

Snoring and Beyond: the Clinical Implications of Sleep Disordered Breathing in Pregnancy

Sushmita Pamidi, MD MSc FRCPC

Assistant Professor of Medicine
Division of Respiratory Medicine
Department of Medicine

McGill University



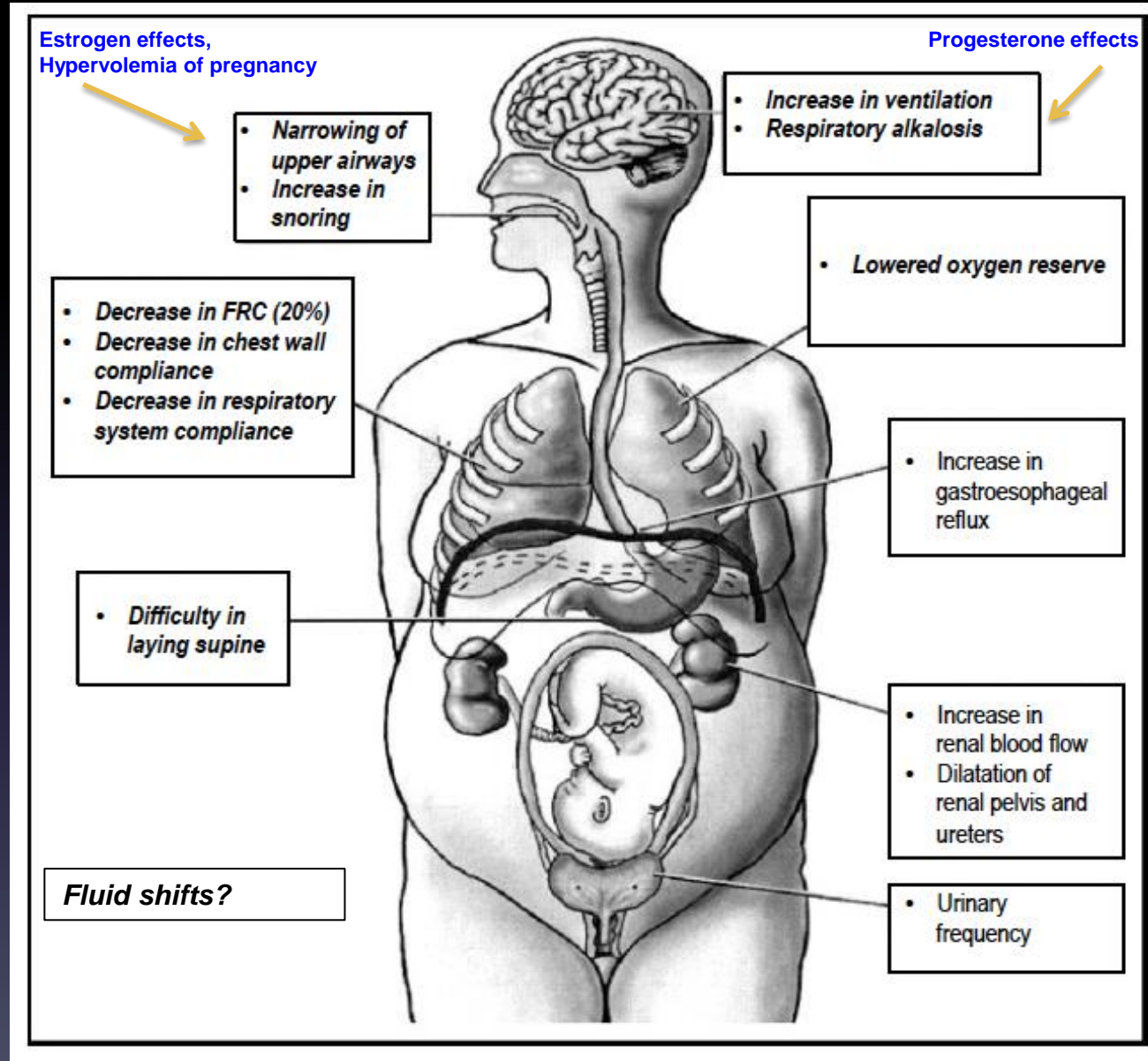
Financial Interest Disclosure

(over the past 24 months)

Sushmita Pamidi

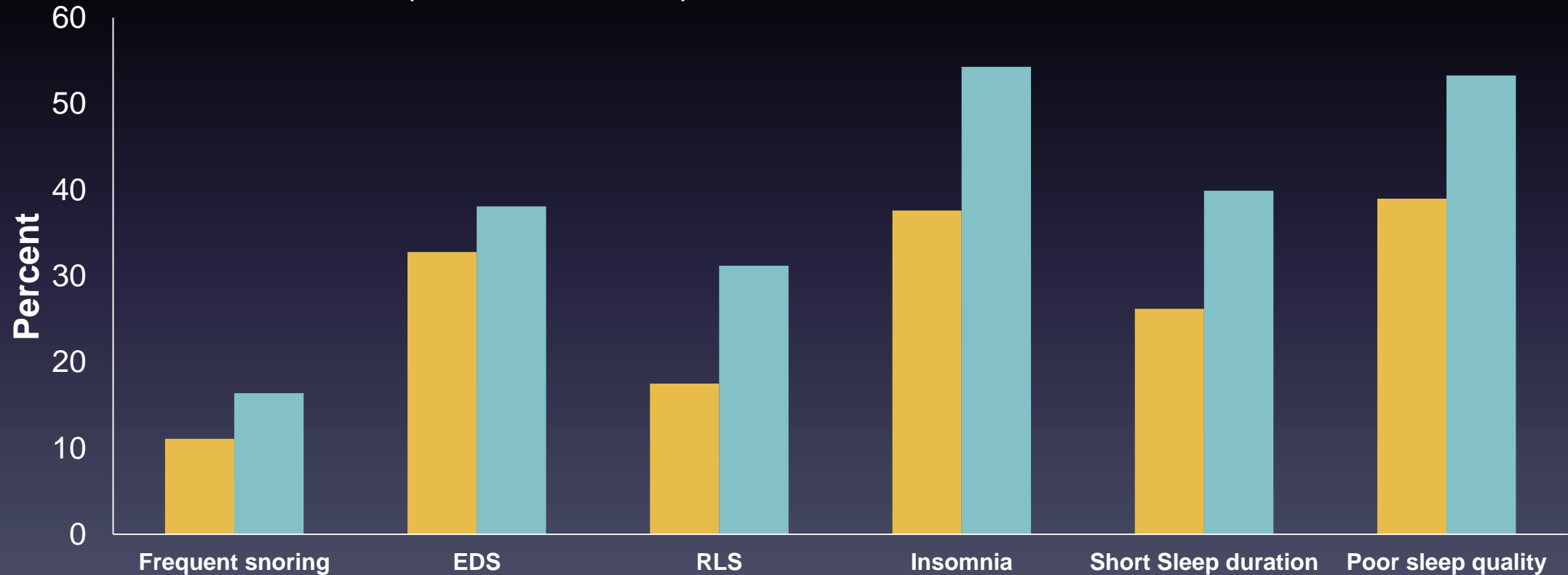
No disclosures

Factors Influencing Sleep in Pregnancy



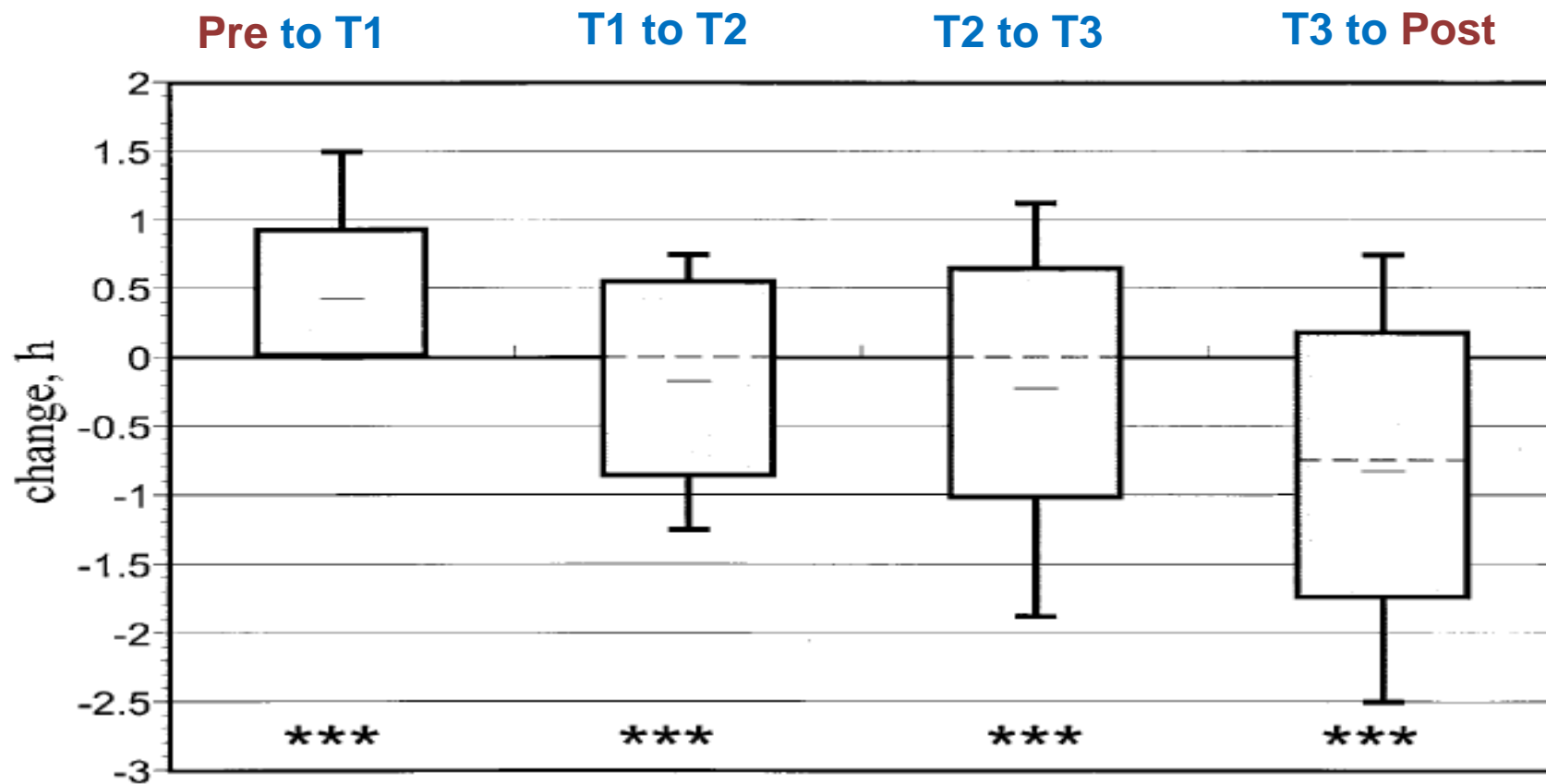
Sleep Complaints in Pregnancy

- Sleep questionnaires administered in **early pregnancy** (6-20 weeks) and in late **3rd trimester** (28-40 weeks)

