were included in this analysis.

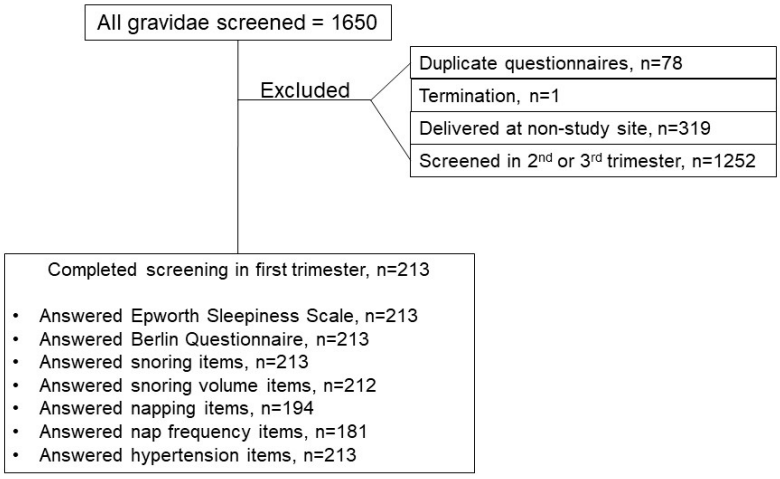

Figure 1. Gravidae included for analysis. Of 1650 gravidae screened, 213 completed screening in the first trimester and were included in the analysis.

Each participant's medical chart was reviewed (MD & KMA7). Miscarriage was defined as a spontaneous abortion at or before 19 6/7 weeks of gestation [2]. Covariates considered in these analyses were age, gravidity, ethnicity, smoking status and history of prior miscarriage. Prior history of miscarriage was defined by participant report of prior miscarriage and review of the medical record. Prepregnancy BMI data was collected where available, but not included in adjusted relative risk calculations due to the low percentage of participants with prepregnancy BMI data available.

Descriptive findings of study sample characteristics and outcomes by responses to questionnaire items are reported. Chi-square tests for independence were performed for categorical variables. Generalized linear models' adjusted relative risks (aRRs) with 95% confidence intervals (CIs) were estimated for age categories, gravidity categories, and ethnicity for associations between questionnaire items and miscarriage or history of miscarriage using a modified Poisson regression approach [25]. When no association was present, aRRs were calculated with all covariates. Analysis stratified by advanced age was also completed. Stata (Stata 15.1, 2017, College Station, TX, USA) was used for analyses. Data related to this article will be shared upon reasonable request to the corresponding author.

3. Results

One thousand, six hundred fifty questionnaires were completed. Of those, two hundred thirteen were from participants who were screened in the first trimester and were included in this analysis. The majority of participants were Hispanic/Latinx (89.7%). One hundred seventy-nine participants had BMI data available for analysis. Over half of participants were overweight (32.4%) or had obesity (31.3%). Most participants were over 25 years of age (73.2%). Few participants reported smoking (2.8%). About one third of participants reported history of miscarriage (36.2%) (Table 1). Napping was most prevalent

in the 20–24-year-old age group (65.9%) and least prevalent in the 25–29-year-old age group (34.5%). Snoring and hypertension were not significantly associated with age.

Table 1. Characteristics of the study population.

