

JCSM

# Journal of Clinical Sleep Medicine

Volume 9, Number 12 | December 15, 2013  
Pages 1229-1362

## IN THIS ISSUE:

**Treatment of Obstructive Sleep Apnea Syndrome with Nasal Positive Airway Pressure Improves Golf Performance**  
Benton; Friedman

*Commentary on Benton and Friedman.*

**Does Treating Obstructive Sleep Apnea in Golfers Improve Their Handicap?**

Richard D. Simon Jr.

**Predictors of Treatment Response to Brief Behavioral Treatment of Insomnia (BBTI) in Older Adults**

Troxel; Conrad; Germain; Buysse

**The Sleep and Technology Use of Americans: Findings from the National Sleep Foundation's 2011 Sleep in America Poll**

Gradisar; Wolfson; Harvey; Hale; Rosenberg; Czeisler

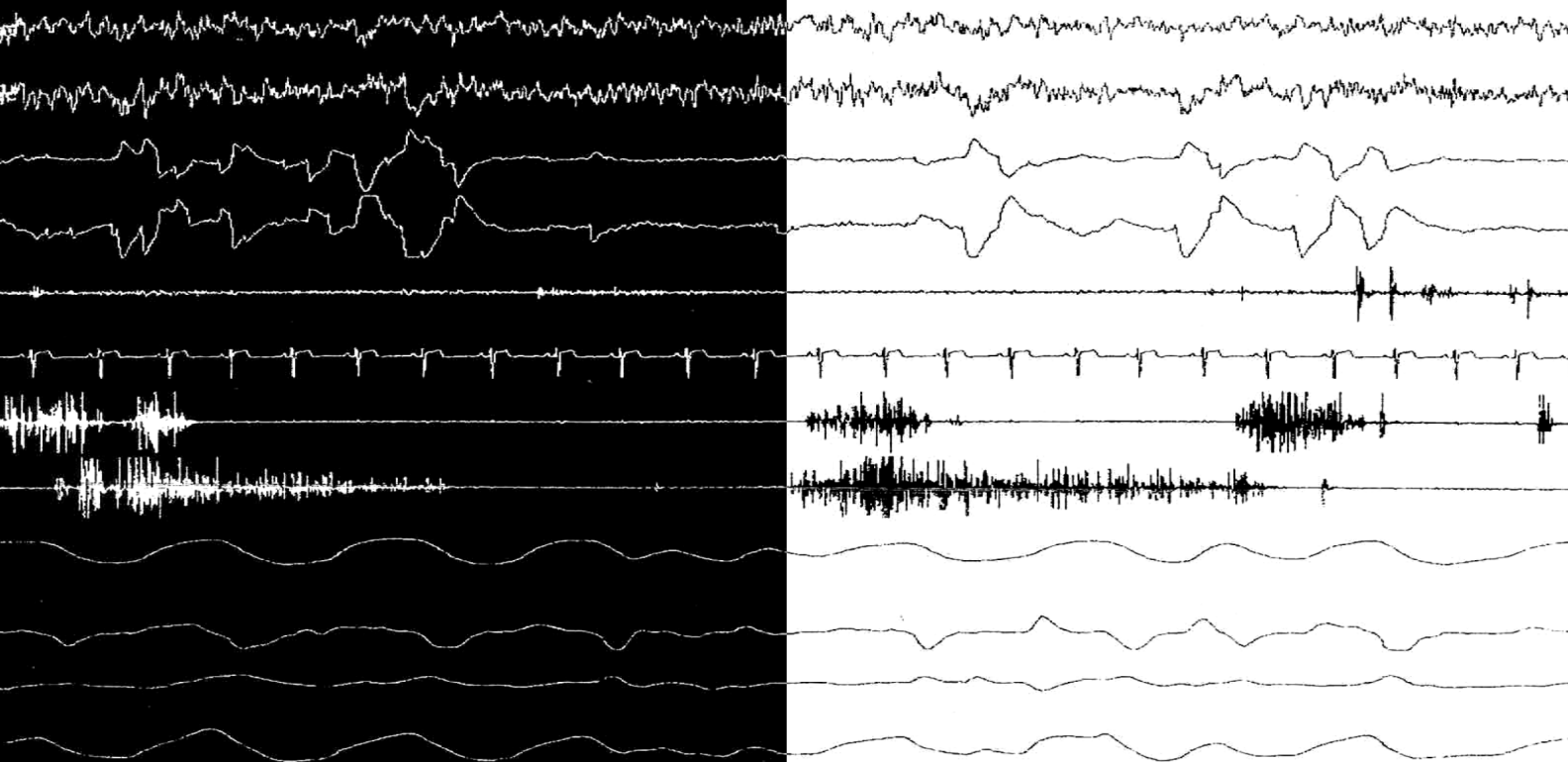
*Commentary on Gradisar et al.*

**The Use of Technology at Night: Impact on Sleep and Health**

Grandner; Gallagher; Gooneratne

**Sleep and Pregnancy-Induced Hypertension: A Possible Target for Intervention?**

Haney; Buysse; Okun



Official Publication of the  
American Academy of Sleep Medicine

[www.aasmnet.org](http://www.aasmnet.org)







## EDITOR

Stuart F. Quan, M.D., F.A.A.S.M., Boston, MA/Tucson, AZ

## DEPUTY EDITOR

Daniel J. Buysse, M.D., F.A.A.S.M., Pittsburgh, PA

## ASSOCIATE EDITORS

|                                                        |                                                      |                                                       |
|--------------------------------------------------------|------------------------------------------------------|-------------------------------------------------------|
| Richard B. Berry, M.D.,<br>F.A.A.S.M., Gainesville, FL | Birgit Högl, M.D.,<br>Innsbruck, Austria             | Amy L. Meoli, M.D., F.A.A.S.M.,<br>Kansas City, MO    |
| Lee K. Brown, M.D., F.A.A.S.M.,<br>Albuquerque, NM     | Conrad Iber, M.D.,<br>Minneapolis, MN                | Robert L. Owens, M.D.,<br>Boston, MA                  |
| Rohit Budhiraja, M.D.,<br>F.A.A.S.M., Tucson, AZ       | Vishesh Kapur, M.D.,<br>F.A.A.S.M., Seattle, WA      | Sairam Parthasarathy, M.D.,<br>F.A.A.S.M., Tucson, AZ |
| Andrew L. Chesson, M.D.,<br>F.A.A.S.M., Shreveport, LA | Douglas B. Kirsch, M.D.,<br>F.A.A.S.M., Brighton, MA | Stephen H. Sheldon, D.O.,<br>F.A.A.S.M., Chicago, IL  |
| David Dinges, Ph.D.,<br>Philadelphia, PA               | Michael Littner, M.D.,<br>F.A.A.S.M., Sepulveda, CA  | Nathaniel F. Watson, M.D.,<br>F.A.A.S.M., Seattle, WA |
| Susan M. Harding, M.D.,<br>F.A.A.S.M., Birmingham, AL  | W. Vaughn McCall, M.D.,<br>F.A.A.S.M., Augusta, GA   |                                                       |

## EXECUTIVE DIRECTOR

Jerome A. Barrett, Darien, IL

## MANAGING EDITOR

Andrew Miller, Darien, IL

## EDITORIAL BOARD

|                                                                                 |                                                              |                                                            |                                                         |                                                              |
|---------------------------------------------------------------------------------|--------------------------------------------------------------|------------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------------|
| Candice A. Alfano, Ph.D.,<br>Houston, TX                                        | Armando Castorena-Maldonado, M.D.,<br>Mexico City, Mexico    | Leila K. Gozal, M.D.,<br>Chicago, IL                       | Matthew T. Naughton, M.D.,<br>Pahran, Australia         | Wolfgang W. Schmidt-Nowara, M.D.,<br>F.A.A.S.M., Dallas, TX  |
| Fernanda R. Almeida, D.D.S., M.Sc.,<br>Ph.D., A.B.D.S.M., Vancouver, BC, Canada | Alejandro D. Chediak, M.D.,<br>F.A.A.S.M., Miami Beach, FL   | Jason P. Kirkness, Ph.D.,<br>Baltimore, MD                 | James M. Parish, M.D.,<br>Scottsdale, AZ                | Shirin Shafazand, M.D., F.A.A.S.M.,<br>Miami, FL             |
| Monica L. Andersen, M.Sc., Ph.D.,<br>Sao Paulo, Brazil                          | Ronald D. Chervin, M.D.,<br>Ann Arbor, MI                    | Meir H. Kryger, M.D., F.A.A.S.M.,<br>West Haven, CT        | Thomas Penzel, Ph.D.,<br>Berlin, Germany                | Aaron E. Sher, M.D.,<br>Albany, NY                           |
| Donna Arand, Ph.D., F.A.A.S.M.,<br>Dayton, OH                                   | Madeline Grigg-Damberger, M.D.,<br>Albuquerque, NM           | Clete A. Kushida, M.D., Ph.D.,<br>F.A.A.S.M., Stanford, CA | Barbara A. Phillips, M.D.,<br>Lexington, KY             | Michael H. Silber, M.B., Ch.B.,<br>F.A.A.S.M., Rochester, MN |
| Kristen Archbold, Ph.D., R.N.,<br>Tucson, AZ                                    | Sally L. Davidson Ward, M.D.,<br>F.A.A.S.M., Los Angeles, CA | Peretz Lavie, Ph.D.,<br>Haifa, Israel                      | Daniel Picchietti, M.D., F.A.A.S.M.,<br>Urbana, IL      | Edward J. Stepanski, Ph.D.,<br>F.A.A.S.M., Memphis, TN       |
| Carol M. Baldwin, Ph.D., R.N.,<br>Tempe, AZ                                     | William C. Dement, M.D., Ph.D.,<br>F.A.A.S.M., Palo Alto, CA | Teofilo L. Lee-Chiong, M.D.,<br>F.A.A.S.M., Denver, CO     | Giora Pillar, M.D., Ph.D.,<br>Haifa, Israel             | Patrick J. Strollo, Jr., M.D.,<br>F.A.A.S.M., Pittsburgh, PA |
| Mary Susan Esther Banks, M.D.,<br>Charlotte, NC                                 | Lawrence J. Epstein, M.D.,<br>F.A.A.S.M., Bedford, MA        | Ching-Chi Lin, M.D.,<br>Taipei, Taiwan                     | Naresh M. Punjabi, M.D., F.A.A.S.M.,<br>Baltimore, MD   | David P. White, M.D., F.A.A.S.M.,<br>Boston, MA              |
| Kenneth R. Casey, M.D., F.A.A.S.M.,<br>Cincinnati, OH                           | Birgit Frauscher, M.D.,<br>Innsbruck, Austria                | Babak Mokhlesi, M.D., M.Sc.,<br>F.A.A.S.M., Chicago, IL    | Daniel O. Rodenstein, M.D., Ph.D.,<br>Brussels, Belgium | B. Tucker Woodson, M.D., F.A.A.S.M.,<br>Milwaukee, WI        |

*Journal of Clinical Sleep Medicine (JCSM)* (Online 1550-9397; Website: [www.aasmnet.org/jcsm](http://www.aasmnet.org/jcsm)) is published online monthly on the 15<sup>th</sup> of the month by the American Academy of Sleep Medicine, 2510 North Frontage Road, Darien, IL 60561-1511, phone (630) 737-9700 and fax (630) 737-9790.

**ANNUAL SUBSCRIPTION RATES:** Subscription rates for Volume 9, 2013: Individual Online (US and International): \$75.00; Institutional Online (US and Inter-

national): \$140.00. Prorated subscriptions are not available. Subscriptions begin with the January issue of the current year. Renewals should be secured as early in the year as possible to avoid uninterrupted service. Questions about subscriptions (including payments, billing procedures, or policy matters) should be directed to the AASM office at (630) 737-9700.

**ADVERTISING:** Digital advertising is available on [www.aasmnet.org/jcsm](http://www.aasmnet.org/jcsm). Please contact the National Sales Ac-

count Executive at [advertising@asmnet.org](mailto:advertising@asmnet.org) for complete information.

**PERMISSION TO REPRODUCE:** Written permission to reproduce, in print or electronically, whole articles or any parts of works, figures or tables published in *JCSM* must be obtained prior to publication. Permission for republication must be arranged through the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, phone (978) 750-8400 or fax (978) 646-8600 or URL <http://www.copyright.com>.

There are royalty fees associated with such permissions.

**REPRINTS:** For author reprints contact the AASM office. For commercial reprint orders contact Cenveo Publisher Services, 4810 Williamsburg Road, #2, Hurlock, MD 21643 or [Reprints2@cadmus.com](mailto:Reprints2@cadmus.com)

**DISCLAIMER:** The statements and opinions contained in editorials and articles in this journal are solely those of

the authors thereof and not of the American Academy of Sleep Medicine, or of its officers, regents, members or employees. The Editor-in-Chief, the American Academy of Sleep Medicine and its officers, regents, members and employees disclaim all responsibility for any injury to persons or property resulting from any ideas or products referred to in articles contained in this journal.

© 2013 American Academy of Sleep Medicine

## Continuing Medical Education Offerings 1232



### ANALYSIS AND PERSPECTIVES

#### Editorials

1233

#### Trust, Verify and Replicate

Stuart F. Quan

1235

#### Should We Treat Nonsleepy Patients with Obstructive Sleep Apnea and Atrial Fibrillation with CPAP?

Alejandro Velasco; Kenneth Nugent



### NEW RESEARCH

#### Scientific Investigations

1237

#### Treatment of Obstructive Sleep Apnea Syndrome with Nasal Positive Airway Pressure Improves Golf Performance

Marc L. Benton; Neil S. Friedman

1243

*Commentary on Benton and Friedman.*

#### Does Treating Obstructive Sleep Apnea in Golfers Improve Their Handicap?

Richard D. Simon Jr.

1245

#### Sleep and Insulin-Like Growth Factors in the Cardiovascular Health Study

Neomi Shah; Tom Rice; Daniel Tracy; Thomas Rohan; Petra Bůžková; Anne Newman; Robert C. Kaplan

1253

#### The Comorbidity of Sleep Apnea and Mood, Anxiety, and Substance Use Disorders among Obese Military Veterans within the Veterans Health Administration

Kimberly A. Babson; A. C. Del Re; Marcel O. Bonn-Miller; Steven H. Woodward

1259

#### Comparing a Combination of Validated Questionnaires and Level III Portable Monitor with Polysomnography to Diagnose and Exclude Sleep Apnea

Effie J. Pereira; Helen S. Driver; Steven C. Stewart; Michael F. Fitzpatrick

1267

#### Excessive Daytime Sleepiness is Associated with Longer Culprit Lesion and Adverse Outcomes in Patients with Coronary Artery Disease

Chi-Hang Lee; Wai-Yee Ng; William Hau; Hee-Hwa Ho; Bee-Choo Tai; Mark Y. Chan; A. Mark Richards; Huay-Cheem Tan

1273

#### Types of Primary Insomnia: Is Hyperarousal Also Present during Napping?

Alexandra D. Pérusse; Isabelle Turcotte; Geneviève St-Jean; Jason Ellis; Carol Hudon; Célyne H. Bastien

1281

#### Predictors of Treatment Response to Brief Behavioral Treatment of Insomnia (BBTI) in Older Adults

Wendy M. Troxel; Tyler S. Conrad; Anne Germain; Daniel J. Buysse

1291

#### The Sleep and Technology Use of Americans: Findings from the National Sleep Foundation's 2011 Sleep in America Poll

Michael Gradisar; Amy R. Wolfson; Allison G. Harvey; Lauren Hale; Russell Rosenberg; Charles A. Czeisler

1301

*Commentary on Gradisar et al.*

#### The Use of Technology at Night: Impact on Sleep and Health

Michael A. Grandner; Rebecca A. Lang Gallagher; Nalaka S. Gooneratne

1303

#### Investigating Reasons for CPAP Adherence in Adolescents: A Qualitative Approach

Priya S. Prashad; Carole L. Marcus; Jill Maggs; Nicolas Stettler; Mary A. Cornaglia; Priscilla Costa; Kristina Puzino; Melissa Xanthopoulos; Ruth Bradford; Frances K. Barg

1315

#### The Accuracy of Eyelid Movement Parameters for Drowsiness Detection

Vanessa E. Wilkinson; Melinda L. Jackson; Justine Westlake; Bronwyn Stevens; Maree Barnes; Philip Swann; Shantha M. W. Rajaratnam; Mark E. Howard

1325

#### Salivary Biomarkers of Physical Fatigue as Markers of Sleep Deprivation

Darren J. Michael; Bianca Valle; Jennifer Cox; John E. Kalns; Donovan L. Fogt

**1333****A Twin Study of Genetic Influences on Diurnal Preference and Risk for Alcohol Use Outcomes**

Nathaniel F. Watson; Dedra Buchwald; Kathryn Paige Harden

**Case Reports****1341****Treatment of Cataplexy in a Three-Year-Old Using Venlafaxine**

Michelle Ratkiewicz; Mark Splaingard

**1343****Does the Clinical Phenotype of Fatal Familial Insomnia Depend on *PRNP* codon 129 Methionine-Valine Polymorphism?**

Sven Rupperecht; Alexander Grimm; Torsten Schultze; Jan Zinke; Panagiota Karvouniari; Hubertus Axer; Otto W. Witte; Matthias Schwab

**1347****Alternobaric Vertigo in a Patient on Positive Airway Pressure Therapy**

Andres Endara-Bravo; Daniel Ahoubim; Edward Mezerhane; R. Alexandre Abreu



## REVIEW ARTICLES

**1349****Sleep and Pregnancy-Induced Hypertension: A Possible Target for Intervention?**

Alyssa Haney; Daniel J. Buysse; Michele Okun



## DEPARTMENTS

**Sleep Medicine Pearls****1358****Nocturnal Oral Movements in a Patient with Schizophrenia**

Justin K. Liegmann; Lourdes M. DelRosso; Romy Hoque

**Erratum****1361**

## CONTINUING MEDICAL EDUCATION OFFERINGS

### Instructions for Earning Credit

Participants may read the selected continuing medical education (CME) articles in this issue of *JCSM* and complete the online CME post-test and evaluation at <http://www.aasmnet.org/JCSM/> within **one year** of the date of publication to receive *AMA PRA Category 1 Credits*.™ Each activity – journal article, post-test, and evaluation – is estimated to take approximately 30 minutes to complete.

The ACCME mandates that accredited providers only offer *AMA PRA Category 1 Credits*.™ to physicians. Non-physicians will be provided with a letter of participation indicating the number of *AMA PRA Category 1 Credits*.™ awarded for the activity in which they participated. Non-physicians requesting letters of participation will be assessed the same fees as physicians requesting *AMA PRA Category 1 Credit*.™ if applicable; visit the journal website for information on applicable fees.

Each journal article designated for CME is worth 0.5 *AMA PRA Category 1 Credits*.™ To earn the credit, physicians must read the article and then correctly answer a minimum of 3 out of 5 post-test questions. Upon successful completion of the post-test, the learner may download a participation letter indicating the number of credits earned.

### Accreditation Statement

The American Academy of Sleep Medicine is accredited by the ACCME to provide continuing medical education for physicians. The American Academy of Sleep Medicine designates this educational activity for a maximum of 0.5 category 1 credits toward the *AMA PRA Category 1 Credits*.™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

### Statement of Educational Purpose/Overall Education Objectives

*JCSM* is a peer-reviewed clinical journal addressing sleep, circadian rhythms, and the diagnosis and treatment of the broad spectrum of sleep disorders. Its mission and educational purpose is to promote the science and art of sleep medicine and sleep research. Sleep disorders medicine draws clinical and scientific applications from a wide variety of primary disciplines, including pulmonology, neurology, psychiatry, psychology, otolaryngology, and dentistry. Readers of *JCSM* should be able to: 1) appraise sleep research in basic science and clinical investigation; 2) interpret new information and updates on clinical diagnosis/treatment and apply those strategies to their practice; 3) analyze articles for the use of sound scientific and medical problems; and 4) recognize the inter-relatedness/dependence of sleep medicine with primary disciplines.

| Articles in this issue that may be read for CME credit                                                                                                                                                                                                                      | Page |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| <b>Treatment of Obstructive Sleep Apnea Syndrome with Nasal Positive Airway Pressure Improves Golf Performance</b><br><i>Objective: Gain insight into non-traditional approaches that may be useful in engaging patients in the evaluation and treatment of their OSAS.</i> | 1237 |
| <b>Predictors of Treatment Response to Brief Behavioral Treatment of Insomnia (BBTI) in Older Adults</b><br><i>Objective: Identify predictors of treatment outcome to Brief Behavioral Treatment of Insomnia.</i>                                                           | 1281 |





## Trust, Verify and Replicate

Stuart F. Quan, M.D., F.A.A.S.M.

Editor, *Journal of Clinical Sleep Medicine*; Division of Sleep Medicine, Harvard Medical School, Boston, MA;  
Arizona Respiratory Center, University of Arizona College of Medicine, Tucson AZ

A number of studies have reported an association between obstructive sleep apnea (OSA) and metabolic syndrome.<sup>1-4</sup> However, until 2 years ago, it was unclear whether metabolic syndrome could be reversed by treatment of OSA with continuous positive airway pressure (CPAP). Studies were uncontrolled, small in size and conflicting in their results.<sup>5,6</sup> Thus, the purported well designed and conducted report in a high profile medical journal in 2011 that metabolic syndrome could be reversed with 12 weeks of CPAP treatment was welcomed by some in the medical community as another piece of evidence supporting the practice to aggressively treat moderate to severe OSA.<sup>7</sup> Nevertheless, there were some doubts expressed about the validity of the results.<sup>8,9</sup> Several weeks ago, the other shoe finally dropped. The authors of the 2011 study retracted their paper writing that they were unable to locate and verify some of their primary data.<sup>10</sup> Although they assert that their conclusions remain valid, this claim is difficult to believe given the reasons for the retraction.

What have we learned about this retraction of a high profile paper? One lesson should be that “replication is a necessity of the scientific process.” One analysis of highly cited clinical research papers found that results were not confirmed in 16% of cases.<sup>11</sup> Were all of these authors guilty of scientific conduct or sloppy research? Most likely not. In many cases they were likely complicit to our worship of the “p value.” In today’s science, results are considered significant and therefore “true” if the p value of a statistical test is less than or equal to 0.05, or less than 1 in 20. Conversely, there is a 1 in 20 chance or less that results are “not true.” This is the most compelling reason for replication. The more times that identical or similar studies find the same results, the greater likelihood that the findings are indeed correct. Other explanations for the failure to replicate include prevailing bias and study design issues.<sup>12</sup> Nevertheless, scientific misconduct and fraud do exist and potentially may adversely influence public opinion concerning scientific research.<sup>13</sup>

The second lesson that should be taken to heart by all of us who participate in research is that we need to take some personal responsibility for papers we co-author. Frequently, co-authors or senior authors are not the primary persons who acquire or analyze the data. As a group, we need to take greater responsibility in verifying and questioning results that do not seem “right,” i.e., difficult to believe, implausible or perhaps too perfect. We also need to take collective responsibility for conducting high quality research including accurate data and analysis.

Finally, for the practitioner, you need to interpret and utilize the results reported in journal articles in the context of your practice and the potential impact on patients. Caution and awaiting

replication is reasonable for most patients. For others with serious or soon to be life-threatening conditions, embracing a new technology or treatment approach may be the only option.

Obviously, the process by which scientific and medical advances are made is imperfect. When asked about nuclear disarmament with the former Soviet Union, President Reagan quoted an old Russian proverb “Trust, but verify.”<sup>14</sup> In the context of medical sciences, we should trust, verify and replicate.

### CITATION

Quan SF. Trust, verify and replicate. *J Clin Sleep Med* 2013;9(12):1233.

### REFERENCES

1. Basoglu OK, Sarac F, Sarac S, Uluer H, Yilmaz C. Metabolic syndrome, insulin resistance, fibrinogen, homocysteine, leptin, and C-reactive protein in obese patients with obstructive sleep apnea syndrome. *Ann Thorac Med* 2011;6:120-5.
2. Coughlin SR, Mawdsley L, Mugarza JA, Calverley PM, Wilding JP. Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. *Eur Heart J* 2004;25:735-41.
3. Drager LF, Lopes HF, Maki-Nunes C, et al. The impact of obstructive sleep apnea on metabolic and inflammatory markers in consecutive patients with metabolic syndrome. *PLoS One* 2010;5:e12065.
4. Parish JM, Adam T, Facchiano L. Relationship of metabolic syndrome and obstructive sleep apnea. *J Clin Sleep Med* 2007;3:467-72.
5. Dorkova Z, Petrasova D, Molcanyiova A, Popovnakova M, Tkacova R. Effects of continuous positive airway pressure on cardiovascular risk profile in patients with severe obstructive sleep apnea and metabolic syndrome. *Chest* 2008;134:686-92.
6. Coughlin SR, Mawdsley L, Mugarza JA, Wilding JP, Calverley PM. Cardiovascular and metabolic effects of CPAP in obese males with OSA. *Eur Respir J* 2007;29:720-7.
7. Sharma SK, Agrawal S, Damodaran D, et al. CPAP for the metabolic syndrome in patients with obstructive sleep apnea. *N Engl J Med* 2011;365:2277-86.
8. Bertisch S, Patel SR. CPAP for obstructive sleep apnea and the metabolic syndrome. *N Engl J Med* 2012;366:963-4.
9. Drager LF, Lorenzi-Filho G. CPAP for obstructive sleep apnea and the metabolic syndrome. *N Engl J Med* 2012;366:964.
10. Sharma SK, Agrawal S, Damodaran D, et al. Retraction: CPAP for the metabolic syndrome in patients with obstructive sleep apnea. *N Engl J Med* 2011;365:2277-86. *N Engl J Med* 2013;369:1770.
11. Ioannidis JP. Contradicted and initially stronger effects in highly cited clinical research. *JAMA* 2005;294:218-28.
12. Ioannidis JP. Why most published research findings are false. *PLoS Med* 2005;2:e124.
13. Jha A. False positives: fraud and misconduct are threatening scientific research: High-profile cases and modern technology are putting scientific deceit under the microscope. *The Guardian* September 13, 2012. <http://www.theguardian.com/science/2012/sep/13/scientific-research-fraud-bad-practice>.
14. <http://www.ask.com/question/who-said-trust-but-verify>. Accessed November 3, 2013.

### DISCLOSURE STATEMENT

Dr. Quan is the Editor-in-Chief of the *Journal of Clinical Sleep Medicine*.







## Should We Treat Nonsleepy Patients with Obstructive Sleep Apnea and Atrial Fibrillation with CPAP?

Alejandro Velasco, M.D.; Kenneth Nugent, M.D.

*Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX*

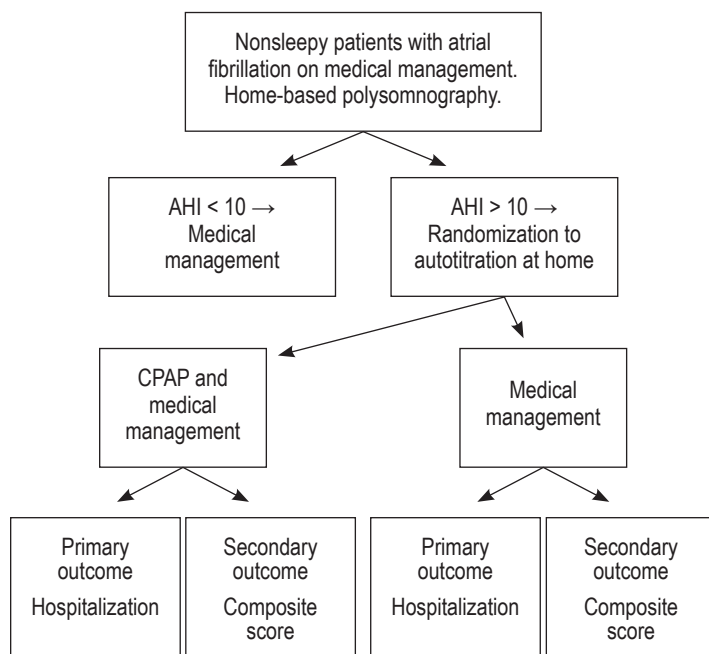
Obstructive sleep apnea (OSA) is a common sleep disorder characterized by partial or complete collapse of the airway leading to abnormal gas exchange, autonomic system imbalance, and frequent arousals during sleep. It occurs in 2% to 7% of our adult population.<sup>1</sup> Atrial fibrillation (AF) is the most common arrhythmia in adults and has an estimated prevalence of 1% to 2%. OSA and AF share several comorbid conditions, such as obesity and advancing age, and OSA is more prevalent in patients with AF after adjusting for other cardiovascular conditions.<sup>2-4</sup> The prevalence of AF is expected to increase 2.5-fold by 2050 as our population ages, and the economic burden it poses will rise accordingly, with a significant fraction of the cost attributed to increased hospitalization rates.<sup>4,5</sup> New therapeutic options are needed to reduce the morbidity and healthcare costs associated with AF, and the treatment of concomitant of OSA offers one potential option.

Even mild unrecognized sleep disordered breathing is associated with cardiovascular events.<sup>6</sup> Stevenson et al. demonstrated that patients with AF had an increased rate of sleep disordered breathing compared to matched controls (68% vs. 38%) in a case-control study using polysomnograms.<sup>7</sup> However, one of the cardinal symptoms used to identify OSA by clinicians is excessive daytime somnolence, a physiological state that is difficult to characterize using questionnaires and is affected by other comorbidities like depression.<sup>8</sup> Recent studies in heart failure patients with OSA have demonstrated that the episodes of apnea do not correlate with sleepiness; this is thought to be caused by an increased sympathetic activity produced by the cardiac dysfunction.<sup>9</sup> This could also occur in patients with AF since somnolence and sense of fatigue may be altered by many factors like hypertension, heart failure, psychiatric and thyroid disorders. A recent meta-analysis demonstrated that OSA was a significant predictor of recurrent atrial fibrillation when OSA was diagnosed with polysomnograms, but not with the Berlin Questionnaire.<sup>10</sup> Since screening tools like the Berlin Questionnaire use daytime somnolence as part of their scoring system, questionnaires may not adequately identify OSA in atrial fibrillation patients. Therefore, some studies have tested the effects of CPAP therapy in nonsleepy patients by using outcome measures which did not depend on symptom assessment. To date, these studies have not shown a significant decrease in blood pressure or major cardiovascular events.<sup>11-14</sup>

However, treating nonsleepy OSA in patients with AF may have beneficial effects for the following reasons. Several

studies have demonstrated that the presence of OSA increases the risk for recurrent AF after using antiarrhythmic drugs, electrical cardioversion, and invasive procedures, such as pulmonary vein isolation for restoring sinus rhythm.<sup>10,15,16</sup> It has been suggested by some authors that the presence of OSA should be considered as a risk factor for stroke in patients with atrial fibrillation.<sup>17</sup> This is based on several prospective cohort studies that have found a significantly increased risk for stroke in patients with OSA. The association of OSA with age, hypertension, atrial fibrillation, and endothelial dysfunction could explain its association with cerebrovascular events. In addition, OSA might increase the risk of stroke by left to right shunting, increases in intracranial pressure, and reduced cerebral blood flow.<sup>18-20</sup>

We think that a randomized controlled pilot study that uses CPAP in patients with permanent atrial fibrillation and abnormal sleep studies independent of sleepiness symptoms could answer important questions about the relationship between the treatment of OSA and AF control and AF outcomes, such as stroke (**Figure 1**). Home-based portable sleep tests can identify sleep apnea and auto titration algorithms can provide effective OSA management at lower costs and greater convenience.<sup>21</sup> Important outcomes would include the rate of cerebrovascular events, cardiac events (CHF, myocardial infarction, hospitalization), AF management (days of hospitalization, number of antiarrhythmic drugs used, interventions), and a quality of life survey. The outcome assessment would likely require a weighted composite score since the event rate for thromboembolic events in patients with AF on anticoagulation prophylaxis is only 2% per year. Alternatively, the outcome could be based on hospitalization rate. In the AFFIRM trial 76.6% of the patients were hospitalized over a three and one-half year period.<sup>22</sup> If CPAP treatment reduced the rate by twenty percent per year, a sample size of 1,200 would be needed for a two-year study. Randomizing nonsleepy patients with OSA into a treatment group and a non-treatment group should not present an ethical dilemma since most of the benefit with CPAP occurs in sleepy patients with OSA, and its role in nonsleepy patients is unknown. A study like this will have difficulties with patient compliance since nonsleepy patients may not perceive symptomatic benefit. Patient education and frequent follow-up could reduce this problem. However, the possibility of reducing the medical and cost burden of atrial fibrillation is a very attractive and warrants consideration.

**Figure 1—Pilot study for CPAP treatment**

Composite score: deaths, stroke, myocardial infarction, and quality of life, based on reference 22.

## CITATION

Velasco A; Nugent K. Should we treat nonsleepy patients with obstructive sleep apnea and atrial fibrillation with CPAP? *J Clin Sleep Med* 2013;9(12):1235-1236.

## REFERENCES

- Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 2008;5:136-43.
- Gami AS, Pressman G, Caples SM, et al. Association of atrial fibrillation and obstructive sleep apnea. *Circulation* 2004;110:364-7.
- Gami AS, Hodge DO, Herges RM, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol* 2007;49:565-71.
- Ball J, Carrington MJ, McMurray JJ, Stewart S. Atrial fibrillation: Profile and burden of an evolving epidemic in the 21st century. *Int J Cardiol* 2013;167:1807-24.
- Coyne KS, Paramore C, Grandy S, et al. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health* 2006;9:348-56.
- Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2001;163:19-25.
- Stevenson IH, Teichtahl H, Cunningham D, Ciavarella1 S, Gordon I, Kalman JM. Prevalence of sleep disordered breathing in paroxysmal and persistent atrial fibrillation patients with normal left ventricular function. *Eur Heart J* 2008;29:1662-9.

- Bixler EO, Vgontzas AN, Lin HM, Calhoun SL, Vela-Bueno A, Kales A. Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. *J Clin Endocrinol Metab* 2005;90:4510-5.
- Taranto Montemurro L, Floras JS, Millar PJ, et al. Inverse relationship of subjective daytime sleepiness to sympathetic activity in patients with heart failure and obstructive sleep apnea. *Chest* 2012;142:1222-8.
- Ng CY, Liu T, Shehata M, Stevens S, Chugh SS, Wang X. Meta-analysis of obstructive sleep apnea as predictor of atrial fibrillation recurrence after catheter ablation. *Am J Cardiol* 2011;108:47-51.
- Barbé F, Mayoralas LR, Durán J, et al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness: a randomized, controlled trial. *Ann Intern Med* 2001;134:1015-23.
- Robinson GV, Smith DM, Langford BA, Davies RJ, Stradling JR. CPAP does not reduce blood pressure in non-sleepy hypertensive OSA patients. *Eur Respir J* 2006;27:1229-35.
- Durán-Cantolla J, Aizpuru F, Montserrat JM, et al.; Spanish Sleep and Breathing Group. Continuous positive airway pressure as treatment for systemic hypertension in people with obstructive sleep apnea: randomized controlled trial. *BMJ* 2010; 341:c5991.
- Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea a randomized controlled trial. *JAMA* 2012;307:2161-8.
- Monahan K, Brewster J, Wang L, et al. Relation of the severity of obstructive sleep apnea in response to anti-arrhythmic drugs in patients with atrial fibrillation or atrial flutter. *Am J Cardiol* 2012;110:369-72.
- Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation* 2003;107:2589-94.
- Yazdan-Ashoori P, Baranchuk A. Obstructive sleep apnea may increase the risk of stroke in AF patients: Refining the CHADS2 score. *Int J Cardiol* 2011;146:131-3.
- Ciccone A, Proserpio P, Roccatagliata DV, et al. Wake-up stroke and TIA due to paradoxical embolism during long obstructive sleep apnoeas: a cross-sectional study. *Thorax* 2013;68:97-104.
- Jennum P, Borgeesen SE. Intracranial pressure and obstructive sleep apnea. *Chest* 1989;95:279-83.
- Loepky JA, Voyles WF, Eldridge MW, Sikes CW. Sleep apnea and autonomic cerebrovascular dysfunction. *Sleep* 1987;10:25-34.
- Rosen CL, Auckley D, Benca R, et al. Multisite randomized trial of portable sleep studies and positive airway pressure autotitration versus laboratory-based polysomnography for the diagnosis and treatment of obstructive sleep apnea: the HomePAP study. *Sleep* 2012;35:757-67.
- AFFIRM Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825-33.

## SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication October, 2013

Accepted for publication October, 2013

Address correspondence to: Kenneth Nugent, 3601 4th Street, Lubbock, TX; Tel: (806) 743-6847; E-mail: kenneth.nugent@ttuhsc.edu

## DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest. There is no off-label investigational use of any equipment or medications.

# Treatment of Obstructive Sleep Apnea Syndrome with Nasal Positive Airway Pressure Improves Golf Performance

Marc L. Benton, M.D., F.A.A.S.M.; Neil S. Friedman, R.N.

Morristown Medical Center, Morristown, NJ

**Study Objectives:** Obstructive sleep apnea syndrome (OSAS) is associated with impairment of cognitive function, and improvement is often noted with treatment. Golf is a sport that requires a range of cognitive skills. We evaluated the impact of nasal positive airway pressure (PAP) therapy on the handicap index (HI) of golfers with OSAS.

**Methods:** Golfers underwent a nocturnal polysomnogram (NPSG) to determine whether they had significant OSAS (respiratory disturbance index > 15). Twelve subjects with a positive NPSG were treated with PAP. HI, an Epworth Sleepiness Scale (ESS), and sleep questionnaire (SQ) were submitted upon study entry. After 20 rounds of golf on PAP treatment, the HI was recalculated, and the questionnaires were repeated. A matched control group composed of non-OSAS subjects was studied to assess the impact of the study construct on HI, ESS, and SQ. Statistical comparisons between pre- and post-PAP treatment were calculated.

**Results:** The control subjects demonstrated no significant change in HI, ESS, or SQ during this study, while the OSAS

group demonstrated a significant drop in average HI (11.3%,  $p = 0.01$ ), ESS, ( $p = 0.01$ ), and SQ ( $p = 0.003$ ). Among the more skilled golfers (defined as  $HI \leq 12$ ), the average HI dropped by an even greater degree (31.5%). Average utilization of PAP was 91.4% based on data card reporting.

**Conclusions:** Treatment of OSAS with PAP enhanced performance in golfers with this condition. Treatment adherence was unusually high in this study. Non-medical performance improvement may be a strong motivator for selected subjects with OSAS to seek treatment and maximize adherence.

**Keywords.** Golf, golf handicap, obstructive sleep apnea, nasal positive airway pressure

**Commentary:** A commentary on this article appears in this issue on page 1243.

**Citation:** Benton ML; Friedman NS. Treatment of obstructive sleep apnea syndrome with nasal positive airway pressure improves golf performance. *J Clin Sleep Med* 2013;9(12):1237-1242.

Obstructive sleep apnea syndrome (OSAS) is characterized by repeated episodes of airway obstruction during sleep, often leading to symptoms such as daytime sleepiness. The severity of this condition is typically determined by factors that include the frequency of the respiratory disturbances (respiratory disturbance index, or RDI, which is comprised of the average number of apneas, hypopneas, and respiratory event-related arousals per hour of sleep), often associated oxygen desaturation, and overall negative impact on restorative sleep and sleep continuity. Optimum treatment of moderate to severe OSAS ( $RDI > 15$ ) usually incorporates nasal positive airway pressure (PAP).<sup>1</sup>

OSAS is a risk factor for hypertension, cardiac disease, stroke, and death.<sup>1-3</sup> It also has negative effects on neurocognitive performance, including memory, concentration, and executive function.<sup>1,4-8</sup> Regular use of PAP reduces the frequency of respiratory disturbances and hypoxemia, and improves overall sleep quality.<sup>9</sup> PAP compliance is typically defined as a minimum of 4 hours of use per night for at least 70% of the nights,<sup>9-11</sup> although some studies indicate that the use of PAP for 6 or more hours per night may be more clearly associated with improvement in sleepiness, daily functioning, and memory.<sup>12</sup> PAP devices commonly incorporate software that measures and records adherence data such as the number of days and duration that the PAP device is used as well as its efficacy, allowing

## BRIEF SUMMARY

**Current Knowledge/Study Rationale:** OSAS is an extraordinarily prevalent medical condition, and there is strong evidence that successful treatment with CPAP positively impacts quality-of-life and many associated morbidities. Achieving high rates of treatment adherence remains challenging, and we felt that investigating the impact that CPAP had on a real-life outcome that has not previously been assessed, golf performance, could offer a unique insight into the potential benefits of therapy. **Study Impact:** Demonstrating that CPAP treatment improves golf performance may serve as a motivator for selected patients to seek and accept therapy for OSAS when they might otherwise remain untreated. Future studies investigating the beneficial impact that treatment of OSAS and other medical conditions has on day-to-day activities may help us in our efforts to reach more patients successfully.

for more accurate assessment of success with treatment. The impact of treatment on daytime sleepiness can be assessed with the Epworth Sleepiness Scale (ESS), a validated questionnaire that can be administered before and after starting PAP therapy to measure changes in daytime sleepiness.<sup>13</sup>

There is conflicting evidence regarding the effect of PAP treatment on the neurocognitive deficits associated with OSAS, ranging from significant benefits to no improvement.<sup>14-16</sup> In these studies the severity of OSAS, the degree of cognitive impairment, the optimal length of PAP treatment, and the specific areas of cognitive improvement vary, making

**Table 1**—Descriptive statistics for clinical variables among OSAS group (n = 12)

|                                     | Mean | Median | Min  | Max   | SD   |
|-------------------------------------|------|--------|------|-------|------|
| Apnea-hypopnea index (AHI)          | 49.8 | 52.8   | 11.7 | 96.0  | 26.6 |
| Respiratory disturbance index (RDI) | 54.1 | 56.5   | 25.2 | 96.0  | 22.3 |
| % night with SpO <sub>2</sub> < 90% | 15.7 | 3.8    | 0.0  | 70.0  | 25.0 |
| Arousal index (events/h)            | 39.6 | 34.9   | 17.9 | 76.0  | 17.0 |
| PAP use (% nights > 4 h)            | 91.4 | 93.7   | 74.1 | 100.0 | 8.2  |
| Average time of PAP use (h/night)   | 6.3  | 6.8    | 4.4  | 7.4   | 1.1  |

**Table 2**—Descriptive statistics for variables in OSAS and control groups

|                                      | OSAS group (n = 12) |        |     | Control group (n = 12) |        |     |
|--------------------------------------|---------------------|--------|-----|------------------------|--------|-----|
|                                      | Mean                | Median | SD  | Mean                   | Median | SD  |
| Age (years)                          | 55.6                | 53.5   | 9.2 | 55.1                   | 55.5   | 7.9 |
| Body mass index (kg/m <sup>2</sup> ) | 29.9                | 30.0   | 3.1 | 25.8                   | 26.6   | 2.8 |
| Initial handicap index               | 12.4                | 12.9   | 3.1 | 12.2                   | 11.7   | 4.7 |

meaningful interpretation of the data difficult. The impact of OSAS and its treatment has been extensively investigated with regard to motor vehicle accidents, medical risks, and academic performance in children.<sup>2,3,9,17</sup> Surprisingly, a relative paucity of data has been published regarding the impact of this condition on athletic and recreational performance.

Golf is an internationally popular sport in which performance is largely dependent on physical and cognitive factors, including concentration, endurance, decision-making and mood control, along with hand-eye coordination and the athleticism of the participant.<sup>18</sup> In this study we used the individual subjects' handicap index (HI) to measure changes in their golf performance. The HI can be used to measure an individual golfer's skill, and it can be used to allow golfers of differing skill levels to compete with each other adjusting for differing skill levels.

In the United States, most avid golfers are adult males, 40-70 years old, which coincides with the population most likely to have OSAS.<sup>1,19</sup> The United States Golf Association (USGA) defines an avid golfer as someone who plays 25 or more rounds of golf per year, and most surveys indicate that approximately 80% of avid golfers are male. The aim of this study was to assess the impact of PAP treatment on the neurocognitive and motor functions, stratified by their playing ability, of avid amateur golfers with moderate-to-severe OSAS. Given the known benefits of PAP therapy to OSAS patients, we expected all golfers to experience an improvement in their HI over the course of this study.

## METHODS

### Patient Selection

Patients were considered for candidacy for the treatment group of this study if they played  $\geq 20$  rounds of golf per year, had undergone an NPSG that demonstrated an RDI  $> 15$ , and had never been successfully treated for OSAS. Between April 2007 and August 2008, a total of 24 participants were enrolled for and completed this study: 12 participants were identified with moderately severe or worse OSAS (RDI  $> 15$ ; **Table 1**). Twelve subjects who were matched for age and HI

(**Table 2**) were selected as non-OSAS control subjects. All of the control subjects had either undergone an NPSG demonstrating a RDI  $< 15$  or were felt to be at very low risk for OSAS based on a detailed evaluation by a board-certified sleep physician prior to their enrollment in the study. The original study design called for 2 control groups, with one group assessed to be at low risk for OSAS, and another group documented to have OSAS but refusing therapy or non-adherent with PAP treatment. The second control group never materialized, as all OSAS patients enrolled in this study were very compliant with their PAP therapy for the duration of the study. Most participants for this study were recruited directly from a busy sleep practice in a non-randomized fashion, with some individuals responding to flyers sent to local golf clubs and/or a newspaper article that was published during the enrollment period. All services were provided using standard outpatient treatment protocols. Billing for all services and equipment was done through healthcare insurance, and no stipends or other inducements were provided for study participation. The Atlantic Health Institutional Review Board approved this study, and all subjects signed an informed consent form at the time of their entry into this study.

### NPSG

Each study consisted of a complete NPSG with a digital sleep system using the international 10-20 electrode placement for recording EEG, EOG, EMG from the chin, ECG, respiratory effort, oximetry, body position, airflow, snoring, and limb movement. During PAP titration studies standard algorithms were utilized to guide changes made in pressure level and modality. Studies were manually scored by a registered sleep technologist and then interpreted by a board-certified sleep physician.

### Study Design

After the subjects signed informed consent, all participants were emailed the initial set of questionnaires. These questionnaires contained queries regarding medical and golf demographics, the ESS, a sleep questionnaire (SQ) developed by the authors to assess sleep-related quality-of-life in an online



**Table 3**—Paired comparison between initial and final total scores from two questionnaires and handicap index in OSAS group (A) and control group (B)

| A                              | Initial |        |     | Final |        |     | p-value |
|--------------------------------|---------|--------|-----|-------|--------|-----|---------|
|                                | Mean    | Median | SD  | Mean  | Median | SD  |         |
| <b>OSAS group (n = 12)</b>     |         |        |     |       |        |     |         |
| Sleep questionnaire (SQ)       | 14.3    | 11.5   | 7.5 | 3.1   | 2.0    | 3.1 | 0.003*  |
| Epworth Sleepiness Scale (ESS) | 11.8    | 9.5    | 6.6 | 5.5   | 5.0    | 3.6 | 0.010*  |
| Handicap index (HI)            | 12.4    | 12.9   | 3.5 | 11.0  | 12.4   | 4.7 | 0.010*  |
| B                              | Initial |        |     | Final |        |     | p-value |
|                                | Mean    | Median | SD  | Mean  | Median | SD  |         |
| <b>Control group (n = 12)</b>  |         |        |     |       |        |     |         |
| Sleep questionnaire (SQ)       | 4.1     | 3.5    | 3.2 | 3.6   | 1.5    | 3.6 | 0.339   |
| Epworth Sleepiness Scale (ESS) | 4.8     | 4.0    | 3.0 | 4.6   | 3.5    | 3.1 | 0.723   |
| Handicap index (HI)            | 12.2    | 11.7   | 4.7 | 12.6  | 11.8   | 4.3 | 0.119   |

\*Statistically significant.

format, a golf questionnaire (GQ) developed by the authors to assess subjective assessment of golf performance, and a golf score template to allow score and other relevant data entry of the first 20 rounds played after treatment initiation. Participants from the OSAS group were titrated onto PAP per Sleep Lab protocol, and received all sleep care under the direct supervision of a board-certified sleep physician. They were seen by the sleep specialist at the time of treatment initiation, 4-6 weeks into treatment, and again 3-6 months afterwards. During each visit subsequent to the initiation of PAP, data card download was acquired when available, and treatment adherence was monitored throughout the duration of their participation in the study. After a total of 20 golf scores were submitted, subjects again completed the ESS, SQ, and GQ.

In order to participate in this study, each individual was required to maintain a handicap with the Golf Handicap and Information Network (GHIN), which is a service of the USGA that calculates and maintains golfer handicaps. The HI is a very complex and specific arithmetic formula that estimates how many strokes above or below par a golfer is likely to score based upon their 10 best scores out of the last 20 rounds that they have played. A number of factors are incorporated into the calculation: the actual number of strokes the golfer reports for each hole of each round that they play, the course rating, the slope rating, and other structured adjustments that are made to player scores that assure that the handicap index reflects playing skill regardless of the actual courses played during each round of golf. The course rating of each course played is a measure of golf course difficulty for scratch golfers, who are skilled golfers likely to score par on each hole played. The slope rating of each course that is played is a measure of difficulty for each golf course for bogey golfers (one more stroke than par per hole) relative to the course rating. Each participant's HI was submitted by them at the time of entry into the study, and it was confirmed at the GHIN website. We utilized templates during the study to collect relevant information from the golfers about each of the 20 rounds that they played, including the dates they played and their scores, along with the slope rating and course rating of each round they played. We used an on-line handicap calculator to determine their HI at the end of their participation in the study, and we

then confirmed that the HI was correct by rechecking their HI on the GHIN website after 20 scores had been submitted.

### Statistical Analyses

Comparisons between pre- (initial) and post-PAP (final) in terms of total score from SQ, ESS, and HI were made using the paired t-test for normally distributed differences and the nonparametric Wilcoxon signed-rank test for non-normally distributed differences. The same statistical comparisons were analyzed in a subset sample including subjects with  $HI \leq 12$ . A p-value < 0.05 was considered significant.

## RESULTS

### Subjects

A total of 41 participants, all male, completed consent forms. Of that total, 24 participants met the criteria for participation in the OSAS group, and 12 of them completed both sets of questionnaires and submitted 20 consecutive golf scores. There were 17 subjects who met the criteria for participation in the control group, which included undergoing either an NPSG that did not demonstrate OSAS or a formal assessment by a board-certified sleep physician identifying him as being at very low risk for having OSAS. Twelve of those participants completed both sets of questionnaires and submitted 20 consecutive golf scores. All subjects who dropped out of this study cited the inconvenience of filling out the questionnaires or submitting the scores, or that they were not playing golf frequently enough to meet the 20-score criterion. All subjects completed this study within 6 months or less of enrollment without seasonal breaks. Three of the 12 golfers in the control group and 2 of the 12 golfers in the OSAS group received golf lessons during their participation in this study.

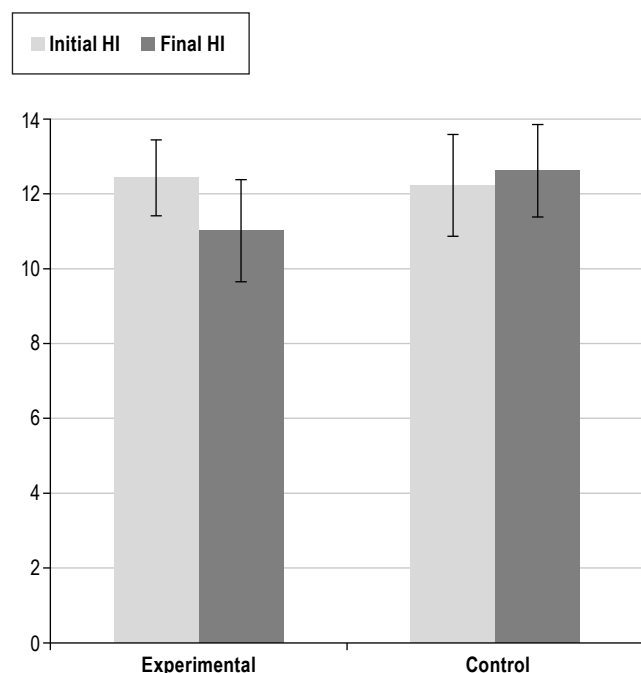
### Treatment Outcomes

The 12 control subjects demonstrated no change in HI, ESS, or SQ throughout their participation in this study (**Table 3B**, **Figure 1**). The active treatment group demonstrated a significant drop in average HI ( $12.4 \pm 3.5$  to  $11.0 \pm 4.7$ ;  $p = 0.01$ ), average ESS ( $11.8 \pm 6.6$  to  $5.5 \pm 3.6$ ;  $p = 0.01$ ), and average

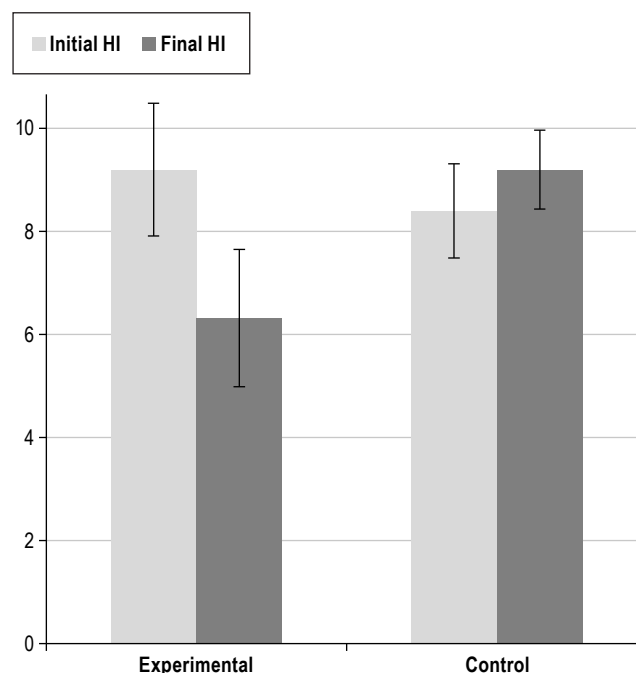
**Table 4**—Subjects with handicap index < 12: paired comparison between initial and final total scores from two questionnaires and handicap index in OSAS group (A) and control group (B)

| A                              | Initial |        |     | Final |        |     | p-value  |
|--------------------------------|---------|--------|-----|-------|--------|-----|----------|
|                                | Mean    | Median | SD  | Mean  | Median | SD  |          |
| <b>OSAS group (n = 5)</b>      |         |        |     |       |        |     |          |
| Sleep questionnaire (SQ)       | 10.8    | 11.0   | 1.9 | 2.8   | 2.0    | 2.6 | 0.004*   |
| Epworth Sleepiness Scale (ESS) | 8.6     | 9.0    | 5.7 | 4.8   | 5.0    | 5.1 | 0.280    |
| Handicap index (HI)            | 9.2     | 9.1    | 2.9 | 6.3   | 6.5    | 3.0 | < 0.001* |
| B                              | Initial |        |     | Final |        |     | p-value  |
|                                | Mean    | Median | SD  | Mean  | Median | SD  |          |
| <b>Control group (n = 6)</b>   |         |        |     |       |        |     |          |
| Sleep questionnaire (SQ)       | 4.8     | 3.5    | 4.2 | 3.5   | 1.0    | 4.3 | 0.082    |
| Epworth Sleepiness Scale (ESS) | 6.2     | 5.5    | 3.6 | 6.0   | 5.5    | 3.5 | 0.842    |
| Handicap index (HI)            | 8.4     | 7.9    | 2.2 | 9.2   | 9.3    | 1.9 | 0.097    |

\*Statistically significant.

**Figure 1**—Comparison of initial and final handicap indexes across all subjects

Bars represent handicap indexes as reported by each of the OSAS subjects (n = 12) and control subjects (n = 12). Averages ± standard error are shown.

**Figure 2**—Comparison of initial and final handicap indexes among skilled golfers

Bars represent handicap indexes as reported by all golfers with an initial handicap index of 12 or less, both in the OSAS group (n = 5) and in the control group (n = 6). Averages ± standard error are shown.

SQ ( $14.3 \pm 7.5$  to  $3.1 \pm 3.1$ ;  $p = 0.003$ ) (Table 3A, Figure 1). Among the better golfers ( $HI \leq 12$ ), the average HI dropped from  $9.2 \pm 2.9$  to  $6.3 \pm 3.0$  ( $p < 0.001$ ) and the average SQ from  $10.8 \pm 1.9$  to  $2.8 \pm 2.6$  ( $p = 0.004$ ). The average ESS among these golfers did not drop significantly (Table 4A, Figure 2).

### Treatment Adherence

Of the 12 subjects with OSAS, digital compliance reporting was obtained from 9 subjects. The remaining 3 participants had PAP devices that did not include digital compliance software, and they all reported 100% compliance with treatment. However, this data was not included in compliance calculations. Throughout the duration of their participation in the

study, the average utilization of PAP was 91.4% of the nights, for an average of 6.3 h per night, as measured by digital compliance reporting (Table 1).

## DISCUSSION

Improvements in the ESS and SQ in the OSAS group confirm that with successful treatment, patients enjoy substantial reductions in daytime somnolence. The post-treatment questionnaire scores of our subjects with OSAS were similar to those without OSAS (Table 3).

The HI dropped significantly following successful treatment of OSAS (Table 3, Figure 1). The majority of improvement was

seen in the better golfers (HI < 12; **Table 4, Figure 2**), with the average HI dropping 32% during the first 20 rounds played after the initiation of PAP therapy. Many of these golfers were in their late 50s and early 60s, at an age when they would be more likely to experience an increasing HI due to the age-related deterioration of their physical skills. Our findings suggest that better golfers have maximized their golf skills, and that the drop in their HI concurrent with treatment of their OSAS was due to enhanced cognitive functioning. Successful treatment of OSAS, therefore, could lead to improved concentration and endurance, along with better decision making, all of which are likely to improve golf performance and lower the HI. These factors were clearly cited by golfers who participated in this study.

