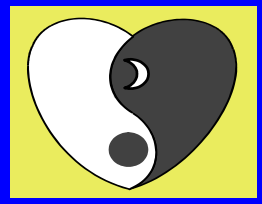
Sleep Apnea and Cardiovascular Disease: Lessons from the Sleep Heart Health Study



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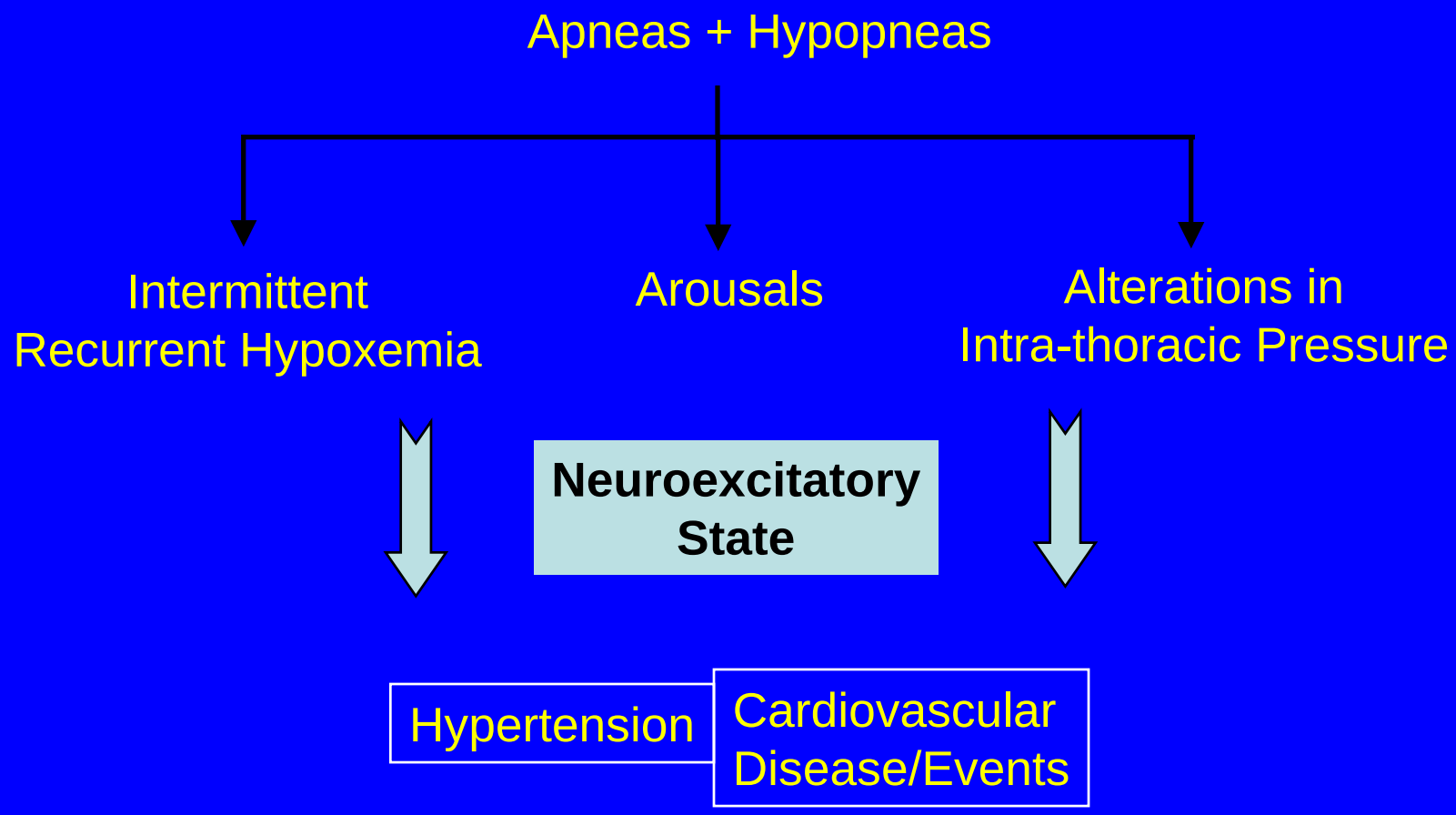
Pathophysiologic Cascade in Sleep Apnea



SHHS: Study Design

- NHLBI sponsored, prospective cohort study
- Addition of sleep assessment to ongoing cohort studies of cardiovascular and respiratory disease established between 1971-1990's
- Use of previous collected data on cardiovascular risk and outcomes
- Updated information on weight, blood pressure, symptoms, medication use, etc…
- Collection of new "baseline" sleep study (1994 – 1999) with repeat sleep study after five years (1999 – 2003)

