Sleep Apnea in Women: How Is It Different?

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Outline

- Prevalence
- Clinical presentation
  - PSG features
  - Symptoms
- Pathophysiology
- Adverse outcomes
- Treatment
  - PAP therapies
  - Non-PAP treatment

Outline

- Prevalence
  - Periods of increased vulnerability to OSA
- Clinical presentation
- Pathophysiology
- Adverse outcomes
- Treatment

Prevalence

- Lower prevalence of OSA in women compared to men
- Specific periods of vulnerability
  - Pregnancy
  - Menopause

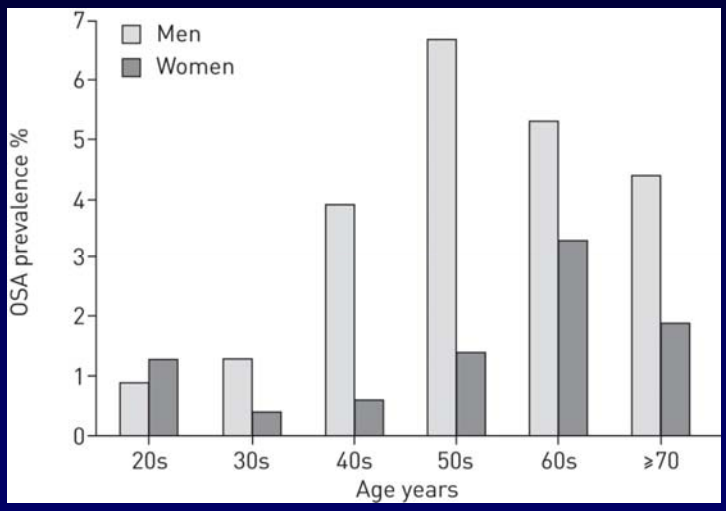
Gender Differences in OSA Prevalence

- Initially 8-10 men:1 woman in clinical populations
- Wisconsin sleep cohort, NEJM 1993
  - 24% of men, 9% of women had OSA (AHI ≥ 5/hour)
  - 4% of men and 2% of women had OSAS (OSA + symptoms)
  - 2013 estimate: 14% of men and 6% of women have OSAS
- Other recent analyses:
  - Data from 9-11 population-based studies estimated OSA prevalence to be 22-27.3% of men, 17-22.5% of women (Franklin et al, J Thor Dis 2015; Theorell-Haglow et al, Sleep Med Rev 2017)
- Overall, ratio of men:women with OSA is ~1.5-3:1
- OSA syndrome estimated at 6% men, 4% women

Epidemiologic Data on OSA

Young **USA** **N = 802**	**4% Men** **2% Women**	**AHI > 5** **EDS** **Age 36-60**
Kripke USA N = 355	9% Men 5% Women	**AHI > 15** **Age 40-64**
Olson Australia N = 2,202	5% Men 1.2% Women	**AHI ≥ 15** **Age 35-69**
Bearpark Australia N = 400	10% Men 7% Women	**AHI ≥ 10** **Age 40-85**

Age Distribution of Prevalence of OSA by Decade



- OSA = AHI ≥15 and daytime symptoms
- Prevalence peaks at age 55 for men, 65 years for women
- Adapted from Bixler et al, AJRCCM 1998 and Bixler et al, AJRCCM 2001

Objectively Measured SDB Increases during Pregnancy

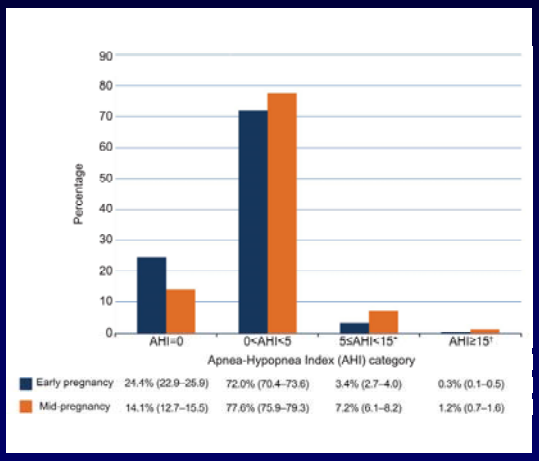
Pien et al, Thorax 2015

- Prospective cohort of 105 women
  - Lab PSG in first (12^1 wks) and third (33^6 wks) trimesters
  - Half had BMI ≥ 30 kg/m^2
- Mean AHI increased from first to third trimester
  - 2.07 (SD 3.01) to 3.74 (5.97) events/hour, p=0.009
- 10.5% of women had AHI≥5 in first trimester
- 26.7% of women had AHI≥5 in third trimester
  - 23 mild, 4 moderate, 1 severe OSA
  - 8 of 55 normal or overweight women had OSA (14.5%)
  - 20 of 50 obese women had OSA (40%)