It is estimated that over 80% of Americans with OSAS have not been diagnosed or effectively treated.<sup>20</sup> For most patients with significant OSAS, PAP is the most effective modality of treatment.<sup>12</sup> Treatment adherence rates with PAP in clinical practice have been measured to range between 40% and 70%.<sup>10,11</sup> Clinicians who treat OSAS devote substantial resources to improving patient adherence, often with poor results. These measures include the addition of heated tubing and humidification, flex technology to reduce peak airway pressures, auto-titrating PAP devices, and aggressive management of nasal congestion. The effectiveness of these and other interventions are widely debated throughout the recent sleep literature.<sup>21-25</sup> Most of the newer PAP devices incorporate sophisticated compliance and efficacy-reporting software, with detailed reports routinely available at the time of office visits as well as via real-time wireless transmission. Some practitioners have developed and implemented comprehensive compliance-enhancement programs with encouraging results. Unfortunately, these efforts are time-consuming, expensive, and not reimbursed by payers, all of which serves as a disincentive to institute programs of this sort.

Avid golfers often go to great lengths to lower their golf scores, often channeling vast amounts of time, money, and effort into those endeavors.<sup>18</sup> Over the last ten years there has been a proliferation of programs available to enhance physical and/or psychological fitness as a means to improve golf performance. Less commonly are those efforts directed in ways that could improve their neurocognitive and motor skills. Identifying and treating OSAS in avid golfers allowed us to measure the impact of treatment on golf performance, which is a real-life outcome that certain patients can relate to.

Treatment adherence was unusually high in our subjects with OSAS despite the absence of specific adherence-enhancement techniques during this study (**Table 2**). It is possible that the potential for improved golf performance may have served a motivational role in increasing treatment compliance. In a number of cases, the participants in this study had previously refused or failed earlier attempts at treatment with PAP, citing a variety of reasons for their unsuccessful experiences.

Major limitations of this study include the small sample size and the fact that patients were not enrolled in a randomized and blinded fashion. However, the 24 subjects who completed this study comprise a representative sampling of avid golfers (most commonly defined as middle-aged, male, playing 25 or more rounds of golf annually, with handicap indexes ranging between 4.9 and 21.4) in the United States. The Epworth Sleepiness Scale, a validated questionnaire that is commonly

used to measure reductions in sleepiness, was used in this study. It has been the experience of the authors that when used to track treatment response to PAP use in OSAS patients, the ESS frequently does not correlate with the clinical assessment of the patient's status. Because of this, we developed a simple 16-question survey (SQ) that can easily be filled out without assistance in an online format, and it contained many of the questions that we routinely ask when assessing response to PAP treatment in our patients. The answers to the SQ correlated with PAP response to a higher degree of statistical significance than the ESS did in this study, particularly in the low HI subjects. We developed a golf questionnaire in an effort to determine if there were specific aspects of playing golf that improved in the OSAS subjects with treatment. No statistically significant findings were observed, but it is possible that a modified version of that questionnaire might yield valuable insight in a larger study. To our knowledge, there are currently no validated questionnaires that investigate the details of playing golf.

The original study design included a second control group which was to consist of subjects with OSAS who either declined treatment with PAP or were found to be non-adherent with therapy during the study period. Due to the small study size and the fact that all of the OSAS subjects exceeded compliance benchmarks, we were unable to include this control group in our data, and this represents another major factor that impacts the interpretation of the data derived from this study. In future studies, it would also make sense to wait one month after PAP therapy has been initiated before assessing the impact of treatment, as many patients need to undergo a period of acclimation and adjustments before the treatment is optimized. Despite these limits, we believe our findings are relevant in the context of OSAS treatment and have strong clinical implications.

## Clinical Implications

This pilot study demonstrated a novel positive treatment outcome that some patients may identify as relevant and important as it pertains to the decisions that they make related to their healthcare. The possibility of improving golf performance may have contributed to high rates of adherence with PAP therapy in this study. Non-traditional methods of motivation could prove successful in convincing patients to seek evaluation for and accept treatment of certain medical conditions, in addition to improving treatment adherence. Enhanced performance in sports, hobbies, social, and professional endeavors should be investigated as possible motivators to improve receptiveness to and adherence with treatment.<sup>26,27</sup> Golf performance, as defined by the HI, appears to improve in a number of subjects related to treatment of their OSAS. It is possible that other discrete aspects of performance enhancement, particularly in work and social environments, may be realized when OSA is successfully treated. Developing tools to assist in the measurement of performance in these areas may facilitate the efforts of providers to more actively engage some of their patients in the evaluation and treatment process.

## REFERENCES

1. Qureshi A, Ballard RD, Nelson HS. Obstructive sleep apnea. *J Allergy Clin Immunol* 2003;112:643-51.



2. Tregear S, Reston, J, Schoelles, K, Phillips, B. Continuous positive airway pressure reduces risk of motor vehicle crash among drivers with obstructive sleep apnea. *Sleep* 2010;33:1373-80.
3. Yaggi HK, Concato J, Kernan WN, et al. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 2005;353:2034-41.
4. Knoepke C, Aloia, M. Proposed mechanisms of cognitive dysfunction in obstructive sleep apnea. *Prim Psychiatry* 2009;16:51-6.
5. Lau EYY, Eskes GA, Morrison DL, et al. Executive function in patients with obstructive sleep apnea treated with continuous positive airway pressure. *J Int Neuropsychol Soc* 2010;16:1077-88.
6. Saunamäki T, Jehkonen M, Huupponen E, Polo O, Himanen S. Visual dysfunction and computational sleep depth changes in obstructive sleep apnea syndrome. *Clin EEG Neurosci* 2009;40:162-7.
7. Saunamäki T, Himanen SL, Polo O, et al. Executive dysfunction in patients with obstructive sleep apnea syndrome. *Eur Neurol* 2009;62:237-42.
8. Twigg GL, Papaioannou I, Jackson M, et al. Obstructive sleep apnea syndrome is associated with deficits in verbal but not visual memory. *Am J Respir Crit Care Med* 2010;182:98-103.
9. Avlonitou E, Kapsimalis F, Varouchakis G, et al. Adherence to CPAP therapy improves quality of life and reduces symptoms among obstructive sleep apnea syndrome patients. *Sleep Breath* 2011;1-7.
10. Richards D, Bartlett DJ, Wong K, Malouff J, Grunstein RR. Increased adherence to CPAP with a group cognitive behavioral treatment intervention: a randomized trial. *Sleep* 2007;30:635-40.
11. Weaver T, Maislin, G, Dinges, DF, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep* 2007;30:711-9.
12. Weaver T, Grunstein R. Adherence to continuous positive airway pressure therapy. *Proc Am Thorac Soc* 2008;5:173-8.
13. Johns M. Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth Sleepiness Scale. *Chest* 1993;103:30-6.
14. Antic N, Catcheside P, Buchan C, et al. The effect of CPAP in normalizing daytime sleepiness, quality of life, and neurocognitive function in patients with moderate to severe OSA. *Sleep* 2011;34:111-9.
15. Quan S, Chan CS, Dement WC, et al. The association between obstructive sleep apnea and neurocognitive performance—the Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep* 2011;34:303-14.
16. Quan SF, Wright R, Baldwin CM, et al. Obstructive sleep apnea-hypopnea and neurocognitive functioning in the Sleep Heart Health Study. *Sleep Med* 2006;7:498-507.
17. Vertes R, Siegel, JM. Time for the sleep community to take a critical look at the purported role of sleep in memory processing. *Sleep* 2005;28:1228-9.
18. Hellström J. Psychological hallmarks of skilled golfers. *Sports Med* 2009;39:845-55.
19. Heerwagen P. Golfer demographics show lots of green. *Quad - State Business Journal* 1997;8:9.
20. Lee W, Nagubadi S, Kryger MH, et al. Epidemiology of obstructive sleep apnea: a population-based perspective. *Expert Rev Respir Med* 2008;2:349-64.
21. Ryan S, Doherty, LS, Nolan, GM, McNicholas, WT. Effects of heated humidification and topical steroids on compliance, nasal symptoms, and quality of life in patients with obstructive sleep apnea syndrome using nasal continuous positive airway pressure. *J Clin Sleep Med* 2009;5:422-7.
22. Worsnop CJ, Miseski S, Rochford PD. Routine use of humidification with nasal continuous positive airway pressure. *Intern Med J* 2010;40:650-6.
23. Smith I, Nadig, V, Lasserson, TJ. Educational, supportive and behavioural interventions to improve usage of continuous positive airway pressure machines for adults with obstructive sleep apnoea. *Cochrane Database Syst Rev* 2009;CD007736.
24. Sparrow D, Aloia M, DeMolles DA, et al. A telemedicine intervention to improve adherence to continuous positive airway pressure: a randomised controlled trial. *Thorax* 2010;65:1061-6.
25. Vennelle M, White, S, Riha, RL, et al. Randomized controlled trial of variable-pressure versus fixed-pressure continuous positive airway pressure (CPAP) treatment for patients with obstructive sleep apnea/hypopnea syndrome (OSAHS). *Sleep* 2010;33:267-71.
26. Taskin U, Yigit O, Acioğlu E, et al. Erectile dysfunction in severe sleep apnea patients and response to CPAP. *Int J Impot Res* 2010;22:134-9.
27. Emsellem HA, Murtagh KE. Sleep apnea and sports performance. *Clinics Sports Med* 2005;24:329-41.

## ACKNOWLEDGMENTS

Author Contributions: Dr. Benton had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Benton contributed to the original idea for the study, subject recruitment, data collection and analysis, manuscript draft and editing. Mr. Friedman contributed to the original idea for the study, data collection and analysis, manuscript draft and editing.

The authors are indebted to Laura Benton and Alison Kole for their help in editing the manuscript, along with Sherin Ibrahim for her contributions to study design. We also thank Rami Bustami for his assistance in statistical analysis, along with Mark Rosen and Christopher Ritchlin for their critical review of the manuscript.

## SUBMISSION & CORRESPONDENCE INFORMATION

**Submitted for publication August, 2013**

**Submitted in final revised form September, 2013**

**Accepted for publication September, 2013**

Address correspondence to: Marc L. Benton, M.D., 300 Madison Ave., Third Floor, Madison, NJ 07940; Tel: (973) 822-2772 (office); Fax: (973) 822-2773; E-mail: mbenton56@hotmail.com

## DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest. There was no off-label or investigational use. Work Performed at the Morristown Medical Center and Atlantic Sleep & Pulmonary Associates, Madison, NJ.

# Does Treating Obstructive Sleep Apnea in Golfers Improve Their Handicap?

Commentary on Benton and Friedman. Treatment of obstructive sleep apnea syndrome with nasal positive airway pressure improves golf performance. *J Clin Sleep Med* 2013;9:1237-1242.

Richard D. Simon Jr., M.D., F.A.A.S.M.

Kathryn Severyns Dement Sleep Disorders Center, Providence St. Mary Medical Center, Walla Walla, WA; Department of Medicine, University of Washington, Seattle, WA

COMMENTARY

Does treating obstructive sleep apnea in golfers improve their handicap? The study by Benton and Friedman suggests that this is the case.<sup>1</sup> If true, one could predict that golfers will be flooding to sleep centers in the near future! Most serious golfers (those who actually have a USGA Handicap and play more than 20 rounds a year) will go to enormous lengths to improve their game, such as by purchasing drivers that cost in excess of \$400, putters that cost in excess of \$200, iron sets that cost in excess of \$1000, fairway metals or rescue clubs that can cost in excess of \$200 each, and range finders that cost in excess of \$200 in addition to paying \$40-over \$200 to play a round of golf. It is not unreasonable for a serious golfer to have several sets of clubs, the total value of which can reach several thousands of dollars (much more than the cost of a simple CPAP unit). The authors are correct in stating that it is highly likely that motivation to have OSA diagnosed and treated among golfers would rise (possibly even “skyrocket”) if better golf and a lower handicap is one of the results.

If this is true, can it be generalized to other sports? Could improvement in athletic performance be a factor that might encourage patients to have OSA diagnosed and treated? Studies suggest that the prevalence of OSA is high in active<sup>2</sup> and retired<sup>3</sup> National Football League players and that the retired players also had an increased prevalence of hypertension and obesity. I am not aware that this has been studied in college football or high school football but it seems likely that, especially in lineman, the prevalence of OSA is high. It also seems that if identification and treatment of OSA would significantly improve athletic performance, that the team that did this would have a significant advantage over teams that ignored the issue, and that players in whom OSA was identified and treated would likely enjoy better long-term health. Unfortunately, there are no studies looking at the athletic outcome of treating OSA in other sports.

But are the results of the study by Benton and Friedman too good to be true? Probably. The study is a pilot study and there are significant design errors such as lack of randomization, lack of blinding to condition (subjects and study personnel), small sample size, questionably appropriate control group, and a 50% dropout in the OSAS group (only

12 of 24 in the OSAS group completed the study) and a 30% dropout rate in the control group (only 12 of 17 in the control group completed the study). I think that the best that can be said of this study is that the results are consistent with the hypothesis that diagnosing and treating OSA in golfers improves golfing scores.

But the study is novel and important. Larger and better-designed studies are clearly warranted to investigate the effects of treatment of OSA on athletic performance. If treating OSA improves athletic performance, I am sure that more people would elect to be evaluated and treated. Athletic performance would improve and, more important, long-term health of the athlete would improve.

## CITATION

Simon RD. Does treating obstructive sleep apnea in golfers improve their handicap? *J Clin Sleep Med* 2013;9(12):1243.

## REFERENCES

1. Benton ML, Friedman NS. Treatment of obstructive sleep apnea syndrome with nasal positive airway pressure improves golf performance. *J Clin Sleep Med* 2013;9:1237-42.
2. George CF, Kab V, Levy AM. Correspondence: Increased prevalence of sleep-disordered breathing among professional football players. *N Engl J Med* 2003;348:367-8.
3. Albuquerque FN, Kuniyoshi FH, Calvin AD, et al. Sleep-disordered breathing, hypertension and obesity in retired National Football League Players. *J Am Coll Cardiol* 2010;56:1432-3.

## SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication October, 2013

Accepted for publication November, 2013

Address correspondence to: Richard D. Simon Jr., M.D., Medical Director, Kathryn Severyns Dement Sleep Disorders Center, Providence St. Mary Medical Center, 401 W. Poplar Street Walla Walla, WA 99362; Tel: (509) 522-5946; Fax: (509) 522-5527; E-mail: richard.simon@providence.org

## DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.



# Sleep and Insulin-Like Growth Factors in the Cardiovascular Health Study

Neomi Shah, M.D., M.P.H.<sup>1,4</sup>; Tom Rice, M.D.<sup>2</sup>; Daniel Tracy, M.P.H.<sup>1</sup>; Thomas Rohan, M.D., Ph.D.<sup>1</sup>; Petra Bůžková, Ph.D.<sup>3</sup>; Anne Newman, M.D., M.P.H.<sup>2</sup>; Robert C. Kaplan, Ph.D.<sup>1</sup>

<sup>1</sup>Albert Einstein College of Medicine, Bronx, NY; <sup>2</sup>University of Pittsburgh School of Medicine, Pittsburgh, PA;

<sup>3</sup>University of Washington, Seattle, WA; <sup>4</sup>Montefiore Medical Center, Bronx, NY

**Study Objectives:** Sleep and sleep disordered breathing (obstructive sleep apnea [OSA]) are known to affect the growth hormone/insulin-like growth factor (GH/IGF) axis. There are few relevant population studies in this area, particularly in the elderly. We conducted this study to investigate the relationship between sleep (architecture and OSA) and circulating IGF-I (insulin-like growth factor-1), IGFBP-1 (insulin-like growth factor binding protein-1), and IGFBP-3 (insulin-like growth factor binding protein-3) levels in an elderly population.

**Design Setting:** Cross-sectional analysis of participants from the year 9 visit of the Cardiovascular Health Study (CHS) who were enrolled in the Sleep Heart Health Study (SHHS).

**Patients or Participants:** 1,233 elderly participants from the CHS and SHHS.

**Measurements and Results:** The mean age of males (n = 526) and females (n = 697) was 77 years. The mean value of IGF-I (ng/mL) in males was 112.4 vs. 97.1 in females (p < 0.01). Mean IGFBP-1 and IGFBP-3 levels were higher in females than males (p < 0.01). As expected, slow wave sleep was better preserved in females compared to males (22% total sleep time vs. 9% total sleep time, p < 0.01). Furthermore, as expected, OSA (apnea-hypopnea index [AHI] ≥ 5/h) was more prevalent in males compared to females (60% vs. 46%, p < 0.01). Multivariable linear regression was used to determine the relationship

between objective sleep parameters and circulating IGF-I, IGFBP-1, and IGFBP-3 levels, with adjustment for age, sex, race, BMI, diabetes, estrogen use, progestin use, and physical activity. We did not detect a significant association between slow wave sleep (SWS) (per 5 min) and IGF-I, IGFBP-1, and IGFBP-3 levels (ng/mL). We found no significant linear association between OSA (AHI ≥ 5/h) and IGF-I, IGFBP-1, and IGFBP-3 levels. Gender-stratification of the entire cohort did not alter these findings. Sensitivity analyses excluding diabetics revealed that moderate OSA (AHI ≥ 5 and < 15) is inversely associated with IGFBP-3 levels in women.

**Conclusions** The relationship between SWS and GH/IGF system is not significant in the elderly. Furthermore, OSA does not appear to adversely influence the GH/IGF axis, as reported in younger individuals. Whether our study findings are due to diminished GH/IGF-I axis activity in elderly needs further investigation by replication in other large population based elderly cohorts.

**Keywords:** Insulin-like growth factors, IGF, IGFBP-3, slow wave sleep, sleep apnea, sleep, elderly, GH/IGF axis

**Citation:** Shah N; Rice T; Tracy D; Rohan T; Bůžková P; Newman A; Kaplan RC. Sleep and insulin-like growth factors in the cardiovascular health study. *J Clin Sleep Med* 2013;9(12):1245-1251.

The growth hormone/insulin-like growth factor (GH/IGF) system comprises a complex endocrine system that is involved in embryonic development, growth, and normal adult physiology. A key mediator of this system, insulin-like growth factor-1 (IGF-I), is important in modulating cell proliferation, differentiation, and survival/apoptosis, and also has insulin-like metabolic effects. GH is the main signal controlling liver production of IGF-I, with reciprocal inhibitory effects of IGF-I on GH secretion. Physiologic regulation of circulating IGF-I is controlled mainly by growth hormone (GH). GH has a pulsatile secretion that varies markedly in a diurnal fashion, with most GH produced during slow wave sleep (SWS) or stage N3 sleep (formerly stages 3 and 4). While GH is known to be pulsatile and the pulsatile secretion seems to be important in some GH effects, it appears that IGF-I levels are more strongly associated with basal GH levels than with pulsatile GH.<sup>1</sup>

Prior studies in the Cardiovascular Health Study (CHS) and other cohorts have implicated circulating levels of IGF-I and

## BRIEF SUMMARY

**Current Knowledge/Study Rationale:** While it is known that sleep and sleep disordered breathing may affect the growth hormone/insulin-like growth factor axis, there are few relevant population studies in this area specifically involving elderly individuals. We conducted this study to investigate the relationship between sleep (architecture and obstructive sleep apnea) and circulating insulin-like growth factor-1, insulin-like growth factor binding protein-1, and insulin-like growth factor binding protein-3 levels in an elderly population.

**Study Impact:** Due to the substantial dependence of the growth hormone/insulin-like growth factor axis on age, it is important to understand the impact of sleep architecture and sleep disordered breathing on circulating insulin-like growth factor-1 and insulin-like growth factor-binding protein levels among elderly patients. This study helps understand the independent impact of sleep architecture and sleep disordered breathing on the growth hormone/insulin-like growth factor axis in an elderly population.

insulin-like growth factor binding proteins (e.g., insulin-like growth factor binding protein-1 [IGFBP-1], insulin-like growth factor binding protein-3 [IGFBP-3], which affect bioactivity

of IGF-I), in risk of cancer, cardiovascular diseases, functional status, and mortality.<sup>2-4</sup>

While it is known that sleep and sleep disordered breathing may affect the GH/IGF factor axis,<sup>5-7</sup> there are few relevant population studies in this area. Prior studies have shown there to be an inverse relationship between the severity of sleep disordered breathing (as measured by the apnea-hypopnea index [AHI]) and IGF-I, and that this relationship appears to be independent of BMI and age.<sup>5-7</sup> Due to the substantial dependence of the GH/IGF axis on age, it is important to understand the impact of sleep architecture and sleep disordered breathing on circulating IGF-I and IGFBP levels among elderly patients for several reasons. First, understanding this relationship may help in determining the cause of altered levels of IGF-I in some older adults.<sup>8</sup> Second, IGF binding proteins have also been linked with circadian regulatory mechanisms<sup>9,10</sup> and these IGF-BPs are of proven relevance to risk of diabetes and death in older adults.<sup>11-13,14</sup> Third, sleep quality, duration, and sleep disordered breathing have been implicated as a risk factor for diabetes and metabolic disorder, and effects of sleep on IGF-I and related mediators may possibly explain this association.<sup>15-21</sup> Fourth, emerging evidence suggests a positive influence of diminished GH/IGF-I axis on longevity (via improved cancer and diabetes related outcomes).<sup>22-24</sup> Whether this is partially mediated by the influence of sleep architecture and sleep disordered breathing on the GH/IGF-I axis is unknown.

We therefore investigated the relationship between sleep architecture and IGF-I, IGFBP-1, and IGFBP-3 levels in an elderly population of CHS participants who were also involved in the Sleep Heart Health Study (SHHS). We examined the relationship between obstructive sleep apnea (OSA) and its associated characteristics, namely hypoxemia and arousal, and circulating IGF-I, IGFBP-1, and IGFBP-3 levels among elderly participants. Due to the major impact of gender on SWS,<sup>25</sup> sleep disordered breathing prevalence,<sup>26</sup> and on the GH/IGF axis,<sup>27-29</sup> we present our primary analyses in a gender stratified manner.

## METHODS

### Study Population

The CHS is a longitudinal cohort study that enrolled 5,888 adults, 65 years and older, from 4 US communities. It consists of an original cohort of 5,201 individuals recruited during 1989-1990 and an additional cohort of African American individuals recruited during 1992-1993. Participants were invited to repeated examinations for collection of data and blood specimens. The examinations were conducted annually through 1999, and again in 2005-2006 on surviving participants. As part of the year 9 CHS visit cycle (1998), a total of 1,350 CHS participants were enrolled into the SHHS. Briefly, the SHHS is a multicenter prospective cohort study evaluating the natural cardiovascular consequences of sleep disordered breathing.<sup>30,31</sup> The study includes 6,441 participants  $\geq 40$  years of age from multiple population-based cohorts. All SHHS participants underwent a baseline examination that included portable sleep monitoring. Our study sample for the present analyses consisted of 1,233 older adults who had objective sleep measurement as part of the SHHS evaluation, as well as circulating IGF-I and IGFBP-3 levels measured as part of an ancillary study to CHS.

All participants provided informed consent, and institutional review board approvals were obtained at all participating institutions.

### Sleep Measurements

The SHHS as described above collected objective sleep data on 6,441 participants (1995-1998) who underwent a full-montage unattended polysomnogram, which provided measurements pertaining to sleep architecture and sleep disordered breathing. Additionally, they completed questionnaires about sleep habits. Apnea was defined as an absence or near absence of airflow  $\geq 10$  seconds. Hypopnea was defined as 70% decrease in airflow plus  $\geq 4\%$  desaturation lasting  $> 10$  seconds. The AHI was calculated as the number of apnea and hypopnea events divided by total sleep time in hours. Hypoxemia variables included average oxygen saturation, lowest oxygen saturation, and T90 (time spent with oxygen saturation less than 90%). Sleep fragmentation was assessed using the arousal index variable. In the SHHS, the arousal index was defined as the total number of arousals per hour of sleep. We excluded arousal index data from sleep studies coded as "sleep wake only" in order to account for technical issues related to EEG scoring of arousals. All sleep studies were scored by the SHHS reading center according to Rechtschaffen and Kales criteria.<sup>32</sup>

### IGF and Other Measurements

Physical and cognitive function tests, questionnaires, laboratory panels, and other key covariates were collected during the CHS study examinations. Laboratory measurements were performed using blood collected using standard procedures after an overnight fast and stored at  $-70^{\circ}\text{C}$ . Measurements of IGFBP-1, IGFBP-3, and IGF-I were performed at the Jewish General Hospital (Montreal, Canada) after an extraction step using ELISA methods (Diagnostics Systems Laboratory, Webster, TX). Assay coefficient of variation was 4% to 6% for IGF-I concentration, and 3% to 5% for IGFBP-3 concentration.<sup>33</sup> Other laboratory measurements such as fasting glucose were measured at the CHS Central Laboratory using standard methods.

### Clinical Variables

Participants were considered to have diabetes at baseline if they reported use of insulin or an oral hypoglycemic agent or if they had fasting serum glucose  $\geq 7.0$  mmol/L (126 mg/dL). Participants were considered to have impaired fasting glucose if their fasting serum glucose level was 110 to 125 mg/dL and they were not on insulin or oral hypoglycemic agents. BMI was calculated as the measured weight in kilograms divided by the square of measured height in meters. Physical activity was measured in the CHS using a validated questionnaire—the Modified Minnesota Leisure-Time Activities Questionnaire.<sup>34,35</sup> The questionnaire was administered by trained interviewers, and inquired about the frequency and duration of participation in 15 leisure-time activities in the 2 weeks preceding a physical examination.

### Analysis

Descriptive statistics including demographic, clinical, and sleep characteristics are reported as mean or median ( $\pm$



standard deviation or range, as appropriate) and are stratified by gender. Skewed variables were log transformed. IGF concentrations (IGF-I, IGFBP-1, and IGFBP-3) are similarly described. Gender-based comparisons of the above noted variables were made using  $\chi^2$ , t-test, or Wilcoxon rank sum analyses, as appropriate. We used linear regression to model sleep variables as predictive of IGF-I, IGFBP-1, and IGFBP-3 levels. Models were adjusted for known determinants of circulating IGF-I, IGFBP-1, and IGFBP-3 concentrations, including sex, race, BMI, diabetes mellitus, physical activity, and use of sex hormones. Because of known gender dimorphism in regulation of the IGF system, we also stratified these analyses by sex. To better assess the relationship between OSA and IGF-I, IGFBP-1, and IGFBP-3, the regression analysis was examined in a restricted sample of non-diabetics and obese participants (obesity defined as a BMI  $\geq 30$  kg/m<sup>2</sup>).

## RESULTS

The study population (n = 1,223) had a mean age of 77.5 years and included 697 women and 526 men. Mean IGF-I levels were higher among men than women (112.4 ng/mL vs. 97.1 ng/mL,  $p < 0.01$ ); however, mean IGFBP-3 levels were higher among women (3835 ng/mL vs. 3460 ng/mL,  $p < 0.05$ ). Overall, women in our cohort had better sleep quality than men. SWS was better preserved in females than males, with females spending 76 min on average in SWS compared to males who spent 29 min ( $p < 0.01$ ). The mean AHI in females was 5.5/h vs. 9.3/h in males ( $p < 0.01$ ). Since the distribution of the AHI variable in our study sample is not normal, we report the log-transformed AHI with addition of 0.01 to those records with a value of 0 for AHI (n = 14). The prevalence of OSA (AHI  $\geq 5$ ) in males was 60% and in females was 46% ( $p < 0.01$ ). The prevalence of moderate OSA (AHI  $\geq 15$ ) was 29% in males, and 16% in females ( $p < 0.01$ ). Women also had a lower arousal index than men (16.8 vs. 20.1,  $p < 0.01$ ), suggesting less sleep fragmentation among women (Table 1).

Tables 2, 3, and 4 show the association between various sleep parameters and IGF-I, IGFBP-1, and IGFBP-3 levels. Table 2 shows the entire cohort, and Tables 3 and 4 show gender-stratified results. We quantified associations as Beta (B), reflecting change in IGF-I, IGFBP-1, or IGFBP-3 for each “unit” change (5 min) in stage 2, slow wave, or REM

**Table 1**—Baseline characteristics of the study sample

|                                              | All Participants (n = 1,223) |                  |        |
|----------------------------------------------|------------------------------|------------------|--------|
|                                              | Females (n = 697)            | Males (n = 526)  | p      |
| Age (years)                                  | 77 (4.5)                     | 77 (4.6)         | 0.23   |
| BMI                                          | 27.4 (5.1)                   | 27.1 (3.8)       | 0.24   |
| Physical activity (kcal during 2 weeks)      | 680 (190-1530)               | 945 (296-1983)   | < 0.01 |
| Diabetic (ADA Definition)                    | 12.6%                        | 18.60%           | 0.02   |
| IGF-I (ng/mL)                                | 97.1 (35.9)                  | 112.4 (35.5)     | < 0.01 |
| IGFBP-1 (ng/mL) <sup>a</sup>                 | 7.7 (3.9-14.0)               | 6.4 (3.5-10.1)   | < 0.01 |
| IGFBP-3 (ng/mL)                              | 3835 (863)                   | 3460 (810)       | < 0.01 |
| Total sleep time in minutes                  | 362 (302-401)                | 337 (298-379)    | < 0.01 |
| AHI                                          | 5.5 (2.1-12.2)               | 9.3 (3.7-19.6)   | < 0.01 |
| Log2(AHI) <sup>a</sup>                       | 2.18 (2.12)                  | 2.88 (2.04)      | < 0.01 |
| AHI $\geq 5$                                 | 45.90%                       | 59.70%           | < 0.01 |
| AHI $\geq 15$                                | 16.20%                       | 28.50%           | < 0.01 |
| AHI $\geq 30$                                | 5.30%                        | 11.00%           | < 0.01 |
| Weekday sleep (h)                            | 7 (1.4)                      | 7.2 (1.3)        | 0.09   |
| Weekend sleep (h)                            | 7.1 (1.5)                    | 7.3 (1.3)        | 0.02   |
| Percent sleep time of SaO <sub>2</sub> < 90% | 0.03 (0.02-2.2)              | 0.6 (0.04-4.0)   | < 0.01 |
| Arousal Index                                | 16.8 (11.6-23.8)             | 20.1 (14.6-28.1) | < 0.01 |

<sup>a</sup>Log-Transformed AHI with addition of 0.01 to those records with a value of 0 for AHI (n = 14).

**Table 2**—Multivariable associations of sleep measures with IGF-I, IGFBP-1 and IGFBP-3 for all participants

| All Participants           | Adjusted for age, gender, race, BMI, diabetes, estrogen use, progestin use, and physical activity |      |                        |      |                       |      |
|----------------------------|---------------------------------------------------------------------------------------------------|------|------------------------|------|-----------------------|------|
|                            | IGF-I (ng/mL)                                                                                     |      | Log2(IGFBP-1) (ng/mL)  |      | IGFBP-3 (ng/mL)       |      |
|                            | B (CI)                                                                                            | p    | B (CI)                 | p    | B (CI)                | p    |
| Log2(AHI) <sup>a</sup>     | 0.20 (-0.99, 1.38)                                                                                | 0.74 | -0.02 (-0.05, 0.01)    | 0.19 | 2.25 (-22.5, 27.0)    | 0.86 |
| AHI ( $\geq 5$ )           | -1.7 (-6.8, 3.4)                                                                                  | 0.51 | -0.03 (-0.17, 0.10)    | 0.61 | -73.1 (-179.0, 32.9)  | 0.18 |
| AHI ( $\geq 15$ )          | -1.5 (-7.3, 4.3)                                                                                  | 0.62 | 0.01 (-0.15, 0.16)     | 0.94 | -70.3 (-189.0, 48.5)  | 0.25 |
| AHI ( $\geq 30$ )          | 2.5 (-6.4, 11.1)                                                                                  | 0.60 | -0.01 (-0.25, 0.22)    | 0.91 | 2.6 (-175.0, 180.3)   | 0.98 |
| AHI Category               |                                                                                                   |      |                        |      |                       |      |
| < 5 (ref)                  | 1                                                                                                 |      | 1                      |      | 1                     |      |
| $\geq 5$ and < 15          | -1.6 (-7.2, 4.1)                                                                                  | 0.59 | -0.04 (-0.19, 0.12)    | 0.64 | -68.0 (-185.0, 48.9)  | 0.25 |
| $\geq 15$ and < 30         | -3.6 (-11.2, 4.0)                                                                                 | 0.35 | -0.04 (-0.24, 0.16)    | 0.71 | -102.6 (-259.8, 54.6) | 0.20 |
| $\geq 30$                  | 1.0 (-8.3, 10.3)                                                                                  | 0.83 | -0.04 (-0.29, 0.21)    | 0.77 | -45.4 (-235.1, 144.3) | 0.64 |
| Stage 1 Time (per 5 min)   | -0.6 (-1.4, 0.3)                                                                                  | 0.17 | -0.01 (-0.03, 0.01)    | 0.52 | 0.2 (-16.6, 16.9)     | 0.98 |
| Stage 2 Time (per 5 min)   | -0.2 (-0.4, 0)                                                                                    | 0.03 | -0.001 (-0.007, 0.004) | 0.59 | -1.5 (-5.6, 2.6)      | 0.48 |
| Stage 3/4 Time (per 5 min) | -0.1 (-0.4, 0.1)                                                                                  | 0.34 | 0.004 (-0.004, 0.011)  | 0.33 | 0.2 (-5.5, 6)         | 0.93 |
| REM Time (per 5 min)       | 0.1 (-0.3, 0.5)                                                                                   | 0.66 | -0.01 (-0.021, 0.002)  | 0.11 | 10.5 (1.2, 19.9)      | 0.03 |

<sup>a</sup>Log-Transformed AHI with addition of 0.01 to those records with a value of 0 for AHI (n = 14).

**Table 3**—Multivariable associations of sleep measures with IGF-I, IGFBP-1 and IGFBP-3 for females

| Female Participants        | Additionally adjusted for BMI, diabetes, estrogen use, progestin use, and physical activity |      |                        |      |                        |      |
|----------------------------|---------------------------------------------------------------------------------------------|------|------------------------|------|------------------------|------|
|                            | IGF-I (ng/mL)                                                                               |      | Log2(IGFBP-1) (ng/mL)  |      | IGFBP-3 (ng/mL)        |      |
|                            | B (CI)                                                                                      | p    | B (CI)                 | p    | B (CI)                 | p    |
| Log2(AHI) <sup>a</sup>     | 0.5 (-0.9, 2)                                                                               | 0.48 | -0.03 (-0.07, 0.01)    | 0.17 | -0.4 (-33.4, 32.6)     | 0.98 |
| AHI (≥ 5)                  | -0.8 (-7.1, 5.6)                                                                            | 0.81 | -0.05 (-0.23, 0.13)    | 0.58 | -69.5 (-208.3, 69.4)   | 0.33 |
| AHI (≥ 15)                 | 0.3 (-7.9, 8.5)                                                                             | 0.94 | -0.18 (-0.4, 0.05)     | 0.13 | -24 (-198.5, 150.6)    | 0.79 |
| AHI (≥ 30)                 | 8.5 (-5.6, 22.7)                                                                            | 0.24 | -0.11 (-0.49, 0.27)    | 0.58 | 192.2 (-92.8, 477.3)   | 0.19 |
| AHI Category               |                                                                                             |      |                        |      |                        |      |
| < 5 (ref)                  | 1                                                                                           |      | 1                      |      | 1                      |      |
| ≥ 5 and < 15               | -1.3 (-8.3, 5.7)                                                                            | 0.71 | 0.01 (-0.19, 0.21)     | 0.77 | -87 (-240.1, 66.1)     | 0.27 |
| ≥ 15 and < 30              | -2.7 (-13, 7.5)                                                                             | 0.60 | -0.2 (-0.48, 0.09)     | 0.25 | -119.3 (-341.1, 102.6) | 0.29 |
| ≥ 30                       | 7.7 (-6.9, 22.2)                                                                            | 0.30 | -0.13 (-0.52, 0.26)    | 0.59 | 140.9 (-153.9, 435.7)  | 0.35 |
| Stage 1 Time (per 5 min)   | -0.1 (-1.3, 1.2)                                                                            | 0.94 | 0.002 (-0.035, 0.039)  | 0.92 | 8.2 (-20.9, 37.3)      | 0.58 |
| Stage 2 Time (per 5 min)   | -0.3 (-0.5, 0)                                                                              | 0.03 | -0.001 (-0.008, 0.006) | 0.80 | -1.2 (-6.6, 4.2)       | 0.66 |
| Stage 3/4 Time (per 5 min) | -0.1 (-0.4, 0.2)                                                                            | 0.46 | 0.003 (-0.006, 0.012)  | 0.48 | -0.3 (-7.2, 6.7)       | 0.94 |
| REM Time (per 5 min)       | -0.1 (-0.7, 0.4)                                                                            | 0.62 | 0 (-0.016, 0.016)      | 0.97 | 12.2 (-0.3, 24.7)      | 0.06 |

<sup>a</sup>Log-Transformed AHI with addition of 0.01 to those records with a value of 0 for AHI (n = 14).

**Table 4**—Multivariable associations of sleep measures with IGF-I, IGFBP-1 and IGFBP-3 for males

| Male Participants          | Additionally adjusted for BMI, diabetes, estrogen use, progestin use, and physical activity |      |                       |      |                        |      |
|----------------------------|---------------------------------------------------------------------------------------------|------|-----------------------|------|------------------------|------|
|                            | IGF-I (ng/mL)                                                                               |      | Log2(IGFBP-1) (ng/mL) |      | IGFBP-3 (ng/mL)        |      |
|                            | B (CI)                                                                                      | p    | B (CI)                | p    | B (CI)                 | p    |
| Log2(AHI) <sup>a</sup>     | -0.4 (-2.4, 1.6)                                                                            | 0.71 | -0.003 (-0.05, 0.044) | 0.89 | 3.2 (-34.3, 40.6)      | 0.87 |
| AHI (≥ 5)                  | -3.8 (-12.4, 4.8)                                                                           | 0.39 | 0.01 (-0.2, 0.22)     | 0.90 | -99.2 (-264.9, 66.5)   | 0.24 |
| AHI (≥ 15)                 | -2.9 (-11.1, 5.3)                                                                           | 0.49 | 0.19 (-0.01, 0.39)    | 0.06 | -128.2 (-289.5, 33)    | 0.12 |
| AHI (≥ 30)                 | -0.1 (-11.3, 11.1)                                                                          | 0.99 | 0.08 (-0.2, 0.37)     | 0.57 | -119.7 (-345.7, 106.2) | 0.30 |
| AHI Category               |                                                                                             |      |                       |      |                        |      |
| < 5 (ref)                  | 1                                                                                           |      | 1                     |      | 1                      |      |
| ≥ 5 and < 15               | -3.1 (-12.9, 6.6)                                                                           | 0.53 | -0.06 (-0.3, 0.17)    | 0.58 | -66.7 (-250, 116.7)    | 0.48 |
| ≥ 15 and < 30              | -5.8 (-17.3, 5.8)                                                                           | 0.33 | 0.13 (-0.15, 0.41)    | 0.36 | -117.6 (-342.8, 107.7) | 0.31 |
| ≥ 30                       | -2.7 (-15.3, 9.9)                                                                           | 0.67 | 0.08 (-0.23, 0.4)     | 0.61 | -174.5 (-427.1, 78)    | 0.18 |
| Stage 1 Time (per 5 min)   | -1 (-2.1, 0.1)                                                                              | 0.07 | -0.02 (-0.04, 0.01)   | 0.22 | -4.4 (-24.7, 16)       | 0.67 |
| Stage 2 Time (per 5 min)   | -0.2 (-0.5, 0.2)                                                                            | 0.36 | -0.002 (-0.01, 0.006) | 0.57 | -1.9 (-8.2, 4.5)       | 0.57 |
| Stage 3/4 Time (per 5 min) | -0.1 (-0.6, 0.4)                                                                            | 0.72 | 0.002 (-0.011, 0.015) | 0.74 | 1.3 (-8.9, 11.6)       | 0.80 |
| REM Time (per 5 min)       | 0.4 (-0.3, 1.1)                                                                             | 0.25 | -0.03 (-0.04, -0.01)  | 0.00 | 8.6 (-5.5, 22.8)       | 0.23 |

<sup>a</sup>Log-Transformed AHI with addition of 0.01 to those records with a value of 0 for AHI (n = 14).

sleep. After adjustment for age, gender, race, BMI, diabetes, estrogen use, progestin use, and physical activity, there were no significant associations between measures of sleep disordered breathing and IGF-I, IGFBP-1, and IGFBP-3 levels. Sleep architecture was also not significantly associated with IGF-I and IGFBP levels. Time spent in stage 1 sleep (5-min increments) was not significantly associated with IGF-I, IGFBP-1, or IGFBP-3 levels. Time spent in stage 2 sleep (5-min increments) was inversely associated with IGF-I levels (B = -0.2, CI = -0.4, 0, p = 0.03) but not with IGFBP-1 or IGFBP-3 levels. Time spent in SWS was also not significantly associated with IGF-I, IGFBP-1, or IGFBP-3 levels in the multivariate model. Time spent in REM sleep was significantly associated with IGFBP-3 levels (B = 10.5, CI 1.2, 19.9, p = 0.03) but not with

IGF-I or IGFBP-1 levels. Beta (B) in the above mentioned analyses reflects change in IGF-I, IGFBP-1, or IGFBP-3 for each “unit” change (5 min) in stage 2, slow wave, or REM sleep.

**Table 3** shows the association between sleep measures and IGF-I, IGFBP-1, and IGFBP-3 levels among *female* participants. After adjustment for age, race, BMI, diabetes, estrogen use, progestin use, and physical activity, there were no associations between measures of sleep disordered breathing and IGF-I, IGFBP-1, or IGFBP-3 levels. The association between time spent in REM sleep and IGFBP-3 levels was similar among females compared to the entire cohort, albeit with attenuated level of statistical significance (B = 12.2, CI -0.3, 24.7, p = 0.06).

**Table 4** shows the association between sleep measures and IGF-I, IGFBP-1, and IGFBP-3 levels among *male* participants.



**Table 5**—Multivariable associations of sleep measures with IGF-I, IGFBP-1 and IGFBP-3 for non-diabetic participants

| Non-Diabetics              | Adjusted for age, gender, race, BMI, estrogen use, progestin use, and physical activity |      |                        |      |                       |      |
|----------------------------|-----------------------------------------------------------------------------------------|------|------------------------|------|-----------------------|------|
|                            | IGF-I (ng/mL)                                                                           |      | Log2(IGFBP-1) (ng/mL)  |      | IGFBP-3 (ng/mL)       |      |
|                            | B (CI)                                                                                  | p    | B (CI)                 | p    | B (CI)                | p    |
| Log2(AHI) <sup>a</sup>     | 0.2 (-1.1, 1.5)                                                                         | 0.75 | -0.02 (-0.05, 0.02)    | 0.29 | -9.3 (-35.8, 17.2)    | 0.49 |
| AHI (≥ 5)                  | -1.5 (-7.1, 4.1)                                                                        | 0.59 | -0.05 (-0.2, 0.1)      | 0.48 | -84.7 (-198, 28.7)    | 0.14 |
| AHI (≥ 15)                 | -3 (-9.5, 3.6)                                                                          | 0.38 | -0.01 (-0.19, 0.16)    | 0.88 | -99.5 (-231.2, 32.2)  | 0.14 |
| AHI (≥ 30)                 | 2.9 (-6.7, 12.4)                                                                        | 0.56 | -0.07 (-0.33, 0.19)    | 0.58 | 41.1 (-151.7, 234)    | 0.68 |
| AHI Category               |                                                                                         |      |                        |      |                       |      |
| < 5 (ref)                  | 1                                                                                       |      | 1                      |      | 1                     |      |
| ≥ 5 and < 15               | -0.8 (-7, 5.4)                                                                          | 0.80 | -0.06 (-0.23, 0.1)     | 0.46 | -63 (-188.4, 62.5)    | 0.33 |
| ≥ 15 and < 30              | -5.4 (-14, 3.1)                                                                         | 0.21 | -0.01 (-0.23, 0.22)    | 0.95 | -185.3 (-358, -12.6)  | 0.04 |
| ≥ 30                       | 1.5 (-8.6, 11.7)                                                                        | 0.77 | -0.1 (-0.38, 0.18)     | 0.47 | -17.9 (-222.5, 186.6) | 0.86 |
| Stage 1 Time (per 5 min)   | -0.88 (-1.79, 0.02)                                                                     | 0.06 | -0.01 (-0.04, 0.01)    | 0.36 | -10.9 (-29.7, 7.8)    | 0.25 |
| Stage 2 Time (per 5 min)   | -0.21 (-0.43, 0.01)                                                                     | 0.06 | -0.001 (-0.007, 0.005) | 0.66 | -1.7 (-6.3, 2.8)      | 0.46 |
| Stage 3/4 Time (per 5 min) | -0.18 (-0.48, 0.12)                                                                     | 0.24 | 0.002 (-0.006, 0.01)   | 0.66 | -0.4 (-6.6, 5.8)      | 0.90 |
| REM Time (per 5 min)       | 0.14 (-0.34, 0.62)                                                                      | 0.57 | -0.01 (-0.02, 0.01)    | 0.40 | 10.7 (0.5, 20.9)      | 0.04 |

<sup>a</sup>Log-Transformed AHI with addition of 0.01 to those records with a value of 0 for AHI (n = 14).

After adjustment for age, race, BMI, diabetes, estrogen use, progestin use, and physical activity, there were no associations between measures of sleep disordered breathing and IGF-I, IGFBP-1, or IGFBP-3 levels. The association between stage 2 sleep and IGF-I levels was not significant in males (B = -0.2, CI -0.5, 0.2, p = 0.36). Similarly, the association between REM sleep and IGFBP-3 was not significant in males (B = 8.6, CI = -5.5, 22.8, p = 0.23). However, unlike females, there is a significant inverse association between REM sleep (5-min increments) and IGFBP-1 (B = -0.03, CI = -0.04, -0.01, p < 0.01).

**Table 5** shows the association between sleep measures and IGF-I, IGFBP-1, and IGFBP-3 levels in non-diabetic individuals. Beta (B) in **Table 5** is changed in IGF-I, IGFBP-1, and IGFBP-3 levels (ng/mL) for each unit of the predictor variable. After adjustment for age, gender, race, BMI, diabetes, estrogen use, progestin use, and physical activity, there were no significant associations between SWS or sleep disordered breathing and IGF-I, IGFBP-1, or IGFBP-3 levels. However, moderate OSA was inversely associated with IGFBP-3 levels (B = -185, CI = -358, -13, p = 0.04). When we stratified this non-diabetic cohort by gender, this association persisted only in females (B = -256, CI = -504, -8, p = 0.04) and not in males (B = -136, CI = -375, 104, p = 0.8) (Data not shown). None of the other sleep disordered breathing variables were associated with IGF-I, IGFBP-1, or IGFBP-3 levels in this gender stratified analysis of non-diabetic individuals. Finally, we investigated the relationship between OSA and IGF-I and IGFBP-3 levels in a restricted sample of obese patients (n = 270 with BMI ≥ 30 kg/m<sup>2</sup>). In this sample of obese patients, we found no significant association between OSA and IGF-I levels (data not shown).

## DISCUSSION

This study evaluated the relationship between sleep (architecture and disordered breathing) and the GH/IGF-I system in an elderly population of patients who were enrolled in the CHS

and who also participated in the SHHS. The major findings of our study are: (a) No significant association was found between SWS and circulating IGF-I, IGFBP-1, or IGFBP-3 levels after adjusting for confounding variables (b) No significant association was detected between measures of sleep disordered breathing and circulating IGF-I, IGFBP-3 or IGFBP-3 levels. (c) Among non-diabetic females, an inverse association was detected between moderate sleep apnea (AHI of 15-30/h) and IGFBP-3 after adjustment for confounding variables.

Numerous studies<sup>27,36,37</sup> support a strong relationship between SWS and increased GH secretion. Increased SWS has also been associated with increased IGF-I levels.<sup>38</sup> In our study of elderly individuals, to the contrary, we found no significant correlation between SWS and IGF-I, IGFBP-1, or IGFBP-3 levels. Based on our study findings, we conclude that the relationship between SWS and the GH/IGF-I axis is not as robust in the elderly as among younger individuals. We found weak yet significant associations between non-SWS and circulating IGF-I and IGFBP-3 levels (**Tables 2-5**). For instance, we found that increased time in stage 2 sleep is associated with reduced IGF-I levels, suggesting an adverse influence of increased stage 2 sleep on IGF-I levels. There was evidence of gender differences, with significance only among females and not males. This suggests that in females, increased stage 2 sleep is associated with reduced IGF-I levels. Similarly, we saw a significant association between time in REM sleep and IGFBP-3 levels, suggesting a positive influence of REM sleep (surrogate for consolidated sleep) on the GH/IGF axis. Gender did not appear to modify this relationship.

We also did not detect a significant association between sleep disordered breathing and IGF-I, IGFBP-1, or IGFBP-3 levels; an association that has been described in prior studies.<sup>5-7</sup> Ursavas et al. has reported a negative correlation between measures of OSA (arousal index, AHI, average desaturation) and IGF-I levels.<sup>7</sup> In that study, the mean age of the study sample was 48.8 years among the control participants and 52 years among those with

sleep apnea. In comparison, the mean age of our study sample is 77.5 years. Therefore, our study is better designed to assess the relationship between sleep and GH/IGF axis in the elderly. Our study is further strengthened by adjusting our multivariable models for important confounding variables including age, BMI, physical activity, and use of sex hormones. We also conducted gender-stratified analyses in addition to sensitivity analyses, excluding obese and diabetic individuals in order to better assess the relationship between sleep and GH/IGF axis. In doing so, we found that although the association between sleep disordered breathing and IGFBP-3 was not significant in the entire cohort or the gender-stratified cohort; there was a significant association in female non-diabetics, where moderate sleep disordered breathing was inversely associated with IGFBP-3 levels. This was not seen in male non-diabetic participants. Therefore, our study demonstrates that the associations between sleep disordered breathing and IGF-I, IGFBP-1, and IGFBP-3 are not significant in an elderly cohort and that sleep disordered breathing likely does not adversely affect the GH/IGF axis (as seen in younger individuals). Our study suggests an inverse association between moderate sleep apnea and IGFBP-3 among female non-diabetics. However, this finding should be interpreted with caution, as a similar association was not seen with mild or severe sleep apnea.

A limitation of our study is that sleep and IGF measures were not collected on the same day but rather within one year of each other. However, in additional analyses we found strong correlation among IGF-I levels within individuals between two study visits conducted 12 months apart ( $r = 0.86$ ). Thus, because IGF-I levels are relatively stable over the short term in the elderly, the measured IGF-I levels used in this study are likely strongly correlated with the measurements that would have been obtained on the same day as the sleep examination. Although we adjusted for potential confounding variables in our regression models, residual confounding by unmeasured variables is possible. In addition, given multiple influences in the elderly that result in relatively low levels of IGFs, it is possible that we may not have had adequate statistical power to detect relatively subtle effects of sleep variables on IGF levels. On the other hand, our study has numerous strengths. It is the first study of its kind to assess an association between sleep architecture and OSA and circulating IGF levels in a population-based sample of elderly participants. The methods of measurement for sleep and IGFs were rigorous as part of two large epidemiological studies namely, the CHS and the SHHS that mutually shared roughly a third of their sample. We were able to adjust for important confounding variables including physical activity which further strengthens our study findings. Finally, our robust sample size with adequate numbers of males and females allowed us to conduct several important secondary data analyses among gender-stratified diabetes and obesity-restricted samples.

In summary, our study did not detect an expected (as seen in younger individuals) significant positive association between SWS and circulating IGF-I, IGFBP-1, or IGFBP-3 levels in our elderly cohort of participants. We also did not observe a significant relationship between various indices of OSA and circulating IGF-I, IGFBP-1, and IGFBP-3 levels among the elderly (as expected among younger individuals). Collectively, our study findings suggest that the relationship between SWS and

the GH/IGF system is weaker in the elderly, and aging appears to dilute the adverse influence of sleep disordered breathing on the GH/IGF system. Future studies are needed to clarify the role of aging on the relationship between sleep and GH/IGF system in order to better understand the implications of circulating levels of IGF-I and IGFBPs in risk of cancer, cardiovascular diseases, functional status, and mortality.

## REFERENCES

1. Faje AT, Barkan AL. Basal, but not pulsatile, growth hormone secretion determines the ambient circulating levels of insulin-like growth factor-I. *J Clin Endocrinol Metab* 2010;95:2486-91.
2. Biernacka KM, Perks CM, Holly JM. Role of the IGF axis in prostate cancer. *Minerva Endocrinol* 2012;37:173-85.
3. Juul A, Scheike T, Davidsen M, Gyllenberg J, Jorgensen T. Low serum insulin-like growth factor I is associated with increased risk of ischemic heart disease: a population-based case-control study. *Circulation* 2002;106:939-44.
4. Empen K, Lorbeer R, Volzke H, et al. Association of serum insulin-like growth factor I with endothelial function: Results from the population-based Study of Health in Pomerania (SHIP). *Eur J Endocrinol* 2010;163:617-23.
5. Gianotti L, Pivetti S, Lanfranco F, et al. Concomitant impairment of growth hormone secretion and peripheral sensitivity in obese patients with obstructive sleep apnea syndrome. *J Clin Endocrinol Metab* 2002;87:5052-7.
6. Johnsen SP, Hundborg HH, Sorensen HT, et al. Insulin-like growth factor (IGF) I, -II, and IGF binding protein-3 and risk of ischemic stroke. *J Clin Endocrinol Metab* 2005;90:5937-41.
7. Ursavas A, Karadag M, Ilcol YO, et al. Low level of IGF-1 in obesity may be related to obstructive sleep apnea syndrome. *Lung* 2007;185:309-14.
8. Sherlock M, Toogood AA. Aging and the growth hormone/insulin like growth factor-I axis. *Pituitary* 2007;10:189-203.
9. Chu LW, Zhu Y, Yu K, et al. Correlation between circadian gene variants and serum levels of sex steroids and insulin-like growth factor-I. *Cancer Epidemiol Biomarkers Prev* 2008;17:3268-73.
10. Amaral IP, Johnston IA. Circadian expression of clock and putative clock-controlled genes in skeletal muscle of the zebrafish. *Am J Physiol Regul Integr Comp Physiol* 2012;302:R193-206.
11. Chen W, Salojin KV, Mi QS, et al. Insulin-like growth factor (IGF)-I/IGF-binding protein-3 complex: therapeutic efficacy and mechanism of protection against type 1 diabetes. *Endocrinology* 2004;145:627-38.
12. Friedrich N, Schneider H, Dorr M, et al. All-cause mortality and serum insulin-like growth factor I in primary care patients. *Growth Horm IGF Res* 2011;21:102-6.
13. Rajpathak SN, He M, Sun Q, et al. Insulin-like growth factor axis and risk of type 2 diabetes in women. *Diabetes* 2012;61:2248-54.
14. Burgers AM, Biermasz NR, Schoones JW, et al. Meta-analysis and dose-response metaregression: circulating insulin-like growth factor I (IGF-I) and mortality. *J Clin Endocrinol Metab* 2011;96:2912-20.
15. Yaggi HK, Araujo AB, McKinlay JB. Sleep duration as a risk factor for the development of type 2 diabetes. *Diabetes Care* 2006;29:657-61.
16. Stamatakis KA, Punjabi NM. Effects of sleep fragmentation on glucose metabolism in normal subjects. *Chest* 2010;137:95-101.
17. Shaw JE, Punjabi NM, Wilding JP, Alberti KG, Zimmet PZ, International Diabetes Federation Taskforce on Epidemiology and Prevention. Sleep-disordered breathing and type 2 diabetes: a report from the International Diabetes Federation Taskforce on Epidemiology and Prevention. *Diabetes Res Clin Pract* 2008;81:2-12.
18. Gottlieb DJ, Punjabi NM, Newman AB, et al. Association of sleep time with diabetes mellitus and impaired glucose tolerance. *Arch Intern Med* 2005;165:863-7.
19. Resnick HE, Redline S, Shahar E, et al. Diabetes and sleep disturbances: findings from the Sleep Heart Health Study. *Diabetes Care* 2003;26:702-9.
20. Botros N, Concato J, Mohsenin V, Selim B, Doctor K, Yaggi HK. Obstructive sleep apnea as a risk factor for type 2 diabetes. *Am J Med* 2009;122:1122-7.
21. Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and type II diabetes: a population-based study. *Am J Respir Crit Care Med* 2005;172:1590-5.
22. Anisimov VN, Bartke A. The key role of growth hormone-insulin-IGF-1 signaling in aging and cancer. *Crit Rev Oncol Hematol* 2013;87:201-23.
23. Jannila RK, List EO, Berryman DE, Murrey JW, Kopchick JJ. The GH/IGF-1 axis in ageing and longevity. *Nat Rev Endocrinol* 2013;9:366-76.

24. Vitale G, Brugts MP, Ogliari G, et al. Low circulating IGF-I bioactivity is associated with human longevity: findings in centenarians' offspring. *Aging (Albany NY)* 2012;4:580-9.
25. Redline S, Kirchner HL, Quan SF, Gottlieb DJ, Kapur V, Newman A. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. *Arch Intern Med* 2004;164:406-18.
26. Krishnan V, Collop NA. Gender differences in sleep disorders. *Curr Opin Pulm Med* 2006;12:383-9.
27. Van Cauter E. Slow wave sleep and release of growth hormone. *JAMA* 2000;284:2717-8.
28. Veldhuis JD, Iranmanesh A. Physiological regulation of the human growth hormone (GH)-insulin-like growth factor type I (IGF-I) axis: predominant impact of age, obesity, gonadal function, and sleep. *Sleep* 1996;19(10 Suppl):S221-4.
29. Veldhuis JD. Gender differences in secretory activity of the human somatotrophic (growth hormone) axis. *Eur J Endocrinol* 1996;134:287-95.
30. Redline S, Sanders MH, Lind BK, et al. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. Sleep Heart Health Research Group. *Sleep* 1998;21:759-67.
31. Quan SF, Howard BV, Iber C, et al. The Sleep Heart Health Study: design, rationale, and methods. *Sleep* 1997;20:1077-85.
32. Rechtschaffen A, Kales A. *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. Los Angeles: UCLA Brain Information Service/Brain Research Institute, 1968.
33. Sanders JL, Ding V, Arnold AM, et al. Do changes in circulating biomarkers track with each other and with functional changes in older adults? *J Gerontol A Biol Sci Med Sci* 2013 June 28. [Epub ahead of print].
34. Taylor HL, Jacobs DR, Jr, Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. *J Chronic Dis* 1978;31:741-55.
35. Folsom AR, Jacobs DR, Jr, Caspersen CJ, Gomez-Marín O, Knudsen J. Test-retest reliability of the Minnesota Leisure Time Physical Activity Questionnaire. *J Chronic Dis* 1986;39:505-11.
36. Van Cauter E, Copinschi G. Interrelationships between growth hormone and sleep. *Growth Horm IGF Res* 2000;10 Suppl B:S57-62.
37. Van Cauter E, Latta F, Nedeltcheva A, et al. Reciprocal interactions between the GH axis and sleep. *Growth Horm IGF Res* 2004;14 Suppl A:S10-7.
38. Prinz PN, Moe KE, Dulberg EM, et al. Higher plasma IGF-1 levels are associated with increased delta sleep in healthy older men. *J Gerontol A Biol Sci Med Sci* 1995;50:M222-6.