	Total	**Miscarriage**	**No Miscarriage**	***p* ***
	N = 213	**N = 28 (13.1%)**	**N = 185 (86.9%)**	
Age				
<19	12 (5.6%)	2 (7.1%)	10 (5.4%)	
20–24	45 (21.1%)	5 (17.9%)	40 (21.6%)	
25–29	64 (30.1%)	6 (21.4%)	58 (31.4%)	0.659
30–34	48 (22.5%)	9 (32.1%)	39 (21.1%)	
35+	44 (20.7%)	6 (21.4%)	38 (20.5%)	
Gravidity				
1	31 (14.6%)	9 (32.1%)	22 (11.9%)	
2	48 (22.5%)	5 (17.7%)	43 (23.2%)	0.006
3–5	120 (56.3%)	10 (35.7%)	110 (59.5%)	
6+	14 (6.6%)	4 (14.3%)	10 (5.4%)	
Race/Ethnicity				
Hispanic	191 (89.7%)	22 (78.6%)	169 (91.4%)	
Black	15 (7.04%)	4 (14.2%)	11 (6.0%)	0.116
Other †	7 (3.3%)	2 (7.14%)	5 (2.7%)	
Smoking				
Yes	6 (2.7%)	3 (10.7%)	3 (1.7%)	0.007
No	204 (97.1%)	25 (89.3%)	179 (98.4%)	
Prior Miscarriage				
Yes	77 (36.2%)	12 (42.9%)	65 (35.1%)	0.428
No	136 (63.9%)	16 (57.1%)	120 (64.9%)	
BMI ‡				
<24.9	65 (30.5%)	1 (3.6%)	64 (34.6%)	
25.0–29.9	58 (27.2%)	0 (0%)	58 (31.4%)	
30+	56 (26.3%)	0 (0%)	56 (30.3%)	<0.001
Missing	34 (16.0%)	27 (96.4%)	7 (3.8%)	
Pregestational DM ‡				
Yes	12 (5.7%)	4 (14.3%)	8 (4.3%)	0.034
No	212 (94.3%)	24 (85.7%)	176 (95.7%)	
Chronic HTN ‡				
Yes	16 (7.5%)	5 (17.9%)	11 (5.9%)	0.026
No	197 (92.5%)	23 (82.1%)	174 (94.1%)	

*: *p*-values based on chi-square tests for independence. Bold font denotes statistical signifance by $p < 0.05$. † Other races included non-Hispanic White, Asian, and American Indian or Alaska Native. ‡ Body mass index (BMI), diabetes mellitus (DM), hypertension (HTN).

In this population, 30.0% (N = 64) of gravidae screened positive on either the ESS or BQ. (Table 2A). Of those, 14.6% (N = 31) of gravidae screened positive on the BQ and 18.8% (N = 40) of gravidae screened positive on the ESS. Only 3.3% (N = 7) screened positive on both the ESS and the BQ (Table 2A). Almost half (N = 88) of gravidae reported napping, greater than half of whom reported napping three or more times weekly (N = 52) (Table 2B). One out of five (21.1%, N = 45) of gravidae reported snoring and 8.9% (N = 19) of gravidae reported hypertension.

Table 2. Participant characteristics by screening questionnaire and by individual questions.