NuMoM2b Sleep-Disordered Breathing Study

Facco et al, Obstet Gyn 2017

- Low overall OSA prevalence
  - 3.6% in early preg
  - 8.3% in mid preg
- Age, BMI, neck circ, race (non-Hisp black), smoking, chronic hypertension significantly associated with AHI
- Generally, OSA was mild
  - Only 6 women with AHI>50/hour



Prevalence of SDB in Women

Bixler et al, AJRCCM 2001

- 1000 women ≥20 yoa evaluated in sleep lab
- Prevalence of OSA 3-5 times higher among postmenopausal women, depending on definition
- Odds for either clinical or AHI-defined OSA no different for women on HRT compared to premenopausal women
- Clear evidence
  - Menopause is a risk factor for OSA
  - HRT associated with reduced risk

Prevalence of Sleep-Disordered Breathing in Women

Bixler et al, AJRCCM 2001

TABLE 2. PREVALENCE OF SDB*

		Sleep Apnea			
	n†	SDC‡	OA/HI ≥ 15	SNORE+§	SNORE‖
Women	1,000	1.2 (0.7, 2.2)	2.2 (1.5, 3.3)	5.4 (4.1, 6.9)	10.4 (8.7, 12.5)
Men	741	3.9 (2.8, 5.6)	7.2 (5.6, 9.3)	17.3 (14.7, 20.2)	17.4 (14.8, 20.3)
Women					
Age, yr					
20–44	455	0.7 (0.2, 2.0)	0.6 (0.2, 2.0)	2.3 (1.3, 4.2)	8.2 (6.0, 11.2)
45–64	376	1.1 (0.4, 2.9)	2.0 (1.0, 4.0)	7.2 (5.0, 10.3)	14.5 (11.3, 18.4)
65–100	169	3.1 (1.3, 7.1)	7.0 (4.0, 11.9)	9.4 (5.8, 14.8)	7.1 (4.1, 12.1)
BMI, kg/cm^2					
< 32.3	814	0.4 (0.1, 1.2)	1.1 (0.5, 2.1)	4.0 (2.8, 5.5)	8.8 (7.0, 11.0)
≥ 32.3	186	4.8 (2.5, 9.0)	7.2 (4.3, 11.9)	11.5 (7.7, 17.0)	17.5 (12.7, 23.6)
Menopause					
Pre	503	0.6 (0.2, 1.8)	0.6 (0.2, 1.8)	3.2 (2.0, 5.2)	7.9 (5.8, 10.6)
Post	497	1.9 (1.0, 3.6)	3.9 (2.5, 6.0)	7.5 (5.5, 10.2)	13.0 (10.3, 16.2)
Hormone replacement					
With	183	0.5 (0.1, 3.8)	1.1 (0.3, 4.3)	3.8 (1.8, 7.7)	9.8 (6.3, 15.1)
Without	314	2.7 (1.4, 5.3)	5.5 (3.4, 8.6)	9.7 (6.9, 13.5)	14.8 (11.3, 19.2)

* Prevalence (95% confidence interval).
† Sample size adjusted for oversampling for sleep laboratory phase and age and BMI based on NHANES III.
‡ SDC criteria: A/HI ≥ 10 and daytime symptoms.
§ SNORE+ = Snoring plus mild sleep-disordered breathing (0 < OA/HI < 15).
‖ SNORE = Snoring plus no sleep-disordered breathing (OA/HI = 0).

