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Predictors of Sleep Disordered Breathing in Pregnancy

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Abstract

Background—Sleep disordered breathing (SDB) is common in pregnancy, but there are limited data on predictors.

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Objectives—The objective of this study was to develop predictive models of SDB during pregnancy.

Study Design—Nulliparous women completed validated questionnaires to assess for symptoms related to snoring, fatigue, excessive daytime sleepiness insomnia and restless leg syndrome. These included questions regarding the timing of sleep and sleep duration, work schedules (e.g., shift work, night work), sleep positions, and previously diagnosed sleep disorders. Frequent snoring was defined as self-reported snoring ≥3 days per week. Participants underwent in-home portable sleep studies for SDB assessment in early (6–15 weeks') and mid-pregnancy (22–31 weeks'). SDB was characterized using an apnea hypopnea index (AHI) that included all apneas, plus hypopneas with ≥3% oxygen desaturation. For primary analyses, an AHI ≥5 events/hour was used to define SDB. Odds ratios and 95% confidence intervals (CIs) were calculated for predictor variables. Predictive ability of the logistic models was estimated using area under the receiver-operating-characteristic curves, along with sensitivities, specificities, and positive and negative predictive values and likelihood ratios.

Results—Among 3705 women who were enrolled, data were available for 3,264 and 2,512 women in early and mid-pregnancy, respectively. The corresponding prevalence of SDB was 3.6% and 8.3%. At each time point in gestation, frequent snoring, chronic hypertension, greater maternal age, BMI, neck circumference, and systolic blood pressure were most strongly associated with an increased risk of SDB. Logistic regression models that included current age, BMI, and frequent snoring predicted SDB in early pregnancy, SDB in mid-pregnancy, and new onset SDB in mid-pregnancy with 10-fold cross-validated AUCs of 0.870, 0.838, and 0.809. We provide a supplement with expanded tables, integrated predictiveness and classification curves, and an Excel predicted probability calculator.

Conclusion(s)—Among nulliparous pregnant women, logistic regression models with just three variables (i.e., age, BMI, and frequent snoring) achieved good prediction of prevalent and incident SDB. These results can help with screening for SDB in the clinical setting and for future clinical treatment trials.

Keywords

home sleep test; methods; pregnancy; sleep-disordered breathing; sleep; prediction

Sleep disordered breathing (SDB), predominantly obstructive sleep apnea, occurs in 10 to 32% of pregnancies (varying with population, diagnostic method, and definition of SDB).[1–3] SDB is a risk factor for pregnancy-related complications including gestational hypertension, preeclampsia, and gestational diabetes mellitus (GDM).[4–6] The presence of SDB is also associated with an increased risk for cardiomyopathy, venous thromboembolism, anesthetic complications, severe maternal morbidity, and maternal mortality.[7] Neonatal complications such as growth restriction[8,9] and preterm delivery[10] are also increased. There is therefore considerable interest in identifying pregnant women with SDB.

SDB is challenging to identify even in a general population, because of limited specificity of SDB symptoms.[11] Women are less likely than men to report sleepiness as a symptom and are more likely to report fatigue and insomnia.[11,12] Questionnaires which have been validated in the general population, are poorly predictive in pregnant women.[2,13] Although

overnight polysomnography is the gold standard for diagnosis, the cost and inconvenience preclude widespread use[14]. Thus, it is desirable to identify pregnant women at increased risk for SDB before obtaining such polysomnography.

A number of studies have attempted to identify predictors of SDB in pregnancy. These studies have been limited by their sample size, limited study population or method of testing for SDB.[3,15] In this study, we sought to develop clinically-feasible prediction models for SDB in a large cohort of nulliparous pregnant women undergoing objective testing for SDB.

Methods

Participants in this study were enrolled in the Sleep Disordered Breathing Substudy of the: Nulliparous Pregnancy Outcomes: Monitoring Mothers-to-Be (nuMoM2b) study. Details of the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b) parent[16] and Sleep Disordered Breathing Substudy methods have been published previously.[17] For the nuMoM2b parent study, which was managed by an independent data-coordinating center, women were recruited at eight clinical sites. Women were eligible for participation in the parent study if they were nulliparous (no prior delivery at 20 weeks of gestation or greater) and had a viable singleton pregnancy at the time of screening ($6–13^6$ weeks of gestation). Participants from the parent study were offered enrollment into the Sleep Disordered Breathing Substudy. The primary aim of the sleep substudy was to evaluate SDB during pregnancy as a risk factor for the development of hypertensive disorders of pregnancy and gestational diabetes.[5] Women were excluded for the following conditions: current SDB treated with continuous positive airway pressure treatment, severe asthma requiring continuous oral steroid therapy for more than 14 days, or a condition requiring oxygen supplementation. After enrollment, participants received routine prenatal care. During study visits, trained research coordinators obtained longitudinal clinical measurements per protocol.[17]

Questionnaires

Sleep questionnaires were completed by all participants in the parent study at the first ($6–13^6$ weeks of gestation) and third study visits ($22–29^6$ weeks). These included questions regarding the timing of sleep and sleep duration, work schedules (e.g., shift work, night work), sleep positions, and previously diagnosed sleep disorders. Frequent snoring was defined as self-reported snoring ≥3 days per week. Questions from validated sleep questionnaires that were collected included: 1) the Berlin Questionnaire (a screening instrument designed to identify adults likely to have OSA through a series of questions pertaining to snoring behavior and wake-time sleepiness);[18] 2) the Epworth Sleepiness Scale (a measurement of daytime sleep propensity, using estimates of the likelihood of dozing off or falling asleep in 8 different sedentary situations);[19,20] 3) the International Restless Legs Syndrome Study Group diagnostic criteria for restless legs syndrome;[21] and 4) the Women's Health Initiative Insomnia Rating Scale (quantifying insomnia symptom severity).[22,23]

Home Sleep Testing

Participants in the nuMoM2b Sleep Disordered Breathing Substudy underwent in-home sleep apnea testing using a six-channel monitor that was self-applied by the participant for a single night at two time points: early pregnancy at 6–15^{6} weeks of gestation (within 2 weeks following nuMoM2b study Visit 1) and mid-pregnancy at 22–31^{6} weeks (within 2 weeks following Visit 3). Sleep study data were downloaded at the study site and electronically transmitted to a central sleep reading center where data were scored by individuals masked to all other study data. A description of the scoring and quality control protocol has been previously published.[17] Sleep studies were scored using the alternative definitions of the American Academy of Sleep Medicine.[24] SDB was characterized using an apnea hypopnea index (AHI) that included all apneas, plus hypopneas with ≥3% oxygen desaturation

