Sleep Disorders in Pregnancy

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- No conflicts of interest



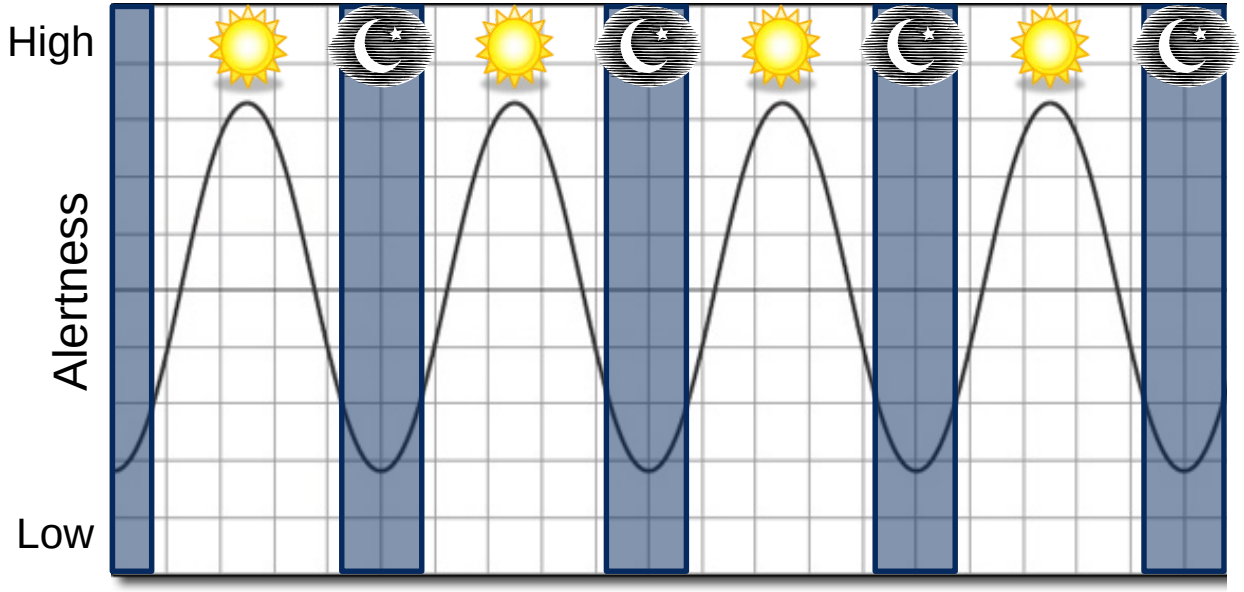



“If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process ever made.”
--Alan Rechschaffen

What Controls Sleep?

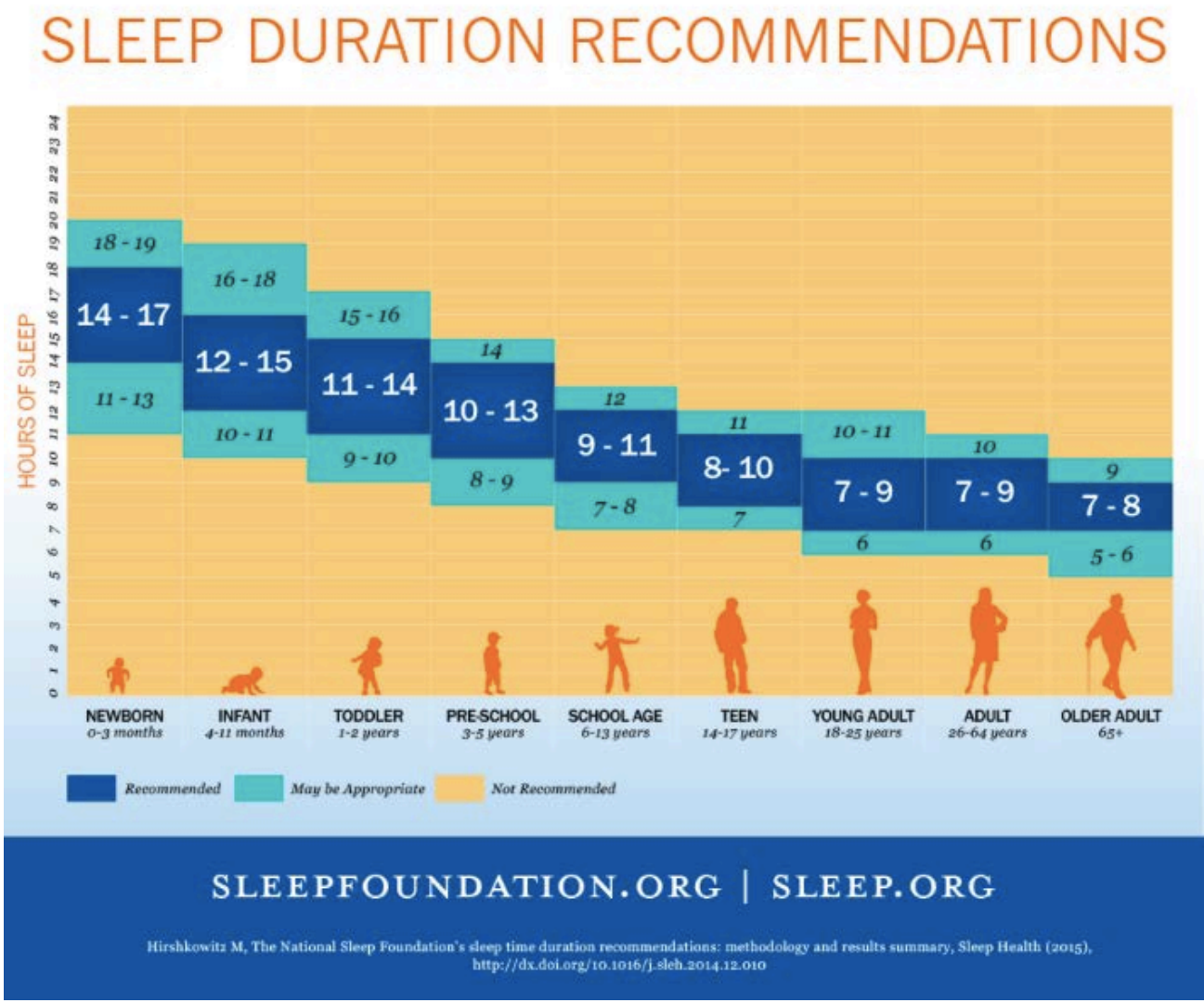
1. How long you have been awake

2. Time of Day

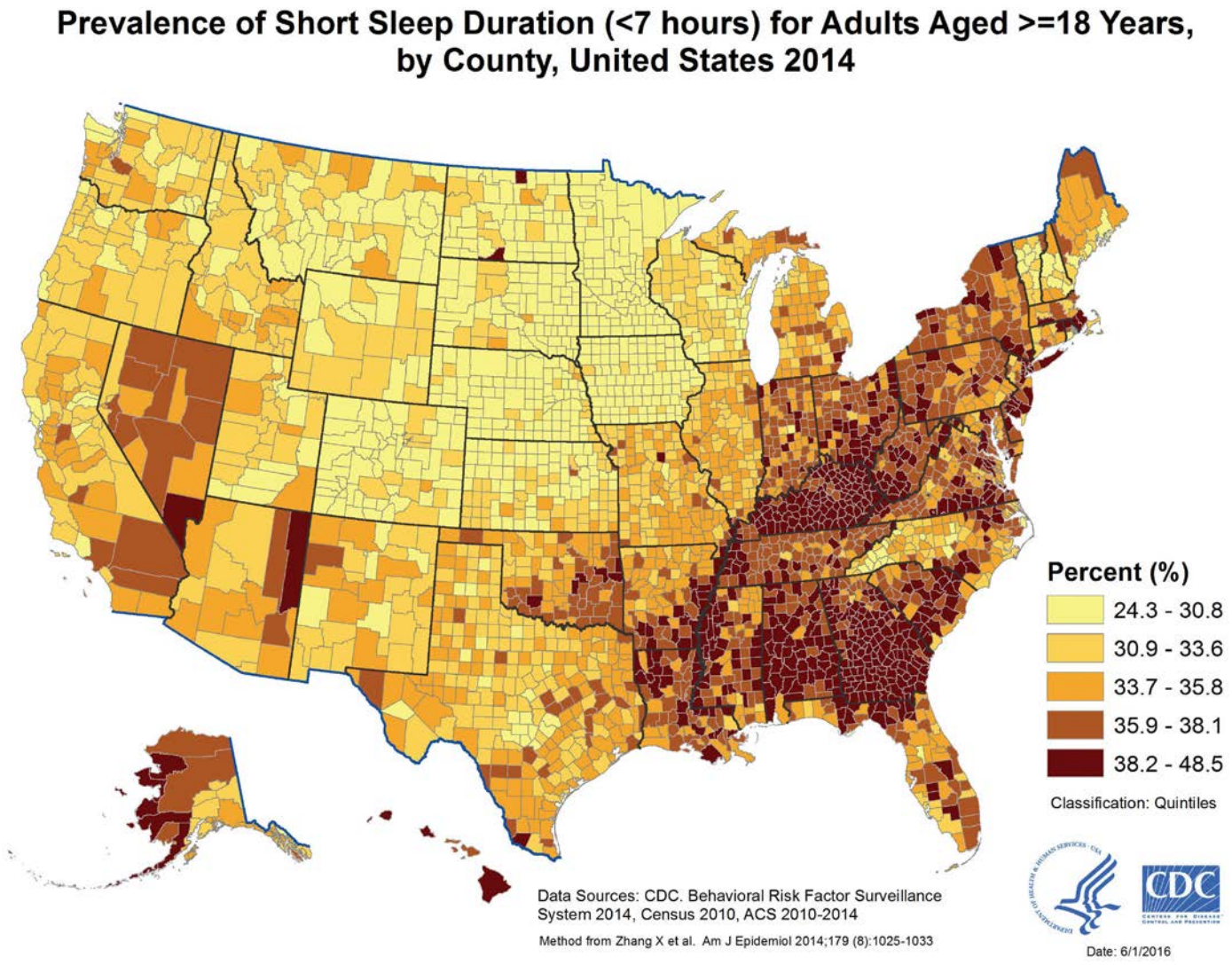


How much sleep is normal?

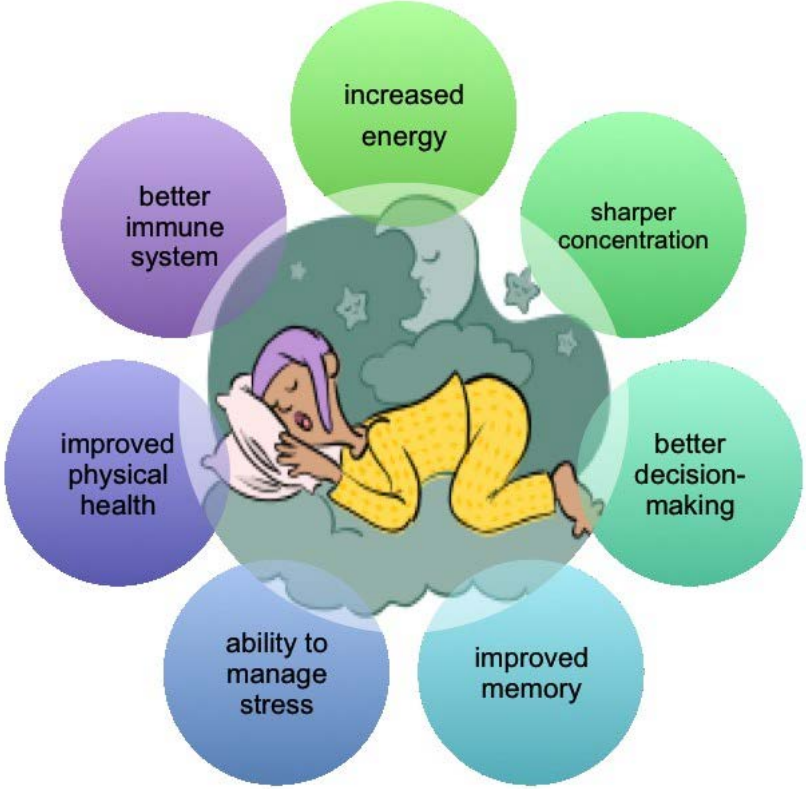
AIM FOR **7-9** hours/night



SHORT SLEEP DURATIONS ARE COMMON



Why is sleep important?



After one night …

- Increased car accidents
- More emotional
- Memory deficits

Chronic sleep loss…

- ↑ cardiovascular disease
- ↑obesity
- ↑ diabetes

Table 3. Age-Adjusted[a] Percentage Reporting Chronic Health Conditions by Sleep Duration—Behavioral Risk Factor Surveillance System, United States, 2014

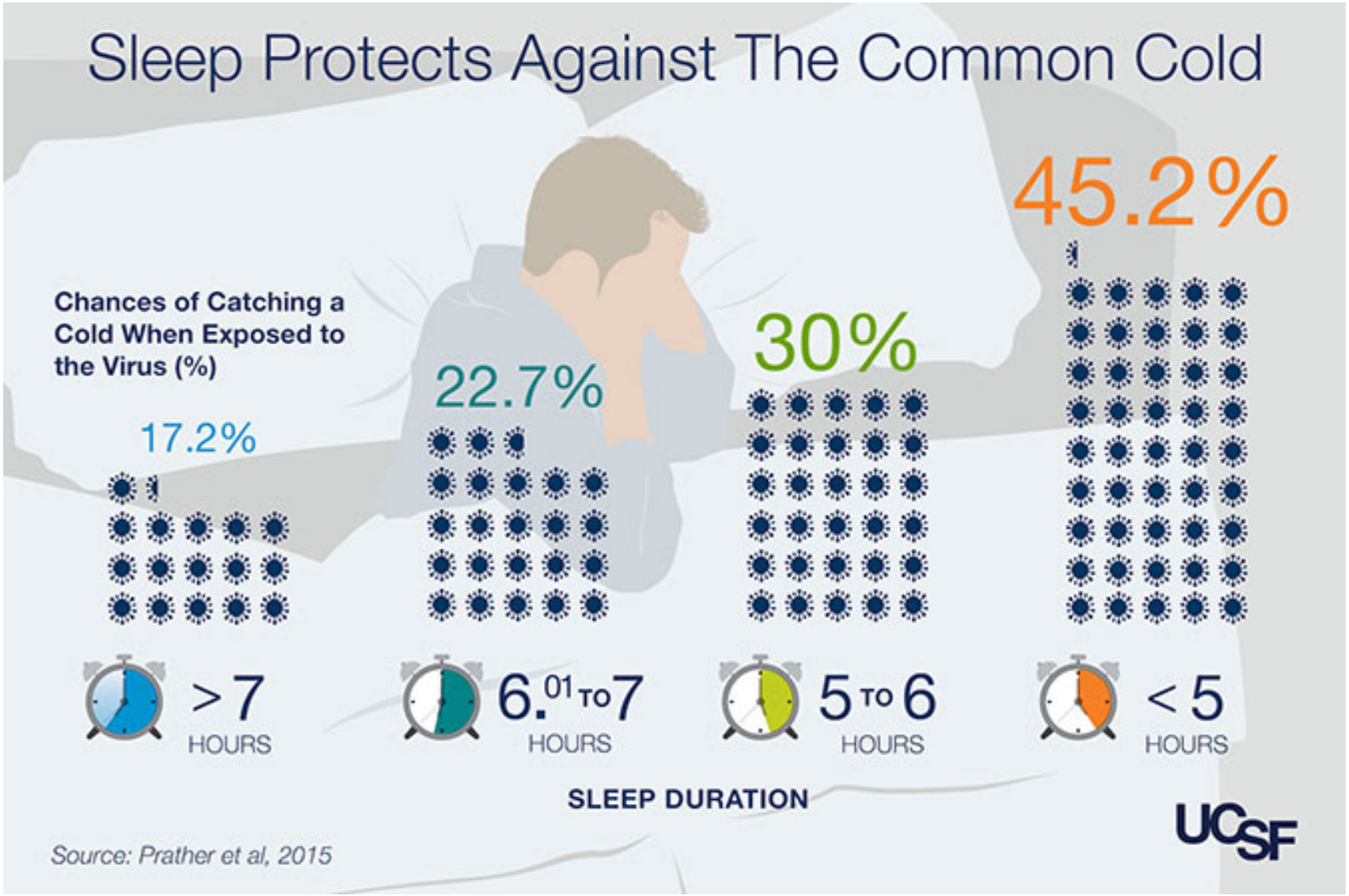
	Short sleep (<7 hours)		Sufficient sleep (≥7 hours)	
Chronic condition	**%**	**95% CI**	**%**	**95% CI**
Heart attack	4.8	(4.6–5.0)	3.4	(3.3–3.5)
Coronary heart disease	4.7	(4.5–4.9)	3.4	(3.3–3.5)
Stroke	3.6	(3.4–3.8)	2.4	(2.3–2.5)
Asthma	16.5	(16.1–16.9)	11.8	(11.5–12.0)
COPD (chronic obstructive pulmonary disease)	8.6	(8.3–8.9)	4.7	(4.6–4.8)
Cancer	10.2	(10.0–10.5)	9.8	(9.7–10.0)
Arthritis	28.8	(28.4–29.2)	20.5	(20.2–20.7)
Depression	22.9	(22.5–23.3)	14.6	(14.3–14.8)
Chronic kidney disease	3.3	(3.1–3.5)	2.2	(2.1–2.3)
Diabetes	11.1	(10.8–11.4)	8.6	(8.4–8.8)

Abbreviations: CI = confidence interval.