	A: Characteristics by Screening Questionnaire											
	Either+ *	**Both− ***	***p***	**BQ+ †**	**BQ−**	***p***	**ESS+ †**	**ESS−**	***p***	**Both+ ‡**	**Either− +**	***p* §**
	N = 64 (30.0%)	**N = 149 (70.0%)**		**N = 31 (14.6%)**	**N = 182 (85.4%)**		**N = 40 (18.8%)**	**N = 173 (81.2%)**		**N = 7 (3.29%)**	**N = 206 (96.7%)**	
Age												
<19	4 (6.3%)	8 (5.4%)		0 (0%)	12 (6.6%)		4 (10.0%)	8 (4.6%)		0 (0%)	12 (5.8%)	
20–24	14 (21.9%)	31 (20.8%)	0.954	5 (16.1%)	40 (22.0%)	0.466	10 (25.0%)	35 (20.2%)	0.486	1 (14.3%)	44 (21.4%)	0.641
25–29	21 (32.8%)	43 (28.9%)		12 (38.7%)	52 (28.6%)		11 (27.5%)	53 (30.6%)		2 (28.6%)	62 (30.1%)	
30–34	13 (20.3%)	35 (23.5%)		8 (25.8%)	40 (22.0%)		6 (15.0%)	42 (24.3%)		1 (14.3%)	47 (22.8%)	
35+	12 (18.8%)	32 (21.5%)		6 (19.4%)	38 (20.9%)		9 (22.5%)	35 (20.2%)		3 (42.9%)	41 (19.9%)	
Gravidity												
1	6 (9.4%)	25 (16.8%)		3 (9.7%)	28 (15.4%)		3 (7.5%)	28 (16.2%)		0 (0%)	31 (15.1%)	
2	18 (28.1%)	30 (20.1%)	0.396	11 (35.5%)	37 (20.3%)	0.201	9 (22.5%)	39 (22.5%)	0.443	2 (28.6%)	46 (22.3%)	0.001
3–5	36 (56.3%)	84 (56.4%)		14 (45.2%)	106 (58.2%)		24 (60.0%)	96 (55.5%)		2 (28.6%)	118 (57.3%)	
6+	4 (6.3%)	10 (6.7%)		3 (9.7%)	11 (6.0%)		4 (10.0%)	10 (5.8%)		3 (42.9%)	11 (5.3%)	
Ethnicity												
Hispanic	53 (82.8%)	138 (92.6%)	0.086	24 (77.4%)	167 (91.8%)	0.051	34 (85.0%)	157 (90.8%)	0.247	5 (71.4%)	186 (90.3%)	0.176
Black	7 (10.9%)	8 (5.4%)		5 (16.1%)	10 (5.5%)		3 (7.5%)	12 (6.9%)		1 (14.3%)	14 (6.8%)	
Other	4 (6.3%)	3 (2.0%)		2 (6.5%)	5 (2.7%)		3 (7.5%)	4 (2.3%)		1 (14.3%)	6 (2.9%)	
Smoking												
1 (1.6%)		5 (3.4%)	0.470	0 (0%)	6 (3.3%)	0.310	1 (2.5%)	5 (2.5%)	0.880	0 (0%)	6 (2.9%)	0.644
No	62 (96.9%)	142 (95.3%)		30 (100%)	174 (95.6%)		39 (97.5%)	165 (97.1%)		7 (100%)	197 (97.0%)	
Prior Miscarriage												
Yes	28 (43.8%)	49 (32.9%)	0.130	18 (58.1%)	59 (32.4%)	0.006	16 (40.0%)	61 (35.3%)	0.574	6 (85.7%)	71 (34.5%)	0.006
No	36 (56.3%)	100 (67.1%)		13 (41.9%)	123 (67.6%)		24 (60.0%)	112 (64.7%)		1 (14.3%)	135 (65.5%)	
BMI †												
<24.9	19 (29.7%)	46 (30.9%)		1 (3.2%)	64 (35.2%)		18 (45.0%)	47 (27.2%)		0 (0%)	65 (31.6%)	
25.0–29.9	16 (25.0%)	42 (28.2%)	0.502	6 (19.4%)	52 (28.6%)	<0.001	11 (27.5%)	47 (27.2%)	0.105	1 (14.3%)	57 (27.7%)	0.132
30+	21 (32.8%)	35 (23.5%)		18 (58.1%)	38 (20.9%)		6 (15.0%)	50 (28.9%)		3 (42.9%)	53 (25.7%)	
Missing	8 (12.5%)	26 (17.4%)		6 (19.4%)	28 (15.4%)		5 (12.5%)	29 (16.8%)		3 (42.9%)	31 (15.1%)	
Pregestational DM †												
Yes	3 (4.8%)	9 (6.0%)	0.713	2 (6.7%)	10 (5.5%)	0.797	2 (5.0%)	10 (5.8%)	0.841	1 (14.3%)	11 (5.4%)	0.315
No	60 (95.2%)	140 (94.0%)		28 (93.3%)	172 (94.5%)		38 (95.0%)	162 (94.2%)		6 (85.7%)	194 (94.6%)	