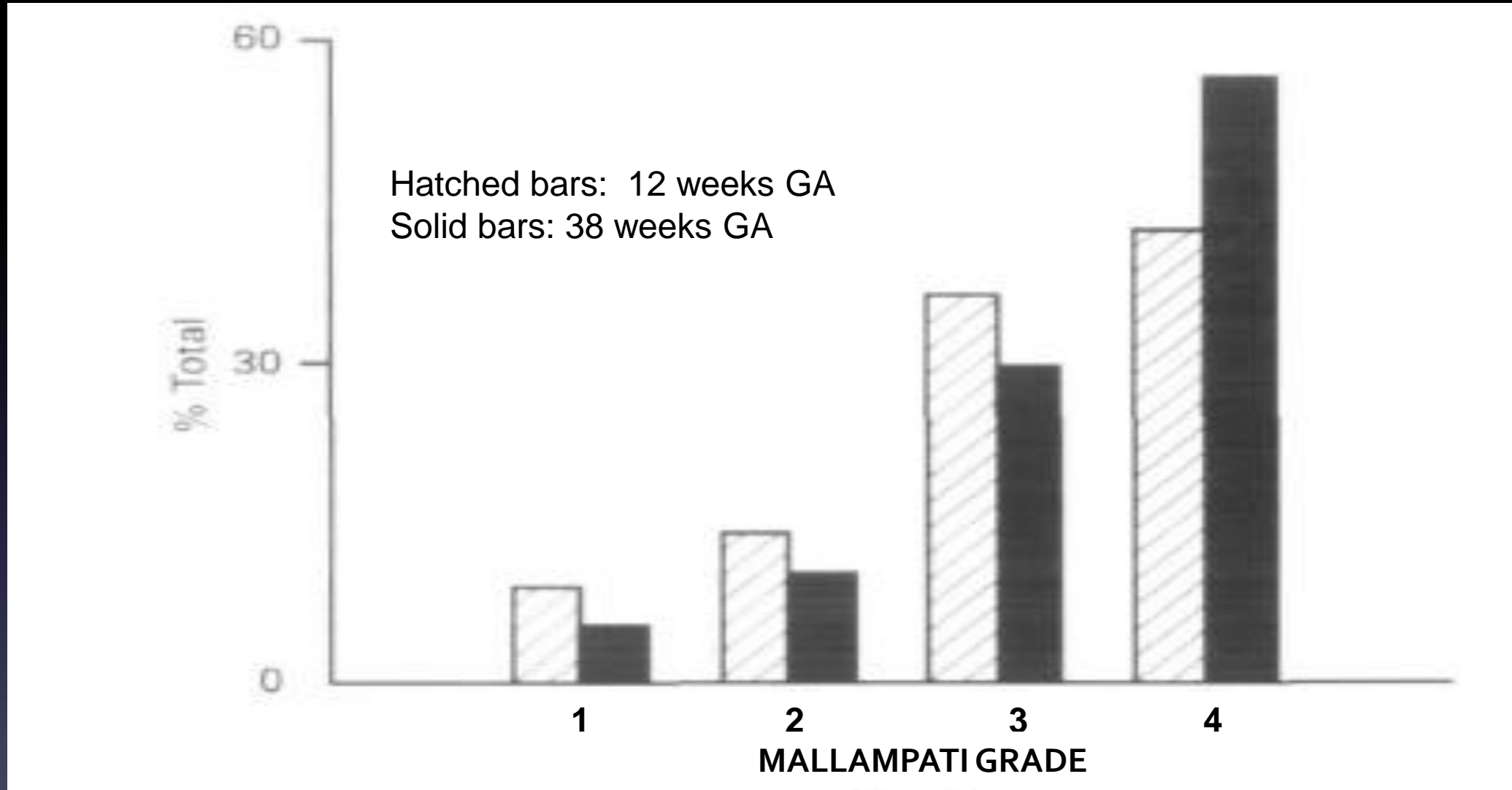


Change in Self-Reported Total Sleep Time During Pregnancy

n=325

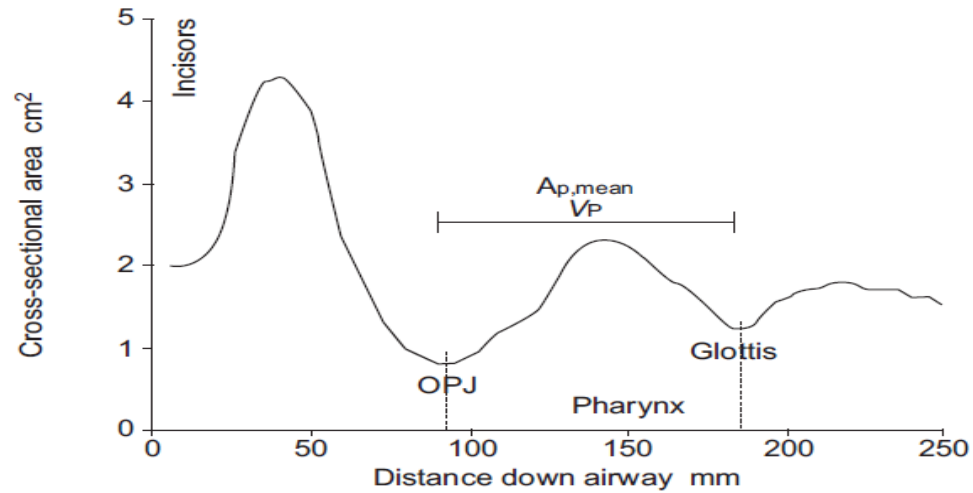


Mallampati Grade Increases As Pregnancy Progresses

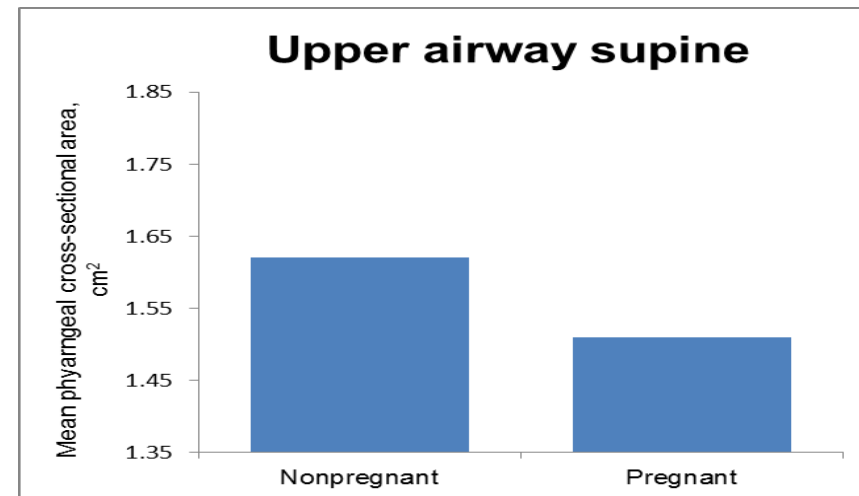
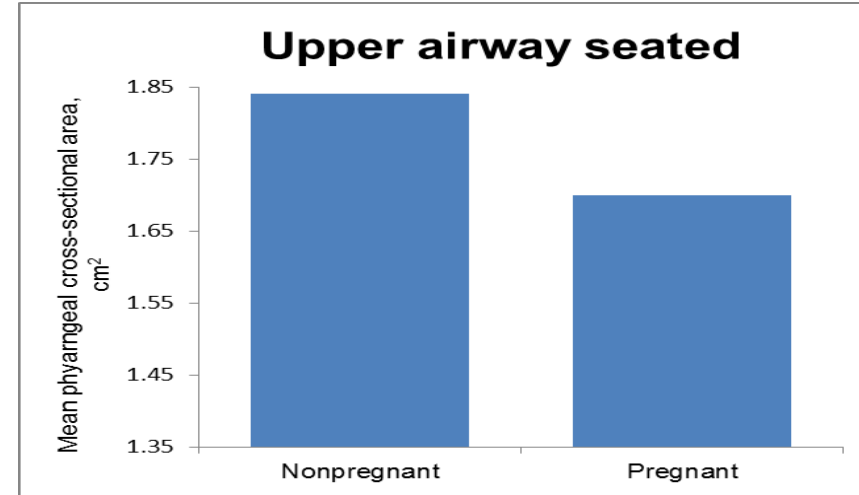


Upper Airway Size in Pregnancy

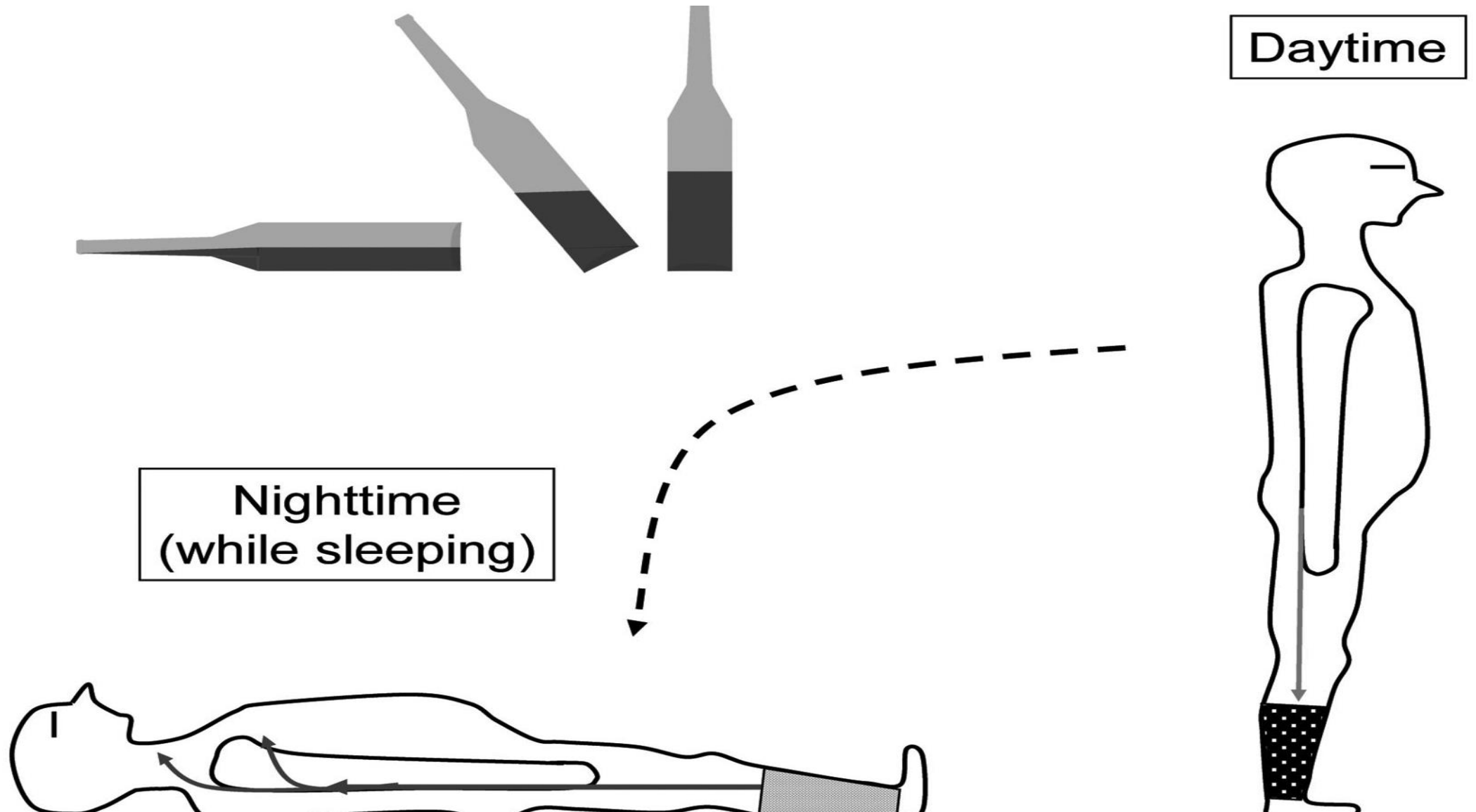
Acoustic reflectometry:



OPJ: Oropharyngeal junction



Nocturnal Fluid Shifts and Sleep Apnea

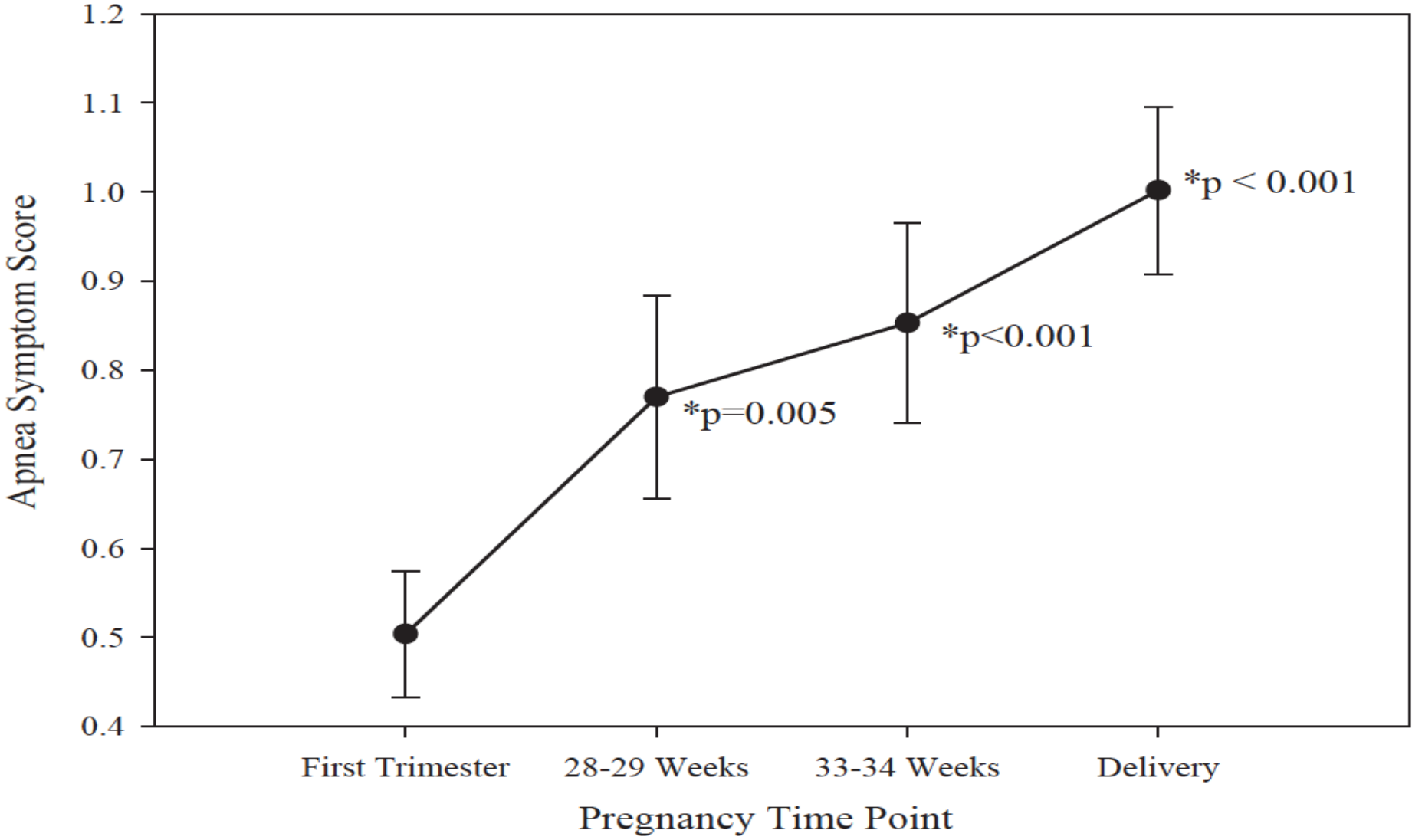


Symptoms of Sleep-Disordered Breathing (SDB) in Men vs. Women

Symptom	Odds Ratio
Loud Snoring	1.8
Snoring disturbs others	2.4
Snorts/gasps	1.9

- Women are 2-3x **less** likely to report symptoms of snoring, gasping and apnea compared to men (adjusted for RDI)