SHHS: Hypothesis

- **Primary hypotheses**

  Sleep apnea → Incident hypertension

  → Increased risk of incident CHD events

  → Increased risk of incident stroke

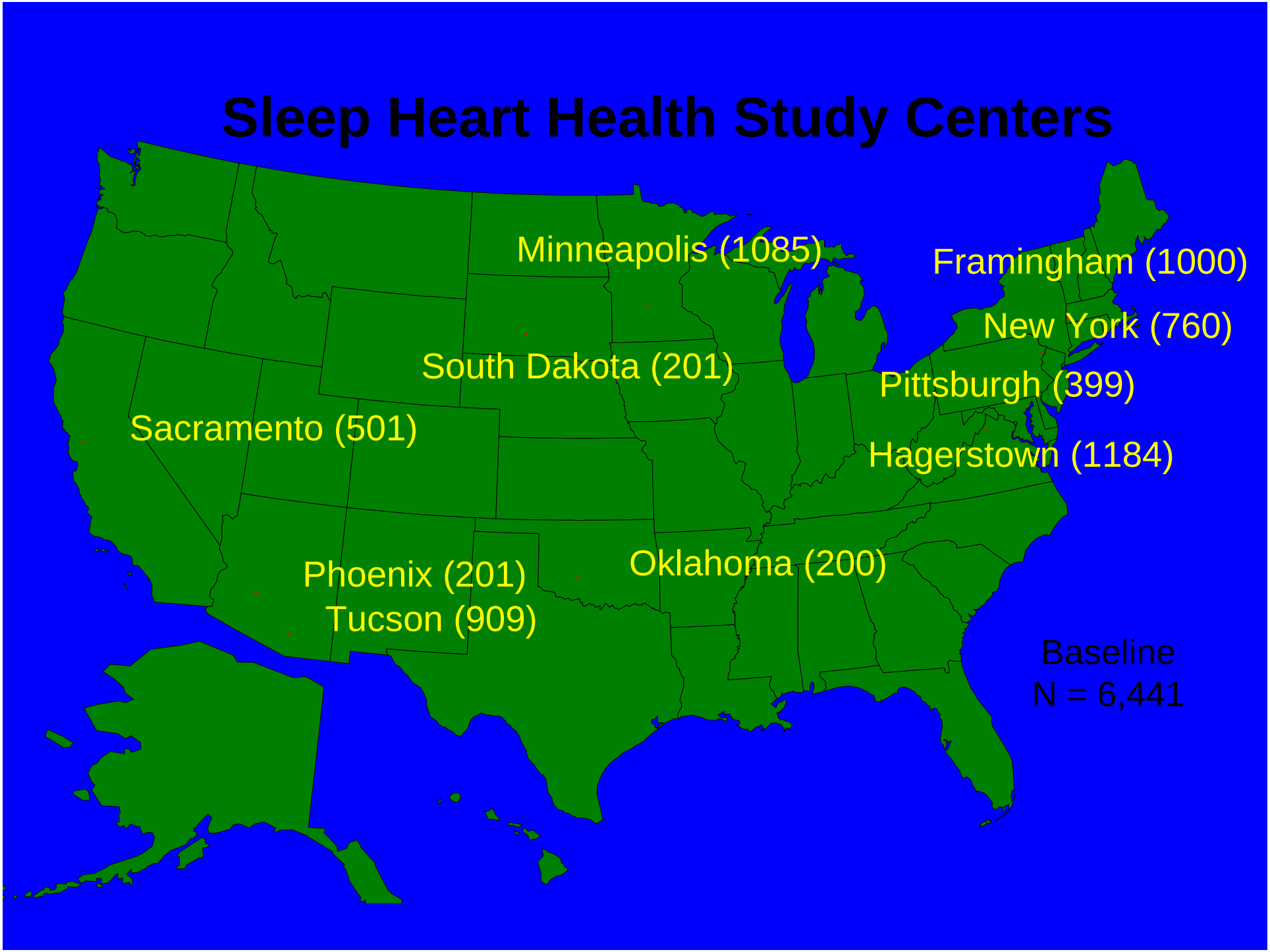
  → Increased risk of all-cause mortality

- **Secondary hypotheses (currently under study)**

  Sleep apnea → Recurrent cardiovascular outcomes

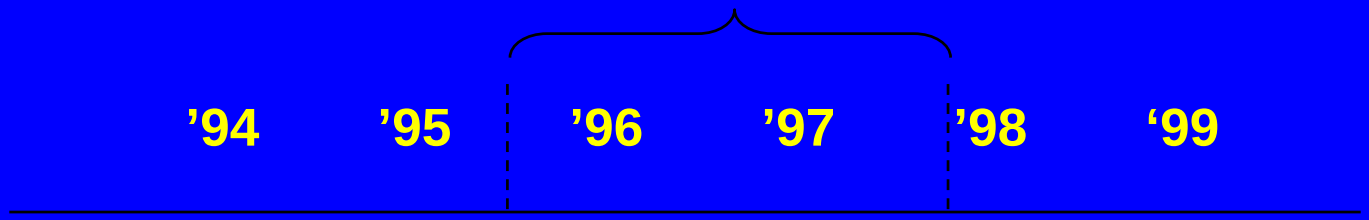
  → Impairment of health-related quality of life