Statistical Analysis

AHI was analyzed as a dichotomous variable with an AHI ≥5 defining SDB.[25] Separate models were developed to predict the following outcomes: 1) SDB at Visit 1, 2) SDB at Visit 3, and 3) new-onset SDB at Visit 3 for those without SDB at Visit 1. Eighty-six potential predictors of interest were specified *a priori* and are summarized in the supplemental materials (Table S1 – descriptive statistics; and Table S2 – single-variable associations with SDB). These were determined by reviewing the published literature in the pregnant and non-pregnant populations, and were included if they were considered well-established risk factors.[1,14,26–28]

The potential predictors of interest were further evaluated by the members of the writing group which included experts in sleep medicine (P.Z., S.R.), maternal fetal medicine (J.L., F.F., R.S.), biostatistics (M.K., B.C., C.P.). Sixteen candidate variables for predictive modelling were selected from the potential predictors of interest based on the writing group's consensus and statistical factors: $p<0.15$ for association with SDB for at least one outcome; magnitude of observed odds ratios; avoidance of sparse numbers of SDB events in predictor response categories (where pooling was not possible) for each outcome, avoidance of potential collinearity among predictor variables, and ease and reliability of measurement in a clinical setting. Chosen candidate predictors are shown in Tables 1 and 2, which are subset from Tables S1 and S2.

Forward selection using logistic regression with $p<0.15$ to enter was used to reduce the candidate list for each outcome. Among candidate predictors, body mass index (BMI), systolic blood pressure, and frequent snoring were collected at both Visit 1 and Visit 3. Of these, only the values measured through Visit 1 were used to model SDB at Visit 1, and for Visit 3 predictions, we used only the Visit 3 measurements to avoid potential collinearity with measurements from Visit 1. Also, the latter reflected the goal of identifying measures that are readily available, acknowledging that many pregnant women initiate prenatal care after the Visit 1 time interval, and thus would not have these measurements from early pregnancy.

After forward selection, further reduction in the number of predictors was pursued to identify parsimonious and easy to apply models without appreciable loss of predictive

performance; these reduced models contained age, BMI, and frequent snoring for each outcome. These models were then examined for non-linearity. Significant quadratic effects for BMI (p=0.0003, p<0.0001, p<0.0001) were found for Visit 1, Visit 3, and Visit 3 new-onset SDB, but their inclusion resulted in observations with undue leverage on the regression. Consequently, because BMI was highly skewed at both visits, we sought a Box-Cox power transformation[29] to better normalize the BMIs for the reduced models. Using the maximum likelihood procedure[30] in SAS PROC TRANSREG, we identified $\lambda = -1.25$ as a reasonable power parameter. We computed the power transformed BMI variables as tBMI = $(BMI^{\lambda} - 1) / \lambda g$, where g = (geometric mean BMI)$^{(\lambda-1)}$ on the BMI values for the models at Visit 1, Visit 3, and new-onset SBD at Visit 3. The geometric means for BMI were 25.8, 28.6, and 28.3. Quadratic terms for BMI became nonsignificant (p=0.86, 0.37, and 0.11) after power transformation. Interactions for frequent snoring with tBMI and with age were nonsignificant (all p>0.22), as was the main effect of weeks of gestation at the sleep assessment (all p>0.20).

Calibration of the final parsimonious models was assessed using the Hosmer-Lemeshow goodness-of-fit test.[31] The models were then internally validated with 10-fold cross-validation to reduce model optimism.[32] Data for a given outcome were randomly divided into 10 subsets (folds); for a given subset, predicted probabilities were calculated based on fitting the model to the 90% not in the subset, and this was repeated for each subset. These predicted probabilities were combined across subsets and performance measures were generated. Classification was assessed using area under the curve (AUC) for the receiver-operating-characteristic (ROC) curve, and the following test characteristics were calculated at selected specificities: predicted probability cutoff, proportion of participants exceeding the cutoff, sensitivity, positive and negative predictive values (PPV, NPV), and positive and negative likelihood ratios (LR+, LR-).

In the logistic regression models, continuous predictors were standardized to zero mean and unit standard deviation so that resulting odds ratios pertain to a one standard deviation difference in the predictor. Except as otherwise stated, all tests were performed at a nominal significance level of $\alpha = 0.05$. All single degree-of-freedom tests were two-sided. No correction was made for multiple comparisons. In a given regression model, participants with missing values for one or more predictors were excluded. Analyses were conducted using SAS 9.4 (SAS Institute, Inc.). This study was approved by the institutional review board at each center, and all women provided informed written consent prior to enrollment.

Results

Among the 10,038 participants of the nuMom2b parent study, 3,705 women enrolled in the Sleep Disordered Breathing Substudy between March 2011 and September 2013. Enrollment data are presented in Figure 1. Among the 3,704 women who attempted a Visit 1 sleep study, 88.1% generated data of quality sufficient to be interpretable.[17] The Visit 3 sleep study was attempted by 2,868 women and 96.6% met criteria for data. Among those with successful Visit 1 studies, 3.5% had SDB. At Visit 3, 8.2% had SDB and 5.2% had new-onset SDB. Among the 837 women without a Visit 3 sleep study (one participant had a Visit 3 study but no Visit 1 study), 65 had a preterm delivery (35 at <20 weeks and 30 at >20

weeks) before the sleep study could be completed, 137 missed the study visit (including the sleep assessment), and 635 had a Visit 3 but did not choose to perform the sleep study. In planning the study, it was assumed and considered in sample size estimations that 25% of women would decline the second sleep study[13]; thus, the participation rate in the Visit 3 sleep study was greater than expected.

Descriptive statistics for candidate predictors by study visit are presented in Table 1. Characteristics were similar between participants with sleep studies at Visit 1 and Visit 3. The prevalence of frequent snoring increased from 18.1% to 25.7% between Visit 1 and Visit 3. Single-variable associations between candidate variables and SDB outcomes are presented in Table 2. All candidate variables had significant associations with at least one of the three outcomes. (Similar tables including all the potential predictors of interest are found in Supplemental tables S1 and S2.).