[a]Age-adjusted to the 2000 US standard population.

The prevalence of each condition is significantly higher ($p<0.05$) for persons reporting short sleep compared with those reporting sufficient sleep.

Sleep Protects Against The Common Cold

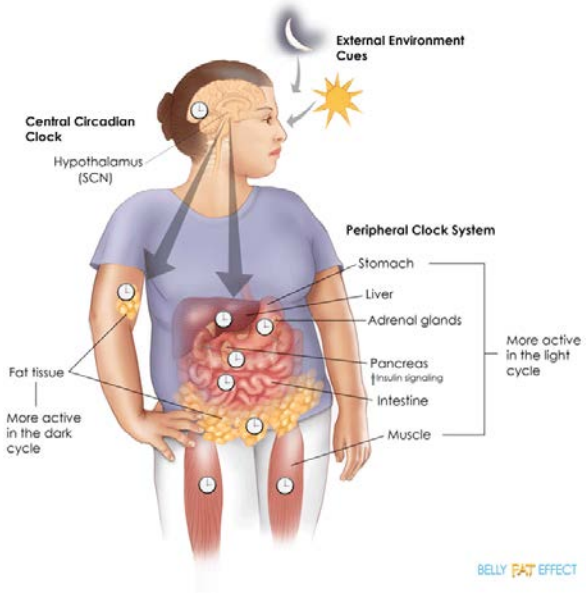


Source: Prather et al, 2015

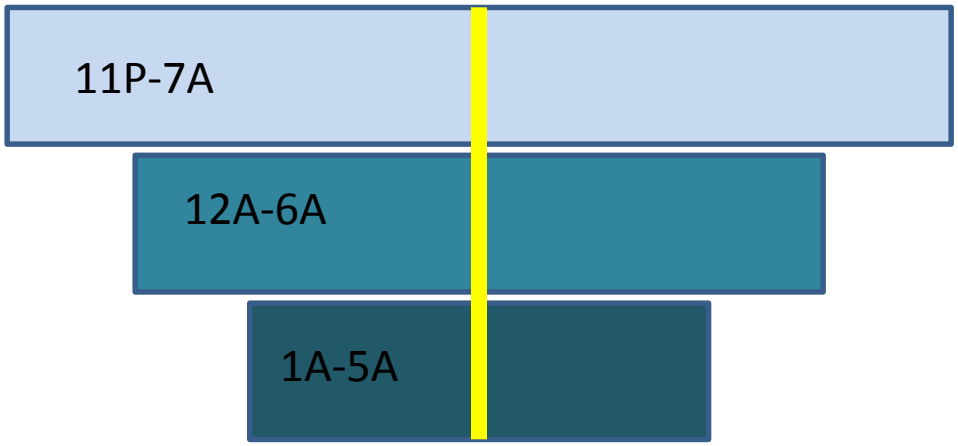
UCSF

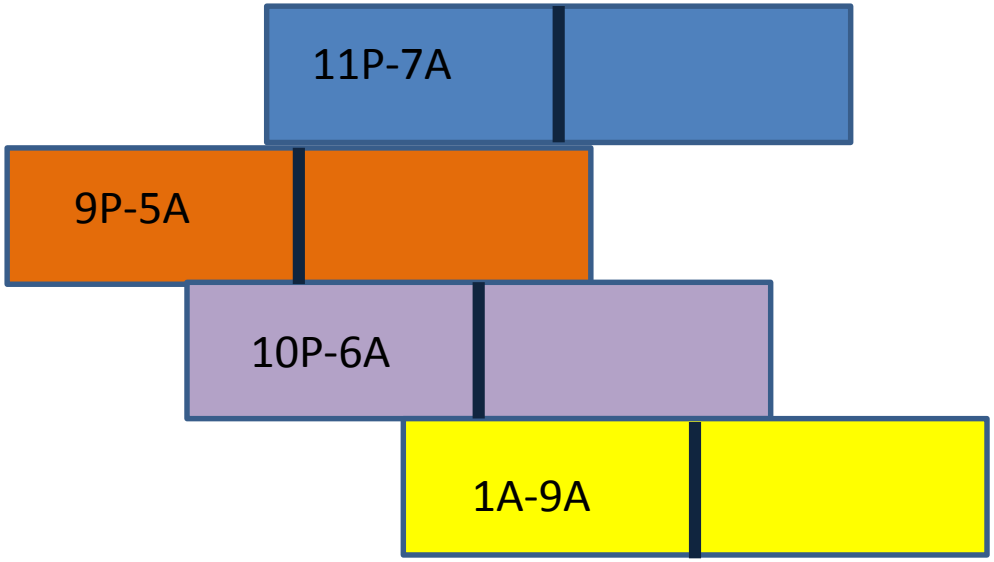
Sleep Timing

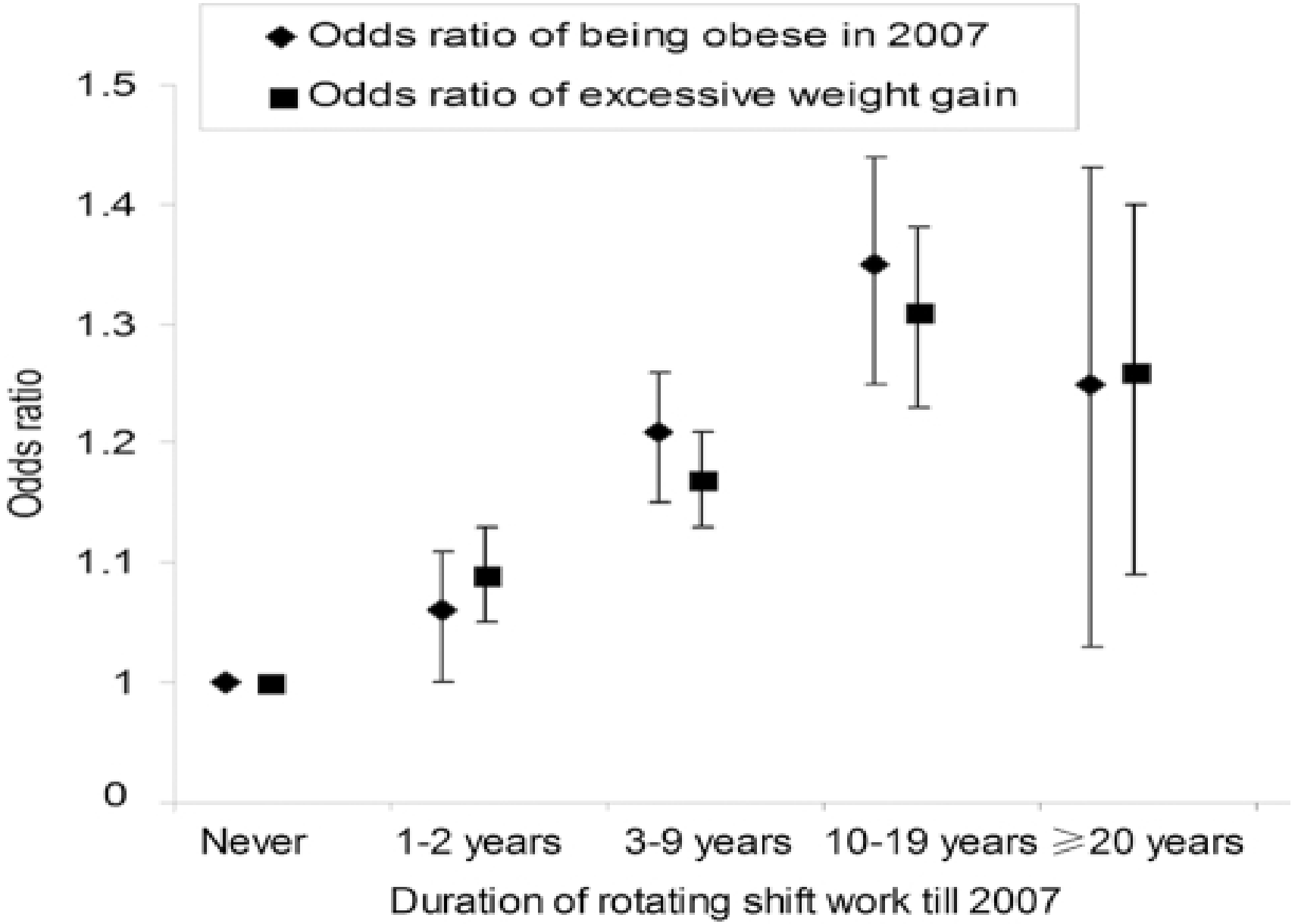
- Circadian Rhythms
- Try to go to bed and wake up around the same time every day (within an hour)
- If your schedule allows it try to go to bed by 11 PM



Sleep Midpoint







Rotating night shift work and risk of obesity and weight gain in Nurses' Health Study II. Pan et al. PLoS Med. 2011 Dec; 8(12): e1001141.

QUALITY MATTERS

- Sleep needs to be adequate in duration/timing but QUALITY is also important
- Poor sleep quality may be due to
  - Getting up multiple times at night because of physical or environmental issues
  - Sleep disorders
    - Sleep apnea
    - Insomnia
    - Restless Legs Syndrome

Sleep Apea

- Apnea Hypopnea Index (AHI)
- SDB= AHI ≥ 5
  - Mild 5-14.9
  - Moderate ≥15-29.9
  - Severe ≥ 30

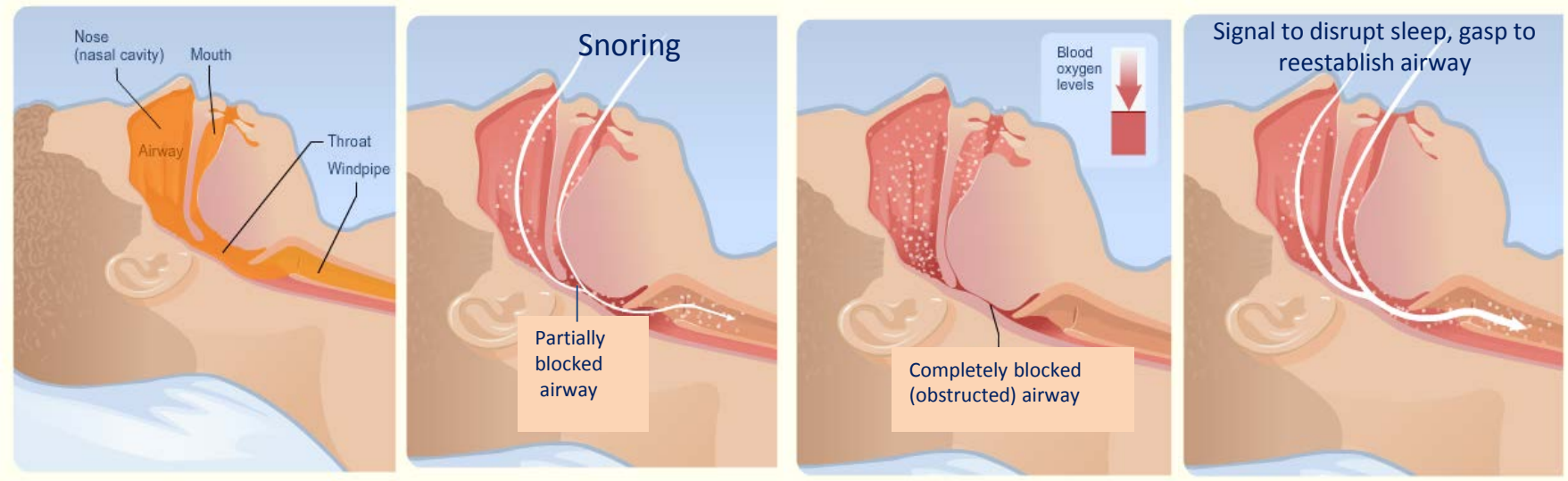
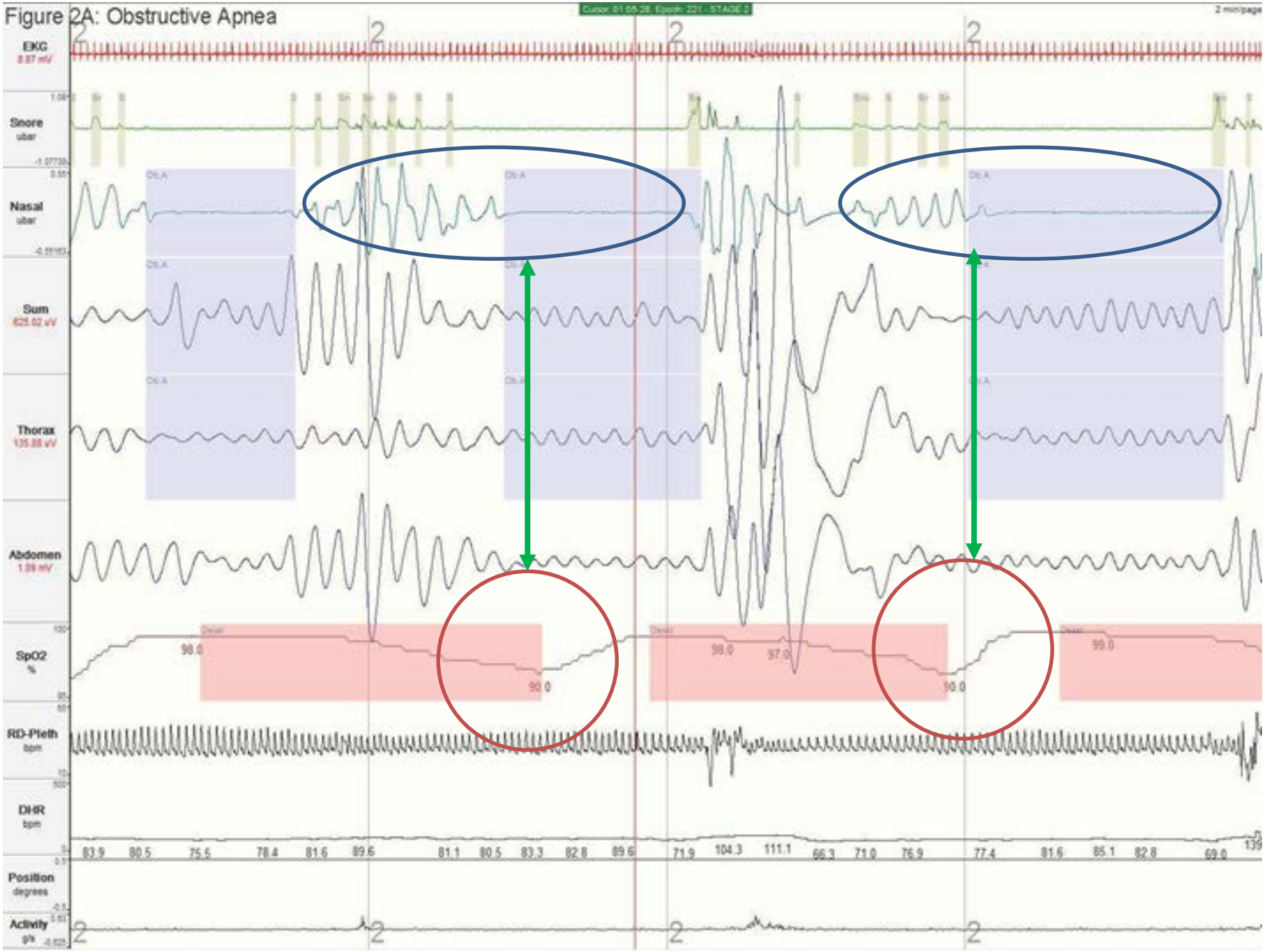
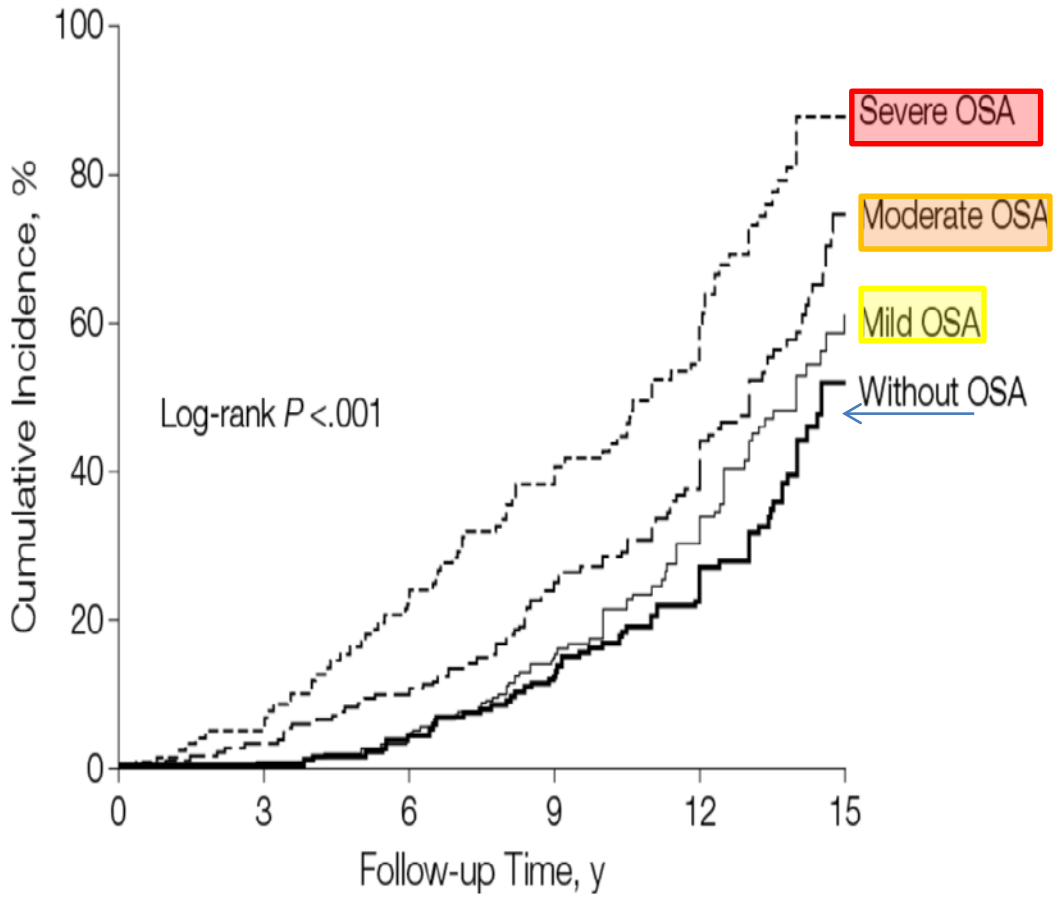