Sleep Heart Health Study Centers



SHHS: Study Design

Baseline Home 18-channel PSG (N = 6,441)



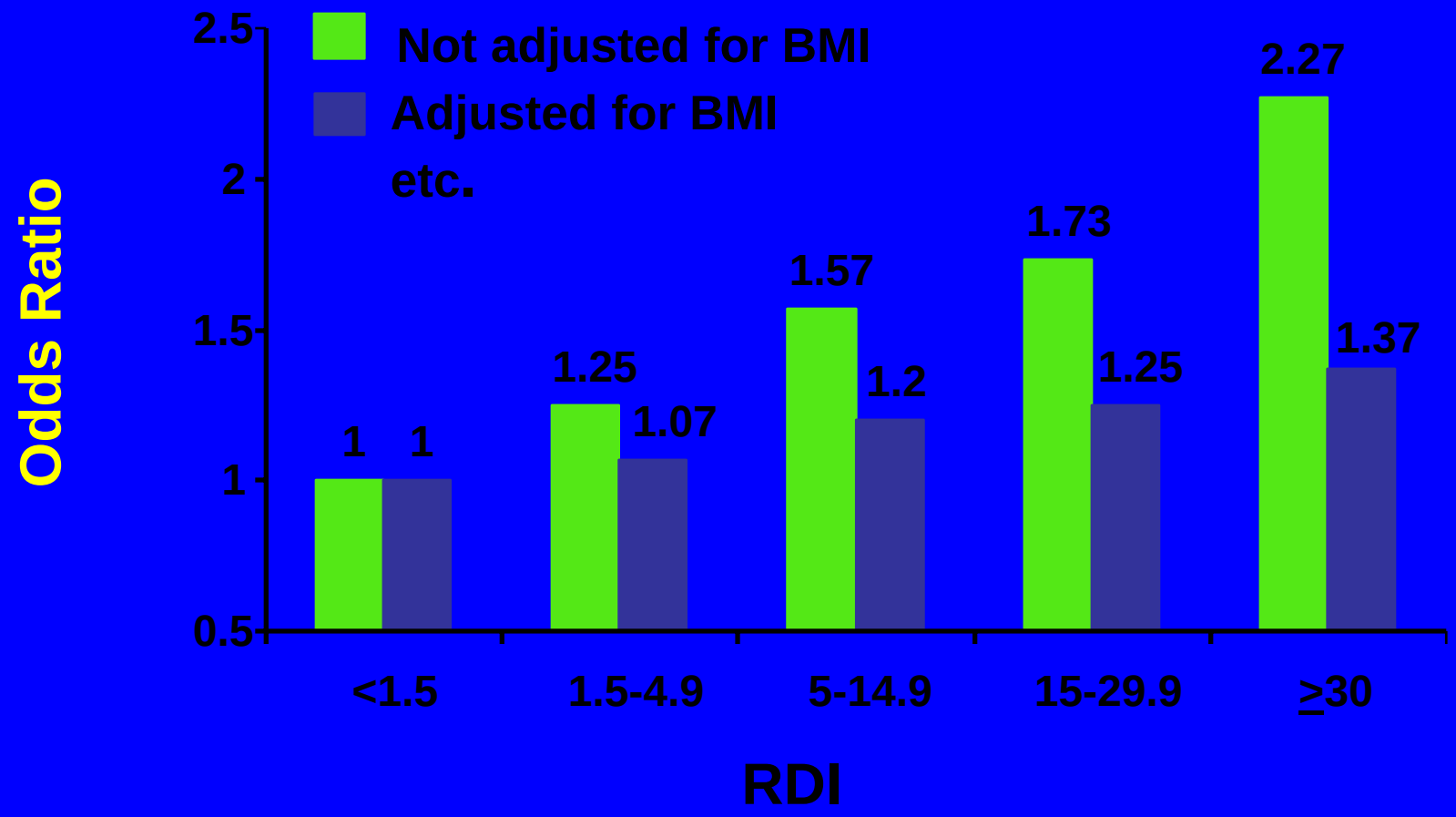
Concurrent publications emphasize sleep results from this assessment period with an emphasis on correlation to Cardiovascular Risk

Outcome Definitions

- **Hypertension:**
  - **Resting blood pressure > 140/90 or**
  - **Current treatment with anti-hypertensive medication**

- **Cardiovascular disease:**
  - **Myocardial infarction**
  - **Angina**
  - **Coronary angioplasty**
  - **Coronary artery bypass surgery**
  - **Congestive heart failure**
  - **Stroke**