Symptoms of OSA Increase Over the Course of Pregnancy

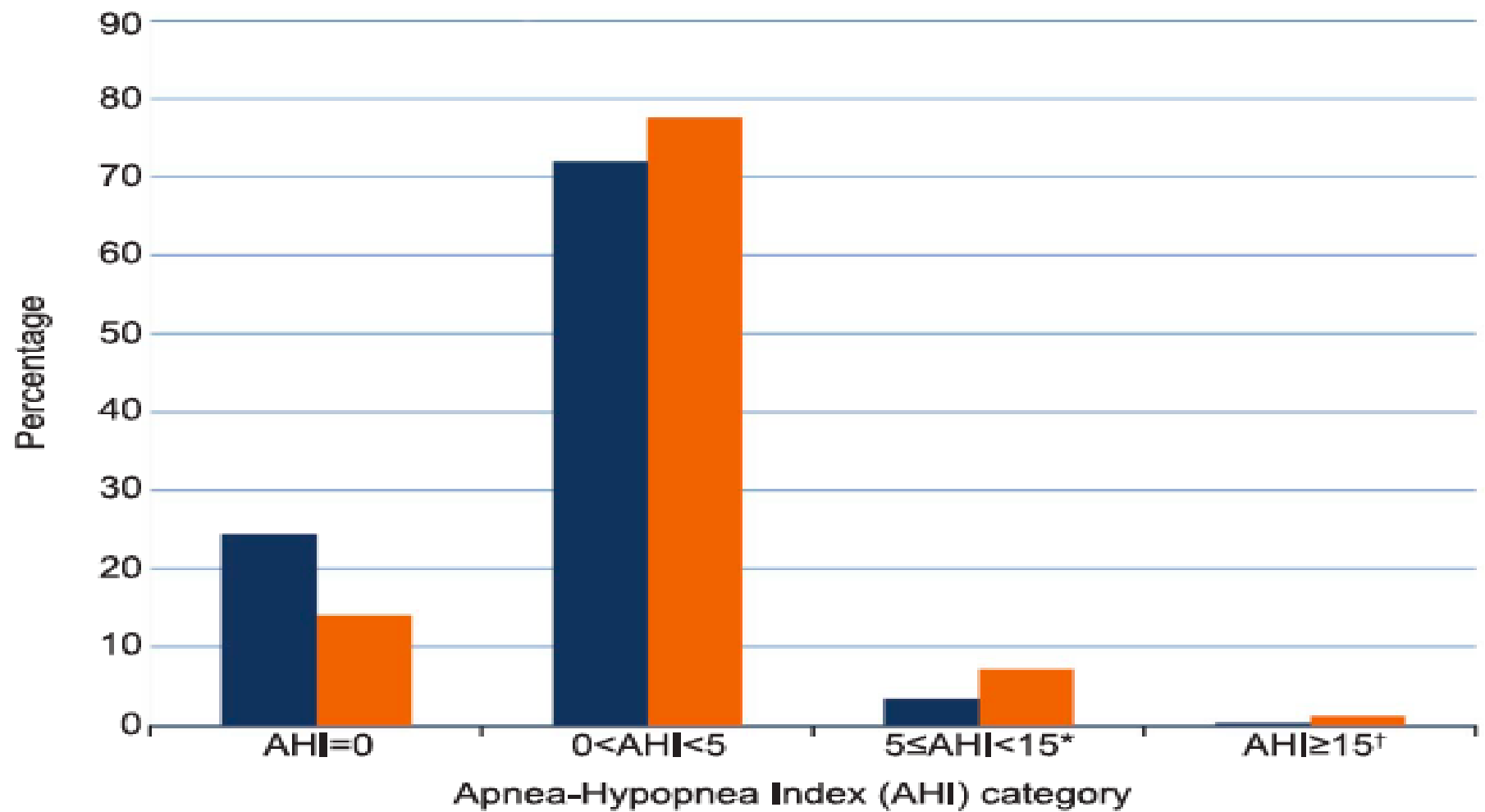


OBSTETRICS

**NuMoM2b Sleep-Disordered Breathing study:
objectives and methods**

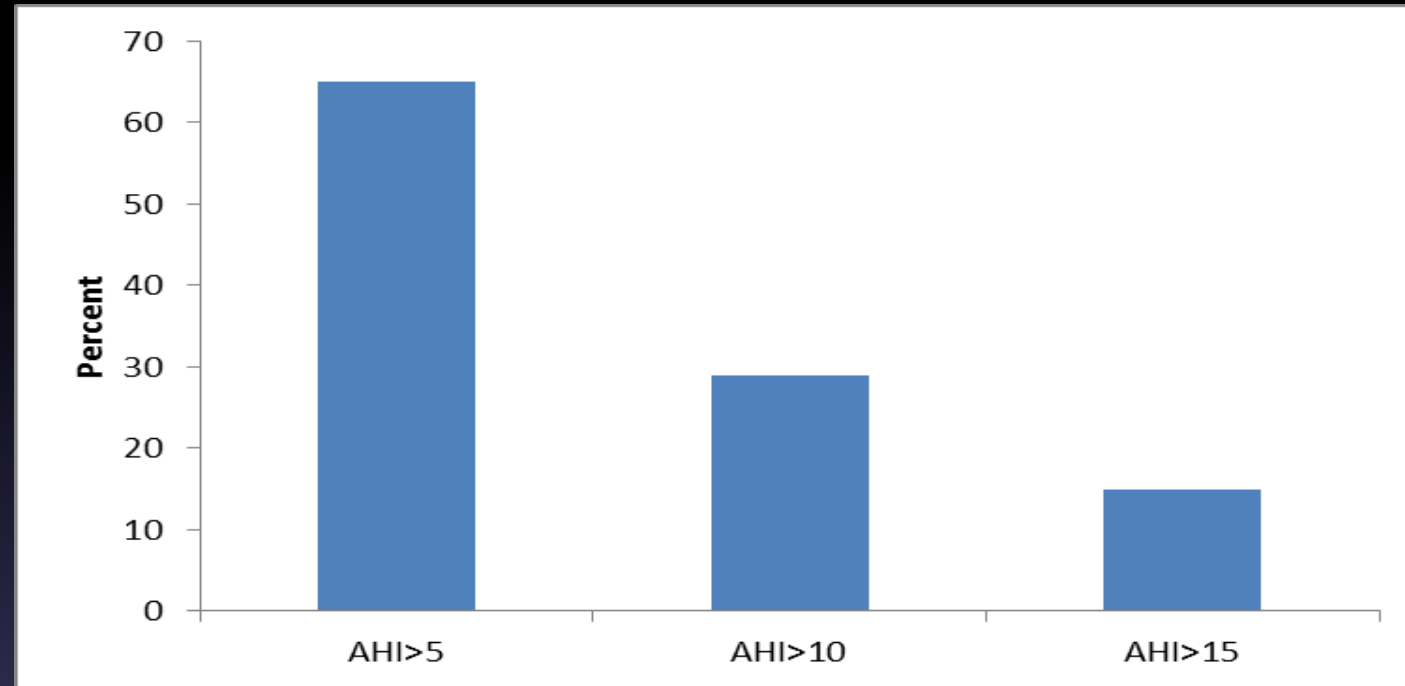
Francesca L. Facco, MD, MS; Corette B. Parker, DrPH; Uma M. Reddy, MD, MPH;
Robert M. Silver, MD; Judette M. Louis, MD, MPH; Robert C. Basner, MD;
Judith H. Chung, MD, PhD; Frank P. Schubert, MD, MS; Grace W. Pien, MD, MSCE;
Susan Redline, MD, MPH; Daniel R. Mobley, RPSGT; Matthew A. Koch, MD, PhD;
Hyagriv N. Simhan, MD, MS; Chia-Ling Nhan-Chang, MD, MS; Samuel Parry, MD;
William A. Grobman, MD, MBA; David M. Haas, MD, MS; Deborah A. Wing, MD;
Brian M. Mercer, MD; George R. Saade, MD; Phyllis C. Zee, MD, PhD

- Prospective cohort of 10,037 nulliparous women with singleton gestations across 8 sites
- Sleep Disordered Breathing substudy recruited 3,702 women to undergo objective level 3 home sleep studies (Sept 2013):
 - Visit 1: 6-15 weeks GA
 - Visit 2: 22-31 weeks GA



Early pregnancy	24.4% (22.9–25.9)	72.0% (70.4–73.6)	3.4% (2.7–4.0)	0.3% (0.1–0.5)
Mid-pregnancy	14.1% (12.7–15.5)	77.6% (75.9–79.3)	7.2% (6.1–8.2)	1.2% (0.7–1.6)

Different Scoring Criteria and AHI Cut-offs Affect Prevalence



Prospective healthy cohort of 3rd trimester women (n=234) using Chicago scoring criteria

Relationship between Symptoms and PSG-based Diagnosis of SDB in Pregnancy

Proportion

Diagnostic test result parameter (%₀, 95% CI)

First trimester

	AHI ≥ 5	AHI ≥ 10	AHI ≥ 15
Sensitivity	37.7 (28.8 to 47.3)	41.7 (27.6 to 56.8)	52.0 (31.3 to 72.2)
Specificity	83.0 (71.0 to 91.6)	73.6 (65.0 to 81.0)	73.0 (65.1 to 80.0)

Third trimester

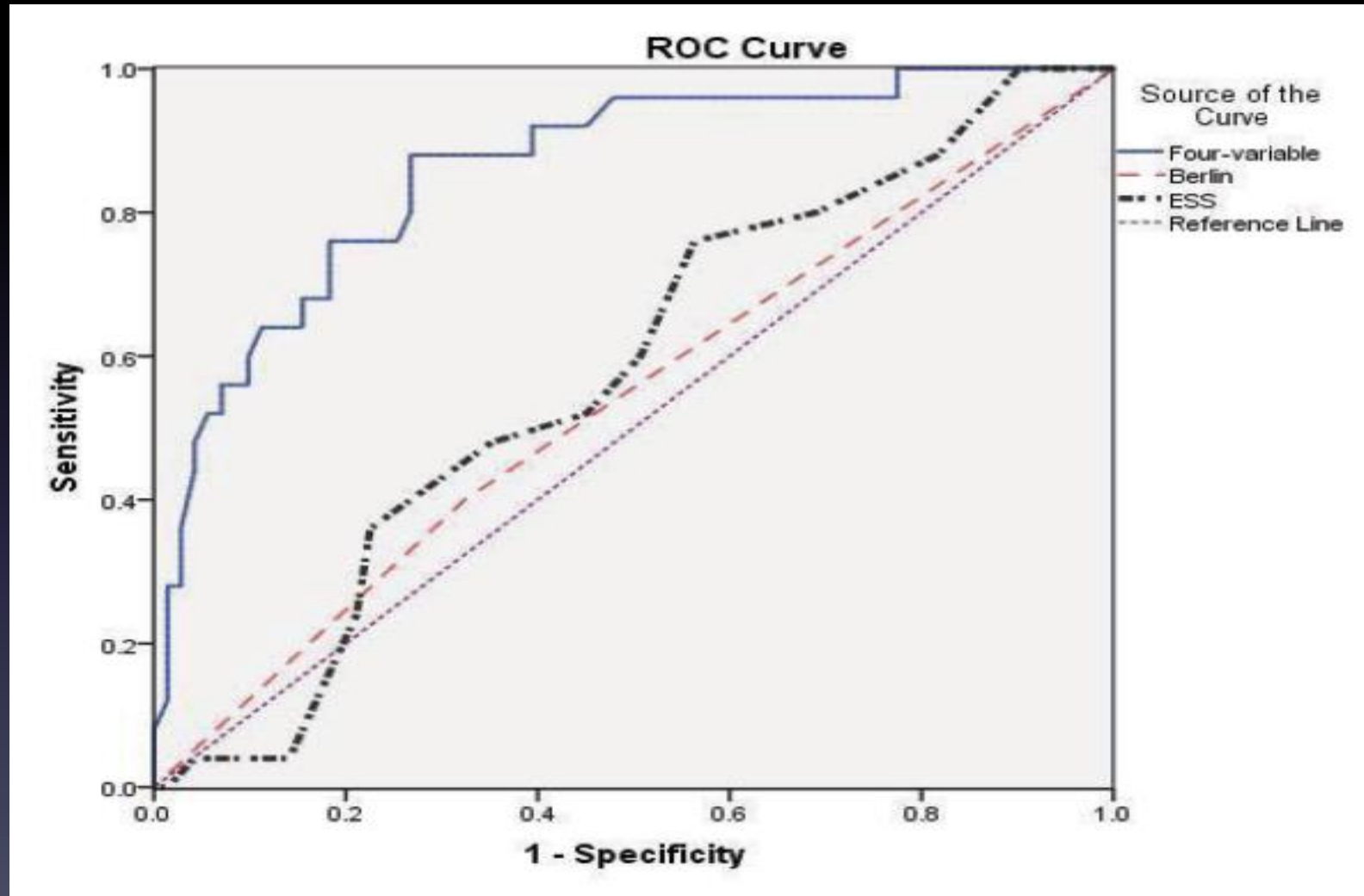
	AHI ≥ 5	AHI ≥ 10	AHI ≥ 15
Sensitivity	57.1 (47.4 to 66.4)	70.6 (56.2 to 82.5)	76.9 (56.3 to 91.0)
Specificity	63.2 (49.3 to 75.5)	58.5 (49.0 to 67.5)	54.5 (46.0 to 62.9)



Screening for SDB in Pregnancy

- Questionnaires of sleepiness (Epworth sleepiness scale; ESS) are not sensitive or specific for SDB, likely due to the high prevalence of daytime sleepiness (up to 65% of pregnant women in the third trimester)
- the Berlin Questionnaire has moderate sensitivity (pooled 0.66) and specificity (pooled 0.63) for predicting SDB
- STOP-Bang has the best specificity (0.85) in the third trimester but has poor sensitivity at only 0.53

Performance of ESS and Berlin in Screening for OSA in Pregnancy



Frequent snoring (> 3x/wk) and AHI > 5: OR 4.4

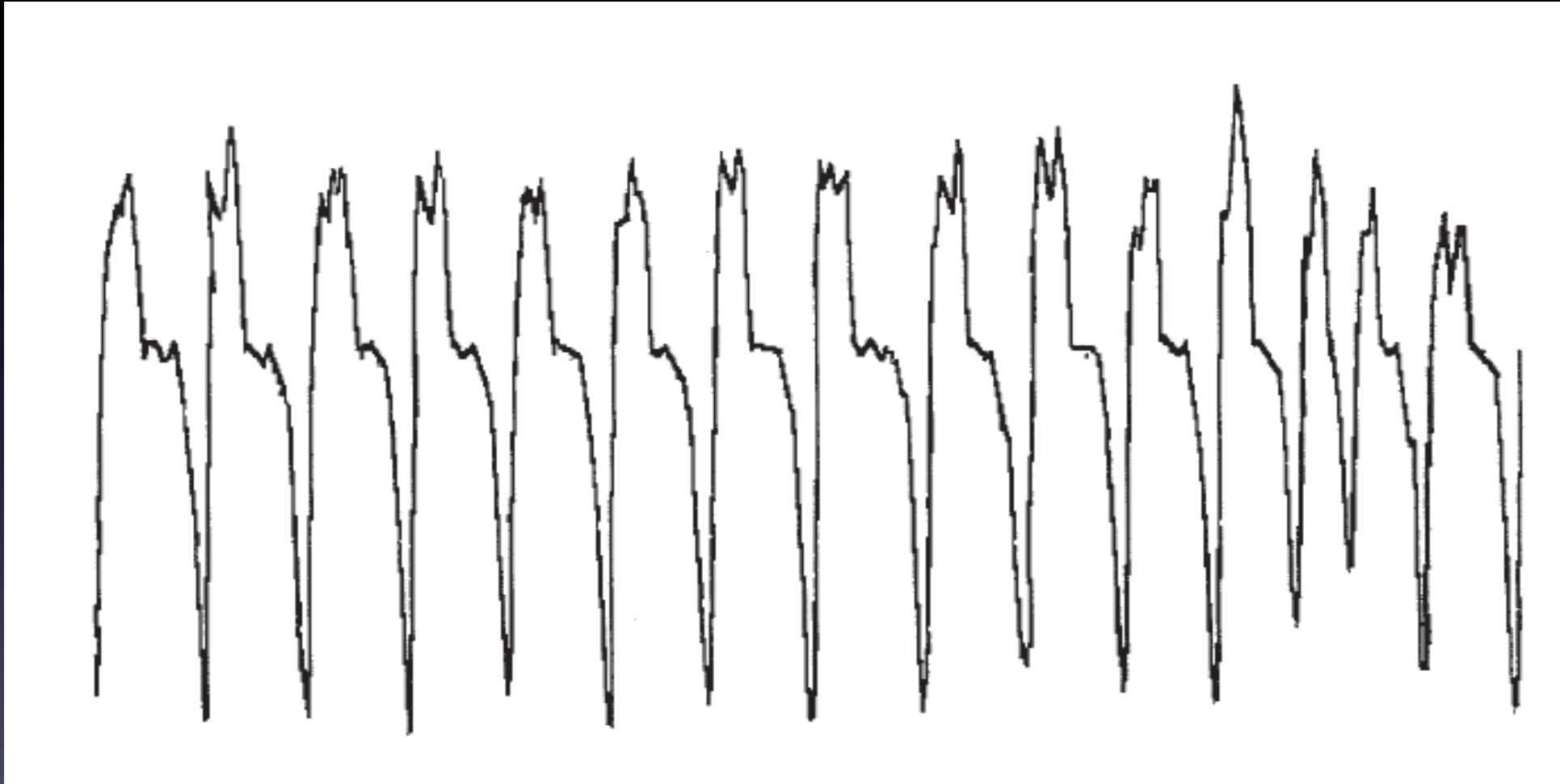
4 variable prediction:
pre-pregnancy BMI, age, chronic hypertension (15 points) and frequent snoring (15 points) → AUC 0.85.