Figure 2A: Obstructive Apnea



OSA and CV Disease

Cumulative Incidence of Hypertension in Participants Without OSA and Untreated Patients With OSA



Marin et al. JAMA. 2012;307(20):2169-2176.
doi:10.1001/jama.2012.3418

T2DM and OSA

TABLE 2. Type 2 Diabetes Mellitus, Diabetic Medication Usage, and Mean HbA1c by OSA Severity

Characteristics	Total Population	No OSA	Mild	Moderate	Severe	*P* Value
T2DM	17.2	6.6	14.1	21.0	28.9	< .001
Diabetic medications	9.3	3.7	8.0	11.4	15.6	< .001
HbA1c (%)	5.68 (0.98)	5.38 (0.72)	5.58 (0.83)	5.76 (0.96)	6.06 (1.22)	< .001

Data are expressed as percentage of cohort or mean (SD). HbA1c = glycosylated hemoglobin; T2DM = type 2 diabetes mellitus.

Kent et al. CHEST. 2014

Short Sleep Duration

Sleep Fragmentation

Circadian Disruption

Sleep apnea- Intermittent hypoxia & Intrathoracic pressure swings

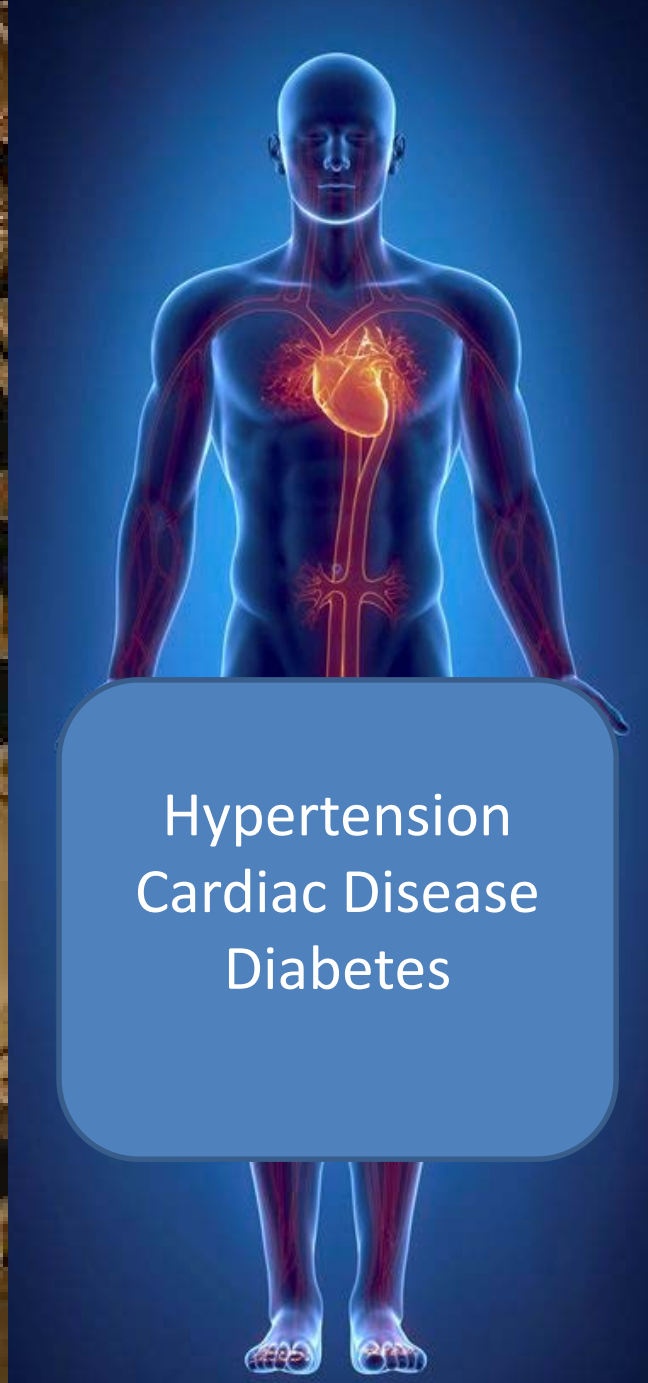
Leptin
Ghrelin

Activation-HPA axis
↓
Cortisol

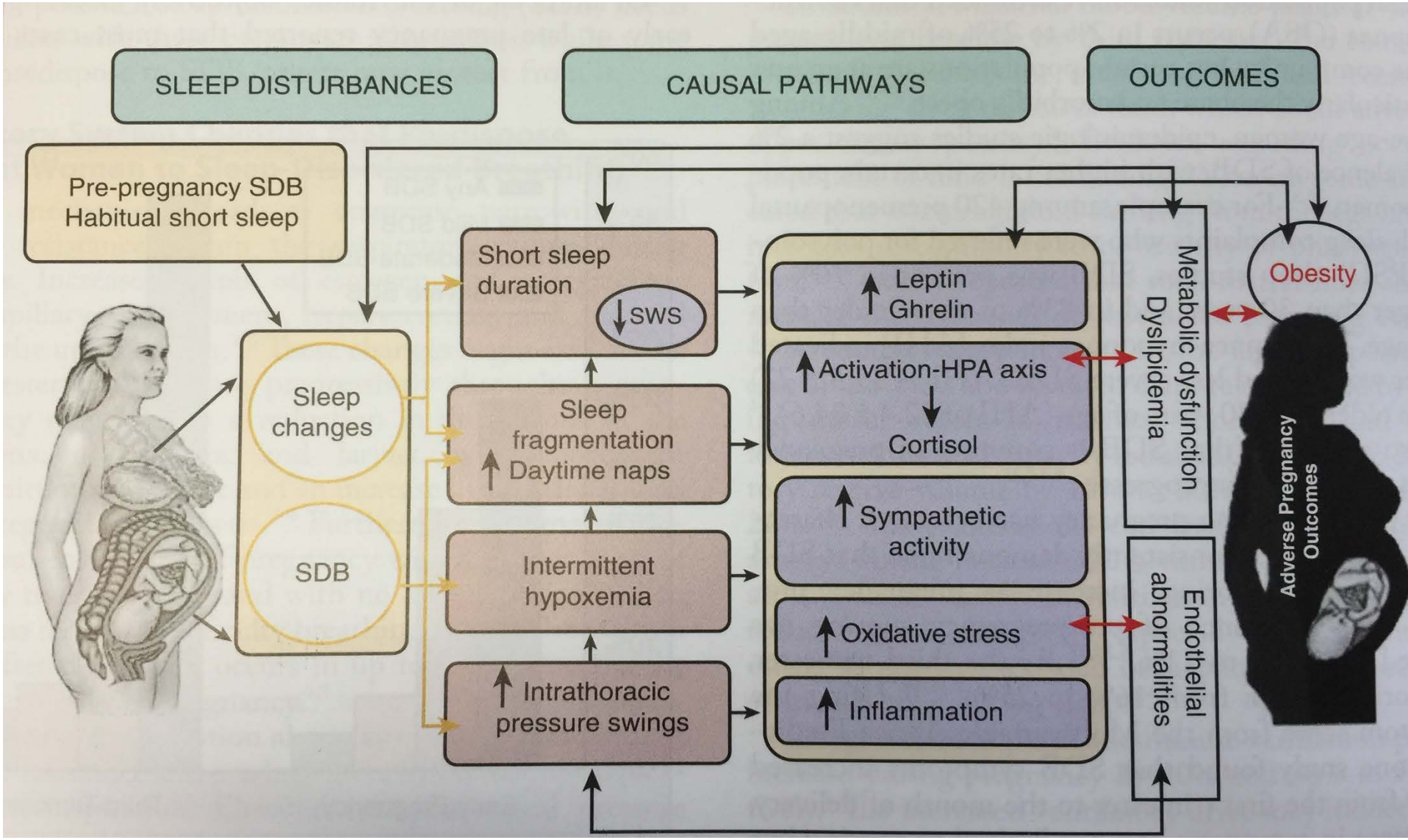
Sympathetic Activity

Oxidative Stress

Inflammation



Hypertension
Cardiac Disease
Diabetes



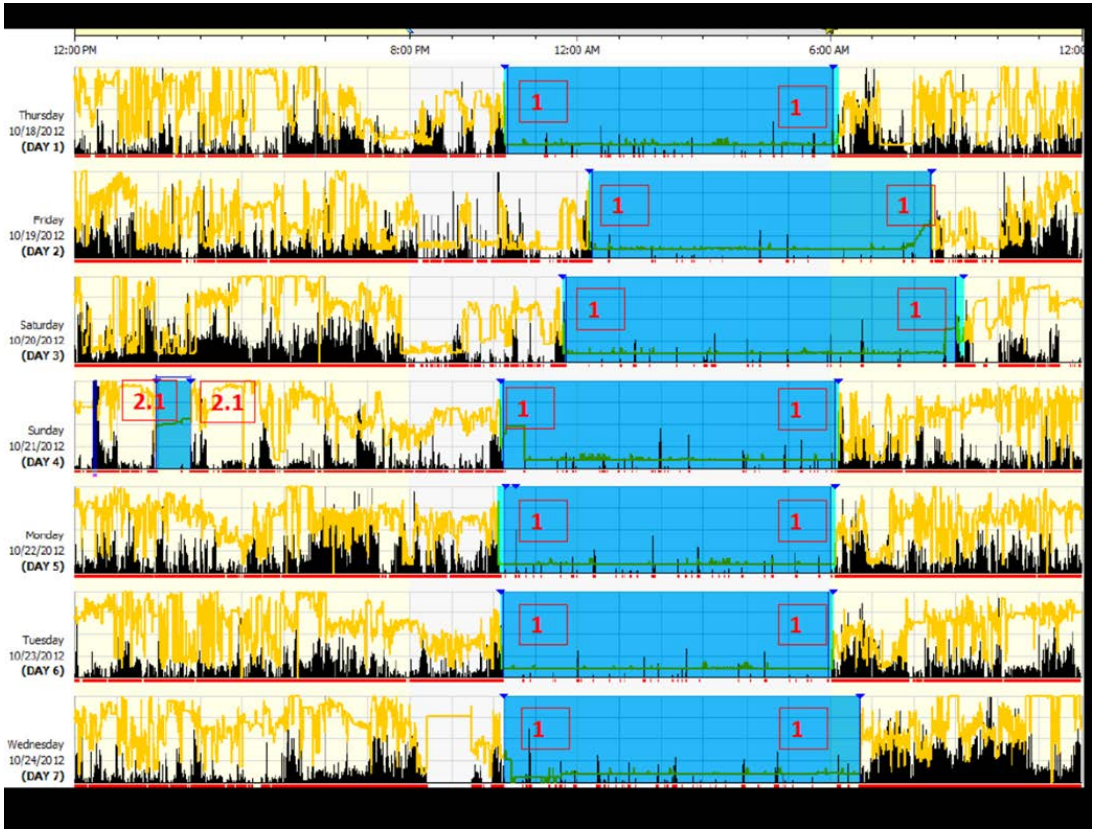
Principles and Practice of Sleep Medicine.
Facco, Francesca; Louis, Judette… Show all.; Knavert, Melissa Pauline; Izci Balserak, Bilgay.
Published January 1, 2017. Pages 1540-1546.e4. © 2017.