Table 3 shows results of forward logistic selection. Visit 3 BMI, maternal age, and frequent snoring captured most of the predictive power for Visit 3 SDB and new-onset Visit 3 SDB, with AUCs at entry of 0.838 and 0.812. Accordingly, they were adopted provisionally as predictors for the parsimonious models. Age and BMI at Visit 1 BMI predicted Visit 1 SDB with an AUC at entry of 0.869. We added frequent snoring at Visit 1 to this provisional set for Visit 1 SDB; this did not improve the AUC but provided consistency with the Visit 3 models. In forward selection, participants were excluded if they were missing data in any of the candidate predictors. For these provisional models, the number of participants excluded for missing predictors was 40 (1.2%), 57 (2.2%), and 50 (2.2%) for the three outcomes.

The provisional parsimonious models were then checked as described in the methods. Each of the three final parsimonious models included (transformed) BMI, maternal age, and frequent snoring. AUCs were 0.875, 0.841, and 0.816, and lack of fit was nonsignificant ($p=0.18$, 0.98, and 0.39), indicating reasonable calibration (lack of bias) for the regressions.

Figure 2 shows 10-fold cross-validated ROC curves for the final parsimonious models. The AUCs for Visit 1, Visit 3, and new-onset Visit 3 were 0.870, 0.838, and 0.809, which were only slightly smaller than the non-validated AUCs. Table 4 provides 10-fold cross-validated performance statistics for these models at selected specificities. Predicted probability cutoffs corresponding to 90% specificity were ≥0.082 for SDB at Visit 1, ≥0.170 at Visit 3, and ≥0.128 for new onset at Visit 3. Testing using these cutoffs, which are each about twice the overall prevalence, would involve referring 11.8%, 13.6%, and 12.1% of patients for objective testing and would yield sensitivities of 61.1%, 54.5%, and 45.8%. Testing with lower specificity would provide greater sensitivity but would involve cutoff probabilities near to or below the overall prevalence; this may be appropriate for designing a screening procedure for a clinical trial.

Integrated predictiveness and classification curves, along with orientation and illustrative examples, are found in the Supplement (Figures S1, S2, and S3). These show the relationships between predicted probability cutoff, proportion of participants at or above the cutoff, and the cross-validated true positive fraction (sensitivity) and false positive fraction (1 minus specificity).[31] Also in the Supplement are expanded versions of Tables 1 and 2

including all the potential predictors of interest and an Excel predicted probability calculator based on the final models, which were internally but not externally validated.

Discussion

In the clinical setting, it is important to have an inexpensive, easy-to-use and rapid tool that can be used to identify women at risk for SDB. We developed predictive models using only three variables – current maternal age, BMI, and frequent snoring – to predict objectively measured SDB in early and mid-pregnancy, including new-onset SDB in mid-pregnancy. These predictors are easily obtainable and assessment of frequent snoring involves the simple questions, “In the last 4 weeks, have you snored?” and if so, “Have you snored 3 or more times a week?”

In nuMoM2b, overnight home sleep apnea testing provided objective assessments of SDB on 3,264 nulliparous pregnant women at 6–15^{6} weeks of gestation (within 2 weeks following nuMoM2b study Visit 1) and 2,512 at 22–31^{6} weeks (within 2 weeks following Visit 3).

This study is the largest to date to prospectively evaluate the risk factors for objectively measured SDB during pregnancy. As others have reported, the Berlin and Epworth Sleepiness Scales, tools, which have been developed and used in the adult nonpregnant population, have low sensitivity and specificity, and are poorly predictive of SDB in pregnant women.[27,33,34] Our model presents a simplified option for identifying these women.

Our findings are similar to those of Facco et al.[27] Using a cohort of 100 women in early pregnancy, Facco et al. devised a scoring system which used four variables to predict SDB: chronic hypertension, age, BMI, and self- reported frequent snoring.[27] In that group, the weighted model predicted objectively-measured OSA with a sensitivity of 86% (95% CI: 66– 95%) and a specificity of 74% (62–83%). Our study has the added benefit of examining mid-pregnancy as well as early pregnancy. One of the oft cited limitations of existing cross sectional studies is the inability to differentiate between pre-existing SDB detected during pregnancy and new-onset SDB in pregnancy.[27,33] Our large sample size and longitudinal study design allowed us the opportunity to address the occurrence and predictors of new-onset SDB in mid-pregnancy. It is also notable that BMI and not pregnancy weight gain was predictive of SDB and new onset SDB. While other studies were not powered to evaluated pregnancy weight gain, their findings stressed the importance of BMI as a predictor.[3,4,27]

Pien et al. also found an increased prevalence of SDB over the course of pregnancy in a group of women who underwent in-laboratory polysomnography, and concluded that age and BMI were the predominant risk factors for SDB regardless of the trimester of pregnancy. [3] Our findings are also consistent with observations in the general population, in which the predictors of age, BMI, and frequent snoring are most predictive of SDB.[35]

As in other reports, excessive daytime sleepiness, a traditionally reported symptom of SDB was not predictive of SDB in this population. The sole such variable which was associated with SDB was the self-reported “nodding off while driving” but reported numbers were

small, and the associations did not meet criteria for inclusion into the candidate list. Our findings are consistent with other reports[2,27,33] and highlight the difficulty of identifying SDB.[36] One exception was self-reported frequent snoring. While most cases of SDB in early pregnancy were predicted by age and BMI, later in pregnancy, the presence of self-reported frequent snoring was associated with the ascertainment of more cases of SDB. The prevalence of self-reported snoring increases over the course of pregnancy, as does the prevalence of SDB, [1,33,37] as we also found in our study. Our results agree with the findings of Shah and colleagues who specifically examined the value of considering symptoms such as fatigue and insomnia as predictor of SDB in women, and we also found that a simpler equation, including age, BMI and snoring frequency provided the best prediction equation.[35]

The strengths of this study are the prospective design, longitudinal assessment of exposures and outcomes in both early and mid-pregnancy, and the sample size. The use of a central sleep reading center allowed for uniform interpretation of sleep data. However, when interpreting our data, a few limitations should be considered. This was a cohort of mostly young healthy women. As such, the prevalence of SDB may have been lower than in a community-based sample. Given this limitation, our model may underestimate the probability of SDB in a cohort with more multiparous and older women. While the gold standard for diagnosis of SDB is overnight polysomnography,[38] the cost and inconvenience of laboratory overnight polysomnography precluded its use in such a large study. Home sleep apnea testing is an acceptable alternative for diagnosis in select populations and has been used increasingly in the general population.[38] However, because total sleep time is usually overestimated during home sleep testing and arousals precipitated by disordered breathing events are not detected (since EEG signals are not usually recorded), AHI may be underestimated. In our study we used a cutoff of AHI ≥5 as abnormal and participants underwent a single night of home sleep testing. One night of sleep may not be truly representative as there has been reported night to night variation in the severity of sleep apnea.[39] Furthermore, the AHI may not identify individuals with airflow limitation, or upper airway resistance syndrome, who despite a low AHI may experience symptoms and adverse health outcomes.