A score of 75 (upper left corner) gave a **SN 86% and SP of 74%**

Pregnancy is Characterized by “milder” OSA

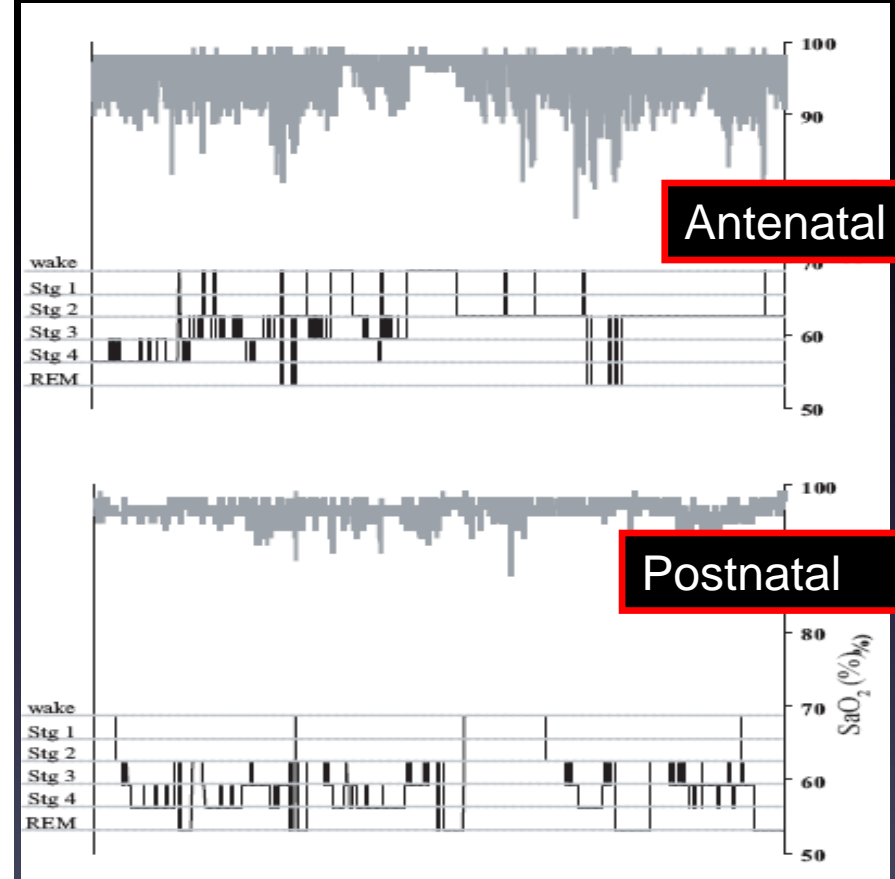
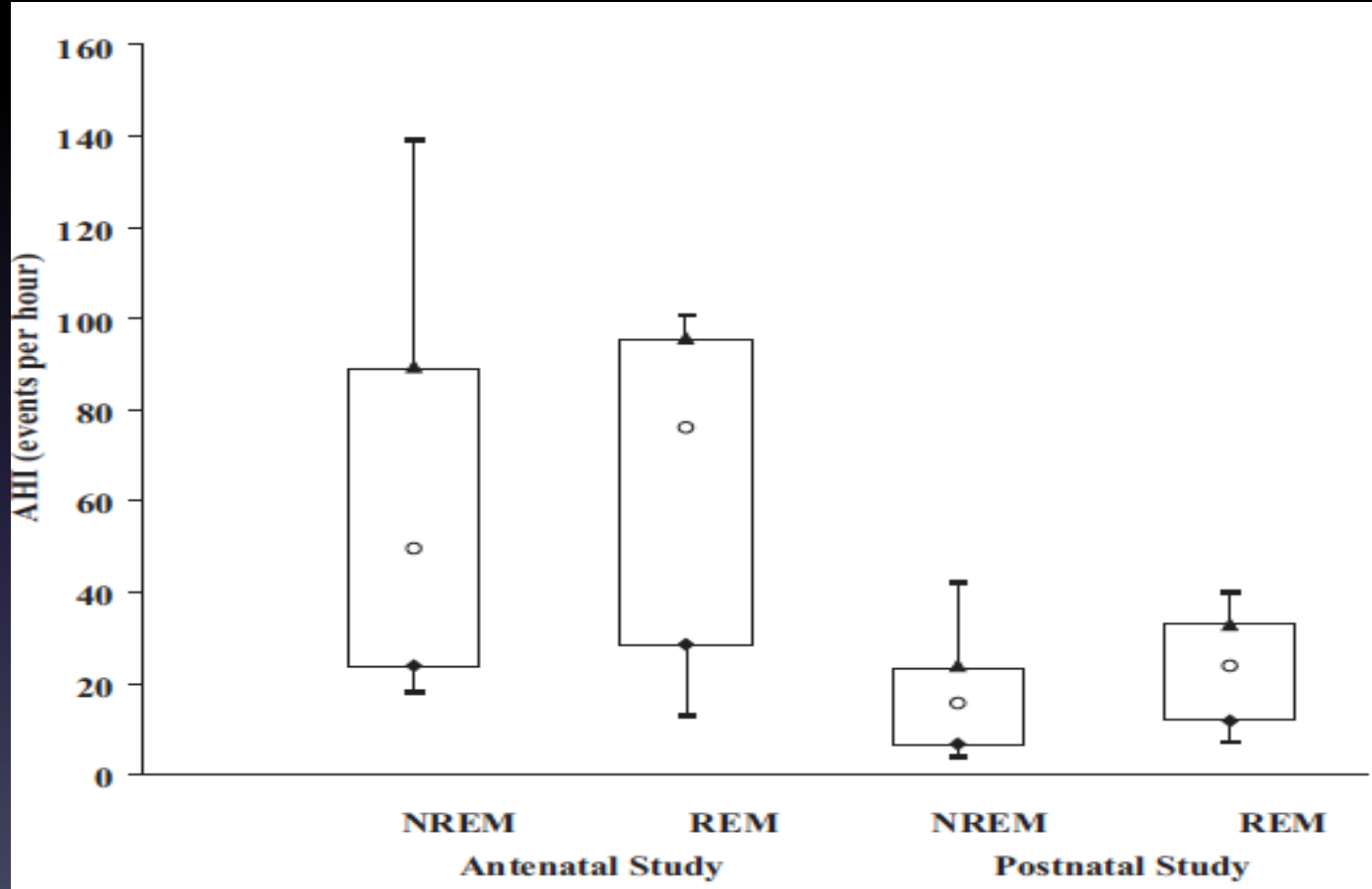
	Third trimester OSA (n=28)	No 3rd trimester OSA (n=77)	p Value
Baseline BMI, kg/m ² (SD)	34.1 (7.9)	28.5 (6.3)	0.002
Gestational weight gain, kg (SD)	7.0 (5.2)	9.6 (5.5)	0.034
Third trimester BMI, kg/m ² (SD)	37.0 (7.4)	32.1 (5.5)	0.003
Third trimester Epworth score (SD)	10.6 (4.1)	9.2 (4.0)	0.129
First trimester AHI, events/h (SD, median)	4.08 (4.55, 2.6)	1.34 (1.74, 0.7)	
Third trimester AHI, events/h (SD, median)	10.97 (7.69, 8.3)	1.11 (1.24, 0.6)	
Apnoea Index	1.79 (3.62)	0.12 (0.25)	
Hypopnoeas with arousal	7.30 (5.26)	0.84 (1.08)	
Hypopnoeas with 3% desaturation	1.89 (2.33)	0.15 (0.37)	

Flow-limitation occurs ~70% of time in preeclampsia patients



-RDI in this group was less than 10/hr

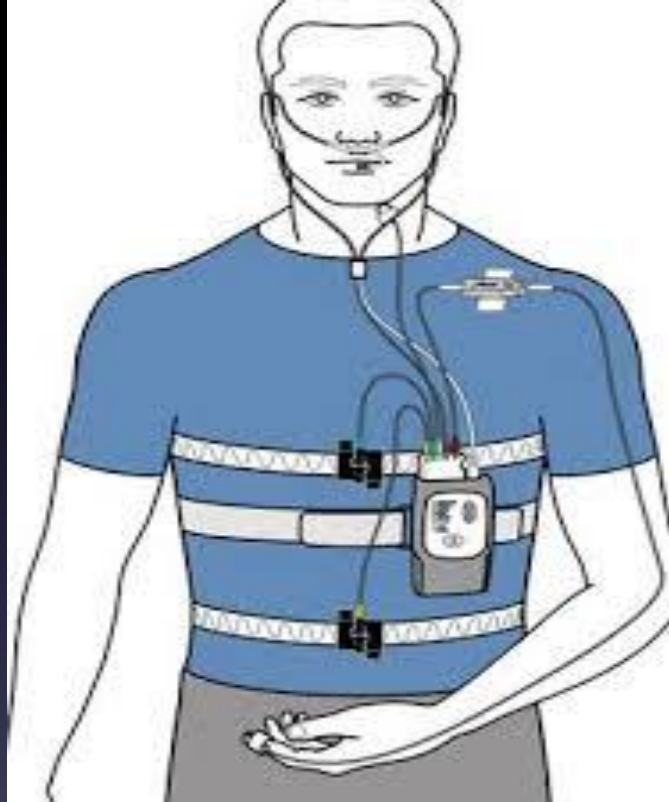
Sleep Apnea Risk Decreases Postnatally



What is the optimal diagnostic tool?

- 20-30% of pregnant women snore by the 3rd trimester
- No standardized way to assess snoring
- 4 million pregnancies/year (US) and 500,000 pregnancies/year (Canada)
- Large diagnostic burden to use level I or II type testing routinely
- Should we include assessments of flow limitation?
- Type III testing?

Level III Study



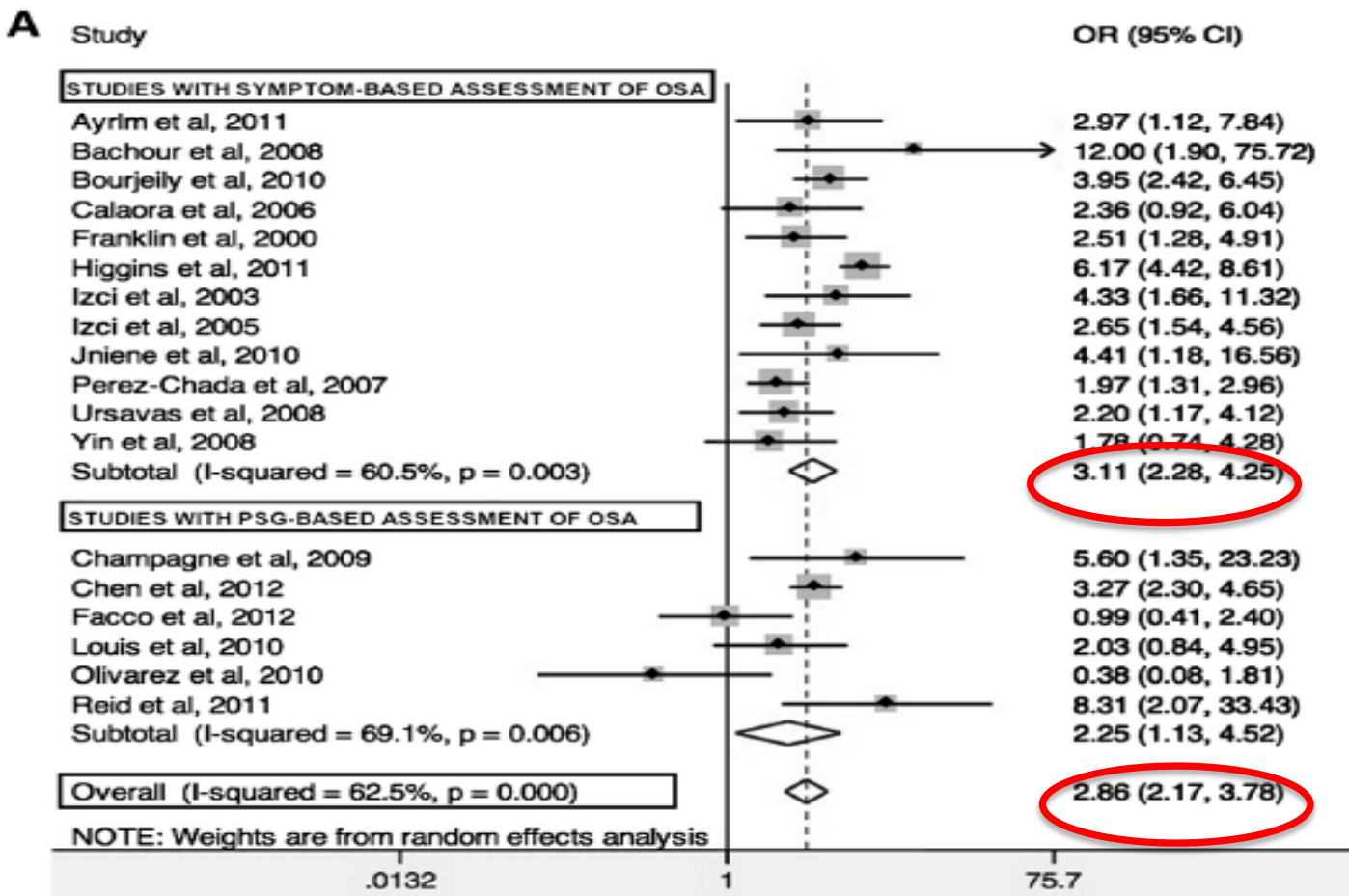
- Convenient, in-home testing
- However, unable to detect hypopneas with arousals

