WHISPER

Women’s Health Initiative Sleep hypoxia Effects on Resilience
## Key Personnel & Expertise

### Wake Forest University Health Sciences:

<table>
<thead>
<tr>
<th>Name</th>
<th>Title/Expertise</th>
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<tbody>
<tr>
<td>Laura D. Baker, PhD</td>
<td>PI; clinical trials, aging, cognitive function &amp; decline, MCI/AD</td>
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<tr>
<td>Sally Shumaker, PhD</td>
<td>WHI SE Regional PI, WHIMS, aging, clinical studies, cognition</td>
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<tr>
<td>Stephen Rapp, PhD</td>
<td>WHIMS PI, aging, cognitive function &amp; decline, MCI/AD</td>
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<tr>
<td>Beverly Snively, PhD</td>
<td>WHI, biostatistics, CVD &amp; cancer events with aging</td>
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<tr>
<td>Daniel Beavers, PhD</td>
<td>WHI, biostatistics, cognitive aging</td>
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<tr>
<td>Kate Hayden, PhD</td>
<td>Epidemiology, aging, cognition</td>
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<tr>
<td>Emily Gower, PhD</td>
<td>Epidemiology, medical co-morbidities, aging</td>
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<tr>
<td>Kaycee Sink, MD</td>
<td>Adjudication of cognitive diagnosis, MCI/AD</td>
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<tr>
<td>Bonnie Sachs, PhD</td>
<td>Adjudication of cognitive diagnosis, MCI/AD</td>
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### Harvard:

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<th>Name</th>
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<tr>
<td>Susan Redline, MD MPH</td>
<td>Sleep, aging, CVD, cancer, cognition, clinical studies, oximetry</td>
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<tr>
<td>Shelley Tworoger, MD</td>
<td>Cancer, aging</td>
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### California Pacific Medical Center Research Institute:

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<th>Name</th>
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<tr>
<td>Katie Stone, PhD</td>
<td>Sleep, aging, CVD, cognition, actigraphy</td>
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Study Rationale

- Compelling epi data linking sleep disordered breathing (SDB), especially intermittent hypoxemia, to increased risk of CVD, cancers, and cognitive decline – but not assessed in prospective studies nor in elderly women.

- Largest study to date (Sleep Heart Health Study) examines predictive value of SDB on health outcomes in younger adults (mean=65yrs), and was not powered to assess in older women (WHISPER women: ~82 yrs old at enrollment)
  
  - 2nd largest prospective study of sleep and health outcomes was MrOS: included only men.

- No study has prospectively examined sleep apnea on incidence of cancer; hypoxemia promotes tumor growth via multiple mechanisms.

- Few studies have prospectively examined predictive value of SDB & other sleep disturbances on cognitive trajectory and incident cognitive impairment (MCI, AD) in elderly adults; new data linking sleep disturbance to $A_\beta$ accumulation in brain – implications for AD pathology.

- WHI offers a time-limited opportunity to study the predictive value of sleep outcomes in a well-characterized cohort of elderly women; approach ensures diverse geographical representation at a fraction of the cost associated with in-person or overnight assessments.
NHLBI approached Shumaker and Rapp several years ago about examining the role of sleep quality on multiple health outcomes in WHI.

- Best assessment device?
- Sleep outcomes that best identify those at greatest risk?

N = 33 women (mean 85.8 yrs) from an elderly WHIMS cohort; included women with mild cognitive impairment.

- Wrist-worn device (Nonin) easy to use → high compliance, high rates of valid data.
- Oxygen desaturation index (# O2 saturation dips of ≥3% per hour of sleep) >10 in 61% of participants indicating mild to moderate SDB.
- Severity linked to increased risks of MCI/AD, CVD, and cancer in other studies led by WHISPER investigators.

Prior Discussions with NHLBI

Preliminary Work Vaughan et al. 2016
Specific Aims

I. Cardiovascular Disease
A. Primary: Test whether increased SDB-related intermittent hypoxemia (IH) – measured by elevated oxygen desaturation index (ODI) – is associated with increased risk of major cardiovascular events (composite outcome of myocardial infarction, stroke, heart failure (HF), cardiovascular mortality).