In conclusion, our results demonstrate that SDB among pregnant women can be predicted in early pregnancy and mid-pregnancy (prevalent and incident SDB) by simple models including current age, BMI, and self-reported frequent snoring. Our models performed well, with AUCs above 0.8. Our findings are important for the practicing clinician who seeks to identify pregnant women at high risk for SDB. Our findings can also help inform the screening of women for future studies of SDB in pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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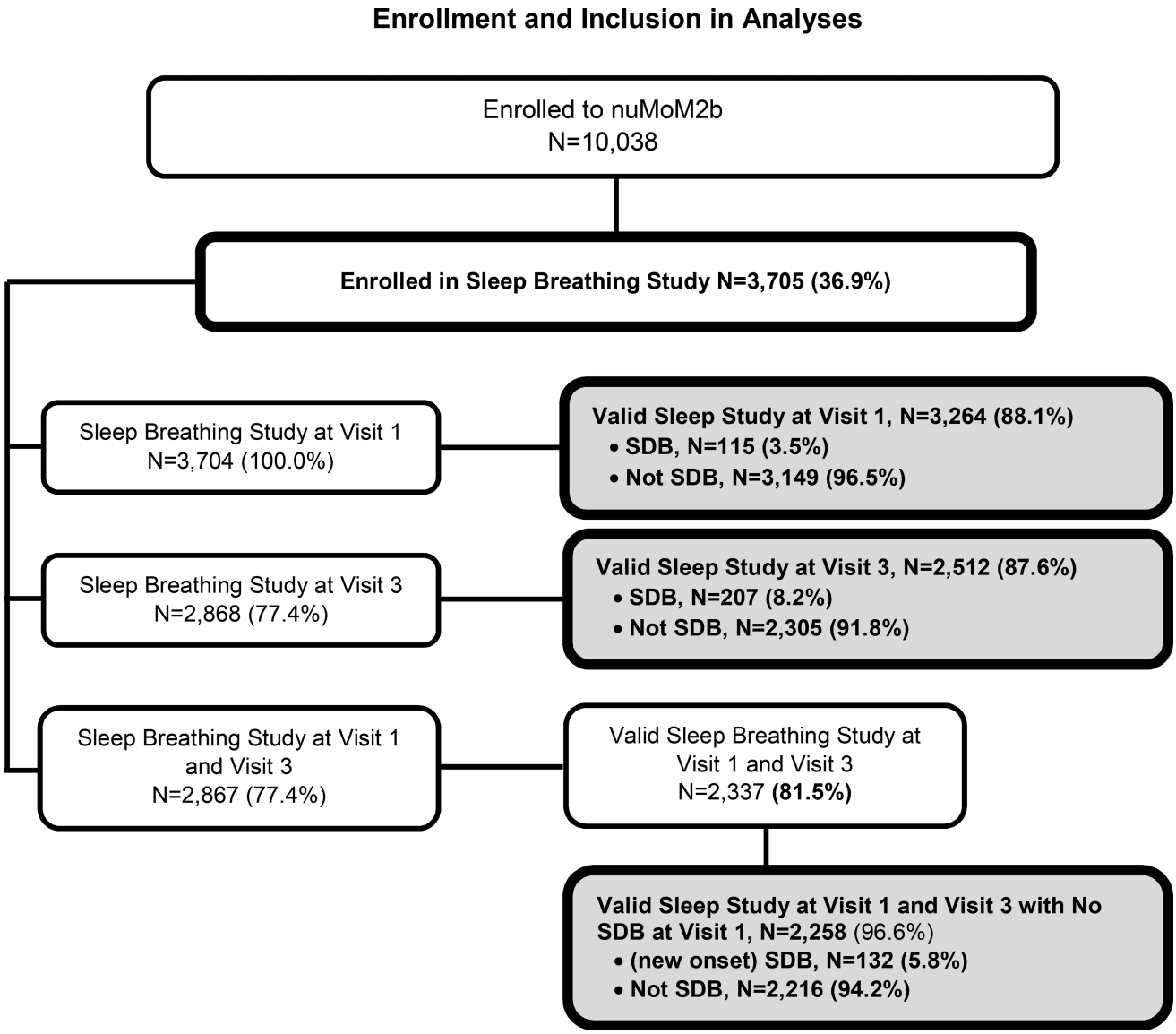

Figure 1.

Flowchart showing enrollment in the Sleep Disordered Breathing Study within the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b) and inclusion in modelling for prediction of SDB at the first study visit and the third study visit, and new onset SDB at the third study visit.