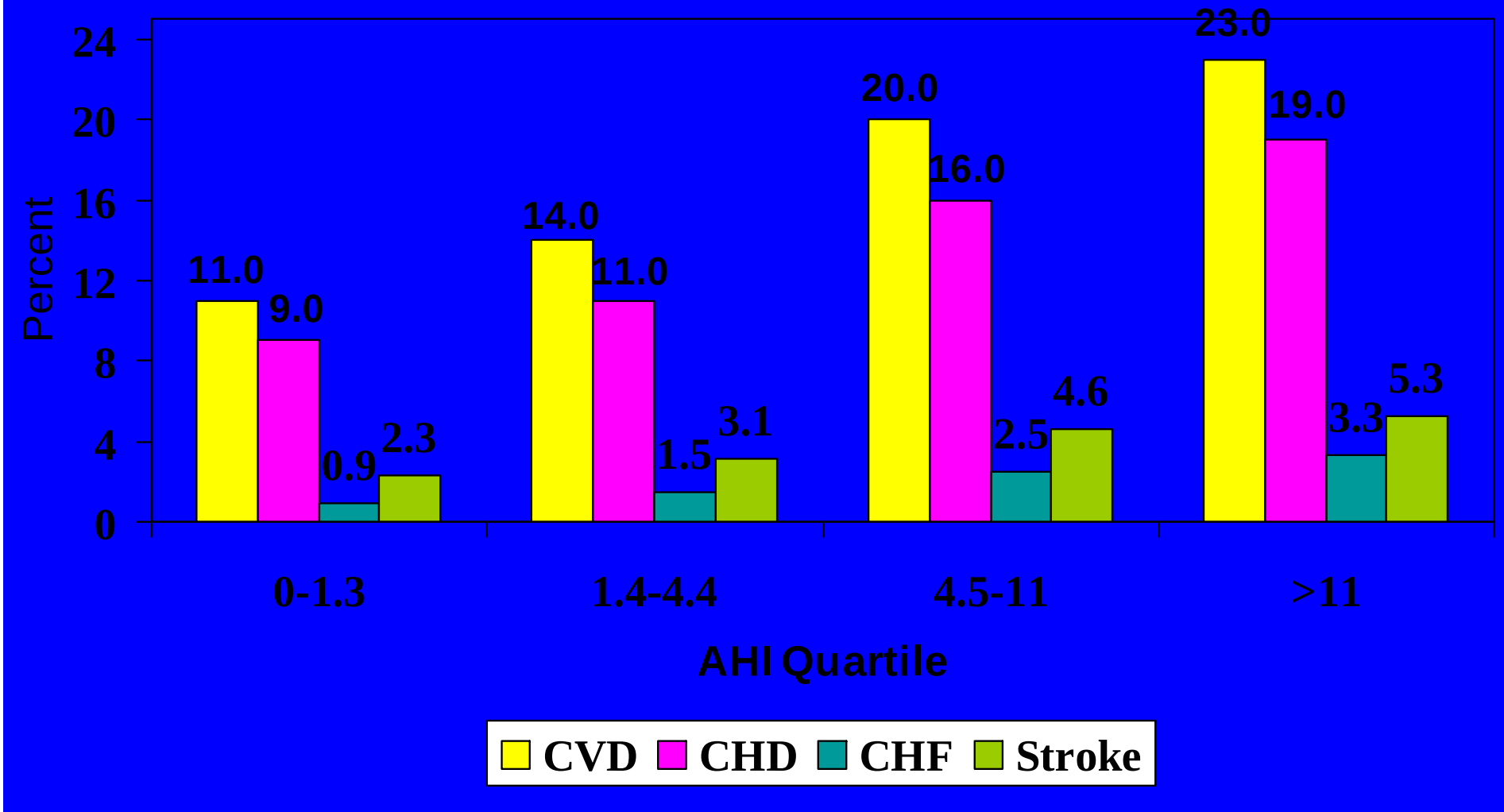
Association: RDI and Hypertension- SHHS Cohort n=6123



(Nieto et al, JAMA 2000;283,1829)

Prevalence of CVD by AHI
SHHS n=6089

(Nieto et al, JAMA 2000;283,1829)