## SUBMISSION & CORRESPONDENCE INFORMATION

**Submitted for publication July, 2013**

**Submitted in final revised form July, 2013**

**Accepted for publication July, 2013**

Address correspondence to: Neomi Shah, M.D., M.P.H., Albert Einstein College of Medicine/Montefiore Medical Center, Department of Medicine - Pulmonary Division, 111 East 210th Street, Klau-3 Pulmonary Sleep Lab, Bronx, NY 10467; Tel: (718) 920-2105; Fax: (718) 652-8590; E-mail: nshah@montefiore.org, neomi.shah@einstein.yu.edu

## DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest. This research was supported by contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, 01HC85086, and grant HL080295 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at <http://www.chs-nhlbi.org/PI.htm>. In addition, this work was supported by SHHS grant HL53934 (for CHS sites of SHHS, i.e. Pittsburgh and Sacramento). Finally, Dr. Shah has received research grant funding from the American Sleep Medicine Foundation (2011-current). Work was performed at the Albert Einstein College of Medicine, Bronx, NY.



# The Comorbidity of Sleep Apnea and Mood, Anxiety, and Substance Use Disorders among Obese Military Veterans within the Veterans Health Administration

Kimberly A. Babson, Ph.D.<sup>1,2</sup>; A. C. Del Re, Ph.D.<sup>1,2</sup>; Marcel O. Bonn-Miller, Ph.D.<sup>1,3,4,5</sup>; Steven H. Woodward, Ph.D.<sup>3</sup>

<sup>1</sup>Center for Health Care Evaluation, VA Palo Alto Health Care System, Menlo Park, CA; <sup>2</sup>Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA; <sup>3</sup>National Center for PTSD, VA Palo Alto Health Care System, Menlo Park, CA; <sup>4</sup>Center of Excellence in Substance Abuse Treatment and Education, Philadelphia VAMC, Philadelphia, PA; <sup>5</sup>Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

**Objectives:** To determine the relations between obstructive sleep apnea (OSA) diagnosis, the likelihood of being diagnosed with a psychological condition, among obese veterans, after accounting for severity of obesity and the correlated nature of patients within facility. We hypothesized that (1) individuals with a diagnosis of OSA would be more likely to receive a diagnosis of (a) mood disorder and (b) anxiety disorder, but not (c) substance use disorder.

**Design:** Cross-sectional retrospective database review of outpatient medical records between October 2009 and September 2010, conducted across all 140 Veterans Health Administration (VHA) facilities.

**Setting:** The entire VA Health Care System.

**Patients or Participants:** Population-based sample of veterans with obesity (N = 2,485,658).

**Main Outcome Measures:** Physician- or psychologist-determined diagnosis of psychological conditions including mood, anxiety, and substance use disorders.

**Results:** Using generalized linear mixed modeling, after

accounting for the correlated nature of patients within facility and the severity of obesity, individuals with a diagnosis of sleep apnea had increased odds of receiving a mood disorder diagnosis (OR = 1.85; CI = 1.71-1.72; p < 0.001), anxiety disorder diagnosis (OR = 1.82; CI = 1.77-1.84; p < 0.001), but not a diagnosis of substance use disorder.

**Conclusions:** Among obese veterans within VA, OSA is associated with increased risk for having a mood and anxiety disorder, but not substance use disorder, with the strongest associations observed for posttraumatic stress disorder (PTSD) and major depressive disorder (MDD). In addition, this relation remained after accounting for severity of BMI.

**Keywords:** Sleep apnea, depression, anxiety, veterans

**Citation:** Babson KA; Del Re AC; Bonn-Miller MO; Woodward SH. The comorbidity of sleep apnea and mood, anxiety, and substance use disorders among obese military veterans within the Veterans Health Administration. *J Clin Sleep Med* 2013;9(12):1253-1258.

Obstructive sleep apnea (OSA), defined as impaired patency of the upper airway during sleep, resulting in apneas (complete cessation of airflow for at least 10 seconds) and/or hypopneas (50% reduction in airflow), is one of the most common forms of sleep disordered breathing (SDB). OSA can result in hundreds of brief arousals from sleep in a single night and affects approximately 2% of women and 4% of men nationwide,<sup>1</sup> with higher rates documented among military veterans (6.5%).<sup>2</sup> Indeed, OSA is one of the most common, yet underdiagnosed, causes of sleep disturbances among veterans, showing no remittance without treatment or lifestyle changes (loss of weight).<sup>3</sup> The nearly twofold difference in prevalence of OSA among veterans, compared to community samples, is thought to be due, at least in part, to two risk factors which are common among veterans: male gender and obesity.<sup>4</sup>

In addition to direct effects (e.g., daytime fatigue, disturbed sleep, irritability, memory problems, and decreased quality of life),<sup>5,6</sup> OSA is associated with a number of indirect physical and psychological complications. Such complications include hypertension, heart disease and heart failure, stroke, insulin resistance and impairments in neurocognitive functioning,

## BRIEF SUMMARY

**Current Knowledge/Study Rationale:** Previous work has documented a relation between sleep apnea and psychopathology, however, limited work has examined this among veterans, a sample of individuals at elevated risk for both sleep apnea and psychopathology. The current study examines the relations between sleep apnea and the likelihood of being diagnosed with a psychological condition among veterans throughout the VA Health Care System.

**Study Impact:** Results indicate a strong association between mood and anxiety disorders and sleep apnea among obese veterans. This highlights the importance of conducting sleep apnea assessments among obese veterans with mood and anxiety disorders (especially MDD and PTSD), as well as conducting anxiety and mood assessments among obese veterans with sleep apnea; such information could aid in the allocation of resources in order to optimize treatments for psychopathology and sleep apnea.

workplace and driving accidents, and elevated psychological symptoms.<sup>7-11</sup> While the associations between OSA and physiological conditions are well established, research is starting to expand our knowledge of the relation between OSA and psychopathology.



## OSA and Mood Disorders

To date the majority of studies investigating the association between OSA and psychopathology have focused on mood disorders, specifically major depressive disorder (MDD). While a few studies have demonstrated a lack of an association between OSA and MDD,<sup>12,13</sup> a majority have pointed, instead, to a strong relation between OSA and MDD.<sup>14,15</sup> For example, community-based epidemiological work has suggested that individuals with MDD are at a five-fold greater risk for having OSA than healthy controls,<sup>16</sup> with between 44.6% and 56% of patients with OSA meeting criteria for MDD.<sup>17,18</sup> Providing further support for the relation between OSA and MDD, intervention studies have demonstrated that treatment of OSA (via continuous positive airway pressure [CPAP] or surgery) results in improvements in depressive symptoms.<sup>19</sup>

## OSA and Anxiety Disorders

Relatively less research has investigated the relation between OSA and anxiety disorders. The work that has been done in this area has demonstrated that 16.7% of military veterans with OSA also had an anxiety disorder.<sup>20</sup> Though the comorbidity between OSA and anxiety is striking, the majority of work conducted on this association has specifically focused on the relation between OSA and posttraumatic stress disorder (PTSD), and to a lesser extent, panic disorder (PD). Indeed, 12.86% of veterans with OSA have a diagnosis of PTSD<sup>20</sup>; and OSA has been associated with nocturnal panic attacks and aggravation of panic symptoms.<sup>21,22</sup> Intervention research further supports this association. Similar to findings with MDD, the treatment of OSA through the use of CPAP reduces symptoms of PTSD and panic.<sup>22-24</sup> Unfortunately, over 50% of veterans with PTSD are non-adherent to CPAP, a significantly lower adherence rate than veterans without PTSD,<sup>25</sup> suggesting that PTSD itself may interfere with successful treatment of OSA.

## OSA and Substance Use Disorders

A relative dearth of research has investigated the relation between OSA and substance use disorders (SUDs), with generally mixed results among existing empirical investigations. Cross-sectional work has suggested a relation between OSA and SUDs, particularly alcohol use disorders.<sup>26</sup> However, epidemiological work among military veterans has found no differences in SUD diagnosis (or alcohol use disorders, specifically) between those with and without OSA.<sup>20</sup> While this finding may have been influenced by differential rates of diagnosis across Veterans Affairs (VA) facilities, further research is clearly needed to better understand the relation between OSA and SUDs.

## Summary

Taken together, previous work has documented a relation between OSA and psychopathology,<sup>27</sup> with the strongest associations being observed for MDD,<sup>16-18</sup> anxiety disorders,<sup>20</sup> and PTSD, specifically.<sup>28</sup> To date, there has been only one study investigating the relation between OSA and psychopathology within the VA Health Care System, which is surprising given the heightened prevalence of OSA among veterans.<sup>2,22</sup> This study was a cross-sectional retrospective review of a centralized VA database between the years 1998 and 2001. The sample

included 4,060,504 military veterans with and without sleep apnea. ICD-9-CM codes were extracted to identify diagnostic status of sleep apnea and psychological conditions. Results from logistic regressions demonstrated that OSA was associated with increased risk for psychological diagnosis including MDD (21.8%), anxiety (16.7%), PTSD (11.9%), and bipolar disorder (3.3%). Two main extensions to this prior work are needed in order to inform our understanding of the relations between OSA and psychopathology among veterans. First, the study by Sharafkhaneh and colleagues<sup>20</sup> did not account for differential diagnosis rates across VA facilities, which may explain the observed associations between OSA and psychological diagnosis. Second, relatively little work has accounted for third factors that may influence the observed associations. For example, it is possible that a common risk factor for both OSA and psychopathology may be driving these relations (e.g., severity of obesity<sup>14</sup>).

## The Role of Severity of Obesity

Obesity is associated with mood, anxiety, and somatoform disorders as well as elevations in psychological distress.<sup>29-31</sup> In addition, obesity is one of the leading risk-factors for OSA.<sup>32</sup> The relation between obesity and OSA is thought to be due to anatomical modifications that result in either upper airway constriction or reduction in lung volume, leading to a loss of caudal traction of the upper airway and pharyngeal collapse.<sup>33</sup> In fact, a one standard deviation increase in body mass index (BMI) has been associated with a 4-fold increase in the prevalence of OSA.<sup>34</sup> Indeed, of those with severe obesity (BMI > 40), the prevalence of OSA ranges between 40% and 90%.<sup>35</sup> Given these associations, there is clearly a need to account for the severity of obesity when assessing relations between OSA and psychological diagnoses.

## Current Study

We sought to replicate and extend the work of Sharafkhaneh<sup>20</sup> by examining the association between OSA and the likelihood of being diagnosed with a psychological condition. We aimed to test these associations among obese veterans across all 140 Veterans Health Administration (VHA) facilities, after accounting statistically for the potentially correlated nature of both patients and diagnostic conventions within each facility as well as severity of obesity (i.e., BMI). We examined these relations among obese veterans only, as we wanted to investigate if the pattern of these relations remained consistent with findings from Sharafkhaneh when examining a population at significant risk for both psychological conditions and OSA.<sup>32</sup> Based on prior research,<sup>20</sup> we hypothesized that individuals with a diagnosis of OSA would be more likely to be diagnosed with (a) mood disorders, and (b) anxiety disorders, but not (c) substance use disorders. In addition, we expected these relations would hold after accounting for severity of obesity (i.e., BMI).

## METHODS

The current study is a retrospective cross-sectional database review of all outpatient medical records collected across each of the 140 VHA facilities for fiscal year (FY) 2010 (October 2009-September 2010). Study procedures were approved by the

VA Palo Alto Health Care System's research office and Stanford University's Human Research Protection program.

## Information Collected

### Data Extraction

Data were obtained from the outpatient VHA Decision Support System (DSS) database. The DSS is a national clinical centralized relational database that includes encounter data from VHA clinical information systems. Patient information, including but not limited to, demographics, diagnoses, procedures, and services provided are updated on a daily basis. In order to construct a database appropriate for the current analyses, SAS v9.2 was used to extract demographic variables, body mass index (BMI), obesity-related physical conditions (ICD-9-CM codes), psychological diagnoses (ICD-9-CM codes), and diagnosis of sleep apnea. A unique identifier (scrambled social security number) was used to obtain complete patient records within the DSS.

### Selection of Participants

Within the DSS we sought to identify veterans at-risk for sleep apnea as a function of obesity. From the 5,576,858 total VHA outpatients seen in FY2010 across the 140 facilities, 64% ( $N = 3,574,765$ ) had at least one record entry of height and weight available to calculate BMI. Previous research using this database has indicated that 90% of within-person repeated measures demonstrated  $< 1$ -inch differences in height and  $< 2\%$  had different values for weight.<sup>36</sup> Based on this work, we included individuals with  $\geq 1$  measurement for height and weight in order to optimize our potential sample size. In the case of multiple values per patient, the largest biologically plausible (i.e., height  $< 84$  inches and weight  $< 700$  pounds), value was used to calculate BMI. The largest weight value was chosen because those fluctuating throughout the year in meeting obesity criteria were considered higher risk than those not meeting criteria at any point during the year. Patients were retained in the final sample ( $n = 2,485,658$ ) if they had a (a) BMI  $\geq 30$ , or (b)  $25 \leq \text{BMI} < 30$  and at least one obesity associated comorbidity (e.g., diabetes, hypertension, hyperlipidemia, heart disease, congestive heart failure, cholelithiasis, osteoarthritis, low back pain, gastroesophageal reflux disease, and obstructive sleep apnea).

## Measures

### Outcome Variables

The primary outcomes of this study included psychological diagnostic status. All diagnoses were made by outpatient health care providers and are based on diagnostic criteria consistent with ICD-9-CM diagnoses. Previous work has vetted the accuracy of diagnoses within VA administrative databases.<sup>37</sup> First, we investigated psychological diagnostic status across broad classifications including (a) mood disorders, (b) anxiety disorders, and (c) substance use disorders (SUDs; see **Table 1** for corresponding ICD-9-CM codes). Second, in the event of a clinically significant finding within a classification, subsidiary analyses were then conducted for each specific disorder (e.g., PTSD, MDD, alcohol use disorder; see **Table 1** for

**Table 1**—ICD-9-CM Diagnostic Codes

| Condition                                                        | ICD-9-CM diagnosis code                                                                                  |
|------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Obesity                                                          | 278.00, 278.01, 259.9, V778                                                                              |
| Sleep Apnea                                                      | 780.57, 786.03, 327.2, 327.20, 327.21, 327.23, 327.29                                                    |
| Diabetes                                                         | 250, 357.2, 362.0, 366.41                                                                                |
| Hypertension                                                     | 401, 402, 403, 404, 405                                                                                  |
| Hyperlipidemia                                                   | 272                                                                                                      |
| Coronary Heart Disease/Ischemic Heart Disease (includes CAD, MI) | 429.1, 429.0, 429.2, 429.9, 410, 411, 412, 413, 414, 440                                                 |
| Congestive heart failure                                         | 402, 404.0, 414.19, 425.4, 428, 429.1, 429.4, 997.1                                                      |
| Cholelithiasis                                                   | 574                                                                                                      |
| Osteoarthritis                                                   | 715                                                                                                      |
| Low back pain                                                    | 722, 724, 846, 847                                                                                       |
| Gastroesophageal reflux disease                                  | 530.11, 530.81, 530.2, 787.1                                                                             |
| Bipolar Disorders                                                | 296.00-296.06, 296.10-296.16, 296.40-296.46, 296.50-296.56, 296.60-296.66, 296.70, 296.80-296.81, 296.89 |
| Major Depressive Disorder                                        | 296.20-296.26, 296.30-296.36                                                                             |
| Panic Disorder                                                   | 300.01                                                                                                   |
| Generalized Anxiety Disorder                                     | 300.02                                                                                                   |
| Phobic Disorders                                                 | 300.20                                                                                                   |
| Agoraphobia                                                      | 200.21, 300.22                                                                                           |
| Social Phobia                                                    | 300.23                                                                                                   |
| Obsessive Compulsive Disorder                                    | 300.30                                                                                                   |
| Posttraumatic Stress Disorder                                    | 309.81                                                                                                   |
| Alcohol Use Disorders                                            | 303.00, 303.90, 305.00-305.03                                                                            |
| Cannabis Use Disorders                                           | 304.30-304.33, 305.20-305.23                                                                             |

Mood Disorder comprised codes for major depressive disorder and bipolar disorders. Anxiety Disorders comprised codes representing panic disorder, generalized anxiety disorder, phobic disorders, agoraphobia, social phobia, obsessive compulsive disorder, and posttraumatic stress disorder. Substance use disorders comprised alcohol and cannabis use disorders.

corresponding ICD-9-CM codes) comprising that classification. All outcomes were binary (0 = absence of diagnosis, 1 = presence of diagnosis).

### Explanatory Variables

To determine patient characteristics associated with psychological diagnostic status, data on patient variables were obtained including: (a) BMI (defined as  $[703 \times \text{weight in pounds}] / \text{height in inches squared}$ ), (b) obesity-related comorbidities (diabetes: ICD-9-CM 250, 357.2, 362.0, 366.41; hypertension (401-405); 8 additional obesity-related comorbidities summarized in **Table 1**), and (c) sleep apnea (see **Table 1** for details). All variables, with the exception of BMI, were binary (0 = absence, 1 = presence).

### Data Analytic Plan

To describe and explore variability in facility-level rates of psychological diagnoses and sleep apnea diagnosis, we calculated the rate of each respective diagnosis (number of patients



with the diagnosis divided by the total number of patients in the facility) in each of the 140 VHA facilities. Next, in order to evaluate the relation between sleep apnea, obesity, and psychological diagnoses (anxiety disorder, mood disorder, substance abuse disorder) we conducted three primary analyses using generalized linear mixed effects models. Independent models were generated for each binary dependent variable (i.e., anxiety disorder, mood disorder, substance use disorder). In the event of a clinically significant finding, subsidiary analyses were conducted for each specific disorder comprising the significant category of psychopathology. Within all models, a random effect for facility was included to account for grouping of patients within VHA facilities. PROC GLIMMIX procedures available within SAS V 9.2 were used to perform estimation and statistical inference for generalized linear mixed effects models.

## RESULTS

### Rates of Diagnosis

In FY2010, PTSD (12.30%) was the most common psychological diagnosis among obese veterans, followed by: MDD (6.40%), SUD (4.19%), bipolar disorder (I and II; 2.63%), generalized anxiety disorder (1.75%), panic disorder (.91%), agoraphobia (.35%), and social anxiety disorder (0.11%). Additionally, 6.68% of obese veterans received a diagnosis of sleep apnea.

### Facility-Level Correlates of Psychological Disorder Diagnosis

In relation to facility-level correlates of psychological diagnosis, the intraclass correlation (ICC) of the intercept-only model indicated that 9.4% of the total variance in mood disorder diagnosis was between facilities rather than explainable by patient factors. Similarly, 10.3% of the total variance in anxiety disorder diagnosis and 20.3% of variance in SUD diagnosis were attributable to differences between facilities.

### Final Model

Results from the final multi-predictor analyses are provided below. Results are discussed in relation to each diagnostic classification (i.e., mood disorders, anxiety disorders, SUDs). Next, in the case of a clinically significant finding, results are presented for each specific disorder comprising the respective classification of psychopathology.

### Mood Disorders

After accounting for the correlated nature of patients within facility, individuals with a diagnosis of sleep apnea were at increased odds of receiving a mood disorder diagnosis (OR = 1.85; CI = 1.80-1.88;  $p < 0.001$ ). Results remained after accounting for BMI, such that after holding BMI constant, a diagnosis of sleep apnea was associated with increased odds of a mood disorder diagnosis (OR = 1.75; CI = 1.62-1.89;  $p < 0.001$ ). In comparison, when holding sleep apnea diagnosis constant, BMI was not associated with the odds of having a mood disorder diagnosis (OR = 1.04; CI = 1.03-1.04). Subsidiary analyses indicated that individuals with a sleep apnea diagnosis

had a 1.4 times ( $p < 0.001$ ) greater likelihood of having a diagnosis of MDD, and a 1.01 times ( $p < 0.001$ ) greater likelihood in having a bipolar disorder diagnosis. Results remained after accounting for BMI such that when holding BMI constant, individuals with sleep apnea had greater odds of having a diagnosis of MDD (OR = 0.59; CI = 0.58-0.60;  $p < 0.001$ ) and to a lesser extent, bipolar disorder (OR = 0.48; CI = 0.46-0.49;  $p < 0.001$ ). Consistent with the primary analysis, results were nonsignificant when holding sleep apnea constant.

### Anxiety Disorders

After accounting for the correlated nature of patients within facility, individuals with a diagnosis of sleep apnea were at greater odds of receiving an anxiety disorder diagnosis (OR = 1.82; CI = 1.77-1.84;  $p < 0.001$ ). Results remained after accounting for BMI, such that after holding BMI constant, a diagnosis of sleep apnea was associated with increased odds of an anxiety disorder diagnosis (OR = 1.71; CI = 1.61-1.82). In comparison, when holding sleep apnea diagnosis constant, BMI was not clinically significantly associated with the odds of having an anxiety disorder diagnosis (OR = 1.02; CI = 1.02-1.02). Subsidiary analyses indicated that individuals with a sleep apnea diagnosis had 1.5-fold greater odds of having a PTSD diagnosis, a 1.3-fold increase in odds of a panic disorder diagnosis, and a 1.2-fold increase in having a diagnosis of both generalized anxiety disorder and agoraphobia (all  $p$ 's  $< 0.001$ ). Results remained after accounting for BMI. Here, when holding BMI constant, individuals with sleep apnea had the greatest odds of having a diagnosis of PTSD (OR = 0.58; CI = 0.58-0.59;  $p < 0.001$ ), followed by panic disorder (OR = 0.55; CI = 0.53-0.56;  $p < 0.001$ ), generalized anxiety disorder (OR = 0.54; CI = 0.53-0.56;  $p < 0.001$ ), and agoraphobia (OR = 0.54; CI = 0.51-0.57;  $p < 0.001$ ). Again, consistent with the primary analysis, results were nonsignificant when holding sleep apnea constant.

### Substance Use Disorders

After accounting for the correlated nature of patients within facility, individuals with a diagnosis of sleep apnea were not at clinically greater odds of receiving a substance use disorder diagnosis (OR = 0.94; CI = 0.92-0.97). Due to the nonsignificant findings, further analyses were not conducted.

## DISCUSSION

Results from this study demonstrate that, among obese veterans in the VA Health Care System, a diagnosis of sleep apnea is associated with increased risk for having a mood or anxiety disorder, but not a substance use disorder. The strongest associations were observed for MDD and PTSD. In addition, results remained after accounting for BMI, such that when holding BMI constant, individuals with sleep apnea had increased odds of both mood and anxiety disorders, specifically MDD, bipolar disorder, PTSD, panic disorder, generalized anxiety disorder, and agoraphobia.

Obese veterans with sleep apnea had clinically significant greater odds of having a mood disorder. This finding is consistent with previous research.<sup>20</sup> In addition, when holding BMI constant, a significant relation emerged for mood disorders. This

indicates that the association between sleep apnea and mood disorders is attributable, at least in part, to factors other than BMI. While mixed results exist for the relation between sleep apnea and MDD, results from specificity analyses supported previous research,<sup>20</sup> indicating an association between sleep apnea and MDD (and to a lesser extent bipolar disorders) as the strongest association within the mood disorders. As results demonstrated that the association was above and beyond BMI, it is unlikely that among this sample BMI was affecting the nature of the relation between sleep apnea and MDD. Two primary theoretical models have been posited to explain this relation. First, some have suggested that the relation between sleep apnea and MDD is explained by depression secondary to a general medication condition.<sup>38</sup> Additional work has suggested that hypoxemia, fragmented sleep, and the daytime consequences of poor sleep (fatigue, excessive daytime sleepiness) have been shown to increase depressed mood.<sup>39</sup> Unfortunately, the cross-sectional nature of the present investigation does not allow for an understanding of the temporal relations of the observed associations.

Obese veterans with sleep apnea also had clinically significant greater odds of having an anxiety disorder. This finding adds to the literature base supporting an association between sleep apnea and anxiety.<sup>20</sup> Further, results remained after accounting for BMI, such that when holding BMI constant, sleep apnea was still associated with anxiety disorders. Consistent with the findings regarding mood disorders, this suggests that the relation between sleep apnea and anxiety is above and beyond the impact of BMI. In terms of specific anxiety disorders, results indicated that sleep apnea had the strongest association with PTSD (followed by panic disorder and generalized anxiety disorder), a consistent finding in the recent literature.<sup>20</sup>

As expected, we did not observe an association between sleep apnea and substance use disorders. This is consistent with previous research conducted among veterans,<sup>20</sup> however, is in contrast to a host of additional work suggesting an association between substance use disorders and sleep apnea.<sup>40,41</sup> This finding may be influenced by data collection methods. This is to say, all data were collected from outpatient VA records. It is possible that individuals with severe substance abuse disorders (a) do not seek treatment within the VA, or (b) are more likely to use inpatient and residential services, which were not included here.

While this study has a number of strengths, including the use of a large sample across the VA health care system, and accounting for differential rates of diagnosis across facilities, there are some limitations which should be considered when interpreting these results. First, the data presented here are cross-sectional in nature and therefore causal or temporal conclusions cannot be made, nor can we identify mechanisms that may be involved in the observed associations. However, as findings have replicated those of Sharafkhaneh and colleagues,<sup>20</sup> future research would now benefit from determining mechanisms that may further explain the differential relations between sleep apnea and mood/anxiety versus substance use disorders. Second, a number of individuals were excluded due to missing height and/or weight assessments. Future research would benefit from more consistent inclusion of these assessments. Third, all data were obtained from a retrospective database review of

ICD-9-CM diagnostic codes. While the reliance on ICD-9-CM diagnostic codes within DSS data introduces the potential for miscoding or misclassification, ICD-9-CM codes have generally been found to be a valid proxy for estimating disorder<sup>42</sup> and have been consistently used within VA research.<sup>20,43</sup> Future research would benefit from the inclusion of longitudinal work using standardized assessments. For example, inclusion of multi-modal assessment would strengthen confidence in diagnoses, especially in relation to sleep apnea. Here, inclusion of a sleep laboratory assessment to confirm sleep apnea status would be beneficial. This form of assessment would also allow for the determination of history and type of sleep apnea, as well as the patients' involvement in treatment for sleep apnea, which our current data cannot provide. Fourth, as our sample was comprised entirely of obese veterans, we may have a restricted range of BMI, which may have affected the observed findings. Finally, the use of an entirely veteran sample may limit the generalizability of the findings. While our prevalence rates of PTSD are consistent with past VA research<sup>20</sup> and VA diagnostic trends,<sup>44</sup> observed rates of MDD were significantly lower than among other VA samples.<sup>20</sup> These findings should be replicated among other VA, as well as non-veteran and female samples.

Despite these limitations, results provide preliminary clinical implications. Namely, findings indicate a strong association between mood and anxiety disorders and sleep apnea among obese veterans. This highlights the importance of conducting sleep apnea assessments among obese veterans with mood and anxiety disorders (especially MDD and PTSD), as well as conducting anxiety and mood assessments among obese veterans with sleep apnea. Such information could aid in the allocation of resources in order to optimize treatments for psychopathology and sleep apnea.

## REFERENCES

1. Vgontzas A, Kales A. Sleep and its disorders. *Annu Rev Med* 1999;50:387-400.
2. Engdahl B, Eberly R, Hurwitz T, Mahowald M, Blake J. Sleep in a community sample of elderly war veterans with and without posttraumatic stress disorder. *Biol Psychiatry* 2000;47:520-5.
3. Ballester E, Badia J, Hernandez L, et al. Evidence of the effectiveness of continuous positive airway pressure in the treatment of sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 1999;159:495-501.
4. Ocasio-Tascon M, Alicea-Colon E, Torres-Palacios A, Rodriguez-Cintrón W. The veteran population: one at high risk for sleep-disordered breathing. *Sleep Breath* 2006;10:70-5.
5. Flemons W, Tsai W. Quality of life consequences of sleep disordered breathing. *J Allergy Clin Immunol* 1997;99:S750-60.
6. Guilleminault C, Partinen M, Querasalva M, Hayes B, Dement W, Ninomurcia G. Determinants of daytime sleepiness in obstructive sleep apnea. *Chest* 1988;94:32-7.
7. Redline S, Strohl K. Recognition and consensus of obstructive sleep apnea hypopnea syndrome. *Otolaryngol Clin North Am* 1999;132:303.
8. Malone S, Liu P, Holloway R, Rutherford R, Xie A, Bradley T. Obstructive sleep apnoea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. *Lancet* 1991;338:1480-4.
9. Partinen M, Guilleminault C. Daytime sleepiness and vascular morbidity at seven-year follow-up in obstructive sleep apnea patients. *Chest* 1988;94:9-24.
10. Quan S, Howard B, Iber C, et al. The Sleep Heart Health Study: design, rationale, and methods. *Sleep* 1997;20:1077-85.
11. Stepnowsky C, Palau J, Zamora T, Ancoli-Israel S, Lored J. Fatigue in sleep apnea: The role of depressive symptoms and self-reported sleep quality. *Sleep Med* 2011;12:832-7.
12. Pillar G, Lavie P. Psychiatric symptoms in sleep apnea syndrome: effects of gender and respiratory disturbance index. *Chest* 1998;114:697-703.

13. Sforza E, de Sant Hilaire Z, Pelissolo, et al. Personality, anxiety and mood traits in patient with sleep-related breathing disorders: effect of reduced daytime alertness. *Sleep Med* 2002;3:139-45.
14. Aloia M, Arnedt J, Smith L, et al. Examining the construct of depression in obstructive sleep apnea syndrome. *Sleep Med* 2005;6:115-21.
15. Peppard P, Szklo-Coxe M, Hla K, et al. Longitudinal association of sleep related breathing disorder and depression. *Arch Intern Med* 2006;166:1709-15.
16. Ohayon M. The effects of breathing-related sleep disorders on mood disturbances in the general population. *J Clin Psychiatry* 2003;64:1195-200.
17. Kales A, Caldwell A, Cadieux R, Vela-Bueno A, Ruch L, Mayes S. Severe obstructive sleep apnea-II: Associated psychopathology and psychosocial consequences. *J Chron Dis* 1985;38:427-34.
18. McCall W, Harding D, O'Donovan C. Correlates of depressive symptoms in patients with obstructive sleep apnea. *J Clin Sleep Med* 2006;2:424-6.
19. Kawahara S, Akashiba T, Akahoshi T, Takasji H. Nasal CPAP improves the quality of life and lessens the depressive symptoms in patients with obstructive sleep apnea syndrome. *Intern Med* 2005;44:422-7.
20. Sharafkhaneh A, Giray N, Richardson P, Young T, Hirshkowitz M. Association of psychiatric disorders and sleep apnea in a large cohort. *Sleep* 2005;23:1405-11.
21. Edlund M, McNamara E, Millman R. Sleep apnea and panic attacks. *Comp Psychiatry* 32:130-2.
22. Takaesu Y, Inoue Y, Komadad Y, Kagimura T, Iimori M. Effects of nasal continuous positive airway pressure on panic disorder comorbid with obstructive sleep apnea syndrome. *Sleep Med* 2012;13:156-60.
23. Krakow B, Lowry C, Germain A, et al. A retrospective study on improvements in nightmares and post-traumatic stress disorder following treatment for co-morbid sleep-disordered breathing. *J Psychosom Res* 2000;49:291-8.
24. Youakim J, Doghranji K, Schutte S. Posttraumatic stress disorder and obstructive sleep apnea syndrome. *Psychosomatics* 1998;39:168-71.
25. El-Solh A, Ayyar L, Akinnusi M, Sachin R, Akinnusi O. Positive airway pressure adherence in veterans with posttraumatic stress disorder. *Sleep* 2010;33:1495-500.
26. Cui R, Tanigawa T, Sakurai S, et al. Associations between alcohol consumption and sleep-disordered breathing among Japanese women. *Respir Med* 2011;105:796-800.
27. Sateia M. Update on sleep and psychiatric disorders. *Chest* 2009;135:1370-9.
28. Maher M, Rego S, Asnis G. Sleep disturbances in patients with posttraumatic stress disorder: Epidemiology, impact and approaches to management. *CNS Drugs* 2006;20:567-90.
29. Baumeister H, Harter M. Mental disorders in patients with obesity in comparison with healthy probands. *Int J Obes* 2007;31:1155-65.
30. Onyike C, Crum R, Lee H, Lyketsos C, Eaton W. Is obesity associated with major depression? Results from the third National Health and Nutrition Examination Survey. *Am J Epidemiology* 2003;158:1139-47.
31. Simon G, Von Korff M, Saunders K, Miglioretti D, et al. Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry* 2006;63:824-30.
32. Young T, Skatrud J, Peppard P. Risk factors for obstructive sleep apnea in adults. *JAMA* 2004;291:2013-6.
33. Schwartz A, Patil S, Laffan A, Polotsky V, Schneider H, Smith P. Obesity and obstructive sleep apnea. Pathogenic mechanisms and therapeutic approaches. *Proc Am Thorac Soc* 2008;5:185-92.
34. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230-5.
35. Frey W, Pilcher J. Obstructive sleep-related breathing disorders in patients evaluated for bariatric surgery. *Obes Surg* 2003;13:676-83.
36. Noel P, Copeland L, Perrin R, et al. VHA corporate data warehouse height and weight data: Opportunities and challenges for health services research. *J Rehab Res Dev* 2010;47:739-50.
37. Szeto H, Coleman R, Gholami P, Hoffman B, Goldstein M. Accuracy of computerized outpatient diagnoses in a veterans affairs general medicine clinic. *Am J Manag Care* 2002;8:37-43.
38. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. (4<sup>th</sup> ed, text revision). Washington DC: American Psychiatric Association, 2000.
39. Pochat M, Ferber C, Lemoine P. Depressive symptomatology and sleep apnea syndrome. *Encephale* 1993;19:601-7.
40. Aldrich M, Brower K, Hall J. Sleep-disordered breathing in alcoholics. *Alcohol Clin Exp Res* 1999;23:134-40.
41. Brower K. Alcohol's effects on sleep in alcoholics. *Alcohol Res Health* 2001;25:110-125.
42. Borzecki A, Wong A, Hickey E, Ash A, Berlowitz D. Identifying hypertension-related comorbidities from administrative data: what's the optimal approach? *Am J Med Qual* 2004;19:201-6.
43. Seal K, Bertenthal D, Miner C, Sen S, Marmer C. Bringing the war back home: Mental health disorders among 103,788 US veterans returning from Iraq and Afghanistan seen at Department Of Veterans Affairs facilities. *Arch Intern Med* 2007;167:476-82.
44. Veterans Health Administration Office of Public Health and Environment Hazards. Analysis of VA health care utilization among U.S. Department of Veterans Affairs, 2009.

## SUBMISSION & CORRESPONDENCE INFORMATION

**Submitted for publication February, 2013**

**Submitted in final revised form July, 2013**

**Accepted for publication July, 2013**

Address correspondence to: Dr. Kimberly Babson, 795 Willow Road (152-MPD), Menlo Park, CA 94025; E-mail: Kimberly.Babson@va.gov

## DISCLOSURE STATEMENT

This was not an industry supported study. This work was supported, in part, by Health Services Research and Development Service funds provided to Drs. Babson and Del Re. The expressed views do not necessarily represent those of the Department of Veterans Affairs. The authors have indicated no financial conflicts of interest.



# Comparing a Combination of Validated Questionnaires and Level III Portable Monitor with Polysomnography to Diagnose and Exclude Sleep Apnea

Effie J. Pereira, B.A.H.; Helen S. Driver, Ph.D.; Steven C. Stewart, Ph.D.; Michael F. Fitzpatrick, M.D., F.A.A.S.M.

Department of Medicine, Queen's University, Kingston, ON, Canada;  
Sleep Disorders Laboratory, Kingston General Hospital, Kingston, ON, Canada

**Study Objectives:** Questionnaires have been validated as screening tools in adult populations at risk for obstructive sleep apnea (OSA). Portable monitors (PM) have gained acceptance for confirmation of OSA in some patients with a high pretest probability of the disorder. We evaluated the combined diagnostic utility of 3 validated questionnaires and a Level III PM in the diagnosis and exclusion of OSA, as compared with in-laboratory polysomnography (PSG) derived apnea hypopnea index (AHI).

**Methods:** Consecutive patients referred to the Sleep Disorders Clinic completed 3 testing components: (1) 3 questionnaires (Berlin, STOP-Bang, and Sleep Apnea Clinical Score [SACS]); (2) Level III at-home PM (MediByte) study; and (3) Level I in-laboratory PSG. The utility of individual questionnaires, the Level III device alone, and the combination of questionnaires and the Level III device were compared with the PSG.

**Results:** One hundred twenty-eight patients participated in the study (84M, 44F), mean  $\pm$  SD age  $50 \pm 12.3$  years, BMI

$31 \pm 6.6$  kg/m<sup>2</sup>. At a PSG threshold AHI = 10, the PM derived respiratory disturbance index (RDI) had a sensitivity and specificity of 79% and 86%, respectively. The sensitivity and specificity for the other screening tools were: Berlin 88%, 25%; STOP-Bang 90%, 25%; SACS 33%, 75%. The sensitivity and specificity at a PSG AHI = 15 were: PM 77%, 95%; Berlin 91%, 28%; STOP-Bang 93%, 28%; SACS 35%, 78%.

**Conclusions:** Questionnaires alone, possibly given a reliance on sleepiness as a symptom, cannot reliably rule out the presence of OSA. Objective physiological measurement is critical for the diagnosis and exclusion of OSA.

**Keywords:** Screening tools, obstructive sleep apnea, questionnaires, portable monitoring, home sleep testing

**Citation:** Pereira EJ; Driver HS; Stewart SC; Fitzpatrick MF. Comparing a combination of validated questionnaires and level III portable monitor with polysomnography to diagnose and exclude sleep apnea. *J Clin Sleep Med* 2013;9(12):1259-1266.

Obstructive sleep apnea (OSA) affects 24% of adult men and 9% adult women in North America.<sup>1-3</sup> A questionnaire-based survey in 2009 by the Public Health Agency of Canada (PHAC) estimated that 22% (5.4 million) of adult Canadians report either being diagnosed with sleep apnea (3%) or are at high risk for OSA (19%).<sup>4</sup> Untreated OSA has been associated with serious long-term medical and neurocognitive complications, including premature death.<sup>5-7</sup>

The recommended diagnostic test for OSA includes an overnight in-laboratory technologist-attended sleep study (Level I polysomnography [PSG]).<sup>8</sup> In addition to monitoring sleep stage by electroencephalography, electro-oculography, and chin electromyography, PSG includes monitoring of electrocardiography, respiratory effort, airflow (nasal pressure and oronasal thermal sensor) and snoring, oxygen saturation, leg movements via electromyography on the anterior tibialis muscles, and body position. This procedure is time- and labor-intensive, and costly. Given the large number of individuals in the population likely to be suffering from OSA, it is not surprising that a great majority remain undiagnosed.<sup>9</sup> It is clear that the challenge of providing a diagnosis of OSA to those suffering from the disorder cannot rely on in-laboratory polysomnography alone, and that simpler and less expensive

## BRIEF SUMMARY

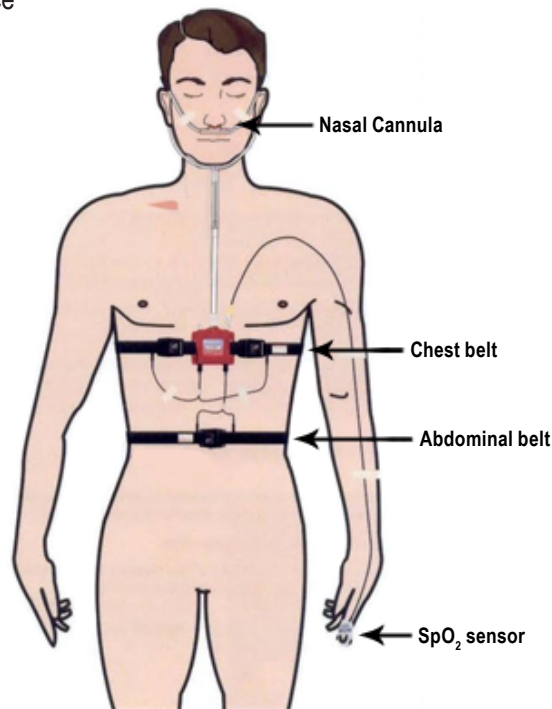
**Current Knowledge/Study Rationale:** Several validated questionnaires are available for screening for obstructive sleep apnea but none has sufficient sensitivity or specificity to mitigate the need for further clinical assessment and testing. Level III portable monitors, while tending to underestimate sleep apnea severity, provide an objective assessment of sleep apnea severity that is often adequate for clinical decision-making. This study evaluated whether one or more previously validated questionnaires, or a combination of these questionnaires with the results from a Level III study, could mitigate the need for polysomnography in patients referred to a sleep disorders clinic.

**Study Impact:** The results demonstrate that the questionnaires were inferior to the Level III study in determining the presence or absence of sleep apnea, and when combined with the information from the Level III study, did not enhance its discriminant ability. These findings strongly suggest that objective physiological monitoring is critically important in the diagnosis and exclusion of obstructive sleep apnea, and cannot be supplanted by questionnaire data.

diagnostic tests are needed. Several such tests for diagnosing OSA, including questionnaires and at-home portable sleep monitors (PM), have been investigated.<sup>10-13</sup>

Several questionnaires have been validated to assist in the stratification of patients as high risk or low risk for OSA based

**Figure 1**—Full set-up for the at-home portable monitoring device



on clinical symptoms and anthropomorphic risk factors.<sup>12-17</sup> Portable monitors that include the recording of oximetry, respiration, heart rate and rhythm, and body position have gained increasing acceptance as a diagnostic tool for sleep apnea. The complexity of physiological measures included range from the equivalent of a full PSG at home without the continuous attendance of a technologist (Level II polysomnography) to overnight pulse oximetry alone (Level IV).<sup>18-20</sup> In a previous report, we demonstrated a high level of agreement for OSA between a Level III portable device and in-laboratory PSG for the diagnosis of OSA, particularly at a threshold AHI of 15 (moderate OSA).<sup>19</sup> Hence, we were curious whether we could harness the screening power of validated questionnaires and the objective physiological measures provided by a Level III device to optimize out-of-laboratory diagnosis of OSA, and potentially obviate the need for PSGs in non-selected referrals to the sleep clinic. We evaluated the combined use of three previously validated questionnaires and a home-based Level III portable monitoring study compared with in-laboratory PSG, for the diagnosis of OSA in consecutive referrals to the sleep clinic.

## METHODS

### Study Participants

Consecutive referrals to the Sleep Disorders Clinic at Kingston General Hospital, Kingston, ON, were invited to participate in the study. All patients were informed that their participation was completely voluntary, and they received nominal compensation for incurred expenses only. The study was approved by Queen's University Health Sciences and the affiliated teaching hospital's research ethics board. Inclusion

criteria included the ability to apply the Level III monitoring equipment without supervision (after brief initial training) and a primary residence within 100 miles of the sleep clinic (for returning the PM equipment). Exclusion criteria included known COPD, congestive heart failure, or uncontrolled asthma.

### Study Design

The study was prospective, involving patients referred to the Kingston General Hospital Sleep Clinic. Study participants were recruited and interviewed by the Research Assistant (EJP), and consenting individuals completed 3 questionnaires: (1) Berlin Questionnaire,<sup>13</sup> (2) Sleep Apnea Clinical Score (SACS),<sup>14</sup> and (3) STOP-Bang.<sup>12</sup> Common features of the questionnaires include physical symptoms of snoring, witnessed episodes of apnea, and hypertension. Based on the Berlin and STOP-Bang questionnaires, respondents were categorized as low or high probability for OSA, while the SACS categorized low (likelihood ratio of  $AHI < 5 = 0.25$ ), intermediate (ratio of  $AHI < 15 = 2.03$ ), or high probability (ratio of  $AHI > 15 = 5.17$ ) of having the disorder.

Upon completion of the questionnaires, participants were shown how to set up the portable monitor. They were asked to wear the Level III portable monitoring device (MediByte; Braebon Medical Corporation, Ottawa, ON) for 2 consecutive nights at home. The first night of recording was used in the analysis, with the second night as a back-up if recording from the first night did not provide sufficient data. The PM device consists of 2 inductance bands for thoracic and abdomen measurement, a nasal cannula pressure transducer airflow signal, finger pulse oximetry, and a body position sensor. The typical at-home set-up is shown in **Figure 1**. Patients were given the option to either manually turn on the device before switching off the lights at night and turn off the device once awake in the morning, or to have the device start and stop automatically at predetermined times.

Following completion of home testing, patients attended the Sleep Disorders Laboratory at Kingston General Hospital for a full overnight PSG. Recordings were conducted using Sandman Elite SD32+ digital sleep recording system (Natus [Embla]; Ottawa, ON), and included 4 EEG channels (C4-A1, C3-A2, O2-A1, F3-A2), 2 EOG channels (ROC-A1, LOC-A2), submental EMG, intercostal (diaphragmatic surface) EMG, bilateral anterior tibialis EMG, ECG, respiratory piezo bands (chest and abdomen), finger pulse oximetry, a vibration snore sensor, nasal pressure airflow, and oronasal thermocouple. PSG recordings were conducted as either a diagnostic study or, in the event of severe OSA, a split-night study. For split-night studies, the initial diagnostic period was followed by the introduction of treatment during the night, and only the diagnostic part of the recording was used for comparison.

Data from the questionnaires and portable monitoring device were manually scored by an experienced scorer (EJP) who was blinded to the results of the in-lab polysomnography. The PSGs were manually scored using standard criteria by registered polysomnographic technologists, who in turn were blinded to results of the questionnaires and the PM device.<sup>20-23</sup> Sixty-four percent of the scored PM data were reviewed by an experienced technologist (HSD) (the concordance between the 2 scorers, EJP and HSD, was 99.2%), and all the PSG studies were reviewed by a sleep specialist. For both PSG and PM data,

**Table 1**—Apnea-hypopnea index (AHI) based on polysomnography (PSG) for questionnaire data for 128 patients

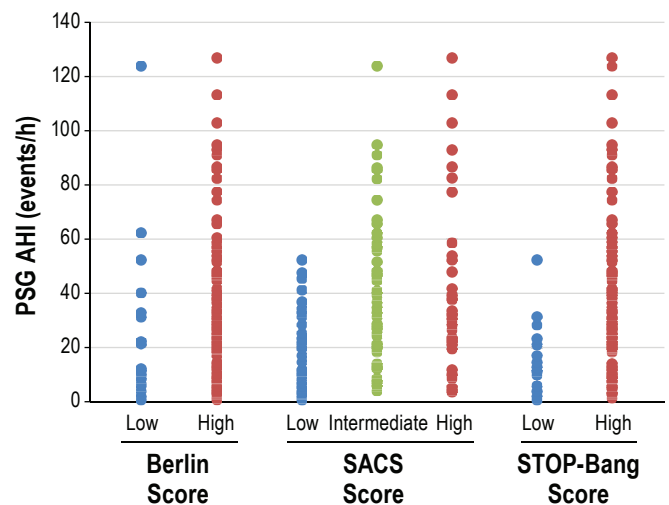
|                                | Mean PSG AHI | SD   |
|--------------------------------|--------------|------|
| <b>Berlin Questionnaire</b>    |              |      |
| Low (n = 19)                   | 24.6         | 29.7 |
| High (n = 109)                 | 34.6         | 27.0 |
| <b>SACS Questionnaire</b>      |              |      |
| Low (n = 36)                   | 18.5         | 15.6 |
| Intermediate (n = 52)          | 38.8         | 27.5 |
| High (n = 40)                  | 38.9         | 31.3 |
| <b>STOP-Bang Questionnaire</b> |              |      |
| Low (n = 17)                   | 14.5         | 13.7 |
| High (n = 111)                 | 36.0         | 28.0 |

apneas were scored as a cessation of airflow  $\geq 50\%$  for  $\geq 10$  sec, and hypopneas were scored as a reduction in pressure-derived airflow of 50% to 90% from baseline for  $\geq 10$  sec followed by  $\geq 3\%$  oxygen desaturation.<sup>20,22</sup> For the PSG, the definition of hypopnea also included  $\geq 50\%$  reduction in pressure-derived airflow amplitude associated with arousal, in the absence of a desaturation  $\geq 3\%$  (alternative criteria).<sup>22</sup> The outcome measure for the PSG data was the apnea-hypopnea index (AHI), which was defined as the number of apneas and hypopneas per hour of sleep, and the outcome measure for the PM data was the respiratory-disturbance index (RDI), defined as the number of apneas and hypopneas per hour of recording time.

## Data Analysis

A dot plot comparison was conducted for the probability rating of sleep apnea based on each questionnaire (Berlin and STOP-Bang as low-high; SACS as low-intermediate-high) as compared to the PSG derived AHI (events/h). Measurement agreement and correlation analysis of the RDI and AHI values based on the PM and PSG, respectively, were obtained and a Bland-Altman plot of agreement was constructed.<sup>24</sup> Multilevel, mixed-effects Poisson regression analysis was used to investigate possible sources of differences between the recording methods, including gender and obesity ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ), while accounting for differences in recording time. The outcome measurement was the observed counts of respiratory events, with the observations nested in individuals—individuals were considered random effects, while recording method, gender, obesity, and their interactions were considered to be fixed effects.

The agreement of each of the 4 screening tools was assessed, compared with PSG, at different threshold AHI threshold values (5, 10, 15, and 30). For each AHI threshold, PM and questionnaire data were rated as true-positive (TP), false-positive (FP), true-negative (TN), or false-negative (FN), allowing for a measure of the sensitivity and specificity for each of the diagnostic screening methods.<sup>25</sup> Receiver operating characteristic (ROC) curves were also plotted to assess the trade-off between false-negatives and false-positives in order to evaluate the area under the curve (AUC), which provides a measure of the diagnostic utility of the screening tools. Likelihood ratios (LR) were calculated to determine the practical significance of the screening measures.

**Figure 2**—Dot plots for each questionnaire rating compared to the polysomnographically (PSG) derived apnea-hypopnea index (AHI) for 128 patients

To evaluate the effectiveness of a combination of questionnaires and PM, 2 separate analyses were conducted: (i) the presence of OSA was defined as scoring high on  $\geq 2$  questionnaires along with a PM RDI  $\geq 10$  events/h, and (ii) the absence of OSA was defined as scoring low on  $\geq 2$  questionnaires along with a PM RDI  $< 10$  events/h. ROC curves, AUC, and LR were also calculated for the combination of screening measures by severity groups based on AHI thresholds 5, 10, 15, and 30 to assess for significance. A stepwise multiple linear regression was used to model the relationship between the various screening tools and the PSG AHI in order to determine the best combination of questionnaires and PM at each AHI threshold value; the PSG AHI was used as the dependent variable, and the questionnaire scores (Berlin and STOP-Bang scored as 0, 1, and SACS scored as 0, 1, 2) and RDI based on the PM as the independent variables.

## RESULTS

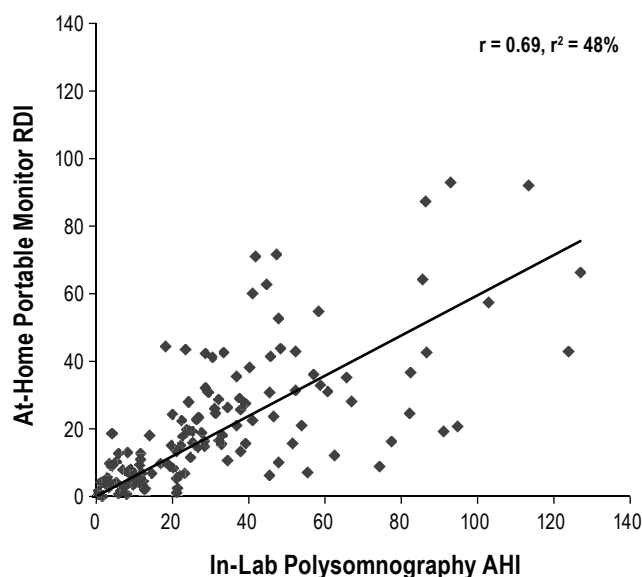
One hundred twenty-eight patients were recruited into the study (84 M, 44 F; mean  $\pm$  SD: age  $50 \pm 12.3$  years, BMI  $31 \pm 6.6 \text{ kg/m}^2$ , neck circumference  $41 \pm 4.4 \text{ cm}$ ). On average, patients reported that they snored (3-5 times a week), felt fatigued (3-4 times a week), and had witnessed apnea (1-2 times a month). The PM data for 13 participants (10%) were analyzed from the second night rather than the first due to unusable or lost data resulting in insufficient ( $< 2$  h) recording time on the first night.

The mean AHI, derived from PSG, for the OSA risk categories determined by the questionnaires is shown in **Table 1**. Dot plots for each questionnaire compared to the PSG AHI are displayed in **Figure 2**; they illustrate a significant overlap and a wide range in the AHI between the different categorical probability ratings for each questionnaire. The mean PSG AHI for each of the questionnaire ratings are provided in **Table 1**.

Objectively recorded data for the PM and PSG are summarized in **Table 2**. The total recording time on PM was longer by

**Table 2**—Portable monitoring (PM) screening measures and polysomnography (PSG) data for 128 patients

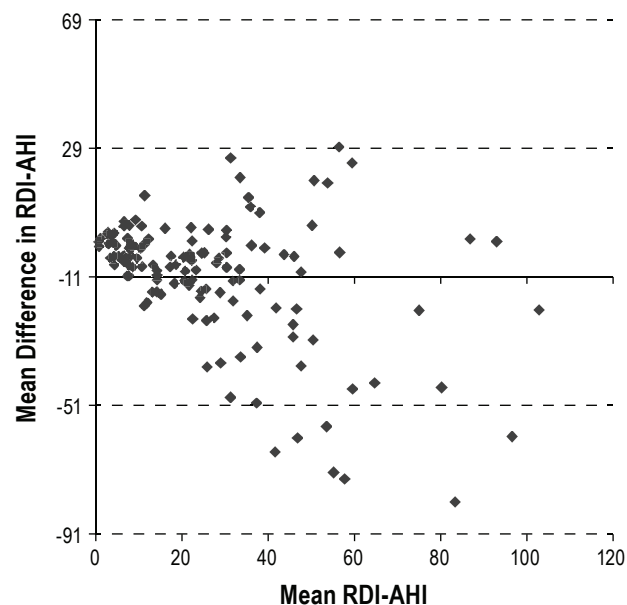
|                                                                                        | PM           | PSG           | p-value |
|----------------------------------------------------------------------------------------|--------------|---------------|---------|
| Respiratory-Disturbance Index (RDI) (events/h) / Apnea-Hypopnea Index (AHI) (events/h) | 21.9 ± 19.9  | 33.1 ± 27.5   | < 0.001 |
| Total Recording Time (TRT) (min)                                                       | 438.4 ± 89.0 | 404.8 ± 103.0 | 0.003   |
| Total Sleep Time (TST) (min)                                                           | N/A          | 304.4 ± 106.6 | —       |

**Figure 3**—Correlation plot for the PM respiratory-disturbance index (RDI) and the PSG apnea-hypopnea index (AHI) for 128 patients

approximately 30 min ( $438 \pm 89$  min) as compared to the PSG ( $405 \pm 103$  min). There was a positive correlation between the PM derived RDI and PSG derived AHI ( $r = 0.69$ ,  $r^2 = 48\%$ ; **Figure 3**).

The Bland-Altman plot (**Figure 4**) shows the mean difference between the PM-RDI and the PSG-AHI, with an under-reporting by the PM of  $-11.2 \pm 19.2$  events/h, with limits of agreement ( $\pm 2$  SD) at  $+29$  and  $-51$ . The mean percent difference between the 2 measures was  $-40\%$ , with limits of agreement at  $+90\%$  and  $-170\%$ . The PM-based RDI under-reported the rate of respiratory events for women and non-obese men by 27% (women:  $p < 0.001$ , IRR = 0.73, 95% CI: 0.70, 0.75; non-obese men:  $p < 0.001$ , IRR = 0.73, 95% CI: 0.70, 0.76), and for obese men by 38% ( $p < 0.001$ , IRR = 0.62, 95% CI: 0.60, 0.64).

The sensitivity and specificity of each screening tool at various PSG-AHI thresholds is displayed in **Table 3**. For a threshold AHI of 10 events/h, the Berlin, SACS, and STOP-Bang questionnaires had sensitivities of 88%, 33%, and 90%, respectively, and specificity of 25%, 75%, and 25%, respectively. The positive (PPV) and negative (NPV) predictive values were 81%-83% and 24%-41%, respectively. In comparison, the PM had a sensitivity of 79% and specificity of 86% (PPV 95%, NPV 53%). Based on the ROC curve for an AHI threshold of

**Figure 4**—Bland-Altman plot examining the difference between the PM RDI and PSG AHI against the mean of the RDI and AHI for 128 patients

The solid line delimits the mean difference (-11), and the dotted lines represent the limits of agreement  $\pm 2$  SDs (29 and -51).

10 (**Figure 5**), the AUC for the PM at 0.82 was higher than that for any of the 3 questionnaires ( $\leq 0.58$ ). For a PSG-derived AHI diagnostic threshold of 15 events/h (moderate OSA), the sensitivity and specificity for each measure was: Berlin 91%, 28%; SACS 35%, 78%; STOP-Bang 93%, 28%; PM 77%, 95% (**Table 3**).