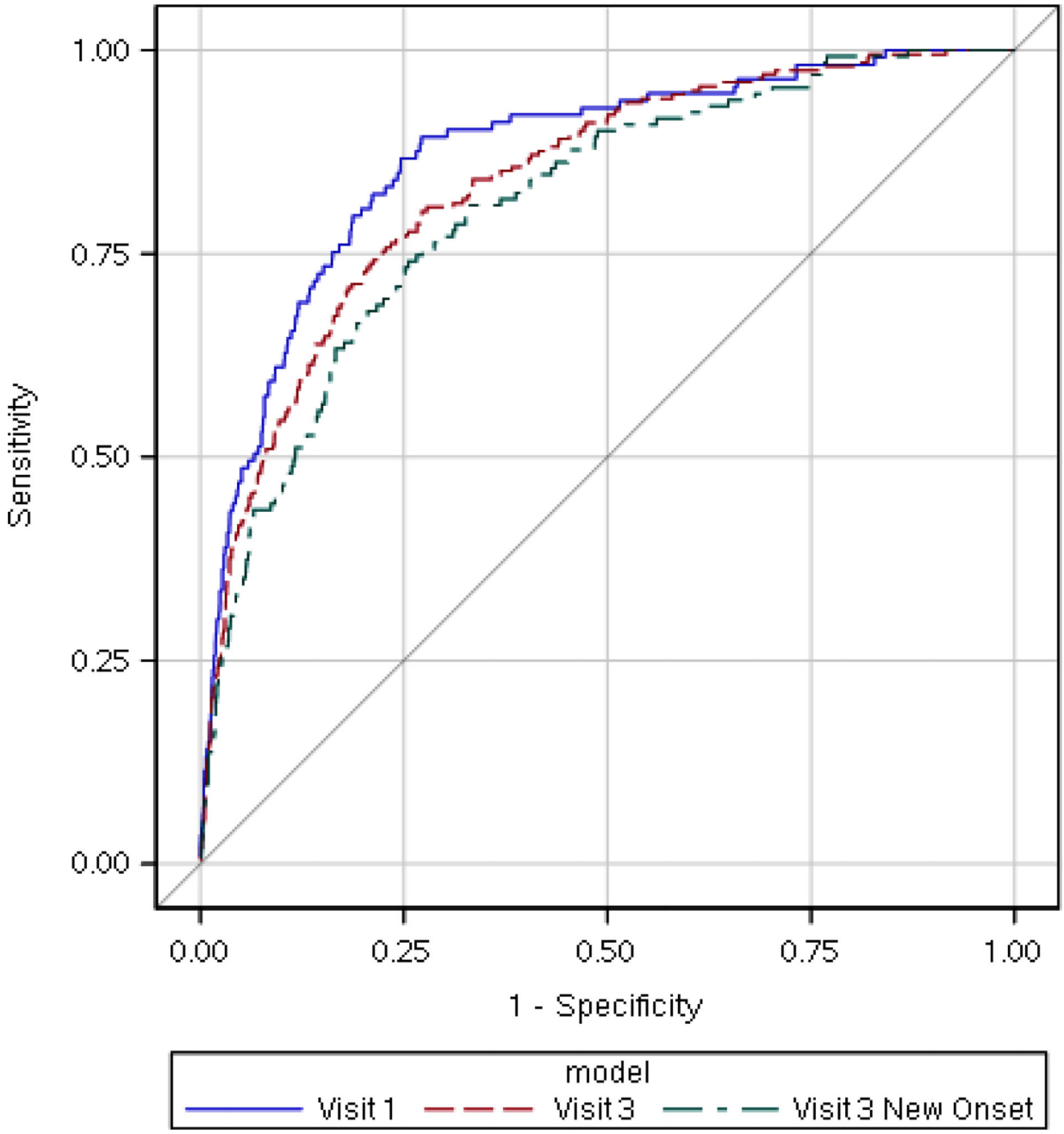

Figure 2.

Ten-fold cross-validated receiver operating characteristic (ROC) curves for the final parsimonious models for prediction of SDB at the first study visit (transformed BMI at V1, maternal age at V1, and frequent snoring at V1; AUC=0.870), SDB at the third study visit (transformed BMI at V3, maternal age at V3, and frequent snoring at V3; AUC=0.838), and new onset SDB at the third study visit (also transformed BMI at V3, maternal age at V3, and frequent snoring at V3; AUC=0.809). BMI was transformed using a Box-Cox power

transformation with $\lambda = -1.25$ (see methods). Frequent snoring was defined as snoring ≥3 days per week during the 4 weeks prior to the visit.

Table 1

Characteristics of the nuMoM2b Sleep Breathing Study Participants at Visit 1 (6^0 to 13^6 weeks' gestation) and Visit 3 (22^0 to 29^6 weeks' gestation)

Candidate predictor variables	Visit 1 N = 3264	Visit 3 N = 2512
Maternal age at Visit 1, in years		
Mean (standard deviation)	26.8 (5.6)	27.0 (5.4)
Category: n (%)		
13–21	679 (20.8)	463 (18.4)
22–35	2,365 (72.5)	1,888 (75.2)
>35	220 (6.7)	161 (6.4)
Maternal race/ethnicity: n (%)		
White, Non-Hispanic	1,971 (60.4)	1,590 (63.3)
Black, Non-Hispanic	416 (12.7)	287 (11.4)
Hispanic	598 (18.3)	424 (16.9)
Asian	123 (3.8)	92 (3.7)
Other	156 (4.8)	119 (4.7)
Education status reported at Visit 1: n (%)		
Less than high school	222 (6.8)	150 (6.0)
Completed high school or GED	410 (12.6)	276 (11.0)
Some college	685 (21.0)	517 (20.6)
Associate or technical degree	360 (11.0)	281 (11.2)
Completed college	911 (27.9)	756 (30.1)
Degree work beyond college	676 (20.7)	532 (21.2)
Smoked during 3 months before became pregnant: n (%)		
Yes	564 (17.3)	412 (16.4)
No	2,698 (82.7)	2,099 (83.6)
Chronic hypertension: n (%)		
Yes	70 (2.2)	57 (2.3)
No	3,065 (97.8)	2,418 (97.7)
Hypothyroidism: n (%)		
Yes	172 (5.5)	136 (5.6)
No	2,958 (94.5)	2,301 (94.4)
Family history * of diabetes: n (%)		
Yes	697 (22.4)	546 (22.2)
No	2,411 (77.6)	1,909 (77.8)
Family history * of heart disease: n (%)		
Yes	260 (11.6)	214 (12.2)
No	1,972 (88.4)	1,543 (87.8)
Family history * of hypertension: n (%)		
Yes	1,017 (45.7)	807 (46.1)

Candidate predictor variables	Visit 1 N = 3264	Visit 3 N = 2512
No	1,210 (54.3)	945 (53.9)
BMI at Visit 1, in kg/m2		
Mean (standard deviation)	26.4 (6.4)	26.4 (6.3)
Category: n (%)		
<25	1,690 (52.4)	1,317 (53.1)
25 to <30	805 (25.0)	591 (23.8)
30 to <35	380 (11.8)	311 (12.5)
≥35	349 (10.8)	263 (10.6)
BMI at Visit 3, in kg/m2		
Mean (standard deviation)	--	29.2 (6.1)
Category: n (%)		
<25	--	644 (26.2)
25 to <30	--	961 (39.1)
30 to <35	--	444 (18.1)
≥35	--	407 (16.6)
Neck circumference at Visit 1, in cm		
Mean (standard deviation)	32.9 (3.0)	32.9 (3.0)
Category: n (%)		
<34	2,095 (67.0)	1,636 (67.5)
34 to 36.5	697 (22.3)	535 (22.1)
>36.5	335 (10.7)	252 (10.4)
Systolic blood pressure at Visit 1, in mm Hg		
Mean (standard deviation)	109.1 (10.7)	109.0 (10.7)
Category: n (%)		
<140	3,190 (99.4)	2,460 (99.4)
≥140	19 (0.6)	14 (0.6)
Systolic blood pressure at Visit 3, in mm Hg		
Mean (standard deviation)	--	110.7 (10.9)
Category: n (%)		
<140	--	2,465 (99.4)
≥140	--	16 (0.6)
Frequent snoring ** in 4 weeks before Visit 1: n (%)		
Yes	409 (18.1)	317 (17.7)
No	1,854 (81.9)	1,475 (82.3)
Frequent snoring ** in 4 weeks before Visit 3: n (%)		
Yes	--	471 (25.7)
No	--	1,361 (74.3)

* Father, mother, brother, sister, half-brother or half-sister.