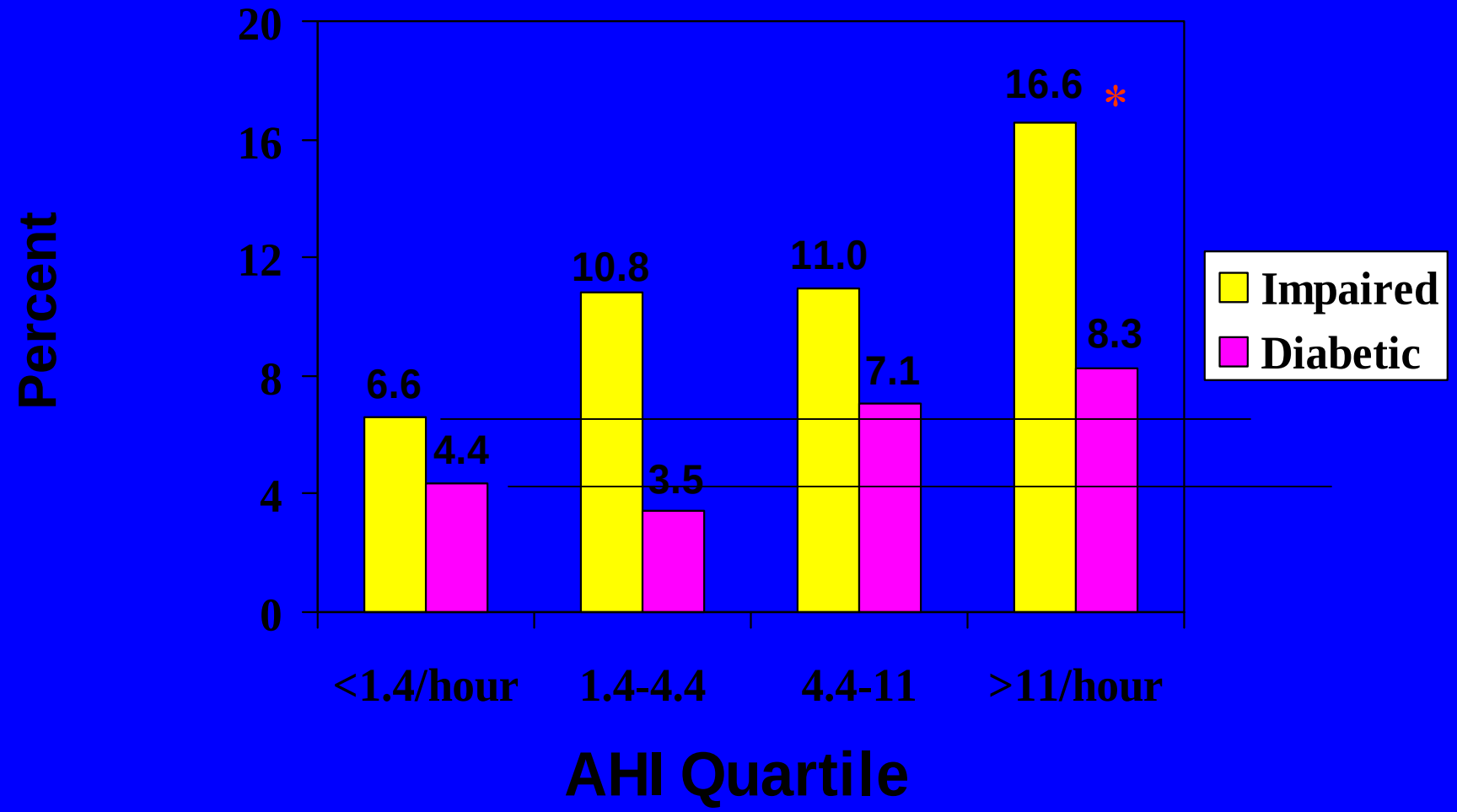
Adjusted Odds Ratio of Prevalent CVD By Quartile of RDI

AHI Quartile	Adjusted OR	95% CI
1st (<1.4)	1.0	
2nd (1.-4.5)	0.98	.77, 1.24
3rd (4.5-11)*	1.28	1.02, 1.61
4th (>11)*	1.42	1.13,1.78

Test for linear trend: p = .015

(Nieto et al, JAMA 2000;283,1829)