Table 2. *Cont.*

Chronic HTN †												
Yes	9 (14.1%)	7 (4.7%)	0.017	9 (29.0%)	7 (3.9%)	<0.001	3 (7.5%)	13 (7.5%)	0.998	3 (42.9%)	13 (6.3%)	<0.001
No	55 (85.9%)	142 (95.3%)		22 (71.0%)	175 (96.2%)		37 (92.5%)	160 (92.5%)		4 (57.1%)	193 (93.7%)	
B: Characteristics by Screening Question												
	Nap+ N = 88 (45.4%)	**Nap− N = 106 (54.6%)**	***p*** **§**	**Nap 3+ N = 52 (49.8%)**	**Nap < 3 N = 129 (50.2%)**	***p***	**Snore+ N = 45 (21.1%)**	**Snore− N = 168 (78.9%)**	***p***	**HTN+ † N = 19 (8.92%)**	**HTN− N = 194 (91.1%)**	***p***
Age												
<19	5 (5.7%)	6 (5.7%)	0.030	2 (3.9%)	8 (6.2%)	0.036	0 (0%)	12 (7.1%)	0.310	1 (5.3%)	11 (5.7%)	0.172
20–24	29 (33.0%)	15 (14.2%)		19 (36.5%)	22 (17.1%)		11 (24.4%)	34 (20.2%)		0 (0%)	45 (23.2%)	
25–29	20 (22.7%)	38 (35.9%)		10 (19.2%)	45 (34.9%)		13 (28.9%)	51 (30.4%)		6 (31.6%)	58 (29.9%)	
30–34	17 (19.3%)	25 (23.6%)		9 (17.3%)	29 (22.5%)		13 (28.9%)	35 (20.8%)		6 (31.6%)	42 (21.7%)	
35+	17 (19.3%)	22 (20.8%)		12 (23.1%)	25 (19.4%)		8 (17.8%)	36 (21.4%)		6 (31.6%)	38 (19.6%)	
Gravidity												
1	17 (19.3%)	12 (11.3%)	0.154	7 (13.5%)	19 (14.7%)	0.724	9 (20.0%)	22 (13.1%)	0.016	5 (26.3%)	26 (13.4%)	0.276
2	23 (26.1%)	20 (18.9%)		15 (28.9%)	27 (20.9%)		16 (35.6%)	32 (19.1%)		2 (10.5%)	46 (23.7%)	
3–5	42 (47.7%)	67 (63.2%)		27 (51.9%)	74 (57.4%)		16 (35.6%)	104 (61.9%)		10 (52.6%)	110 (56.7%)	
6+	6 (6.8%)	7(6.6%)		3 (5.8%)	9 (7.0%)		4 (8.9%)	10 (6.0%)		2 (10.5%)	12 (6.2%)	
Ethnicity												
Hispanic	75 (85.2%)	98 (92.5%)	0.126	45 (86.5%)	116 (89.9%)	0.261	36 (80.0%)	155 (92.3%)	0.055	13 (68.4%)	178 (91.8%)	0.006
Black	10 (11.4%)	4 (3.8%)		6 (11.5%)	7 (5.4%)		6 (13.3%)	9 (5.4%)		4 (21.1%)	11 (5.7%)	
Other	3 (3.4%)	4 (3.8%)		1 (1.9%)	6 (4.7%)		3 (6.7%)	4 (2.4%)		2 (10.5%)	5 (2.6%)	
Smoking												
Yes	3 (3.5%)	3 (2.9%)	0.815	2 (3.9%)	4 (3.1%)	0.789	0 (0%)	6 (3.6%)	0.201	2 (10.5%)	4 (2.1%)	0.035
No	84 (96.6%)	102 (97.1%)		49 (96.1%)	124 (96.9%)		44 (100%)	160 (96.4%)		17 (89.5%)	187 (97.9%)	
Prior Miscarriage												
Yes	29 (33.0%)	40 (37.7%)	0.489	20 (38.5%)	45 (34.9%)	0.650	18 (40.0%)	59 (35.1%)	0.545	7 (36.8%)	70 (36.1%)	0.948
No	59 (67.1%)	66 (62.3%)		32 (61.5%)	84 (65.1%)		27 (60.0%)	109 (64.9%)		12 (63.2%)	124 (63.9%)	
BMI †												
<24.9	32 (36.4%)	27 (25.5%)	0.093	22 (42.3%)	33 (25.6%)	0.057	7 (15.6%)	58 (34.5%)	0.023	3 (15.8%)	62 (32.0%)	0.008
25.0–29.9	18 (20.5%)	34 (32.1%)		11 (21.2%)	39 (30.2%)		11 (24.4%)	47 (28.0%)		1 (5.3%)	57 (29.4%)	
30+	27 (30.7%)	25 (23.6%)		15 (28.9%)	33 (25.6%)		15 (33.3%)	41 (24.4%)		9 (47.4%)	47 (24.2%)	
Missing	11 (12.5%)	20 (18.9%)		4 (7.7%)	24 (18.6%)		12 (26.7%)	22 (13.1%)		6 (31.6%)	28 (14.4%)	