** Snoring ≥3 days per week

Table 2

Statistics for Candidate Predictor Variables for Visit 1 (6^0 to 13^6 weeks' gestation) and Visit 3 (22^0 to 29^6 weeks' gestation): Numbers and Proportions of Participants with Sleep Disordered Breathing (SDB; AHI ≥5), Means by SDB Status, and Odds Ratios for Associations between Candidate Predictor Variables and SDB

Candidate predictor variables	Visit 1 N = 3264		Visit 3 N = 2512		New Onset at Visit 3 N = 2258*	
	Descriptive Statistic	Odds Ratio** (95% CI)	Descriptive Statistic	Odds Ratio** (95% CI)	Descriptive Statistic	Odds Ratio** (95% CI)
Total: n (%) SDB	115 (3.5)		207 (8.2)		132 (5.8)	
Maternal age at Visit 1, in years						
Mean (standard deviation)						
SDB	29.7 (5.9)	1.7 (1.4, 2.0)	29.8 (5.5)	1.7 (1.5, 2.0)	29.8 (5.1)	1.8 (1.5, 2.1)
no SDB	26.7 (5.6)	reference	26.7 (5.3)	reference	26.7 (5.3)	reference
P-value		<.0001		<.0001		<.0001
Category: n (%) SDB						
13–21	11 (1.6)	0.5 (0.2, 0.9)	13 (2.8)	0.3 (0.2, 0.5)	8 (1.9)	0.3 (0.1, 0.6)
22–35	82 (3.5)	reference	162 (8.6)	reference	107 (6.3)	reference
>35	22 (10.0)	3.1 (1.9, 5.1)	32 (19.9)	2.6 (1.7, 4.0)	17 (12.6)	2.1 (1.2, 3.7)
P-value		<.0001		<.0001		<.0001
Maternal race: n (%) SDB						
White Non-Hispanic	66 (3.3)	reference	124 (7.8)	reference	83 (5.8)	reference
Black Non-Hispanic	22 (5.3)	1.6 (1.0, 2.6)	32 (11.1)	1.5 (1.0, 2.2)	17 (7.1)	1.2 (0.7, 2.1)
Hispanic	15 (2.5)	0.7 (0.4, 1.3)	25 (5.9)	0.7 (0.5, 1.2)	17 (4.3)	0.7 (0.4, 1.2)
Asian	6 (4.9)	1.5 (0.6, 3.5)	14 (15.2)	2.1 (1.2, 3.9)	9 (10.7)	1.9 (0.9, 4.0)
Other	6 (3.8)	1.2 (0.5, 2.7)	12 (10.1)	1.3 (0.7, 2.5)	6 (5.6)	1.0 (0.4, 2.3)
P-value		0.1738		0.0126		0.2131
Education status reported at Visit 1: n (%) SDB						
Less than high school	8 (3.6)	reference	8 (5.3)	reference	3 (2.3)	reference
Completed high school or GED	18 (4.4)	1.2 (0.5, 2.9)	17 (6.2)	1.2 (0.5, 2.8)	8 (3.3)	1.4 (0.4, 5.5)
Some college	28 (4.1)	1.1 (0.5, 2.5)	36 (7.0)	1.3 (0.6, 2.9)	23 (4.9)	2.2 (0.6, 7.4)
Associate or technical degree	19 (5.3)	1.5 (0.6, 3.5)	39 (13.9)	2.9 (1.3, 6.3)	24 (9.6)	4.5 (1.3, 15.3)
Completed college	24 (2.6)	0.7 (0.3, 1.6)	66 (8.7)	1.7 (0.8, 3.6)	45 (6.6)	3.0 (0.9, 9.8)

Candidate predictor variables	Visit 1 N = 3264		Visit 3 N = 2512		New Onset at Visit 3 N = 2258*	
	Descriptive Statistic	Odds Ratio** (95% CI)	Descriptive Statistic	Odds Ratio** (95% CI)	Descriptive Statistic	Odds Ratio** (95% CI)
Degree work beyond college	18 (2.7)	0.7 (0.3, 1.7)	41 (7.7)	1.5 (0.7, 3.2)	29 (6.0)	2.7 (0.8, 9.1)
P-value		0.1459		0.0067		0.0227
Smoked during 3 months before became pregnant: n (%) SDB						
Yes	30 (5.3)	1.7 (1.1, 2.6)	48 (11.7)	1.6 (1.1, 2.3)	28 (8.0)	1.5 (1.0, 2.3)
No	85 (3.2)	reference	159 (7.6)	reference	104 (5.5)	reference
P-value		0.0120		0.0064		0.0685
Chronic hypertension: n (%) SDB						
Yes	9 (12.9)	4.2 (2.0, 8.6)	18 (31.6)	5.5 (3.1, 9.8)	11 (24.4)	5.5 (2.7, 11.1)
No	105 (3.4)	reference	188 (7.8)	reference	121 (5.6)	reference
P-value		0.0001		<.0001		<.0001
Hypothyroidism: n (%) SDB						
Yes	11 (6.4)	1.9 (1.0, 3.7)	22 (16.2)	2.3 (1.4, 3.7)	14 (11.8)	2.3 (1.3, 4.1)
No	101 (3.4)	reference	178 (7.7)	reference	114 (5.5)	reference
P-value		0.0443		0.0007		0.0058
Family history*** of diabetes: n (%) SDB						
Yes	42 (6.0)	2.1 (1.4, 3.2)	62 (11.4)	1.7 (1.2, 2.3)	36 (7.6)	1.5 (1.0, 2.2)
No	70 (2.9)	reference	137 (7.2)	reference	90 (5.2)	reference
P-value		0.0001		0.0018		0.0480
Family history*** of heart disease: n (%) SDB						
Yes	20 (7.7)	2.3 (1.4, 3.8)	26 (12.1)	1.6 (1.0, 2.5)	13 (7.3)	1.3 (0.7, 2.3)
No	69 (3.5)	reference	124 (8.0)	reference	81 (5.8)	reference
P-value		0.0015		0.0452		0.4298
Family history*** of hypertension: n (%) SDB						
Yes	53 (5.2)	1.8 (1.2, 2.9)	87 (10.8)	1.7 (1.2, 2.4)	56 (7.8)	1.8 (1.2, 2.8)
No	35 (2.9)	reference	62 (6.6)	reference	37 (4.4)	reference
P-value		0.0058		0.0018		0.0051
BMI at Visit 1, in kg/m2						
Mean (standard deviation)						