Menopausal Status and SDB

Young et al, AJRCCM 2003

- Female subjects from Wisconsin Sleep Cohort Study
  - 30-60 yoa; baseline in 618, 364 had ≥1 follow-up
  - After exclusions, 589 women, 1035 studies
- Crude odds ratio for AHI≥5: 1.66 in perimenopausal women, 2.82 in peri/post, 3.22 in postmenopausal women
- Adjusted OR for AHI≥5 showed increased risk for all peri and postmenopausal groups
  - HRT users with lower odds of SDB compared to perimenopausal and postmenopausal non-HRT users
  - More recent analyses suggest HRT findings may have been due to “healthy user” bias (Mirer et al, Ann Epi 2015)

Menopausal Status and SDB in the WSCS

Young et al, AJRCCM 2003

TABLE 2. ASSOCIATION OF MENOPAUSAL STATUS AND SLEEP-DISORDERED BREATHING DEFINED BY FREQUENCY OF APNEA AND HYPOPNEA EPISODES PER HOUR OF SLEEP (APNEA–HYPOPNEA INDEX)*

	Odds Ratio (95% CI)	
	AHI of 5 or More versus AHI of Less Than 5	AHI of 15 or More versus AHI of Less Than 5
Unadjusted model		
Premenopause	Reference category	
Perimenopause	1.66 (1.05, 2.60)	1.18 (0.83, 1.69)
Peri/Postmenopause	2.82 (1.41, 5.65)	1.82 (1.04, 3.21)
Postmenopause	3.22 (2.23, 4.66)	2.59 (1.64, 4.09)
Adjusted model*		
Premenopause	Reference category	
Perimenopause	1.23 (0.68, 2.22)	1.07 (0.52, 2.20)
Peri/postmenopause	1.80 (0.79, 4.12)	3.13 (1.06, 9.20)
Postmenopause	2.60 (1.41, 4.81)	3.49 (1.38, 8.78)
Age, 5 yr	1.17 (0.98, 1.38)	1.10 (0.82, 1.48)
BMI, kg/m²	1.14 (1.11, 1.17)	1.20 (1.15, 1.25)

Definition of abbreviation: AHI = apnea–hypopnea index; BMI = body mass index.

* Model is also adjusted for alcohol, education, smoking, hypertension, exercise, cardiovascular disease, and self-rated evaluation of health; further adjustment with body habitus measures other than BMI did not alter the odds ratios. Covariates were all modeled as continuous, with the exception of variables for hypertension (yes = systolic blood pressure of 140 or more, diastolic blood pressure of 90, or more or using hypertensive medication) and cardiovascular disease (yes = self-reported myocardial infarction, coronary artery disease, atherosclerosis, heart failure), and smoking (current = yes).

Wisconsin Sleep Cohort Data

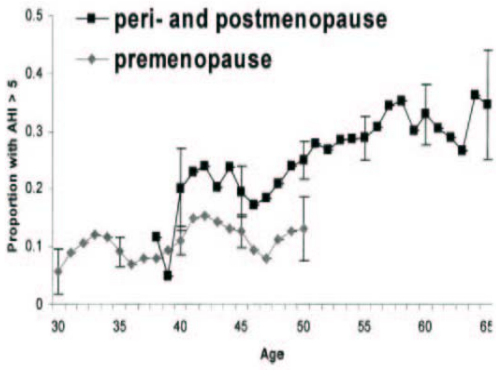


Figure 1. Prevalence of sleep-disordered breathing (SDB) indicated by apnea–hypopnea index (AHI) of 5 or greater for premenopausal women and perimenopausal plus postmenopausal women by age. Values represent a 5-year moving average.

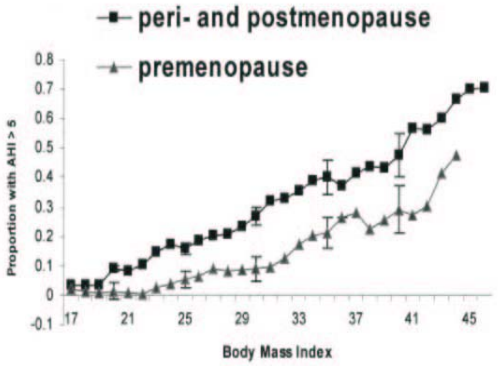


Figure 2. Prevalence of SDB indicated by an AHI of 5 or greater for premenopausal women and perimenopausal plus postmenopausal women by body mass index (BMI). Values represent a 5-unit moving average.