B. Secondary: (i) Test whether short sleep duration, reduced sleep efficiency, and poor sleep quality are associated with increased risk of major CVD events (composite outcome); (ii) Test whether elevated ODI, short sleep duration, and reduced sleep efficiency and poor sleep quality (sleep exposures) are associated with incident stroke and HF.

II. Cancer
A. Primary: Test whether increased SDB-related IH is associated with increased risk of cancer (excluding non-melanoma skin cancer).

B. Secondary: (i) Test whether short sleep duration and poor sleep quality are associated with increased cancer risk; (ii) Test whether sleep exposures are associated with cancer of the breast, and with cancer aggressiveness, as measured by cancer stage and hormone receptor status.

III. Cognitive Decline
A. Primary: Test whether increased SDB-related IH is associated with a faster rate of cognitive decline (composite outcome of global cognition, episodic memory, executive function test scores).

B. Secondary: (i) Test whether short sleep duration, reduced sleep efficiency and adverse sleep exposures (including SDB-related IH) are associated with a faster rate of cognitive decline; (ii) Test whether sleep exposures are associated with increased risk of mild cognitive impairment or dementia; (iii) Examine strength of associations between sleep exposures and episodic memory vs. other cognitive domains.
Study Design

Overview

• Large-scale prospective clinical study of 5000 older women (mean [SD] age = 82 [6.2] years) from the ongoing WHI Extension Study

• All correspondence with participants by phone and by mail; no clinic visits

• Utilize extensive rich resources available through the WHI and other funded studies (i.e., COSMOS) to maximize cost efficiency
Study Design

Baseline (N = 5000)

1. Sleep Assessment using simple sensitive wrist-worn devices

- Oximetry: continuous measurements of blood oxygen desaturation obtained over 2 consecutive nights to quantify nocturnal intermittent hypoxemia, a key feature of SDB

- Actigraphy: continuous measurements of motion via tri-axial accelerometer obtained for 4 consecutive 24-hour periods (overlapping oximetry) to quantify total sleep/wake time, number of awakenings, sleep efficiency and fragmentation, and frequency of daytime naps

2. Cognitive Assessment via telephone using well-established and validated protocols, and trained/experienced examiners; previously developed for WHIMS follow-up studies
Study Design

Follow-up

- **Adjudicated CVD** (annually, 4 years of f/u)
  - MI, stroke, HF, coronary revascularization
  - Cardiovascular mortality

- **Adjudicated Cancers** (annually, 4 years of f/u)
  - Incidence of all cancers, breast cancer
  - Cancer aggressiveness (stage, hormone receptor status)

- **Cognitive Assessment** (annually, 3 years of f/u; 8% attrition per year)
  - Global measures of cognition, episodic memory, executive function, subjective memory complaints, dementia questionnaire
  - Adjudication to identify mild cognitive impairment (MCI), Alzheimer’s disease, and other dementias
WHI EXTENSION STUDY *  
N=93,540

Medical Record Cohort (MRC)  
(adjudicated CVD events)

Self-Report Cohort  
(no adjudication)

WHISPER  
N=6500

Grant Year 1 (N=5000)
- sleep assessments (oximetry, actigraphy)
- ‘baseline’ cognitive assessment via telephone

Grant Year 2
- Telephone cognitive assessment
- Adjudicated CVD events (data sharing with MRC/COSMOS)
- Adjudicated cancers (data sharing with WHI through NCI support)

Grant Year 3
- Telephone cognitive assessment
- Adjudicated CVD events (data sharing with MRC/COSMOS)
- Adjudicated cancers through WHISPER

COSMOS  
(adjudicates CVD events)  
N=12,000 Women

Grant Year 4
- Telephone cognitive assessment
- Adjudicated CVD events (data sharing with MRC/COSMOS while available)
- Adjudicated cancers through WHISPER
Participants

• Targeting N=5000 with a valid sleep assessment, conducted soon after enrollment

• Inclusion Criteria

  ✓ No history of clinically significant CVD (MI, stroke, HF)
  ✓ No diagnosis of cancer within the last 2 years (non-melanoma skin cancer ok)
  ✓ No users of CPAP or supplemental oxygen
  ✓ No diagnosis of dementia
Table 2. Estimated Power in Aims 1 and 2 to Detect Between-Group Differences in Event Rates in a Total of 5000 Women with Complete Baseline Data and Average Follow-up Duration of 4 Years*