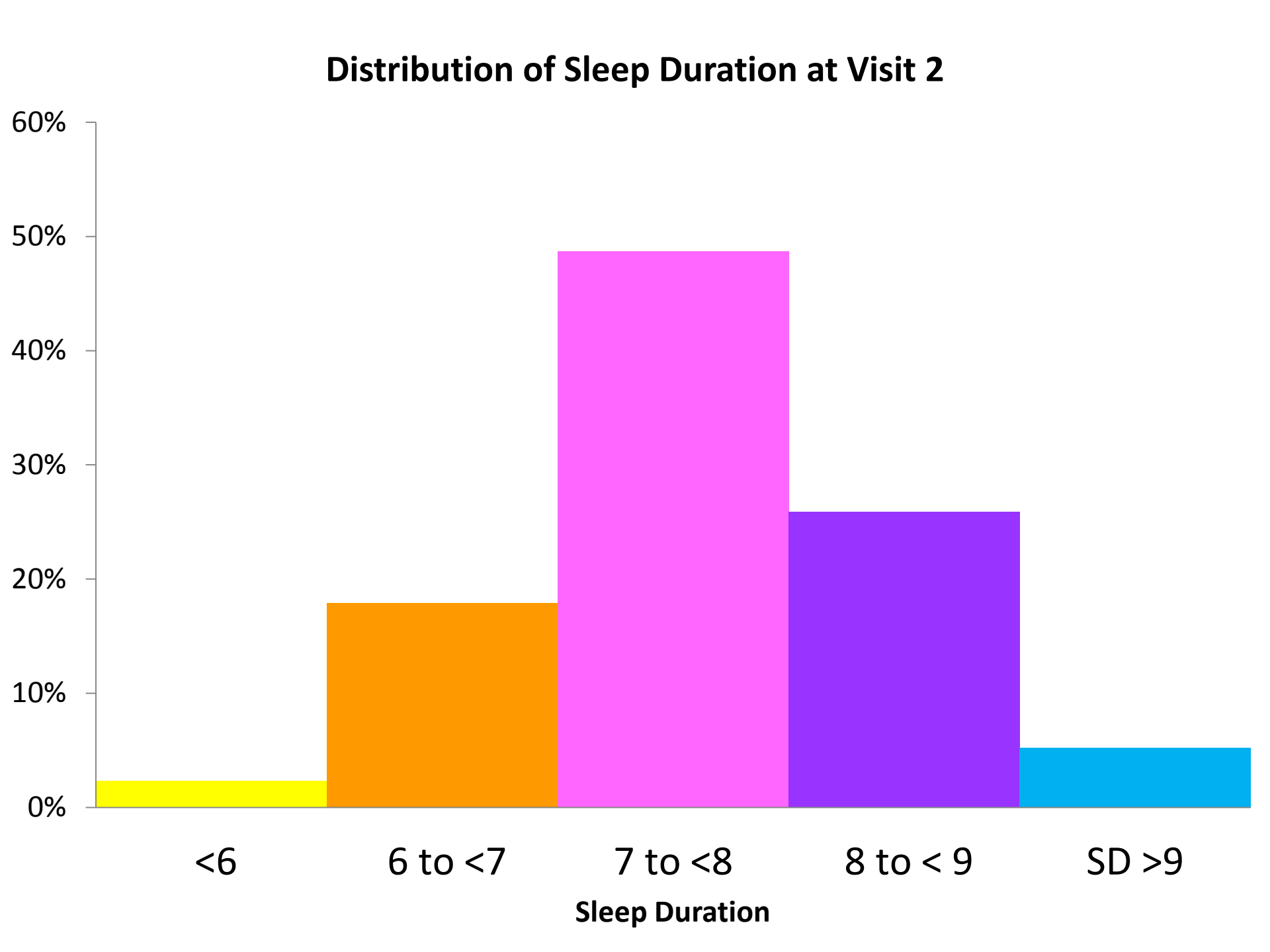
SLEEP AND PREGNANCY


zzzzz

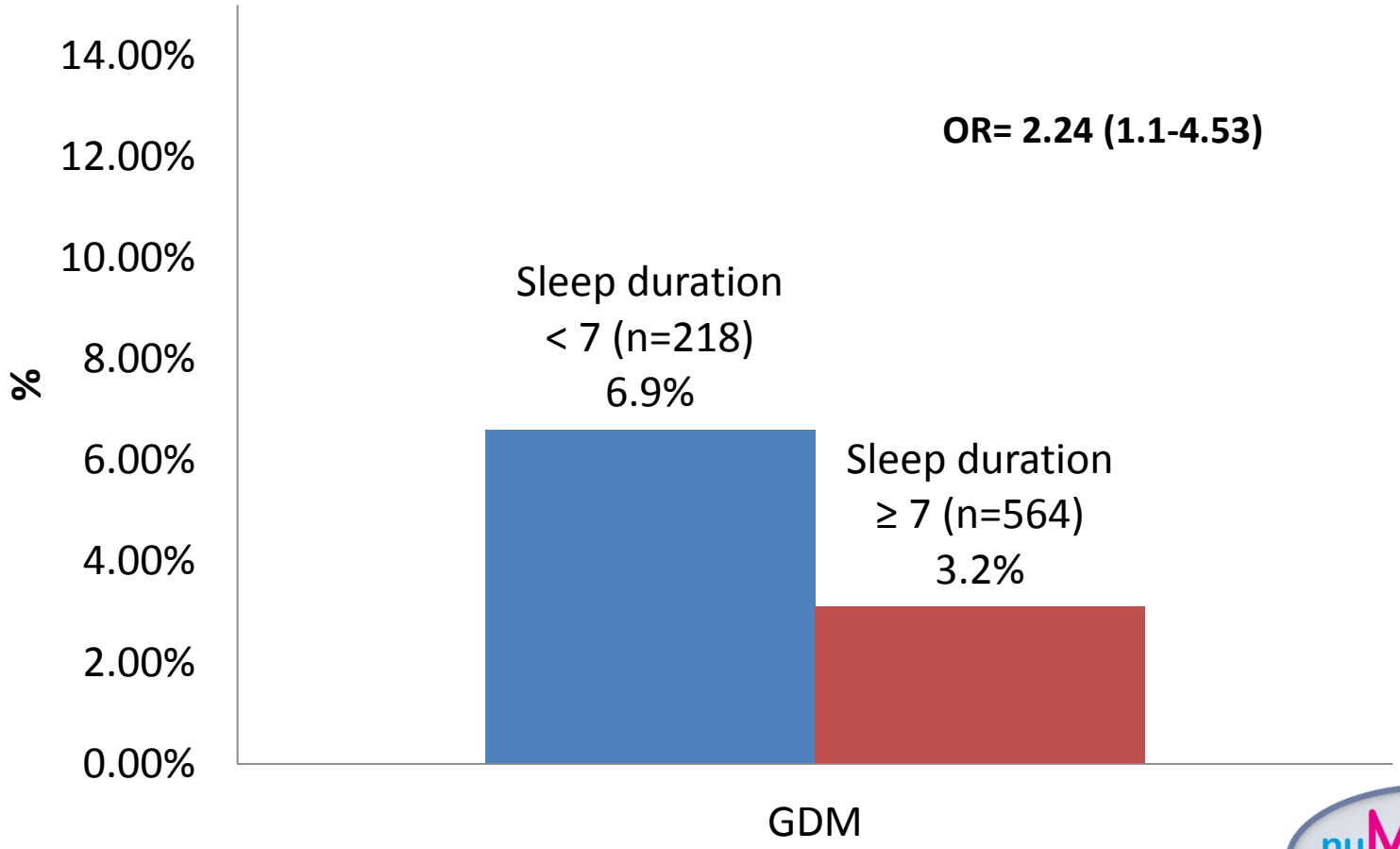
NuMoM2b Sleep Duration Study

Actiwatch (Philips Respironics)



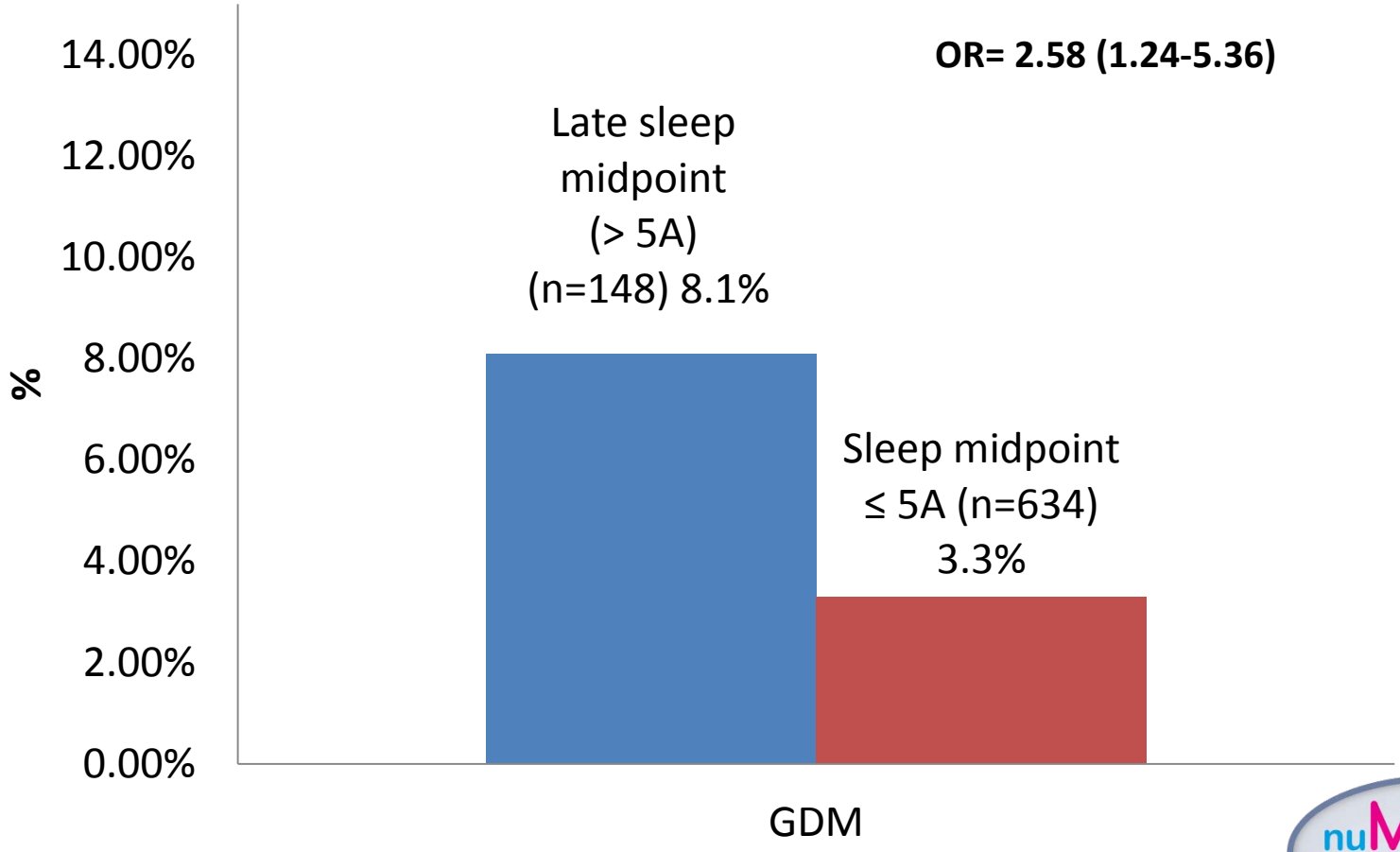

Distribution of Sleep Duration at Visit 2
60%
50%
40%
30%
20%
10%
0%
<6
6 to <7
7 to <8
8 to < 9
SD >9
Sleep Duration

Short Sleep and Gestational Diabetes Risk



Facco et al, 2015, SMFM Abstract # 256

Late Sleep Midpoint (> 5 AM) and Gestational Diabetes Risk



nuMOM2b
Nulliparous Pregnancy Outcomes Study Monitoring Mothers-to-be

Facco et al, 2015, SMFM Abstract # 256

TABLE 4

Association of sleep duration and timing with gestational diabetes

Sleep characteristic categories	Gestational diabetes n/N (%)	Crude OR, point estimate (95% CI) N = 782	Adjusted OR, point estimate (95% CI), after adjustment for:					
			Age, linear and quadratic N = 782	BMI, linear and quadratic N = 772	Race/ethnicity, 4 categories N = 782	White, non-Hispanic, yes/no N = 782	Frequent snoring, yes/no N = 669	Employment schedule, 3 categories N = 741
Sleep duration								
<7 h	15/218 (6.9)	2.24 (1.11–4.53)	2.26 (1.12–4.58)	2.12 (1.04–4.30)	2.31 (1.13–4.73)	2.25 (1.10–4.60)	2.29 (0.97–5.39)	2.42 (1.16–5.06)
≥7 h	18/564 (3.2)	1.00	1.00	1.00	1.00	1.00	1.00	1.00
		P value = .0246	*P* value = .0232	*P* value = .0380	*P* value = .0220	*P* value = .0266	*P* value = .0586	*P* value = .0190
Sleep midpoint								
>5 AM	12/148 (8.1)	2.58 (1.24–5.36)	3.87 (1.74–8.59)	2.41 (1.15–5.07)	2.61 (1.22–5.57)	2.62 (1.23–5.58)	2.84 (1.16–6.99)	3.71 (1.50–9.21)
≤5 AM	21/634 (3.3)	1.00	1.00	1.00	1.00	1.00	1.00	1.00
		P value = .0114	*P* value = .0009	*P* value = .0202	*P* value = .0132	*P* value = .0124	*P* value = .0229	*P* value = .0047

OR given to show association between gestational diabetes and sleep characteristic, without consideration of covariates and with separate adjustment for: age; BMI; race/ethnicity categories; white, non-Hispanic race/ethnicity; frequent snoring noted before pregnancy; and employment schedule (regular day shift, some form of shift work, unemployed). For race/ethnicity, Asian and other are collapsed.

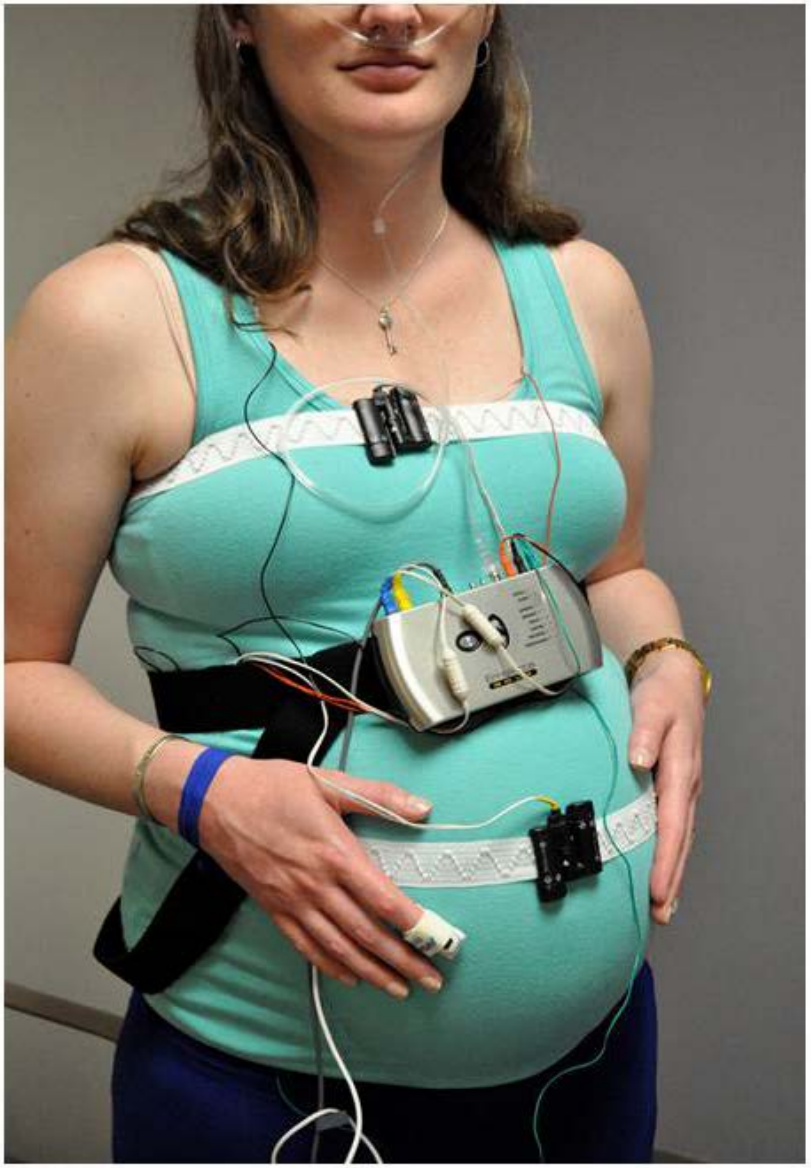
BMI, body mass index; *CI*, confidence interval; *OR*, odds ratio.

Facco et al. Sleep duration in pregnancy associated with risk of gestational diabetes. Am J Obstet Gynecol 2017.