Table 2. *Cont.*

Pregestational DM [†]											
Yes	7 (8.0%)	5 (4.7%)	0.351	3 (5.8%)	6 (4.7%)	0.763	3 (6.8%)	9 (5.4%)	0.709	3 (15.8%)	9 (4.7%)	0.045
No	81 (92.1%)	101 (95.3%)		49 (94.2%)	122 (95.3%)		41 (93.2%)	159 (94.6%)		16 (84.2%)	184 (95.3%)	
Chronic HTN	[†]											
Yes	6 (6.8%)	8 (7.5%)	0.859	1 (1.9%)	13 (10.1%)	0.063	7 (15.6%)	9 (5.4%)	0.021	NA	NA	
No	82 (93.2%)	99 (92.5%)		51 (98.1%)	116 (89.9%)		38 (84.4%)	159 (94.6%)				

*: Either refers to screening positive on either BQ or ESS. [†]: Berlin Questionnaire (BQ), Epworth Sleepiness Scale (ESS), body mass index (BMI), diabetes mellitus (DM), hypertension (HTN). [‡]: Both refers to screening positive on both BQ and ESS. [§]: Bold font signifies statistical significance by $p < 0.05$.

The percentage of gravidae who miscarried by screening tool or item is shown in Table 3. Unadjusted analyses indicate that screening positive on both Epworth and Berlin ($p = 0.018$), snoring ($p = 0.042$) and hypertension ($p = 0.013$) were associated with increased miscarriage. Napping more than 3 times per week was associated with decreased miscarriage ($p = 0.045$). There was no association between napping and higher Epworth scores ($p = 0.173$). Results of stratified analysis for advanced maternal age (age $\geq$ 35) were similar to results of the overall analysis (results available upon request). Table 3 also shows relative risk for miscarriage by screening tool or item adjusted for confounding variables including age, ethnicity, gravidity, prior miscarriage history, and smoking status. Screening positive on both questionnaires, snoring, and hypertension were not associated with miscarriage after adjustment for confounding variables. Napping was not significantly associated with decreased miscarriage after adjustment for age alone ($p = 0.066$). After adjusting for age, ethnicity, gravidity, prior miscarriage history and smoking, napping was associated with decreased miscarriage with gravidae who napped one-third less likely to miscarry as gravidae who did not ($p = 0.007$) (Table 3).

Table 3. Miscarriage outcomes by OSA screening questionnaires and individual questions about snoring, hypertension, and napping.