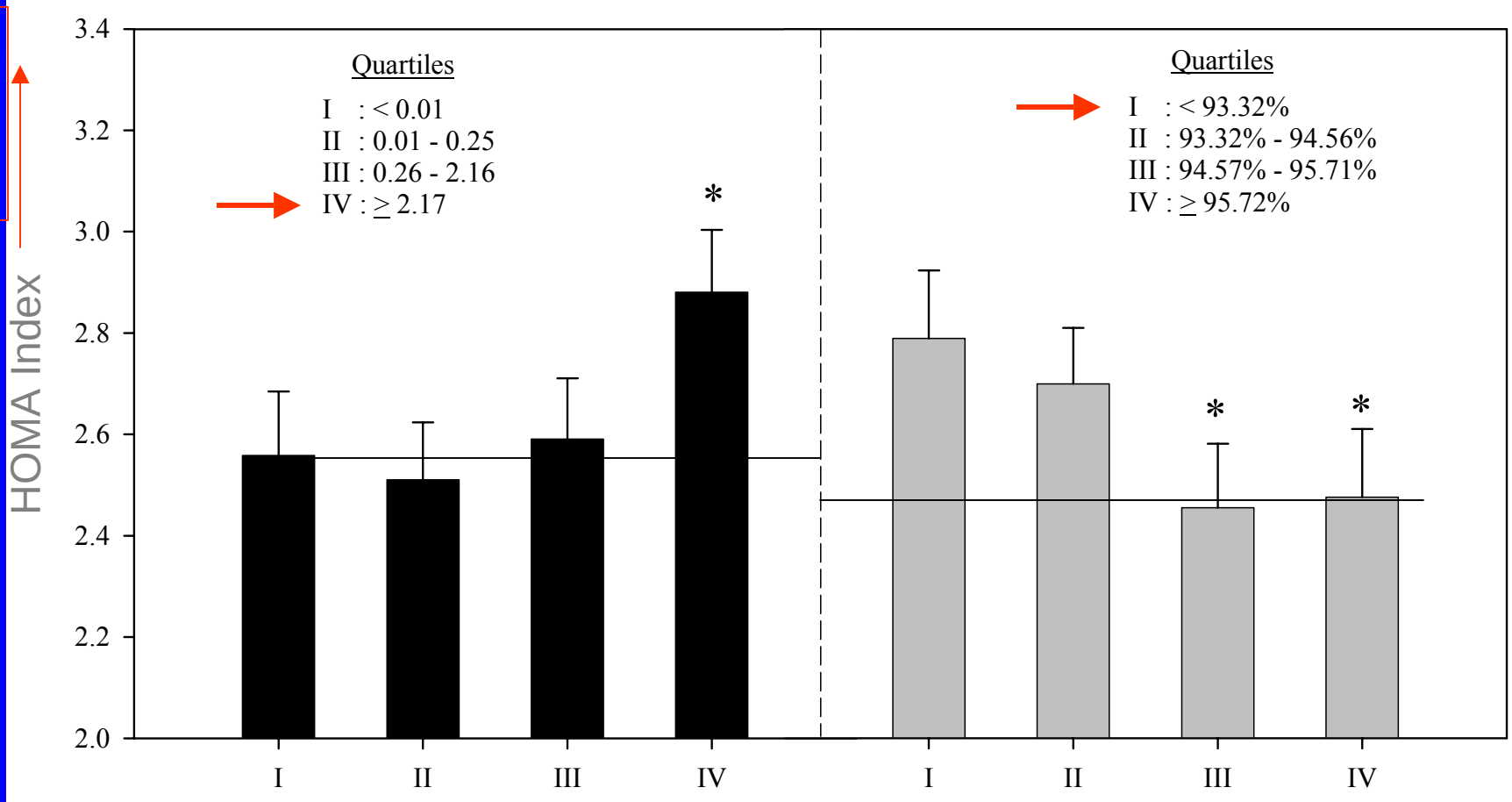
AHI and Impaired Insulin Resistance or Diabetic State (community-based cohort)



Punjabi et al, 2003

Hypoxemia and Insulin Resistance

Punjabi et al, 2003



*p < 0.05 for comparisons to the first quartile; † Adjusted for age, gender, sex, smoking status, BMI, and waist circumference

Snoring at time 0 with 10yr Risk of developing Diabetes

Nurses Health Study

Snoring Category	Adjustment by Age and BMI	+Adjustment for diabetes/sleep variables
Occasional	RR 1.48 (CI: 1.29-1.70)	RR 1.41 (CI: 1.22-1.63)
Regular	RR 2.25 (CI: 1.91-2.66)	RR 2.03 (CI: 1.71-2.40)

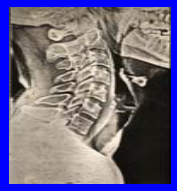
Al-Delaimy et al, 2002

THEORY

Adapted from Strohl et al, 1993

ENVIRONMENTAL STRESSOR ⟷ GENETIC PREDISPOSITION

FOOD AVAILABILITY
ALCOHOL
SLEEP (LOSS)



AHI
O2 SAT%
AROUSALS

\+

\+

FAT DEPOSITION,
ACCUMULATION

\+

CELLULAR RESPONSES

CORTISOL, EPINEPHRINE,
INSULIN, GLUCOSE, LEPTIN

Apneas, Hypopneas, and Prevalent HTN

- Hypopnea index was independently associated with prevalent HTN
- Sensitivity analyses with varying thresholds for defining a hypopnea showed a significant association between HTN and hypopnea index based on a ΔSaO_2 criteria as low as 2%
- In contrast, apnea index was not associated with prevalent HTN status

Conclusions at this Point in the SHHS

- RDI and in this cohort Hypopneas are associated with prevalent hypertension and cardiovascular disease
- Events with ΔSaO_2 as low as 2% may be related with adverse health consequences
- Ongoing longitudinal analyses will delineate whether the observed cross-sectional associations are causal

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- **Field Site Staff**
- **Participants**

The Significance of Sleep Apnea in Cardiovascular Disease Lessons from the Sleep Heart Health Study

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1. To list the pathophysiologic pathways relevant to cardiovascular changes associated with sleep disordered breathing.
2. To the chronic cardiovascular conditions and cardiovascular risk factors associated with sleep-disordered breathing (SDB), with particular reference to the Sleep Heart Health Study.