nuMOM2b

Nulliparous Pregnancy Outcomes Study
Monitoring Mothers-to-be

Sleep-Disordered Breathing Substudy

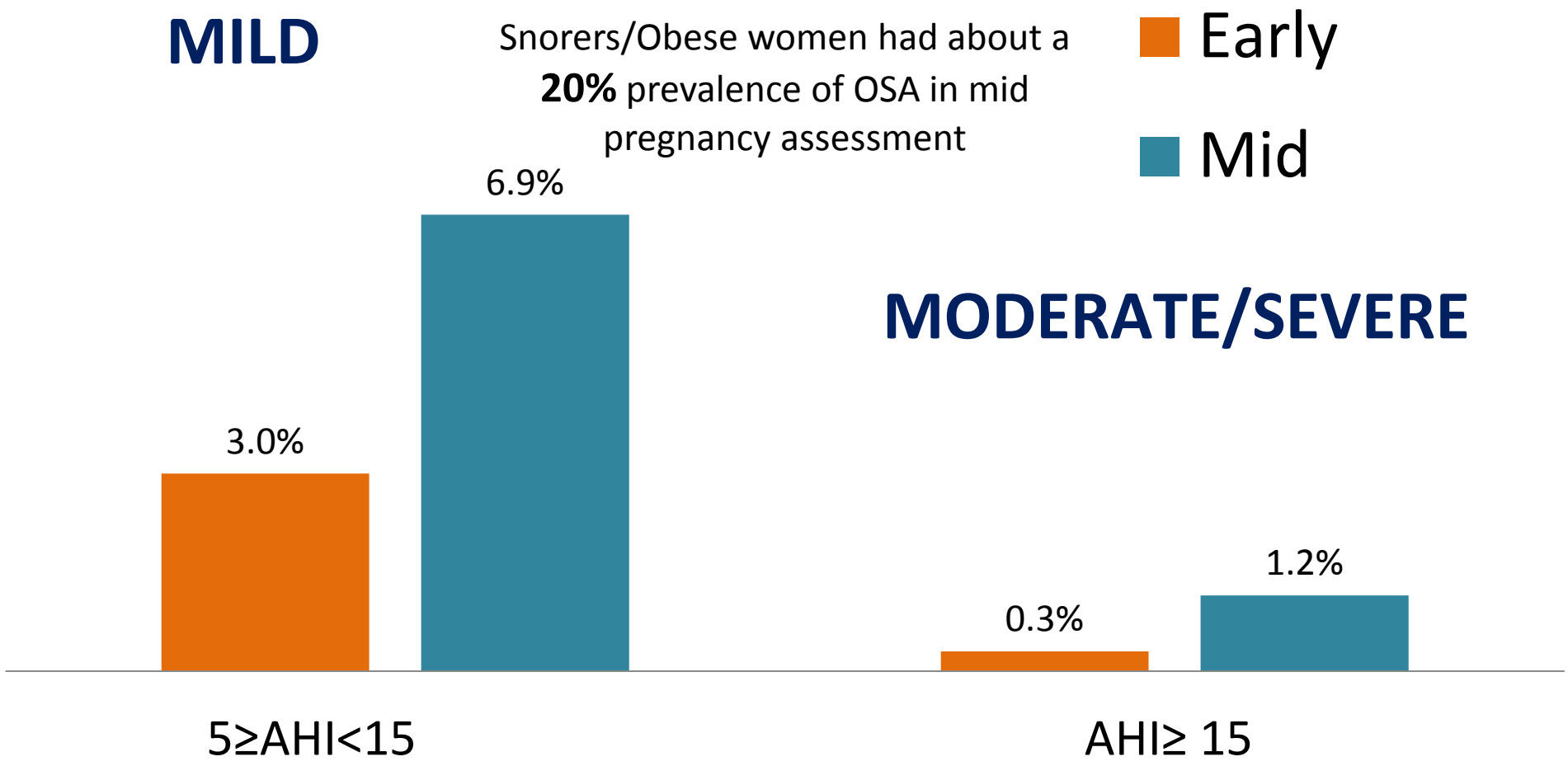


SDB Prevalence in Nulliparous Women

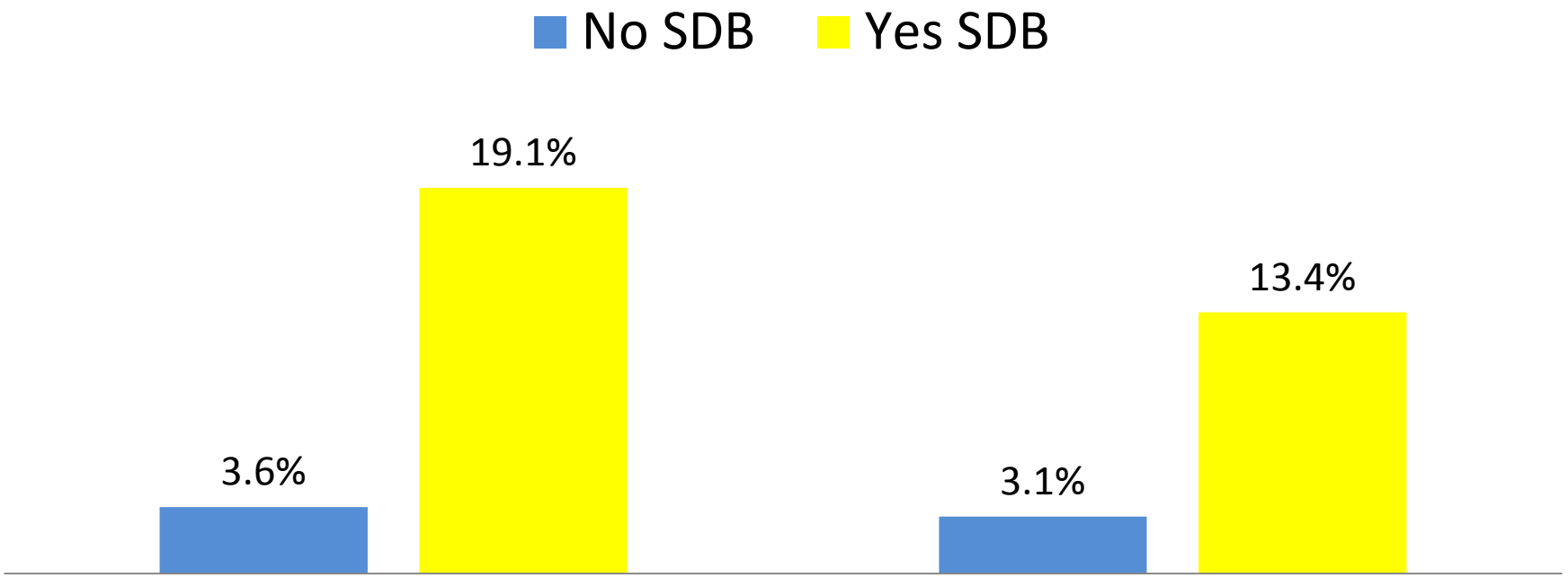
AHI ≥ 5

3.6% in early pregnancy

8.3% in mid pregnancy

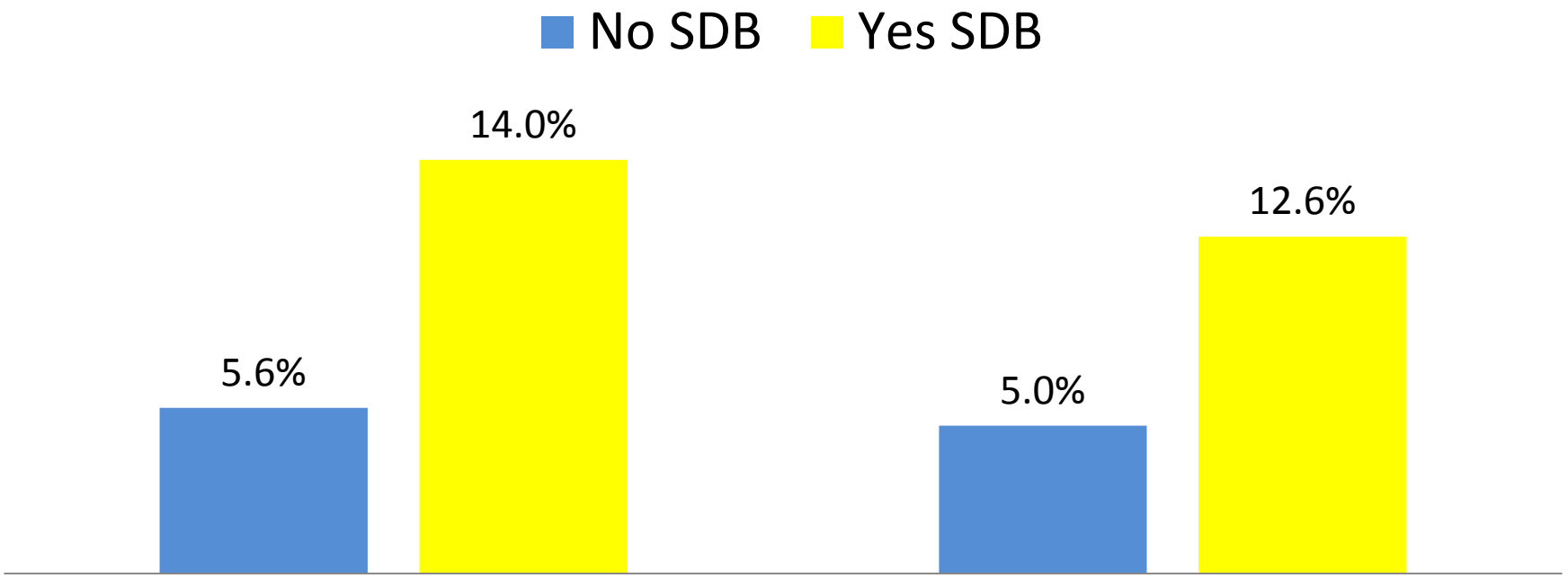


Incidence of Gestational Diabetes



EARLY PREGNANCY	p-value	MID-PREGNANCY	p-value
Adjusted OR 3.47 (1.95, 6.19)	**<0.001**	**Adjusted OR 2.79 (1.63, 4.77)**	**<0.001**

Incidence of Preeclampsia



EARLY PREGNANCY	p-value	MID-PREGNANCY	p-value
Adjusted OR 1.94 (1.07, 3.51)	**0.03**	**Adjusted OR 1.95 (1.18, 3.23)**	**0.01**

Sleep Health

A **Modifiable** Risk Factor for Adverse Pregnancy Outcomes?

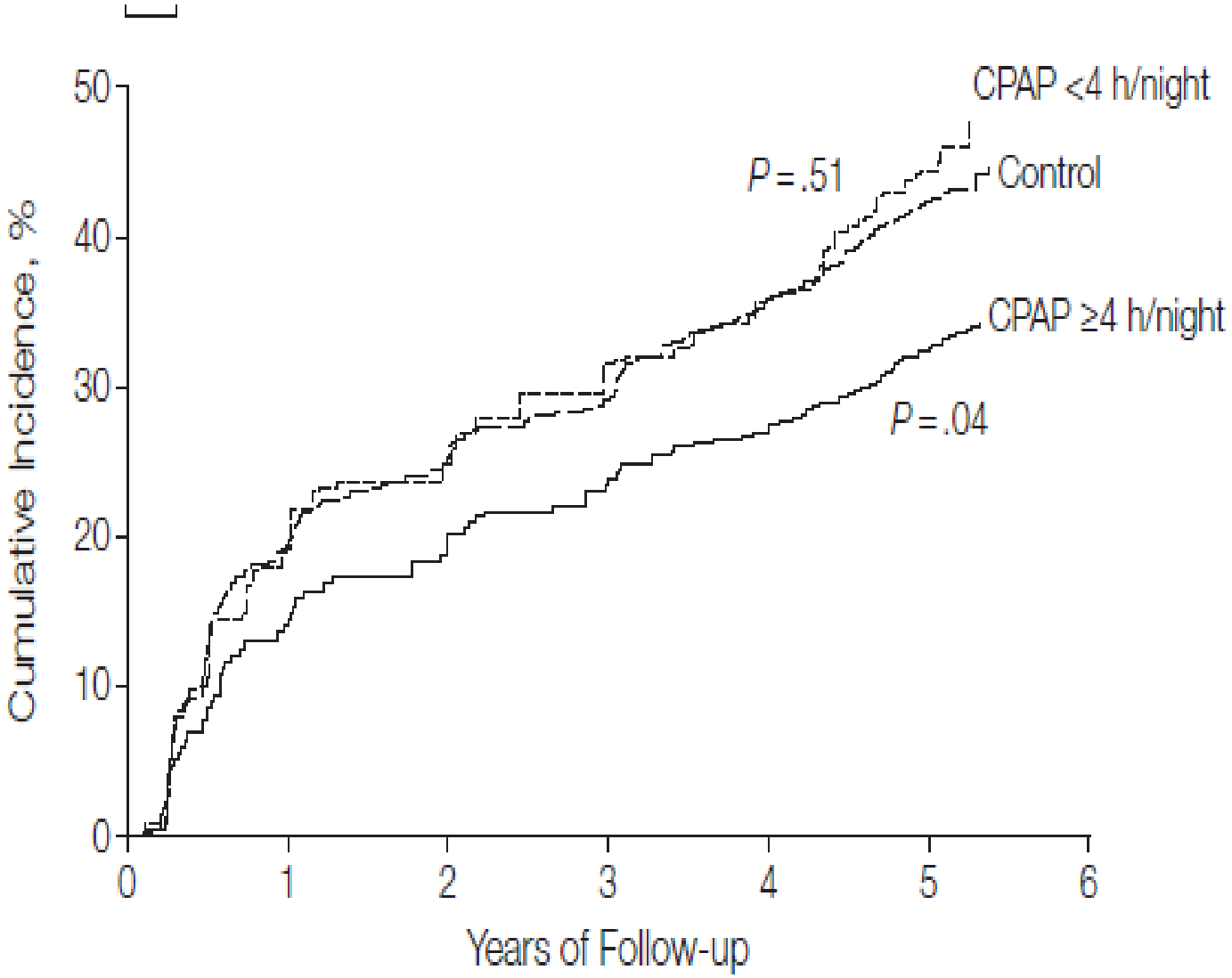
Continuous **P**ositive **A**irway **P**ressure
CPAP

- Sleep apnea is a potentially modifiable pregnancy risk factor
- Opportunity to study if OSA treatment with CPAP can reduce the frequency of hypertensive disorders of pregnancy

CPAP Trials in Non-Pregnant Cohorts

- Normalization of AHI
- Improved Sleep Quality
- Less daytime sleepiness, improved daytime functioning
- CV and metabolic health ???

Figure 2. Cumulative Incidence of Hypertension or Cardiovascular Events During Follow-up



Barbe et al. JAMA. 2012;307(20):2161-2168. doi:10.1001/jama.2012.4366.

Original Investigation

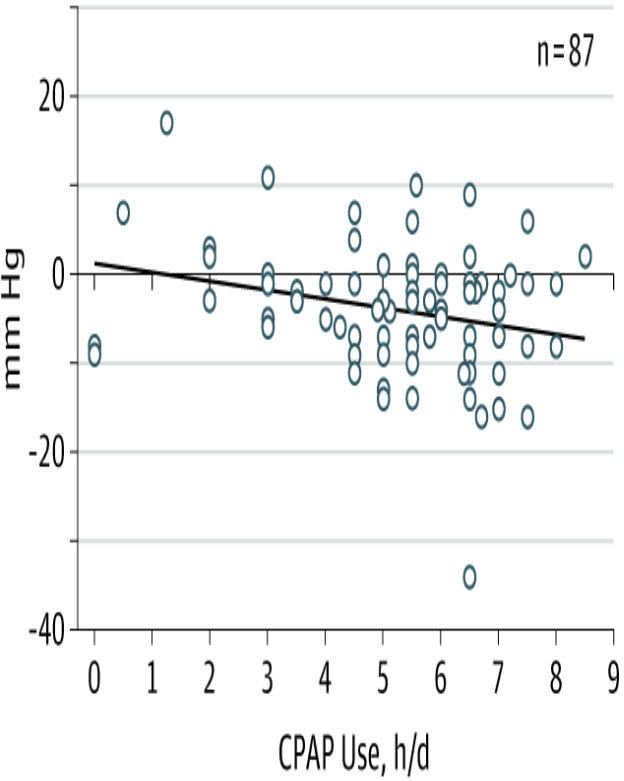
Effect of CPAP on Blood Pressure in Patients With Obstructive Sleep Apnea and Resistant Hypertension

The HIPARCO Randomized Clinical Trial

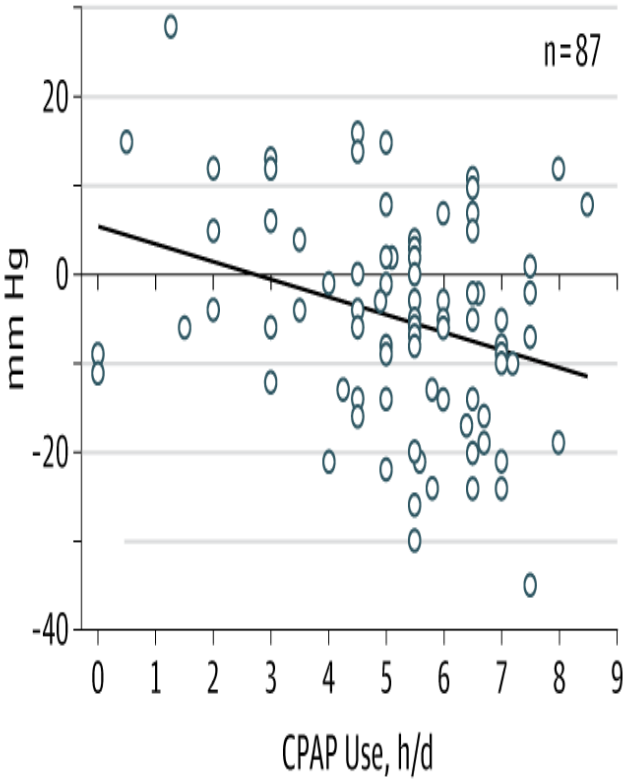
JAMA. 2013;310(22):2407-2415.

Miguel-Angel Martínez-García, MD, PhD; Francisco Capote, MD, PhD; Francisco Campos-Rodríguez, MD, PhD; Patricia Lloberes, MD, PhD;