Outline

- Prevalence
- Clinical presentation
  - Differences in PSG features
  - Differences in symptoms
- Pathophysiology
- Adverse outcomes
- Treatment

Clinical Presentation

- Differences in PSG features
- Differences in symptoms

Apnea/Hypopnea Event Characteristics

- When matched by age and BMI, women with OSA have fewer SDB events compared to men
  - Postmenopausal women had similar apnea frequency and desats compared to men age >50
- Higher proportion of hypopneas, lower proportion of apneas in women compared to men
- Women have shorter events, with milder oxygen desaturations
- Comparing pre/post menopausal women, post women had longer events with larger desats

Disease Characteristics and Severity

- In women, OSA events cluster in REM compared to non REM
  - Men and women have similar OSA severity in REM
  - Women have milder SDB in non-REM sleep
- Men may be more likely to have positional SDB
- Overall, women are more likely to have mild or moderate disease
  - Women more likely to have REM-related disease

Clinical Presentation

- When asked, women referred for PSG are ***as likely as men*** to report sleepiness and snoring, snorting, gasping or apneas
- Several studies show no gender differences in symptoms after matching or adjusting for age, AHI, BMI
- ***Women with symptoms of SDB remain less likely to be diagnosed and treated for OSA***
  - Despite more frequent doctor visits and hospitalizations prior to OSA diagnosis than men
  - Lindberg E et al, Sleep Med 2017

Why Are Women Underdiagnosed with OSA Compared to Men?

- Women with OSA are more likely to have a history of depression or hypothyroidism and to complain primarily of insomnia
  - Providers need to inquire about SDB symptoms
- Women tend to have less severe OSA compared to men
- Women seem to be distributed among different clinical phenotypes of OSA (e.g. Sleepy, Minimally Symptomatic, Difficulty Sleeping in ISAC cohort) similarly to men
  - Ye et al, ERJ 2014

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Gender Differences in Upper Airway Anatomy and Function

- Smaller tongue, soft palate and lateral fat pads in women
  - Volumes are associated with OSA severity
- Smaller tongues, soft palate size and shorter airway length in females associated with less collapsible upper airway
- Shorter pharyngeal length may reduce risk for OSA
- Conflicting data about gender differences in upper airway dilator muscle activity

Sex Differences in Association of Regional Obesity with Severity of OSA

Simpson L et al, Sleep 2010

- 60 men and 36 women suspected of OSA
- % of fat and lean tissue, and bone density measured using DXA
- Among women, % fat in neck and BMI explained 33% of variance in AHI
- Among men, % abdominal fat and neck:waist ratio accounted for 37% of variance in AHI
- *Distribution* of fat, rather than increased total fat mass, associated with AHI

How Do Female Reproductive Hormones Affect Ventilatory Responses?

- Several studies have examined HRT effects on OSA postmenopausally
  - Conflicting results from small trials
  - Large observational studies suggest a protective effect – d/t healthy cohort effect?
- Estrogen and progesterone enhance respiratory chemosensitivity (i.e. ventilatory responses to CO_2 and O_2 levels)
  - May offset sleep state-dependent reductions in respiratory drive affecting OSA devt
- Progesterone
  - Stimulates central ventilatory drive, enhances resp response to **acute** hypoxia in wake
  - Changes in ventilatory responses to acute hypoxia and hypercarbia (respiratory changes expected in OSA) do not vary with gender or menstrual phase
- Overall, only modest gender differences in waking responses to hypoxic and hypercapnic challenges
  - Unlikely to contribute substantially to gender differences in OSA severity

How Do Female Reproductive Hormones Affect Ventilatory Responses?

- Gender differences in response to *episodic* hypoxia and hypercapnia may affect sleep apnea
- Several studies have demonstrated larger ventilatory response to hypercarbia ("high loop gain") in the setting of episodic hypoxia in males than females
  - Greater ventilatory response upon arousal
  - Males had more significant hypocapnia upon awakening from apneic event
  - This promotes development of central apnea with respiratory instability, as CO_2 falls below apneic threshold
  - How reproductive hormones play a role is still not well understood
- Sympathetic drive in response to arousal has been seen to change more in males relative to premenopausal females

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OSA Outcomes

- Are there differences between women and men in risk for adverse outcomes associated with OSA?
- Several studies with attenuated or non-significant associations between OSA and cardiometabolic outcomes in women

Sleep Apnea And Hypertension: Are There Sex Differences?