Sensitivity and specificity were also calculated for a combination of the screening tools (presence of OSA = high risk for  $\geq 2$  questionnaires and PM RDI  $\geq 10$  events/h; absence of OSA = low risk for  $\geq 2$  questionnaires and PM RDI  $< 10$  events/h) and are provided in **Table 3**. For an AHI threshold of 10 events/h, the combination of questionnaires and PM had a sensitivity of 71% and specificity of 89% for the presence of OSA (PPV = 96%, NPV = 46%), and a sensitivity of 94% and specificity of 25% for excluding OSA (PPV = 82%, NPV = 54%). The AUC for the combination of questionnaires and portable monitor was 0.80 (**Figure 6**) for the presence of OSA and 0.59 (**Figure 7**) for the absence of OSA. Positive and negative likelihood ratios for each individual screening tool along with the combination of the questionnaires and portable monitor are displayed in **Table 4**.

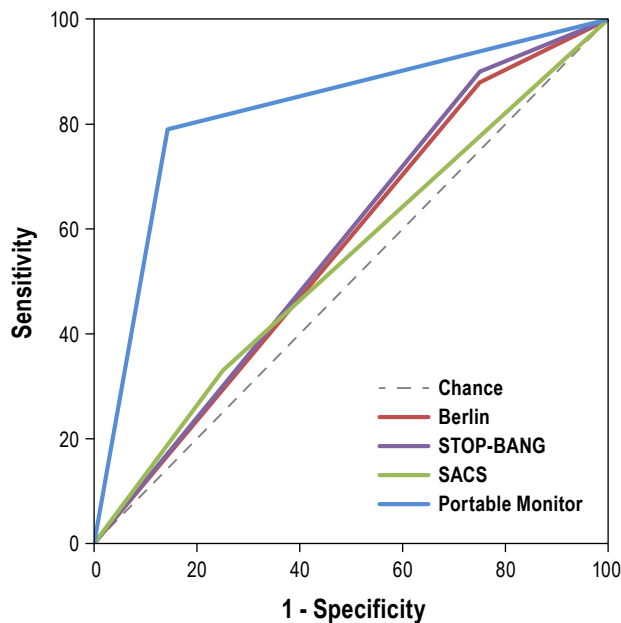
Stepwise multiple regression analyses were used to examine the relationship between the PSG AHI and the various screening tools. A model using all 3 questionnaires and the portable monitor produced an  $R^2 = 0.487$ ,  $F_{4,123} = 29.22$ ,  $p < 0.001$ . Of all 4 screening tools, the portable monitor was the only screening device with a statistically significant regression coefficient,  $b = 0.91$ ,  $\beta = 0.658$ ,  $p < 0.001$ . In fact, none of the questionnaires contributed significantly to the multiple regression model,  $p$ -values  $> 0.35$ ; combined, the questionnaires accounted for less than 1% of the variation of the regression.



**Table 3**—Sensitivity (Sen; %), specificity (Spec; %), positive predictive value (PPV; %), and negative predictive value (NPV; %) for the individual and combination of questionnaires and portable monitoring device based on the polysomnography (PSG) apnea-hypopnea index (AHI) threshold points for 128 patients

|                                                       | AHI ≥ 5 (N = 116) |      |      |      | AHI ≥ 10 (N = 100) |      |      |      | AHI ≥ 15 (N = 88) |      |      |      | AHI ≥ 30 (N = 56) |      |      |      |
|-------------------------------------------------------|-------------------|------|------|------|--------------------|------|------|------|-------------------|------|------|------|-------------------|------|------|------|
|                                                       | Sen               | Spec | PPV  | NPV  | Sen                | Spec | PPV  | NPV  | Sen               | Spec | PPV  | NPV  | Sen               | Spec | PPV  | NPV  |
| <b>Individual</b>                                     |                   |      |      |      |                    |      |      |      |                   |      |      |      |                   |      |      |      |
| Berlin                                                | 86                | 25   | 91.7 | 15.8 | 88                 | 25   | 80.7 | 36.8 | 91                | 28   | 73.4 | 57.9 | 89                | 18   | 45.9 | 68.4 |
| SACS                                                  | 33                | 83   | 95.0 | 11.4 | 33                 | 75   | 82.5 | 23.9 | 35                | 78   | 77.5 | 35.2 | 36                | 72   | 50.0 | 59.1 |
| STOP-Bang                                             | 90                | 42   | 93.7 | 29.4 | 90                 | 25   | 81.1 | 41.2 | 93                | 28   | 73.9 | 64.7 | 96                | 21   | 48.6 | 88.2 |
| Portable Monitor                                      | 87                | 67   | 96.2 | 34.8 | 79                 | 86   | 95.1 | 53.3 | 77                | 95   | 97.1 | 65.5 | 50                | 93   | 84.8 | 70.5 |
| <b>Combination</b>                                    |                   |      |      |      |                    |      |      |      |                   |      |      |      |                   |      |      |      |
| Presence of OSA:<br>high ≥ 2 Qs &<br>PM ≥ 10 events/h | 63                | 92   | 98.6 | 20.3 | 71                 | 89   | 95.9 | 46.3 | 77                | 85   | 91.9 | 63.0 | 82                | 61   | 62.2 | 81.5 |
| Absence of OSA:<br>low ≥ 2 Qs &<br>PM < 10 events/h   | 93                | 42   | 93.9 | 38.5 | 94                 | 25   | 81.7 | 53.8 | 97                | 25   | 73.9 | 76.9 | 100               | 18   | 48.7 | 100  |

**Figure 5**—Receiver operating characteristic (ROC) curves for each of the three questionnaires and the PM at a PSG AHI cutoff of 10 events/h



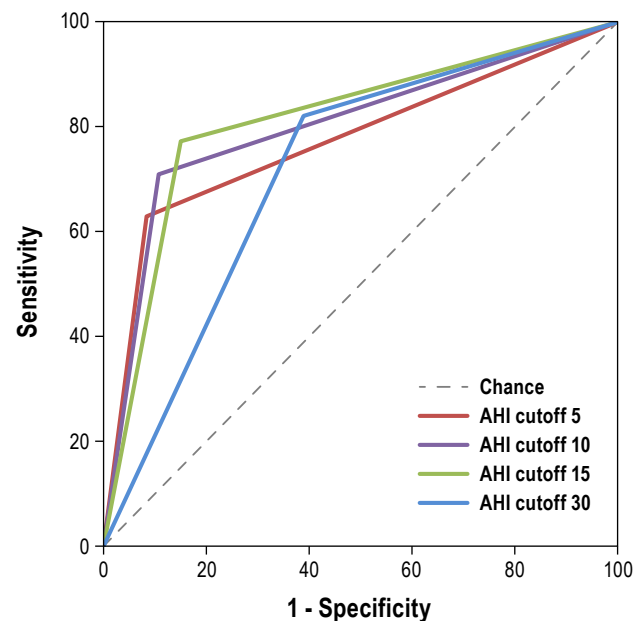
Area under the curve (AUC): Berlin = 0.565; SACS = 0.540; STOP-Bang = 0.575; PM = 0.824.

Our analysis is estimated to have had 90% power ( $1 - \beta$  error probability) of detecting a Cohen's effect size  $f^2$  of 0.1 (medium effect size), given a sample size of 128 patients and  $\alpha$  error probability of 0.05.

## DISCUSSION

This study demonstrated that in a consecutive series of patients referred to a hospital-based sleep clinic, questionnaires that have been previously well-validated in other populations were not accurate in determining the presence or

**Figure 6**—Receiver operating characteristic (ROC) curves for identifying OSA at various PSG AHI cutoffs based on the combination of ≥ 2 high-scoring questionnaires and a PM RDI ≥ 10 events/h

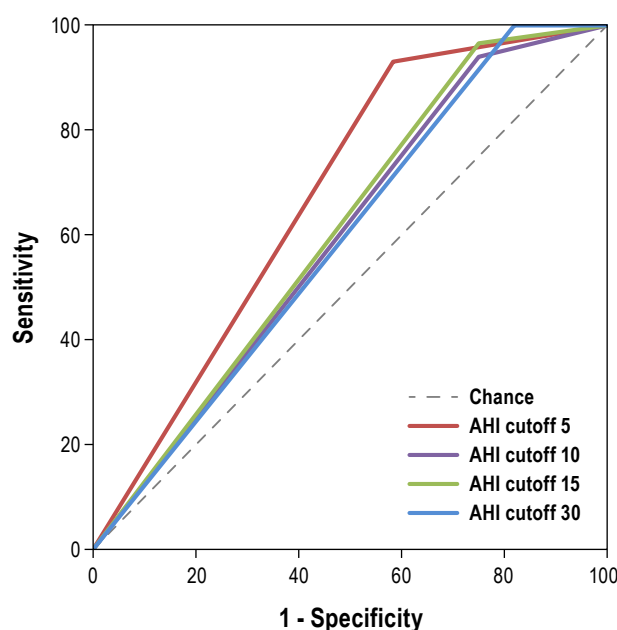


Area under the curve (AUC): AHI 5 = 0.773; AHI 10 = 0.801; AHI 15 = 0.811; AHI 30 = 0.716.

absence of OSA. None of the three questionnaires used had adequate sensitivity (proportion of patients with OSA who screen positive) and specificity (proportion without OSA who screen negative) to render them sufficiently reliable in a clinical setting to rule in or to rule out OSA—two of the questionnaires (Berlin and STOP-Bang) were found to have a high sensitivity for OSA but low specificity, while the SACS had higher specificity but low sensitivity for OSA. Overall, the portable monitor was found to perform significantly better in the identification as well as the exclusion of OSA than any

**Table 4**—Likelihood ratio positive (LR+) and likelihood ratio negative (LR-) for the individual and combination of questionnaires and portable monitoring device based on the polysomnography (PSG) apnea-hypopnea index (AHI) threshold points for 128 patients

|                                                                 | AHI $\geq 5$ (N = 116) |     | AHI $\geq 10$ (N = 100) |     | AHI $\geq 15$ (N = 88) |     | AHI $\geq 30$ (N = 56) |     |
|-----------------------------------------------------------------|------------------------|-----|-------------------------|-----|------------------------|-----|------------------------|-----|
|                                                                 | LR+                    | LR- | LR+                     | LR- | LR+                    | LR- | LR+                    | LR- |
| <b>Individual</b>                                               |                        |     |                         |     |                        |     |                        |     |
| Berlin                                                          | 1.1                    | 0.6 | 1.2                     | 0.5 | 1.3                    | 0.3 | 1.1                    | 0.6 |
| SACS                                                            | 2.0                    | 0.8 | 1.3                     | 0.9 | 1.6                    | 0.8 | 1.3                    | 0.9 |
| STOP-Bang                                                       | 1.5                    | 0.2 | 1.2                     | 0.4 | 1.3                    | 0.2 | 1.2                    | 0.2 |
| Portable Monitor                                                | 2.6                    | 0.2 | 5.5                     | 0.2 | 15.5                   | 0.2 | 7.2                    | 0.5 |
| <b>Combination</b>                                              |                        |     |                         |     |                        |     |                        |     |
| Presence of OSA:<br>high $\geq 2$ Qs &<br>PM $\geq 10$ events/h | 7.6                    | 0.4 | 6.6                     | 0.3 | 5.2                    | 0.3 | 2.1                    | 0.3 |
| Absence of OSA:<br>low $\geq 2$ Qs &<br>PM $< 10$ events/h      | 1.6                    | 0.2 | 1.3                     | 0.2 | 1.3                    | 0.1 | 1.2                    | 0.0 |

**Figure 7**—Receiver operating characteristic (ROC) curves for **excluding OSA** at various PSG AHI cutoffs based on the combination of  $\geq 2$  low-scoring questionnaires and a PM RDI  $< 10$  events/h

Area under the curve (AUC): AHI 5 = 0.674; AHI 10 = 0.595; AHI 15 = 0.608; AHI 30 = 0.590.

of the individual questionnaires or combination of questionnaires with portable monitoring.

The accuracy and reliability of questionnaires used to screen for OSA appears to vary depending on the patient population studied and the diagnostic AHI threshold used.<sup>14,16,27</sup> In contrast to the present study of patients referred to a sleep clinic, in community screening the Berlin questionnaire had a high sensitivity (85%) and specificity (95%) at an AHI threshold of 5 events/h.<sup>27</sup> However, Netzer reported that when the AHI threshold for the diagnosis of OSA was raised to 15 events/h, sensitivity levels were reduced to 54%.<sup>13</sup> A decrease in specificity with increasing AHI was mirrored in the STOP-Bang

questionnaire, where specificity dropped from 56% to 43% with a change in AHI from 5 to 15 events/h, respectively.<sup>12</sup> Compared to questionnaire responses, portable monitors have shown a consistently high degree of sensitivity and specificity even at higher AHI thresholds with a bias of underreporting the OSA severity.<sup>19,28,29</sup> Our findings also showed a low negative predictive value for the portable monitor, both with and without the addition of the questionnaires, suggesting that the monitor may be able to establish a diagnosis of OSA with a high degree of certainty, but that it may not be able to conclusively rule out OSA. Guidelines from the Canadian Thoracic Society and Canadian Sleep Society have suggested that portable monitors be used in patients with a high pretest probability of OSA, and previous research has shown these devices to have a moderately high negative predictive value (71% to 100%) for patients with a high likelihood of having the disorder.<sup>20,29,31</sup> It had been our belief that the NPV of this objective diagnostic method would be increased with the addition of subjective questionnaires, but it appears that the portable monitor alone still outperformed the combination of the portable monitor and questionnaires in negative predictive value.

A potential contributing factor to the underreporting of OSA severity with the PM as compared with PSG is that the denominator is total sleep time for PSG and total recording time for the PM. By recalculating the PSG scored apnea and hypopnea index in the present study using total recording time rather than total sleep time as the denominator, there was an improvement in the performance of the PM such that the PM underreported the rate of respiratory events for women by only 5% ( $p = 0.001$ , IRR = 0.95, 95% CI: 0.91, 0.98), for obese men by 14% ( $p < 0.001$ , IRR = 0.86, 95% CI: 0.83, 0.88), and did not underestimate the AHI for non-obese men ( $p = 0.42$ , IRR = 0.99, 95% CI: 0.95, 1.02).

Different scoring rules for hypopneas have been found to affect the resultant AHI.<sup>32</sup> The highest AHI was based on 1999 ("Chicago") scoring criteria (hypopnea based on  $\geq 50\%$  decrease in airflow or  $< 50\%$  reduction in airflow associated with a 3% oxygen desaturation and/or arousal), followed by the alternative criteria that was used in this study ( $\geq 50\%$  pressure-derived airflow reduction and  $\geq 3\%$  desaturation or arousal) and lowest using recommended criteria for hypopneas ( $\geq 30\%$

pressure-derived airflow reduction and  $\geq 4\%$  desaturation).<sup>21,22</sup> The authors suggested that the AHI cutoff of 5 events/h using AASM recommended criteria is approximately equivalent to an AHI of 15 events/h using the 1999 hypopnea definition and 10 events/h using the alternative AASM definition.<sup>32</sup> Scoring of hypopneas in our study was based on the AASM alternative criteria, but without the option of identifying arousals on the PM, which contributed to underreporting by this screening tool.

We have demonstrated that objective data from a portable monitor was superior to questionnaires in the identification and exclusion of OSA. Recently the Centers for Medicare and Medicaid Services and a position statement from the Canadian Thoracic Society and Canadian Sleep Society have endorsed the use of portable monitors as a means of providing sufficient evidence for the diagnosis of OSA, under defined circumstances and with specific patient populations.<sup>31</sup> These rulings, and the results of the current study, support the judicious use of portable monitors in the diagnosis of OSA, in association with appropriate clinical assessment.

Many patients with OSA are only minimally symptomatic. In the Sleep Heart Health Study, the average Epworth Sleepiness Scale (ESS) score of patients with severe OSA (AHI > 30) was within normal limits.<sup>32</sup> Indeed two-thirds of patients with severe OSA had an ESS within normal limits, while 21% with an AHI < 5 (normal) had an ESS score that was higher than normal.<sup>32</sup> Hence, the reliance of sleepiness as a symptom to determine the presence or absence of OSA is fraught with uncertainty. In addition, although obesity increases the propensity to OSA for simple anatomical reasons, many patients with OSA are not overweight.<sup>33</sup> It is our belief that the overlap in symptom profile and anthropomorphic features between individuals with OSA and those without underpins the weak discriminant ability of screening questionnaires for OSA (as demonstrated in the current study), even when anthropomorphic data is added. A critical factor here is the current uncertainty as to whether asymptomatic or minimally symptomatic OSA carries similar cardiovascular consequences to symptomatic patients with the OSA syndrome; if not, then the detection of clinically important OSA—based on symptoms—may prove to be adequate.<sup>34</sup>

It is important to acknowledge the limitations of the current study. Although our patient group was recruited from a series of consecutive referrals to the sleep clinic, our data did not come from a community-based random sample, and as such, our results may not be generalizable to the general population. Further research would be required to determine whether or not the sensitivity and specificity of the portable monitor would be maintained when testing more heterogeneous groups. It is also possible that our findings are specific to the particular brand of portable monitor used for the study (MediByte; Braebon Medical Corporation) and may not be as generalizable to other Level III devices. As such, it would be important to test patients without a high pretest probability of OSA on other portable monitors to further validate our findings. In addition, although the portable monitor and PSG had a moderately positive correlation for AHI, there were significant outliers in our data—which could potentially relate to the presence of other sleep disorders, particularly movement disorders and periodic limb movements. There are potential advantages of the use of at-home PM studies over in-lab PSG; for example, home sleep

testing may better represent habitual sleep habits, including posture, as compared to in-laboratory testing, where patients are likely to spend more time sleeping supine.<sup>35</sup> In-laboratory testing may also underrepresent habitual alcohol consumption at night, because of the need to drive to the sleep laboratory. Hence, the systematic underestimation of the RDI by PM, that does not include instrumentation for measurement of the sleep-wake state, may be balanced to some extent by the less than perfect reflection of true sleep-related habits provided by the “gold standard” PSG.

In conclusion, the current study demonstrated poor discriminant ability for OSA among previously validated questionnaires, and emphasizes the need for objective physiological monitoring in the identification and exclusion of OSA. Furthermore, in the current study, the use of questionnaire data did not further enhance the diagnostic utility of a Level III portable monitor for the diagnosis and exclusion of OSA.

## REFERENCES

1. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* 1997;20:705-6.
2. Young T, Palta M, Dempsey J, Skatrud J, Wever S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Eng J Med* 1993;328:1230-15.
3. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002;165:1217-39.
4. Sleep Apnea Rapid Response Survey, The Canadian Community Health Survey. Statistics Canada. Centre for Chronic Disease Prevention and Control, Public Health Agency of Canada, 2009. <http://www.statcan.gc.ca/daily-quotidien/091208/dq091208d-eng.htm>.
5. Lee W, Nagubadi S, Kryger MH, Mokheles B. Epidemiology of obstructive sleep apnea: a population-based perspective. *Expert Rev Respir Med* 2008;2:349-64.
6. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2001;163:19-25.
7. Turkington PM, Sircar M, Allgar V, Elliott MW. Relationship between obstructive sleep apnoea, driving simulator performance, and risk of road traffic accidents. *Thorax* 2001;56:800-5.
8. Fleetham J, Ayas N, Bradley D, et al. Canadian Thoracic Society 2011 guideline update: Diagnosis and treatment of sleep disordered breathing. *Can Respir J* 2011;18:25-47.
9. Pack AI. Advances in sleep-disordered breathing. *Am J Respir Crit Care Med* 2006;173:7-15.
10. Banno K, Kryger MH. Factors limiting access to services for sleep apnea patients. *Sleep Med Rev* 2004;8:253-5.
11. Pang KP, Terris DJ. Screening for obstructive sleep apnea: An evidence-based analysis. *Am J Otolaryngol* 2006;27:112-8.
12. Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology* 2008;108:812-21.
13. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 1999;131:485-91.
14. Flemons WW, Whitelaw WA, Brant R, Remmers JE. Likelihood ratios for a sleep apnea clinical prediction rule. *Am J Respir Crit Care Med* 1994;150:1279-85.
15. Harding SM. Prediction formulae for sleep-disordered breathing. *Curr Opin Pulm Med* 2001;7:381-5.
16. Ahmadi N, Chung SA, Gibbs A, Shapiro CM. The Berlin questionnaire for sleep apnea in a sleep clinic population: relationship to polysomnographic measurement of respiratory disturbance. *Sleep Breath* 2008;12:39-45.
17. Chung F, Yegneswaran B, Liao P, et al. Validation of the Berlin questionnaire and American Society of Anesthesiologists checklist as screening tools for obstructive sleep apnea in surgical patients. *Anesthesiology* 2008;108:822-30.
18. Collop NA, Anderson WM, Boehlecke B, et al. Clinical guideline for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. *J Clin Sleep Med* 2007;3:737-47.

19. Driver HS, Pereira EJ, Bjerring K, et al. Validation of the MediByte® type 3 portable monitor compared with polysomnography for screening of obstructive sleep apnea. *Can Respir J* 2011;18:137-43.
20. Collop NA, Tracy SL, Kapur V, et al. Obstructive sleep apnea devices for out-of-center (OOC) testing: technology evaluation. *J Clin Sleep Med* 2011;7:531-48.
21. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999;22:667-89.
22. Iber C, Ancoli-Israel S, Chesson A, Quan SF for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications, 1<sup>st</sup> ed. Westchester, IL: American Academy of Sleep Medicine, 2007.
23. Rechtschaffen A, Kales A. Manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Bethesda, MD: National Institutes of Health (NIH Publ. No. 204), 1968.
24. Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. *Statistician* 1983;32:307-17.
25. Flemons WW, Littner MR. Measuring agreement between diagnostic devices. *Chest* 2003;124:1535-42.
26. Gafsou B, Marsac L, Fournier JL, Beloucif S, Baillard C. Validation of the STOP-Bang questionnaire as screening tools for obstructive sleep apnea in patients scheduled for bariatric surgery. *Eur J Anesthesiology* 2010;27:13.
27. Sharma SK, Vasudev C, Sinha S, Banga A, Pandey RM, Handa KK. Validation of the modified Berlin questionnaire to identify patients at risk for the obstructive sleep apnoea syndrome. *Indian J Med Res* 2006;124:281-90.
28. Ng SS, Chan TO, To KW, et al. Validation of Embletta portable diagnostic system for identifying patients with suspected obstructive sleep apnoea syndrome (OSAS). *Respirology* 2010;15:336-42.
29. Verse T, Pirsig W, Junge-Hulsing B. Validation of the POLY-MESAM seven-channel ambulatory recording unit. *Chest* 2000;117:1613-8.
30. Blackman A, McGregor C, Dales R, et al. Canadian Sleep Society / Canadian Thoracic Society position paper on the use of portable monitoring for the diagnosis of obstructive sleep apnea/ hypopnea in adults. *Can Respir J* 2010;17:229-32.
31. Gottlieb DJ, Whitney CW, Bonekat WH, et al. Relation of sleepiness to respiratory disturbance index: the Sleep Heart Health Study. *Am J Respir Crit Care Med* 1999;159:502-7.
32. Ruehland WR, Rochford PD, O'Donoghue FJ, Pierce RJ, Singh P, Thornton AT. The new AASM criteria for scoring hypopneas: Impact on the apnea hypopnea index. *Sleep* 2009;32:150-7.
33. White DP. Pathogenesis of obstructive and central sleep apnea. *Am J Respir Crit Care Med* 2005;172:1363-70.
34. Comondore VR, Cheema R, Fox J, et al. The impact of CPAP on cardiovascular biomarkers in minimally symptomatic patients with obstructive sleep apnea: a pilot feasibility randomized crossover trial. *Lung* 2009;187:17-22.
35. Iber C, Redline S, Kaplan Gilpin AM, et al. Polysomnography performed in the unattended home versus the attended laboratory setting - Sleep Heart Health Study methodology. *Sleep* 2004;27:536-40.

## ACKNOWLEDGMENTS

The authors thank BRAEBON Medical Corporation for providing MediByte units for the purposes of the study, and the technologists at Kingston General Hospital Sleep Disorders Laboratory for assistance.

## SUBMISSION & CORRESPONDENCE INFORMATION

**Submitted for publication January, 2013**

**Submitted in final revised form July, 2013**

**Accepted for publication July, 2013**

Address correspondence to: Michael F. Fitzpatrick, 102 Stuart Street, Queen's University, Division of Respiratory & Critical Care Medicine, Kingston, ON, K7L 3N6; Tel: (613) 548-2379; Fax: (613) 549-1459; E-mail: mike.fitzpatrick@queensu.ca

## DISCLOSURE STATEMENT

This was not an industry supported study. This research was conducted at the Sleep Disorders Laboratory, Kingston General Hospital, Kingston, ON, and has been funded by the Innovation Fund, the Ontario Ministry of Health and the William M. Spear Foundation from Queen's University. The authors have indicated no financial conflicts of interest. There was no off-label or investigational use.



## Excessive Daytime Sleepiness is Associated with Longer Culprit Lesion and Adverse Outcomes in Patients with Coronary Artery Disease

Chi-Hang Lee, M.D.<sup>1,2</sup>; Wai-Yee Ng, B.Sc.<sup>3</sup>; William Hau, Ph.D.<sup>2</sup>; Hee-Hwa Ho, MB.BS.<sup>4</sup>; Bee-Choo Tai, Ph.D.<sup>2,3</sup>; Mark Y. Chan, MB.BS.<sup>1,2</sup>; A. Mark Richards, M.D., Ph.D.<sup>1,2</sup>; Huay-Cheem Tan, MB.BS.<sup>1</sup>

<sup>1</sup>Department of Cardiology, National University Heart Centre, Singapore; <sup>2</sup>Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore; <sup>3</sup>Saw Swee Hock School of Public Health, National University of Singapore, National University Health System, Singapore; <sup>4</sup>Department of Cardiology, Tan Tock Seng Hospital, Singapore

**Study Objectives:** We assessed whether excessive daytime sleepiness was associated with coronary plaque phenotype and subsequent adverse cardiovascular events.

**Methods:** Prospective cohort study. Intravascular ultrasound (IVUS) examination of the culprit coronary stenosis was performed. The Epworth Sleepiness Scale (ESS) questionnaire was administered, and the patients were divided into 2 groups—(1) sleeper and (2) less sleepy—based on the ESS score. Adverse cardiovascular outcomes were defined as cardiac death, myocardial infarction, stroke, unplanned revascularization, or heart failure admission.

**Results:** One hundred seventeen patients undergoing urgent or non-urgent coronary angiography were recruited. Compared with the less sleepy group (ESS ≤ 10, n = 87), the sleeper group (ESS > 10, n = 30) had higher serum levels of total cholesterol and of low-density-lipoprotein cholesterol (p < 0.05 for both). The IVUS examinations indicated coronary stenoses were longer in the sleeper group than in the less

sleepy group (p = 0.011). The cumulative incidence of adverse cardiovascular events at 16-month follow-up was higher in the sleeper than the less sleepy group (12.5% versus 6.9%, p = 0.03). Cox regression analysis adjusting for age and smoking showed increased hazard of adverse cardiovascular events in sleeper group as compared to less sleepy group (HR = 3.44, 95% CI 1.01-11.72).

**Conclusion:** In patients presenting with coronary artery disease, excessive daytime sleepiness based on ESS > 10 was associated with longer culprit lesions and future adverse cardiovascular events.

**Keywords:** Sleepiness, coronary artery disease, intravascular ultrasound, outcomes

**Citation:** Lee CH; Ng WY; Hau W; Ho HH; Tai BC; Chan MY; Richards AM; Tan HC. Excessive daytime sleepiness is associated with longer culprit lesion and adverse outcomes in patients with coronary artery disease. *J Clin Sleep Med* 2013;9(12):1267-1272.

### BRIEF SUMMARY

**Current Knowledge/Study Rationale:** There are limited data on the prognostic implication of excessive daytime sleepiness in patients with coronary artery disease. In this prospective observational study, we determined the association between excessive daytime sleepiness (ESS > 10), coronary plaque phenotype, and subsequent adverse cardiovascular outcomes.

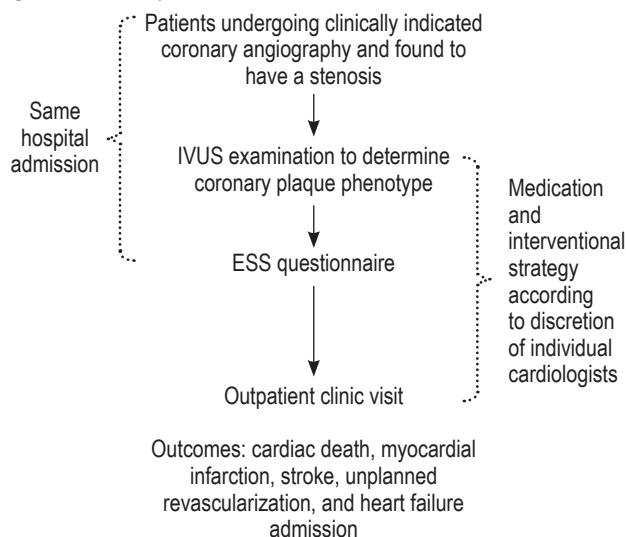
**Study Impact:** The patients were classified into sleeper and less sleepy groups according to their baseline ESS scores (> 10 versus ≤ 10), and we found that the sleeper group was associated with longer lesion lengths. After adjusting for potential confounders, the hazard of adverse cardiovascular events was 3-fold in the sleeper as compared to the less sleepy groups.

Excessive daytime sleepiness is a prevalent health problem that affects 18% of the general population in the United States.<sup>1</sup> This condition increases the risk of road traffic accidents and causes serious economic consequences due to poor work performance.<sup>2,3</sup> In the clinical context, excessive daytime sleepiness is a common but nonspecific symptom that accompanies neurological, psychiatric, kidney, and cardiopulmonary disorders. Excessive sleepiness is also a side effect of certain medications and a consequence of insufficient sleep duration. The pathological consequences of excessive daytime sleepiness are complex and remain incompletely understood. Previous epidemiological studies have found that elderly people who reported having frequent excessive daytime sleepiness had a higher risk of subsequent adverse cardiac and cerebrovascular events than those who reported never having excessive daytime sleepiness. This pattern remained evident even after adjusting for confounding factors.<sup>4-7</sup>

In most of these previous studies,<sup>4-6</sup> excessive daytime sleepiness was self-reported as a qualitative variable, and some degree of misclassification or overlapping with fatigue could not be excluded. The Epworth Sleepiness Scale (ESS) was developed more than 20 years ago to gain a more objective measure of

sleepiness, and is now the most widely used measure of excessive daytime sleepiness.<sup>8</sup> The ESS is frequently administered to patients to estimate their risk of obstructive sleep apnea and thus guide decisions regarding overnight polysomnography. The questionnaire also enables the evaluation of responses to treatment for patients diagnosed with obstructive sleep apnea. The ESS has been validated against in-laboratory polysomnography on community individuals in general practice settings.<sup>9,10</sup>



**Figure 1—Study flowchart**

However, it remains unknown whether excessive daytime sleepiness, as measured by high ESS scores, can predict adverse outcomes in patients with cardiovascular conditions. In this prospective observational study, we determined the association between excessive daytime sleepiness (ESS > 10), coronary plaque phenotype, and subsequent adverse cardiovascular outcomes in a cohort of patients presenting with symptomatic coronary artery disease. Specifically, we targeted patients in whom a stenosis was detected by coronary angiography so that an intravascular ultrasound (IVUS) catheter could be used to assess their plaque phenotype.

## METHODS

### Study Design and Patients

This prospective study was conducted at 2 tertiary centers (the National University Heart Centre and Tan Tock Seng Hospital) in Singapore between February 2011 and March 2013. The participants were selected from among patients aged 21 years and older who were undergoing coronary angiography for stable coronary artery disease or acute coronary syndromes, including myocardial infarction with or without ST-segment elevation, and had been found to have  $\geq 1$  significant ( $> 50\%$  visual estimation) de novo stenosis in a native coronary artery. Criteria for exclusion from the study included known obstructive sleep apnea (based on previous polysomnography), cardiogenic shock (systolic blood pressure  $< 90$  mm Hg), chronic renal failure with dialysis treatment, previous treatment of the target vessel, being a foreign patient who could not attend the outpatient clinic for follow-up, or inability to provide informed consent. The angiographic exclusion criteria were angiographically visible residual thrombus despite thrombus aspiration or thrombectomy, a heavily calcified lesion, a tortuous vessel, chronic total occlusion, a significant left main lesion, or a distal lesion that was too small to accommodate an IVUS catheter. The National Healthcare Group Domain Specific Review Board approved

the study's research protocol (reference: C/2010/00341), and informed consent was obtained from the subjects. Recruited patients underwent IVUS examination of the culprit lesions. During the same hospital admission, the ESS questionnaire was administered to the patients to determine their degree of excessive daytime sleepiness. A flow chart of this study is shown in **Figure 1**.

### Intravascular Ultrasound Examination

Consenting patients were formally enrolled into the study after identification of the culprit lesion by coronary angiography. A guiding catheter was used to selectively cannulate the ostium of the target coronary artery. Immediately after advancing the guidewire, but before balloon predilation, a 20-MHz, 3.5-French phased-array IVUS catheter (Eagle Eye Gold, Volcano Corp., Rancho Cordova, CA, USA) was inserted into the mid- to distal segment of the target coronary artery. The IVUS catheter was automatically pulled back to the ostium of the guiding catheter using a motorized pull-back device at a speed of 0.5 mm/s (R-100 Pullback Device, Volcano Corp.). All images were recorded in digital format on a DVD for subsequent offline quantitative analysis by 2 investigators (CHL, WH), who were blinded to the ESS data. Any discrepancies between the analyses of the 2 investigators were resolved by consensus.

### Intravascular Ultrasound Analyses

Conventional gray-scale quantitative IVUS analyses were performed according to the IVUS expert consensus document.<sup>11</sup> The following parameters were measured in the culprit lesions in the target coronary artery: (i) external elastic membrane area ( $\text{mm}^2$ ), (ii) minimal lumen diameter (mm), (iii) minimal lumen area ( $\text{mm}^2$ ), and (iv) plaque burden ( $\text{mm}^2$ ).

The virtual-histology-IVUS images were analyzed according to the published guidelines to determine the tissue composition of the lesions.<sup>11</sup> The 4 virtual-histology-IVUS plaque components were color-coded and displayed on the virtual-histology-IVUS console, with fibrous tissue shown in green, fibro-fatty tissue in light-green, dense calcium in white, and the necrotic core in red. Volumetric measurements using Simpson's rule were performed over the entire region of interest by tracing the external elastic membrane and the lumen border. The volumetric values for each of the 4 plaque components and the culprit lesion plaque volume were then automatically calculated using VIAS 3.0 offline analysis software (Volcano Corp.).<sup>12</sup> Thin-cap fibroatheroma was defined as a plaque with  $> 10\%$  confluent necrotic core, with  $> 30$  degrees of the necrotic core abutting the lumen in  $\geq 3$  consecutive frames.<sup>13</sup>

### Epworth Sleepiness Scale and Data Collection

Patients presenting with ST-elevation myocardial infarction were treated with urgent percutaneous coronary intervention. These patients were not only under time pressure, but were in pain and distress, and may have been medicated with opiates that affect decision-making. To standardize the protocol, the ESS questionnaire was administered to all patients after the angiography and intervention procedures. The recruited patients were approached by a dedicated research assistant and

asked to complete the ESS questionnaire in the cardiac ward. The ESS is a validated questionnaire that asks subjects to rate their likelihood of falling asleep in several common situations. In this questionnaire, patients rate their perceived likelihood of falling asleep in 8 everyday situations, and their answers give a score of between 0 and 24 points. Based on the ESS score, the recruited patients who completed the ESS were divided into either (1) the sleeper group ( $ESS > 10$ ) or (2) the less sleepy group ( $ESS \leq 10$ ).

The following demographic and clinical information were collected prospectively: ethnicity, gender, age, height, weight, body mass index, clinical presentation (such as ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, unstable angina, or stable angina), cardiovascular risk factors (such as smoking, diabetes mellitus, hypertension, hyperlipidemia, or family history of premature coronary artery disease), previous cardiovascular conditions (such as previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass surgery), laboratory investigation results, and detailed angiographic findings.

### Clinical Follow-Up

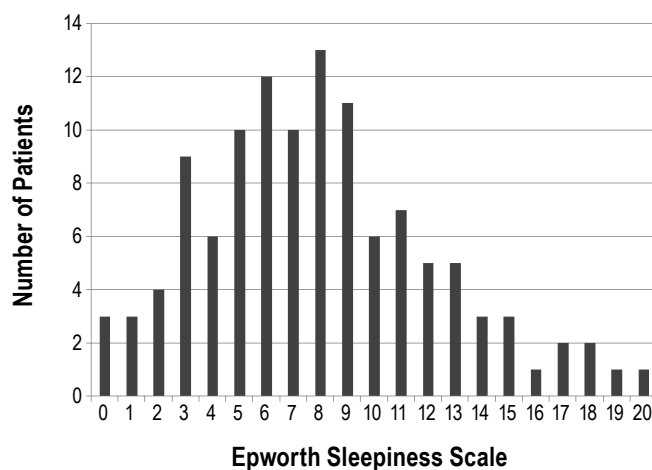
After hospital discharge, all of the recruited patients made regular visits to an outpatient clinic. The physicians conducting the outpatient clinic were not part of the study team, and were blinded to the results of the ESS data. The cardiovascular outcome data were collected by a dedicated research assistant via telephone calls or clinic chart reviews, and all of the information was entered prospectively. Adverse cardiovascular events were defined as cardiac death, myocardial infarction, stroke, unplanned revascularization, or heart failure requiring hospitalization. To verify the events, source documents of the patients who had experienced adverse cardiovascular events were reviewed by the investigators.

### Statistical Analysis

We summarized the distribution of the continuous normally distributed clinical and laboratory procedural characteristics of the patients using the mean and standard deviation. The differences in the means of the sleeper and less sleepy groups were compared using an independent sample *t* test. For skewed continuous variables, the median and interquartile ranges were used to summarize the distribution, with comparisons between groups made with the Mann-Whitney test. For categorical variables, the Fisher exact test was used to compare differences in proportions.

For the analysis of time-to-adverse events, each participant's survival time was calculated from the date of index admission to the date when an adverse event first occurred. Patients who did not have an adverse event were censored on February 15, 2013. The Kaplan-Meier cumulative incidence curves were plotted and the difference in cumulative incidence of adverse event rates between the sleeper and less sleepy groups was compared using the log rank test. The Cox proportional hazards regression was then applied to adjust for body mass index and smoking in the time-to-adverse-event analysis. All of the statistical analyses were carried out using STATA version 10.0 (StataCorp LP, College Station, TX, USA), assuming a two-sided test with a 5% level of significance.

**Figure 2**—Distribution of Epworth Sleepiness Scale score



## RESULTS

### Baseline Demographic and Clinical Characteristics

Among the 118 recruited patients, 117 completed the ESS and formed the study population. The distribution of the ESS scores is shown in **Figure 2**. The median ESS score was 8 (interquartile range 5-11). The baseline demographic and clinical characteristics of the sleeper ( $ESS > 10$ ,  $n = 30$ ) and less sleepy ( $ESS \leq 10$ ,  $n = 87$ ) groups are shown in **Table 1**. The majority of the study patients were male. About 30% of the recruited patients had diabetes mellitus, but none had undergone previous coronary artery bypass grafting. The most common clinical presentations were ST-elevation myocardial infarction ( $n = 45$ ) and non-ST-elevation myocardial infarction ( $n = 38$ ). Compared with the less sleepy group, the sleeper group had higher serum levels of total and low-density-lipoprotein cholesterol. There were no significant differences between the sleeper and less sleepy groups with respect to full blood count, renal biochemistry, peak creatine kinase levels (for patients with acute myocardial infarction), or glycosylated hemoglobin levels (for patients with diabetes mellitus) (data not shown).

### Angiographic and Intravascular Ultrasound Characteristics

There were no significant differences between the sleeper and less sleepy groups in the angiographic complexity of their coronary artery disease. Likewise, the incidence of multivessel coronary artery disease, location of culprit lesions, and left ventricular ejection fraction were similar between the 2 groups. The incidence of treatment for coronary artery disease using drug-eluting stents was similar between the sleeper and less sleepy groups. The IVUS findings are shown in **Table 2**. The culprit lesions were longer and had more fibrofatty tissues in the sleeper than in the less sleepy group. Slightly more than half of the culprit lesions were thin-cap fibroatheroma, with no difference in lesion type between the sleeper and less sleepy groups (data not shown).

**Adverse Cardiovascular Events**

The median follow-up duration was 16 months (95% CI: 14.4-17.6). Complete data on follow-up were available for

all 117 patients. Among the 30 patients in the sleepier group, 9 patients developed 10 adverse cardiovascular events. These included 2 cardiac deaths, 2 myocardial infarctions, 4 target

**Table 1—Patient demographics and clinical characteristics**

| Characteristics                                  | Overall (n = 117) | Sleepier (n = 30) | Less Sleepy (n = 87) | p value |
|--------------------------------------------------|-------------------|-------------------|----------------------|---------|
| Age in years, mean (SD)                          | 54.2 (8.6)        | 54.6 (9.3)        | 53.9 (8.5)           | 0.722   |
| Male sex, n (%)                                  | 103 (88.0)        | 26 (86.7)         | 77 (88.5)            | 0.753   |
| Body mass index in kg/m <sup>2</sup> , mean (SD) | 25.6 (4.0)        | 25.8 (4.3)        | 25.6 (4.0)           | 0.780   |
| Cardiovascular risk factors, n (%)               |                   |                   |                      |         |
| Smoking                                          | 54 (46.2)         | 12 (40.0)         | 42 (48.3)            | 0.526   |
| Hypertension                                     | 62 (53.0)         | 18 (60.0)         | 44 (50.6)            | 0.404   |
| Diabetes mellitus                                | 35 (29.9)         | 12 (40.0)         | 23 (26.4)            | 0.173   |
| Hyperlipidemia                                   | 91 (77.8)         | 25 (83.3)         | 66 (75.9)            | 0.456   |
| Family history of coronary artery disease        | 34 (29.1)         | 6 (20.0)          | 28 (32.2)            | 0.249   |
| Concomitant conditions, n (%)                    |                   |                   |                      |         |
| Previous myocardial infarction                   | 22 (18.8)         | 6 (20.0)          | 16 (18.4)            | 0.794   |
| Previous percutaneous coronary intervention      | 24 (20.5)         | 7 (23.3)          | 17 (19.5)            | 0.794   |
| Chronic renal failure                            | 3 (2.6)           | 1 (3.3)           | 2 (2.3)              | 1.000   |
| Previous stroke                                  | 3 (2.6)           | 0 (0.0)           | 3 (3.5)              | 0.569   |
| Ethnicity, n (%)                                 |                   |                   |                      |         |
| Chinese                                          | 75 (64.1)         | 20 (66.7)         | 55 (63.2)            | 0.382   |
| Malay                                            | 23 (19.7)         | 8 (26.7)          | 15 (17.2)            |         |
| Indian                                           | 16 (13.7)         | 2 (6.7)           | 14 (16.1)            |         |
| Other                                            | 3 (2.6)           | 0 (0.0)           | 3 (3.5)              |         |
| Clinical presentations, n (%)                    |                   |                   |                      | 0.900   |
| ST-elevation myocardial infarction               | 45 (38.5)         | 10 (33.3)         | 35 (40.2)            |         |
| Non-ST-elevation myocardial infarction           | 38 (32.5)         | 10 (33.3)         | 28 (32.2)            |         |
| Unstable angina                                  | 4 (3.4)           | 1 (3.3)           | 3 (3.5)              |         |
| Stable angina                                    | 30 (25.6)         | 9 (30.0)          | 21 (24.1)            |         |
| Serum cholesterol, mm/dL                         |                   |                   |                      |         |
| Total cholesterol                                | 4.9 (1.1)         | 5.4 (1.0)         | 4.8 (1.1)            | 0.009   |
| Triglyceride                                     | 1.5 (1.1-2.2)     | 1.5 (1.1-2.2)     | 1.5 (1.1-2.1)        | 0.818   |
| Low-density-lipoprotein cholesterol              | 3.1 (1.0)         | 3.4 (0.9)         | 3.0 (0.9)            | 0.020   |

**Table 2—Intravascular ultrasound findings**

| Characteristics                            | Overall (n = 117)   | Sleepier (n = 30)   | Less Sleepy (n = 87) | p value |
|--------------------------------------------|---------------------|---------------------|----------------------|---------|
| Proximal reference                         |                     |                     |                      |         |
| External elastic membrane, mm <sup>2</sup> | 16.4 (5.7)          | 16.3 (5.2)          | 16.4 (5.9)           | 0.917   |
| Lumen area, mm <sup>2</sup>                | 8.4 (3.7)           | 8.3 (3.0)           | 8.5 (4.0)            | 0.873   |
| Plaque burden, mm <sup>2</sup>             | 48.8 (12.9)         | 48.3 (13.1)         | 48.8 (12.9)          | 0.867   |
| Minimal lumen area site                    |                     |                     |                      |         |
| External elastic membrane, mm <sup>2</sup> | 15.4 (6.2)          | 16.0 (5.8)          | 15.2 (6.5)           | 0.535   |
| Lumen area, mm <sup>2</sup>                | 2.60 (2.30-3.30)    | 2.60 (2.40-3.40)    | 2.50 (2.30-3.20)     | 0.382   |
| Lumen diameter, mm                         | 1.70 (1.60-1.80)    | 1.60 (1.60-1.80)    | 1.70 (1.60-1.80)     | 0.915   |
| Plaque burden, mm <sup>2</sup>             | 76.2 (10.7)         | 77.6 (10.9)         | 75.8 (10.6)          | 0.440   |
| Distal reference                           |                     |                     |                      |         |
| External elastic membrane, mm <sup>2</sup> | 11.9 (7.7-17.2)     | 11.7 (7.6-15.6)     | 12.3 (7.9-17.4)      | 0.616   |
| Lumen area, mm <sup>2</sup>                | 5.9 (4.5-7.5)       | 5.9 (4.9-6.7)       | 6.0 (4.4-7.8)        | 0.927   |
| Plaque burden, mm <sup>2</sup>             | 47.8 (13.5)         | 46.7 (14.9)         | 48.2 (13.1)          | 0.595   |
| Lesion length, mm                          | 25.5 (18.2-38.1)    | 35.5 (23.0-42.6)    | 23.6 (17.2-35.2)     | 0.011   |
| Plaque volume, mm <sup>3</sup>             | 221.5 (135.7-354.6) | 243.6 (155.1-362.1) | 191.8 (123.1-316.8)  | 0.156   |
| Tissue composition                         |                     |                     |                      |         |
| Fibrous tissue, mm <sup>3</sup>            | 76.3 (47.2-139.8)   | 108.1 (65.0-142.3)  | 67.2 (43.9-134.1)    | 0.058   |
| Fibrofatty tissue, mm <sup>3</sup>         | 15.8 (8.6-26.2)     | 18.2 (14.0-27.2)    | 13.5 (6.9-24.8)      | 0.016   |
| Necrotic core, mm <sup>3</sup>             | 30.2 (16.1-64.2)    | 38.2 (27.9-67.9)    | 27.1 (14.4-57.3)     | 0.141   |
| Dense calcium, mm <sup>3</sup>             | 11.0 (3.6-19.0)     | 13.1 (8.2-23.8)     | 9.9 (2.8-18.0)       | 0.096   |

vessel revascularizations, 1 stroke, and 1 heart failure admission. Among the 87 patients in the less sleepy group, 2 patients developed 4 adverse cardiovascular events. These included 2 myocardial infarctions and 2 target vessel revascularizations. The Kaplan-Meier cumulative incidence of adverse cardiovascular events is shown in **Figure 3**. The event rate at 16 months was higher in the sleeper than the less sleepy group (12.5% versus 6.9%,  $p = 0.03$ ). The Cox regression analysis adjusting for age and smoking showed increased hazard of adverse event in sleeper group as compared to less sleepy group (HR = 3.44, 95% CI 1.01-11.72).

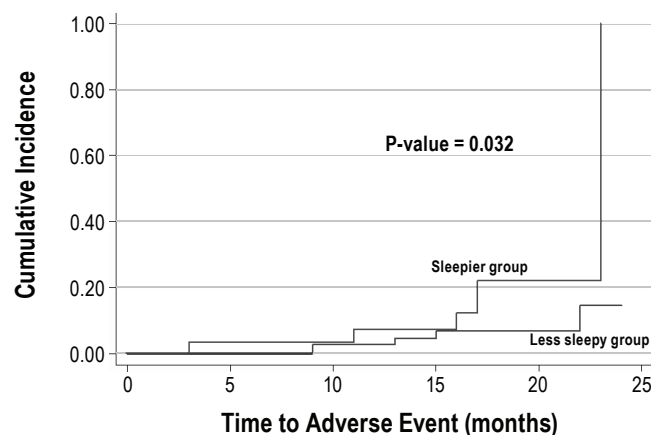
## DISCUSSION

We report the relationships between excessive daytime sleepiness, coronary plaque phenotype, and incidence of subsequent adverse cardiovascular events in a cohort of patients presenting with symptomatic coronary artery disease. A total of 117 patients underwent an IVUS interrogation of coronary stenosis and answered the ESS questionnaire during the same hospital admission. All of the recruited patients were treated according to standard clinical practice. The patients were classified into sleeper and less sleepy groups according to their baseline ESS scores ( $> 10$  versus  $\leq 10$ ), and we found that the sleeper group was associated with longer lesion lengths. After adjusting for potential confounders, the hazard of adverse cardiovascular events was 3-fold in the sleeper as compared to the less sleepy groups.

The evaluation of excessive daytime sleepiness is often performed in the diagnosis of obstructive sleep apnea. In the general population, the association between excessive daytime sleepiness and obstructive sleep apnea has been clearly demonstrated. However, in patients with cardiovascular disorders, this association has proven to be weak.<sup>14-16</sup> A possible factor that could explain in this discrepancy is the presence of “transient” obstructive sleep apnea in patients presenting with acute cardiovascular conditions. In addition, myocardial ischemia or heart failure alone can lead to fatigue and excessive daytime sleepiness, even in the absence of obstructive sleep apnea.<sup>17,18</sup> Cardiac medications such as  $\beta$ -blockers can also lead to excessive daytime sleepiness. As a result of these entangled relationships, the true prognostic implication of excessive daytime sleepiness in patients presenting with cardiovascular disease has been inadvertently neglected.

Excessive daytime sleepiness is among the most frequent sleep complaints in the general population, yet the data on the effects of excessive daytime sleepiness on subsequent cardiovascular outcomes are limited. In the 1990s, the Cardiovascular Health Study reported that excessive daytime sleep was associated with subsequent cardiovascular mortality in otherwise healthy elderly women.<sup>6</sup> A recent French study of over 7,000 healthy community-dwelling elderly subjects found that frequent excessive daytime sleepiness was independently associated with future vascular events, stroke, and cardiovascular mortality.<sup>4,5</sup> However, in the aforementioned studies, objective tools such as ESS were not used, and subjects with pre-existing cardiovascular disorders were excluded.<sup>4,6</sup> The aim of this study was thus to extend these results by exploring the association between baseline excessive daytime sleepiness and subsequent

**Figure 3**—Kaplan-Meier cumulative incidence curves



|                   | Number at risk |    |    |    |    |   |
|-------------------|----------------|----|----|----|----|---|
| Less sleepy group | 87             | 79 | 62 | 43 | 18 | 0 |
| Sleeper group     | 30             | 25 | 24 | 20 | 5  | 0 |

cardiovascular outcomes in patients presenting with coronary artery disease. We hypothesized that excessive daytime sleepiness is associated with complex coronary plaque phenotype and future adverse cardiovascular events.

Based on a median ESS scores ( $> 10$  versus  $\leq 10$ ), we divided the patients into sleeper and less sleepy groups. The incidence of adverse cardiovascular events in the sleeper group was significantly higher than in the less sleepy group in our cohort of middle-aged (mean age 54) and predominantly male patients (88%), even after adjustment for potential confounding factors. The exact mechanisms for this association remain incompletely understood, but heightened sympathetic drive and elevated levels of circulating catecholamines, oxidative stress, endothelial dysfunction, and systemic inflammation have been reported as possible mechanisms.<sup>19-22</sup> Our findings corroborate those of previous studies on healthy elderly people. If our observations are verified in larger-scale studies, then conducting the ESS questionnaire could be a simple and inexpensive tool to risk-stratify patients presenting with symptomatic coronary artery disease.

One of the strengths of this study is its use of IVUS rather than coronary angiography to assess the coronary plaque phenotype. As an intrinsic attempt to preserve the lumen and perfusion, the coronary arteries often develop outward remodeling in response to accumulations of atherosclerotic plaques. Thus, the early phase of coronary atherosclerosis is often undetectable by conventional coronary angiography, which depicts the lumen but not the vessel wall. In contrast, IVUS is an intracoronary imaging technique that provides a three-dimensional tomographic view, and is superior to conventional coronary angiography in the assessment of coronary plaque phenotype.<sup>23</sup>

This study included patients with relatively severe forms of coronary artery disease, as is evidenced by the high proportion of patients with diabetes mellitus (30%), previous myocardial infarction (19%), and previous percutaneous coronary intervention (21%). In addition, 70% of the patients presented with acute myocardial infarction (ST- or non-ST- elevation myocardial



infarction). Rather than resulting from selection bias, this pattern represents the current trend in the management of coronary artery disease. Recent data have suggested that in patients with stable angina, routine invasive management with angiography and percutaneous coronary intervention does not provide any incremental benefit compared with medical therapy alone.<sup>24</sup> Thus, in recent years there have been fewer patients with stable angina undergoing coronary angiography, and acute myocardial infarction represents the most common indication of coronary angiography in our institutions.

This study has several limitations. This is a preliminary and hypothesis generating study due to the relatively small study size. The ESS scores were based on the patients' own responses, which were not validated by other family members. However, the number of family members differed among the patients, and the responses given by different family members may vary, which would make such validation unreliable. Also, Singapore is a multiethnic country, and its population includes Chinese, Malays, and Indians. The ESS was administered in English, and although English is the common language among people living in Singapore, it is not the mother tongue for many of them. The levels of language proficiency may have influenced the participants' understanding and interpretation of the ESS questionnaire. Further, the physicians conducting the outpatient clinic visits were blinded to the ESS data, but had access to the IVUS images. Although IVUS is a highly specialized interventional field that most outpatient physicians do not refer to, we could not exclude the possibility that some outpatient physicians may have modified their treatment after reviewing the IVUS images, and that such shifts in treatment may have ultimately changed the natural history of the patients' conditions. Finally, all of the patients in this study underwent clinically indicated coronary angiography, because angiography is a prerequisite for IVUS examinations. Thus, it may not be possible to extrapolate the results of this study to patients who are treated in more conservative ways.

In conclusion, we found that excessive daytime sleepiness (ESS > 10) was associated with longer lesion length in patients presenting symptomatic coronary artery disease. As of the completion of a 16-month follow-up period, the sleepier group was associated with significantly more adverse cardiovascular events than the less sleepy group. In the future, large-scale studies are warranted that target the association between the ESS and a diagnosis of obstructive sleep apnea, and the effects of coronary artery disease treatment on the degree of excessive daytime sleepiness.

## REFERENCES

- Swanson LM, Arnedt JT, Rosekind MR, et al. Sleep disorders and work performance: findings from the 2008 National Sleep Foundation Sleep in America poll. *J Sleep Res* 2011;20:487-94.
- Hillman DR, Murphy AS, Pezzullo L. The economic cost of sleep disorders. *Sleep* 2006;29:299-305.
- Connor J, Norton R, Ameratunga S, et al. Driver sleepiness and risk of serious injury to car occupants: population-based case control study. *BMJ* 2002;324:1125.
- Blachier M, Dauvilliers Y, Jaussent I, et al. Excessive daytime sleepiness and vascular events: the Three City Study. *Ann Neurol* 2012;71:661-7.
- Empana JP, Dauvilliers Y, Dartigues JF, et al. Excessive daytime sleepiness is an independent risk indicator for cardiovascular mortality in community-dwelling elderly: the Three City Study. *Stroke* 2009;40:1219-24.

- Newman AB, Spiekerman CF, Enright P, et al. Daytime sleepiness predicts mortality and cardiovascular disease in older adults. The Cardiovascular Health Study Research Group. *J Am Geriatr Soc* 2000;48:115-23.
- Boden-Albala B, Roberts ET, Bazil C, et al. Daytime sleepiness and risk of stroke and vascular disease: findings from the Northern Manhattan Study (NOMAS). *Circ Cardiovasc Qual Outcomes* 2012;5:500-7.
- Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991;14:540-5.
- Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea: the Epworth Sleepiness Scale. *Chest* 1993;103:30-6.
- Lee SJ, Kang HW, Lee LH. The relationship between the Epworth Sleepiness Scale and polysomnographic parameters in obstructive sleep apnea patients. *Eur Arch Otorhinolaryngol* 2012;269:1143-7.
- Mintz GS, Nissen SE, Anderson WD, et al. American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2001;37:1478-92.
- Garcia-Garcia HM, Mintz GS, Lerman A, et al. Tissue characterisation using intravascular radiofrequency data analysis: recommendations for acquisition, analysis, interpretation and reporting. *EuroIntervention* 2009;5:177-89.
- Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;364:226-35.
- Arzt M, Young T, Finn L, et al. Sleepiness and sleep in patients with both systolic heart failure and obstructive sleep apnea. *Arch Intern Med* 2006;166:1716-22.
- Albuquerque FN, Calvin AD, Sert Kuniyoshi FH, et al. Sleep-disordered breathing and excessive daytime sleepiness in patients with atrial fibrillation. *Chest* 2012;141:967-73.
- Capodanno D, Cumbo M, Marchese A, et al. Daytime sleepiness does not predict sleep apnoea in patients with coronary artery disease. *Int J Cardiol* 2011;151:248-50.
- Skinner MA, Choudhury MS, Homan SD, et al. Accuracy of monitoring for sleep-related breathing disorders in the coronary care unit. *Chest* 2005;127:66-71.
- Schiza SE, Simantirakis E, Bouloukaki I, et al. Sleep disordered breathing in patients with acute coronary syndromes. *J Clin Sleep Med* 2012;8:21-6.
- Irwin M, Thompson J, Miller C, et al. Effects of sleep and sleep deprivation on catecholamine and interleukin-2 levels in humans: clinical implications. *J Clin Endocrinol Metab* 1999;84:1979-85.
- Mullington JM, Haack M, Toth M, et al. Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. *Prog Cardiovasc Dis* 2009;51:294-302.
- Lusardi P, Mugellini A, Preti P, et al. Effects of a restricted sleep regimen on ambulatory blood pressure monitoring in normotensive subjects. *Am J Hypertens* 1996;9:503-5.
- Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999;354:1435-9.
- Lee CH. Intravascular ultrasound guided percutaneous coronary intervention: a practical approach. *J Interv Cardiol* 2012;25:86-94.
- Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503-16.