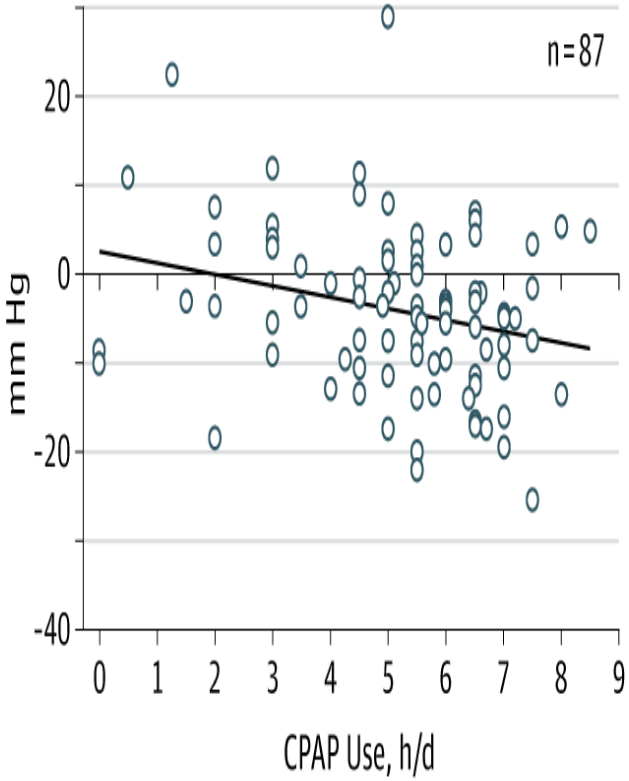
Change in diastolic blood pressure



Change in systolic blood pressure



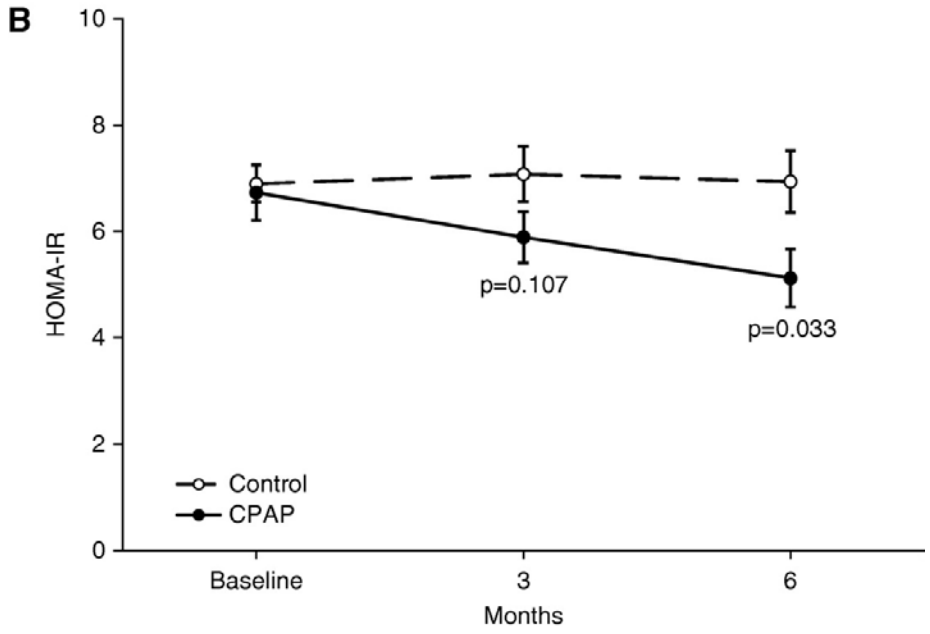
Change in 24-h mean blood pressure



American Journal of Respiratory and Critical Care Medicine

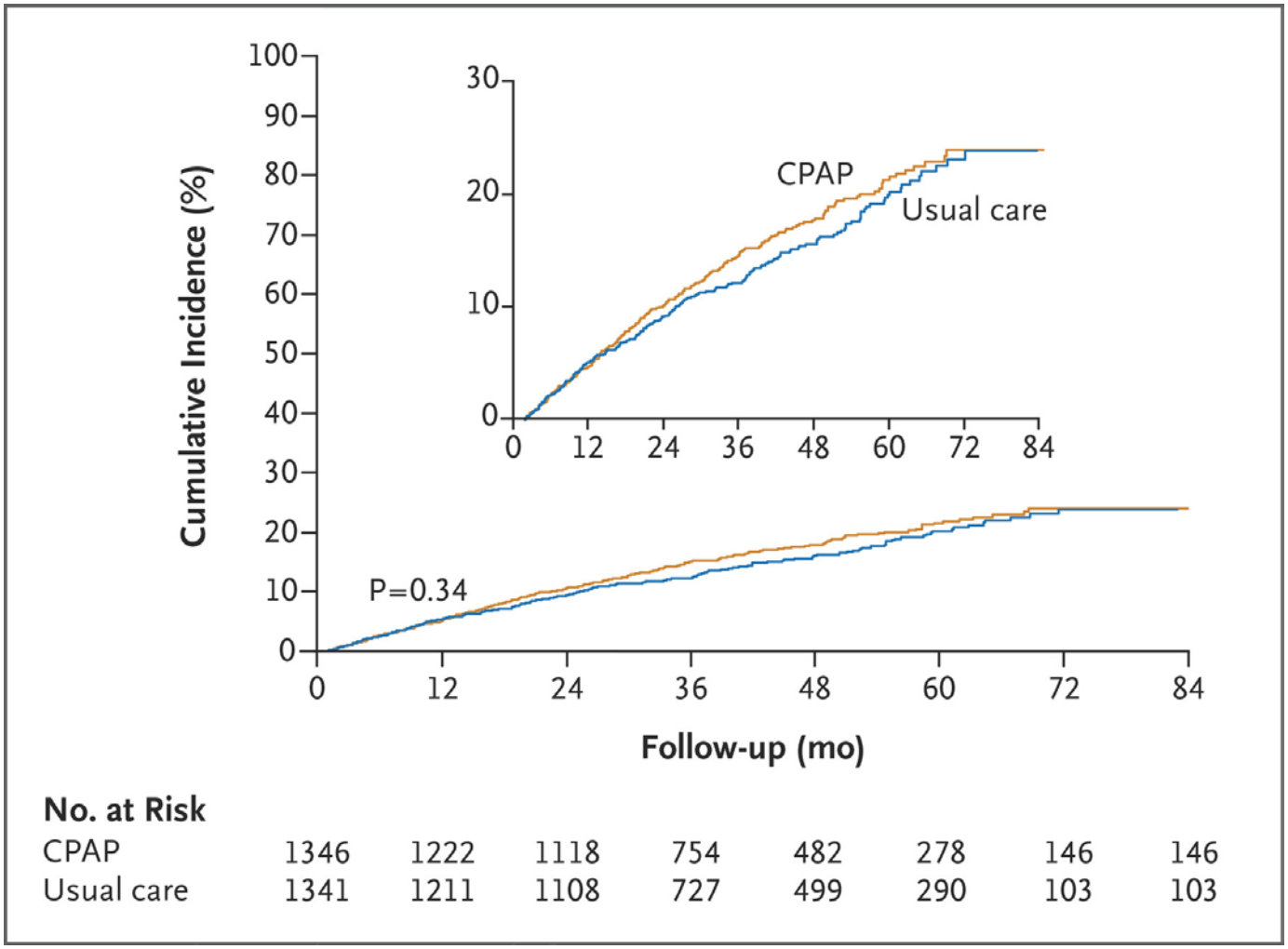
Effect of Continuous Positive Airway Pressure on Glycemic Control in Patients with Obstructive Sleep Apnea and Type 2 Diabetes. A Randomized Clinical Trial

Elisabet Martínez-Cerón [1,2], Beatriz Barquiel [3], Ana-Maria Bezos [4], Raquel Casitas [1,2], Raúl Galera [1,2], Cristina García-Benito [5], Angel Hernanz [6], Alberto Alonso-Fernández [7], and Francisco Garcia-Rio [1,2,8]



SAVE TRIAL

Therapy with CPAP plus usual care, as compared with usual care alone, did not prevent cardiovascular events in patients with moderate-to-severe obstructive sleep apnea **and established cardiovascular disease**



McEvoy et al. NEJM. 2016.

CPAP & Pregnancy

- CPAP and pregnancy data extremely limited
- Pregnancy is an ideal scenario in which to better understand the role of CPAP as a **preventative strategy** in reducing cardio-metabolic morbidity

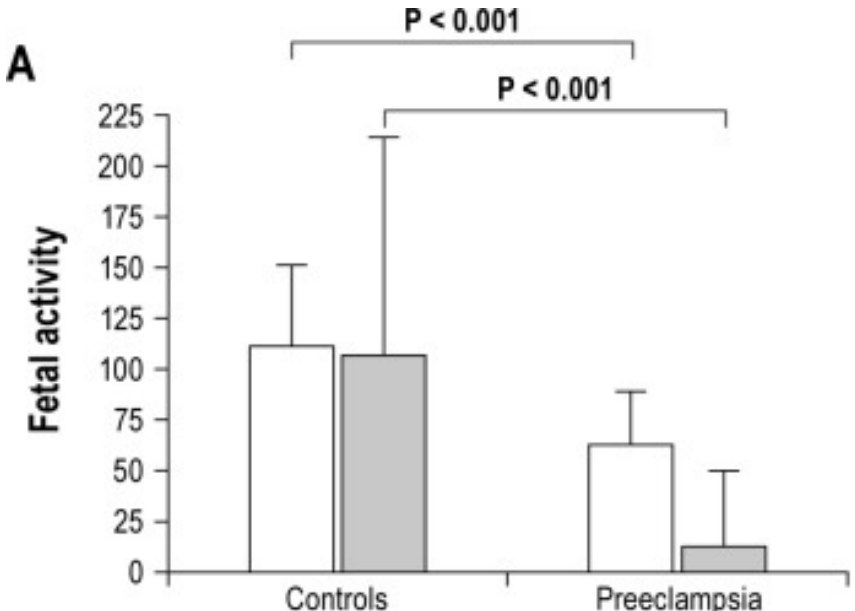
SLEEP

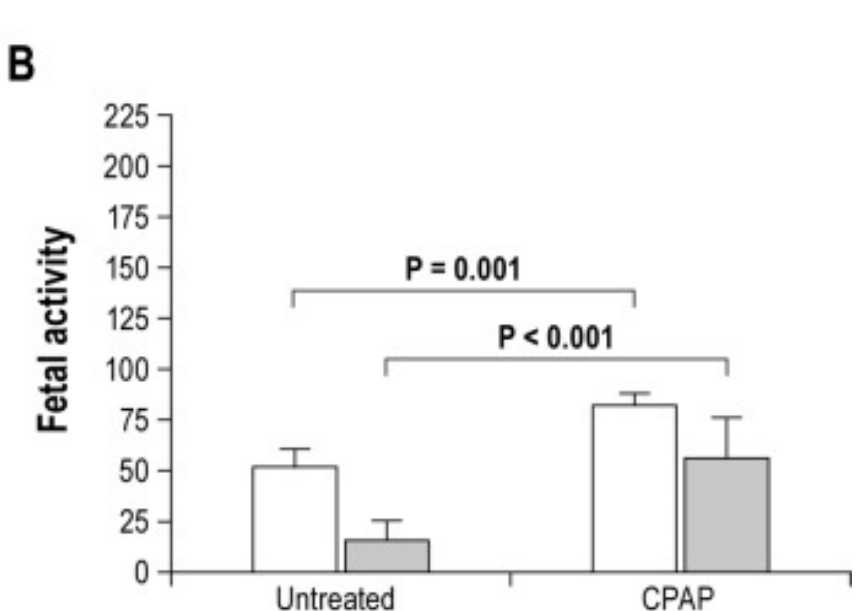
Sleep. 2013 Jan 1; 36(1): 15–21.
Published online 2013 Jan 1. doi: 10.5665/sleep.2292
PMCID: PMC3524539

Treatment of Sleep Disordered Breathing Reverses Low Fetal Activity Levels in Preeclampsia

Diane M. Blyton, PhD,[1] Michael R. Skilton, PhD,[2] Natalie Edwards, PhD,[1,*] Annemarie Hennessy, PhD,[3] David S. Celermajer, PhD,[1] and Colin E. Sullivan, PhD[1]

- 10 Preeclamptic Women
- Fetal Movement Senor
  - White bars fetal movements
  - Grey bars fetal hiccups





ELSEVIER

Sleep Medicine 9 (2007) 15–21

SLEEP MEDICINE

www.elsevier.com/locate/sleep

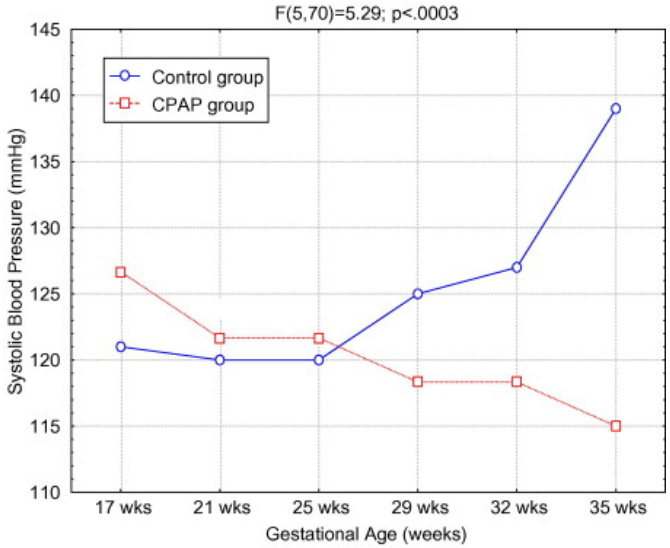
Original article

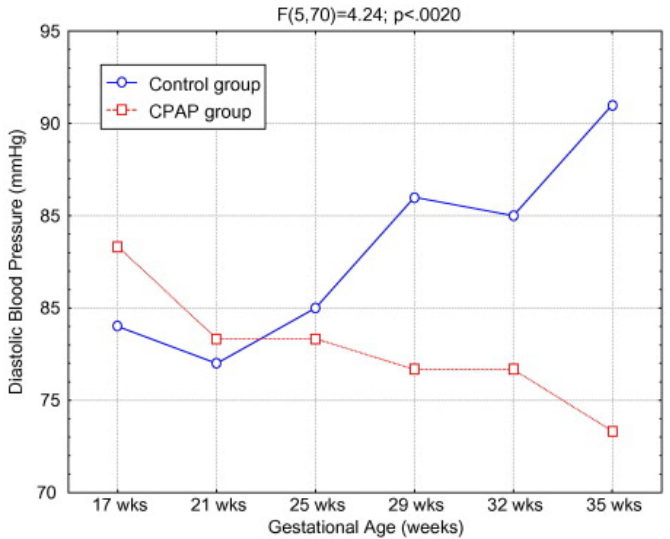
Pre-eclampsia and nasal CPAP: Part 2. Hypertension during pregnancy, chronic snoring, and early nasal CPAP intervention

Dalva Poyares [a,b], Christian Guilleminault [b,*], Helena Hachul [a], Luciane Fujita [a] Shanon Takaoka [b], Sergio Tufik [a], Nelson Sass [a]

[a] *Federal University of Sao Paulo Sleep Disorders Center, Brazil*
[b] *Stanford University Sleep Medicine Program, 401 Quarry Road, Suite 3301, Stanford, CA 94305, USA*

- Pregnancy women with CHTN
- Early pregnancy intervention
- 7 CPAP, 9 Controls
- Better BP control





Reduced Nocturnal Cardiac Output Associated with Preeclampsia is Minimized with the Use of Nocturnal Nasal CPAP

Diane M. Blyton, MSc[1,2]; Colin E. Sullivan, PhD[1]; Natalie Edwards, PhD[1]

[1]The University of Sydney; [2]Royal Prince Alfred Hospital, Sydney

- 24 severe pre-E
- Randomized
  - 12 CPAP, 12 no treatment
- 15 controls nulliparous
- Cardiac output reductions minimized and total peripheral resistance decreased with CPAP

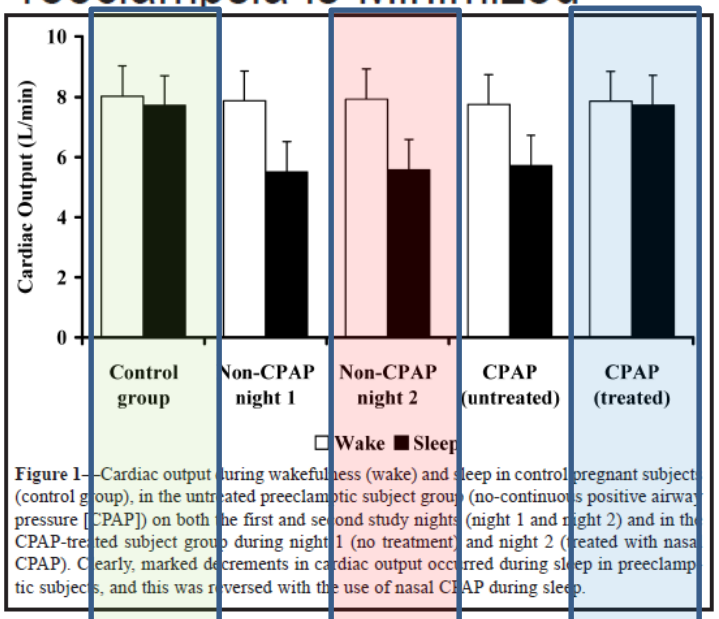


Figure 1—Cardiac output during wakefulness (wake) and sleep in control pregnant subjects (control group), in the untreated preeclamptic subject group (no-continuous positive airway pressure [CPAP]) on both the first and second study nights (night 1 and night 2) and in the CPAP-treated subject group during night 1 (no treatment) and night 2 (treated with nasal CPAP). Clearly, marked decrements in cardiac output occurred during sleep in preeclamptic subjects, and this was reversed with the use of nasal CPAP during sleep.

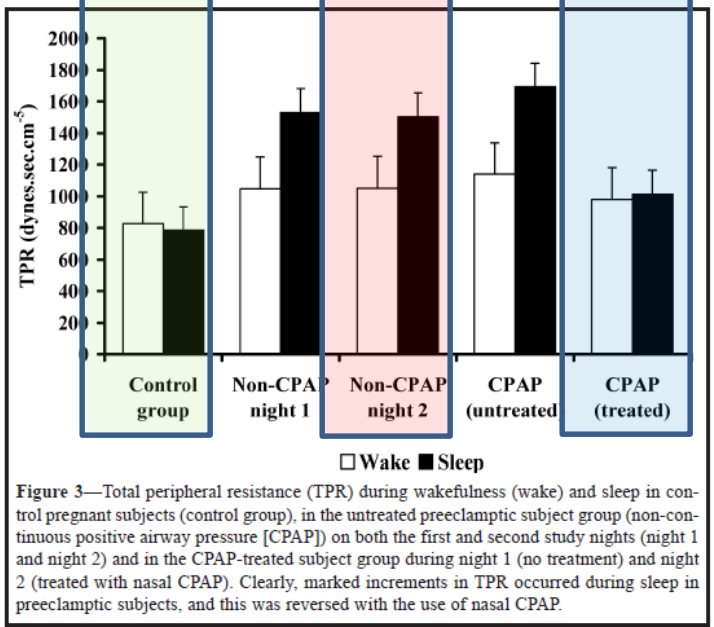


Figure 3—Total peripheral resistance (TPR) during wakefulness (wake) and sleep in control pregnant subjects (control group), in the untreated preeclamptic subject group (non-continuous positive airway pressure [CPAP]) on both the first and second study nights (night 1 and night 2) and in the CPAP-treated subject group during night 1 (no treatment) and night 2 (treated with nasal CPAP). Clearly, marked increments in TPR occurred during sleep in preeclamptic subjects, and this was reversed with the use of nasal CPAP.