Cano-Pumarega I et al, Chest 2017

- 1155 normotensive middle-aged men and women
- Prospectively studied over 7.5 years
- Among men, RDI ≥ 14/hour associated with increased risk for stage 2 hypertension (SBP≥160/DBT≥100)
- No significant association among women
- Authors acknowledged milder OSA among women was likely to affect results

Prospective Study of OSA & Incident CHD and Heart Failure (SHHS)

Gottlieb DJ et al, Circulation 2010

- 4422 subjects (1927 men, 2495 women) followed for median of 8.7 years
- OSA significantly associated with new CHD among men < 70 years of age after adjustment for age, race, BMI, smoking
  - *Not* significant after adjustment for DM and lipids
  - No significant association for women, or men >70
- OSA also associated with incident heart failure among men only

OSAH and Incident Stroke (SHHS)

Redline S et al, AJRCCM 2010

- 5422 participants followed for median 8.7 years
- Men with SDB at greater risk of ischemic strokes with increasing AHI
  - Men in highest AHI quartile (>19) with adjusted hazard ratio of 2.86 (1.1-7.4) compared to baseline
- No similar association seen among women, though a threshold effect seen above AHI>25

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  - PAP therapy
  - Non-PAP treatment

PAP Therapy

- Women may require lower PAP pressures compared to men after matching for BMI, severity of OSA
  - Consistent with less collapsible airway (lower Pcrit pressure) in women
  - Leveraged to create a women-specific auto-PAP treatment algorithm resulting in lower mean PAP pressures
- Conflicting data about whether PAP usage patterns differ, gender impact on CPAP acceptance and adherence

Study of a Novel APAP Algorithm for Treatment of OSA in Women

McArdle et al, Sleep 2015

- Novel, female-specific autotitrating algorithm tested in 20 premenopausal women on long term CPAP treatment
  - Increased sensitivity to flow limitation
  - Slower lower pressure rise and decay response to flow limitation
  - Lower cap on pressure response to obstructive apneas
  - Minimum CPAP pressure based on moving data window
- Female-specific algorithm delivered lower 95th percentile pressure compared to standard algorithm (10.6±1.7 v 11.6±2.6 cm H_2O)
  - Residual AHI (1.2 [0.60-1.85] v. 1.15 [0.40-2.85]) and ODI3% (0.85 [0.25-1.5] v 0.5 [0.25-2.55]) not significantly different between algorithms

Treatment: PAP Therapy

- CPAP therapy appears equally effective for women and men in treating symptoms such as sleepiness, sleep maintenance insomnia, mood, functional status
- In one recent study, elevated levels of a systemic inflammation marker (CRP) improved more quickly w/ CPAP use in men than women – very preliminary
  - Mermigkis C et al, Sleep Breath 2012
- Very little data on whether gender affects treatment effects on cardiometabolic outcomes

Non-PAP Therapies

- Few studies examining efficacy of non-PAP therapies for OSA
- One clinical study examined oral appliances
  - Marklund et al, Chest 2004
  - 619 consecutive OA patients with snoring or OSA
  - Women more than twice as likely to have treatment success
  - Attributed to women enlarging their palate more with mandibular advancement than men (despite narrower pharynx)
- Speculation about role of HRT
  - ***Not*** recommended

Change in OSA with Weight Change

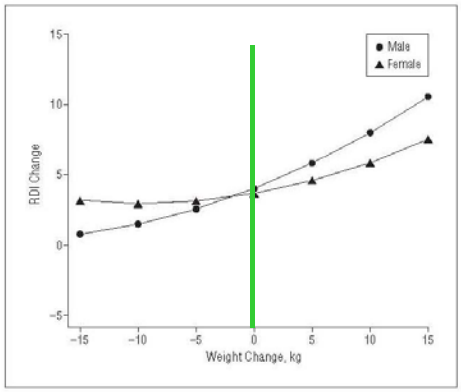

Figure 2. Change in Respiratory Disturbance Index (RDI) by change in weight.

Newman et al, Arch Int Med 2005 (from WSCS)

- Sleep Ahead study
  - 1 year results: intensive lifestyle intervention more effective in reducing AHI in men than women (Foster et al, Arch Int Med 2009)
  - 4 year results: no gender differences in magnitude of change in AHI with weight loss (Kuna et al, Sleep 2013)

Take Home Messages

- OSA remains less prevalent among women compared to men – but prevalence is very high
  - Postmenopausal status increases the risk for OSA
  - OSA remains underdiagnosed in women
- Symptoms may not be “classic” OSA presentation – perhaps bc of milder disease, comorbidities
- Outcomes, or at least their timing, may differ
  - Effects of OSA may occur later
  - Shorter duration of disease, less severe disease

Take Home Messages

- CPAP appears equally effective for women and men
- Conflicting data on the relationship between weight loss and OSA severity in women v. men
- More attention being focused on whether CPAP approach should be different for women v. men
  - Little work on gender differences in outcomes