## ACKNOWLEDGMENTS

The authors gratefully acknowledge the assistance of Miss Pei-Ee Lee and Miss Venesa Loh with the recruitment of patients.

## SUBMISSION & CORRESPONDENCE INFORMATION

**Submitted for publication July, 2013**

**Submitted in final revised form July, 2013**

**Accepted for publication July, 2013**

Address correspondence to: Dr. Chi-Hang Lee, M.D., F.R.C.P., Department of Cardiology, National University Heart Centre, Singapore, 1E Kent Ridge Road, NUHS Tower Block Level 9, Singapore 119228; Tel: +65 67722493; Fax: +65 68722998; E-mail: mdclchr@nus.edu.sg

## DISCLOSURE STATEMENT

This was not an industry supported study. This study was funded by the Academic Research Fund (grant number R172-000-239-112) of the Ministry of Education, Singapore. The authors have indicated no financial conflicts of interest.



## Types of Primary Insomnia: Is Hyperarousal Also Present during Napping?

Alexandra D. Pérusse, B.A.<sup>1,2</sup>; Isabelle Turcotte, Ph.D.<sup>1,2</sup>; Geneviève St-Jean, Ph.D.<sup>1,2</sup>; Jason Ellis, Ph.D.<sup>3</sup>; Carol Hudon, Ph.D.<sup>1</sup>; Célyne H. Bastien, Ph.D.<sup>1,2</sup>

<sup>1</sup>École de psychologie, Université Laval, Québec, Canada; <sup>2</sup>Laboratoire de Neurosciences Comportementales Humaines du Centre de Recherche de l'Institut Universitaire en Santé Mentale de Québec, Québec, Canada;

<sup>3</sup>Northumbria Centre for Sleep Research, Northumbria University, Newcastle, UK

**Study Objectives:** The objective of this study was to identify if hyperarousal is a 24-hour phenomenon in insomnia by comparing sleep during napping between good sleepers (GS) and Insomnia sufferers (INS) (subdivided into paradoxical "PARA-I" and psychophysiological "PSY-I") following a mentally challenging battery of cognitive tests.

**Design:** Cross-sectional comparisons of GS, PSY-I, and PARA-I.

**Setting:** Participants slept for 4 consecutive nights in the laboratory where PSG was recorded. Upon awakening on mornings 2 and 3, cognitive testing (lasting 90-120 min) was administered, followed by a 20-minute nap.

**Participants:** Fourteen PSY-I, 12 PARA-I, and 23 GS completed the study, comprising home questionnaires, clinical interviews, night PSG recordings, cognitive testing, and nap PSG recordings. All participants were between 25 and 50 years of age and met inclusion criteria for PSY-I, PARA-I, or GS.

**Interventions:** N/A.

**Measurements and Results:** On objective nap parameters,

GS had a longer total sleep time (TST;  $p = 0.008$ ) and better sleep efficiency (SE;  $p = 0.009$ ), than PSY-I and PARA-I, and both groups of INS were awake significantly longer than GS ( $p = 0.003$ ). Also, PARA-I took significantly more time than GS to fall asleep ( $p = 0.014$ ). Subjectively reported sleepiness was comparable across the three groups. Positive relationships were observed between SE over the night and SE over the nap the following day.

**Conclusions:** Results show that GS sleep better than INS during naps following prolonged cognitive testing, suggesting that, in INS, hyperarousal predominates over mental fatigue resulting from these tests. These results may parallel what is observed at night when INS experience increased cognitive load but are unable to fall asleep.

**Keywords:** Insomnia, napping, hyperarousal

**Citation:** Pérusse AD; Turcotte I; St-Jean G; Ellis J; Hudon C; Bastien CH. Types of primary insomnia: is hyperarousal also present during napping? *J Clin Sleep Med* 2013;9(12):1273-1280.

Primary insomnia is one of the most prevalent sleep disorders.<sup>1</sup> In fact, between 30% and 48% of the general population occasionally reports insomnia related symptoms, and more than 13% suffers from chronic primary insomnia.<sup>2,3</sup> Important consequences resulting from this sleep disorder include fatigue, daytime sleepiness, confusion, sudden mood changes, and cognitive alterations.<sup>2</sup> The *International Classification of Sleep Disorders Second Edition (ICSD-2)*<sup>4</sup> differentiates 11 types of insomnia; paradoxical insomnia (PARA-I) and psychophysiological insomnia (PSY-I) being the most prevalent types. PARA-I is characterized by misperceptions in sleep quality and quantity. Individuals suffering from PARA-I complain about sleep difficulties although objective sleep measures (polysomnography; PSG) appear to be normal.<sup>5</sup> On the other hand, PSY-I is characterized by "relatively" good perceptions of sleep duration and quality along with "real" sleep onset and/or sleep maintenance difficulties and/or early morning awakenings.<sup>1</sup> The maintenance of PSY-I results from the conditioning between sleep related stimuli (e.g. bedroom) and anxious thoughts concerning possible sleep disturbances.<sup>6,7</sup> This conditioning contributes to the elevated cognitive activation that is typically reported in insomnia sufferers (INS).<sup>8</sup> Irrespective of insomnia types, a difficulty in napping is one of the core

### BRIEF SUMMARY

**Current Knowledge/Study Rationale:** This study was done to determine if there are differences in napping characteristics between GS and INS. These measures will allow us to identify if hyperarousal is a 24-hour phenomenon in INS.

**Study Impact:** In this study, INS were more hyperaroused during their naps than GS, suggesting that the high level of hyperarousal characterizing INS influences their functioning not only during the night, but also during the day. Also, this study contributes to a better understanding of the phenomenon of hyperarousal and results confirm once more that insomnia is a 24-hour problem in the hyperarousal domain.

features of insomnia.<sup>9-14</sup> Thus, napping difficulties might be similar to sleep difficulties observed in INS during the night. There is also a possibility that napping reflects the hyperarousal phenomenon that characterizes insomnia. These hypotheses remain to be tested.

There are several models which have attempted to explain insomnia. One of the most popular is the neurocognitive model of insomnia.<sup>15</sup> In this model, the authors state that in order to diminish sleep difficulties, INS tend to develop maladaptive behaviors, such as increasing the time spent in bed and going to bed earlier.<sup>15</sup> These strategies are not efficient since they

contribute to the elevation of somatic, cognitive and cortical activations.<sup>16</sup> Cognitive activation is characterized by intrusive thoughts before sleep and cortical activation is measured by cortical activity across different frequency bands. The hyperarousal of somatic, cognitive and cortical functions contributes to alterations in sensorial and information processing and the formation of long-term memories. Although the neurocognitive model of insomnia<sup>15</sup> has been supported by numerous studies measuring quantitative EEG during the night,<sup>17,18</sup> it has not yet been validated during naps. Therefore, a study on nap characteristics in insomnia would allow us to identify if hyperarousal is a phenomenon that influences not only nocturnal sleep, but also diurnal sleep. Several studies using a multiple sleep latency test (MSLT) protocol reported data on objective sleep during naps in insomnia, but these variables predominantly relate to sleep onset latency. While some studies failed to find significant differences in MSLT sleep-onset latencies between primary INS and good sleepers (GS),<sup>19,20</sup> others showed that INS had longer MSLT sleep-onset latencies than GS,<sup>13,14</sup> even though INS reported higher levels of sleepiness.<sup>12</sup> Other studies found that following sleep deprivation, INS had longer sleep onset latencies during daytime naps compared to GS.<sup>9-11</sup> Previous results thus tend to imply that hyperarousal is a 24-hour phenomenon in insomnia.

It is also possible that the degree of hyperarousal during naps in INS is influenced by activities completed before napping. Knowing the impact of cognitive testing on napping could contribute to the development of new strategies to help INS nap more efficiently when managing their sleep disorder and its associated consequences. To date, the link between activities completed before a nap and hyperarousal is unknown. In the present study, a battery of mentally challenging tasks was administered to participants before their naps. These tasks would most likely contribute to mental fatigue prior going to sleep since they lasted for 90 to 120 minutes and required a high and constant level of concentration. As such, we believe that mentally exhausting tasks before napping may serve as an analogy of insomnia in GS and/or increase cognitive load in INS, which should, according to the neurocognitive model,<sup>15</sup> contribute to the exacerbation of hyperarousal and delay sleep onset. To our knowledge, prolonged cognitive testing has never been administered to INS, as well as GS, before a nap. However, in some studies, cognitive tasks were completed before bedtime at night.<sup>21,22</sup> In general, it was observed that after cognitive testing, GS took significantly longer to fall asleep than those who did not complete them. Nonetheless, these studies failed to observe significant between group differences on other sleep parameters such as total sleep time and sleep stage distribution.

Finally, the relationship existing between sleep parameters during the night and the corresponding nap in insomnia has been seldom studied. In one study, it was reported that the shorter the objective total sleep time was during the night, the longer it took for INS to fall asleep during the day and the greater their daytime alertness was,<sup>14</sup> suggesting that hyperarousal predominates over sleepiness in insomnia. Another study failed to find significant positive relationships, in a population of GS, between nocturnal sleep variables and sleep variables over a nap the next day.<sup>23</sup> Therefore, it would be interesting to investigate the relationship between subjective sleepiness before a nap

and objective sleep variables over a nap protocol in INS since studies on this component are limited.<sup>12</sup> This would allow us to determine if subjective sleepiness contributes to the level of hyperarousal typically observed in INS. There is a possibility that the subjective perception of sleepiness is enough to exacerbate the level of hyperarousal, contributing to a diminution in the quality and quantity of sleep.

Even though sleep and nap difficulties have commonly been reported in PARA-I and PSY-I alike, significant differences between these two categories of insomnia still exist in their clinical presentation. To date, naps have rarely been studied in a population of INS and when they have been, types of INS were undifferentiated. Thus, napping difficulties reported in previous studies were generalized to all types of insomnia, independently of the specific classifications. However, it is possible that one of the types of insomnia (PSY-I or PARA-I) do not face napping difficulties, especially when considering that the objective nocturnal sleep of PARA-I often mirrors that of GS.<sup>5</sup> Therefore, individuals suffering from PARA-I and PSY-I should be classified and divided into two independent groups. This clustering would provide a more representative understanding of napping in insomnia.

## Objectives and Hypotheses

This study aims primarily at determining if there are significant differences in objective sleep parameters (sleep onset latency [SOL], wake after sleep onset [WASO], number of awakenings, total sleep time [TST], total wake time [TWT], and sleep efficiency [SE]) during naps among three groups of sleepers: PSY-I, PARA-I, and GS after completing a cognitively demanding battery of tests. It was assumed that this battery of tests would contribute to a state of mental exhaustion and/or an increase in cognitive load since testing lasted for a long period (90-120 min) and required an elevated and constant level of concentration. Mental exhaustion should facilitate sleep during napping, whereas high cognitive loading should delay sleep onset by exacerbating the hyperarousal level already present in INS. Therefore, since PSY-I and PARA-I should be more cognitively loaded after testing, we hypothesized that they would have poorer sleep during naps compared to GS, suggesting that hyperarousal predominates over mental exhaustion. Since PARA-I and GS usually have similar sleep profiles, objective sleep parameters of naps would be worse for PSY-I than PARA-I. Therefore, this study seeks empirical validation of the neurocognitive model of insomnia during napping.

This study also aimed at determining the influence of nocturnal sleep parameters on the ability to nap the next day. We suggested that a negative relationship would exist between nocturnal SE and SE during a nap for GS. In fact, the better the participant slept during the night, the harder it would be for him/her to fall asleep during a morning nap, since sleep homeostasis has been reset. Conversely, since PSY-I and PARA-I should be more hyperaroused than GS, we hypothesized that a positive relationship would exist between SE of the nocturnal sleep and the nap, confirming previous findings.<sup>14</sup> Consequently, the less they slept, the harder it would be for them to fall asleep during a nap the next day.

Finally, this research will allow us to determine if the three groups differ on subjective sleepiness (The Stanford Sleepiness

Scale [SSS])<sup>24</sup> following cognitive testing. Since PSY-I should have the poorest objective sleep parameters on nights before cognitive testing and PARA-I should have the feeling of a bad night's sleep, both groups should be more tired, and therefore should report higher levels of sleepiness than GS. Independently of sleepers' group, a positive relationship would also exist between the SE during nap and scores on the SSS.

## METHODS

### Participants

Participants were divided in 3 groups: 14 PSY-I, 12 PARA-I, and 23 GS. All participants were aged between 25 and 50 years. To be included in the PSY-I group, participants had to meet the following criteria: (a) a subjective complaint of insomnia characterized by difficulties initiating and/or maintaining sleep; (b) the insomnia must have been present  $\geq 3$  nights a week for  $> 6$  months; (c) a complaint of  $\geq 1$  daytime consequence attributed to insomnia; (d) distress or significant difficulties in social and/or occupational functioning; and (e)  $SE \leq 85\%$ . Participants in the PARA-I group had to meet the same inclusion criteria as those of the PSY-I group, but their objective SE had to be  $\geq 85\%$  and their TST had to exceed 390 minutes. An important discrepancy also had to be present between subjective and objective sleep variables: TST ( $\geq 60$  min discrepancy) and SE ( $\geq 15\%$  discrepancy). For this study, GS had to report sleeping  $\geq 7$  h per night, satisfaction with their sleep, and no subjective sleep complaints. In addition to not meeting criteria for insomnia, GS had to report not using sleep-promoting agents and having a subjective  $SE \geq 85\%$ .

Exclusion criteria for all participants were: (a) a significant medical disorder, (b) major psychopathology, (c) other sleep disorders, (d) strong dependency to tobacco, (e) ongoing psychological treatment, (f) use of a medication known to affect sleep, (g) score  $\geq 23$  on the Beck Depression Inventory (BDI),<sup>25</sup> or (h) a score  $\geq 15$  on the Beck Anxiety Inventory (BAI).<sup>26</sup> These criteria were consistent with those of the ICSD-2 and those of Bastien and colleagues.<sup>27</sup>

### Procedure

All participants were recruited through media advertisements as well as email sent to the Laval's university community. Following a brief telephone screening interview, eligible participants were sent a set of questionnaires to evaluate psychological symptoms (BAI and BDI) and sleep difficulties (Insomnia Severity Index [ISI],<sup>16</sup> Dysfunctional Beliefs and Attitudes About Sleep [DBAS-16]<sup>28</sup> and 2 weeks of sleep diaries<sup>16</sup>) that they completed at home. Those who met the inclusion criteria for any of the 3 groups were invited to the sleep laboratory for a clinical interview. Upon arrival to the sleep laboratory, informed consent was obtained. The Structured Clinical Interview for DSM-IV (SCID-IV)<sup>29</sup> was administered to rule out major psychopathologies and the Insomnia Diagnosis Interview (IDI)<sup>16</sup> to explore the nature of insomnia symptoms. These evaluations were conducted respectively by a graduate student in a clinical psychology program (GSJ) and a sleep specialist (CHB). Participants meeting the study criteria underwent four consecutive nights of PSG recordings in the sleep laboratory.

The mornings following nights 2 and 3, participants completed a battery of cognitive tests lasting between 90 to 120 minutes. The battery was composed of the following event-related potentials paradigms: go/no-go, distraction, and distraction delay. This procedure was approved by the ethics comity of the Centre de Recherche de l'Institut Universitaire en Santé Mentale de Québec (CER; # 183).

### Go/NoGo Protocol

During this test, 2 types of auditory stimuli were presented to participants. Stimulus 1 was standard and frequent in occurrence and stimulus 2 was rare and either easy "target 1" or difficult "target 2." Sounds all had the same duration of 40 ms, a rising time of 2 ms, and an intensity of 70 dB. The inter-stimulus interval varied from 1.3 to 1.7 seconds. Four conditions were presented to participants: (1) Go easy consists of stimulus 1 and target 1; (2) Go difficult consists of stimulus 1 and target 2; (3) NoGo easy (same stimuli as Go easy); and (4) NoGo difficult (same stimuli as Go difficult). Each condition consisted of 200 trials. Instructions differed for each condition: (A) Go conditions: participants have to detect target sounds and ignore standard ones; (B) NoGo conditions: they have to ignore target sounds and detect standard ones.

### Distraction

This test consisted of 7 white letters appearing one after the other on a black computer screen. The stimuli were presented for 800 ms each, with an inter-stimulus interval of 200 ms. Participants were instructed to memorize those letters, and after the last one appeared they had to write the letters in the correct order. There were 2 different conditions, totalling 15 trials each, each trial lasting approximately 7 seconds. During the first condition, office-like noises (e.g., telephone, background noises of people chatting) were played while the letters appeared. During the second condition no noises were played.

### Distraction Delay

This test is similar to the distraction paradigm, except participants had to memorize numbers instead of letters. There was a 10-sec delay before they were allowed to write down the numbers. There were three conditions consisting of 20 trials each, each trial lasting approximately 17 seconds. In the first condition, while waiting, participants heard a one-syllable non-relevant verbal sound. During the second, the sounds comprised 2 different syllables and there were 5 syllables in the third condition.

After cognitive tests, participants completed the SSS. Altogether, cognitive testing lasted between 90 to 120 min, including a 10-min break halfway through the protocol. Tests were followed by a 20-min nap opportunity during which PSG was recorded. Participants were instructed to try napping and were allowed out of bed if not asleep after 15 min (all participants stayed in bed for 20 min). This procedure was followed on both experimental days.

### Measures

To evaluate psychological symptoms, the BAI, BDI, and the SCID-IV were used. To portray sleep difficulties, at-home questionnaires; the ISI and DBAS-16 were completed by



participants. Adequate psychometric properties have been reported for both questionnaires in previous studies.<sup>28,30,31</sup> Also, the IDI was used to evaluate the presence of insomnia and its contributing factors. The SSS was completed on mornings 2 and 3 after cognitive testing. This scale was used to evaluate the level of sleepiness of participants after a cognitive demand and just before napping opportunity.

Prior to the nights in the laboratory, participants completed a 2-week sleep diary.<sup>16</sup> The sleep diary assesses subjective sleep quality, so participants had to report their sleep habits, such as the number of awakenings, the length of each awakening, the time spent in bed. From these raw data, the following subjective variables were derived: SOL, the amount of time it took to fall asleep; WASO, the amount of time spent awake after sleep onset; frequency of awakenings (FNA), the number of awakenings during the night; TWT, obtained by the sum of SOL and WASO; TST, the subtraction between the time in bed (TIB) and TWT; and SE, the ratio of TST over TIB.

### PSG Recordings

PSG was recorded during 4 nights and 2 naps. The same montage was used for every recording. A standard PSG montage was used including electroencephalography (EEG; F3, F4, Fz, C3, C4, Cz, P3, P4, Pz, O1, and O2), electromyography (EMG; electrodes on chin), electrocardiography (ECG; electrode on heart) and electro-oculography (EOG; one electrode on the supraorbital ridge of the right eye and another on the infraorbital ridge of the left eye) recordings. Reference electrodes were fixed on the mastoids and the ground was on the forehead. On the first night, leg EMG (electrodes on tibialis) and breathing devices were used to detect breathing disorders and limb movements. The inter-electrode impedance was maintained < 5 k $\Omega$ . To amplify the signal from the electrodes, a Grass Model 15A54 amplifier system (Astro-Med Inc., West Warwick, USA; gain 10000; bandpass 0.3-100 Hz) was used, and PSG signals were digitized at a sampling rate of 512 Hz with the commercial product Harmonie (Stellate system, Montreal, Canada). PSG recordings during sleep and nap were visually scored (Luna, Stellate system, Montreal, Canada) by experienced sleep technicians using Rechtschaffen and Kales' criteria<sup>32</sup> at 20-sec epochs.

In the present study, the objective sleep variables of interest were: SOL, defined as time from lights out to the first epoch of stage 1 sleep; WASO, the time spent awake after sleep onset; TWT, total time spent awake during the nap; TST, the time spent sleeping from lights out to lights on; number of awakenings after sleep onset and; and SE, the ratio of TST over TIB.

### Statistical Analyses

One-way ANOVAs were used to compare groups on socio-demographic variables, psychological characteristics, and subjective sleep variables from the sleep diary. Independent samples t-tests were then performed on significant main effects. Repeated measures ANOVAs were used to compare groups on objective sleep parameters of nights (duration of each sleep stage and SOL) and on objective sleep parameters of naps (SOL, WASO, number of awakenings, and TWT). Bonferroni post hoc analyses were then performed on significant main effects. Repeated measures ANCOVAs were computed to compare groups on the other sleep parameters of nights (WASO,

TST, TWT, and SE) and naps (SE and TST). Age was used as a covariate since it was significantly different between groups, and it was correlated with WASO (night 2:  $R = 0.39$ ,  $p = 0.006$ ; night 3:  $R = 0.29$ ,  $p = 0.045$ ), TWT (night 2:  $R = 0.37$ ,  $p = 0.009$ ; night 3:  $R = 0.27$ ,  $p = 0.059$ ), SE (nap 1:  $R = -0.30$ ,  $p = 0.032$ ; nap 2:  $R = -0.28$ ,  $p = 0.065$ ; night 2:  $R = -0.40$ ,  $p = 0.005$ ; night 3:  $R = -0.28$ ,  $p = 0.051$ ), and TST (nap1:  $R = -0.30$ ,  $p = 0.041$ ; nap 2:  $R = -0.26$ ,  $p = 0.080$ ; night 2:  $R = -0.42$ ,  $p = 0.003$ ; night 3:  $R = -0.35$ ,  $p = 0.014$ ). A Sidak correction was then performed on significant main effects of groups. Bilateral Pearson correlations were computed between SE of night and SE of its corresponding nap and between the SSS score and SE during the nap. Significance levels were set at 0.05.

Variables of participants who did not fall asleep during naps were included in the above statistical analyses; since all participants stayed in bed for the full 20 min, a value of 20 was attributed for SOL for those who did not sleep.

## RESULTS

### Socio-demographic, Psychological Measures, and Subjective Sleep Variables

Statistical analyses showed that PSY-I, PARA-I and GS were similar in gender ( $p = 0.291$ ), and education ( $p = 0.900$ ). GS were significantly younger than PSY-I and PARA-I ( $p = 0.050$ ), age varying between 25 and 49. There was no significant difference between INS groups concerning the duration of insomnia ( $p = 0.260$ ), ranging from 0.25 to 30 years. Analyses also revealed that the severity of insomnia symptoms measured by the ISI varied between 0 and 9 and was significantly greater in PSY-I and PARA-I than GS ( $p < 0.001$ ). Both groups of INS reported more depressive symptoms (BDI scores ranging from 0 to 20 [ $p = 0.001$ ]), and anxiety symptoms (BAI scores ranging from 0 to 15 [ $p = 0.002$ ]), than GS; and scores on the DBAS-16 were significantly higher for PSY-I and PARA-I than GS ( $p < 0.001$ ), with scores ranging from 17 to 108. Finally, analyses revealed significant differences among groups for all variables on the sleep diary ( $p < 0.001$ ), values for SOL varying from 1.72 to 116.79 min, from 0 to 105.36 min for WASO, from 223 to 552 min for TST, and from 51.90% to 99.90% for SE. Again, INS reported longer SOL and WASO while reporting shorter TST and lower SE than GS. Therefore, subjectively, INS had poorer sleep quality and quantity than GS. **Table 1** illustrates means and SDs for each of the above variables.

### Objective Sleep Parameters and Subjective Sleepiness Measures

No significant differences between groups were found for all objective sleep parameters of nights ( $0.208 \geq p \geq 0.293$ ); SOL ranging from 0.67 to 75.33 min, SE from 68% to 97%, WASO from 3.33 to 151.33 min, TST from 349 to 519.33 min, and TWT from 6.33 to 131 min. For the duration of sleep stages, no effect of groups was found for any stages ( $0.253 \geq p \geq 0.813$ ). The duration of stage 1 varied from 0 to 267 min, from 147.33 to 360 min for stage 2, from 0 to 68.67 min for stage 3, from 0 to 49.67 for stage 4, and from 65.67 to 169.33 for REM sleep. Since no significant differences were found between groups for objective sleep parameters on either night, no sleep patterns

**Table 1**—Means (SD) of sociodemographic, psychological data and subjective sleep variables of psychophysiological INS (PSY-I), paradoxical INS (PARA-I), and good sleepers (GS)

|                           | PSY-I (n = 14)              | PARA-I (n = 12)             | GS (n = 23)                   | F        | p         |
|---------------------------|-----------------------------|-----------------------------|-------------------------------|----------|-----------|
| Gender                    |                             |                             |                               | 1.27     | 0.291     |
| Female                    | 7                           | 9                           | 11                            |          |           |
| Male                      | 7                           | 3                           | 12                            |          |           |
| Age (years)               | 36.00 (8.17)                | 36.50 (8.70)                | 30.96 (5.82) <sup>a,b</sup>   | 3.21     | 0.050*    |
| Education (years)         | 16.31 (3.77)                | 16.17 (4.11)                | 16.70 (2.68)                  | 0.11     | 0.900     |
| Insomnia duration (years) | 11.31 (11.62)               | 7.03 (5.46)                 | —                             | t = 1.16 | 0.260     |
| Questionnaires            |                             |                             |                               |          |           |
| ISI                       | 6.14 (1.35)                 | 7.83 (1.12)                 | 1.09 (1.08) <sup>a,b</sup>    | 157.98   | < 0.001** |
| BDI                       | 10.00 (6.02)                | 8.83 (5.31)                 | 3.35 (3.59) <sup>a,b</sup>    | 9.28     | 0.001**   |
| BAI                       | 8.44 (4.36)                 | 6.63 (4.47)                 | 3.17 (3.06) <sup>a,b</sup>    | 7.61     | 0.002*    |
| DBAS-16                   | 85.79 (14.42)               | 74.18 (13.34)               | 54.77 (22.64) <sup>a,b</sup>  | 12.53    | < 0.001** |
| Sleep diary               |                             |                             |                               |          |           |
| SOL                       | 31.94 (25.3)                | 45.75 (35.47)               | 11.94 (8.83) <sup>a,b</sup>   | 9.37     | < 0.001** |
| WASO                      | 31.93 (21.94)               | 49.05 (32.87)               | 7.10 (8.91) <sup>a,b</sup>    | 17.31    | < 0.001** |
| TST                       | 410.29 (43.94) <sup>b</sup> | 331.21 (52.16) <sup>a</sup> | 462.89 (44.41) <sup>a,b</sup> | 32.09    | < 0.001** |
| SE                        | 82.18 (5.35) <sup>b</sup>   | 69.14 (11.07) <sup>a</sup>  | 93.22 (3.94) <sup>a,b</sup>   | 51.89    | < 0.001** |

<sup>a</sup>Significant difference with PSY-I; <sup>b</sup>significant difference with PARA-I; \*p ≤ 0.05; \*\*p ≤ 0.001. ISI, Insomnia Severity Index; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; DBAS-16, Dysfunctional Beliefs and Attitudes about Sleep; SOL, sleep onset latency; WASO, wake after sleep onset; TST, total sleep time; SE, sleep efficiency.

**Table 2**—Means (SD) of polysomnographic objective sleep parameters of nights of psychophysiological INS (PSY-I), paradoxical INS (PARA-I), and good sleepers (GS)

|                                             | PSY-I (n = 14) |                | PARA-I (n = 12) |                | GS (n = 23)    |                | F    | p     |
|---------------------------------------------|----------------|----------------|-----------------|----------------|----------------|----------------|------|-------|
|                                             | Night 2        | Night 3        | Night 2         | Night 3        | Night 2        | Night 3        |      |       |
| <b>Objective sleep parameters of nights</b> |                |                |                 |                |                |                |      |       |
| SOL                                         | 13.38 (12.30)  | 13.67 (12.45)  | 6.47 (5.77)     | 8.50 (7.78)    | 9.81 (15.86)   | 9.20 (6.57)    | 1.36 | 0.268 |
| WASO                                        | 38.55 (31.41)  | 42.52 (39.76)  | 47.25 (33.07)   | 38.75 (32.98)  | 23.03 (20.53)  | 24.78 (29.79)  | 1.62 | 0.210 |
| TST                                         | 437.71 (52.15) | 437.64 (47.00) | 425.81 (30.36)  | 424.97 (33.00) | 454.57 (33.76) | 453.64 (28.55) | 1.63 | 0.208 |
| TWT                                         | 51.93 (36.82)  | 56.19 (43.78)  | 53.72 (34.96)   | 47.25 (34.51)  | 32.84 (29.68)  | 33.98 (33.72)  | 1.34 | 0.273 |
| SE (%)                                      | 88.36 (7.87)   | 87.71 (8.32)   | 87.83 (6.65)    | 89.00 (6.73)   | 9.09 (5.95)    | 91.83 (5.91)   | 1.26 | 0.293 |
| <b>Duration of sleep stages (minutes)</b>   |                |                |                 |                |                |                |      |       |
| Stage 1                                     | 12.88 (7.79)   | 13.74 (11.93)  | 11.56 (6.85)    | 33.14 (74.24)  | 11.01 (7.35)   | 10.71 (8.13)   | 1.42 | 0.253 |
| Stage 2                                     | 288.55 (34.89) | 281.83 (46.84) | 281.47 (32.30)  | 280.17 (34.00) | 301.61 (32.67) | 287.19 (40.24) | 0.94 | 0.397 |
| Stage 3                                     | 22.43 (14.52)  | 21.83 (19.25)  | 18.92 (20.43)   | 21.11 (21.87)  | 25.29 (20.09)  | 22.78 (16.95)  | 0.21 | 0.813 |
| Stage 4                                     | 2.02 (4.17)    | 2.79 (4.11)    | 3.61 (6.15)     | 4.20 (10.07)   | 5.01 (10.28)   | 4.72 (10.86)   | 0.38 | 0.684 |
| REM                                         | 111.83 (28.54) | 117.45 (26.72) | 110.25 (24.16)  | 108.39 (19.24) | 111.64 (21.54) | 121.16 (21.47) | 0.52 | 0.597 |

SOL, sleep onset latency; WASO, wake after sleep onset; TST, total sleep time; TWT, total wake time; SE, sleep efficiency.

between groups could be identified. See **Table 2** for more details on objective sleep parameters of both nights.

On objective sleep parameters of naps (naps were treated separately), analyses revealed main effect of groups for SOL (p = 0.008), values ranging from 0 to 20 minutes. Post hoc analyses indicated that PARA-I had a significantly longer SOL than GS (p = 0.014), and the difference between PSY-I and GS was marginally significant (p = 0.078), PSY-I having a longer SOL than GS. A significant difference was also found for TWT (p = 0.003), with PSY-I (p = 0.019), and PARA-I (p = 0.010) spending significantly more time awake during their naps than GS. Values of TWT varied from 0.33 to 20 minutes. No main effects of groups were observed for WASO (p = 0.110) and number of awakenings (p = 0.427),

with WASO varying from 0 to 19.67 min and number of awakenings from 0 to 3.

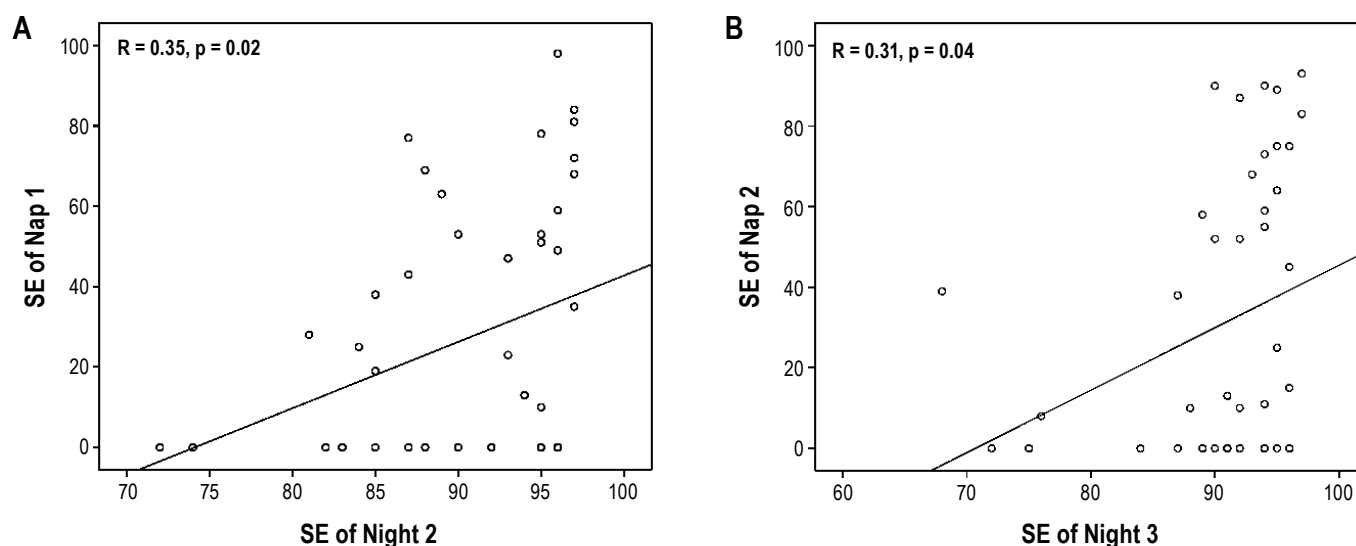
When controlling for age, analyses showed a significant group effect for TST (p = 0.008), where TST was significantly shorter for PSY-I (p = 0.021) and PARA-I (p = 0.034) than GS. Values of TST ranged between 0 to 20 min. Finally, values of SE varied from 0 to 98% and was significantly different between groups (p = 0.009), SE being significantly higher for GS than PSY-I (p = 0.025) and PARA-I (p = 0.036). Conversely, when analyses compared objective measures from the first nap with those of the second one, no main effect of naps was found. Therefore, objective nap measures were similar on both napping opportunities. In sum, analyses on objective sleep parameters of naps showed that GS had a better capacity to nap than PARA-I and



**Table 3**—Means (SD) of polysomnographic objective sleep parameters of naps and subjective sleepiness of psychophysiological INS (PSY-I), paradoxical INS (PARA-I), and good sleepers (GS)

|             | PSY-I (n = 14) |               | PARA-I (n = 12) |               | GS (n = 23)                  |                              | F    | p      |
|-------------|----------------|---------------|-----------------|---------------|------------------------------|------------------------------|------|--------|
|             | Nap 1          | Nap 2         | Nap 1           | Nap 2         | Nap 1                        | Nap 2                        |      |        |
| # who slept | 6              | 5             | 3               | 4             | 17                           | 17                           |      |        |
| SOL         | 12.19 (8.26)   | 12.83 (9.25)  | 15.80 (6.96)    | 13.93 (7.94)  | 6.80 (8.39) <sup>b</sup>     | 5.59 (8.30) <sup>b</sup>     | 5.42 | 0.008* |
| WASO        | 8.07 (3.39)    | 11.13 (6.95)  | 9.00 (5.48)     | 7.44 (2.17)   | 5.65 (3.81)                  | 5.62 (4.00)                  | 2.47 | 0.110  |
| Awakenings  | 0.50 (0.91)    | 0.08 (0.29)   | 0.50 (1.08)     | 0.40 (0.84)   | 0.27 (0.46)                  | 0.14 (0.47)                  | 0.87 | 0.425  |
| TST         | 3.44 (4.36)    | 2.86 (5.33)   | 1.97 (3.65)     | 3.63 (5.05)   | 9.42 (7.06) <sup>a,b</sup>   | 9.85 (7.70) <sup>a,b</sup>   | 5.50 | 0.008* |
| TWT         | 16.56 (4.57)   | 17.36 (5.35)  | 18.87 (3.44)    | 16.73 (4.69)  | 11.35 (6.64) <sup>a,b</sup>  | 11.00 (7.53) <sup>a,b</sup>  | 6.76 | 0.003* |
| SE (%)      | 17.25 (22.23)  | 14.08 (26.74) | 9.20 (17.34)    | 17.40 (24.10) | 44.73 (32.95) <sup>a,b</sup> | 47.00 (35.92) <sup>a,b</sup> | 5.31 | 0.009* |
| SSS         | 3.14 (0.95)    | 2.79 (0.89)   | 3.00 (1.12)     | 3.33 (1.00)   | 2.65 (1.23)                  | 2.57 (0.73)                  | 1.65 | 0.204  |

<sup>a</sup>Significant difference with PSY-I; <sup>b</sup>significant difference with PARA-I; \* $p \leq 0.05$ . SOL, sleep onset latency; WASO, wake after sleep onset; TST, total sleep time; TWT, total wake time; SE, sleep efficiency; SSS, Stanford Sleepiness Scale.

**Figure 1**

(A) Correlation between sleep efficiency (SE) of night 2 and SE of nap 1. (B) Correlation between SE of night 3 and SE of nap 2.

PSY-I. See **Table 3** for more comprehensive details on objective parameters of naps.

For the subjective sleepiness measure, analyses revealed no effect of groups for the SSS ( $p = 0.204$ ), and scores varied from 1 to 5. **Table 3** illustrates means and SDs for subjective sleepiness before naps from the SSS.

### Correlations between Objective and Subjective Measures

Bilateral Pearson correlation between SE of night 2 and SE of nap 1 was significant ( $R = 0.35$ ,  $p = 0.015$ ). Also, SE of night 3 and SE of nap 2 were significantly positively correlated ( $R = 0.31$ ,  $p = 0.038$ ). For both bilateral Pearson correlations, Mahalanobis distances confirmed the absence of bivariate outliers at a critical value of  $p \leq 0.001$ . **Figure 1** illustrate these relationships on scatterplots. When analyses were computed on each group separately, no significant correlations were found between night 2 and nap 1 (PSY-I:  $R = 0.38$ ,  $p = 0.201$ ; PARA-I:  $R = 0.22$ ,  $p = 0.500$ ; GS:  $R = 0.24$ ,  $p = 0.276$ ) as

well as between night 3 and nap 2 (PSY-I:  $R = 0.40$ ,  $p = 0.179$ ; PARA-I:  $R = 0.26$ ,  $p = 0.467$ ; GS:  $R = 0.15$ ,  $p = 0.509$ ).

No significant correlation was found between the SSS and SE of nap 1 ( $R = 0.22$ ,  $p = 0.313$ ) as well as with SE of nap 2 ( $R = 0.33$ ,  $p = 0.129$ ). Mahalanobis distances revealed no bivariate outliers for both correlations at the critical value of  $p \leq 0.001$ . When bilateral Pearson correlations were performed on each group independently, no significant correlations were found between SSS and SE of nap 1 (PSY-I:  $R = 0.18$ ,  $p = 0.568$ ; PARA-I:  $R = -0.22$ ,  $p = 0.517$ ; GS:  $R = 0.22$ ,  $p = 0.313$ ) or between SSS and SE of nap 2 (PSY-I:  $R = 0.19$ ,  $p = 0.543$ ; PARA-I:  $R = 0.25$ ,  $p = 0.483$ ; GS:  $R = 0.33$ ,  $p = 0.129$ ).

### DISCUSSION

In the present study, GS and INS, classified in psychophysiological and paradoxical types, were compared on sleep parameters and characteristics during naps following a mentally challenging battery of cognitive tests. Socio-demographic data

revealed that both groups of INS were significantly older than GS. Until now, there has been no data available to our knowledge to illustrate the impact of age on PSG recordings variables during a single nap. However, a review paper on MSLT revealed that age contributed to a significant increase in MSLT latency.<sup>33</sup> Since groups were significantly different in age, this was factored in our statistical design. Therefore, we could ensure the significant difference of age between groups did not contribute to the significant differences between groups found for some nap parameters.

Results failed to show significant differences between GS, PSY-I, and PARA-I on objective sleep parameters during both nights of PSG recording. These results might be explained by the fact that INS usually sleep better in the laboratory than at home and that GS have a poorer sleep quality in the laboratory. Therefore, sleep patterns of these two populations during laboratory PSG recordings tend to be similar, and the differences that actually exist between them are attenuated. The poorer quality of sleep obtained by GS during laboratory nights might result in some kind of partial sleep deprivation, which could explain why GS slept better during their naps following prolonged cognitive testing compared to both groups of INS. In fact, GS fell asleep significantly faster, their TST was longer, their TWT was shorter, and their SE was greater than PSY-I and PARA-I. Conversely, our results also suggest that for INS, hyperarousal appears to predominate over mental exhaustion following cognitive testing. One explanation might be that completing the battery of cognitive tests increased the cognitive load, which in turn contributed to hyperactivation of cognitive functions in INS, and prevented them from falling asleep. As for GS, prolonged cognitive testing most likely did not contribute to cognitive arousal but more to mental fatigue, as they slept relatively well during naps. Results obtained for objective sleep parameters during naps support the neurocognitive model of insomnia stating that cognitive arousal contributes to poor sleep in insomnia.<sup>15</sup> These results may parallel what is observed at night when INS experience cognitive loading and are unable to fall asleep. This finding suggests that the neurocognitive model is not only applicable to nighttime sleep but also to napping, and it could be an explanation for the inability to nap characterizing INS.<sup>15,34</sup>

Data from the SSS completed at the end of cognitive testing and before napping support previous observations and confirm the present hypothesis, that hyperarousal contributes to the inability to nap. In fact, even though the analyses did not reach significance for the SSS, PSY-I had higher scores than PARA-I and GS, and the scores of PARA-I on the SSS were greater than GS. These results suggest that after prolonged cognitive testing PSY-I reported being the sleepest, followed by PARA-I and then GS. So, both groups of INS subjectively reported being sleepy, but they were, in general, unable to nap, which suggests again that hyperarousal predominates over sleepiness in insomnia. That said, it could be suggested that GS were as mentally exhausted as PSY-I and PARA-I after testing, but since they were not as cognitively aroused, they slept better. There is also the possibility that partial sleep deprivation explains napping abilities in GS.

We found significant positive correlations between SE during the night and SE of the nap on the next day. As such, it appears that the better participants slept during the night, the

better was their ability to nap the next day. The opposite is also true; a low SE for the night led to a low SE during nap on the following day. These results are difficult to reconcile with the literature presented earlier and with other results. Still, nightly and daily sleep efficiencies varied together only when the total sample was taken as a whole and not when groups were studied independently. It is possible that the few observations in each group lead to a lack of power, hence a lack of within-group significant relationship between night and day. Nonetheless, it is also possible than instead of varying with the present night of sleep, daily SE might vary with the SE of the subsequent night of sleep. As is often acknowledged in CBT-I (in the sleep restriction module and/or sleep hygiene instructions<sup>16</sup>), napping during the day may well influence or borrow on the following night of sleep in INS but not on the nocturnal SE of GS. Our sample had more GS than INS as a whole and might just reflect this last statement. Still, this hypothesis remains to be tested in a larger sample and also on subsequent days and nights.

Alternatively, one might argue that for INS, a greater sleep pressure would build up as a result of the quality of sleep during the night, which would equate to a better nap opportunity the next day. However, the fact that INS tend to increase their time spent in bed in order to increase their sleeping time would most likely contribute to an elevation of hyperarousal, which would diminish the nap opportunity. Additionally, a 20-minute window was used for the naps, similar to a MSLT protocol. Maybe it is not long enough to fall asleep when participants are tired; the time required to fall asleep might be higher in this case. There is also the possibility that SE during the nap would have been normal after a bad night sleep if participants were allowed to nap as long as they wish and if the time pressure to fall asleep was removed. However, the observation obtained in the present study confirmed results previously found.<sup>14</sup>

In general, the results have shown no significant differences between PSY-I and PARA-I for nap parameters. Even though diagnostic criteria for PSY-I and PARA-I are different,<sup>4</sup> there is a possibility that the level of hyperarousal during the day is similar for both groups of INS, which would explain why no significant differences were found between these two groups for objective nap parameters. Also, if levels of hyperarousal are independent of the amount of nocturnal sleep obtained objectively, it would explain the subjective reports of poor sleep in PARA-I.<sup>5</sup> Nonetheless, the distinction between PSY-I and PARA-I is not as clear when hyperarousal is taken into account. Future studies on objective nap parameters in INS should take this into consideration and combine PSY-I and PARA-I since there is a possibility that hyperarousal influences to a comparable extent the quality of naps in both types of insomnia. However, this hypothesis also remains to be tested.

The small number of participants in each group limits the interpretations of our results. Therefore, we have to be careful when generalizing and a replication with a larger sample is warranted. Also, to ensure participants actually experienced mental fatigue after completing the battery of cognitive tests, a scale of mental exhaustion should have been used. This would have allowed determining as to whether mental exhaustion contributed to the difficulty in napping in INS. Moreover, we also assume that cognitive testing had an impact on sleep characteristics of naps, but it is possible that the same results would

have been obtained in the absence of mentally exhausting tests. Therefore, the presence of a nap not preceded by cognitive testing would have been useful to identify if the results obtained were influenced by the tests or if they had no impact on naps. It would have allowed us to determine if diagnosis alone was sufficient to explain between-group differences on sleep parameters during naps or if prolonged cognitive tests contributed to the results.

To conclude, it seems that INS, independent of type, are more hyperaroused than GS during napping. This observation suggests that the high level of hyperarousal characterizing insomnia influences their functioning not only during the night, but also during the day. Finally, this study contributes to a better understanding of the phenomenon of hyperarousal and gives some insights for future research in the field of insomnia. Additionally, these results confirm once more that insomnia is a 24-hour problem, particularly in the hyperarousal domain. Nonetheless, more studies need to explore nap parameters in a population of INS in order to support these results.

## REFERENCES

1. Bastien CH. Insomnia: Neurophysiological and neuropsychological approaches. *Neuropsychol Rev* 2011;21:22-40.
2. Ohayon MM. Epidemiology of insomnia: What we know and what we still need to learn. *Sleep Med Rev* 2002;6:97-111.
3. Morin CM, LeBlanc M, Bélanger L, Ivers H, Mérette C, Savard J. Prevalence of insomnia and its treatment in Canada. *Can J Psychiatry* 2011;56:540-8.
4. American Academy of Sleep Medicine. *International classification of sleep disorders, 2nd ed; diagnostic and coding manual*. Westchester, IL: American Academy of Sleep Medicine, 2005.
5. Edinger JD, Bonnet MH, Bootzin RR, et al. Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group. *Sleep* 2004;27:1567-96.
6. Espie CA. Insomnia: Conceptual issues in the development, persistence, and treatment of sleep disorders in adults. *Annu Rev Psychol* 2002;53:215-43.
7. Harvey AG. A cognitive model of insomnia. *Behav Res Ther* 2002;40:869-93.
8. Wicklow A, Espie CA. Intrusive thoughts and their relationship to actigraphic measurement of sleep: toward a cognitive model of insomnia. *Behav Res Ther* 2000;38:679-93.
9. Bonnet MH, Arand DL. 24-hour metabolic rate in insomniacs and matched normal sleepers. *Sleep* 1995;18:581-8.
10. Bonnet MH, Arand DL. The consequences of a week of insomnia II: patients with insomnia. *Sleep* 1998;21:359-68.
11. Bonnet MH, Arand DL. Activity, arousal, and the MSLT in patients with insomnia. *Sleep* 2000;23:205-12.
12. Edinger JD, Means MK, Carney CE, Krystal AD. Psychomotor performance deficits and their relation to prior nights' sleep among individuals with primary insomnia. *Sleep* 2008;31:599-607.
13. Roehrs TA, Randall S, Harris E, Maan R, Roth T. MSLT in primary insomnia: Stability and relation to nocturnal sleep. *Sleep* 2011;34:1647-52.
14. Stepanski E, Zorick F, Roehrs T, Young D, Roth T. Daytime alertness in patients with chronic insomnia compared with asymptomatic control subjects. *Sleep* 1988;11:54-60.
15. Perlis ML, Giles DE, Mendelson WB, Bootzin RR, Wyatt JK. Psychophysiological insomnia: the behavioural model and a neurocognitive perspective. *J Sleep Res* 1997;6:179-88.
16. Morin CM. *Insomnia: psychological assessment and management*. New York: Guilford Press, 1993.
17. Krystal AD, Edinger JD, Wohlgemuth WK, Marsh GR. NREM sleep EEG frequency spectral correlates of sleep complaints in primary insomnia subtypes. *Sleep* 2002;25:630-40.

18. Merica H, Blois R, Gaillard JM. Spectral characteristics of sleep EEG in chronic insomnia. *Eur J Neurosci* 1998;10:1826-34.
19. Seidel WF, Ball S, Cohen S, Patterson N, Yost D, Dement WC. Daytime alertness in relation to mood, performance, and nocturnal sleep in chronic insomniacs and noncomplaining sleepers. *Sleep* 1984;7:230-8.
20. Sugerman JL, Stern JA, Walsh JK. Daytime alertness in subjective and objective insomnia: some preliminary findings. *Biol Psychiatry* 1985;20:741-50.
21. Gross RT, Borkovec TD. Effects of a cognitive intrusion manipulation on the sleep-onset latency of good sleepers. *Behav Ther* 1982;13:112-6.
22. Wuyts J, De Valck E, Vandekerckhove M, et al. The influence of pre-sleep cognitive arousal on sleep onset processes. *Int J Psychophysiol* 2012;83:8-15.
23. McDevitt EA, Alaynick WA, Mednick SC. The effect of nap frequency on daytime sleep architecture. *Physiol Behav* 2012;107:40-4.
24. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of sleepiness: A new approach. *Psychophysiology* 1973;10:431-6.
25. Beck AT, Steer RA, Brown GK. *Manual for Beck Depression Inventory II (BDI-II)*. San Antonio, TX: Psychological Corporation, 1996.
26. Beck AT, Steer RA. *Beck Anxiety Inventory Manual*. San Antonio, TX: Psychological Corporation, 1993.
27. Bastien CH, Guimond S, St-Jean G, Lemelin S. Signs of insomnia in borderline personality disorder individuals. *J Clin Sleep Med* 2008;4:462-70.
28. Morin CM, Vallières A, Ivers H. Dysfunctional beliefs and attitudes about sleep (DBAS): Validation of a brief version (DBAS-16). *Sleep* 2007;30:1547-54.
29. Williams JBW, Gibbon M, First MB, et al. The structured clinical interview for DSM-III (SCID). 2. Multisite test-retest reliability. *Arch Gen Psychiatry* 1992;49:630-6.
30. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001;2: 297-307.
31. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: Psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;34:601-8.
32. Rechtschaffen A, Kales A. *A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects*. Los Angeles: Brain Information Service/Brain Research Institute, University of California, 1968.
33. Arand D, Bonnet M, Hurwitz T, Mitler M, Rosa R, Sangal B. The clinical use of the MSLT and MWT. *Sleep* 2005;28:123-44.
34. Moul DE, Nofzinger EA, Pilkonis PA, Houck PR, Miewald JM, Buysse DJ. Symptom report in chronic severe insomnia. *Sleep* 2002;25:548-58.

## ACKNOWLEDGMENTS

The authors thank Sonia Petit for analysing PSG recordings and all the research assistants who helped in cognitive testing and data entry.

## SUBMISSION & CORRESPONDENCE INFORMATION

**Submitted for publication February, 2013**

**Submitted in final revised form July, 2013**

**Accepted for publication July, 2013**

Address correspondence to: Célyne H. Bastien, Ph.D., Pavillon Félix-Antoine-Savard, 2325 rue des Bibliothèques, Bureau 1012, Université Laval, Québec, Qc, G1V 0A6; Tel: +1-418-656-2131, ext. 8344; Fax: +1-418-656-3646; E-mail: celyne.bastien@psy.ulaval.ca

## DISCLOSURE STATEMENT

This was not an industry supported study. This study was supported by the Canadian Institutes of Health Research (CIHR; # 49500, 86571) and les Fonds de Recherche en Santé du Québec (FRSQ; # 23028). The authors have indicated no financial conflicts of interest. The study was conducted at Laboratoire de Neurosciences Comportementales Humaines du Centre de Recherche de l'Institut Universitaire en Santé Mentale de Québec, Québec, Canada.

## Predictors of Treatment Response to Brief Behavioral Treatment of Insomnia (BBTI) in Older Adults

Wendy M. Troxel, Ph.D.<sup>1</sup>; Tyler S. Conrad, B.A.<sup>2</sup>; Anne Germain, Ph.D.<sup>2</sup>; Daniel J. Buysse, M.D., F.A.A.S.M.<sup>2</sup>

<sup>1</sup>Behavioral and Policy Sciences, RAND Corporation, Pittsburgh, PA;

<sup>2</sup>Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA

**Study Objectives:** The extant literature on predictors of treatment response to behavioral treatments for insomnia is equivocal and limited in scope. The current study examined demographic, clinical, and sleep characteristics as predictors of clinically significant treatment response to brief behavioral treatment of insomnia (BBTI) in older adults with insomnia.

**Methods:** Thirty-nine older adults with insomnia (67% females, mean age: 72.54 years) were randomized to BBTI treatment. Treatment outcomes were defined according to 2 criteria: (1) "response," defined as change in Pittsburgh Sleep Quality Index (PSQI) score  $\geq 3$  points or increase in sleep diary sleep efficiency  $\geq 10\%$ ; or (2) remission, defined as absence of a clinical diagnosis of insomnia according to standard diagnostic criteria. Logistic regression examined whether baseline demographic, clinical, or sleep characteristics predicted treatment outcomes at 1 month follow-up.

**Results:** Demographic variables did not predict treatment outcomes for either criterion. Higher anxiety, depression,

poorer sleep quality, and longer polysomnography (PSG)-assessed sleep latency predicted greater likelihood of response at follow-up ( $p < 0.05$ ). Longer sleep duration at baseline (measured by sleep diary and PSG) predicted greater likelihood of the remission at follow-up ( $p < 0.05$ ).

**Conclusion:** Patients with insomnia who have greater distress at baseline or prolonged sleep latency are more likely to show positive response to BBTI. In contrast, short sleepers at baseline are less likely to have resolution of insomnia diagnosis following BBTI, perhaps due to the sleep restriction component of the treatment. Identifying the characteristics that predict positive BBTI treatment outcomes can facilitate personalized behavioral treatments to improve outcomes.

**Keywords:** Insomnia, behavioral treatment, treatment response, predictors, cognitive-behavioral

**Citation:** Troxel WM; Conrad TS; Germain A; Buysse DJ. Predictors of treatment response to brief behavioral treatment of insomnia (BBTI) in older adults. *J Clin Sleep Med* 2013;9(12):1281-1289.

Insomnia is a chronic and persistent sleep disorder which affects approximately 10% of the adult population, and up to 20% in geriatric populations.<sup>1,2</sup> Over the past 20 years, robust and consistent evidence has demonstrated that behavioral interventions (under the umbrella of cognitive behavioral therapy for insomnia; CBTI) are comparably efficacious and perhaps more enduring than pharmacologic interventions.<sup>3</sup> Despite the well-documented benefits of CBTI, pharmacotherapy remains the front-line treatment for insomnia in many primary care settings, in part due to the lack of trained CBTI clinicians. To address this challenge, our group recently demonstrated the efficacy of a variant of CBTI, called brief behavioral treatment of insomnia (BBTI),<sup>4</sup> in a sample of older adults with insomnia. BBTI is shorter in duration than traditional CBTI and designed to be delivered by a nurse with limited training in sleep medicine. The improvements seen with BBTI (effect sizes ranging from 0.62-0.96 for quantitative sleep parameters) were comparable in magnitude to those reported in a meta-analysis of CBTI and other behavioral interventions for insomnia in older adults.<sup>5</sup> As with traditional CBTI, however, there was considerable variability in treatment response to BBTI. In other words, though treatment was efficacious overall, not all patients demonstrated significant improvement. Identifying characteristics of individuals who are more or less likely to benefit from

### BRIEF SUMMARY

**Current Knowledge/Study Rationale:** Research on predictors of treatment response following behavioral treatment of insomnia is equivocal and limited in scope. The current study includes a broad assessment of demographic, clinical, and sleep characteristics as predictors of treatment response to brief behavioral treatment of insomnia (BBTI) in a sample of older adults with insomnia.

**Study Impact:** Identifying patient characteristics that predict favorable treatment outcomes to behavioral treatment of insomnia is critical to tailor treatment efforts and optimize treatment outcomes. The current study demonstrated that higher levels of depression and anxiety predicted better treatment response to BBTI, whereas shorter sleep latency and shorter total sleep time predicted poorer treatment outcomes.

a given treatment is of critical clinical importance in order to maximize patient benefits and cost-effectiveness, and minimize side effects. Therefore, the purpose of the present study is to identify predictors of treatment response to BBTI.

Although this is the first study to examine predictors of response to BBTI, previous research has examined the influence of several demographic, clinical, and psychiatric variables on treatment response to CBTI. For the most part, however, prior results are equivocal, perhaps due to methodological differences across studies. For instance, age has not been consistently



related to treatment response, with a handful of studies reporting older age being related to poorer outcome<sup>6-8</sup> and other studies showing no influence of age on treatment response,<sup>9-11</sup> perhaps due to differences in study eligibility criteria (including a varying range of ages for “older” or “younger” participants) or statistical control for medical comorbidities, which are particularly common in older adults. Indeed, once screened for medical comorbidities, older patients have been shown to respond similarly to their younger counterparts.<sup>12</sup> These findings suggest that older age does not portend poorer treatment response; however, comorbidities associated with increasing age may account for age differences in treatment outcome.

Differences in eligibility criteria may also account for equivocal findings with regard to baseline clinical characteristics. For instance, in a clinical effectiveness trial, which included patients representative of those presenting in clinical practice, Espie and colleagues found that higher levels of baseline depression and anxiety and initial insomnia severity predicted greater treatment response.<sup>13</sup> In contrast, the majority of clinical trials of CBTI, which have been conducted in highly controlled research trials with more stringent eligibility criteria, have shown higher severity and longer duration of insomnia associated with poorer response,<sup>8</sup> while still other studies have shown no relation to treatment response.<sup>7,14</sup> Thus, given the conflicting nature of these results and that the vast majority of insomnia patients can be characterized as comorbid cases (particularly among older adults), further investigation of predictors of treatment response in samples more characteristic of the general insomnia population is warranted.