Candidate predictor variables	Visit 1 N = 3264		Visit 3 N = 2512		New Onset at Visit 3 N = 2258*	
	Descriptive Statistic	Odds Ratio** (95% CI)	Descriptive Statistic	Odds Ratio** (95% CI)	Descriptive Statistic	Odds Ratio** (95% CI)
SDB	36.7 (8.3)	2.9 (2.5, 3.4)	33.4 (7.6)	2.5 (2.2, 2.8)	31.1 (6.2)	2.0 (1.7, 2.2)
no SDB	26.0 (6.0)	reference	25.8 (5.8)	reference	25.7 (5.8)	reference
P-value		<.0001		<.0001		<.0001
Category: n (%) SDB						
<25	8 (0.5)	reference	28 (2.1)	reference	24 (2.0)	reference
25 to <30	12 (1.5)	3.2 (1.3, 7.8)	41 (6.9)	3.4 (2.1, 5.6)	35 (6.4)	3.5 (2.0, 5.9)
30 to <35	33 (8.7)	20.0 (9.2, 43.7)	60 (19.3)	11.0 (6.9, 17.6)	38 (14.6)	8.6 (5.0, 14.6)
≥35	60 (17.2)	43.7 (20.7, 92.2)	76 (28.9)	18.7 (11.8, 29.6)	34 (16.8)	10.1 (5.9, 17.5)
P-value		<.0001		<.0001		<.0001
BMI at Visit 3, in kg/m2						
Mean (standard deviation)						
SDB	--	--	35.7 (6.7)	2.5 (2.2, 2.8)	33.9 (6.0)	2.0 (1.8, 2.3)
no SDB	--	--	28.6 (5.7)	reference	28.5 (5.7)	reference
P-value	--	--		<.0001		<.0001
Category: n (%) SDB						
<25	--	--	8 (1.2)	reference	7 (1.2)	reference
25 to <30	--	--	37 (3.9)	3.2 (1.5, 6.9)	31 (3.5)	3.1 (1.3, 7.0)
30 to <35	--	--	54 (12.2)	11.0 (5.2, 23.4)	39 (10.0)	9.5 (4.2, 21.5)
≥35	--	--	103 (25.3)	26.9 (13.0, 56.0)	54 (16.5)	16.8 (7.5, 37.4)
P-value	--	--		<.0001		<.0001
Neck circumference at Visit 1, in cm						
Mean (standard deviation)						
SDB	36.8 (4.6)	2.8 (2.3, 3.3)	35.5 (3.9)	2.3 (2.0, 2.6)	34.6 (2.7)	1.8 (1.6, 2.2)
no SDB	32.8 (2.8)	reference	32.7 (2.8)	reference	32.6 (2.7)	reference
P-value		<.0001		<.0001		<.0001
Category: n (%) SDB						
<34	23 (1.1)	reference	62 (3.8)	reference	50 (3.3)	reference
34 to 36.5	32 (4.6)	4.3 (2.5, 7.5)	73 (13.6)	4.0 (2.8, 5.7)	50 (10.6)	3.5 (2.3, 5.2)
>36.5	56 (16.7)	18.1 (11.0, 29.8)	65 (25.8)	8.8 (6.0, 12.9)	27 (13.9)	4.7 (2.9, 7.8)

Candidate predictor variables	Visit 1 N = 3264		Visit 3 N = 2512		New Onset at Visit 3 N = 2258*	
	Descriptive Statistic	Odds Ratio** (95% CI)	Descriptive Statistic	Odds Ratio** (95% CI)	Descriptive Statistic	Odds Ratio** (95% CI)
P-value		<.0001		<.0001		<.0001
Systolic blood pressure at Visit 1, in mm Hg						
Mean (standard deviation)						
SDB	116.5 (13.3)	1.9 (1.6, 2.3)	115.0 (11.8)	1.8 (1.6, 2.1)	114.0 (11.3)	1.7 (1.4, 2.0)
no SDB	108.8 (10.5)	reference	108.5 (10.4)	reference	108.5 (10.4)	reference
P-value		<.0001		<.0001		<.0001
Category: n (%) SDB						
<140	107 (3.4)	reference	197 (8.0)	reference	126 (5.7)	reference
≥140	5 (26.3)	10.3 (3.6, 29.1)	6 (42.9)	8.6 (3.0, 25.1)	4 (36.4)	9.5 (2.7, 32.8)
P-value		<.0001		<.0001		0.0004
Systolic blood pressure at Visit 3, in mm Hg						
Mean (standard deviation)						
SDB	--	--	116.6 (11.7)	1.8 (1.5, 2.0)	115.4 (10.8)	1.6 (1.4, 1.9)
no SDB	--	--	110.2 (10.6)	reference	110.1 (10.6)	reference
P-value	--	--		<.0001		<.0001
Category: n (%) SDB						
<140	--	--	201 (8.2)	reference	131 (5.9)	reference
≥140	--	--	4 (25.0)	3.8 (1.2, 11.7)	1 (8.3)	1.5 (0.2, 11.3)
P-value	--	--		0.0230		0.7224
Frequent snoring**** in 4 weeks before Visit 1: n (%) SDB						
Yes	35 (8.6)	3.9 (2.5, 6.2)	64 (20.2)	4.0 (2.8, 5.7)	39 (14.3)	3.6 (2.3, 5.5)
No	43 (2.3)	reference	87 (5.9)	reference	59 (4.4)	reference
P-value		<.0001		<.0001		<.0001
Frequent snoring**** in 4 weeks before Visit 3: n (%) SDB						
Yes	--	--	106 (22.5)	6.5 (4.6, 9.2)	67 (16.8)	6.1 (4.0, 9.2)
No	--	--	58 (4.3)	reference	40 (3.2)	reference
P-value	--	--		<.0001		<.0001

*Participants with AHI <5 at V1.

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** Odds ratios for continuous predictors are computed by logistic regression for a 1-standard deviation difference.

*** Father, mother, brother, sister, half-brother or half-sister.

**** Snoring ≥3 days per week

Table 3

Summary of logistic modelling of sleep disordered breathing (AHI>5) with forward selection (p<0.15 to enter) for the first study visit (V1), third study visit (V3), and new onset SDB at the third study visit (V3). Frequent snoring was defined as snoring ≥3 days per week during the 4 weeks prior to the visit.