<table>
<thead>
<tr>
<th>Events</th>
<th>True overall event rate per 100 person-years</th>
<th>Hazard Ratio</th>
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<tbody>
<tr>
<td></td>
<td>1.25</td>
<td>1.50</td>
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<tr>
<td>Cardiovascular †</td>
<td>3.3</td>
<td>0.814</td>
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<tr>
<td>All cancer ‡</td>
<td>2.2</td>
<td>0.582</td>
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<tr>
<td>Stroke</td>
<td>0.9</td>
<td>0.319</td>
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<tr>
<td>Breast cancer ‡</td>
<td>0.8</td>
<td>0.257</td>
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* Estimated statistical power for nonparametric testing at alpha=0.05 (two-tailed).
† Based on composite outcome of myocardial infarction, coronary artery revascularization, stroke, heart failure, and cardiovascular mortality.
‡ Estimated power for testing among participants cancer-free for the first 6 months of follow-up, i.e., those not diagnosed with cancer, excluding non-melanoma skin cancer; thus, for both total cancer and breast cancer, fewer than 5,000 are included in these between-group comparisons.

Table 3. Estimated Power in Aim 3 to Detect Between-Group Differences in 4000 Women (1600 with SDB) with Complete Data for Cognitive Outcomes Both at Baseline and the 3-Year Follow-up*

variance with standardized composite outcome (mean=0, SD=1) and α=0.05 (two-tailed)
Clinical Relevance

- Vast majority of sleep disturbances are undiagnosed and untreated – implications for prevalence of health complications and morbidity

- Study will assess clinical utility of 3 targets for intervention: overnight oxygenation, sleep duration, and sleep quality
  - Each target can be addressed with different therapeutic approaches
  - New strategies under development to treat sleep apnea that are less burdensome than CPAP

- Study will test whether a simple, home-based sleep assessment identifies those at greatest risk of poor health outcomes 4 years later, and thus at high priority for early intervention

- Findings may support addition of a simple sleep assessment to routine clinical care in older adults
A0 Review of >500K WHISPER Application
~ Cancer, Heart, and Sleep Epidemiology B Study Section ~

*As per NHLBI PO (Ludlam), general tone of the review was very positive

**Noted Strengths**

- Highly significant
- Focus on older women
- Objective measures of sleep
- Innovative & feasible
- Investigative team and environment are strong
- Excellent collaboration record of investigators
- Well-adjudicated CVD & cancer outcomes
- Valid and reliable cognitive outcomes
- Use of telephone-based cognitive assessment & certification protocols
- Adjudication of cognitive impairment and dementia
- Strong longitudinal design
- Oversampling of minorities
- Statistical power is ‘good’
- Strengths ‘far outweigh’ minor to moderate weaknesses
Noted Weaknesses

- Potential impact of ‘reverse causality’ on outcomes
- Potential for loss to f/u or differential attrition due to exposure or outcome
- Healthy cohort bias and impact on generalization
- Some concerns about telephone cognitive testing & validity of data
- Concerns about validity of self-report BMI
- Study Section did not have a problem with multiple ‘primary’ aims across the Funding decisions

Other Points that Impact Likelihood of Funding ...

- NIA has agreed to cost-sharing, which will significantly increase chance of funding if we receive a good score on our resubmission
- No difference in NHLBI pay-lines for standard and large budget R01s
## Proposed Timeline

### WHISPER Timeline

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<tr>
<td>Participant Enrollment</td>
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<td>Sleep Studies</td>
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<td>Data Collection: CVD, Cancer, Mortality</td>
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<td>Baseline &amp; Follow-up Cognitive Assessments</td>
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<td>Cognitive Diagnosis Adjudication</td>
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<td>Data Quality Monitoring &amp; Clean-up</td>
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<td>Data Analysis</td>
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<td>Preparation of Manuscripts &amp; Presentations</td>
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<td>Dissemination of Findings</td>
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<td>Study Close-out</td>
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**COSMOS**
- WHI Medical Records Cohort
- NCI-Supported Cancer Adjudication
Ancillary Studies to WHISPER

it’s not too early to start planning …

Contact:

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