SDB in Pregnancy and Health Outcomes

Maternal sleep-disordered breathing and adverse pregnancy outcomes: a systematic review and metaanalysis

Sushmita Pamidi, MD; Lancelot M. Pinto, MD, MSc; Isabelle Marc, MD; Andrea Benedetti, PhD; Kevin Schwartzman, MD, MPH; R. John Kimoff, MD

FIGURE 2
Unadjusted and adjusted ORs for SDB and gestational hypertension or preeclampsia



Obstructive sleep apnoea and its association with gestational hypertension

K. Champagne*, K. Schwartzman*, L. Opatrny[#], P. Barriga[†], L. Morin⁺, A. Mallozzi⁺, A. Benjamin⁺ and R.J. Kimoff[§]

TABLE 4 Adjusted odds ratio (OR) for each variable and its association with gestational hypertension

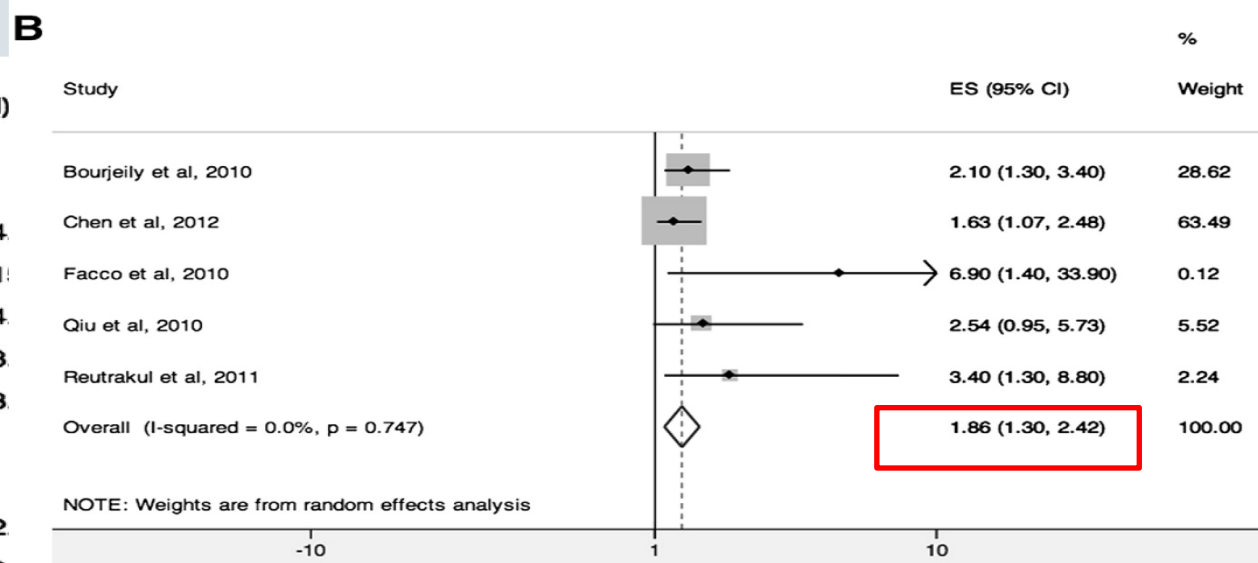
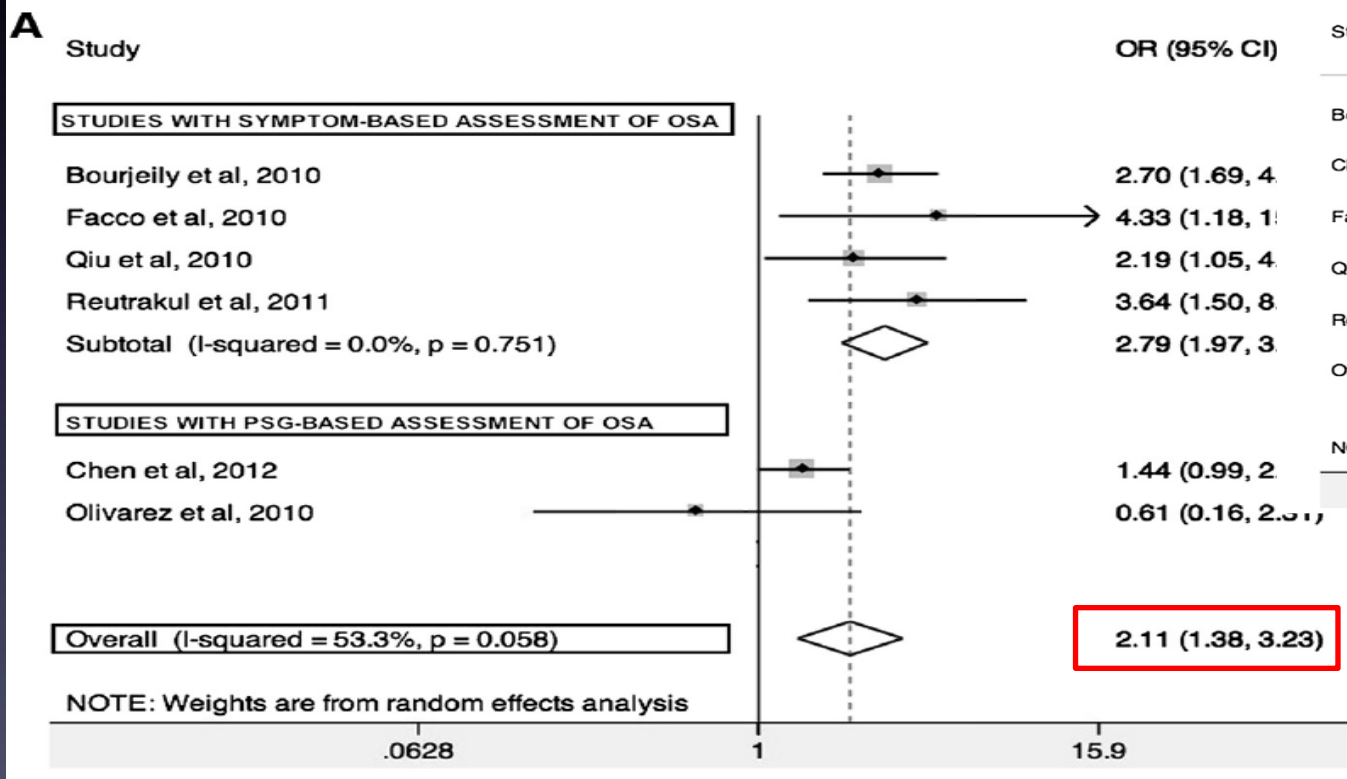
Variables	Adjusted OR (95% CI)	p-values
Sleep apnoea [#] versus no sleep apnoea	7.5 (3.5–16.2)	<0.0001
BMI per 1 kg·m ⁻² increase	1.2 (1.1–1.4)	0.001
Maternal age per 1-yr increase	1.2 (0.95–1.4)	0.14
Pregnancy status		
Previous pregnancy but no live birth	12.8 (3.5–46.0)	<0.0001
First pregnancy	3.4 (0.25–45.5)	0.35
Previous live birth [†]	1	
Gestational age		
20–27 weeks	1.1 (0.4–3.2)	0.80
27–34 weeks	0.8 (0.5–1.2)	0.32
>34 weeks [†]	1	

OBSTETRICS

Maternal sleep-disordered breathing and adverse pregnancy outcomes: a systematic review and metaanalysis

Sushmita Pamidi, MD; Lancelot M. Pinto, MD, MSc; Isabelle Marc, MD; Andrea Benedetti, PhD; Kevin Schwartzman, MD, MPH; R. John Kimoff, MD

FIGURE 3
Unadjusted and adjusted ORs for association between SDB and gestational diabetes



Sleep-Disordered Breathing and Gestational Diabetes Mellitus

A meta-analysis of 9,795 participants enrolled in epidemiological observational studies

MIGUEL ANGEL LUQUE-FERNANDEZ, PHD¹
 PAUL A. BAIN, PHD²
 BIZU GELAYE, PHD¹

SUSAN REDLINE, MD, MPH³
 MICHELLE A. WILLIAMS, SCD¹

Diabetes Care 36:3353–3360, 2013

Author, (year)	Adjusted OR (95%CI)	%, Weight
----------------	---------------------	-----------

BMI adjusted:

Bourjeily G. (2010)	2.10 (1.30, 3.40)	23.34
Facco F. (2010)	6.90 (1.40, 33.95)	7.06
Reutrakul S. (2011)	3.40 (1.31, 8.85)	13.87
Chen Y-H. (2012)	1.63 (1.07, 2.48)	24.69
Subtotal (I-squared = 32.6%, p = 0.217)	2.17 (1.45, 3.25)	68.96

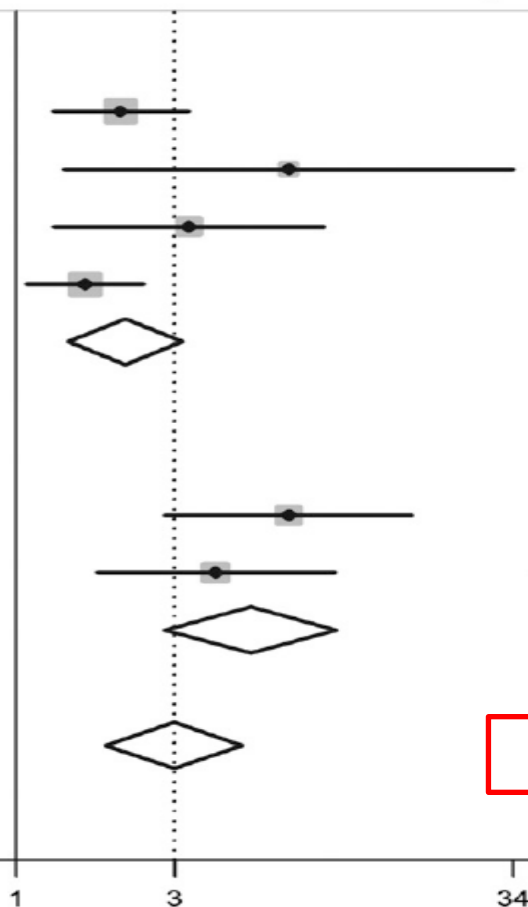
Analysis stratified by BMI:

Qiu C. (2010)	6.90 (2.87, 16.59)	15.17
O'Brien L. (2012)	4.12 (1.78, 9.53)	15.86
Subtotal (I-squared = 0.0%, p = 0.405)	5.27 (2.87, 9.66)	31.04

Pooled summary OR:

Overall (I-squared = 61.2%, p = 0.024)	3.06 (1.89, 4.96)	100.00
----------------------------------------	--------------------------	--------

NOTE: Weights are from random-effects analysis



Obstructive Sleep Apnea and Severe Maternal-Infant Morbidity/Mortality in the United States, 1998-2009

Judette M. Louis, MD, MPH¹; Mulubrhan F. Mogos, PhD²; Jason L. Salemi, MPH²; Susan Redline, MD, MPH³; Hamisu M. Salihu, MD, PhD^{1,2}

SLEEP 2014;37(5):843-849.

- ~55 million pregnancy-related hospital discharges using 1998-2009 annual data from the Nationwide Inpatient Sample (NIS)
- Used ICD-9-CM codes to identify maternal-fetal complications and diagnosis of OSA
- OSA significantly associated with complications, including GDM

Outcomes	Rate ^a		OR (95% CI)			
	OSA	No OSA	Model 1 ^b	Model 2 ^c	Model 3 ^d	Model 4 ^e
Maternal, pregnancy-related						
Cesarean section ^f	430.51	251.28	2.26 (2.09–2.43)	2.05 (1.87–2.24)	1.29 (1.17–1.42)	1.12 (1.01–1.23)
Gestational diabetes ^g	191.29	45.08	5.03 (4.50–5.62)	3.85 (3.43–4.31)	2.02 (1.79–2.28)	1.89 (1.67–2.14)