	Miscarriage	***p***	**Adjusted RR ***	***p***
Either+ (N = 64) Both− (N = 149)	6 (9.38%) 22 (14.8%)	0.286	0.54 (0.22–1.33)	0.182
BQ+ ‡ (N = 31) BQ− (N = 182)	4 (12.9%) 24 (13.2%)	0.966	0.59 (0.20–1.74)	0.343
ESS+ ‡ (N = 40) ESS− (N = 173)	5 (12.5%) 23 (13.3%)	0.893	0.97 (0.35–2.66)	0.946
Both+ (N = 7) Either− (N = 206)	3 (42.9%) 25 (12.1%)	0.018 *	1.95 (0.43–8.83)	0.385
Snore+ (N = 45) Snore− (N = 168)	10 (22.2%) 18 (10.7%)	0.042	1.64 (0.79–3.38)	0.183
HTN+ ‡ (N = 19) HTN− (N = 194)	6 (31.6%) 22 (11.3%)	0.013	1.78 (0.82–3.90)	0.144
Nap+ (N = 88) Nap− (N = 106)	7 (7.95%) 19 (17.9%)	0.045	0.44 (0.18–1.05)	0.007
Nap 3+ (N = 52) Nap < 3 (N = 129)	2 (3.85%) 20 (15.5%)	0.030	0.24 (0.05–1.03)	0.055

* Adjusted using a modified Poisson regression for significant associations as seen in Table 2A,B or for all covariates if there was no significant association. ‡ Berlin questionnaire (BQ), Epworth sleepiness scale (ESS), hypertension (HTN).

4. Discussion

Elevated scores on screening questionnaires for both obstructive sleep apnea and excessive sleepiness in the first trimester of pregnancy were significantly associated with miscarriage in our study before adjustment for confounding variables. This finding aligns with the findings of recent publications and emerging hypotheses about the association between miscarriage and sleep disordered breathing [6,26], and suggest the "sleepy" apnea phenotype may be particularly relevant to likelihood of pregnancy loss [27]. One recent retrospective study found a significant association between apnea-hypopnea index and miscarriage, and between BMI and miscarriage [6]. It has been hypothesized that sleep disordered breathing may act as a mediating factor in the relationship between weight and miscarriage [26]. Gravidae with obstructive sleep apnea can experience intermittent hypoxemia, leading to increased oxidative stress [28]. This increase in oxidative stress can contribute to endothelial dysfunction and increased pro-inflammatory cytokines, which has been linked to adverse pregnancy outcomes, including miscarriage [29–31]. Furthermore,

sleep disordered breathing has been demonstrated in multiple studies to be associated with placental abnormalities consistent with chronic hypoxia and underperfusion [32,33]. Recent in vitro studies have demonstrated that intermittent hypoxia inhibits trophoblast motility and proliferation and induces apoptosis via the endoplasmic reticulum stress signaling pathway [34].

However, our results did not support an association between elevated scores on screening questionnaires and miscarriage after adjusting for confounders. The lack of association between miscarriage and screening positive on the BQ or ESS individually here could mean that they are inadequate screening tools during pregnancy. Given these plausible hypotheses for how sleep disordered breathing may be associated with miscarriage, it is important to delineate how to best screen gravidae for sleep disordered breathing. In recent meta-analyses, the prevalence of sleep disordered breathing in pregnancy has been estimated to be between 4% to 32% [9]. However, the commonly used Berlin Questionnaire and Epworth Sleepiness Scale have been shown to perform poorly in the general obstetric population [14,15]. The lack of association between miscarriage and elevated scores on the BQ or ESS individually here could be due to their poor performance in this population as a screening tool for either obstructive sleep apnea or excessive sleepiness alone, but raise the interesting hypothesis that symptomatic gravidae at risk of sleep apnea who also have hypersomnolence are the specific population that should be prioritized for objective sleep apnea testing. Recent review articles have suggested using snoring and chronic hypertension as risk factors prompting testing of gravidae for obstructive sleep apnea [13,35]. These risk factors are consistent with our findings on individual item analysis. However, a standardized and validated questionnaire for the obstetric population could be an asset in detecting sleep disordered breathing in the clinical setting; one such questionnaire, published after the enrollment period of this prospective study, has been validated in pregnancy and is used clinically in some settings [19,36,37].