Aside from patient characteristics, the operational definition of treatment response varies widely and may influence the clinical significance of treatment response.<sup>15</sup> To date, most studies assess treatment response via change in clinically relevant quantitative sleep parameters (e.g., sleep latency, wakefulness after sleep onset, sleep efficiency) measured via sleep diaries and/or actigraphy.<sup>7,16</sup> Although these quantitative criteria have the utility of being well recognized and relatively well standardized in terms of research diagnostic criteria,<sup>17</sup> their clinical utility is somewhat limited as current clinical diagnostic criteria are based on the clinical complaint of insomnia with daytime impairment, and do not specify quantitative parameters (e.g., sleep latency > 30 min). Moreover, quantitative criteria may not adequately reflect the patient's experience of clinically significant improvement. For instance, Currie and colleagues demonstrated that 57% of patients met treatment response criteria based on significant reductions in Pittsburgh Sleep Quality Index (PSQI) scores after 7 weeks of treatment; however, only 18% were considered fully recovered from their sleep problems, based on reliable change in PSQI scores and clinical criteria for normative values on diary-assessed quantitative sleep parameters (e.g., total sleep time, sleep efficiency) and PSQI scores < 5.<sup>18</sup> Reimann and Perlis have also recently advocated for outcome data that can be interpreted in terms of clinical relevance, such as percentages of responders/non-responders or those meeting/not-meeting insomnia diagnostic criteria at follow-up.<sup>19</sup>

Finally, few previous investigations have examined physiological predictors of treatment response. In a sample of middle-aged adults with insomnia, Krystal and Edinger found that lower peak delta and a more gradual decline of delta across

NREM periods prior to treatment predicted a greater subjective response to CBTI.<sup>20</sup> Given age-related changes in sleep architecture and micro-architecture, particularly with regard to the levels and slope of decline in delta activity and the putative role of homeostatic sleep pressure as a mechanism of change in behavioral insomnia treatments, examination of the role of delta activity as a predictor of treatment response in older adults may provide useful insights into how to further improve or refine behavioral insomnia treatments.

In summary, prior research on predictors of treatment response to CBTI have not identified a reliable set of predictors to treatment response, and no prior study has examined predictors of response to BBTI. Several methodological characteristics of the BBTI clinical trial offer unique opportunities to address unresolved issues in the extant literature on predictors of treatment response to CBTI. In particular, the BBTI trial includes older adults recruited from the community and ranging in age from 62 to 88 years, which offers the opportunity to examine predictors of treatment response in an older adult population. In addition, to maximize generalizability of the results and in contrast to most prior clinical trials of behavioral treatments of insomnia, the BBTI trial did not exclude based on the presence of other co-occurring medical or psychiatric conditions, which more accurately reflects the vast majority of insomnia cases. The current study incorporates a broader assessment of demographic, clinical, and physiological predictors of treatment response than has been considered in prior research. Finally, the current study includes treatment response criteria that are intended to more closely reflect clinically relevant domains of improvement.

## METHODS

### Overview

These data were collected as part of a study of older adults with chronic insomnia (symptoms present  $\geq 1$  month) and their response to a brief behavioral treatment for insomnia (BBTI; AG 20677; Buysse, PI). Detailed study procedures have been published previously.<sup>4,21</sup> Briefly, participants were recruited from a single primary care practice in the Pittsburgh area or from community advertisements. Following screening and baseline assessments, participants were randomly assigned to an active treatment condition (BBTI) or information-control condition. Given the current study focus on predictors of BBTI treatment outcome, participants included in the present analyses ( $n = 39$ ) were insomnia patients who were randomized to BBTI treatment. Predictors of treatment outcome were collected at the baseline assessment and included demographic and clinical characteristics assessed by questionnaires, and sleep characteristics assessed by sleep diaries, actigraphy, and polysomnography. Treatment response was determined after 4 weeks of treatment. The University of Pittsburgh Biomedical Institutional Review Board approved this study. All participants provided written informed consent.

### Participants

Eligibility criteria required that participants be at least 60 years of age and meet the general criteria for insomnia in the Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup>



Edition, Text Revision (DSM-IV-TR)<sup>22</sup> and the International Classification of Sleep Disorders, 2<sup>nd</sup> Edition (ICSD-2),<sup>23</sup> A structured clinical interview was used to determine eligibility, i.e., the presence/absence of insomnia disorder and other sleep disorders. As part of the interview, we administered an insomnia symptom checklist (see supplemental material, **Figure S3**) to specifically examine DSM-IV and ICSD-2 criteria. Specifically, insomnia criteria included: presence of a sleep complaint lasting for at least one month (median duration of symptoms was 351 weeks; minimum = 35 weeks; maximum = 2,860 weeks); adequate opportunity and circumstances for sleep; and evidence of significant distress or daytime impairment. The checklist was administered at both time points and was used to determine the presence/absence of insomnia post-treatment.

To optimize the clinical relevance and generalizability of the study, participants were eligible if they had stable, co-occurring medical or psychiatric disorders. Therefore, most of our participants had comorbid insomnia. The following exclusion criteria were applied: presence of dementia (identified by history or a score < 25 on the Folstein Mini Mental Status Exam)<sup>24</sup> or delirium; previously undiagnosed and untreated depressive, anxiety, psychotic, or substance use disorders (those with stably treated depressive and anxiety disorders were not excluded); untreated severe obstructive sleep apnea syndrome (apnea-hypopnea index [AHI] > 20), restless legs syndrome or other sleep disorders (those with stably-treated sleep disorders were not excluded); hospitalization within the past 2 weeks; ongoing chemotherapy or other cancer treatment; and terminal illness with life expectancy less than 6 months.

## Intervention

Detailed descriptions of BBTI efficacy data and therapeutic guidelines have been previously reported.<sup>4,21</sup> The manualized intervention consists of a single 45- to 60-min in-person, individual session, followed by a 30-min follow-up session 2 weeks later, and 20-min phone sessions after 1 and 3 weeks of treatment. All sessions were conducted by a master's level mental health nurse. BBTI shares many features of standard CBTi; however, it is distinct in its explicit behavioral focus (i.e., primary treatments are stimulus control and sleep restriction), its relatively short duration including 2 phone call sessions, its delivery by a nurse without prior training in behavioral sleep medicine, and the provision of a hard-copy workbook which includes the treatment rationale and specific written instructions for prescribed sleep behaviors. All intervention sessions were audiotaped. An independent evaluator randomly rated 33% of the audiotapes using a checklist of the 4 treatment elements specified in the treatment manual to rate treatment fidelity. BBTI sessions contained 97% (SD = 3.2) of intended BBTI treatment elements.

## Treatment Predictors

Baseline predictors of treatment outcome were assessed prior to treatment initiation and included data from interviews and questionnaires, sleep diaries, wrist actigraphy, and polysomnography (individual methods described below).

## Demographics

Demographic characteristics including age, sex, marital status, race/ethnicity, and education were assessed by self-report.

## Baseline Clinical Characteristics

Depressive symptoms were assessed with the 17-item Hamilton Rating Scale for Depression (HRSD).<sup>25</sup> The HRSD is a clinician-administered interview scale that assesses the presence and severity of 17 symptoms of depression experienced in the past week using a varied response format ranging from 0-2 to 0-4 (with higher scores indicating greater depression severity), and exhibits well-documented reliability and validity.<sup>26</sup> Anxiety symptoms were assessed using the Hamilton Anxiety Rating Scale (HRSA),<sup>27</sup> a widely used and well-validated interview scale that assesses 14 symptoms of anxiety.<sup>28</sup> Three items on the HRSD and 1 item on the HRSA pertaining to sleep disturbance were removed from all subsequent analyses to avoid confounding with the outcomes. Given research suggesting that people's beliefs and expectations with respect to behavioral treatments play a crucial role in shaping their experiences and outcomes of that treatment, we administered a modified, 4-item version of the Credibility and Expectancy Questionnaire (CEQ)<sup>29</sup> to all participants prior to their first treatment session, but after a brief description of each treatment condition (BBTI or information-control was provided). Example items were: "How sensible/logical does this intervention seem?" and "how much improvement in your sleep do you think will occur because of this type of treatment?" The 4 items were standardized and summed, yielding a total score with excellent internal consistency ( $\alpha = 0.85$ ).

Medical comorbidities were evaluated with a comorbidity questionnaire developed at the Center for Research on Chronic Disorders at the University of Pittsburgh School of Nursing. This measure is adapted from the Charlson Comorbidity Index<sup>30</sup> but includes a wider range of conditions, which were grouped into 17 categories (e.g., arthritis, cancer, coronary heart disease, diabetes).

Information regarding participants' use of medications known to affect sleep or wake functions (benzodiazepines, hypnotics, antidepressants, antipsychotics, anxiolytics, stimulants, antihistamines, decongestants, corticosteroids, diuretics) was collected via self-report and included as a potential predictor of treatment outcome.

## Baseline Sleep Characteristics

The *Pittsburgh Sleep Quality Index (PSQI)*<sup>31</sup> was used as a measure of global sleep quality. The PSQI is a widely-used, well-validated, self-report scale, used to assess sleep quality in the past month. Global PSQI score was utilized, with a total possible range from 0 (good sleep quality) to 21 (poor sleep quality). In the current sample, PSQI scores ranged from 6-16; (skewness = 0.34; kurtosis -0.61).

The *Pittsburgh Sleep Diary (PghSD)*<sup>32</sup> is a prospective self-report measure of daytime activities, sleep behaviors, and sleep parameters. Previous research has demonstrated that the PghSD is sensitive to differences between sleep disorder patients and good sleeper controls, and to behavioral treatment effects in insomnia patients.<sup>32,33</sup> The PghSD was administered via paper and pencil and collected for 2 weeks (mean = 13 days, SD = 1.49) at baseline. Baseline sleep diary sleep latency (SL), wakefulness after sleep onset (WASO), and total sleep time (TST), averaged over 2 weeks of baseline data collection, were evaluated as predictors of treatment outcome. Sleep diary sleep

efficiency (SE; calculated as the ratio of time spent asleep/time in bed) collected after treatment was utilized in the definition of treatment response (as defined below).

*Wrist actigraphy* was measured with the Minimitter Actiwatch-64 device (Respironics, Inc., Murrysville, PA), which was worn concurrently with the collection of sleep diary data (mean = 13.86 days; SD = 1.49). Actigraphs are wrist-watch-sized, motion-sensitive monitors worn on the participant's nondominant arm that can be used to provide a behavioral measure of sleep-wake patterns. Actigraphy data were collected in 1-min epochs and analyzed with the validated Actiware Version 5.04 software program. Actigraphy variables evaluated as predictors of treatment outcome included SL, WASO, and TST (expressed in minutes). We used definitions provided by the Actiware software for these variables, which rely on values for bedtime and rise time from the sleep diary.

*Visually scored and Quantitative EEG Sleep.* Polysomnography (PSG) was conducted in participants' homes at their habitual sleep times using Compumedics Siesta units (Compumedics Limited, Abbotsford, Victoria, Australia). One screening PSG night was used to rule out severe obstructive sleep apnea or periodic limb movements (i.e., participants with apnea-hypopnea index [AHI] > 20 or periodic limb movement arousal index [PLMA-I] > 20, [according to American Academy of Sleep Medicine Task Force standards] were excluded). Visual sleep stage scoring was conducted in 20-sec epochs by trained PSG sleep technologists with established reliability, using standard scoring criteria<sup>34</sup>; this study was conducted prior to the AASM 2007 scoring rules. Visually scored PSG measures evaluated as predictors of treatment outcome were averaged over nights 2 and 3 and included SL, WASO, TST, AHI, and PLMA-I. In addition, quantitative EEG analysis<sup>35</sup> was performed to quantify average power in the delta (0.05-4.0 Hz) range and slope of delta activity across the night, given previous associations between visually scored delta activity and treatment response.<sup>20</sup> Modified periodograms were computed using the fast Fourier transform (FFT) of non-overlapping 4-sec epochs of the sleep EEG. NREM EEGs were binned into 5-min averages across each NREM period. Any 5 min epoch that had > 4 min of artifact was removed, as well as one peak epoch from each NREM period. The one peak epoch was removed since we often saw extreme blips at beginning or end of NREM period that we believed to be artifact due to sleep staging. The peak and average delta in each NREM period was calculated from the remaining epochs. A mixed effects repeated measures analysis of variance was used to model peak and average delta across NREM periods using random intercept and slope. A natural log transformation was used on both peak and average delta in the analyses. Models were run using whole group and each subject's model-based estimate of their intercept and slope as predictors in a logistic regression.

## Treatment Outcomes

There are no universally accepted criteria for assessing response or remission in insomnia treatment studies.<sup>36</sup> For the current study, outcomes were chosen because they met the following criteria which are thought to be indicative of clinically significant change: (1) outcomes correspond to approximately 1 standard deviation of the pretreatment values (i.e., a

"large effect" according to Cohen's D of approximately 1.0); (2) outcomes are consistent with mean change values in published clinical trials; and (3) outcomes correspond to a change score of approximately -8 on the Insomnia Severity Index.<sup>37</sup> Specifically, for the current study we focused on 2 binary treatment outcomes: (1) response/remission versus partial response or nonresponse; and (2) clinical remission, defined as the participant no longer meeting DSM-IV-TR and ICSD-2 criteria for insomnia disorder after treatment using a structured interview and checklist (described above). As reported in the BBTI efficacy study,<sup>4</sup> the response/remission category consisted of those participants who had a change in PSQI score  $\geq 3$  points or increase in diary SE  $\geq 10\%$  (response) or remission defined as response criterion plus final PSQI score of  $< 5$  and sleep diary SE of  $> 85\%$ , corresponding to "good sleep" values.<sup>31</sup> The partial response or nonresponse category consisted of those who showed improvement in PSQI or SE but worsening in the other measure or change in PSQI  $< 3$  points and increase in sleep diary SE  $< 10\%$ , respectively. For the current study, we refer to these categories as "response" (inclusive of response or remission) versus "non-response" (inclusive of partial or nonresponse).

## Analyses

Sleep variables with non-normal distributions (i.e., sleep latency across all methods and diary-assessed WASO) were normalized using logarithmic transformations prior to analyses. Logistic regression models regressed each of the individual baseline variables on response or clinical remission criteria. Statistical analyses were conducted using IBM SPSS software, version 19. Statistical significance was set at a p-value of  $p < 0.05$ .

## RESULTS

**Table 1** describes sample characteristics for the 39 participants randomized to BBTI. As reported in Buysse et al., 67% of those randomized to BBTI met criteria for response/remission after 4 weeks of treatment, and 55% no longer met diagnostic criteria for insomnia after treatment.<sup>4</sup>

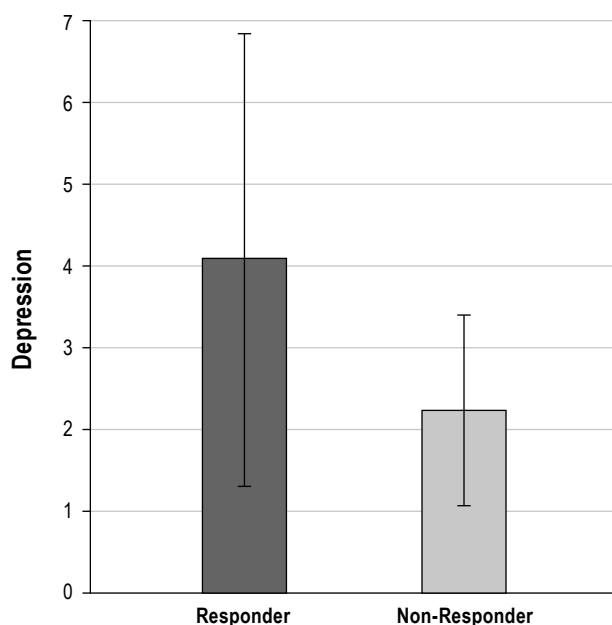
Logistic regression models which regressed baseline demographic, clinical, or sleep characteristics on response criteria are reported in **Table 2**. Higher levels of depression and anxiety were associated with higher likelihood of treatment response (as shown in **Figures 1** and **2**, respectively). In addition, poorer quality sleep at baseline, as indicated by higher PSQI scores, was associated with greater likelihood of treatment response. For visual purposes, **Figure 3** displays mean baseline PSQI values for responders versus non-responders. There was also a significant association between PSG-assessed sleep latency and treatment response, such that patients with longer sleep latency at baseline were more likely to respond to BBTI. None of the demographic, sleep diary, actigraphy, or remaining PSG or clinical measures predicted treatment response.

As shown in **Table 3**, the only significant predictors of clinical remission were total sleep time as assessed by sleep diary and in-home PSG. As shown in **Figure 4**, participants with longer PSG-assessed TST or longer diary-assessed TST at baseline were more likely to meet clinical remission criteria at post-treatment. Follow-up analyses which used the cutoff of  $\leq 6$  h of sleep (i.e., short sleepers) versus those with  $> 6$  h of sleep, showed an

**Table 1**—Baseline demographic and clinical characteristics of sample<sup>a</sup>

| Characteristic                                    | BBTI Treatment Group (N = 39) |
|---------------------------------------------------|-------------------------------|
| Age                                               | 72.54 (6.61)                  |
| Female (%)                                        | 26 (66.70)                    |
| White (%)                                         | 36 (92.30)                    |
| Education (%)                                     |                               |
| ≤ High School                                     | 7 (17.9)                      |
| Trade or Technical School                         | 4 (10.3)                      |
| College                                           | 15 (38.5)                     |
| Postgraduate                                      | 13 (33.3)                     |
| Medical and Psychiatric Status                    |                               |
| Currently Taking Sleep Medications (%)            | 12 (30.8)                     |
| Duration of Insomnia Symptoms (weeks)             | 634.9 (680.1)                 |
| Number of Chronic Health Conditions               | 5.6 (2.8)                     |
| Hamilton Rating Scale for Depression <sup>b</sup> | 7.46 (2.6)                    |
| Hamilton Rating Scale for Anxiety                 | 5.38 (2.03)                   |

<sup>a</sup>Data are reported as number (percentage) or mean (SD). <sup>b</sup>Averages are from the Hamilton Rating Scale for Depression with sleep items removed.

**Figure 1**—Mean Hamilton Rating Scale for Depression score according to responder status

increased odds of non-remission, among those defined as short sleepers by PSG (OR = 4.8; CI: 1.04-21.79) or diary (OR = 8.05; CI: 1.70-38.1). However, these analyses should be interpreted with caution due to the relatively small cell sizes for this categorical definition of short sleepers (n = 20 and n = 17, respectively, for PSG and diary), and the wide confidence interval.

## DISCUSSION

Despite the well-documented efficacy of CBT for insomnia, behavioral treatments remain under-utilized, in part due to the

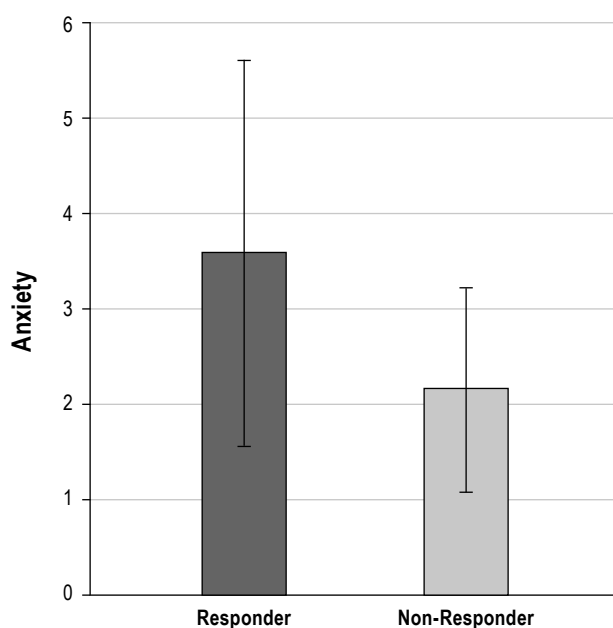
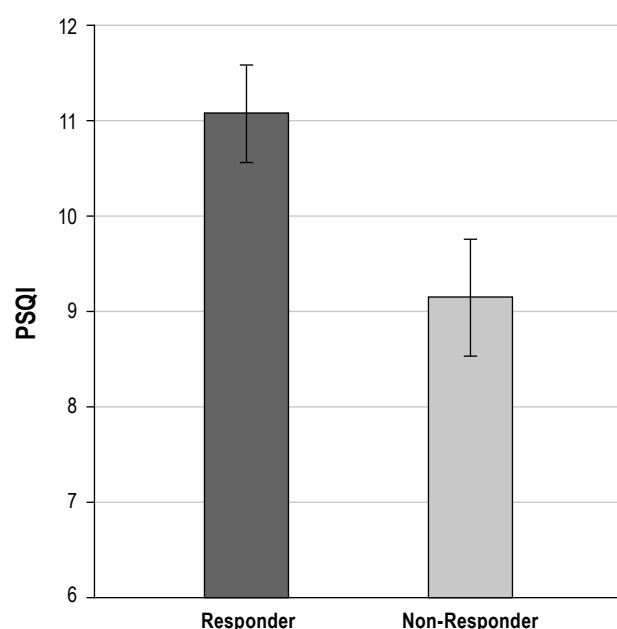
**Table 2**—Bivariate logistic regression predicting the odds of treatment response after brief behavioral treatment for insomnia (BBTI; N = 39)

|                                             | Odds Ratio (95% CI) |
|---------------------------------------------|---------------------|
| <b>Demographic Characteristics</b>          |                     |
| Age                                         | 1.03 (0.93, 1.15)   |
| Sex                                         | 2.33 (0.58, 9.37)   |
| Race                                        | 1.00 (0.08, 12.16)  |
| Marital Status                              | 1.87 (0.49, 7.18)   |
| Education                                   | 0.61 (0.11, 3.23)   |
| <b>Clinical Characteristics</b>             |                     |
| Sleep Medications                           | 0.59 (0.14, 2.42)   |
| Duration of Insomnia                        | 0.54 (0.14, 2.06)   |
| Anxiety                                     | 1.69 (1.04, 2.75)*  |
| Depression                                  | 1.53 (1.01, 2.30)*  |
| Physical Health Comorbidity                 | 0.90 (0.69, 1.17)   |
| Treatment Expectancy                        | 1.09 (0.86, 1.39)   |
| <b>Sleep Characteristics</b>                |                     |
| Subjective Sleep                            |                     |
| Daytime Sleepiness                          | 0.94 (0.73, 1.20)   |
| Sleep Quality                               | 1.40 (1.01, 1.93)*  |
| Sleep Diary                                 |                     |
| Sleep Latency† <sup>c</sup>                 | 2.02 (0.90, 4.52)   |
| Wakefulness After Sleep Onset† <sup>d</sup> | 1.22 (0.88, 1.68)   |
| Sleep Duration <sup>d</sup>                 | 1.00 (0.99, 1.01)   |
| Actigraphy <sup>d</sup>                     |                     |
| Sleep Latency†                              | 0.99 (0.37, 2.64)   |
| Wake After Sleep Onset                      | 0.99 (0.96, 1.02)   |
| Sleep Duration                              | 1.01 (1.00, 1.03)   |
| Polysomnography                             |                     |
| Visually Scored Measures <sup>e</sup>       |                     |
| Sleep Latency†                              | 4.59 (1.08, 19.48)* |
| Wake After Sleep Onset                      | 1.22 (0.88, 1.68)   |
| Sleep Duration                              | 1.00 (0.99, 1.02)   |
| Apnea-Hypopnea Index                        | 1.11 (0.96, 1.29)   |
| Periodic Leg Movement Index                 | 0.88 (0.75, 1.03)   |
| Quantitative Sleep Measures                 |                     |
| Average Delta                               | 0.48 (0.08, 2.90)   |
| Delta Slope                                 | 4.87 (0.00, 6.69)   |

\*p ≤ 0.05. †Variables transformed prior to analysis. <sup>c</sup>N = 38. <sup>d</sup>N = 37.

lack of specialty trained clinicians. Such challenges to dissemination have motivated considerable efforts to develop variants of CBTi that can be more easily disseminated to broader clinical practice.<sup>38</sup> BBTi has been shown to be efficacious for the treatment of older adults, most of whom have other comorbid medical or psychiatric conditions, with effect sizes comparable to those of CBTi. Although BBTi has been shown to be efficacious overall, this is the first study to examine a wide range of potential predictors of treatment response to BBTi.

Consistent with prior research on predictors of response to CBTi, we found no reliable evidence for differential treatment response according to demographic characteristics. However, these results may be due to the fact that the sample was restricted

**Figure 2**—Mean Hamilton Rating Scale for Anxiety score according to responder status**Figure 3**—Mean PSQI score according to responder status

in terms of age and composed primarily of educated, Caucasian older adults. Although a handful of previous studies<sup>6-8,14</sup> have indicated poorer treatment response among older adults versus younger adults, these findings may be more indicative of higher rates of co-occurring medical or psychiatric conditions in older adults. A strength of the current study was that to maximize generalizability of the findings to older adults with insomnia, we did not exclude participants with stable or treated co-occurring medical or psychiatric conditions or mild to moderate OSA or PLMs. The presence of such comorbidities also did not predict treatment response in this sample. In contrast, consistent with

**Table 3**—Bivariate logistic regression predicting the odds of remission after brief behavioral treatment for insomnia (BBTI; N = 39)

|                                    | Odds Ratio (95% CI) |
|------------------------------------|---------------------|
| <b>Demographic Characteristics</b> |                     |
| Age                                | 1.03 (0.93, 1.15)   |
| Sex                                | 0.92 (0.24, 3.52)   |
| Race                               | 0.00 (0.00, –)      |
| Marital Status                     | 2.64 (0.69, 10.18)  |
| Education                          | 0.57 (0.09, 3.55)   |
| <b>Clinical Characteristics</b>    |                     |
| Sleep Medications                  | 1.04 (0.26, 4.26)   |
| Duration of Insomnia               | 0.60 (0.16, 2.23)   |
| Anxiety                            | 1.02 (0.73, 1.44)   |
| Depression                         | 0.97 (0.74, 1.26)   |
| Physical Health Comorbidity        | 1.15 (0.89, 1.50)   |
| Treatment Expectancy               | 0.86 (.68, 1.09)    |
| <b>Sleep Characteristics</b>       |                     |
| Subjective Sleep                   |                     |
| Daytime Sleepiness                 | 1.23 (0.95, 1.57)   |
| Sleep Quality                      | 1.07 (0.84, 1.37)   |
| Sleep Diary                        |                     |
| Sleep Latency†*                    | 0.80 (0.39, 1.67)   |
| Wake After Sleep Onset††           | 1.22 (0.89, 1.66)   |
| Sleep Duration†                    | 0.99 (0.97, 1.00)*  |
| Actigraphy†                        |                     |
| Sleep Latency†                     | 0.71 (0.28, 1.83)   |
| Wake After Sleep Onset             | 0.98 (0.96, 1.01)   |
| Sleep Duration                     | 1.00 (0.98, 1.01)   |
| Polysomnography                    |                     |
| Visually Scored Measures*          |                     |
| Sleep Latency†                     | 0.94 (0.40, 2.25)   |
| Wake After Sleep Onset             | 1.01 (1.00, 1.02)   |
| Sleep Duration                     | 0.98 (0.97, 1.00)*  |
| Apnea-Hypopnea Index               | 0.93 (0.81, 1.06)   |
| Periodic Leg Movement Index        | 0.93 (0.80, 1.08)   |
| Quantitative Sleep Measures        |                     |
| Average Delta                      | 0.48 (0.08, 2.90)   |
| Delta Slope                        | 0.00 (0.00, 1.42)   |

\*p &lt; 0.05. †Variables transformed prior to analysis. \*N = 37. †N = 36.

Espie effectiveness trial,<sup>13</sup> higher clinical distress at pre-treatment, as indicated by higher depression and anxiety scores and poorer sleep quality, were associated with greater likelihood of meeting the response criteria at follow-up. Importantly, these distress characteristics were only associated with the more subjectively defined response criteria, but not by the insomnia criteria defined by structured interview, whereas PSG- or diary-assessed short sleep duration predicted the clinician-assessed outcome of remission. The fact that distress measures predicted better treatment response may reflect regression to the mean (i.e., greater opportunity for improvement with higher baseline values) or perhaps greater motivation among this subset who is most distressed by their insomnia. However, supplemental

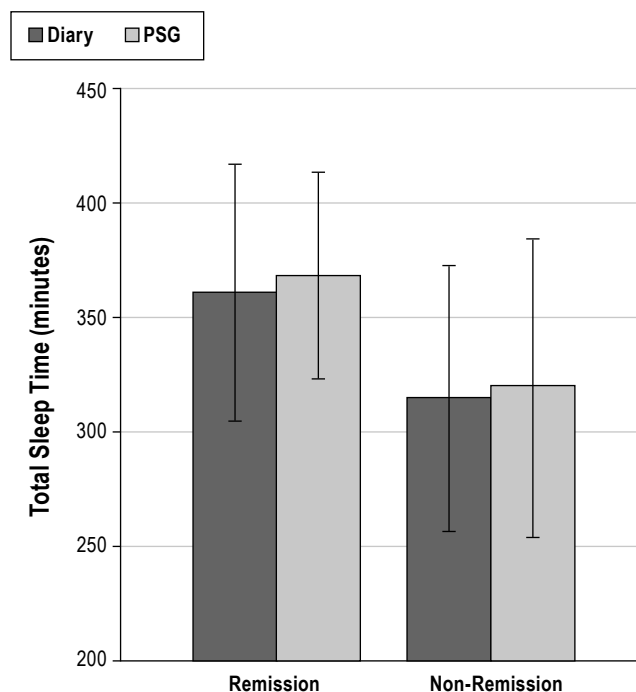


analyses conducted in the control condition demonstrated that among patients in the information-control condition, higher PSQI scores at baseline were associated with poorer treatment response (see **Figure S2**), which argues against regression to the mean. We also found that PSG-assessed prolonged sleep latency at baseline predicted higher likelihood of treatment response in the BBTI group, perhaps again due to greater motivation to change as well as opportunity for improvement, given that behavioral techniques including sleep compression are particularly effective at reducing sleep latency.

These findings are in contrast, to findings for the remission criteria, based on clinician-assessed diagnostic criteria, which showed that longer sleep diary and PSG-assessed total sleep time predicted greater likelihood of remission. Actigraphy-assessed sleep duration showed a similar pattern of results for remission, but did not reach statistical significance. Actigraphy or diary-assessed sleep latency and WASO were not associated with response or remission. These findings regarding short sleep duration have important clinical implications because they suggest that the possibility that individuals with shorter sleep durations may benefit less from behavioral sleep treatments (including BBTI), which utilize sleep restriction as a primary component of treatment. For safety reasons, including increased risk of falls associated with short sleep duration in older adults,<sup>39</sup> the BBTI protocol did not restrict time in bed less than 6 hours per night, even if pretreatment total sleep time is estimated at 6 hours. Thus, given these safety constraints, the strength of the sleep restriction component may be diminished in these patients. Recent evidence from Vgontzas' laboratory suggests that there may be a synergistic effect of insomnia with short sleep duration on a wide variety of adverse outcomes, including poorer cognitive functioning and mortality.<sup>40,41</sup> Thus, insomnia patients presenting with short sleep durations present a specific clinical challenge, given that they may fail to benefit as much from behavioral treatments of insomnia and are at greater risk for associated morbidities. On the other hand, the short duration of follow-up in this study (4 weeks) may have contributed to the finding linking short sleep duration with poor treatment outcome. For these patients, longer follow-up periods may be necessary to allow sufficient time for the benefits of sleep restriction to be realized. In contrast to the findings of Krystal and Edinger,<sup>20</sup> we did not find evidence for an effect of overall delta activity or slope of delta activity across the night on treatment outcomes. Several methodological differences may account for the discrepancy in results. In particular, Krystal's findings were based on a smaller sample ( $N = 16$ ) of primarily middle-aged adults (mean age = 56), whereas the current findings were based on a sample of 39 older adults all over the age of 60 (mean age = 72). Given age-related declines in peak delta activity and blunted delta dynamics (i.e., lesser slope) throughout the night, our findings which were restricted to older adults may reflect a lack of range in delta activity and subsequent reduction in power. In addition, the two studies used similar, but not identical, methods for calculating delta EEG activity. Nevertheless, given the putative role of homeostatic sleep pressure as a mechanism of change in behavioral sleep treatments, future research is needed to examine the impact of sleep micro-architecture and dynamics in broader clinical samples.

These findings must be interpreted within the context of study limitations. First, findings may not generalize beyond

**Figure 4**—Diary or PSG-assessed total sleep time according to remission status



older, predominantly Caucasian adults with insomnia, who were recruited from the community or a primary care practice, and who volunteered to participate in research. Second, although the relatively inclusive recruitment strategy is a strength of the study, the enhanced generalizability of results also introduces greater heterogeneity and potential confounds, such as the inclusion of patients with mild to moderate levels of sleep disordered breathing or periodic leg movements, which may have influenced the results. Although, the study characterized a wide range of pretreatment demographic, clinical, sleep, and neurophysiologic indicators of treatment response, we did not measure all potentially informative treatment predictors, such as motivation for change (although we did assess treatment expectancies, which was not related to outcome). As previously mentioned, the relatively short follow-up (4 weeks) may have implications for the results, particularly with regard to the sleep duration finding. There are limitations with regard to the definition criteria for treatment response. Specifically, treatment response was based, in part, on change in PSQI scores, which is a general measure of sleep quality, rather than a measure specific to insomnia severity, such as the Insomnia Severity Index (ISI).<sup>37</sup> However, only a subset of the sample ( $N = 17$ ) completed the ISI. Finally, the magnitude of observed effects may be partially attributable to the use of a single clinician. Whether similar effects would be observed across different clinicians, with different professional backgrounds and varying levels of experiences cannot be ascertained. On the other hand, delivery by a single therapist has the advantage of minimizing inter-therapist variability.

These limitations notwithstanding, the current findings contribute to our understanding of *in whom* behavioral treatments for insomnia are most likely to benefit. This question is absolutely critical as there continues to be a substantial gap between the solid

evidence base supporting behavioral treatments for insomnia and the actual use of such treatments in clinical practice. Our findings also suggest that even complex insomnia cases, including those with comorbid mood or sleep disorders or medical conditions may benefit from a brief behavioral treatment delivered by a mental health nurse without prior training in sleep medicine, rather than a doctoral-level clinical psychologist. These findings also provide convergent evidence from sleep diaries and PSG to suggest that insomnia patients with short sleep duration or with short sleep latency may be a specific subset of the patient population that requires different treatment approaches, with more extended follow-up, such as adjunctive pharmacotherapy or multi-component behavioral strategies which rely more on cognitive techniques (e.g., thought restructuring) or other behavioral techniques (e.g., relaxation or mindfulness-based approaches). Alternatively, it is possible that these patients would benefit from the sleep restriction component of BBTI if limits regarding the minimum time in bed (set at 6 hours for this protocol) were removed; however, safety issues are a concern. In summary, identifying predictors of treatment response to behavioral treatments for insomnia is critical in order to refine treatment algorithms to optimize treatment response, improve patient adherence and satisfaction, most efficiently allocate resources (including specialty trained clinicians), and ultimately reduce the economic and public health burden of insomnia.

## ABBREVIATIONS

AASM, American Academy of Sleep Medicine  
 AHI, apnea-hypopnea index  
 BBTI, brief behavioral treatment of insomnia  
 CBTI, cognitive behavioral therapy for insomnia  
 CCI, Charlson Comorbidity Index  
 CEQ, Credibility and Expectancy Questionnaire  
 DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> Edition, Text Revision  
 EEG, electroencephalography  
 FFT, fast Fourier transformation  
 HRSA, Hamilton Rating Scale for Anxiety  
 HRSD, Hamilton Rating Scale for Depression  
 ICSD-2, International Classification of Sleep Disorders, 2<sup>nd</sup> Edition  
 ISI, Insomnia Severity Index  
 NREM, non-rapid eye movement  
 PghSD, Pittsburgh Sleep Diary  
 PLMA-I, periodic leg movement with arousal index  
 PSG, polysomnography  
 PSQI, Pittsburgh Sleep Quality Index  
 SE, sleep efficiency  
 SL, sleep latency  
 TST, total sleep time  
 WASO, wakefulness after sleep onset

## REFERENCES

- Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. Sleep complaints among elderly persons: an epidemiologic study of three communities. *Sleep* 1995;18:425-32.
- Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA* 1989;262:1479-84.
- Morin CM, Bootzin RR, Buysse DJ, Edinger JD, Espie CA, Lichstein KL. Psychological and behavioral treatment of insomnia: An update of recent evidence (1998-2004). *Sleep* 2006;29:1398-414.
- Buyse DJ, Germain A, Moul DE, et al. Efficacy of brief behavioral treatment for chronic insomnia in older adults. *Arch Intern Med* 2011;171:887-95.
- Irwin MR, Cole JC, Nicassio PM. Comparative meta-analysis of behavioral interventions for insomnia and their efficacy in middle-aged adults and in older adults 55+ years of age. *Health Psychol* 2006;25:3-14.
- Alpers J, Biglan A. Self administered treatment of sleep onset insomnia and the importance of age. *Behav Ther* 1979;10:337-46.
- Edinger JD, Stout AL, Hoelscher TJ. Cluster analysis of insomniacs' MMPI profiles: relation of subtypes to sleep history and treatment outcome. *Psychosom Med* 1988;50:77-87.
- Gagne A, Morin CM. Predicting treatment response in older adults with insomnia. *J Clin Geropsychol* 2001;7:131-43.
- Chambers MJ, Alexander SD. Assessment and prediction of outcome for a brief behavioral insomnia treatment program. *J Behav Ther Exp Psychiatry* 1992;23:289-97.
- Espie CA, Inglis SJ, Tessler S, Harvey L. The clinical effectiveness of cognitive behaviour therapy for chronic insomnia: Implementation and evaluation of a sleep clinic in general medical practice. *Behav Res Ther* 2001;39:60.
- Van Houdenhove L, Buysse B, Gabriels L, Van den Bergh O. Treating primary insomnia: Clinical effectiveness and predictors of outcomes on sleep, daytime function and health-related quality of life. *J Clin Psychol Med Settings* 2011;18:312-21.
- Morin CM, Kowatch RA, Barry T, Walton E. Cognitive-behavior therapy for late-life insomnia. *J Consult Clin Psychol* 1993;61:137-46.
- Espie CA, Inglis SJ, Harvey L. Predicting clinically significant response to cognitive behavior therapy for chronic insomnia in general motor practice: Analyses of outcome data at 12 months posttreatment. *J Consult Clin Psychol* 2001;69:58-66.
- Lacks P, Powlishta K. Improvement following behavioral treatment for insomnia: Clinical significance, long-term maintenance, and predictors of outcome. *Behav Ther* 1989;20:117-34.
- Vincent N, Penner S, Lewycky S. What predicts patients' perceptions of improvement in insomnia? *J Sleep Res* 2006;15:301-8.
- Blivise DL, Friedman L, Nekich JC, Yesavage JA. Prediction of outcome in behaviorally based insomnia treatments. *J Behav Ther Exp Psychiatry* 1995;26:17-23.
- Lichstein KL, Durrence HH, Taylor DJ, Bush AJ, Riedel BW. Quantitative criteria for insomnia. *Behav Res Ther* 2003;41:427-45.
- Currie SR, Wilson KG, Curran D. Clinical significance and predictors of treatment response to cognitive-behavior therapy for insomnia secondary to chronic pain. *J Behav Med* 2002;25:135-53.
- Riemann D, Perlis ML. The treatments of chronic insomnia: a review of benzodiazepine receptor agonists and psychological and behavioral therapies. *Sleep Med Rev* 2009;13:205-14.
- Krysl AD, Edinger JD. Sleep EEG predictors and correlates of the response to cognitive behavioral therapy for insomnia. *Sleep* 2010;33:669-77.
- Troxel WM, Germain A, Buysse DJ. Clinical management of insomnia with Brief Behavioral Treatment (BBTI). *Behav Sleep Med* 2012;10:266-79.
- American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-IV-TR). fourth edition, text revision*. Washington, DC: American Psychiatric Association, 2000.
- American Academy of Sleep Medicine. *International classification of sleep disorders, second edition (ICSD-2): diagnostic and coding manual*. Westchester, IL: American Academy of Sleep Medicine, 2005.
- Folstein MF, Folstein SW, McHugh PR. Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-98.
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62.
- Prien RF, Carpenter LL, Kupfer DJ. The definition and operational criteria for treatment outcome of major depressive disorder: A review of the current research literature. *Arch Gen Psychiatry* 1991;48:796-800.
- Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;32:50-5.
- Shear MK, Vander Bilt J, Rucci P, et al. Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale. *Depress Anxiety* 2001;13:166-78.
- Borkovec TD, Nau SD. Credibility of analogue therapy rationales. *J Behav Ther Exp Psychiatry* 1972;3:257-60.

30. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies. *J Chron Dis* 1987;40:373-83.
31. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193-213.
32. Monk TH, Reynolds CF, Kupfer DJ, et al. The Pittsburgh Sleep Diary. *J Sleep Res* 1994;3:111-20.
33. Germain A, Moul DE, Franzen PL, et al. Effects of a brief behavioral treatment for late-life insomnia: Preliminary findings. *J Clin Sleep Med* 2006;2:403-6.
34. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Washington DC: US Government Printing Office, 1968.
35. Brunner DP, Vasko RC, Detka CS, Monahan JP, Reynolds CF, Kupfer DJ. Muscle artifacts in the sleep EEG: Automated detection and effect on all-night EEG power spectra. *J Sleep Res* 1996;5:155-64.
36. Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM. Recommendations for a standard research assessment of insomnia. *Sleep* 2006;29:1155-73.
37. Yang M, Morin CM, Schaefer K, Wallenstein GV. Interpreting score differences in the Insomnia Severity Index: using health-related outcomes to define the minimally important difference. *Curr Med Res Opin* 2009;25:2487-94.
38. Perlis ML, Smith MT. How can we make CBTI and other BSM services widely available? *J Clin Sleep Med* 2008;4:11-3.
39. Stone KL, Ancoli-Israel S, Blackwell T, et al. Actigraphy-measured sleep characteristics and risk of falls in older women. *Arch Intern Med* 2008;168:1768-75.
40. Fernandez-Mendoza J, Calhoun S, Bixler EO, et al. Insomnia with objective short sleep duration is associated with deficits in neuropsychological performance: a general population study. *Sleep* 2010;33:459-65.
41. Vgontzas AN, Liao D, Pejovic S, et al. Insomnia with short sleep duration and mortality: the Penn State cohort. *Sleep* 2010;33:1159-64.

## SUBMISSION & CORRESPONDENCE INFORMATION

**Submitted for publication February, 2013**

**Submitted in final revised form July, 2013**

**Accepted for publication August, 2013**

Address correspondence to: Wendy M. Troxel, Ph.D., 4570 Fifth Avenue, Suite 600, Pittsburgh, PA 15213; Tel: (412) 683-2300 ext: 4427; Fax: (412) 683-2800; E-mail: wtroxel@rand.org

## DISCLOSURE STATEMENT

This was not an industry supported study. Funding for this research was provided by National Institutes of Health grants AG020677 (PI: Timothy Monk, Ph.D., D.Sc.), MH024652 (PI: Daniel Buysse, M.D.), RR024153 (PI: Daniel Buysse, M.D.), and K23HL093220 (PI: Wendy M. Troxel, Ph.D.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Dr. Buysse serves as a paid consultant for Merck, Philips, and Transcept Pharmaceuticals, Inc., and he has been paid for lectures at international, non-CME educational meetings supported by Servier and Astellas. The other authors have indicated no financial conflicts of interest.





# The Sleep and Technology Use of Americans: Findings from the National Sleep Foundation's 2011 Sleep in America Poll

Michael Gradisar, Ph.D., F.A.A.S.M.<sup>1</sup>; Amy R. Wolfson, Ph.D.<sup>2</sup>; Allison G. Harvey, Ph.D.<sup>3</sup>; Lauren Hale, Ph.D.<sup>4</sup>,  
Russell Rosenberg, Ph.D., F.A.A.S.M.<sup>5,6</sup>; Charles A. Czeisler, Ph.D., M.D.<sup>7</sup>

<sup>1</sup>Flinders University, School of Psychology, Adelaide, Australia; <sup>2</sup>College of the Holy Cross, Department of Psychology, Worcester, MA; <sup>3</sup>University of California, Berkeley, CA; <sup>4</sup>Stony Brook University, Department of Preventive Medicine, Stony Brook, NY; <sup>5</sup>Atlanta School of Sleep and Medicine Technology, Atlanta, GA; <sup>6</sup>National Sleep Foundation, Washington, DC; <sup>7</sup>Division of Sleep Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA; Division of Sleep Medicine, Harvard Medicine School, Boston, MA

**Study Objectives:** To describe the technology use and sleep quality of Americans, and the unique association between technology use and sleep disturbances.

**Methods:** Interviews were conducted via random digit dialing (N = 750) or the Internet (N = 758). 1,508 Americans (13-64 years old, 50% males) matched to 2009 U.S. Census data provided complete interviews. The sample was further divided into adolescents (13-18 years, N = 171), young adults (19-29 years, N = 293), middle-aged adults (30-45 years, N = 469), and older adults (46-64 years, N = 565) to contrast different generations' technology use. Participants answered a 47-item semi-structured survey, including questions about their sleep habits, and the presence and use of technology in the hour before bed in the past 2 weeks.

**Results:** Nine of 10 Americans reported using a technological device in the hour before bed (e.g., TVs the most popular; 60%). However, those under 30 years of age were more likely to use cell phones (72% of adolescents, 67% of young adults) than those over 30 years (36% of middle-aged, and 16% of older adults). Young adults' sleep patterns were significantly

later than other age groups on both weekdays and weekend nights. Unlike passive technological devices (e.g., TV, mp3 music players), the more interactive technological devices (i.e., computers/laptops, cell phones, video game consoles) used in the hour before bed, the more likely difficulties falling asleep ( $\beta = 9.4$ ,  $p < 0.0001$ ) and unrefreshing sleep ( $\beta = 6.4$ ,  $p < 0.04$ ) were reported.

**Conclusions:** Technology use near bedtime is extremely prevalent in the United States. Among a range of technologies, interactive technological devices are most strongly associated with sleep complaints.

**Keywords:** Sleep, sleep disturbances, technology, electronic media, interactive devices

**Commentary:** A commentary on this article appears in this issue on page 1301.

**Citation:** Gradisar M; Wolfson AR; Harvey AG; Hale L; Rosenberg R; Czeisler CA. The sleep and technology use of Americans: findings from the National Sleep Foundation's 2011 Sleep in America Poll. *J Clin Sleep Med* 2013;9(12):1291-1299.

## BRIEF SUMMARY

**Current Knowledge/Study Rationale:** To date, there has not been a large-scale survey across generations using comprehensive measures of sleep and technology use close to bedtime.

**Study Impact:** Americans' use of technology near sleep is highly prevalent, and related to sleep difficulties, especially in younger age groups (i.e., < 30 years of age).

The emergence of the computer chip and the rapid technological advances that ensued have enhanced industrialized societies' ability to work and play. Indeed, in the 1970s, technology was hoped to promote a 4-day work week by reducing the physical strain of labor, thus providing more time for leisure.<sup>1</sup> Personal computers (PCs) began to enter homes in the early 1980s, and ownership has increased steadily; nearly 8 of 10 Americans now own a PC.<sup>2,3</sup> Video game console ownership paralleled PC ownership in homes in the 1980s, and in 2011 approximately US\$17.8 billion was spent on video game hardware.<sup>4</sup> In the mid-1990s, 2 of 10 Americans had personal access to the developing Internet.<sup>3</sup> Now, 7 of 10 Americans have access to the Internet in their homes.<sup>3</sup> However, it is the once-humble cell phone that is now ubiquitous worldwide. In 2011, there were 6 billion cell phone subscriptions worldwide—enough for 87% of the world's population.<sup>5</sup> These technological devices have become smaller and therefore more portable. One exception is that television screen dimensions have grown. However, "watching TV" may now be performed on smaller devices (e.g., cell phones) due to increased multi-functionality.

For example, in addition to making phone calls, cell phones now allow the user to instant message, listen to music, send emails, play games, and surf the Internet. Furthermore, technological devices have become more affordable, thus allowing more users to access technology as we enter the second decade of the new millennium.

The affordability and portability of technology has seen these devices move into bedrooms. In the 2006 Sleep in America Poll, 97% of US teens had at least one technological device in their bedroom, with mp3 players being the most popular (90%) followed by TVs (57%), video games and cell phones (42%), and computers (28%) with Internet access (21%).<sup>6</sup>

Prevalence rates from other countries sometimes match those found in the USA. (e.g., 60% of Israeli adolescents have a TV in their bedroom; 60% have a computer in their bedroom).<sup>7</sup> More recent US data demonstrate that media presence in the bedroom has increased. For example, 33% of young people (8-18 years) now have Internet access in their bedroom.<sup>8</sup> For adults, 30% of Belgians had a TV in their bedroom and 25% had Internet access in their bedroom,<sup>9</sup> and these figures double for Korean adults.<sup>10</sup> Evening use of these devices in Japan have also ranged from 48% to 60%.<sup>11</sup> In terms of concern about sleep and health, it is not the mere presence of these devices in the bedroom, but more importantly, when, and the extent to which these devices are used. Despite longstanding recommendations that stimulating activities should be avoided when preparing for bed,<sup>12</sup> several studies have shown that technology use still occurs regularly before bed.<sup>6,7,12-16</sup> However, these studies have not comprehensively assessed the range of technological devices used in the bedroom in the hour before bed and their associations with sleep. Accordingly, the first aim of the present study is to describe the technology use of Americans in their bedrooms in the hour before bed using a national poll of adults. A second aim is to describe Americans' self-reported sleep habits and sleep quality. The third aim of the present study is to investigate associations between technology use and sleep.

Several mechanisms have been proposed for how evening technology use may affect sleep.<sup>17,18</sup> One of these mechanisms is that the use of stimulating technological devices may cause hyperarousal that interferes with healthy sleep initiation. Stimulating technological devices may include those devices with which the user is frequently interacting, such as video consoles, cell phones, and computers. Such interactions may impede the natural withdrawal of sympathetic nervous system activity necessary for sleep onset.<sup>19-21</sup> In contrast, other devices may involve "passive observation" and require little input from the user of the device (e.g., watching TV, listening to music). Therefore, we hypothesize that use of stimulating technological devices in the hour before bed will be associated with sleep problems (i.e., difficulty initiating sleep, unrefreshing sleep). Furthermore, difficulty maintaining sleep may occur from devices that wake individuals. Van den Bulck found that 10% to 20% of adolescents use their cell phone or are awakened by incoming calls/text messages after lights out.<sup>22,23</sup> Therefore, the effects of cell phones on maintaining sleep will also be investigated.

## METHODS

### Participants

The sample consisted of 1,508 participants, ages 13-64 years, who resided in the United States (50% males, 50% females). Of the total sample, 37% resided in the South, 23% in the West, 22% in the Midwest, and 17% in the Northeast. Over the previous month, 64% percent of the total sample was employed, 22% were enrolled as students, and 19% were neither (see footnote 1). Approximately half the sample was married (54%), a third were single (33%), and the remaining participants were either divorced (6%), in a de facto relationship (4%), separated (2%), or widowed (1%). The majority of Americans sampled

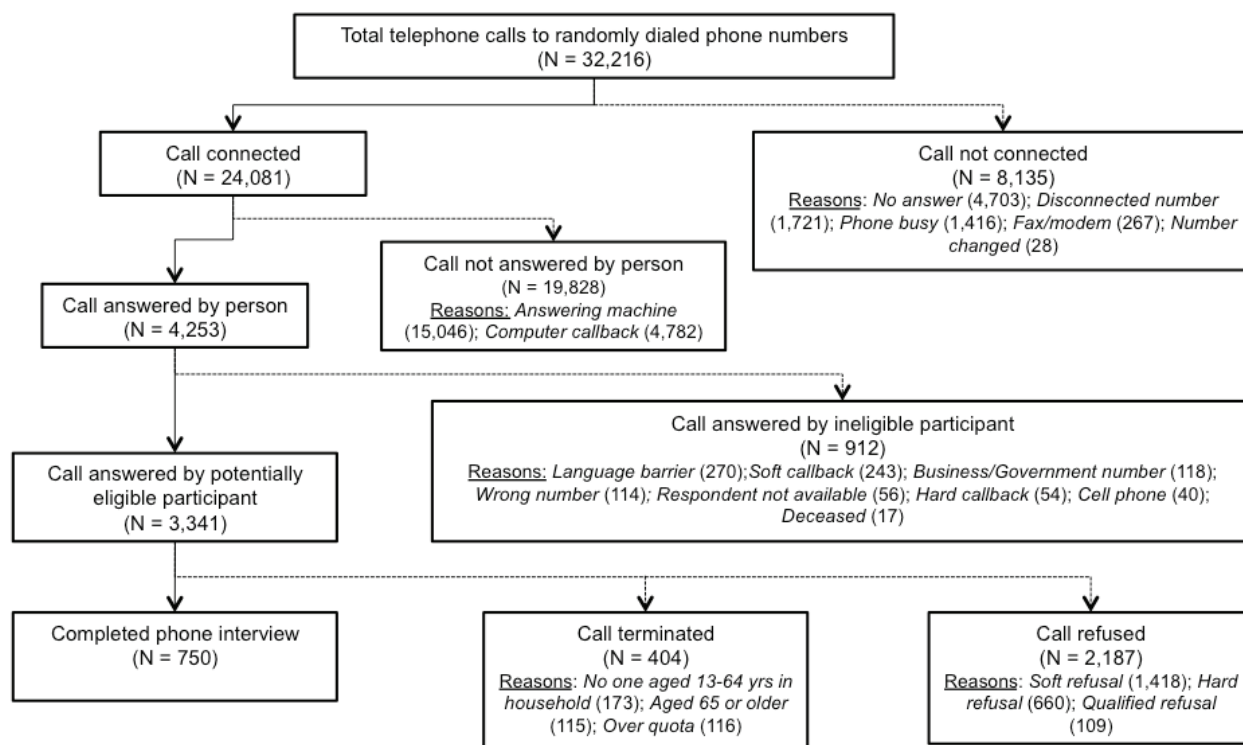
were white/Caucasian (81%), followed by African American (7%) Asian (6%), Hispanic (4%) or American Indian (1%) (see footnote 2). Since one of the objectives of the study was to compare the sleep habits and technology use of Americans across different age groups, the sample was split into the categories of adolescents (13-18 years, N = 171, 11.3% of the total sample), young adults (19-29 years, N = 293, 19.4% of the sample), middle-aged adults (30-45 years, N = 469, 31.1% of the sample), and older adults (46-64 years, N = 575, 38.2% of the sample).

Approximately half the sample completed phone surveys (N = 750), and the remaining participants completed the survey on the web (N = 758). These multiple methods were performed because telephone sampling tends to over-represent older populations, and thus the web-sampling would provide a better representation of younger populations. Consistent with that expectation, younger populations were more likely to complete web surveys than phone surveys (adolescents: N = 50 for phone vs. N = 113 for web; young adults: N = 71 for phone vs. N = 161 for web), yet older populations were more likely to complete phone surveys than web surveys (middle adults: N = 268 for phone vs. N = 201 for web; older adults: N = 353 for phone vs. N = 294 for web). Random digital dialing (RDD) was performed by SDR Consulting, Inc. (Atlanta, USA) to generate a set of phone numbers. **Figure 1** presents a flowchart of participant recruitment via RDD as per STROBE guidelines.<sup>24</sup> The overall phone response rate for the 2011 Poll was 2.3% (see footnote 3), with a cooperation rate of 23.3% (see footnote 4), a refusal rate of 11.9% (see footnote 5), and a contact rate of 17.6% (see footnote 6).<sup>25</sup> The maximum sampling error for the total sample was  $\pm 2.5$  percentage points (95% CI). This study was exempt from institutional review board approval as the research conducted by the National Sleep Foundation (a not-for-profit organization) involved observations of public behavior where human subject data were de-identified.<sup>26</sup>

### Measures

The survey instrument consisted of 47 structured questions with coded responses. The survey opened with several questions targeting key demographic information (i.e., age, region, employment, gender), followed by questions reporting participants' sleep habits on weekdays and non-working days (including daytime naps) over the past 2 weeks. Further questions assessed sleep quality (e.g., *On how many nights would you say "I had a good night's sleep"?*), sleep need (e.g., *On average how many hours of sleep do you need to function at your best the next day?*), and the impact of not getting enough sleep on occupational/vocational performance and relationships with significant others. The survey included the Epworth Sleepiness Scale<sup>27</sup> to assess daytime sleepiness. Participants were also asked about the frequency of drowsy driving, and coping behaviors (e.g., average daily caffeine consumption). The frequency of sleep problems (difficulty falling asleep, difficulty maintaining sleep, unrefreshing sleep) was asked (e.g., *In the past 2 weeks, would you say you had difficulty falling asleep?*), with responses measured on a 4-point Likert scale ranging from *"every night or almost every night"* to *"never."*

Eleven questions asked participants about the presence and use of various technological devices in the bedroom (e.g., TV,

**Figure 1**—Flowchart of participant recruitment using Random Digit Dialing to arrive at N = 750 quota

cell phones, computer/laptops, video/computer games) in the hour before bed in the past 2 weeks. Questions were also asked about the types of activities performed on these devices in the hour before bed (but not limited to use in the bedroom), the content viewed, and sleep interruptions resulting from technological devices during the night. Presence and use of technological devices was answered in a Yes/No format, and frequency of technology use was typically answered on a Likert scale ranging from “Never” to “Every night or almost every night.”

Not all questions were asked for all participants. For example, if a participant indicated they did not use a particular device before bed (e.g., cell phone), they then skipped questions related to particular functions and content on such a device. For ethical reasons, adolescents were not asked particular questions that older participants were (e.g., whether not getting enough sleep affected their intimate or sexual relations). The survey instrument appears in full in the Appendix of the 2011 Summary of Findings (<http://www.sleepfoundation.org/article/sleep-america-polls/2011-communications-technology-use-and-sleep>).