Abbreviations used in this section and presentation

AHI = apnea-hypopnea index; CI = confidence interval; CPAP = continuous positive airway pressure; HTN = hypertension; NREM = nonrapid eye movement; OR= Odds Ratio; RDI = respiratory disturbance index; REM = rapid eye movement; SDB = sleep-disordered breathing; SHHS = Sleep Heart Health Study

Definitions.

Obstructive sleep apnea syndrome is characterized by recurrent episodes of complete upper airway obstruction (apnea) or partial upper airway obstruction (hypopnea) during sleep, leading to disturbed sleep and excessive daytime sleepiness (hypersomnolence). More than 5 respiratory events per hour of sleep has traditionally been used as the cutoff between normal and abnormal. The sum of apneas and hypopneas per hour of sleep (apnea-hypopnea index [AHI]) and the sum of all respiratory events per hour of sleep (respiratory disturbance index [RDI]) are commonly used summary statistics for SDB.

Apnea is defined as a pause in breathing (absence of airflow) lasting $\geq$ 10 s. Central apneas are defined by the lack of respiratory effort on chest and abdominal gauges, while obstructive apneas are defined by presence of effort. *Hypopneas* are defined by reduction in airflow for $\geq$ 10 s, with or without a consequence such as arousal or oxygen desaturation. *Respiratory effort-related arousals* are characterized by increasing effort (in the absence of airflow changes that meet the criteria for an apnea or hypopnea) leading to arousal from sleep. While the definition of apnea is fairly universal, the definition of hypopnea (*eg*, the amount of airflow decrement required, the need for arousal, the need for desaturation, the amount of desaturation required) has varied among clinical and research laboratories, and respiratory effort-related arousals are by no means universally measured. In addition to differing definitions, techniques for monitoring airflow and effort also vary across laboratories. In response to these issues, the American Academy of Sleep Medicine Clinical Practice Review Committee has proposed a consensus definition for hypopnea similar to that used in the SHHS, although whether the AHI or RDI alone is the best metric to define SDB remains controversial.

Chronic Cardiovascular Disorders Associated With SDB.

As a group, patients with SDB in the SHHS have an increased risk of HTN, ischemic heart disease, congestive heart failure, and stroke. The converse is also true: namely, patients with these disorders have an increased risk for SDB. Early reports suggested a link between SDB and cardiovascular disease, and more recent epidemiologic studies have better controlled for multiple risk factors. The SHHS is the largest prospective cohort study to date, enrolling more than 6,000 participants from existing cohorts of cardiovascular and respiratory disease across the United States. Inclusion criteria included age > 40 years, with increased sampling of snoring individuals between ages 40 and 65 years to maximize the prevalence of SDB in the final population. All minorities were recruited. Exclusion criteria were treatment of SDB with CPAP, tracheostomy, and current home oxygen therapy. Participants completed questionnaires on sleep habits, sleepiness, and quality of life; the parent cohorts provided information on cardiovascular risk factors. All subjects received a home visit, which included a health interview, assessment of medication use, blood pressure measurement, and anthropomorphic measurements. Full, unattended polysomnography was performed, with studies scored at a central location using strict criteria for respiratory disturbances, arousals, and other events. Respiratory events used in the calculation of the AHI included apneas, defined as complete or near-complete cessation of airflow by oronasal thermocouples, and hypopneas, defined as decrease in airflow of $\geq$ 30% of baseline accompanied by $\geq$ 4% oxygen desaturation. The initial data were analyzed cross-sectionally, with and without adjusting for multiple potential confounding factors including demographics (age, race, sex), anthropomorphic measures (body mass index, waist-hip ratio, neck circumference), alcohol use, cigarette smoking, HTN (self-reported HTN, use of antihypertensive medications, measured blood pressure), self-reported diabetes, and measured plasma lipid levels, depending on the cardiovascular outcome of interest. Cross-sectional analysis of the SHHS cohort is thus enormously helpful in identifying associations between SDB and cardiovascular disease. Future longitudinal analysis will address SDB as a predictor of cardiovascular outcomes.

Limitations of observational studies such as the SHHS include lack of precision of the measurements used to define variables of interest and multiple sources of bias. Causality cannot be determined in cross-sectional analyses. Odds ratios are subject to error, as unknown confounders cannot be corrected for. Also, odds ratios may be subject to overcorrection, if the confounders controlled for in these studies are really intermediates in the pathway to end-stage disease. For example, if SDB causes HTN and this resultant HTN is the mechanism by which SDB leads to other cardiovascular outcomes, controlling for HTN may obscure a true relationship between SDB and cardiovascular disease. Similarly, if SDB directly leads to central obesity or diabetes, adjustment for these factors may be inappropriate. Long-term prospective studies, intervention studies, and animal models are therefore also needed to sort out possible mechanisms and confounders.