Step	Variable entered	P-value at entry	AUC after inclusion in model	P-value in final selection model
Sleep disordered breathing at V1*:				
1	BMI (kg/m^2) at V1	<0.0001	0.8594	<0.0001
2	Age (years) at V1	<0.0001	0.8691	<0.0001
3	Education	0.0173	0.8713	0.0343
4	Race/ethnicity	0.0740	0.8725	0.0928
5	Neck circumference at V1 (cm)	0.0862	0.8725	0.0826
6	Family history of heart disease	0.1071	0.8752	0.1107
Sleep disordered breathing at V3**:				
1	BMI (kg/m^2) at V3	<0.0001	0.8016	<0.0001
2	Age (years) at V3	<0.0001	0.8257	<0.0001
3	Frequent snoring at V3	<0.0001	0.8379	<0.0001
4	Race/ethnicity	0.0056	0.8416	0.0077
5	Education	0.0113	0.8474	0.0116
6	History of hypothyroidism	0.0182	0.8498	0.0169
7	Family history of diabetes mellitus	0.0170	0.8520	0.0222
New onset sleep disordered breathing at V3***:				
1	BMI (kg/m^2) at V3	<0.0001	0.7606	<0.0001
2	Frequent snoring at V3	<0.0001	0.7907	<0.0001
3	Age (years) at V3	<0.0001	0.8119	<0.0001
4	Family history of diabetes mellitus	0.0219	0.8154	0.0190
5	History of hypothyroidism	0.0166	0.8191	0.0280
6	Education	0.0461	0.8279	0.0520

*Variables not selected for SDB at V1 were: smoking during 3 months before became pregnant, chronic hypertension, hypothyroidism, family history of diabetes, family history of hypertension, systolic blood pressure at V1, and frequent snoring in the 4 weeks before V1.

**Variables not selected for SDB at V3 were: smoking during 3 months before became pregnant, chronic hypertension, family history of heart disease, family history of hypertension, neck circumference at V1, and systolic blood pressure at V3,

***Variables not selected for new onset SDB at V3 were: race/ethnicity, smoking during 3 months before became pregnant, chronic hypertension, family history of heart disease, family history of hypertension, neck circumference at V1, and systolic blood pressure at V3,

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Table 4

Ten-fold cross-validated performance of final parsimonious models for prediction of SDB at the first study visit (V1), third study visit (V3), and new onset SDB at the third study visit (V3) at selected specificities. Predictor variables are transformed BMI at V1, maternal age at V1, and frequent snoring at V1 for SDB at V1; and transformed BMI at V3, maternal age at V3, and frequent snoring at V3 for both SDB and new onset SDB at V3. BMI was transformed using a Box-Cox power transformation with $\lambda = -1.25$ (see methods). Frequent snoring was defined as snoring ≥3 days per week during the 4 weeks prior to the visit.

SDB model	nominal specificity	predicted probability cutoff	percentage of participants	Sens	Spec	PPV	NPV	LR+	LR-
V1	50%	≥0.008	51.5%	92.9%	50.0%	6.3%	99.5%	1.86	0.14
	55%	≥0.010	46.6%	92.0%	55.0%	6.9%	99.5%	2.05	0.14
	60%	≥0.013	41.8%	92.0%	60.0%	7.7%	99.5%	2.30	0.13
	65%	≥0.017	36.9%	90.3%	65.1%	8.6%	99.5%	2.58	0.15
	70%	≥0.022	32.1%	89.4%	70.0%	9.8%	99.5%	2.98	0.15
	75%	≥0.029	27.1%	86.7%	75.0%	11.2%	99.4%	3.47	0.18
	80%	≥0.038	22.1%	80.5%	80.0%	12.8%	99.1%	4.03	0.24
	85%	≥0.055	17.0%	72.6%	85.0%	15.0%	98.8%	4.84	0.32
	90%	≥0.082	11.8%	61.1%	90.0%	18.2%	98.5%	6.11	0.43
	95%	≥0.139	6.5%	46.9%	95.0%	25.5%	98.0%	9.41	0.56
V3	50%	≥0.031	53.4 %	91. 6%	50. 0%	14. 1%	98. 5%	1.8 3	0.1 7
	55%	≥0.037	48.6%	89.1%	55.0%	15.1%	98.3%	1.98	0.20
	60%	≥0.045	43.8%	86.1%	60.0%	16.2%	98.0%	2.15	0.23
	65%	≥0.053	39.0%	84.2%	65.0%	17.7%	97.9%	2.41	0.24
	70%	≥0.065	34.1%	80.7%	70.0%	19.5%	97.6%	2.69	0.28
	75%	≥0.080	29.2%	76.7%	75.0%	21.6%	97.3%	3.07	0.31
	80%	≥0.101	24.2%	71.3%	80.0%	24.2%	96.9%	3.57	0.36
	85%	≥0.126	19.0%	63.9%	85.0%	27.7%	96.3%	4.27	0.42
	90%	≥0.170	13.6%	54.5%	90.0%	32.8%	95.7%	5.45	0.51
	95%	≥0.258	8.0%	41.6%	95.0%	42.9%	94.8%	8.37	0.61
new onset V3	50%	≥0.027	52.4 %	90. 1%	50. 0%	10. 2%	98. 8%	1.8 0	0.2 0
	55%	≥0.031	47.4%	86.3%	55.0%	10.8%	98.4%	1.92	0.25
	60%	≥0.036	42.5%	83.2%	60.0%	11.6%	98.3%	2.08	0.28

SDB model	nominal specificity	predicted probability cutoff	percentage of participants	Sens	Spec	PPV	NPV	LR+	LR-
	65%	≥0.042	37.7%	80.9%	65.0%	12.7%	98.2%	2.31	0.29
	70%	≥0.050	32.8%	77.1%	70.0%	14.0%	98.0%	2.57	0.33
	75%	≥0.061	27.8%	72.5%	75.0%	15.5%	97.7%	2.90	0.37
	80%	≥0.075	22.7%	66.4%	80.0%	17.3%	97.4%	3.32	0.42
	85%	≥0.094	17.4%	56.5%	85.0%	19.2%	96.9%	3.77	0.51
	90%	≥0.128	12.1%	45.8%	90.0%	22.5%	96.3%	4.60	0.60
	95%	≥0.187	6.7%	33.6%	95.0%	29.9%	95.8%	6.77	0.70

Sens = sensitivity, Spec = specificity, PPV = positive, predictive value, NPV = negative predictive value, LR+ = positive likelihood ratio, LR− = negative likelihood ratio.