## Procedure

In 2010, the National Sleep Foundation assembled an expert panel of sleep researchers, chaired by one of us (RR). Panel members were informed of the 2011 Sleep in America Poll objectives, and together developed the survey instrument over a series of conference calls. WB&A Market Research were contracted to conduct the 2011 Sleep in America Poll. Professional interviewers conducted phone interviews mainly on weekdays (17:00 to 21:00), Saturdays (10:00-14:00), and Sundays (16:00-20:00). Remaining phone surveys were

conducted on weekdays (09:00-17:00). A sample of cell phones was included with landline phones to reach the growing trend of cell phone-only households.<sup>28</sup> Phone surveys were completed on average in 18.0 min. No equivalent data were available for surveys completed on the web. Web surveys were conducted via an E-Rewards online panel of registrants. All surveys were conducted with the respondents themselves (i.e., including adolescents). The survey was introduced as “the annual Sleep in America Poll” conducted on behalf of the National Sleep Foundation. Potential respondents were informed of the confidentiality of any information they provided. Data were collected from late October 2010 to late November 2010. To reduce the impact of age on the results, data were weighted based on age so as to be comparable to 2009 U.S. Census data estimates.<sup>29</sup>

## Statistical Analyses

Independent z-tests were used to compare outcome variables (reported as percentages) across the 4 age groups.<sup>30</sup> Significant differences between groups occurred when the z-statistic exceeded 1.96 (using 95% confidence interval). Z-scores > 2.57 were significant using 99% confidence interval. A series of linear regressions were used to assess the unique contributions from various aspects of technology use on sleep while controlling for significant covariates (i.e., age, gender, ambient light, naps, caffeine consumption). The “amount of technology used” was the main predictor variable and is defined as the total number of devices used in the hour before bed, which resulted from the question, “Thinking about the past 2 weeks, on a typical night which of the following are in your bedroom and you use in the hour before trying to go to sleep?” This predictor variable was further split into the number of interactive technological devices used (i.e.,



computers/laptops, cell phone, video gaming) and the number of passive technological devices used (i.e., TV, reading, mp3 music players) to test the hypothesis that stimulating devices are more likely to relate to difficulties sleeping. Statistical significance was set at  $\alpha = 0.05$ . When statistical significant differences were detected, standardized regression coefficients (i.e., standardized beta [ $\beta$ ]) were reported. The  $\beta$  represents the change in the dependent variable (sleep difficulty) for every one standard deviation change in the independent variable (number of technology items used). Due to the high variability in the way technology use is measured, standardizing the beta coefficient allows for easier comparisons across studies.

## RESULTS

### Technology Presence and Use

For the entire sample, 90% of Americans reported using some form of technological device in the bedroom in the hour before trying to sleep. Of those aged under 30 years, technology use was even more prevalent (96% of adults younger than 30 years used some form of technology). For the overall sample, TVs were the most commonly used (60%), then cell phones (39%), followed by computers/laptops (36%), electronic music devices (29%), telephones (21%), video game consoles (8%) and lastly e-book readers (6%). There were, however, notable age differences.

Although 39% of the entire sample used cell phones in their bedroom in the hour before bed, 72% of adolescents and 67% of young adults used cell phones, both significantly more than middle adults (30–45 years: 36%), and older adults (46–64 years: 16%); all  $z$ s  $\geq 8.78$ . Similar significant patterns emerged for computers/laptops (both adolescents and young adults 60% vs. older adults 22%) and electronic music devices (adolescents = 64% and young adults 43% vs. older adults = 17%; all  $z$ s  $\geq 7.91$ ). Although not as prevalent, video game consoles were used significantly more by under 30s (adolescents = 23%; young adults = 18% vs. older adults = 1%; all  $z$ s  $\geq 6.78$ ).

Several other significant demographic differences were found for devices used in the bedroom in the hour before bed. Females were more likely than males to use the telephone (24% vs. 18%), and read printed books (54% vs. 43%) and e-book readers (7% vs. 4%; all  $z$ s  $\geq 2.56$ ). Conversely, males were more likely to use a video gaming console (12% vs. 3%;  $z = 6.74$ ). Single Americans were about twice as likely to use a computer/laptop (45% vs. 24%), cell phone (52% vs. 21%), electronic music device (34% vs. 17%), or videogame console (9% vs. 2%) than married Americans (all  $z$ s  $\geq 4.88$ ). African Americans were more likely to watch TV (76%) than white Americans (59%) and Asian Americans (49%), and use a telephone compared to all other Americans (53% vs.  $\leq 29\%$ ; all  $z$ s  $\geq 3.75$ ). Asian Americans were more likely to use a computer/laptop (68%) than all other groups (32% to 49%; all  $z$ s  $\geq 2.79$ ). African Americans and Hispanic Americans (both 61%) used cell phones more than white Americans (34%) and Asian Americans (45%; all  $z$ s  $\geq 2.29$ ). White Americans were less likely to use an electronic music device (24%) than all other groups (40% to 49%) and a video gaming console (6%, vs. 13 and 20% for Asian Americans and Hispanic Americans, respectively;

all  $z$ s  $\geq 1.96$ ). These percentages mirror some findings from a previous Sleep in America Poll.<sup>16</sup>

When investigating specific activities performed in the hour before bed (but not necessarily in the bedroom) for the entire sample, watching TV was the most common activity performed at least a few nights a week (79%). This was followed by: doing homework on the computer (68%); surfing the Internet (54%); reading a printed book/magazine (48%); doing work on the computer (40%); personal emailing (39%); social networking (38%); text messaging (38%); talking on the phone (29%); watching a video (21%); work-related e-mailing (19%); video gaming (19%); listening to music (18%); and reading on an e-book (5%). Nearly the entire sample (97%) reported performing at least one of these activities in the hour before bed.

### Sleep Habits, Sleep Quality

**Figure 2** presents the weekday and non-workday sleep habits of the various age groups. Young adults went to bed significantly later than all other age groups on both weekdays and weekends, and adolescents went to bed significantly later on weekends than groups over 30 years of age. Wake times were reasonably consistent across age groups with 2 exceptions. On weekdays, young adults rose significantly later than all other age groups, and on weekends middle adults rose later than adolescents and older adults.

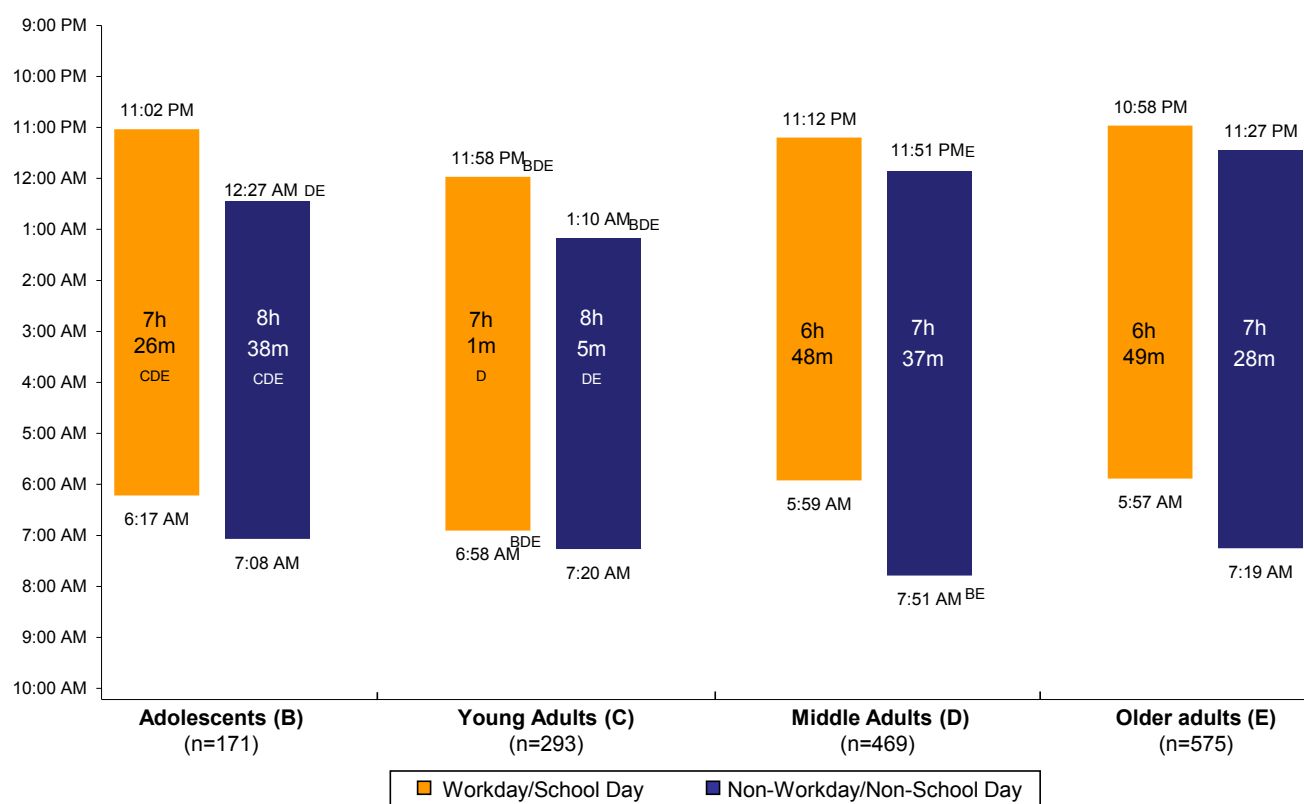
As total sleep time varies as a function of age,<sup>31</sup> whether participants were obtaining enough sleep to meet their needs was also measured. Overall, 35% of the sample reported getting enough sleep on weeknights, whereas roughly 6 in 10 Americans (63%) claimed they were not getting enough sleep to function properly. This was particularly true for adolescents (67%), young adults (67%), and middle adults (65%) compared to older adults (58%). For those Americans reporting insufficient sleep ( $N = 420$ ), 94% reported at least some impact on at least one of the following: mood, school work, family life or home responsibilities, work, social life or leisure activities, and/or intimate/sexual relations (see **Figure 3**). Of these Americans, 51% reported not obtaining enough sleep had a *major* impact on one of these areas of functioning. Of Americans who drive, 37% reported they had driven drowsy in the past month. One in 2 young adults reported this occurred at least once a month, which was significantly more than every other age group (older adults = 28%; middle adults = 30%; adolescents = 40% [see footnote 7]).

### Associations between Technology Use and Sleep Problems

We explored possible associations between technology use and sleep using a series of linear regressions (**Table 1**). The amount of technology use before bed (the greater the number of technological devices used in the bedroom in the hour before bed) did not predict any unique variance in bedtimes on weeknights after controlling for demographic (age and gender) or other sleep hygiene variables (light in the bedroom, naps, and caffeine consumption) known to also affect sleep ( $t_{1467} = 1.09$ ,  $p > 0.05$ ). Since we hypothesized that certain technological devices could be more engaging and thus lead to later bedtimes (e.g., cell phone), regression analyses were performed for each device; however, none contributed significant variance to weeknight bedtimes. Of



**Figure 2**—Self-reported sleep habits on weekdays and weekends between adolescents (B), young adults (C), middle adults (D) and older adults (E)



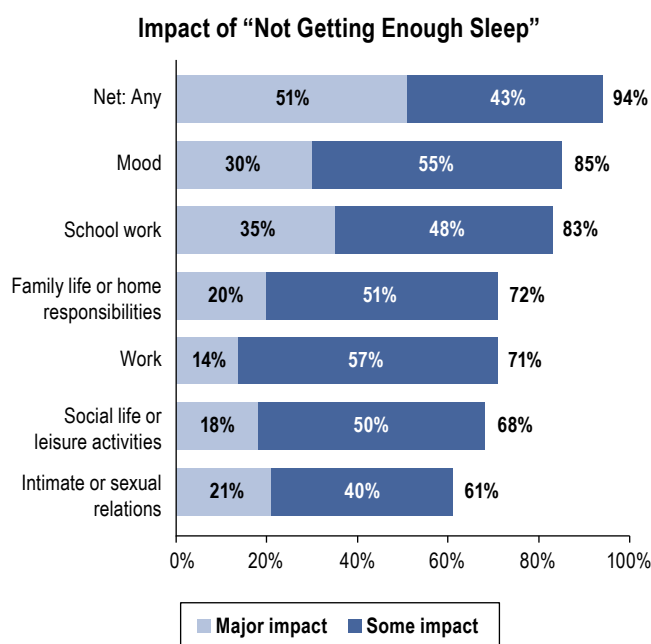
Values on top of bars represent mean bedtimes; values within bars represent mean total sleep times; values below bars represent mean rise times; alphabetic letters adjacent to means represent significant differences between age groups. For example, CDE adjacent to 7h 26m in adolescents' school day total sleep time means this value is significantly different to young- (C), middle- (D), and older adults (E).

all variables considered, only napping (on weekends) was significantly related to later bedtimes in each analysis ( $\beta = 5.7\%$ – $6.2\%$ ; all  $p < 0.05$ ). Interestingly, frequent nappers (napping  $> 3$  times in past 2 weeks) were more likely to use interactive technological devices before bed ( $F_{1,1504} = 6.88$ ,  $p = 0.009$ ), suggesting significant overlap between napping and using stimulating technological devices when predicting bedtimes.

After controlling for covariates, we found that the amount of media used in the bedroom in the hour before bed was significantly related to difficulty falling asleep ( $t_{1460} = 3.07$ ,  $p = 0.002$ ,  $\beta = 8.4$ ). Thus, the more Americans were poly users of technology before bed, the more severe was their difficulty initiating sleep. As these electronic media consisted of both passive (TV, reading, mp3 music players) and interactive devices (computers/laptops, cell phone, video gaming), separate analyses were performed to assess whether the stimulating devices were more associated with difficulty sleeping. Passive devices did not significantly contribute to difficulty falling asleep ( $t_{1460} = 1.73$ ,  $p = 0.08$ ); however, interactive devices did ( $t_{1460} = 3.29$ ,  $p = 0.001$ ,  $\beta = 9.4$ ). This significance primarily resulted from using video gaming consoles ( $\beta = 10.6$ ,  $p < 0.0001$ ), but also from cell phones ( $\beta = 6.4$ ,  $p = 0.03$ ) and computers/laptops ( $\beta = 5.5$ ,  $p = 0.049$ ).

Of all technological devices to interrupt sleep during the night, cell phones were the only devices targeted in the 2011 Poll.

**Figure 3**—Significant impacts on areas of functioning from not getting enough sleep



**Table 1**—Linear regression analyses for technology use predicting bedtimes and sleep difficulties after controlling for covariates

|                                | Bedtimes |       |         |                |      | Difficulty Falling Asleep |      |         |                |        | Difficulty Maintaining Sleep |      |         |                |        | Unrefreshing Sleep |       |         |                |        |
|--------------------------------|----------|-------|---------|----------------|------|---------------------------|------|---------|----------------|--------|------------------------------|------|---------|----------------|--------|--------------------|-------|---------|----------------|--------|
|                                | B        | SE    | $\beta$ | R <sup>2</sup> | p    | B                         | SE   | $\beta$ | R <sup>2</sup> | p      | B                            | SE   | $\beta$ | R <sup>2</sup> | p      | B                  | SE    | $\beta$ | R <sup>2</sup> | p      |
| <b>Demographic</b>             |          |       |         |                |      |                           |      |         |                |        |                              |      |         |                |        |                    |       |         |                |        |
| Age                            | -1.21    | 2.13  | -0.02   | —              | 0.57 | -0.01                     | 0.00 | -0.08   | —              | 0.004  | 0.02                         | 0.00 | 0.30    | —              | 0.0001 | -0.01              | -0.01 | -0.10   | —              | 0.001  |
| Gender                         | -89.41   | 57.04 | -0.04   | —              | 0.12 | 0.23                      | 0.05 | 0.12    | —              | 0.0001 | 0.26                         | 0.08 | 0.13    | —              | 0.002  | 0.19               | 0.05  | 0.11    | —              | 0.0001 |
| <b>Sleep Hygiene</b>           |          |       |         |                |      |                           |      |         |                |        |                              |      |         |                |        |                    |       |         |                |        |
| Light                          | -12.03   | 31.91 | -0.01   | —              | 0.71 | 0.02                      | 0.03 | 0.02    | —              | 0.40   | 0.12                         | 0.04 | 0.11    | —              | 0.006  | 0.07               | 0.03  | 0.07    | —              | 0.01   |
| Caffeine                       | 5.76     | 5.59  | 0.03    | —              | 0.30 | 0.00                      | 0.01 | 0.01    | —              | 0.85   | 0.01                         | 0.01 | 0.04    | —              | 0.35   | 0.01               | 0.01  | 0.04    | —              | 0.16   |
| Naps (weekday)                 | 31.57    | 35.09 | 0.03    | —              | 0.37 | 0.05                      | 0.03 | 0.04    | —              | 0.14   | 0.00                         | 0.05 | 0.00    | —              | 0.96   | 0.09               | 0.03  | 0.09    | —              | 0.003  |
| Naps (weekend)                 | 96.36    | 45.77 | 0.06    | —              | 0.04 | 0.07                      | 0.04 | 0.05    | —              | 0.09   | 0.07                         | 0.07 | 0.05    | —              | 0.30   | -0.01              | 0.04  | -0.01   | —              | 0.88   |
| <b>Technology Use</b>          |          |       |         |                |      |                           |      |         |                |        |                              |      |         |                |        |                    |       |         |                |        |
| Total                          | -21.54   | 18.63 | -0.03   | 0.01           | 0.25 | 0.05                      | 0.02 | 0.08    | 0.04           | 0.002  |                              |      | na      |                |        | 0.03               | 0.02  | 0.05    | 0.05           | 0.048  |
| Passive                        | -42.69   | 31.51 | -0.04   | 0.01           | 0.18 | 0.05                      | 0.03 | 0.05    | 0.04           | 0.08   |                              |      | na      |                |        | 0.03               | 0.03  | 0.03    | 0.05           | 0.28   |
| Interactive                    | -17.10   | 29.93 | -0.02   | 0.01           | 0.57 | 0.08                      | 0.03 | 0.09    | 0.05           | 0.001  |                              |      | na      |                |        | 0.05               | 0.03  | 0.06    | 0.05           | 0.04   |
| <b>Cell Phones<sup>a</sup></b> | na       |       |         |                |      | na                        |      |         |                |        | 0.21                         | 0.05 | 0.18    | 0.16           | 0.0001 | na                 |       |         |                |        |

Total, the total amount of pre-sleep devices used in the hour before bed; Passive, passive devices used in the hour before bed (i.e., TV, mp3 music players, reading); Interactive, interactive devices used in the hour before bed (i.e., computers/laptops, cell phones, videogame consoles); na, not applicable as the only device measured for interrupting sleep was cell phones; <sup>a</sup>N = 555, otherwise N = 1,468; gender was coded male = 1, female = 2.

Twenty-two percent of the entire sample reported going to sleep with their cell phone ringers on in their bedroom. Furthermore, 10% were awakened *at least a few nights a week*, with awakenings occurring more in adolescents (18%) and young adults (20%). When investigating the association between leaving cell phones on and Americans' ratings of their difficulty maintaining sleep, a linear regression analysis was performed only for those who kept their cell phone in their bedroom overnight and left their ringer on (N = 331). After adjusting for demographic and sleep hygiene variables, being awakened by one's cell phone uniquely contributed towards Americans' perception of their difficulty in maintaining sleep ( $\beta = 17.9$ ,  $p < 0.0001$ ).

The same pattern emerged when assessing various forms of technology use on Americans' reporting unrefreshing sleep. The more media used in the bedroom before bed was related to the frequency of reporting unrefreshing sleep ( $t_{1461} = 1.98$ ,  $p = 0.048$ ,  $\beta = 5.4$ ), which was primarily accounted for by the use of interactive technological devices ( $t_{1466} = 2.17$ ,  $p = 0.04$ ,  $\beta = 6.1$ ) but not passive activities ( $t_{1466} = 1.06$ ,  $p > 0.05$ ).

## DISCUSSION

The findings from the 2011 Sleep in America Poll show technology use in the hour before bed is common practice, with 90% of Americans engaging with technology. Furthermore, many Americans are reporting inadequate sleep. Up to two-thirds of adolescents (13–18 years) and adults (19– to 29-year-olds) reported inadequate sleep on weeknights. Between 8.5 to 9.25 hours has been recommended for adolescents and 7–8.2 hours for adults.<sup>32–35</sup> Significant, and even dangerous, daytime consequences (37% of Americans had driven drowsy in the past month) were frequently reported by those experiencing inadequate sleep. The analyses from the present study show evening technology use is associated with sleep, such that more technology use is associated with poorer sleep. While the present study was cross-sectional, precluding conclusions regarding a causal relationship, the findings are consistent with the potential mechanisms by which technology use may

affect sleep, including bedtime displacement, cognitive and physiological arousal, light and electromagnetic transmissions from technological devices, and devices interrupting the maintenance of nocturnal sleep.<sup>17,18</sup> The present study was able to assess some of these mechanisms.

## Links between Technology Use and Sleep

Although previous studies have found that later bedtimes are related to the use of TVs, computers, videogames, and the Internet,<sup>9,14,36</sup> the present study did not find evidence of any technological devices contributing to later bedtimes. This may have occurred due to the present study accounting for other variables known to affect bedtimes, including caffeine consumption,<sup>37,38</sup> bedroom lighting,<sup>39,40</sup> and napping.<sup>41,42</sup> Of these variables, napping was the only variable to be significantly related to bedtimes. We note previous studies that demonstrated a link between evening technology use and bedtimes did not statistically control for such confounding variables,<sup>14,36</sup> which may account for differences between study findings.

The greater number of technological devices used in the hour before bed was related to higher ratings of difficulties initiating sleep. The strength of this association was greatest for stimulating activities, such as using videogame consoles, cell phones, and computers/laptops. These results suggest that once Americans do decide to go to bed, they have significant difficulty sleeping if they have used stimulating technologies shortly beforehand. The cognitive<sup>43,44</sup> and physiological arousal<sup>45,46</sup> from using such devices may interfere with Americans' preparation for sleep. Similar findings occurred for reports of unrefreshing sleep, with the greater likelihood of reporting such poor sleep quality being related to the use of interactive technological devices before bed. However, we cannot exclude the possible contributions of other factors such as screen light<sup>47</sup> and electromagnetic transmissions<sup>48</sup> from the same devices. Although more research is needed to better understand why such devices are related to sleep initiation difficulties, it is clear that Americans should schedule passive activities in between their use of interactive technological devices and sleep (i.e.,

passive technological devices; TV, electronic music devices, books), as these showed weaker associations with sleep.

One surprising finding from the present study was the extent to which Americans are going to sleep with their cell phone *turned on* in their bedroom. Of those who reported that they use their cell phone before bed (22%), 57% leave their ringer on (10% of the entire sample), which is associated with difficulty returning to sleep after an awakening. One in ten Americans reported being awakened at least a few nights a week, with younger people awakened by their cell phones (adolescents = 18%, young adults = 20%). These figures concur with previous findings.<sup>22,23</sup> The inability to maintain sleep may be due to these Americans performing behaviors during the night (e.g., texting) that are arousing and incompatible with sleep. The problem could be worse than our study suggests, as only cell phones were targeted in this Poll. Many Americans reported using other technological devices when awake during the night (e.g., computers/laptops); however, it was not clear if these devices woke them up with alerting sounds, or whether people woke spontaneously and used these devices until re-initiating sleep. This may have implications for the quality of Americans' sleep.

### Implications for Evening Technology Use

Since the 1970s, stimulus control therapy instructions have stated that the bed (and bedroom) should only be used for sleep and sexual activity.<sup>49,50</sup> The findings from the 2011 Sleep in America Poll indicate that 9 of 10 Americans surveyed are not following this basic recommendation. However, the present study's findings offer correlative evidence that some forms of technology confer weak effects on sleep (i.e., passive activities; watching TV, reading). Use of these devices may challenge the notion of using the bed only for sleep. Passive devices may be helpful as they are a pleasurable activity that fills the void while waiting to fall asleep.<sup>51,52</sup> Conversely, a sleep tip considered "common sense"<sup>53</sup> and imbedded within the principles of sleep hygiene is that one should avoid stimulating activities before bedtime.<sup>12,54</sup> The present study demonstrated that the use of stimulating activities with technological devices that involve interactivity (cell phones, laptops, videogame consoles) were associated with difficulty falling asleep and unrefreshing sleep. With the high proportion of Americans who use technology close to bedtime, combined with the significant impact on daily functioning as a result of inadequate sleep, a clear delineation is needed between devices that are acceptable, or not, in the hour before bed.

### Limitations of the Present Study

There are several limitations of the present study. Although efforts were made to match participant characteristics to 2009 US Census data,<sup>29</sup> the present Poll nevertheless contains a small proportion of error variance that limits generalizability to the population. Our response rate may be considered low, yet we note most surveys do not conform to STROBE guidelines,<sup>24</sup> and thus report liberal rates akin to cooperation rates (i.e., do not include "calls not connected" and "calls not answered by a person"; see **Figure 1**). The Poll was presented as a "sleep survey," hence introducing a possible self-selection bias.<sup>55,56</sup> It may be likely that those Americans with a vested interest in sleep (e.g., those with sleep problems) may have been more inclined to participate. Although the web survey gained access

to participants who may be difficult to recruit via phones, it could be argued that further selection bias may exist in that these participants may be more likely to own and use multiple technological devices. However, using a singular recruitment method could result in sampling biases which would slant findings more so than multiple methods. We therefore believe viewing the multiple methods as a confound needs to be reframed. It is likely that future surveys of technology use will incorporate multiple methods to balance any biases due to over-represented younger or older people. We did report age group differences between web and phone surveys, but any further analysis of differences on technology use between these two methods is likely a function of age (i.e., younger age groups use technology and are more likely to complete web surveys). Data on the number of e-surveys undeliverable, deliverable but not commenced, and not completed were unavailable, thus making it difficult to assess any biases in sampling. Due to informed consent concerns, the Poll did not assess children's use of technology ( $\leq 12$  years). Further insights may be found for younger children's susceptibility to technology-induced sleep problems.<sup>57</sup> Hopefully, many parents are implementing the American Pediatric Association's recommendation of less than two hours of screen time per day,<sup>58</sup> but are not using this screen time in their child's bedtime routine. We note that the wake-up time for the adolescent group is earlier than those reported from recent reviews.<sup>59,60</sup> More data are required to assess whether adolescents who use technology report unique sleep patterns. The Poll used a cross-sectional design; thus the scope for determining cause and effect is limited (e.g., do Americans have difficulties falling asleep due to using interactive technological devices—or—do Americans who have preexisting difficulties falling asleep have an affinity for interactive technological devices?). Our self-reported sleep items are not ideal, and although ambitious, future large surveys of sleep and technology could use more valid time-use diaries. In summary, we recognize that the published summary of findings and media release from the 2009 National Sleep Foundation Poll has received criticism for not adhering to various scientific principles (e.g., extrapolating "sleep problem" to "insomnia"; "Poll-pushed" questions; lack of transparency of sampling biases; lack of statistical analyses controlling for extraneous variables).<sup>61</sup> The present study represents a scientific presentation of the 2011 National Sleep Foundation results, which should be viewed in conjunction with the growing number of field surveys and experimental laboratory studies in this area to understand the weight of evidence for the role of technology use on sleep in modern society.

### Concluding Remarks

The technology use of Americans in their bedrooms is prevalent, especially in the hour before attempting sleep. To our surprise, technology use during the sleep period was much higher than expected. Analysis of different age groups demonstrated that those who use technology in the hour before bedtime are younger than 30 years of age. These groups also report the largest amounts of sleep problems. These findings suggest that technology use is emerging as a possible contributing factor to sleep disturbance in the twenty-first century. Future research should investigate whether adolescents (13-18 year olds) and young adults (19-29 year olds) will continue evening technology

use into late adulthood, and what effects their modeling of technology use will have on future generations to come.

## FOOTNOTES

1. < 1% refused to answer.
2. < 2% refused to answer.
3. Response rate is total completed interviews of the total calls dialed (750 of 32,216).
4. Cooperation rate is total completed interviews (750) of total calls to potentially eligible participants (3341) plus deceased (17) and language barrier (270) call dispositions, minus calls terminated (-404) (750 of 3224).
5. Refusal rate is the total number refusing the interview (2187) of all potentially eligible participants (3341) plus deceased (17), language barrier (270), answering machines (15046), and not available (56) dispositions, minus calls terminated (-404) (2,187 of 18,326).
6. Contact rate is the percentage of participants reached by interviewers of the total calls connecting, including answering machines and no answers (3,224 of 18,613).
7. These findings are derived from data of only adolescents who drive.

## REFERENCES

1. Hedges JN. A look at the 4-day workweek. *Monthly Lab Rev* 1971;94:33-7.
2. Economics and Statistics Administration and National Telecommunications and Information Administration. *Exploring the digital nation: computer and internet use at home*. Washington, DC: U.S. Department of Commerce, 2011.
3. United States Census Bureau. *Households with a computer and internet use: 1984 to 2009*. Washington, DC: U.S. Census Bureau, 2010.
4. Gartner, Inc. Market trends: gaming ecosystem, 2011. Stamford, CT: Gartner, Inc., 2011.
5. International Telecommunication Union. The world in 2011-ICT facts and figures. ITU, Geneva, Switzerland, 2011.
6. National Sleep Foundation. 2006 Sleep in America Poll: summary of findings. Washington, DC: National Sleep Foundation, 2006.
7. Shochat T, Flint-Bretler O, Tzischinsky O. Sleep patterns, electronic media exposure and daytime sleep-related behaviours among Israeli adolescents. *Acta Paed* 2010;99:1396-1400.
8. Kaiser Family Foundation. *Generation M2: media in the lives of 8- to 18-year-olds*. Menlo Park, CA: Henry J. Kaiser Family Foundation, 2010.
9. Custers K, van den Bulck J. Television viewing, Internet use, and self-reported bedtime and rise time in Adults: implications for sleep hygiene recommendations from an exploratory cross-sectional study. *Behav Sleep Med* 2012;10:96-105.
10. Stewart K, Choi HP. PC-Bang (Room) culture: a study of Korean college students' private and public use of computers and the Internet. *Trends in Communication* 2003;11:61-77.
11. Suganuma N, Kikuchi T, Yanagi K, et al. Using electronic media before sleep can curtail sleep time and result in self-perceived insufficient sleep. *Sleep Biol Rhythms* 2007;5:204-14.
12. Hauri P. *Current concepts: the sleep disorders*. Kalamazoo, MI: The Upjohn Company, 1977.
13. Adam EK, Snell EK, Pendry P. Sleep timing and quantity in ecological and family context: a nationally representative time-diary study. *J Fam Psychol* 2007;21:4-19.
14. Brunborg GS, Mentzoni RA, Molde H, et al. The relationship between media use in the bedroom, sleep habits and symptoms of insomnia. *J Sleep Res* 2011;20:569-75.
15. Mesquita G, Reimao R. Nightly use of computer by adolescents: its effect on quality of sleep. *Arq Neuropsiquiatr* 2007;65:428-32.
16. National Sleep Foundation. 2010 Sleep in America Poll: summary of findings. Washington, DC: National Sleep Foundation, 2010.
17. Cain N, Gradisar M. Electronic media use and sleep in school-aged children and adolescents: a review. *Sleep Med* 2010;11:735-42.
18. Gradisar M, Short M. Sleep hygiene and environment: role of technology. In: Wolfson AR, Montgomery-Downs H, eds. *The Oxford Handbook of Infant, Child, and Adolescent Sleep and Behavior*. Oxford, UK: Oxford University Press, 2013.
19. Freedman RR, Sattler HL. Physiological and psychological factors in sleep-onset insomnia. *J Abnorm Psychol* 1982;91:380-9.
20. Gradisar M, Lack L, Wright H, Harris J, Brooks A. Do chronic primary insomniacs have impaired heat loss when attempting sleep? *Am J Physiol Regul Integr Comp Physiol* 2006;290:R1115-21.
21. Monroe L. Psychological and physiological differences between good and poor sleepers. *J Abnorm Psychol* 1967;72:255-64.
22. Van den Bulck J. Text messaging as a cause of sleep interruption in adolescents: evidence from a cross-sectional study. *J Sleep Res* 2003;12:263.
23. Van den Bulck J. Adolescent use of mobile phones for calling and for sending text messages after lights out: results from a prospective cohort study with a one-year follow-up. *Sleep* 2007;30:1220-3.
24. Von Elm E, Altman DG, Egger M; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61:344-9.
25. American Association for Public Opinion Research. Response rate – an overview. Accessed July 9 2012. [www.aapor.org/Response\\_Rates\\_An\\_Overview1.htm](http://www.aapor.org/Response_Rates_An_Overview1.htm).
26. U.S. Department of Human and Health Services. Code of Federal Regulations, Title 45: Public Welfare, Part 46: Protection of human subjects. Washington, DC: Department of Human and Health Services, 2009.
27. Johns M. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991;14:540-5.
28. Blumberg SJ, Luke JV. *Wireless substitution: Early release of estimates from the National Health Interview Survey, July December 2009*. National Center for Health Statistics, May 2010.
29. United States Census Bureau. *American Community Survey: 2009 data release*. Washington, DC: U.S. Census Bureau, 2010.
30. Stark PB. Approximate hypothesis tests: the z test and the t test. University of California, Berkeley, 2013. Accessed July 18 2013. <http://www.stat.berkeley.edu/~stark/SticiGui/Text/zTest.htm>.
31. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of qualitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep* 2004;27:1255-73.
32. National Sleep Foundation. *Adolescent sleep needs and patterns*. Washington, DC: National Sleep Foundation, 2000.
33. National Sleep Foundation. How much sleep do we really need? National Sleep Foundation, Washington, DC, 2011. Accessed June 25 2012. <http://www.sleepfoundation.org/article/how-sleep-works/how-much-sleep-do-we-really-need>.
34. Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 2003;26:117-26.
35. Carskadon MA, Harvey K, Duke P, Anders TF, Litt IF, Dement WC. Pubertal changes in daytime sleepiness. *Sleep* 1980;2:453-60.
36. Van den Bulck J. Television viewing, computer game playing, and internet use and self-reported time in bed and time out of bed in secondary-school children. *Sleep* 2004;27:101-4.
37. Pollak CP, Bright D. Caffeine consumption and weekly sleep patterns in US seventh-, eighth-, and ninth graders. *Pediatrics* 2003;111:42-6.
38. Sanchez-Ortuno M, Moore N, Taillard J, et al. Sleep duration and caffeine consumption in a French middle-aged working population. *Sleep Med* 2005;6:247-51.
39. Palmer CR, Kripke DF, Savage HC Jr, Cindrich LA, Loving RT, Elliott JA. Efficacy of enhanced evening light for Advanced Sleep Phase Syndrome. *Behav Sleep Med* 2003;1:213-6.
40. Peixoto CAT, da Silva AGT, Carskadon MA, Louzada FM. Adolescents living in homes without electric lighting have earlier sleep times. *Behav Sleep Med* 2009;7:73-80.
41. Fukuda K, Ishihara K. Routine evening naps and night-time sleep patterns in junior high and high school students. *Psychiatry Clin Neurosci* 2002;56:229-30.
42. Gradisar M, Wright H, Paine S, Robinson J, Gamble A. Adolescent napping behaviour: Comparisons of school week and weekend patterns. *Sleep Biol Rhythms* 2008;6:183-6.
43. Mathiak K, Weber R. Toward brain correlates of natural behavior: fMRI during violent video games. *Hum Brain Mapp* 2006;27:948-56.
44. Weaver E, Gradisar M, Dohnt H, Lovato N, Douglas P. The effect of pre-sleep video game playing on adolescent sleep. *J Clin Sleep Med* 2010;6:184-9.



45. Higuchi S, Motohashi Y, Liu Y, Maeda A. Effects of playing a computer game using a bright display on presleep physiological variables, sleep latency, slow wave sleep and REM sleep. *J Sleep Res* 2005;14:267-73.
46. Ivarsson M, Anderson M, Akerstedt T, Lindblad F. Playing a violent television game affects heart rate variability. *Acta Paed* 2009;98:166-72.
47. Cajochen C, Frey S, Anders D, et al. Evening exposure to a light-emitting diodes (LED)-backlit computer screen affects circadian physiology and cognitive performance. *J Appl Physiol* 2011;110:1432-38.
48. Wood AW, Loughran SP, Stough C. Does evening exposure to mobile phone radiation affect subsequent melatonin production? *Int J Radiation Biol* 2006;82:69-76.
49. Bootzin RR. A stimulus control treatment for insomnia. *Proc Am Psychol Assoc* 1972;395-6.
50. Bootzin RR, Rider SP. Behavioral techniques and biofeedback for insomnia. In: Pressman MR, Orr WC, eds. *Understanding sleep: the evaluation and treatment of sleep disorders*. American Psychological Association, 1997.
51. Eggermont S, van den Bulck J. Nodding off or switching off? The use of popular media as a sleep aid in secondary-school children. *J Paed Child Health* 2006;42:428-33.
52. McEvoy GF, Vincent CS. Who reads and why? *J Communication* 2006;30:134-40.
53. Perlis ML, Sharpe M, Smith MT, Greenblatt D, Giles D. Behavioral treatment of insomnia: treatment outcome and the relevance of medical and psychiatric morbidity. *J Behav Med* 2001;24:281-96.
54. American Academy of Sleep Medicine. *The international classification of sleep disorders: diagnostic and coding manual*. 2nd edition. Westchester, IL: American Academy of Sleep Medicine, 2005.
55. Daley M, Morin CM, LeBlanc M, Grégoire JP, Savard J. The economic burden of insomnia: direct and indirect costs for individuals with insomnia syndrome, insomnia symptoms, and good sleepers. *Sleep* 2009;32:55-64.
56. Smyth JM. Beyond self-selection in video game play: an experimental examination of the consequences of massive multiplayer online role-playing game play. *Cyberpsychol Behav* 2007;10:717-21.
57. Dworak M, Schierl T, Bruns T, Strüder HK. Impact of singular excessive computer game and television exposure on sleep patterns and memory performance of school-aged children. *Pediatrics* 2007;120:978-85.
58. American Academy of Pediatrics Committee on Communications. Media violence. *Pediatrics* 1995;95:949-51.
59. Crowley SJ, Acebo C, Carskadon MA. Sleep, circadian rhythms, and delayed sleep phase in adolescence. *Sleep Med* 2007;8:602-12.
60. Gradisar M, Gardner G, Dohnt H. Recent worldwide sleep patterns and problems during adolescence: a review and meta-analysis of age, region, and sleep. *Sleep Med* 2011;12:110-8.
61. Webb WB. Opinion polls and science. *Sleep* 2010;33:865-6.

## ACKNOWLEDGMENTS

The authors thank Ms. Jennifer Williams (Marketing & Communications Manager, National Sleep Foundation) and Mr. David Cloud (CEO, National Sleep Foundation),

Mr. Tom Kowalczyk, Mr. Steve Markenson and Ms. Bethany Black (WB&A Market Research), and the 1,508 adolescents and adults who participated in the 2011 Sleep in America Poll. A summary of findings of the 2011 Sleep in America Poll can be downloaded from the National Sleep Foundation website ([www.sleepfoundation.org](http://www.sleepfoundation.org)).

## SUBMISSION & CORRESPONDENCE INFORMATION

**Submitted for publication March, 2013**

**Submitted in final revised form July, 2013**

**Accepted for publication August, 2013**

Address correspondence to: Michael Gradisar, Flinders University, GPO Box 2100, Adelaide, South Australia, Australia; Tel: +61 8 8201 2192; Fax: +61 8 8201 3877; E-mail: [grad0011@flinders.edu.au](mailto:grad0011@flinders.edu.au)

## DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Rosenberg has research grant funding from Merck, Pfizer, Astra Zeneca, Philips/Respironics, and Vanda Pharmaceuticals. Dr. Czeisler has received consulting fees/served as a paid member of scientific advisory boards for Actelion, Ltd., Avera Pharmaceuticals, Inc., Bombardier Inc., Boston Celtics, Cephalon, Inc., Columbia River Bar Pilots, Delta Airlines, Eli Lilly and Co., Federal Motor Carrier Safety Administration (FMCSA), U.S. Department of Transportation, Fedex Kinko's, Fusion Medical Education, LLC, Garda Síochána Inspectorate, Global Ground Support, Hypnion, Inc. (acquired by Eli Lilly and Co. in April 2007), Johnson & Johnson, Koninklijke Philips Electronics, N.V., Minnesota Timberwolves, Morgan Stanley, Norfolk Southern, Portland Trail Blazers, Respironics, Inc., Sanofi-Aventis Groupe, Sepracor, Inc., Sleep Multimedia, Inc., Sleep Research Society, Somnus Therapeutics, Inc., Takeda Pharmaceuticals, Vanda Pharmaceuticals, Inc., Vital Issues in Medicine, Warburg-Pincus, and Zeo Inc. Dr. Czeisler owns an equity interest in Lifetrac, Inc., Somnus Therapeutics, Inc., Vanda Pharmaceuticals, Inc., and Zeo Inc. Dr. Czeisler received royalties from the Massachusetts Medical Society/New England Journal of Medicine, McGraw Hill, the New York Times Penguin Press, and Philips Respironics. Dr. Czeisler has clinical trial research contracts from Cephalon, Inc., Merck & Co., Inc., and Pfizer, Inc.; an investigator-initiated research grant from Cephalon, Inc.; and his research laboratory at the Brigham and Women's Hospital has received unrestricted research and education funds for research expenses from Cephalon, Inc., Koninklijke Philips Electronics, N.V., ResMed, and the Brigham and Women's Hospital. Dr. Czeisler is the incumbent of an endowed professorship provided to Harvard University by Cephalon, Inc. and holds a number of process patents in the field of sleep/circadian rhythms, details of which are available on request. Since 1985, Dr. Czeisler has also served as an expert witness on various legal cases related to sleep and/or circadian rhythms. The other authors have indicated no financial conflicts of interest.



## The Use of Technology at Night: Impact on Sleep and Health

Commentary on Gradisar et al. The sleep and technology use of Americans: findings from the National Sleep Foundation's 2011 Sleep in America Poll. *J Clin Sleep Med* 2013;9:1291-1299.

Michael A. Grandner, Ph.D.<sup>1,2</sup>; Rebecca A. Lang Gallagher, M.S.Ed.<sup>1,2</sup>; Nalaka S. Gooneratne, M.D., M.Sc., F.A.A.S.M.<sup>2,3</sup>

<sup>1</sup>Behavioral Sleep Medicine Program, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; <sup>2</sup>Center for Sleep and Circadian Neurobiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; <sup>3</sup>Division of Geriatric Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Since mankind first tamed fire, we have been using artificial light to extend the waking day. As technology has progressed, our relationship with the night has changed. With widespread use of electric lights, the night has essentially become optional. But this is not an ideal perspective for health and well-being. Adverse outcomes arise from extending wakefulness<sup>1,2</sup> or even shifting it later.<sup>3,4</sup> In recent years, the use of electronic devices in the bedroom has increased dramatically. However, not much is known at the population level about who uses technology in the bedroom, what sort of technology is used, how much is used, and how this use affects sleep.

In this issue of *JCSM*, Gradisar and colleagues report results of the 2011 Sleep in America Poll conducted by the National Sleep Foundation, which focused on technology use and relationships to sleep.<sup>5</sup> The results show that approximately 90% of Americans report some technology use in the hour before bed. Although television was the most popular overall, young adults were more likely to be using cell phones. Other demographic differences existed as well, with younger adults being more likely to use computers/laptops and video game consoles. Differences regarding gender, race/ethnicity and relationship status were also reported.

The authors also found that technology use was associated with sleep patterns. For example, the more types of devices used, the more individuals reported difficulty falling asleep and maintaining sleep, especially if the use of technology was active. Regarding intrusions into sleep, 22% reported going to sleep with cell phone ringers on in their bedroom and 10% reported awakenings at least a few nights per week due to their phone. Among those with the ringer on, being awakened by the cell phone was significantly associated with difficulty maintaining sleep.

This study had a number of important strengths. The random sample contributes to the generalizability of these findings. Also, this study represents one of the first times that technology use in the bedroom is surveyed, especially relative to sleep. In addition to its strengths, a number of significant limitations suggest future research directions. For example, the lack of precision in the survey instrument makes conclusions difficult to draw. For example, using a phone or tablet or computer could indicate a passive activity (e.g., watching a movie, browsing the internet) or an interactive one (e.g., communicating with people, playing video games, social networking). Some activities may

have varying degrees of interactivity; for example, playing a video game or talking on the phone may be more impactful on sleep than texting or browsing the internet. In addition, future research that includes more standard assessments of sleep would aid in interpretations of results and more complex statistical analyses will more thoroughly elucidate relationships.

The landscape of technology use in the bedroom is changing rapidly. We need to design research studies that will effectively assess patterns of use in the real world. For example, it is plausible that individuals who use smartphones are using them in the bedroom—to check emails, send texts, use social networks, play games, or simply use its alarm to wake up in the morning. Perhaps more carefully assessing quantity and timing of passive versus active consumption of technology would be helpful, as would be assessing interruptions by and uses of devices in the middle of the night.

One particular challenge in conducting this type of research is that individual users may themselves not be able to recall specific events in granular detail. An individual user may text for a few minutes, check e-mails, watch a video, then send additional texts before going to bed, all within 15-20 minutes. Indeed, it may be that the only way to accurately capture this data would be through monitoring applications installed on the devices themselves. This requires that researchers not only understand the possible technologies in play, but they may also need to directly manipulate/measure them, with the consent of the user.

Despite these challenges, the issue of technology relative to sleep is an important one. Nearly all adults, especially young adults, use technology before bed. As the possibilities increase for talking, texting, browsing, emailing, working, playing, posting, and reading before bed, and as a portal to information and social networks becomes an arm's reach away in the middle of the night, and as the devices that go "beep" in the night become more common in the bedroom, it is important for sleep researchers to understand how these changing patterns of use affect sleep and, in turn, health and well-being.

### CITATION

Grandner MA; Gallagher RAL; Gooneratne NS. The use of technology at night: impact on sleep and health. *J Clin Sleep Med* 2013;9(12):1301-1302.

## REFERENCES

1. Grandner MA, Patel NP, Gehrman PR, Perlis ML, Pack AI. Problems associated with short sleep: Bridging the gap between laboratory and epidemiological studies. *Sleep Med Rev* 2010;14:239-47.
2. Penev PD. Update on energy homeostasis and insufficient sleep. *J Clin Endocrinol Metab* 2012;97:1792-801.
3. Roenneberg T, Allebrandt KV, Mrosovsky M, Vetter C. Social jetlag and obesity. *Curr Biol* 2012;22:939-43.
4. Abe T, Inoue Y, Komada Y, et al. Relation between morningness-eveningness score and depressive symptoms among patients with delayed sleep phase syndrome. *Sleep Med* 2011;12:680-4.
5. Grandner M, Wolfson AR, Harvey AG, Hale L, Rosenberg R, Czeisler CA. The sleep and technology use of americans: findings from the National Sleep Foundation's 2011 Sleep in America Poll. *J Clin Sleep Med* 2013;9:1291-9.

## SUBMISSION & CORRESPONDENCE INFORMATION

**Submitted for publication November, 2013**

**Accepted for publication November, 2013**

Address correspondence to: Michael A. Grandner, Ph.D., University of Pennsylvania, Center for Sleep and Circadian Neurobiology, 3624 Market Street, Suite 205, Philadelphia, PA 19104; Tel: (215) 615-1756; Fax: (215) 701-1831; E-mail: grandner@gmail.com

## DISCLOSURE STATEMENT

This was not an industry supported study. This work was supported by the National Heart, Lung and Blood Institute (K23HL110216), the National Institute of Environmental Health Sciences (R21ES022931), and the University of Pennsylvania CTSA (UL1RR024134). The authors have indicated no financial conflicts of interest.



## Investigating Reasons for CPAP Adherence in Adolescents: A Qualitative Approach

Priya S. Prashad, M.D., M.S.C.E.<sup>1</sup>; Carole L. Marcus, MB.BCh., F.A.A.S.M.<sup>1</sup>; Jill Maggs, Ed.D., M.Med.Sci.<sup>1</sup>; Nicolas Stettler, M.D., M.S.C.E.<sup>2</sup>; Mary A. Cornaglia<sup>1</sup>; Priscilla Costa, M.S.<sup>1</sup>; Kristina Puzino, B.A.<sup>1</sup>; Melissa Xanthopoulos, Ph.D.<sup>1</sup>; Ruth Bradford<sup>1</sup>; Frances K. Barg, Ph.D., M.Ed.<sup>3</sup>

<sup>1</sup>*Sleep Center, The Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA;* <sup>2</sup>*Exponent, Inc. Washington, DC;* <sup>3</sup>*Department of Family Medicine and Community Health, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

**Study Objectives:** Adolescents with obstructive sleep apnea syndrome (OSAS) represent an important but understudied subgroup of long-term continuous positive airway pressure (CPAP) users. The purpose of this qualitative study was to identify factors related to adherence from the perspective of adolescents and their caregivers.

**Methods:** Individual open-ended, semi-structured interviews were conducted with adolescents (n = 21) and caregivers (n = 20). Objective adherence data from the adolescents' CPAP machines during the previous month was obtained. Adolescents with different adherence levels and their caregivers were asked their views on CPAP. Using a modified grounded theory approach, we identified themes and developed theories that explained the adolescents' adherence patterns.

**Results:** Adolescent participants (n = 21) were aged 12-18 years, predominantly male (n = 15), African American (n = 16), users of CPAP for at least one month. Caregivers were mainly mothers (n = 17). Seven adolescents had high use (mean use

381 ± 80 min per night), 7 had low use (mean use 30 ± 24 min per night), and 7 had no use during the month prior to being interviewed. Degree of structure in the home, social reactions, mode of communication among family members, and perception of benefits were issues that played a role in CPAP adherence.

**Conclusions:** Understanding the adolescent and family experience of using CPAP may be key to increasing adolescent CPAP adherence. As a result of our findings, we speculate that health education, peer support groups, and developmentally appropriate individualized support strategies may be important in promoting adherence. Future studies should examine these theories of CPAP adherence.

**Keywords:** Qualitative, interviews, adolescent, CPAP adherence  
**Citation:** Prashad PS; Marcus CL; Maggs J; Stettler N; Cornaglia MA; Costa P; Puzino K; Xanthopoulos M; Bradford R; Barg FK. Investigating reasons for CPAP adherence in adolescents: a qualitative approach. *J Clin Sleep Med* 2013;9(12):1303-1313.

Obstructive sleep apnea syndrome (OSAS) affects approximately 2% of children and adolescents.<sup>1</sup> OSAS in children may result in severe complications if left untreated, such as growth failure, pulmonary hypertension, neurocognitive deficits, behavioral problems, and attention deficit hyperactivity disorder.<sup>2-6</sup>

In young children, OSAS can often be treated with adenotonsillectomy. However, in adolescents, adenotonsillectomy may not be effective, as adenoids and tonsils involute with age<sup>7,8</sup> and obesity is more likely to be present. While weight loss may be an effective treatment for OSAS in this age group, it is difficult to achieve and maintain, particularly for those with severe obesity. Therefore, continuous positive airway pressure (CPAP) has become the mainstay of treatment of OSAS in adolescents.

CPAP is an effective treatment for OSAS in adolescents, but adherence remains a challenge.<sup>9-12</sup> CPAP adherence patterns of adolescents have not been extensively studied, but studies of medication adherence in other adolescent groups, such as asthmatics, epileptics, and diabetics have demonstrated poor adherence.<sup>13,14</sup> Poor adherence in adolescents may be related to not understanding or not perceiving the benefits of the treatment, wanting to conform to peers, and rebelling against authority.<sup>15</sup> In addition, adolescents may have little parental supervision of CPAP use. Because of a lack of published literature, we performed an exploratory study from the perspective of

adolescents and their caregivers. To our knowledge, this is the first study focused on the adolescent age group.

The purpose of the study was to identify and explore factors that influenced adolescent CPAP use, using a modified grounded theory approach.<sup>16</sup> Grounded theory is a qualitative method that seeks to generate theories from the data, to offer explanations for the phenomenon being explored.

### BRIEF SUMMARY

**Current Knowledge/Study Rationale:** Continuous positive airway pressure (CPAP) is an effective treatment for obstructive sleep apnea syndrome (OSAS) in adolescents, when used, but adherence is a challenge. The purpose of the current study was to identify and explore factors that influenced adolescent CPAP use.

**Study Impact:** This is one of the first studies to provide information about reasons for continuous positive airway pressure (CPAP) adherence and nonadherence in adolescents, a growing group of CPAP users who have been understudied.

### METHODS

This exploratory study consisted of qualitative semi-structured interviews and a download of the adolescent's adherence data from his or her CPAP machine during the previous month.

**Table 1**—Details of the study participants

| Participant number | Age | Gender | Body mass index z-score | AHI (events/h)* | SpO <sub>2</sub> nadir (%)* | Years prescribed CPAP | Age at time of CPAP prescription (years) | Caregiver participating in study |
|--------------------|-----|--------|-------------------------|-----------------|-----------------------------|-----------------------|------------------------------------------|----------------------------------|
| No use             |     |        |                         |                 |                             |                       |                                          |                                  |
| 1                  | 16  | female | 2.89                    | 14              | 86                          | 3                     | 13                                       | Mother                           |
| 2                  | 18  | male   | 2.33                    | 14.6            | 90                          | 4                     | 15                                       | Aunt                             |
| 4                  | 16  | male   | 3.12                    | 27.8            | 50.6                        | 3                     | 13                                       | Mother                           |
| 6                  | 17  | female | 2.5                     | 8.1             | 88                          | 1                     | 16                                       | Mother                           |
| 11                 | 18  | female | 2.89                    | 7.3             | 87                          | 3                     | 16                                       | Mother                           |
| 14                 | 14  | male   | 2.71                    | 5.4             | 85                          | 4                     | 10                                       | Mother                           |
| 16                 | 12  | female | 0.28                    | 5.9             | 84                          | 6                     | 6                                        | Mother                           |
| Low use            |     |        |                         |                 |                             |                       |                                          |                                  |
| 3                  | 14  | female | 2.42                    | 6.6             | 85                          | 4                     | 10                                       | Mother                           |
| 5                  | 17  | male   | 2.93                    | 6.8             | 81                          | 3                     | 14                                       | Father                           |
| 7                  | 17  | male   | 2.61                    | 20.6            | 83                          | 0.5                   | 16                                       | Mother                           |
| 9                  | 16  | male   | 2.42                    | 46.6            | 72                          | 0.5                   | 15                                       | Father                           |
| 12                 | 16  | male   | 2.99                    | 75.4            | 68                          | 0.75                  | 15                                       | Mother                           |
| 13                 | 12  | female | 2.73                    | 78.3            | 72                          | 0.25                  | 12                                       | Mother                           |
| 15                 | 18  | male   | 1.04                    | 5.7             | 92                          | 2                     | 16                                       | Mother                           |
| High use           |     |        |                         |                 |                             |                       |                                          |                                  |
| 8                  | 15  | male   | 2.84                    | 70.5            | 17.8                        | 7                     | 8                                        | Mother                           |
| 10                 | 13  | male   | 3.05                    | 42.9            | 70                          | 10                    | 3                                        | Mother                           |
| 17                 | 13  | male   | 3.12                    | 21.4            | 60                          | 8                     | 5                                        | Mother                           |
| 18                 | 13  | male   | 2.52                    | 4               | 85                          | 1                     | 12                                       | Mother                           |
| 19                 | 13  | male   | 2.54                    | 46.3            | 72                          | 0.5                   | 13                                       | Mother                           |
| 20                 | 16  | male   | 1.4                     | 11.2            | 91                          | 5                     | 11                                       | Mother                           |
| 21                 | 16  | male   | 2.84                    | 13.7            | 53                          | 8                     | 9                                        | Mother                           |

\*Apnea-hypopnea index (AHI) and oxyhemoglobin desaturation (SpO<sub>2</sub>) nadir: data represent wide variation as the baseline studies were conducted at different time periods and at different sleep laboratories.

As experienced physicians in pediatric sleep medicine, it was impossible to set aside our preconceived notions regarding CPAP adherence. As a consequence, we acknowledged these notions and used them to generate a tentative framework from which we developed the initial interview questions. This framework led us to explore issues of stress, parenting style, family structure and organization, behavior and emotional problems, knowledge about OSAS, and the purpose and benefits of treatment with CPAP. We used these notions to identify and explore factors that may act as barriers and facilitators of CPAP use.

Details of the study participants are shown in **Table 1**. Each participant had been diagnosed with OSAS by polysomnography. All participants had been prescribed CPAP therapy as part of their usual care for at least one month prior to recruitment. Details of how long the study participants had been prescribed CPAP are shown in **Table 1**. Participants were purposively recruited across the spectrum of adherence. We also included a caregiver for each adolescent in the study, defined as a parent, relative, or other adult with the responsibility of caring for the adolescent. Exclusion criteria included non-English speakers, developmental delays, and the presence of another severe chronic medical condition.

Approval was obtained from the Children's Hospital of Philadelphia Institutional Review Board. Parental/guardian informed consent was obtained, as well as child assent for those younger than 18 years of age. Participants were provided reimbursement for their time.

Each individual semi-structured interview was conducted by one of three interviewers conversant with qualitative

methodology and interviewing techniques. The approach used was to ask questions exploring the issues within the framework developed for the study. The semi-structured nature of the interview was piloted with a related caregiver and adolescent. Their feedback helped us identify appropriate language and phrases that would be understood by the participants. Examples of the type of questions used to explore these issues are shown in **Table 2**. By using a semi-structured approach, we ensured that the same topics were explored with each family; however, the interviewers had the scope to be responsive to the issues that arose during the interview and to ask more probing questions. Most interviews were audio recorded, transcribed verbatim, and reviewed by the interviewer for accuracy. Three interviewees refused to have their interviews audio recorded, so notes were taken instead. In addition, the interviewers took field notes and noted general impressions for each interview, which were used in the analysis process. The mean time for interviews was 30 minutes.