Any napping and napping three or more times weekly were associated with lower rates of miscarriage. The association of napping at all did persist after adjusting for all other potentially confounding variables. These findings could be explained by the small sample size screened in the first trimester or by the frequency of multifactorial fatigue in pregnancy, which may make these questions a poor indicator of objective hypersomnolence or sleep disturbance in pregnancy. It may also be that napping counteracts some effects of hypersomnolence.

Strengths of our study include a sample of participants with known histories and outcomes which were manually entered into the database by obstetric physicians (KMA7 and MD). The prospective nature of the study also ensured that responses to subjective questions, such as fatigue and napping, were accurate as minimal recall was required to answer questions.

The most significant limitation of this study was the small proportion of gravidae who completed the questionnaire in the first trimester. This may have particularly limited our ability to adjust for confounding variables. Prepregnancy BMI data was also missing for a substantial number of those included, thus we were not able to adjust for this potentially important factor. This is a limitation noted in recent meta-analyses of sleep disordered breathing in pregnancy [14]. Here, BMI data was missing for more gravidae with miscarriage than those with ongoing pregnancy. While referral for positive screens occurred within a few days of questionnaire completion, data entry was delayed. Confirming the pregravid weight required in-depth review of scanned paper records, and this step was unfortunately not always performed in pregnancies that had already miscarried because these pregnancies were not included in the primary analysis [16]. Additionally, because this questionnaire was completed at a prenatal visit, gravidae who miscarried prior to the first prenatal visit were not included in our sample. Gravidae with prior history of miscarriage may also be more likely to seek earlier pregnancy care and thus complete the questionnaire than gravidae with no history of miscarriage; however, the overall miscarriage rate in the study population (13.9%) is within the range of estimated rates in the general population

(10–26%) [38–40]. In future studies, recruiting gravidae earlier in pregnancy or screening or testing prior to pregnancy could provide further evidence to elucidate the association between sleep disordered breathing and miscarriage. The lack of objective diagnostic data is a limitation of this study. Though gravidae were referred for polysomnography, few were able to undergo further testing, which is reflective of resource limitations at the study site [15,16]. Treatment of sleep disordered breathing and its effect on miscarriage was not evaluated in this analysis. This population was majority Hispanic/Latinx, which is an understudied population, so this contribution is needed. However, this also limits the generalizability of our findings. Future research evaluating treatment of objectively diagnosed sleep disordered breathing, especially associated with symptomatic excessive sleepiness in the obstetric population could address this limitation.

5. Conclusions

As noted in recent publications on sleep disordered breathing in pregnancy, data on obstructive sleep apnea in early pregnancy, and specifically miscarriage, are limited [6,14]. This study contributes to the available evidence on this topic. In the context of prior hypotheses and available evidence, our study suggests a possible association between obstructive sleep apnea, excessive sleepiness phenotype, and miscarriage. Although it is not known whether treatment would alter pregnancy outcomes, it is reasonable to consider screening gravidae for sleep disordered breathing at the initiation of prenatal care or at preconception consultations. Further studies are needed to clarify this association with larger sample sizes and more available data on confounding variables such as BMI, as well as to evaluate potential screening tools and feasible diagnostic and treatment modalities.

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Institutional Review Board Statement: The parent study was approved by the Institutional Review Board at Baylor College of Medicine (IRB H-19183) and was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was obtained from all participants at the time of the parent study. This current secondary analysis was determined to be exempt from approval by the Minimal Risk Health Sciences Institutional Review Board at the University of Wisconsin–Madison.

Informed Consent Statement: Informed consent was obtained from all participants at the time of the parent study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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