MFMU SLEEP Trial

- RCT
- Nulliparous women who have a BMI ≥ 30 and/or who snore will be identified and asked to perform a home sleep test to identify sleep apnea positive subjects (AHI ≥ 5)
- OSA + women will be randomized
  - Auto-titrating CPAP
  - Sleep hygiene control (i.e., usual care)

- **Primary hypothesis of this trial is that treatment of OSA with CPAP in pregnancy will result in a reduction in the rate of hypertensive disorders of pregnancy**

Screen

- Rate of OSA much higher in women obese women and those with self reported snoring
- nuMoM2b **25%** of women reported frequent snoring
- Snorers/Obese women had about a **20%** prevalence of OSA in mid pregnancy assessment

Timing of Screen

- Balance
  - Optimize cost-effective screening (later in pregnancy)
  - Optimal treatment effect (earlier in pregnancy)
- 16w 0 d-20w 6 d gestation

Exclusion

- Age < 18
- Previously prescribed, current or planned therapy for sleep apnea
- Inability to sleep in a stable place with access to the CPAP machine at least 5 nights/week
- Current use prescribed sleeping pills for insomnia
- Current use of opiates
- Active drug use, alcohol use, unstable psychiatric condition
- Severe asthma requiring continuous oral steroid therapy for more than 14 days in past 6 months
- Conditions requiring oxygen supplementation

Exclusion

- Current use of antihypertensive medications to treat chronic hypertension
- Chronic renal disease with Cr > 1.3
- Antiphospholipid antibody syndrome
- Acute liver disease
- Thrombocytopenia < 100K
- Active vaginal bleeding more than spotting
- Known chromosomal/genetic/major malformation of the fetus
- Uterine malformations
- Participation in another interventional study that influences preE, GDM
- Delivery/care planned at a non-network site

Diagnose Sleep Apnea via Home Sleep Test (HST)

Severe Sleep Apnea & Hypoxemia Exclusions-Urgent Alerts

- If severe sleep apnea exclusion (AHI ≥ 30),nocturnal hypoxemia (02 sat ≤ 90% ≥ 10 % of recording time)
  - Anticipated less than 1%

CPAP vs. Sleep Hygiene Control

- Auto titrating-CPAP
  - Informational handout about healthy sleep
  - CPAP machine with appropriate mask, education about CPAP
  - Weekly follow-up
- Sleep Hygiene Control (i.e., usual care)
  - Informational handout
  - Sleep resources
  - Monthly follow-up

When you're in a rush to meet work, school, family, or household responsibilities, do you cut back on your sleep, thinking it won't be a problem? Like many people, you might think that sleep is merely a "down time" when the brain shuts off and the body rests. Think again.

What Is Sleep?

Sleep was long considered just a block of time when your brain and body shut down. Thanks to sleep research studies done over the past several decades, it is now known that sleep has distinct stages that cycle throughout the night in predictable patterns. Your brain and body functions stay active throughout sleep, but different things happen during each stage. For instance, certain stages of sleep are needed for us to feel well rested and energetic th
help us learn or make mem

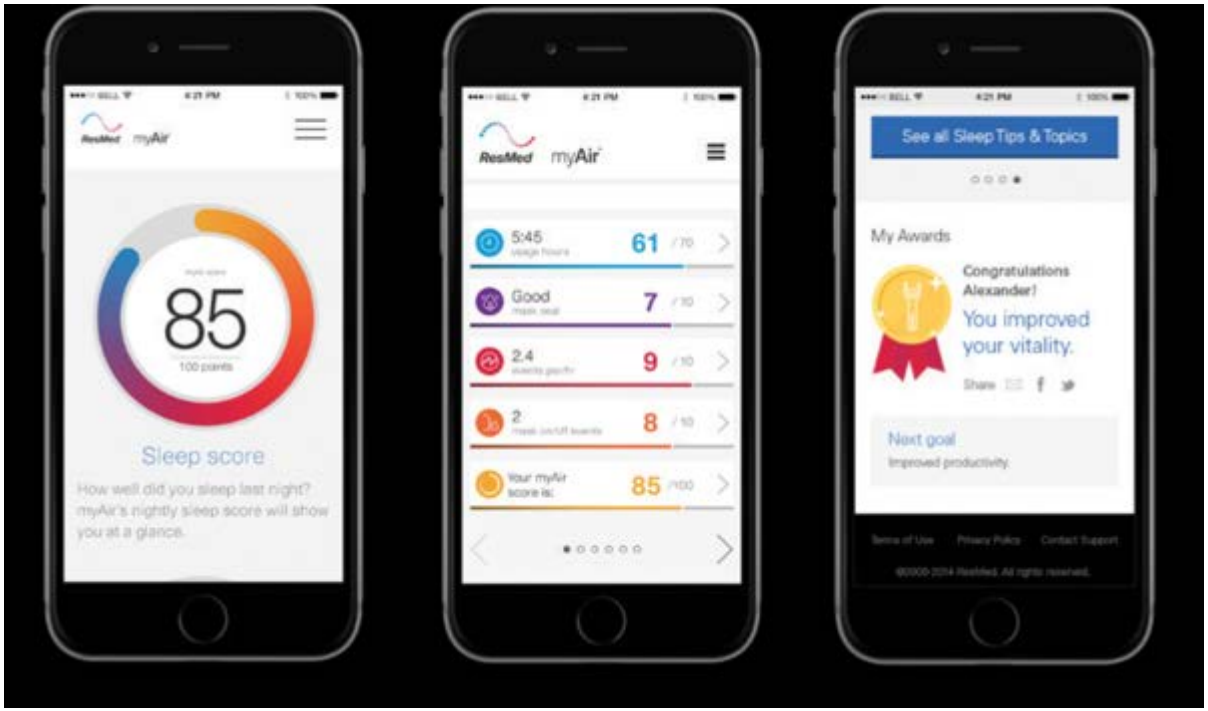
In brief, a number of vital
help people stay healthy a
On the other hand, not get
dangerous—*for example*, y
a car crash if you drive wh

How Much Sleep Is Enough?

Sleep needs vary from person to person, and they change throughout the life cycle. Most adults need 7–8 hours of sleep each night. Newborns, on the other hand, sleep between 16 and 18 hours a day, and children in preschool sleep between 11 and 12 hours a day. School-aged children and teens need at least 10 hours of sleep each night.

Some people believe that adults need less sleep as they get older. But there is no evidence to show that older people can get by with less sleep than younger people. As people age, however, they often get less sleep or they tend to spend less time in the deep, restful stage of sleep. Older people are also more easily awakened.

Compliance Monitoring for CPAP



-Compliance incentive

Primary Outcome

- Hypertensive disorders of pregnancy a composite of:
  - Gestational hypertension diagnosed before the onset of labor (antepartum)
  - Preeclampsia
  - Superimposed Preeclampsia
  - HELLP
  - Eclampsia

Secondary Outcomes

- Gestational diabetes by GTT criteria- GTT to be performed at or after 24 weeks gestation
- Preterm birth- < 34 weeks, <37 weeks, spontaneous, indicated
- Birthweight

Blood Analytes

- Mechanistic lab assays in the domains of :
  - Inflammation
  - Oxidative stress
  - Endothelial dysfunction
  - Angiogenesis
  - Hormonal mechanisms of energy regulation

Placental Collection

- Samples can be collected up to 72 hours after delivery as long as they have been stored in a 4 degree Celsius freezer between delivery and pickup.
- Samples will be stored for future histological analysis and analysis of stable proteins via immunohistochemistry.

Sample Size Assumptions

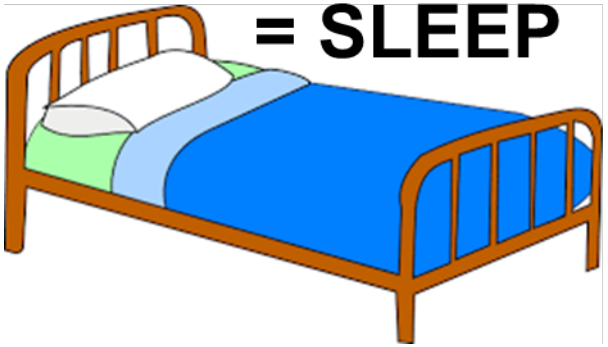
- 90% power to detect 30% reduction in reduction in the frequency of hypertensive disorders of pregnancy in women who get active-CPAP therapy
- nuMoM2b data -incidence of hypertensive disorders among women with OSA =20%
- 20% of women will use the device so infrequently over the course of the entire pregnancy that we would expect them to have an outcome frequency the same as in the control arm
- 1-2% cross over

Sample Size

- 1350 women/group (2700)
- Identify 1.33 women (BMI ≥ 30 and or snore) for every woman who agrees to the sleep test
  - 75% consent to sleep test
- Identify 1.25 women with a positive sleep test for every women who randomizes
  - 80% still eligible, and consent to randomization

Interventions to Improve Sleep

- Education
- Behavioral Interventions



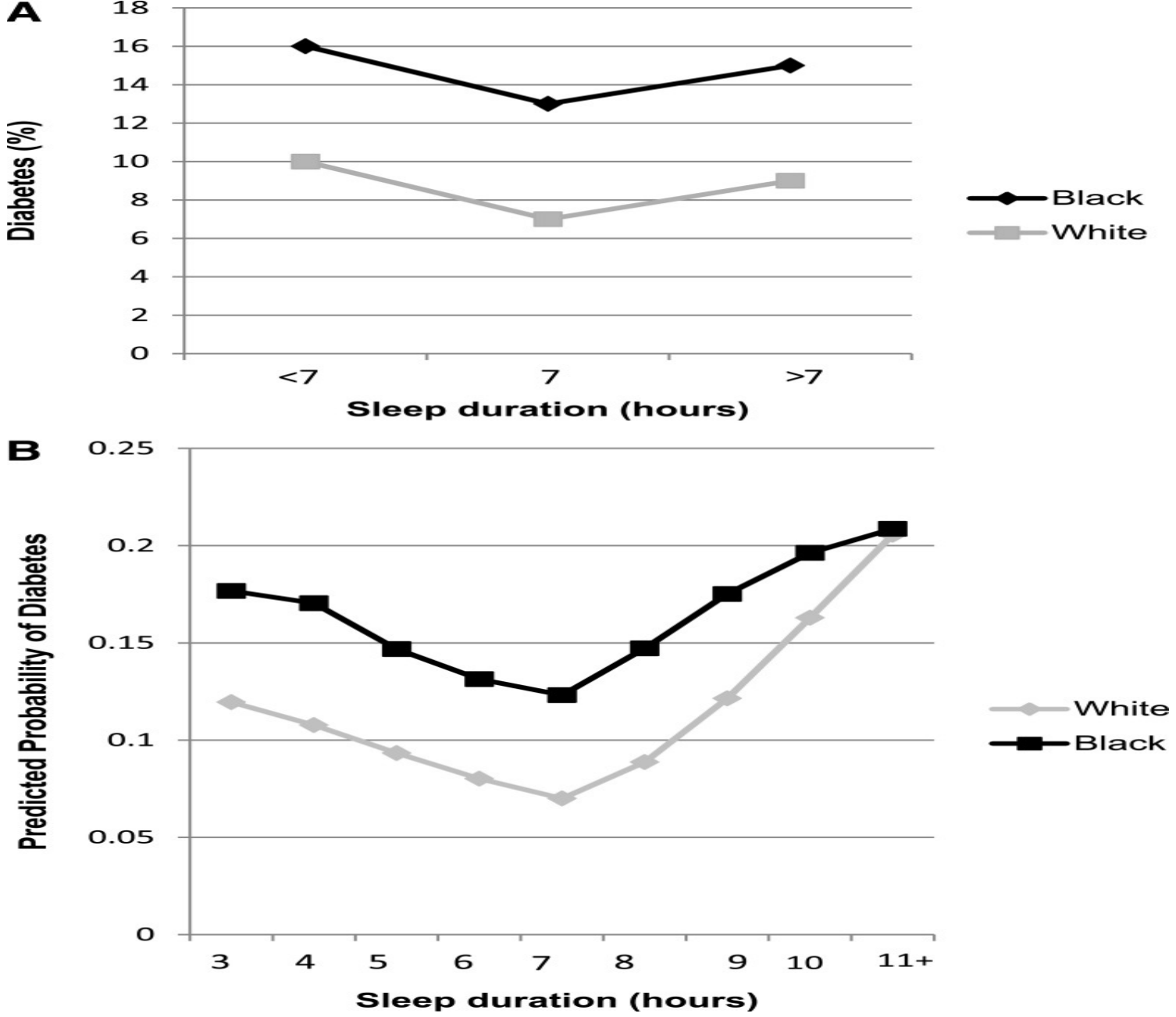
Continuous **P**ositive **A**irway **P**ressure

CPAP

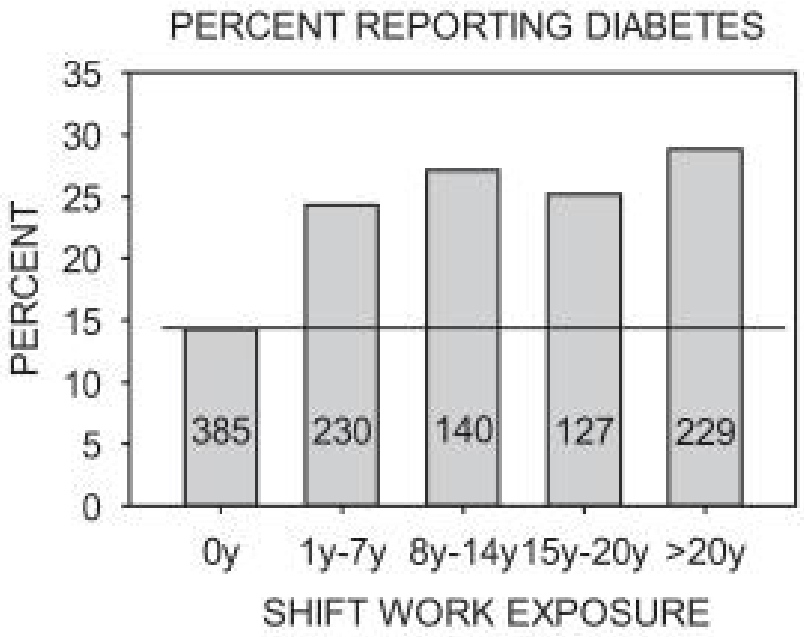
CPAP & Pregnancy

- CPAP and pregnancy data extremely limited
- Pregnancy is an ideal scenario in which to better understand the role of CPAP as a **preventative strategy** in reducing cardio-metabolic morbidity

Questions?



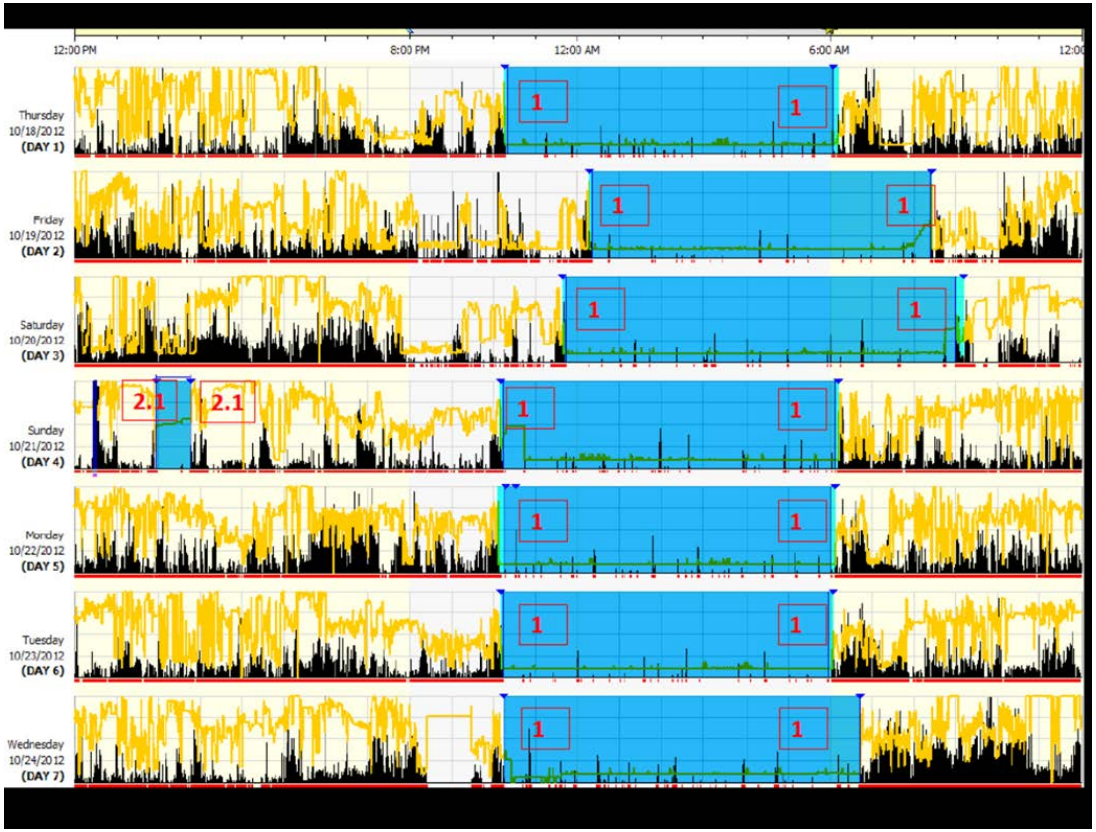
Association Between Sleep Duration and Diabetes in Black and White Adults
Jackson et al. Diabetes Care. 2013 Nov; 36(11): 3557–3565.