Adjusted for obesity

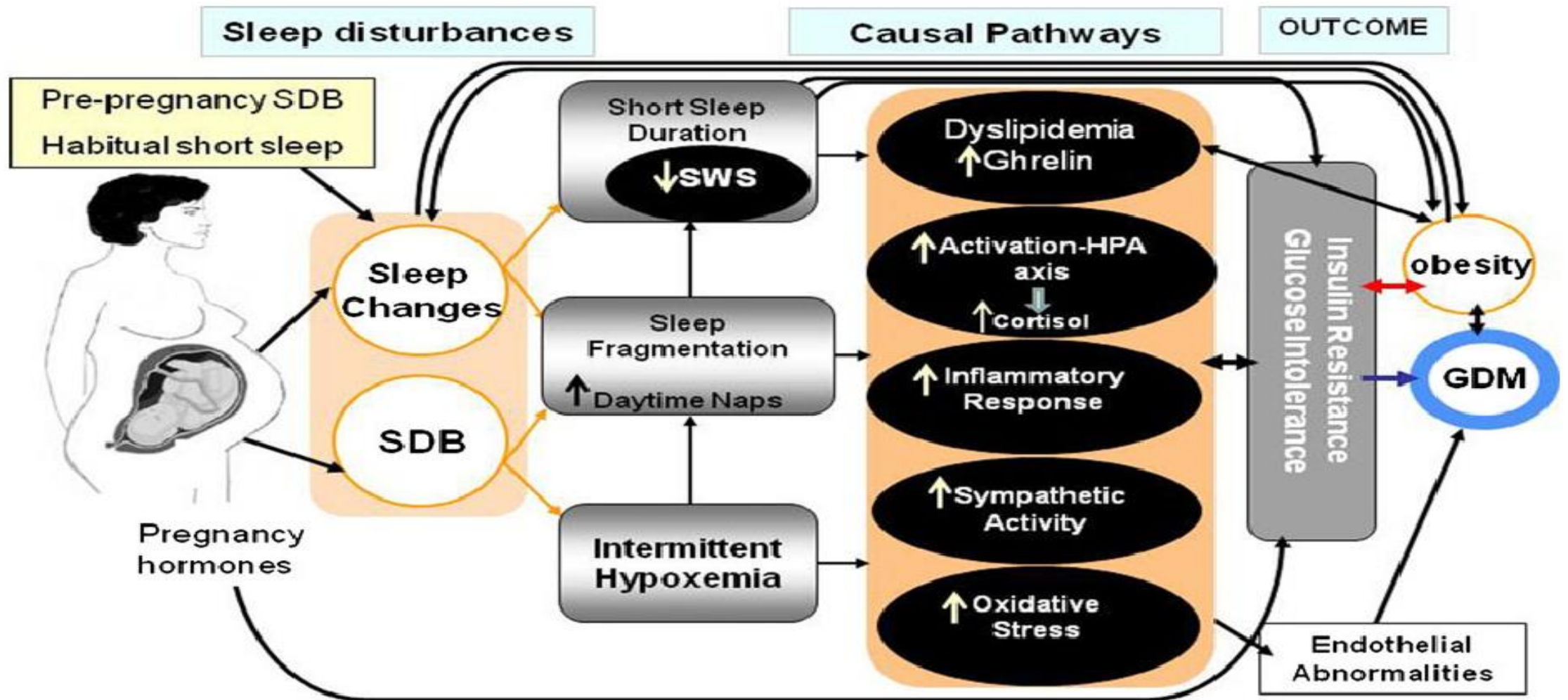
Adjusted for comorbidities

Association Between Sleep-Disordered Breathing and Hypertensive Disorders of Pregnancy and Gestational Diabetes Mellitus

Francesca L. Facco, MD, MSCI, Corette B. Parker, DrPH, Uma M. Reddy, MD, MPH, Robert M. Silver, MD, Matthew A. Koch, MD, PhD, Judette M. Louis, MD, MPH, Robert C. Basner, MD, Judith H. Chung, MD, PhD, Chia-Ling Nhan-Chang, MD, Grace W. Pien, MD, MSCE, Susan Redline, MD, MPH, William A. Grobman, MD, MBA, Deborah A. Wing, MD, MBA, Hyagriv N. Simhan, MD, David M. Haas, MD, MS, Brian M. Mercer, MD, Samuel Parry, MD, Daniel Mobley, RPSGT, Shannon Hunter, MS, George R. Saade, MD, Frank P. Schubert, MD, MS, and Phyllis C. Zee, MD, PhD

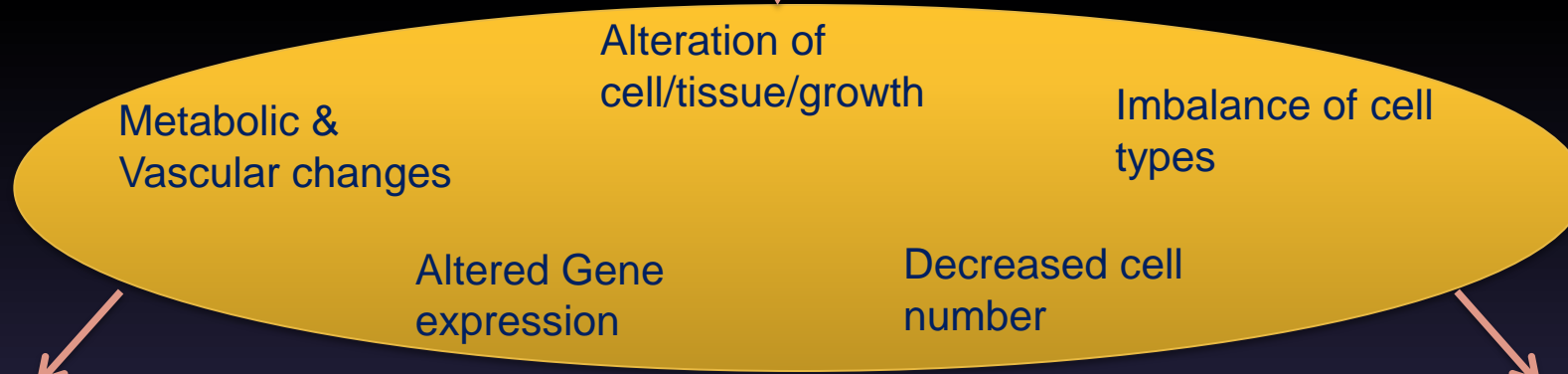
All Apneas and Hypopneas With 3% Oxygen Desaturation/h (AHI)	n/N (%)	Crude OR		Adjusted OR	
		Estimate (95% CI)	P	Estimate (95% CI)	P
Preeclampsia					
Early pregnancy (n=3,131)					
Less than 5 (referent)	170/3,017 (5.6)	1.00	<.001	1.00	.03
5 or greater	16/114 (14.0)	2.73 (1.58–4.74)		1.94 (1.07–3.51)	
0 (referent)	42/763 (5.5)	1.00	.004	1.00	.16
Greater than 0 to less than 5	128/2,254 (5.7)	1.03 (0.72–1.48)	Trend tests: .02 linear .50 quadratic	0.96 (0.66–1.39)	
5 to less than 15	14/105 (13.3)	2.64 (1.39–5.02)		1.79 (0.89–3.61)	
15 or greater	2/9 (22.2)	4.90 (0.99–24.34)		2.74 (0.51–14.73)	

Potential Causal Pathways Linking Maternal Sleep-Disordered Breathing and Gestational Diabetes and Gestational Hypertension/Pre-eclampsia



Maternal, placental, fetal factors

IUGR



Perinatal Effects:

Mortality
Perinatal depression
Hypoglycemia
Hypothermia
RDS
Infection
Pulm HTN

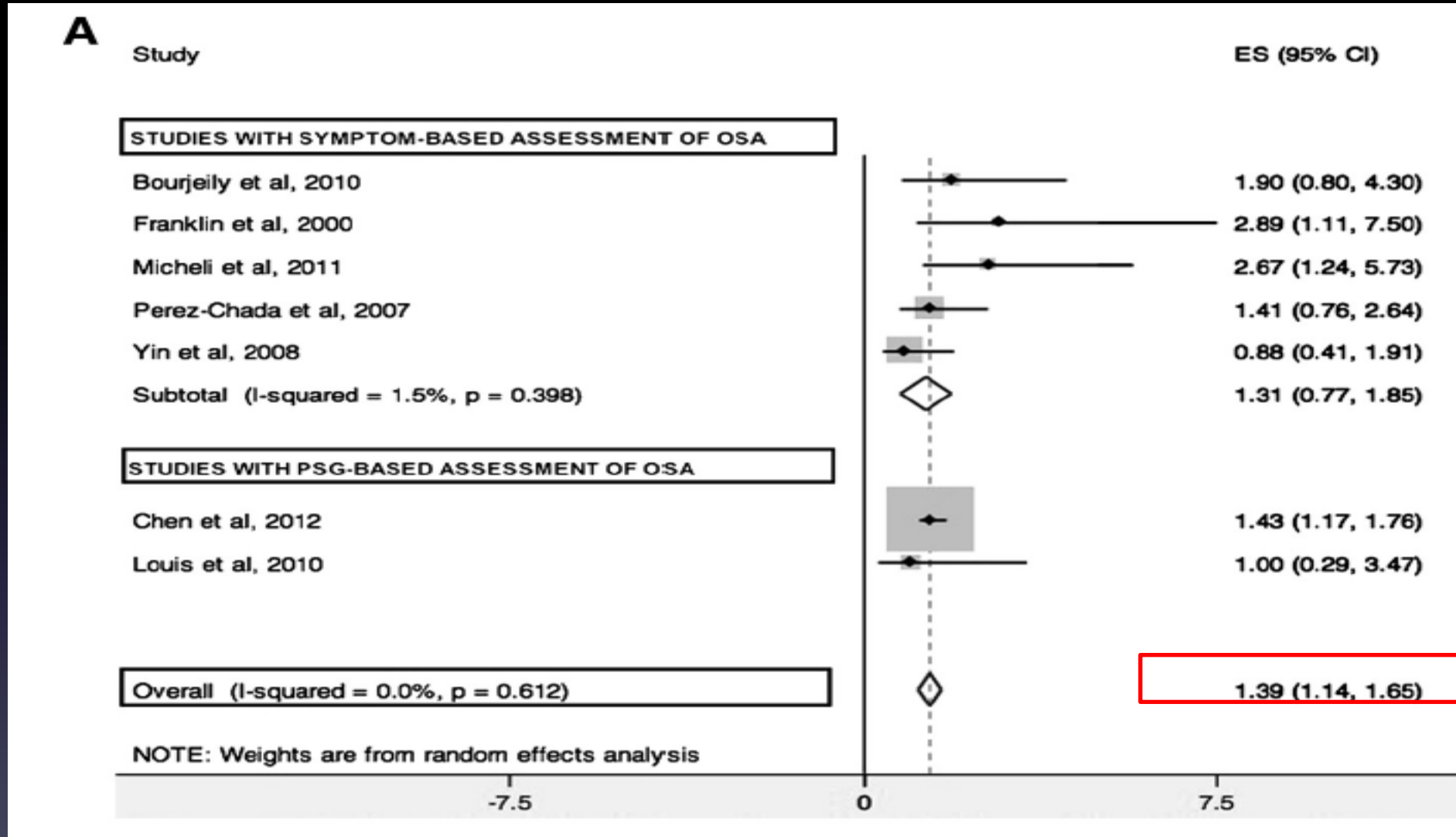
Childhood Effects:

Poor growth
Neurologic sequelae
SIDS (?)

Adult Effects:

HTN
Type 2 DM
CAD

Maternal SDB and Low Infant Birth Weight



Effects of Maternal Obstructive Sleep Apnoea on Fetal Growth: A Prospective Cohort Study

	Cases (n = 14)	Controls (n = 27)	P value
Respiratory Disturbance Index	7.9 (6.1–13.8)	2.2 (1.3–3.5)	<.001
Apnoea Hypopnoea Index	6.2 (4.9–11.7)	1.4 (0.6–2.6)	<.001
Oxygen Desaturation Index ≥3%	3.4 (1.5–9.4)	0.4 (0.1–1.0)	<.001
Oxygen Desaturation Index ≥4%	1.9 (0.7–5.1)	0.1 (0.0–0.3)	<.001
Number of desaturations ≥3%	16.5 (9.3–38.5)	3.0 (1.0–5.0)	<.001
Number of desaturations ≥4%	9.5 (4.0–23.5)	1.0 (0.0–2.0)	<.001
Largest oxygen desaturation (%)	6 (5.0–8.3)	4 (3.0–5.0)	.001
Minimum O2 (%)	90 (88–90.3)	91 (90–93)	.044
%Total Sleep Time below 95%	34.7 (12.0–58.2)	17.2 (4.4–56.5)	.25
%Total Sleep Time below 90%	0.1 (0–0.1)	0 (0–0)	.003

customised centile >33% between 32 weeks and term)

Birthweight <10 th centile	2 (14%)	3 (11%)	1
Fall in customised centile >33% between 32 weeks and term	4 (29%)	0 (0%)	<0.01
Apgar ≤7 at 5 min	0	1 (4%)	1.0
Admission SCN/NICU	0	1 (3.7%)	1.0

Obstructive Sleep Apnea and Severe Maternal-Infant Morbidity/Mortality in the United States, 1998-2009

Judette M. Louis, MD, MPH¹; Mulubrhan F. Mogos, PhD²; Jason L. Salemi, MPH²; Susan Redline, MD, MPH³; Hamisu M. Salihu, MD, PhD^{1,2}

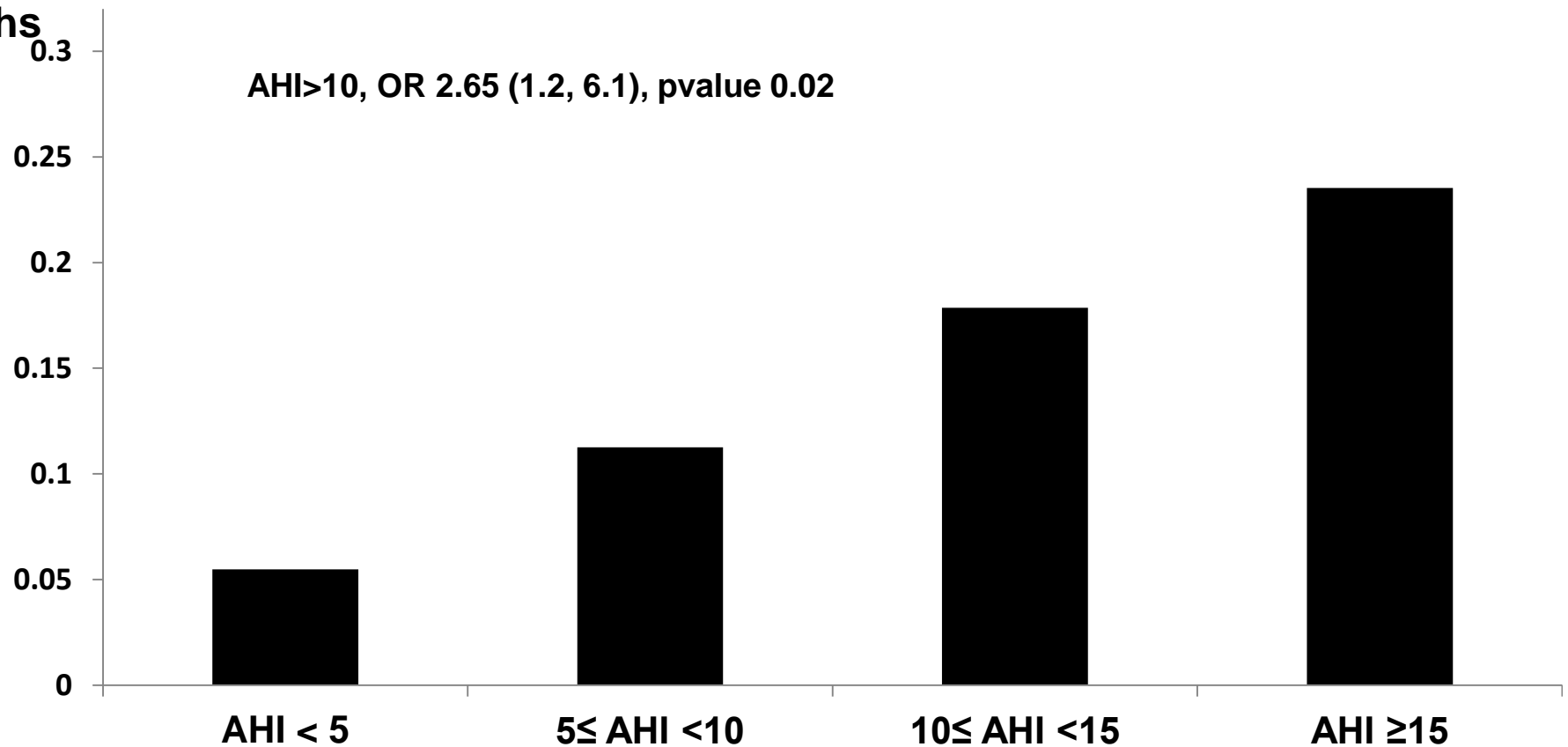
¹*Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Morsani College of Medicine, University of South Florida, Tampa, FL;* ²*Maternal and Child Health Comparative Effectiveness Research Group, Department of Epidemiology and Biostatistics, College of Public Health, University of South Florida, Tampa, FL;* ³*Division of Sleep Medicine, Department of Medicine, Harvard Medical School, Brigham and Women's Hospital and Beth Israel Deaconess Medical Center, Boston, MA*