Hypertension. A clear independent association between SDB and HTN was found in the cross-sectional analysis of the SHHS, with an increasing prevalence of HTN with increasing AHI, after adjustment for demographics, anthropomorphic measures, alcohol intake, and smoking. The odds ratio for HTN, comparing the highest category of AHI ($\geq$ 30/h) with the lowest category of AHI (< 1.5/h) was 1.37 (95% confidence interval [CI], 1.03 to 1.83). Associations of HTN with SDB were seen in men and women, in older and younger individuals, in normal-weight and overweight individuals, and across ethnic groups. Similar associations have been found in other cross-sectional studies. In the only prospective study reported to date, the Wisconsin Sleep Cohort Study, a dose-response relationship was found between SDB and the presence of HTN 4 years later. Even after adjustment for baseline HTN status, age, sex, anthropomorphic measures, alcohol intake, and smoking, as compared with an AHI reference category of 0/h, the odds of developing HTN at 4 years were increased almost 50% for a baseline AHI of 0.1 to 4.9/h, twofold for an AHI of 5.0 to 14.9, and almost threefold for an AHI of $\geq$ 15/h. Some, but not all, intervention studies with CPAP have shown that CPAP decreases diurnal HTN. The lack of concordance may be due to the fact that not all individuals with SDB have HTN, and CPAP may be most effective in the subgroup of patients who are hypertensives. In one randomized, placebo-controlled, crossover trial of the effects of CPAP on 24-h blood pressure in 68 patients with SDB who were not taking antihypertensive medications, CPAP was associated with a small but significant decrease in blood pressure. The fall in diastolic blood pressure was 1.5 mm Hg for the group as a whole and 5.0 mm Hg in patients with 4% desaturation frequencies of > 20/h.

Coronary Heart Disease. Self-reported coronary heart disease was, at most, modestly associated with SDB in the cross-sectional analysis of the SHHS cohort. In the multivariably adjusted model that included demographics, anthropomorphic measures, cigarette smoking, HTN, diabetes, and lipid levels as covariates, the odds ratio of coronary heart disease in the highest quartile of SDB (AHI > 11/h) vs the lowest quartile of SDB (AHI 0 to 1.3/h) was 1.22 (95% CI, 0.93 to 1.59). Based on statististical testing of covariates and concern regarding possible overadjustment for hypertension, a parsimonious model was created, eliminating smoking, body mass index, and all hypertension variables. In the parsimonious model, the odds ratio of coronary heart disease (highest vs lowest quartile) was 1.27 (95% CI, 0.99 to 1.62). No prospective studies have been reported. In a small, uncontrolled series, CPAP has been reported to decrease nocturnal ischemic events in patients with SDB and coexistent ischemic heart disease.

Congestive Heart Failure. Congestive heart was clearly associated with SDB in the SHHS cohort.[36] In the multivariably adjusted model, there was more than a twofold increase in the odds of congestive heart failure in the highest vs the lowest quartile of SDB (odds ratio, 2.22; 95% CI, 1.11 to 4.37), with similar findings in the parsimonious model (odds ratio, 2.38; 95% CI, 1.22 to 4.62). In one small intervention study in individuals with SDB and idiopathic dilated cardiomyopathy, treatment with CPAP was associated with improvement in left ventricular function

Stroke. Stroke was modestly associated with SDB in the SHHS cohort. There was a > 50% increased odds of stroke in the highest vs the lowest quartiles of SDB (odds ratio 1.55, 95% CI 0.96 to 2.50, in the multivariably adjusted model and odds ratio 1.58, 95% CI 1.02 to 2.46, in the parsimonious model). The current evidence for an association between stroke and SDB has recently been reviewed.

Impact on Clinical Decisions.

These data are cross-sectional in nature and do not define either a sub-group at risk or an indication to treat sleep apnea independent of neurocognitive dysfunction, as treatments for these chronic cardiovascular conditions currently exist and are backed by rather large clinical trials and experience. In regard to specific treatment of SDB, these data do not answer questions about whom to treat, what modality to use for treatment, and what the goals of therapy should be. CPAP therapy was recommended for patients with an RDI of 5/h to 30/h and coexistent neurocognitive symptoms (sleepiness) or documented cardiovascular disease including nocturnal angina, ischemic heart disease, or stroke. CPAP was also recommended for all patients with an RDI of $\geq$ 30/h, regardless of symptoms, based on the risk of HTN in this group. Current reports continue to support these recommendations. Elucidating the underlying mechanisms linking SDB to cardiovascular disease, understanding the cut points, if any, at which patients have an increased risk of cardiovascular disease, and evaluating specific therapies in light of the outcomes of cardiovascular disease are essential for determining appropriate therapy for SDB. The level of SDB that mandates treatment in order to prevent cardiovascular consequences is an important clinical question that is, as yet, unanswered.

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