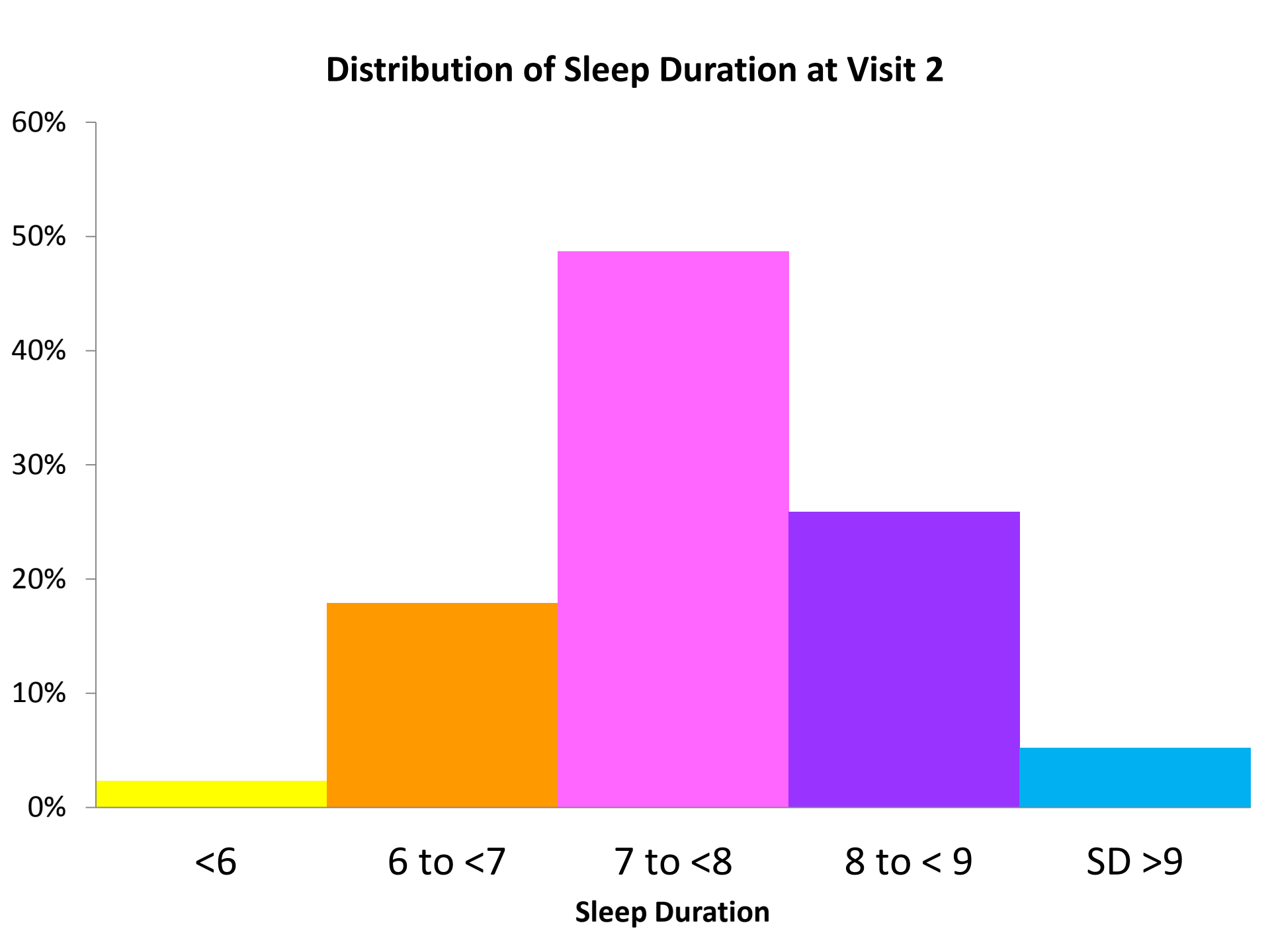


Monk et al. J Biol Rhythms. 2013 Oct; 28(5): 356–359.

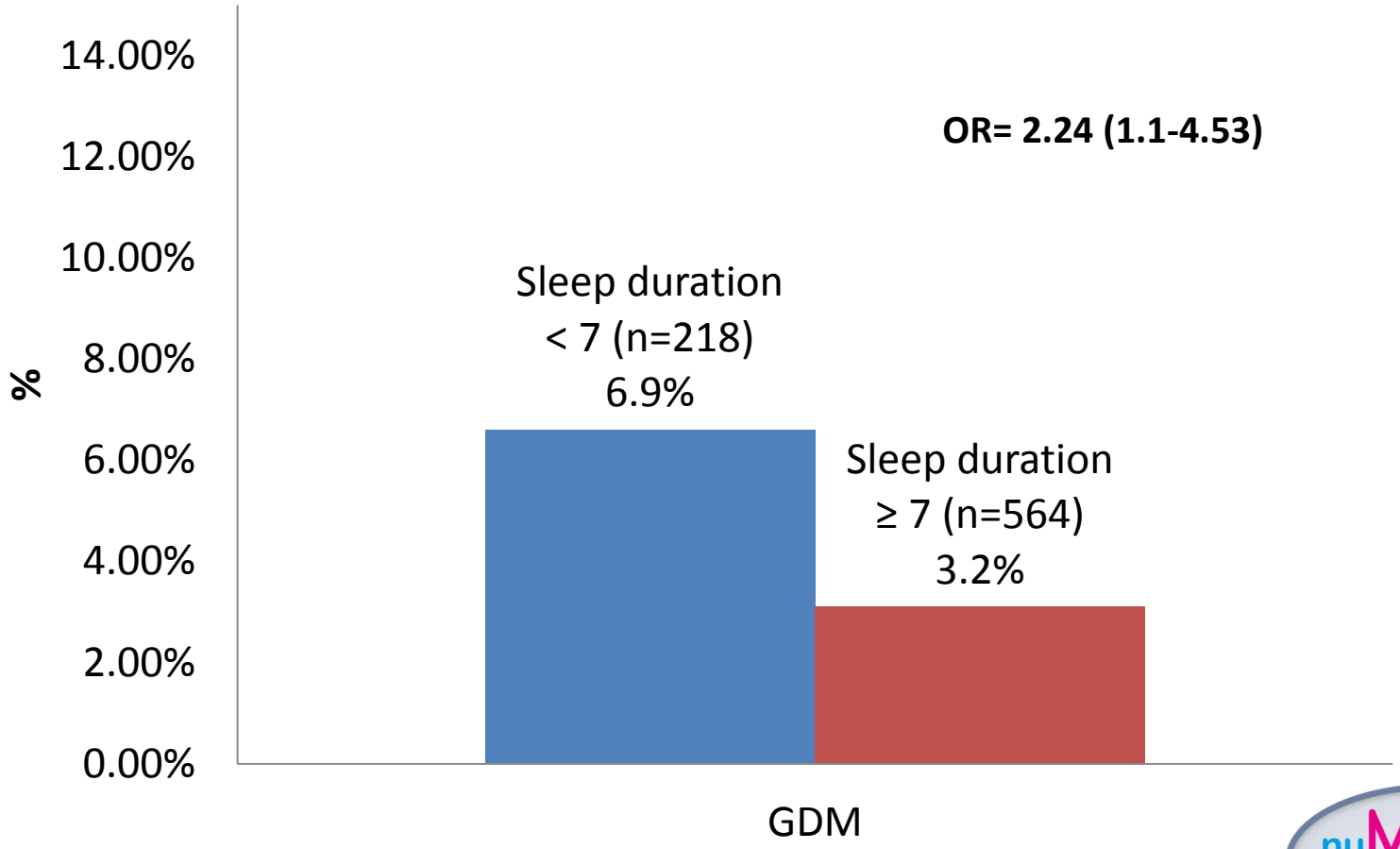
NuMoM2b Sleep Duration Study

Actiwatch (Philips Respironics)



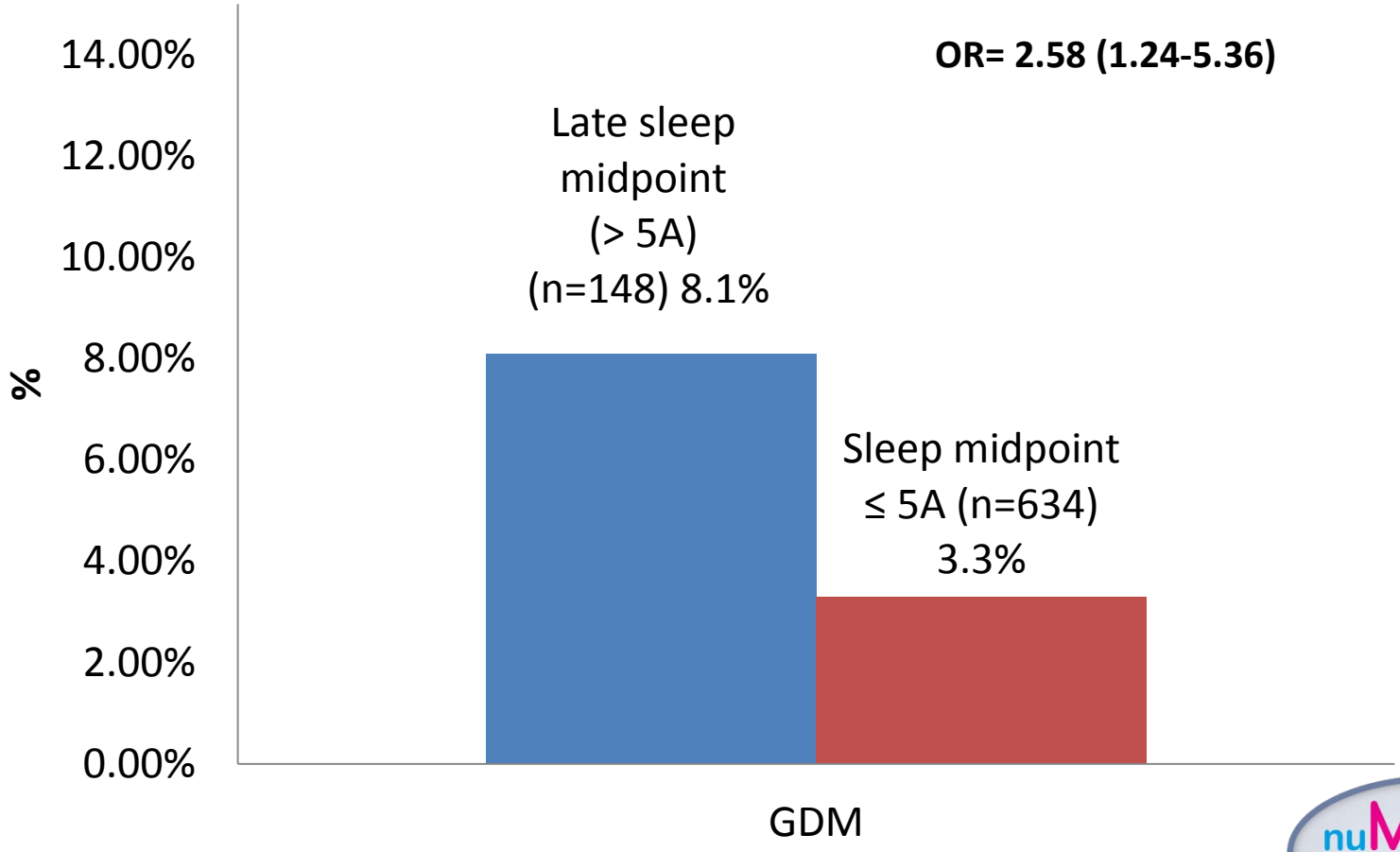

Distribution of Sleep Duration at Visit 2
60%
50%
40%
30%
20%
10%
0%
<6
6 to <7
7 to <8
8 to < 9
SD >9
Sleep Duration

Short Sleep and Gestational Diabetes Risk



Facco et al, 2015, SMFM Abstract # 256

Late Sleep Midpoint (> 5 AM) and Gestational Diabetes Risk



nuMOM2b
Nulliparous Pregnancy Outcomes Study Monitoring Mothers-to-be

Facco et al, 2015, SMFM Abstract # 256

TABLE 4

Association of sleep duration and timing with gestational diabetes

Sleep characteristic categories	Gestational diabetes n/N (%)	Crude OR, point estimate (95% CI) N = 782	Adjusted OR, point estimate (95% CI), after adjustment for:					
			Age, linear and quadratic N = 782	BMI, linear and quadratic N = 772	Race/ethnicity, 4 categories N = 782	White, non-Hispanic, yes/no N = 782	Frequent snoring, yes/no N = 669	Employment schedule, 3 categories N = 741
Sleep duration								
<7 h	15/218 (6.9)	2.24 (1.11–4.53)	2.26 (1.12–4.58)	2.12 (1.04–4.30)	2.31 (1.13–4.73)	2.25 (1.10–4.60)	2.29 (0.97–5.39)	2.42 (1.16–5.06)
≥7 h	18/564 (3.2)	1.00	1.00	1.00	1.00	1.00	1.00	1.00
		P value = .0246	*P* value = .0232	*P* value = .0380	*P* value = .0220	*P* value = .0266	*P* value = .0586	*P* value = .0190
Sleep midpoint								
>5 AM	12/148 (8.1)	2.58 (1.24–5.36)	3.87 (1.74–8.59)	2.41 (1.15–5.07)	2.61 (1.22–5.57)	2.62 (1.23–5.58)	2.84 (1.16–6.99)	3.71 (1.50–9.21)
≤5 AM	21/634 (3.3)	1.00	1.00	1.00	1.00	1.00	1.00	1.00
		P value = .0114	*P* value = .0009	*P* value = .0202	*P* value = .0132	*P* value = .0124	*P* value = .0229	*P* value = .0047

OR given to show association between gestational diabetes and sleep characteristic, without consideration of covariates and with separate adjustment for: age; BMI; race/ethnicity categories; white, non-Hispanic race/ethnicity; frequent snoring noted before pregnancy; and employment schedule (regular day shift, some form of shift work, unemployed). For race/ethnicity, Asian and other are collapsed.

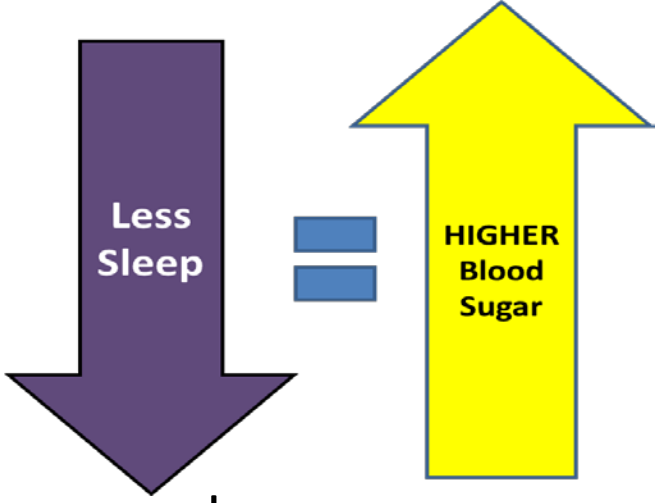
BMI, body mass index; *CI*, confidence interval; *OR*, odds ratio.

Facco et al. Sleep duration in pregnancy associated with risk of gestational diabetes. Am J Obstet Gynecol 2017.

Gestational Diabetes Mellitus: *Original Research*

Sleep Duration and Blood Glucose Control in Women With Gestational Diabetes Mellitus

Roxanna Twedt, MD, Megan Bradley, MD, Danielle Deiseroth, Andrew Althouse, PhD, and Francesca Facco, MD



- Shorter sleep duration was associated with worse glucose control
- 2-6 mg/dL increase in glucose observed per hour less of sleep

Table 2. Relationships Between Continuous Sleep Exposures and Glucose

		Unadjusted			Adjusted*		
Glucose Outcome	Exposure	β†	95% CI	*P*	β	95% CI	*P*
Fasting	Sleep time	−2.52	−4.35 to −0.69	.008	−2.09	−3.98 to −0.20	.03
Breakfast	Sleep time	−3.72	−7.01 to −0.43	.03	−3.05	−6.52 to 0.42	.09
Lunch	Sleep time	−4.32	−8.16 to −0.48	.03	−4.62	−8.75 to −0.50	.03
Dinner	Sleep time	−5.97	−9.14 to −2.79	<.001	−6.07	−9.42 to −2.73	.001