Outcomes	Rate ^a		OR (95% CI)			
	OSA	No OSA	Model 1 ^b	Model 2 ^c	Model 3 ^d	Model 4 ^e
Fetal/infant						
Early-onset delivery	101.15	65.33	1.62 (1.43–1.84)	1.40 (1.24–1.61)	1.32 (1.16–1.50)	1.20 (1.06–1.37)
Poor fetal growth	21.88	15.92	1.39 (1.10–1.74)	1.26 (1.01–1.59)	1.28 (1.02–1.62)	1.21 (0.96–1.53)
Stillbirth	8.05	6.29	1.28 (0.84–1.95)	1.04 (0.68–1.58)	1.07 (0.70–1.62)	1.01 (0.66–1.53)

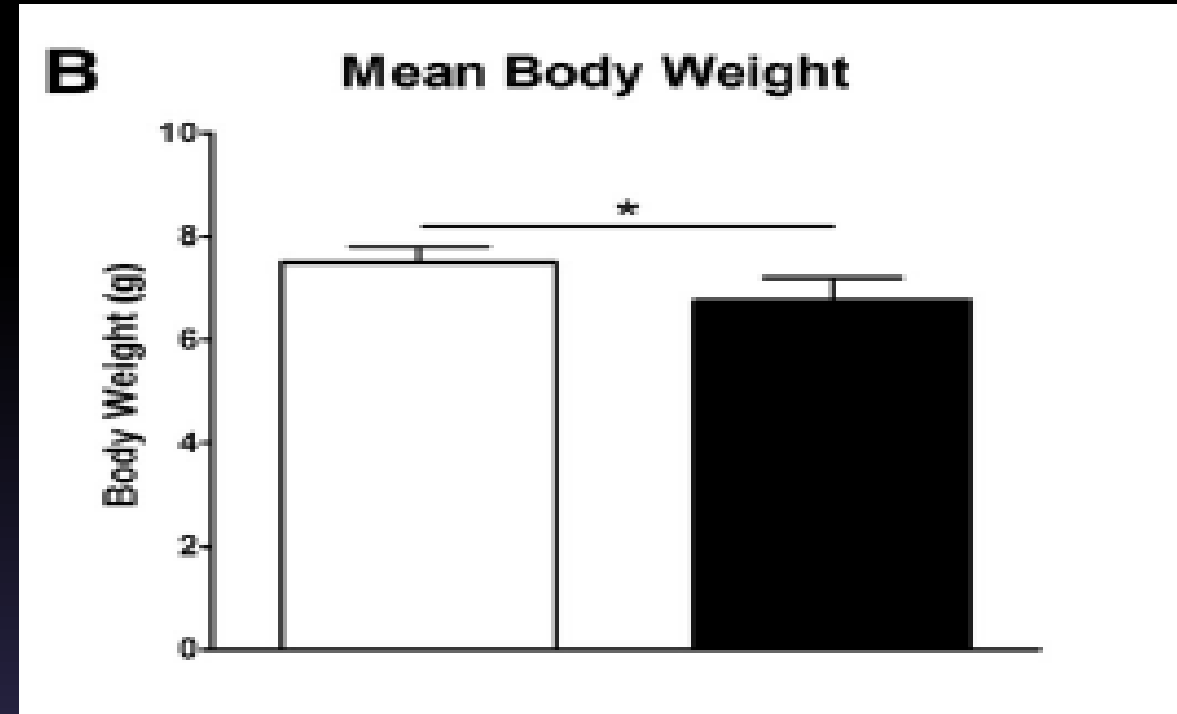
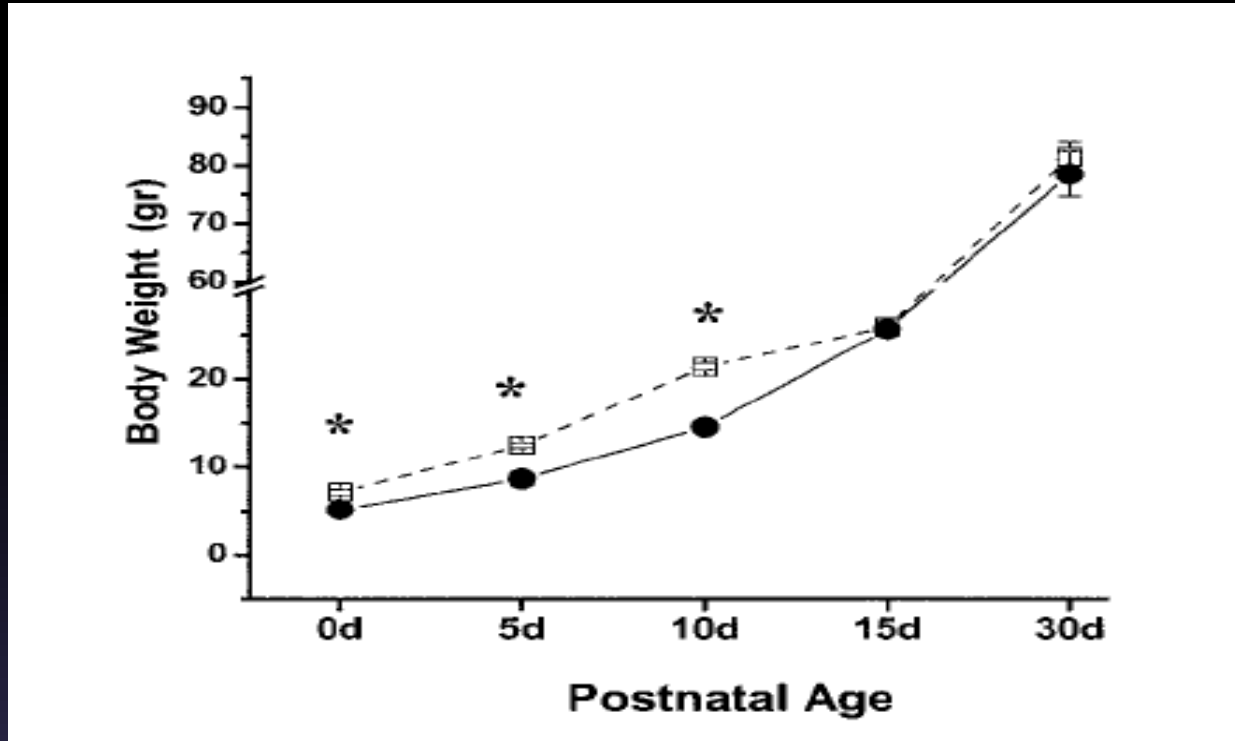
Maternal sleep-disordered breathing and the risk of delivering small for gestational age infants: a prospective cohort study

Sushmita Pamidi,¹ Isabelle Marc,² Gabrielle Simoneau,^{3,4} Lorraine Lavigne,¹ Allen Olha,¹ Andrea Benedetti,^{3,4} Frédéric Sériès,⁵ William Fraser,⁶ François Audibert,⁶ Emmanuel Bujold,² Robert Gagnon,⁷ Kevin Schwartzman,^{1,3,4} R John Kimoff¹

Proportion of SGA births



Animal Studies



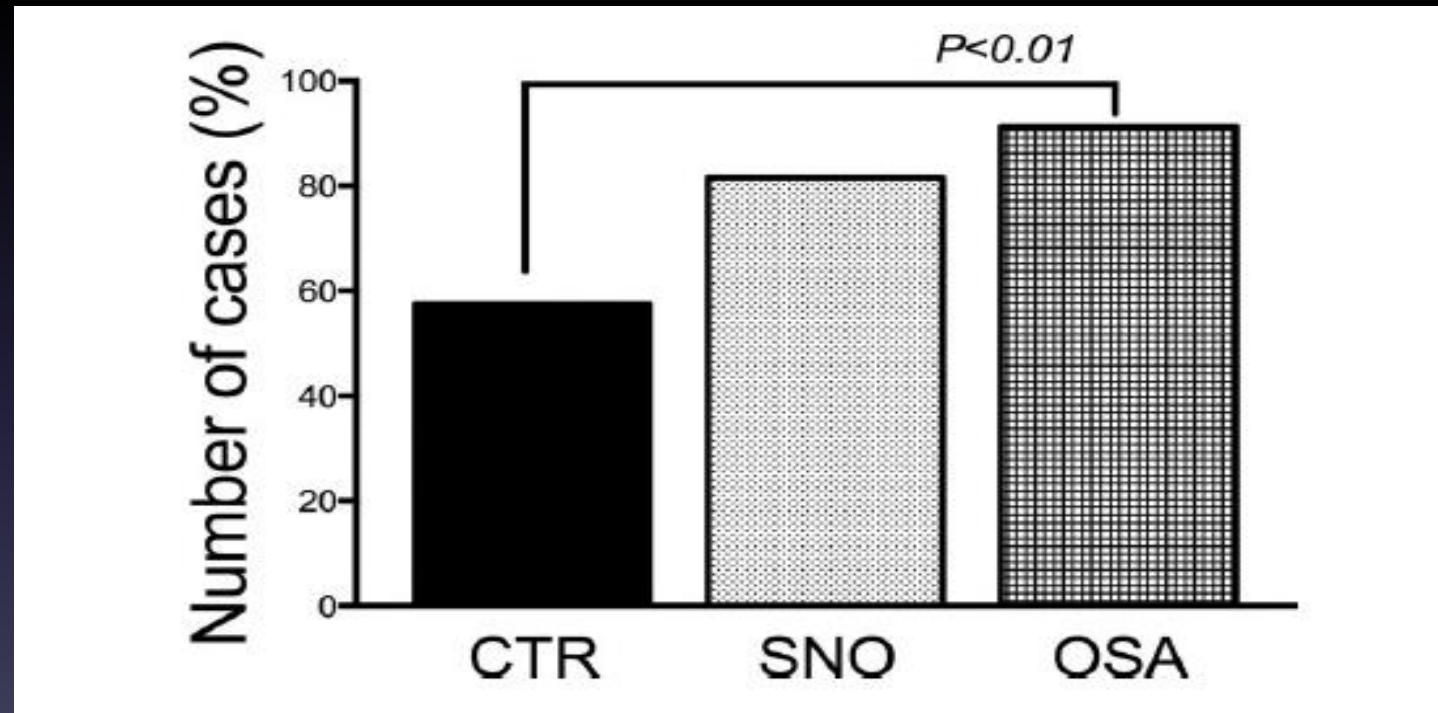
- pups of rats exposed to intermittent hypoxia

- pups of rats in room air during gestation

Iqbal et al., AJOG 2013

Fetoplacental Hypoxia

Carbonic Anhydrase IX (Tissue Hypoxia Marker)



Treatment Options

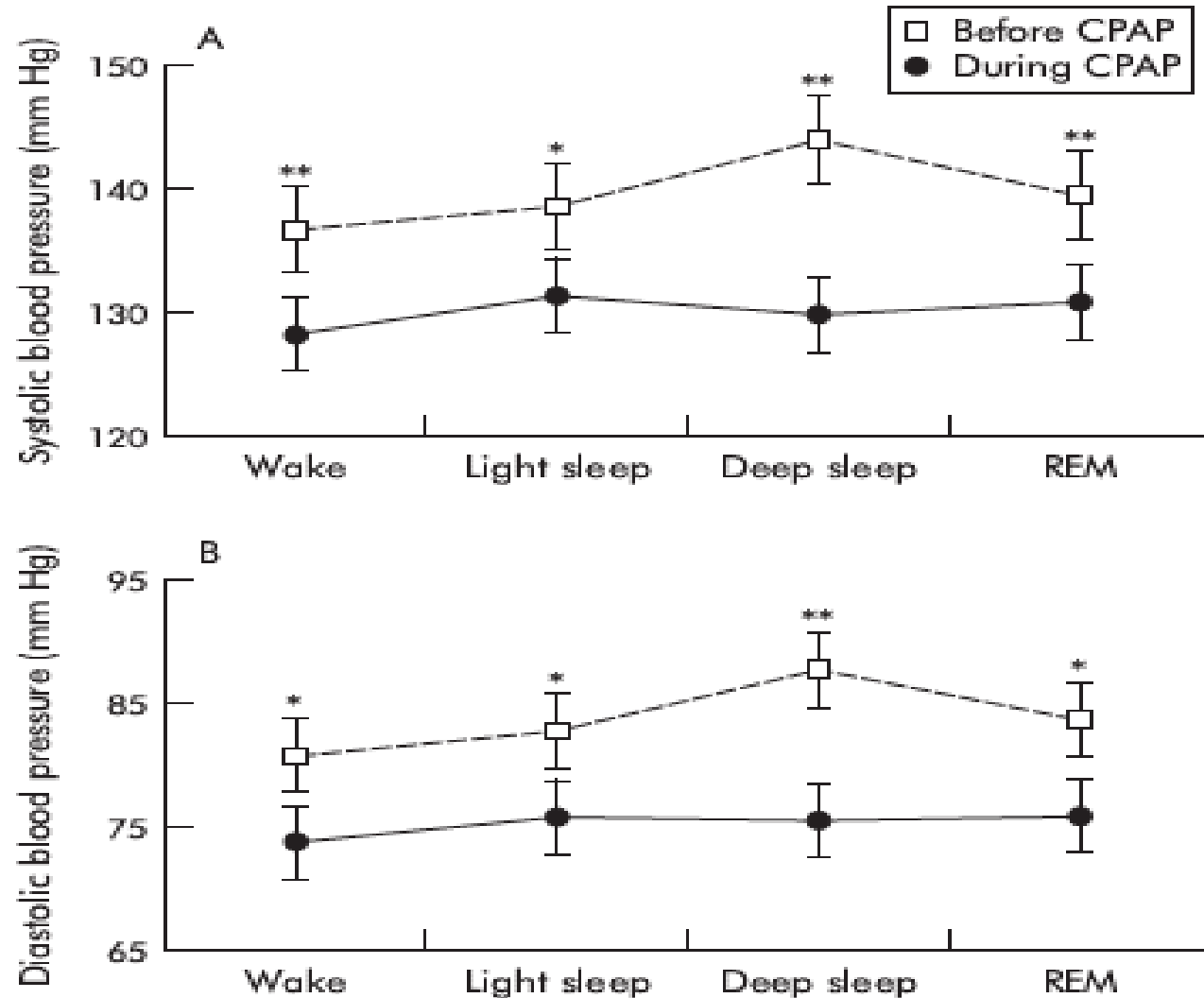
- Lack of RCTs
- CPAP – lower compliance?
 - milder OSA
 - inability to lie supine
 - nasal rhinitis/congestion
- Role for alternatives to therapy: oral appliances?

Sleep disordered breathing and pregnancy

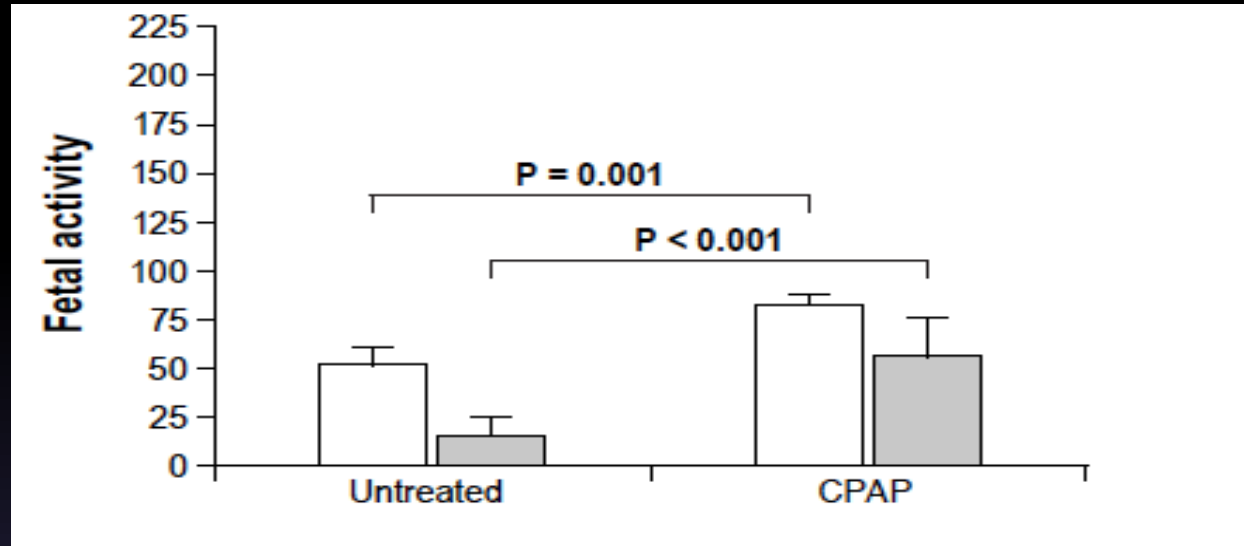
N Edwards, P G Middleton, D M Blyton, C E Sullivan

Thorax 2002;**57**:555–558

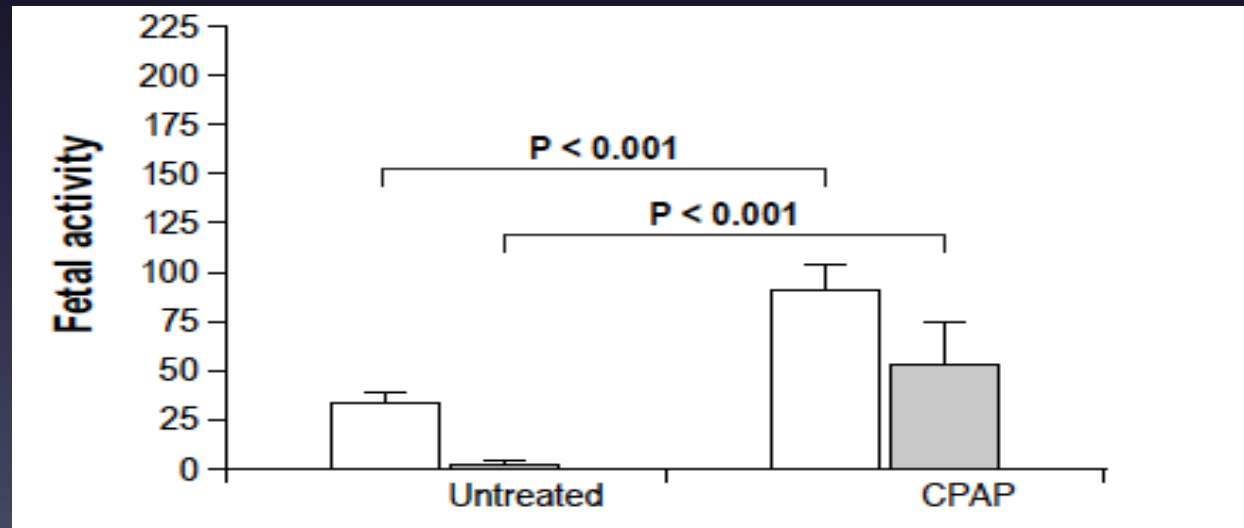
Pre-eclampsia
patients treated with
auto-PAP



Maternal SDB and Fetal Activity



NREM sleep

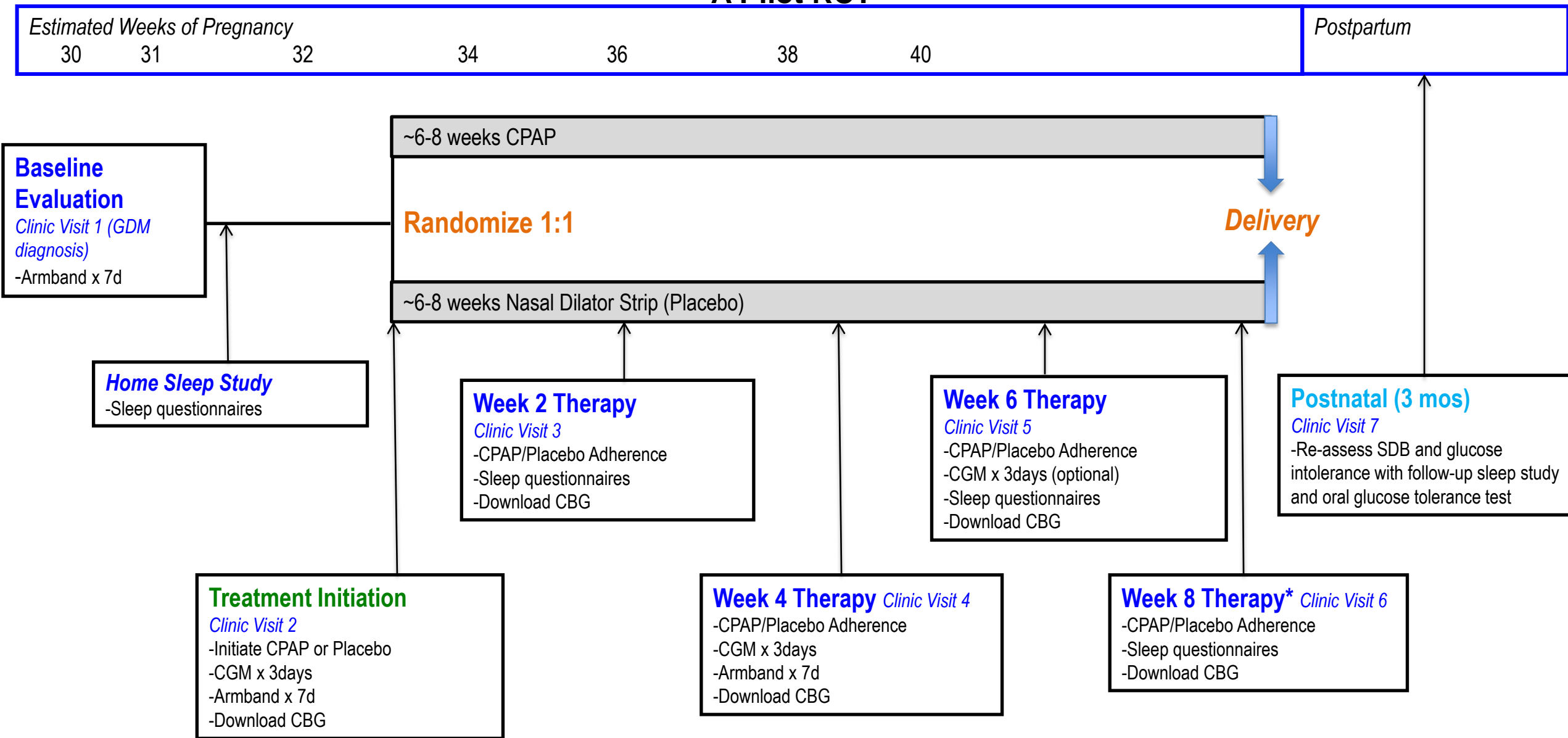


REM sleep

Future Research Directions

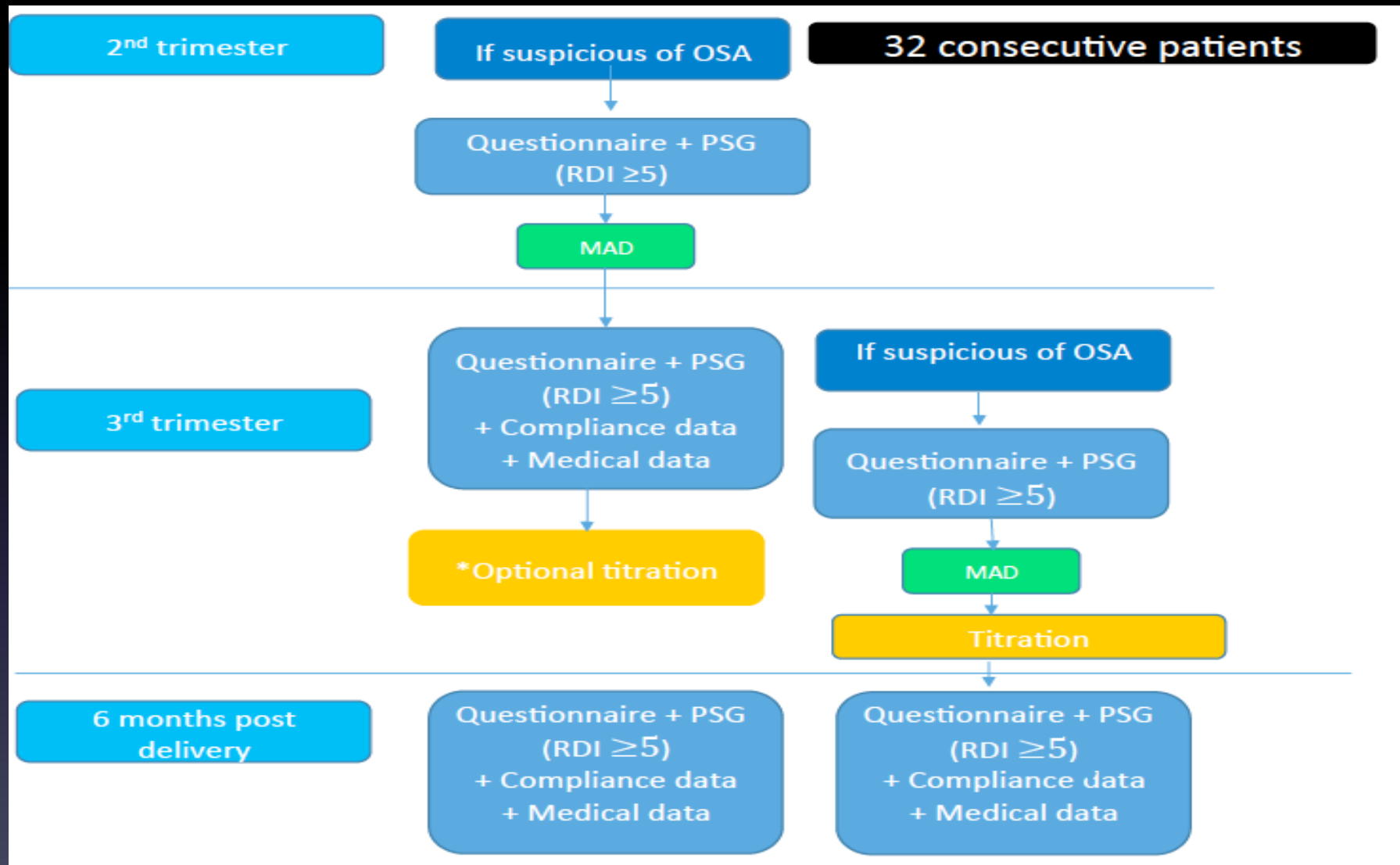
- Comparing ambulatory vs. level I/II studies against health outcomes
- Role of biomarkers and screening in targeting high risk women; at what stage of pregnancy should OSA testing occur?
- Mechanisms of SDB in pregnancy
- Natural history of SDB in females (pre- and post- pregnancy)
- Randomized-controlled trials
 - CPAP and oral appliances

Effectiveness of CPAP for Improving Glucose Control in Gestational Diabetes – A Pilot RCT



* Possible only if participant has not delivered; If continuous glucose monitoring (CGM) not available on any visits, the most recent downloaded capillary blood glucose (CBG) measurements will be used as surrogate measures of glycemia

Oral Appliances in Pregnancy



Acknowledgements

- R. John Kimoff, MD
- Isabelle Marc, MD PhD
- Lorraine Lavigne, RN
- Allen Olha, RPSGT
- Lancelot Pinto, MD
- Nelly Huynh, PhD
- Léa Drouin-Gagné
- Ahamed Khalyfa



Centre universitaire
de santé McGill



McGill University
Health Centre