The decision to use modified grounded theory for the analysis<sup>16</sup> was made because the framework was created using the researchers' experience and the analysis was inevitably influenced by this experience. Five of the authors read the transcribed text and looked for the factors that had been previously identified as being potentially relevant to CPAP use, as well as allowing other factors to emerge. The authors were conscious of a need to understand the meaning of the responses within the context provided by the participants. In order to facilitate this understanding, interim analyses were informally conducted by the lead investigator and the interviewers after each interview

which allowed for the identification of themes to explore in depth in subsequent interviews. We decided to invite for interview all eligible families who attended the sleep center during the study period until we reached saturation (where no new themes were emerging). In order that all the coders had a shared understanding of the concept and context that underpinned each code, we developed what we termed a “codebook” to help insure the integrity and reliability of the coding. Each transcript was independently coded by the 5 authors using NVivo 9.0 software (Doncaster, Victoria), and 85% agreement was found among the coders. Remaining differences in coding were discussed and resolved among the coders. Two authors then refined the factors and categories and created themes and theories (**Table 3**). These revised themes and theories were reviewed and validated by one of the 5 original coders. Records were kept that demonstrate an audit trail of the data processing and reveal how the theories emerged from the data.

Objective adherence data from the previous month was obtained from the adolescents’ CPAP machines using Encore Pro2 software (Phillips Respironics, Murraysville, PA). In order to explore potential differences between adolescent users, participants were divided into those with high use, low use, and no use based on tertiles of number of minutes used per night. The adherence data was downloaded at the end of the interview and independently reviewed with the adolescent and caregiver, and used to further explore adherence.

## RESULTS

Using the departmental CPAP database, 36 families with adolescents who met the eligibility criteria during the study period were approached. 28 (78%) agreed to participate. Seven of these did not come to their study appointments, and thus, 21 adolescents (including one set of twins) were enrolled along with 20 caregivers. Mean CPAP use was  $381 \pm 80$  (SD) (range 213–468) min/night for adolescents with high use ( $n = 7$ ),  $30 \pm 24$  (range 8–65) min/night for adolescents with low use ( $n = 7$ ), and zero min/night for adolescents with no use ( $n = 7$ ).

By comparing adolescents with high, low, and no use, we identified factors associated with CPAP adherence that differentiated use in the groups. This led us to create 4 theories of CPAP use. We postulate that each of the following factors has an effect on CPAP adherence: (1) The extent and nature of structure in the home and family, (2) style of communication between caregivers and adolescents, (3) social reactions and attitudes, and (4) adolescent perception of benefits. Exemplar quotes for each theme can be found in **Tables 4–7**.

### The Extent and Nature of Structure in the Home/Family Affects CPAP Adherence (Table 4)

#### Family Organization and Structure

Adolescents with high use described having a stable family structure. Their caregivers were able to organize routines that incorporated CPAP use into their daily lives. When problems occurred, the caregivers were able to identify the issues and work to resolve them, sometimes in creative ways. For example, one participant described how family meetings were used to address concerns.

**Table 2**—Examples of semi-structured interview questions for adolescents

- 1) Who all lives at home? What things are most important to you in your life?
- 2) Tell me a little about your relationship with your caregiver. Give me an example.
- 3) Who else besides your family knows you use CPAP? How do you feel about them knowing this?
- 4) How do you feel when you wear your mask? If you could change your mask or machine in any way, what would you do?
- 5) What was it like using CPAP at the beginning? How has that changed from now?
- 6) Is your caregiver around at bedtime? Does he/she check/remind you to use CPAP? How does that affect your relationship with him/her?
- 7) What kinds of things does your family do to stay healthy?
- 8) What determines whether you wear or not wear your CPAP machine at night?
- 9) What is your sleeping pattern like with and without using CPAP? How do you feel after the nights you wear it?
- 10) Tell me about the causes of stress in your life. Does your having to use CPAP play any role in them?

#### Routine

Adolescents with low and no use described a lack of stability in their family life, and unsuccessful attempts by their caregivers to incorporate CPAP use into their daily lives. For example, a caregiver felt challenged to create a better nighttime routine to enable her daughter to use her CPAP machine.

Adolescents with high use demonstrated an awareness or knowledge of what is needed for nightly CPAP use. Clearly, having CPAP incorporated into nighttime routines means it is less likely to be forgotten. Adolescents with low or no use described not wanting to use their CPAP machines and deliberately forgetting to use them at night.

### Style of Communication between Caregivers and Adolescents Affects CPAP Adherence (Table 5)

#### Communication

Communication methods about CPAP differed between adolescents with high versus low and no use and their caregivers. Adolescents with high use were not disquieted by their caregivers’ reminders to use CPAP. These reminders were appreciated by them and found to be helpful. Consistency was identified as being important by participant 11, who divided her time between different parental homes.

Adolescents with low and no use described that yelling by their caregivers would decrease their motivation for use. They felt that this showed that their caregivers did not understand how difficult it was for the adolescents to use CPAP.

#### Parenting Style

The caregivers of adolescents with high use described an authoritative parenting style, e.g. explaining why it was important to use CPAP and then giving their adolescents the choice whether to use it or not. Four of 7 of the adolescents with high use have been using the device since they were much younger, less than 10 years old, and are currently

**Table 3**—Development of coding, themes, and theories from the initial theories

| Initial theory              | Initial coding categories           | Themes                                     | Grounded theory                                                                            |
|-----------------------------|-------------------------------------|--------------------------------------------|--------------------------------------------------------------------------------------------|
| Organization                | Problem solving                     | Family Organization and Structure          | The Extent and Nature of Structure in the Home/Family Affects CPAP Adherence               |
|                             | Family values                       |                                            |                                                                                            |
|                             | Family chaos structure              |                                            |                                                                                            |
|                             | Forgetting or laziness              |                                            |                                                                                            |
|                             | Broken equipment                    |                                            |                                                                                            |
|                             | Being accustomed to CPAP            | Routine                                    |                                                                                            |
|                             | Routine                             |                                            |                                                                                            |
| Communication               | Nagging/fighting                    | Communication                              | Style of Communication between Caregivers and Adolescents Affects Motivation and Adherence |
|                             | Trust or respect                    |                                            |                                                                                            |
|                             | Modeling                            | Parenting Style                            |                                                                                            |
|                             | Parenting style                     |                                            |                                                                                            |
|                             | Rebellion/invulnerability           | Desire to Please/Self Respect              | Social Reactions and Attitudes Affect CPAP Adherence                                       |
|                             | Desire to please                    |                                            |                                                                                            |
| Health awareness or beliefs | Behavior/emotional problems         |                                            | Adolescent Perceptions of Benefits Affects Motivation for CPAP Use                         |
|                             | Shame                               |                                            |                                                                                            |
|                             | Family health beliefs and practices |                                            |                                                                                            |
|                             | Caregiver or adolescent stress      | Stress                                     |                                                                                            |
|                             | Fear                                | Fear of Consequences to Health with No Use |                                                                                            |
| Benefits or deterrents      | Understanding importance of CPAP    | Benefits of CPAP                           |                                                                                            |
|                             | Physical or psychological need      |                                            |                                                                                            |
|                             | Adverse side effects of CPAP        |                                            |                                                                                            |
|                             | Daytime sleepiness                  |                                            |                                                                                            |
|                             | Night time sleep issues             |                                            |                                                                                            |
|                             | Mood/energy                         |                                            |                                                                                            |
|                             | School performance                  |                                            |                                                                                            |

using it and cleaning it largely without parental supervision (**Table 1**).

By contrast, the caregivers of the adolescents with low and no use exemplified an authoritarian parenting style. The quote from the mother of participant 1 typifies this style in her response to asking about strategies used to encourage adherence. Since 13/14 of these adolescents were prescribed CPAP at an older age (> age 10; **Table 1**), they were initially trusted to use CPAP independently. When caregivers discovered that they had not been using it, caregivers tried to facilitate use by punishment and threats. These scenarios rarely resulted in the adolescent exhibiting the desired behaviors. Indeed, these punishments and threats appeared to have the opposite effect.

### **Social Reactions and Attitudes Affect CPAP Adherence (Table 6)**

#### ***Desire to Please/Self-Respect***

Within the theme of social reactions and attitudes that affect CPAP adherence, was a sub-theme of desire to please which

seemed closely linked to the notion of self-respect. Adolescents with high use revealed an awareness of their caregivers' concerns about their health and the consequences of having sleep apnea. They expressed a desire to alleviate their caregivers' anxiety by using CPAP.

Rebellious attitudes were noted by the caregivers of the participants with low or no use. Parental promotion of CPAP use can become an issue of contention. Within our participants, we found that teenagers who described rebellious attitudes tended to be lower users. Adolescents with low and no use were influenced by their peers' knowledge of them having a CPAP machine. These users appeared to be ashamed about having to use CPAP and expressed wanting to be like peers. Their desire to conform to peer norms was also noted by caregivers.

Some participants did not express any need to use CPAP. A sub-theme of invulnerability was related to the theme of adolescent perception of benefits affects motivation. This feeling of invulnerability in the adolescents was recognized by their caregivers too.



**Table 4**—Relationship between quotes, themes and theory: the extent and nature of structure in the home/family affects CPAP adherence

| Themes                            | High user quotes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Low user quotes                                                                                                                                                                                                                                                                                                          | Non user quotes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Family Organization and Structure | <p>Mother of Participant 18: "... this is our routine...take everything and shut all the lights out completely. Put the machine on."</p> <p>Participant 8: "...Sometimes I'd be watching TV and just fall asleep...she'll come in and check and then she'll probably...if she see that I don't have it on..."</p> <p>Participant 9: "His mask is broken and they were supposed to order it, but they never did. So I taped it up the last couple nights."</p> <p>Participant 8: "she'll probably have a talk with everybody and stuff like that. There will probably be a family meeting or something like that, everybody telling me that I should use it and stuff like that, so, or something like that."</p> | <p>Participant 3: "It's not really a schedule, it's just like whenever...I can be very, uh... nocturnal, and like, want to sleep all day and stay up all night."</p> <p>Participant 5: "[I use it] more on the weekdays because I live at my mom's house."</p>                                                           | <p>Participant 11: "It was probably laziness or just forgetfulness, or, I'd be sleeping at my friends' houses for extended periods of time and purposely forget my machine so I didn't have to use it at their house."</p> <p>Participant 14: "I start getting on it again, but once them pieces start missing I kinda was like forget it."</p> <p>Participant 6: "Actually that was last when I used it probably when I lived with my dad. He was very consistent, more so than my mom was."</p> <p>Mother of Participant 1: "She wants to sit and watch TV. 'No, because you got the same TV in your room...get in your bed and get comfortable. When you start falling asleep put the mask on, ...I'll come in there and cut your TV off or your brother will cut your TV off.' She still won't do it."</p> <p>Participant 16: "Because sometimes I do forget to put it on or I just fall asleep or I don't wanna put it on that night, so I don't put it on. [Also], the weekends to me is like a break from school and stuff, so I just don't wear it."</p> |
| Routine                           | <p>Participant 8: "Like, the more you do something the more your body get used to doin' it, so, I'm ...used to wearin' it and I remember more that I got to put on...my mask when I go to sleep."</p> <p>Participant 10: "...When I get tired I either go to sleep by myself or I put the mask on...because I know I'll go to sleep faster."</p> <p>Participant 10: "...I put it on when I watch TV because if I watch TV I fall asleep. The machine is on while I'm watching TV. I never slept without my mask."</p>                                                                                                                                                                                            | <p>Participant 4: "...Like I might like, I might have everything set up or something and I'm, I start watching TV and just fall asleep and forget about putting it on...even when it's right there..."</p> <p>Participant 13: "I feel kind of annoying. Because I'm not used to sleeping with something on my face."</p> | <p>Participant 16: "So when I stay up late...I don't go to sleep until like 4:00... I really didn't get that much sleep so I wouldn't have no point in putting it on"</p> <p>Participant 6: "I didn't bring it and her mom asked me why I didn't bring it and I was like, "I just didn't feel like it." But I usually do bring it to my friends' house if I've been using it, I bring it, but, recently, I haven't used it...at all..."</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

## Stress

Stress within a family was linked to CPAP use. High use appeared to decrease stress. While adolescents with low and no use did not perceive lack of CPAP adherence to be an issue related to stress, adolescents' lack of use was seen as a factor in increasing the stress in the lives of the caregivers.

## Adolescent Perception of Benefits Affects Motivation for CPAP Adherence (Table 7)

### Fear of Consequences to Health with No Use

Adolescents with high use seemed to be motivated by fear of the consequences of not using CPAP. Adolescents with low and no use appeared indifferent to the knowledge of the consequences of not using CPAP. They expressed indifference about their lack of use being detrimental to their health.

### Benefits of CPAP

Adolescents with high use consistently described receiving benefits from CPAP use. They appeared to be untroubled by the

adverse side effects they suffered. However, adolescents with low and no use were more variable in noticing benefits from CPAP, which may have been due to inconsistent use. They complained about discomfort and saw this as a reason for disuse.

## Review of CPAP Downloads with Participants

In adolescents with low and no use, being shown evidence of their lack of use provoked surprise. The low use participants were especially astonished about their lack of use. Their expressions showed a belief that they thought they had been using their CPAP machines more. Participant 12 said, "I like I had the machine set up ...So I guess I was using it and I take it off when I was asleep." Participant 15 said, "I usually would think that I would have it on long, but then I see it don't look like I have it on that long at all."

Caregivers expressed surprise and concern when presented with the evidence of low or no use. The mother of participant 13 responded that she thought her daughter was using her CPAP machine most nights. After seeing the download of her daughter's CPAP use during the past month, she said "She has to use it more, ...I'm gonna stay on top of it."

**Table 5**—Relationship between quotes, themes and theory: the style of communication between caregivers and adolescents affects CPAP adherence

| Themes          | High user quotes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Low user quotes                                                                                                                                                                                                                   | Non user quotes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Parenting Style | <p>Mother of Participant 18: <i>"I tell him or remind him of the consequences and let it go, and let him make the choice."</i></p> <p>Participant 18: <i>"Like she'll come in and make sure I have it on...if...I'm ready to go to sleep, she just reminds me to make sure that I put it on. I think it's helpful because it shows that she cares."</i></p> <p>Mother of Participant 18: <i>"Don't force it. Let it be their decision...You want to nudge, but just to hammer it wouldn't be a good idea, because what will happen is they won't do it at all."</i></p> | <p>Father of Participant 9: <i>"I told him, he had to use it every night or else I take... his PlayStation 3. It works good, but except middle of the night... the mask always off of his face and he say he don't know."</i></p> | <p>Mother of Participant 1: <i>"You can't go out for the weekend"...that don't work. So I feel like sometimes she don't care and she don't care what nobody say..."</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Communication   | <p>Participant 19: <i>"Sometimes – she will come in and tell me "make sure you put your mask on"... I tell her "I will" but sometimes she don't tell me because she knows I put it on."</i></p> <p>Participant 18: <i>"I think she understands that I forget. She's trying to help me get in the mind frame of making sure that I don't forget. So it's like I think she does understand, but she wants to help me so that way I don't keep forgetting."</i></p>                                                                                                        | <p>Participant 9: <i>"...I do put it on. I just don't know how it ends up off me...I don't remember taking it off. When I don't use it, they yell at me."</i></p>                                                                 | <p>Participant 1: <i>"Like yelling at me and stuff like that just to put it on...just tell me...don't yell at me."</i></p> <p>Participant 16: <i>"Because she'll tell me to put my mask on, but then when I don't put it on she'll holler at me or say go put my mask on. But when I tell her that it leaves marks on my face or something like that, she says well you have to put it on and I just don't want to. She don't...she's not aware of it, that I don't want to."</i></p> <p>Participant 11: <i>"My dad said 'If you don't use that damn machine I'm gonna ground you'.... He would drill it into my head and every night he'd call me because he'd be at work...I'd be like 'alright, bye'...And then I'd just fall asleep...He was very consistent, more so than my mom was..."</i></p> <p>Participant 16: <i>"when I don't put it on she'll holler at me... But when I tell her that it leaves marks on my face...she says well you have to put it on and I just don't want to. She's...not aware of it, that I don't want to."</i></p> <p>Mother of Participant 1: <i>"Punishment. Taking away things from her...you can't spend the night out...I done tried to punish her...that don't work. 'You can't go out for the weekend'...that don't work. So I feel like sometimes she don't care...and I done punished her...it just don't work."</i></p> |

## DISCUSSION

Little is known about the perspectives of adolescent CPAP users and their caregivers. This is important as adherence in this age group is often poor. Gaining these insights may be of benefit to clinicians in identifying factors to explore with adolescent patients and their families to facilitate optimal use.

### The Extent and Nature of Structure in the Home/Family Affects CPAP Adherence

Adolescents may have difficulty adhering to treatment regimens devised by health professionals and parents because of poorly developed abstract thinking. This problem may manifest as a poor ability to plan and prepare for different situations using abstract concepts<sup>17</sup>; therefore, family organization is key. Bender found in a quantitative study that

non-adherence, to  $\beta$ -agonists and corticosteroids in 24 asthmatic children, increased with the level of disorganization or dysfunction within the family.<sup>18</sup> Our qualitative results support this conclusion with CPAP adherence: for families of adolescents with high use, CPAP use was considered an important family priority by both the caregivers and the adolescents. Also, households with an adolescent with high use maintained an organized structure for managing CPAP use, e.g., caregiver present at bedtime and facilitating the adolescents using CPAP away from home.

Youth with behavior problems are especially at risk for poor adherence. According to family process theories, behaviorally disordered youth tend to lack routines in their lives, which is hypothesized to compromise their compliance with a daily, multifaceted treatment regimen.<sup>19</sup> Greening found it is important that clinicians help families recognize the critical aspects of the child's medical regimen and to integrate the treatment

**Table 6**—Relationship between quotes, themes and theory: social reactions and attitudes affect CPAP adherence

| Themes                        | High user quotes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Low user quotes                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Non user quotes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Desire to Please/Self Respect | <p>Mother of Participant 8: <i>"I think she [mother] understands it more than I do...why it is important to wear it, so... I just use it and she's happy; I'm happy, so, we're all happy."</i></p> <p>Participant 18: <i>"...from what I understand it does, it'll help me be alive longer, it'll help me with my health. So it'll contribute more to my life and my family and things."</i></p> <p>Participant 8: <i>"Sometimes I stop breathing at night, and I really scared her, and I don't like my mom being scared and upset and stuff...so I started using it."</i></p> | <p>Participant 9: <i>"I don't know. I just didn't feel like wearing it."</i></p> <p>Participant 12: <i>"When I first got it, I really didn't like using it. So I guess that's why I wasn't really using it."</i></p>                                                                                                                                                                                                                                                      | <p>Participant 1: <i>"I just end up not wearing it because she [mother] just irritates...when I get mad, I just want to go to sleep."</i></p> <p>Participant 16: <i>"...sometimes I do forget to put it on or I just fall asleep or I don't wanna put it on that night...I just was being stubborn...so I don't put it on."</i></p> <p>Participant 11: <i>"I'd be sleeping at my friends' houses for extended periods of time and purposefully forget my machine."</i></p> <p>Mother of Participant 4: <i>"He's always been very negative with it. ...He doesn't want to use anything that alters him from being normal."</i></p> <p>Participant 4: <i>"You know you're gasping for air. Put the mask on!" She won't do it. She just don't wear it. It's like to me she don't care."</i></p> |
| Stress                        | <p>Participant 8: <i>"I'm used to it now, so it doesn't really stress me out or make me upset or anything."</i></p> <p>Participant 18: <i>"No. I actually think it will decrease it because it's like a good night's sleep with help everything go flower, smoother I wake up in the morning, I'm refreshed...I don't feel like I've been working in my sleep. I just feel good when I wake up."</i></p>                                                                                                                                                                        | <p>Mother of Participant 15: <i>"If you're at home with me now and I have to fight with you to wear it, when you go to college who is going to fight with you to wear it? So you probably won't wear it. So that is a very big stressor for me."</i></p> <p>Participant 9: <i>"I just feel more stressful, like, ever since I started using it... it makes me kind of more mad...Like when I use the machine...i just wake up in like a bad mood, like I'm lost."</i></p> | <p>Mother of Participant 1: <i>"It's really a problem, and I know if she'd wear that mask she'd get a good night rest... it's just a task...because she don't get enough rest. She won't wear the mask...it's depressing and I cry a lot"</i></p> <p>Mother of Participant 1: <i>"And when she don't wear it, she wets the bed. When she do wear it, she don't pee the bed...It bothers me. It's a big issue to me."</i></p>                                                                                                                                                                                                                                                                                                                                                                 |

plan into the child's and family's current routine activities.<sup>20</sup> If a routine does not exist, it may be beneficial for the clinical team to facilitate the development of a routine with the family that incorporates CPAP.

### Style of Communication between Caregivers and Adolescents Affects CPAP Adherence

Starting in early adolescence, parents and adolescents begin to have less interactions and spend less time together outside the home than they did previously and children's conformity to their peers peaks, reflecting the importance of social acceptance.<sup>21</sup> This distancing in parent-adolescent relations has a functional value for adolescents in that it fosters their independence, prompts them to try more things on their own, and develops their sense of efficacy.<sup>22</sup> Caregivers may view their adolescents as emerging adults and may expect their adolescent to use CPAP independently without support and supervision. Of note, most high users initiated CPAP during childhood rather than adolescence, when their parents may have played a more active role.

Parenting style can contribute to adolescent adherence patterns. Family environments that encourage autonomy and the early adolescent's role in family decision making are

associated with self-esteem, self-reliance, satisfaction with school and student-teacher relations, positive school adjustment, and advanced moral reasoning.<sup>23</sup> Recognizing the emerging adult autonomy of an adolescent is a factor that can contribute to optimal use by encouraging a sense of self-respect and self-discipline and fostering mature and responsible health decision-making. Conversely, a parenting style that is coercive, authoritarian, and not attuned to the adolescent's need for autonomy and input is associated with self-consciousness and lowered self-esteem which can have negative implications for CPAP adherence.<sup>24</sup>

Research from several investigators<sup>25-27</sup> suggests that adolescents' relationships with their parents can be also be stressful during early and middle adolescence due to developmental changes. This stress is often focused on issues of control and autonomy within the family, which are renegotiated during this developmental period. Ideally, the renegotiation process would be a smooth transition for both adolescents and parents, but as children mature and take more responsibility for their own lives; it is not easy for parents to determine the optimal level of autonomy versus control. According to the stage-environment fit perspective, one would predict strained relationships

**Table 7**—Relationship between quotes, themes and theory: adolescent perception of benefits affects motivation for CPAP adherence

| Themes                                     | High user quotes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Low user quotes                                                                                                                                                                                                                                                                 | Non user quotes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Fear of Consequences to Health with No Use | <p>Participant 18: “It actually motivates me because I think it’s scary that I stop breathing at night and that I could not wake up in the morning if I don’t have the machine on...So that is motivation to me, because the fact that I would like to stay alive. So that’s definitely motivation.”</p> <p>Participant 10: “...if I go to sleep and I don’t have it on I go into a deep sleep and I stop breathing, And then I wake up...My mask is uncomfortable, but I can’t sleep with it off. I can’t take it off and go to sleep.”</p> <p>Participant 19 “Because it helps me stay alive when I sleep so I won’t die in my sleep.”</p> | <p>Participant 12: “I just didn’t like using it. So I, I didn’t know how serious it was.”</p> <p>Participant 15: “I don’t think anything would happen to my health.”</p>                                                                                                        | <p>Participant 6: “Eventually, I’ll just be tired, I guess. I don’t really know. I haven’t really thought about that [laughs]... if [my doctor did tell me what would happen] I wasn’t paying attention. My mom probably knows.”</p> <p>Mother of Participant 4: “He wants to hide it [CPAP]. He doesn’t want to use it. I find it all over the house disassembled. If you put it on him and you leave the room he takes it off. He’s...just totally non-compliant with it.”</p>                                                                                                                                                                                                    |
| Benefits of CPAP                           | <p>Participant 18: “It actually motivates me because I think it’s scary that I stop breathing at night and that I could not wake up in the morning if I don’t have the machine on...So that is motivation to me, because the fact that I would like to stay alive. So that’s definitely motivation.”</p> <p>Participant 10: “...if I go to sleep and I don’t have it on I go into a deep sleep and I stop breathing, And then I wake up...My mask is uncomfortable, but I can’t sleep with it off. I can’t take it off and go to sleep.”</p>                                                                                                 | <p>Participant 9: “I feel the same as without the mask.”</p> <p>Participant 3: “...I was told that if I wear it now I won’t have to later...that motivated me to wear it for a while, but, lately... it’s annoying.”</p> <p>Participant 13: “To me it’s just all the same.”</p> | <p>Participant 4: “I feel that I’m breathing better without it. My mother said I need it. I feel normal. I feel okay when I wake up in the morning... [without CPAP]”</p> <p>Participant 12: “...I just be like, probably don’t really need it. But...when I started coming back for appointments and they saw I wasn’t using it, then really they told me like I really, really need it.”</p> <p>Participant 6: “I don’t pay attention because I don’t like doing school work so it’s kind of just like either way I’m like, ‘I don’t want to move. I just want to lay here.’”</p> <p>Participant 14: “I think I’d be the same, because I never feel myself stop breathing...”</p> |

wherever there is a poor fit between the child’s desire for increasing autonomy and the opportunities for independence and autonomy provided by the child’s parents.<sup>28</sup>

Monaghan found that an authoritative parenting style was associated with significantly less parenting stress than authoritarian or permissive parenting styles.<sup>29</sup> In our study, an authoritative parenting style was more common among caregivers of adolescents with high use and an authoritarian style was more likely to be demonstrated by caregivers of no and low use adolescents. Our findings were consistent with studies of other treatment regimens which found that caregivers with an authoritative parenting style were associated with improved treatment adherence.<sup>30-32</sup> For adolescents with low and no use, there were some caregivers who would try to assist with using CPAP, but their authoritarian parenting style led them to have expectations that were unrealistic resulting in little or no CPAP use. This phenomenon has been described in the literature as “Miscarried Helping.”<sup>33</sup> DiMatteo also found that social support from caring family members, family cohesiveness, and positive family interaction patterns strongly affect adherence. Conversely, family conflict and negative feelings in the family can serve as powerful factors related to non-adherence, as well as by being upsetting and stressful.<sup>34</sup> Effective communication is important in the parental promotion of CPAP adherence.

Offering occasional reminders and checking on adolescents at bedtime as a means of encouraging the establishment of

CPAP into their routines seems to promote adherence. Berating or nagging appeared to have the opposite effect than intended.

There was a difference in the age CPAP was prescribed between the high users and low and no users (**Table 1**). We believe this shows the difficulty of introducing CPAP in the adolescent age group. Introducing CPAP prior to adolescence, when children’s behaviors are more malleable and parents have greater influence and control,<sup>28</sup> is likely to be less challenging, although can still take time for the child to become accustomed to using the mask and machine. When CPAP is prescribed at a younger age, there is a longer opportunity for it to become a routine part of the adolescent’s life and the patient may have a better sense of the benefits of use. Introducing CPAP use during adolescence may be especially challenging because of rebellion and emerging autonomy, as discussed below.

### Social Reactions and Attitudes Affect CPAP Adherence

Concerns about health contributed to stress levels in participants’ families. Although high stress levels in the families of low and no users may not have been entirely attributable to poor adherence, poor CPAP use was a cause of stress for the caregivers. Becoming aware of family stressors is important so that the health care providers consider the social situation of the families to begin the conversation that despite having other stresses how can they best support the family in using CPAP and making its use a priority. The way CPAP is initiated may be



important to facilitate adherence. Adding CPAP to a family that is already coping with significant stressors may only magnify stress in the household and impede actual use of CPAP.

Some high users attributed the reasons for their regular use of CPAP to a desire to please their caregivers. They expressed concern about their parents' anxiety about their OSAS and did not want to upset them. They seemed to have a greater sense of self-worth than the low and no users and had a sense of responsibility for their own and their parents' well-being. Encouraging self-respect and fostering a sense of responsibility would appear to be a helpful strategy for increasing adherence.

The participant-caregiver relationship also appeared to play a role in adherence. Within the high users, most participants described cohesive family relationships. Although a close relationship with the parent facilitates adherence in young adolescents, if the parent is overprotective, it may prove challenging for the adolescent to achieve autonomy and assume responsibility for their CPAP use. Overprotection has been shown to cause social isolation and interfere with the development of individual ability for self-care.<sup>35</sup>

A normal facet of adolescence is to rebel against authority and to challenge limits set by family caregivers. One of the main tasks of adolescence is to become an autonomous individual. The drive for autonomy stems from biological processes marking the transition to a more adult role (puberty and increasing cognitive maturity) and from shifts in social roles and expectations. As adolescents become physically mature, they begin to question family rules and roles, leading to conflicts.<sup>21</sup> CPAP use provides an opportunity for rebellion. While adolescents may rebel against parental and adult societal expectations, they want to conform to peer norms.

Another aspect of the developmental process is a feeling of invulnerability. Adolescents possess little ability to appreciate consequences of current life style decisions and actions. They see themselves as being invulnerable, a notion that has been described in the literature as being "bullet proof."<sup>17</sup> This notion is linked to the adolescent perceptions of the benefits of CPAP.

### Adolescent Perception of Benefits Affect Motivation for CPAP Adherence

Less daytime sleepiness, sleeping better, having more energy, improved school performance, and decrease in enuresis were some of the benefits associated with adolescent CPAP adherence. Caregivers and adolescents of the low and no CPAP use groups reported more subtle benefits from using CPAP than their high use counterparts. Some of the adolescents with high use described having a physical or psychological need for using CPAP, e.g., believing it was what made them fall asleep or reporting they would wake up choking and gasping if they fell asleep without using it. Having an understanding of the importance of using CPAP was associated with high use, which highlights the need for healthcare providers to educate CPAP users and their families as fully as possible about the purpose and benefits of CPAP, as well as the physical and neurobehavioral consequences of untreated OSAS.

Discomfort with using CPAP was described by all the adolescents, but only adolescents in the low and no use groups described this as a significant barrier to adherence. Nasal congestion, skin irritation, a poor mask fit, and intolerance to air

pressure are all well-known side effects of CPAP use that were mentioned by all the adolescents. As part of the educational initiation processes for CPAP, it is essential to provide anticipatory guidance about the potential complications of CPAP. Further, it is important for clinicians to explain that potential remedies exist for these complications and that the family should contact the medical team if the adolescent experiences any of the side effects. While some of these complications may improve with increased use of CPAP, others may be addressed by the health care team (e.g., mask fit, chronic nasal congestion, skin irritation). Identifying potential barriers and providing support to problem solve barriers may facilitate adherence.

As previously discussed, some adolescents are non-adherent because of a feeling of invulnerability; however, the adolescents with high use described fear as a motivator for adherence. They expressed being afraid of the consequences of not using CPAP (e.g. death, not being able to breathe, adverse effects on their hearts). Bond et al.'s Health Belief Model predicted that the benefits-costs and cues constructs were related to compliance if benefits were high and costs were low. The greatest compliance was achieved with low perceived threat and high perceived benefits-costs. Our findings fit this model. High use adolescents expressed knowledge of fear of consequences, or high threat, for lack of use and had a perception of high benefits and low cost regarding their CPAP use. Adolescents with low or no use perceived low benefit, high cost, and high threat, but the level of threat was not adequate motivation to overcome the high cost of use which may be linked to the adolescent perception of invulnerability.<sup>36</sup>

### Strengths and Limitations

This was a small study and as is the case with qualitative research, the findings do not presume to be generalizable. Rather, we have generated grounded theories that we offer for further exploration and evaluation. Nonetheless, we feel that these theories merit consideration by clinicians in helping families develop strategies that will promote CPAP use. Despite purposively sampling across the spectrum of adherence, we do recognize it was not demographically representative, and the population was primarily inner city families. Following the analysis, it became apparent there was a difference in the age at which CPAP was prescribed for the high users (**Table 1**); ideally, we should have also purposively recruited more high users who started CPAP during adolescence and additional low and no users who were prescribed CPAP at a younger age in order to represent a broader range of experience using CPAP in adolescence. Another potential weakness that is common to all studies involving interviewing was self-selection of participants, which could create volunteer bias in our sample. There is a risk that participants will offer responses that they feel are desired by the interviewer. We attempted to minimize this risk by carrying out the interviews in a non-judgmental and open way and by emphasizing that there were no right or wrong answers and that the interviewer was genuinely interested in the participants' experiences and opinions.

Our findings were strengthened by the use of objective adherence data facilitating an open discussion about actual use. Objective measurement of adherence is less prone to bias, owing to the tendency of parents and children to overestimate adherence on self-report.<sup>37</sup>

## CONCLUSION

Adherence to medical regimens in adolescents has long been recognized as problematic. For sleep clinicians, CPAP adherence in adolescents has been a concern that is likely to grow due to the current obesity epidemic and an increase in referrals to sleep specialists of adolescents with OSAS. Understanding the adolescent and family experience of using CPAP may be the key to developing more effective mechanisms to promote adherence. Issues that need to be considered are parenting style, family dynamics, and communication. Health education, combined with family involvement in developing strategies that facilitate CPAP use within their family context, are important components of promoting adherence. Since many adolescents appear reluctant to make their peers aware of their CPAP use, peer support groups may help promote adherence. All support strategies need to take into account the developmental process of adolescence and should be tailored to the individual and his or her family.

## REFERENCES

1. Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. Risk factors for sleep-disordered breathing in children. Associations with obesity, race, and respiratory problems. *Am J Respir Crit Care Med* 1999;159:1527-32.
2. Marcus CL, Carroll JL, Koerner CB, Hamer A, Lutz J, Loughlin GM. Determinants of growth in children with the obstructive sleep apnea syndrome. *J Pediatr* 1994;125:556-62.
3. Guilleminault C, Eldridge FL, Simmons FB, Dement WC. Sleep apnea in eight children. *Pediatrics* 1976;58:23-30.
4. Somers VK, White DP, Amin R, et al. Sleep Apnea and Cardiovascular Disease: An American Heart Association/American College of Cardiology Foundation Scientific Statement From the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing In Collaboration With the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *J Am Coll Cardiol* 2008;52:686-717.
5. Beebe DW, Byars KC. Adolescents with obstructive sleep apnea adhere poorly to positive airway pressure (PAP), but PAP users show improved attention and school performance. *PLoS One*;6:e16924.
6. Beebe DW, Ris MD, Kramer ME, Long E, Amin R. The association between sleep disordered breathing, academic grades, and cognitive and behavioral functioning among overweight subjects during middle to late childhood. *Sleep* 2010;33:1447-56.
7. Kliegman RM, Behrman RE, Jenson HB, Stanton BF, eds. *Nelson textbook of pediatrics*. 18th ed. Philadelphia: Saunders, 2007.
8. Zitelli BJ, Davis HW, eds. *Atlas of pediatric physical diagnosis*. 5th ed. Philadelphia: Mosby/Elsevier, 2007.
9. Marcus CL, Rosen G, Ward SL, et al. Adherence to and effectiveness of positive airway pressure therapy in children with obstructive sleep apnea. *Pediatrics* 2006;117:e442-51.
10. Marcus CL, Beck SE, Traylor J, et al. Randomized, double-blind clinical trial of two different modes of positive airway pressure therapy on adherence and efficacy in children. *J Clin Sleep Med* 2012;8:37-42.
11. Sawyer AM, Deatrick JA, Kuna ST, Weaver TE. Differences in perceptions of the diagnosis and treatment of obstructive sleep apnea and continuous positive airway pressure therapy among adherers and nonadherers. *Qual Health Res* 2010;20:873-92.
12. Simon SL, Duncan CL, Janicke DM, Wagner MH. Barriers to treatment of paediatric obstructive sleep apnoea: Development of the adherence barriers to continuous positive airway pressure (CPAP) questionnaire. *Sleep Med* 2012;13:172-7.
13. Orrell-Valente JK, Jarlsberg LG, Hill LG, Cabana MD. At what age do children start taking daily asthma medicines on their own? *Pediatrics* 2008;122:e1186-92.
14. Chigier E. Compliance in adolescents with epilepsy or diabetes. *J Adolesc Health* 1992;13:375-9.

15. Difeo N, Meltzer LJ, Beck SE, et al. Predictors of positive airway pressure therapy adherence in children: a prospective study. *J Clin Sleep Med* 2012;8:279-86.
16. Charmaz K. Grounded theory: objectivist and constructivist methods. In: Denzin NK, Lincoln YS, eds. *The handbook of qualitative research*. 2nd ed. Thousand Oaks, CA: Sage Publications, 2000:509-35.
17. Suris JC, Michaud PA, Viner R. The adolescent with a chronic condition. Part I: developmental issues. *Arch Dis Child* 2004;89:938-42.
18. Bender B, Milgrom H, Rand C, Ackerson L. Psychological factors associated with medication nonadherence in asthmatic children. *J Asthma* 1998;35:347-53.
19. Fiese BH, Tomcho TJ, Douglas M, Josephs K, Poltrock S, Baker T. A review of 50 years of research on naturally occurring family routines and rituals: Cause for celebration? *J Fam Psychol* 2002;16:381-90.
20. Greening L, Stoppelbein L, Konishi C, Jordan SS, Moll G. Child routines and youths' adherence to treatment for type 1 diabetes. *J Pediatr Psychol* 2007;32:437-47.
21. Eccles JS. The development of children ages 6 to 14. *Future Child* 1999;9:30-44.
22. Collins, WA. Parent-child relationships in the transition to adolescence: Continuity and change in interaction, affect, and cognition. In: Montemayor R, Adams GR, Gullotta TP, eds. *From childhood to adolescence: A transitional period?* Beverly Hills, CA: Sage Publications, 1990: 85-106.
23. Eccles JS, Lord S, Buchanan, CM. School transitions in early adolescence: What are we doing to our young people? In: Graber JA, Brooks-Gunn J, Petersen AC, eds. *Transitions through adolescence: Interpersonal domains and context*. Hillsdale, NJ: Lawrence Erlbaum Associates, 1996:251-84.
24. Leahy RL. Parental practices and the development of moral judgment and self-image disparity during adolescence. *Dev Psychol* 1981;17:580-94.
25. Buchanan CM, Eccles JS, Becker JB. Are adolescents the victims of raging hormones? Evidence for activation effects of hormones on moods and behavior at adolescence. *Psychol Bull* 1992;111:62-107.
26. Paikoff RL, Brooks-Gunn J. Do parent-child relationships change during puberty? *Psychol Bull* 1991;110:47-66.
27. Steinberg L. Interdependence in the family: Autonomy, conflict, and harmony in the parent-adolescent relationship. In: Feldman SS, Elliott GR, eds. *At the threshold: The developing adolescent*. Cambridge, MA: Harvard University Press, 1990:255-76.
28. Eccles JS, Midgley C, Wigfield A, et al. Development during adolescence: The impact of stage-environment fit on young adolescents' experiences in schools and in families. *Am Psychol* 1993;48:90-101.
29. Monaghan M, Horn I, Alvarez V, Cogen F, Streisand R. Authoritative parenting, parenting stress, and self-care in pre-adolescents with type 1 diabetes. *J Clin Psychol Medical Settings*;19:255-61.
30. Rhee H, Wenzel J, Steeves RH. Adolescents' psychosocial experiences living with asthma: a focus group study. *J Pediatr Health Care* 2007;21:99-107.
31. George M, Rand-Giovannetti D, Eakin MN, Borrelli B, Zettler M, Riekert KA. Perceptions of barriers and facilitators: Self-management decisions by older adolescents and adults with CF. *J Cyst Fibros* 2010;9:425-32.
32. Guilfoyle SM, Goebel JW, Pai ALH. Efficacy and flexibility impact perceived adherence barriers in pediatric kidney post-transplantation. *Fam Syst Health* 2011;29:44-54.
33. Carden SR. Working with Families of Adolescents with Diabetes, CME Disclosures. Presented at the 60th Scientific Sessions of the American Diabetes Association 2000; San Antonio, TX.
34. DiMatteo MR. The role of effective communication with children and their families in fostering adherence to pediatric regimens. *Patient Educ Couns* 2004;55:339-44.
35. Wysocki T. Diabetes mellitus in the transition to adulthood: adjustment, self-care, and health status. *J Dev Behav Pediatr* 1992;13:194-201.
36. Bond GG, Aiken LS, Somerville SC. The health belief model and adolescents with insulin-dependent diabetes mellitus. *Health Psychol* 1992;11:190-8.
37. Bender BG, Bartlett SJ, Rand CS, Turner C, Wamboldt FS, Zhang L. Impact of interview mode on accuracy of child and parent report of adherence with asthma-controller medication. *Pediatrics* 2007;120:e471-7.

## ACKNOWLEDGMENTS

We would like to thank Dr. Renée H. Moore from the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania for her assistance with the study design and mentorship; Shimrit Keddem and Katie Kellom from the Mixed-Methods Research Laboratory at the University of Pennsylvania for their expertise with NVivo 9.0 software; and the patients and their families for their participation in the study. Financial Support: NIH T32-HL007713-19 & R01HL58585

**SUBMISSION & CORRESPONDENCE INFORMATION**

**Submitted for publication March, 2013**

**Submitted in final revised form August, 2013**

**Accepted for publication August, 2013**

Address correspondence to: Priya Prashad, Suite 9NW50, 34th and Civic Center Blvd., Philadelphia, PA, 19104; Tel: (267) 426-5842; Fax: (267) 426-9234; E-mail: prashadps@hotmail.com

**DISCLOSURE STATEMENT**

This was not an industry supported study. Carole Marcus, Jill Maggs, Mary Anne Cornaglia, and Ruth Bradford have research support in the form of loaned equipment from Philips Respironics and Ventus, not related to the current study. Nicolas Stettler works at a scientific consulting firm that does work for various companies. None of his work has been related to the topic of this study or devices described in it. The other authors have indicated no financial conflicts of interest. Financial Support: NIH T32-HL007713-19 & R01HL58585





# The Accuracy of Eyelid Movement Parameters for Drowsiness Detection

Vanessa E. Wilkinson, Ph.D.<sup>1</sup>; Melinda L. Jackson, Ph.D.<sup>1,2</sup>; Justine Westlake, B.A./BAppSci (Hons)<sup>1</sup>;  
Bronwyn Stevens, BBNSc, PGradDip (Psych)<sup>1</sup>; Maree Barnes, MB.BS<sup>1</sup>; Philip Swann, Ph.D.<sup>3</sup>; Shantha M. W. Rajaratnam, Ph.D.<sup>4,5,6</sup>;  
Mark E. Howard, MB.BS., Ph.D.<sup>1</sup>

<sup>1</sup>Institute for Breathing & Sleep, Department of Respiratory & Sleep Medicine, Austin Health, Victoria, Australia; <sup>2</sup>Melbourne School of Psychological Sciences, The University of Melbourne, Victoria, Australia; <sup>3</sup>Department Road Safety, Victoria, Australia; <sup>4</sup>School of Psychology and Psychiatry, Monash University, Clayton, Victoria, Australia; <sup>5</sup>Division of Sleep Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA; <sup>6</sup>Division of Sleep Medicine, Department of Medicine, Harvard Medical School, Boston, MA

**Study Objectives:** Drowsiness is a major risk factor for motor vehicle and occupational accidents. Real-time objective indicators of drowsiness could potentially identify drowsy individuals with the goal of intervening before an accident occurs. Several ocular measures are promising objective indicators of drowsiness; however, there is a lack of studies evaluating their accuracy for detecting behavioral impairment due to drowsiness in real time.

**Methods:** In this study, eye movement parameters were measured during vigilance tasks following restricted sleep and in a rested state ( $n = 33$  participants) at three testing points ( $n = 71$  data points) to compare ocular measures to a gold standard measure of drowsiness (OSLER). The utility of these parameters for detecting drowsiness-related errors was evaluated using receiver operating characteristic curves (ROC) (adjusted by clustering for participant) and identification of optimal cutoff levels for identifying frequent drowsiness-related errors (4 missed signals in a minute using OSLER). Their accuracy was tested for detecting increasing frequencies of behavioral lapses on a different task

(psychomotor vigilance task [PVT]).

**Results:** Ocular variables which measured the average duration of eyelid closure (inter-event duration [IED]) and the ratio of the amplitude to velocity of eyelid closure were reliable indicators of frequent errors (area under the curve for ROC of 0.73 to 0.83,  $p < 0.05$ ). IED produced a sensitivity and specificity of 71% and 88% for detecting  $\geq 3$  lapses (PVT) in a minute and 100% and 86% for  $\geq 5$  lapses. A composite measure of several eye movement characteristics (Johns Drowsiness Scale) provided sensitivities of 77% and 100% for detecting 3 and  $\geq 5$  lapses in a minute, with specificities of 85% and 83%, respectively.

**Conclusions:** Ocular measures, particularly those measuring the average duration of episodes of eye closure are promising real-time indicators of drowsiness.

**Keywords:** Behavioral lapses, drowsiness, fatigue, ocular measures, eye blinks

**Citation:** Wilkinson VE; Jackson ML; Westlake J; Stevens B; Barnes M; Swann P; Rajaratnam SMW; Howard ME. The accuracy of eyelid movement parameters for drowsiness detection. *J Clin Sleep Med* 2013;9(12):1315-1324.

Drowsiness as a result of sleep deprivation, circadian effects, or sleep disorders is a major risk factor for motor vehicle and occupational accidents.<sup>1,2</sup> Objective indicators of drowsiness may allow sleepy individuals to be identified in real time in the laboratory, occupational settings, and on the road, with the potential to intervene and prevent accidents. Ideally, indicators of drowsiness for this purpose should be able to detect brief periods of inattention, which may result in an individual failing to respond to hazards in the environment. The lack of validated real-time objective indicators of drowsiness for field research and operational settings, such as driving, restricts both the ability to accurately assess drowsiness in these settings and the development of field-based interventions for drowsiness. Initial laboratory studies have suggested that some ocular measures may be good indicators of drowsiness<sup>3-5</sup>; however, there is a paucity of detailed evaluation of the utility of different ocular measures for this purpose.

Electroencephalography (EEG) is the gold standard method for quantifying sleep state (awake versus sleep). Although EEG changes occur with drowsiness in the wake state (increased

## BRIEF SUMMARY

**Current Knowledge/Study Rationale:** Objective indicators of drowsiness have the potential to identify drowsy drivers. This study evaluated the accuracy of ocular measures for detecting drowsiness-related behavioral impairment in real-time.

**Study Impact:** Several ocular measures, particularly those measuring the average duration of episodes of eye closure, were found to be accurate in the real-time detection of behavioral impairment in the laboratory. Ocular measures are promising indicators of real-time drowsiness.

alpha and theta activity),<sup>6</sup> they are difficult to measure in field settings due to signal artifact, are not readily amenable to real-time signal processing and are not highly predictive of impaired behavior due to drowsiness.<sup>7</sup> These features have hindered the use of EEG for assessing drowsiness in field settings and the potential to use it to provide real-time drowsiness monitoring.

Changes in the frequency, amplitude, and duration of blinks and episodes of slow eye closure occur in response to increased drowsiness caused by sleep deprivation and circadian rhythm effects.<sup>8-11</sup> While blink duration in rested conditions lasts for less

than 200 ms, sleep deprivation results in increased blink duration, episodes of slow eye closure lasting more than 500 ms, and increased proportion of time the eyes are closed.<sup>10,12</sup> The proportion of time the eyes are at least 80% closed (PERCLOS) increases in drowsy participants during task performance and is reported to correlate well with vigilance and simulated driving tasks in the laboratory.<sup>5-7</sup> Technological development has enabled more detailed measurement of eyelid movements in real time. Initial reports suggest that the velocity and amplitude of eyelid movements provide useful indicators of drowsiness and that the use of multiple eyelid closure metrics may improve the prediction of drowsiness.<sup>10,13</sup> There is, however, a paucity of studies evaluating the ability of these measures to detect impaired vigilance as a result of drowsiness. In this study we evaluated the ability of a range of eye movement parameters to detect impaired vigilance (frequent behavioral lapses) following restricted sleep.

## METHODS

Participants undertook objective assessment of vigilance and drowsiness with concurrent measurement of eyelid movement parameters following a normal night of sleep and a night restricted to 4 h time in bed in a randomized crossover design.

### Participants

Healthy participants aged between 18-70 years were recruited. Participants underwent a medical review and were excluded if they had a chronic medical condition that might affect neurocognitive or motor function or be a contraindication to sleep restriction including sleep disorders and chronic neurological or psychiatric conditions. Participants were also excluded if they were heavy smokers, consumed on average  $\geq 5$  caffeinated beverages a day, had significant daytime sleepiness (Epworth Sleepiness Scale [ESS]  $> 11$ ),<sup>14</sup> had a high risk of sleep apnea on a validated screening survey,<sup>15</sup> or had visual impairment which was not corrected with glasses.

The study protocol was approved by the Austin Health Human Research Ethics Committee and was registered on the Australian New Zealand Clinical Trials Registry.

### Protocol

Participants attended the Sleep Laboratory, Austin Hospital, Heidelberg, for an initial medical screening, to obtain written informed consent and for familiarization with tasks and fitting of Optalert Drowsiness Measurement System (ODMS) equipment. ODMS glasses were fitted by an experienced researcher trained in this technique to confirm correct measurement of ocular data.

Two separate days of testing were conducted in random order,  $\geq 1$  week apart. Participants were instructed to maintain an 8-h in bed sleep schedule (22:00-06:00), confirmed by sleep diary, for the week preceding the testing session. A baseline session was performed while participants were in a rested state. On the night prior to the sleep restriction session, participants restricted their time in bed to 4 h (02:00-06:00). Sleep restriction was confirmed via actigraphy (SenseWear Body Monitoring System armband, Pittsburgh, USA) and a sleep diary kept for the preceding week.

Participants undertook one 1.5-h performance test battery in the rested state (baseline session) and 2 performance

test batteries following one night of sleep restriction (sleep restriction sessions in the morning (SR-AM) and afternoon (SR-PM)). Eighteen participants commenced this sequence with the baseline session prior to the sleep restriction sessions, and 21 participants commenced the sequence with the sleep restriction sessions. Three testing sessions were conducted to sample a range of impairments due to drowsiness and circadian factors. Performance measures were conducted at 09:00 (baseline and SR-AM) and 13:00 (SR-PM). The test battery consisted of objective vigilance tests in addition to exploratory drowsiness and performance questionnaires, which are not presented in this analysis. Testing was conducted in randomized order in a soundproofed room with dim lighting as per maintenance of wakefulness test (MWT) protocol.<sup>16</sup> There was a short break in between tests to check ocular signals and adjust as required. Vigilance testing included the 40-min Oxford Sleep Resistance Test (OSLER), and 10-min psychomotor vigilance task (PVT). Continuous ODMS recording occurred during these testing sessions, in addition to video monitoring to ensure synchronization of ODMS measures with vigilance testing measures.

### Outcome Measures and Data Analysis

A two-step process of analysis was undertaken. In Step 1, cutoff values for ocular measures of the ODMS for predicting drowsiness-related impairment were derived using the OSLER as the gold standard. In Step 2, the sensitivity, specificity, and area under the ROC curve were calculated using these cutpoints, using the PVT as a gold standard.

#### Step 1: Derivation of Cutoff Values

Ocular measures were evaluated for their accuracy in detecting drowsiness-related impairment and cutoff values for detecting impairment were developed. Eyelid movement parameters were measured using the ODMS (Optalert, Sleep Diagnostics Pty Ltd, Melbourne, Australia). This device records 8 ocular variables using infrared light from a light-emitting diode positioned below and in front of the eye on a pair of glasses hardwired to a laptop.<sup>17</sup> ODMS is reported to be fully functional regardless of the position or movement of the person's head, and in sunlight or darkness.<sup>18</sup>

The following ocular variables were calculated as an average on a minutely basis:

- *Inter-Event Duration (IED)*: blink duration measured from the point of maximum closing velocity to maximum opening velocity of the eyelid measured in seconds.
- *Percent Time with Eyes Closed (%TEC)*: proportion of time eyes are closed, determined from the velocity of eyelid movement during eyelid closure.
- *Blink Total Duration (BTD)*: duration of blinks measured in seconds from the start of closing to complete re-opening.
- *Negative Amplitude-Velocity Ratio (-AVR)*: the ratio of the maximum amplitude to maximum velocity of eyelid movement for the reopening phase of blinks.
- *Positive Amplitude-Velocity Ratio (+AVR)*: the ratio of the maximum amplitude to maximum velocity of eyelid movement for the closing phase of blinks.

- *Percent Long Closures (%LC)*: proportion of time eyes are fully closed > 10 ms.
- *Duration of Ocular Quiescence (DOQ)*: duration of no movements between eyelid and ocular movement events, including blinks, saccades and smooth pursuit.
- *Johns Drowsiness Scale (JDS)*: a composite measure of drowsiness calculated using weighted values of the other recorded ocular variables. JDS is calculated on a scale from zero to ten, with higher scores indicative of increased drowsiness.<sup>17</sup>

The OSLEP was used as the gold standard for indicating drowsiness and determining ocular measure cutoff values. OSLEP is a portable, computerized, non-assisted method of monitoring wakefulness through responses to presented stimuli occurring every 3 sec seconds over a 40-min time period, which has been found to be reliable in measuring sleep onset.<sup>19</sup> The OSLEP was designed as a simplified version of the maintenance of wakefulness test (MWT), a laboratory-based EEG method of determining an individual's ability to remain awake and the current recommended method of assessing whether people with sleep disorders have the ability to safely drive a vehicle.<sup>20,21</sup> Sleep onset is defined as no response to 7 consecutive OSLEP stimuli (absent response for 18-21 sec); however,  $\geq 4$  consecutive missed stimuli (absent response for 9-12 sec) is strongly predictive of microsleeps (brief occurrences of theta lasting between 3 and 15 sec).<sup>22</sup>

OSLEP and concurrent ocular measures were analyzed in 1-min bins. Overall OSLEP misses per minute and consecutive misses within each minute were identified. Consecutive misses which crossed a minute bin were attributed to the minute in which the missed signals began. Data from the OSLEP was compared to the corresponding time matched ocular variables in one minute bins. Data were excluded from sessions if the ODMS signal quality was poor (low amplitude), and for some instances of failure of time matching data to ocular variables.

### Statistical Analysis for Derivation of Cutoff Values

Statistical analyses were conducted using STATA 11 (StataCorp, College Station, TX: StataCorp LP). Receiver operating characteristic (ROC) curve analysis was conducted for each ocular variable, using data from all 3 testing sessions, to assess the ability of each variable to identify missed OSLEP signals occurring during any 1-min bin. This analysis was undertaken for (1)  $\geq 4$  consecutive missed signals on the OSLEP in a minute, and (2)  $\geq 4$  total missed signals on the OSLEP in a minute. Data were clustered by participant during statistical analysis to account for the multiple minutes of OSLEP replication for each participant.<sup>23,24</sup> Cutoff values to determine a level of drowsiness resulting in drowsiness-related deterioration in vigilance for each ocular variable were determined using the peak of the ROC curve to determine the optimum sensitivity and specificity combination. In addition, high sensitivity cutoff values were determined using the highest sensitivity with a specificity of  $\geq 50\%$  and the high specificity cutoff values were determined using the highest specificity with a sensitivity of  $\geq 50\%$ . Lastly, logistic regression models were fitted using the ocular variables with the highest discrimination for detection of missed signals on the OSLEP (IED, BTM, %TEC, +AVR).

### Step 2: Validation of Cutoff Values

The ability of the ocular variables with the greatest discrimination in detecting frequent missed signals on the OSLEP (IED, BTM, +AVR, and JDS) were then evaluated for the ability (sensitivity and specificity) of their OSLEP determined cutoff levels to detect different frequencies of lapses per minute on the PVT. The PVT is a hand-held reaction time task which assesses sustained attention through measuring reaction time to a visual stimulus, presented at varying intervals approximately 10 times per minute.<sup>25</sup> Impaired attention is a reliable consequence of drowsiness, with the PVT showing results characteristic of decreased attention such as slowed reaction times and increases in errors and lapses.<sup>26-28</sup> A review of 141 articles utilizing the PVT found the 10-min PVT to be the optimal length and the outcome of number of lapses to be the most frequently used and the most reliable measure when evaluating the effect of sleep loss.<sup>29</sup> PVT files were inspected for errors (reaction time < 100 ms) which were removed from the analysis. PVT and concurrent ocular measures were again analyzed in 1-min bins. Lapses (reaction time > 500 ms) were identified and the number of lapses per minute was determined for each minute.

### Statistical Analysis for Validation of Cutoff Values

Data from the PVT were compared to the corresponding time matched ocular variables in 1-min bins. The sensitivity and specificity of each ocular variable was calculated for detecting different frequencies of lapses (1 to  $\geq 5$ ) in any minute.

## RESULTS

Thirty-nine participants were recruited with data utilized from the 33 participants who completed the protocol (29 male, mean age 41.4 [ $\pm 12.9$ ], mean BMI 27.5 [ $\pm 5.3$ ], and a median ESS score of 5 [IQR 4-8]). The mean hours of sleep prior to the baseline testing was 6.5 ( $\pm 1.0$ ) and prior to the sleep restricted testing was 4.0 ( $\pm 0.1$ ) (confirmed by actigraphy).

### OSLEP Misses and Ocular Variables: ROC Curve Analysis

A summary of outcome measures for the OSLEP and PVT is presented in **Table 1** and ocular variables during these tasks in **Table 2** for baseline, SR-AM, SR-PM, and an overall compilation of all data.

ROC area under the curve (AUC) and 95% confidence intervals (CIs) clustered by participant are presented in **Table 3** for analysis of ocular variables compared to  $\geq 4$  consecutive missed signals on OSLEP (equates to 12 sec) and to  $\geq 4$  overall missed signals on the OSLEP by minute.

The variables measuring blink duration (IED and BTM) had good discriminatory ability for detecting frequent drowsiness-related missed signals, as did the JDS (**Table 3, Figures 1 and 2**). The ratio of the amplitude to velocity of eyelid movement during eyelid closure (+AVR) was also an accurate discriminator and was better than the ratio during re-opening at the end of the blink (-AVR). The measures of proportion of time with eyes closed had moderate to poor discriminatory ability (%TEC and %LC).

Logistic regression models fitted for ocular variables with the highest discrimination for detection of drowsiness-related

errors (IED, BTD, %TEC, +AVR) (**Figure 3**) displayed good discriminatory ability in detecting drowsiness via 4 consecutive (ROC AUC = 0.76) and 4 overall (ROC AUC = 0.824) missed signals in one minute. However, the ROC AUC for these models was found to be lower than for the use of the IED variable alone (**Table 3**), and further analysis using these models was not undertaken.

### Ocular Variable Cutoff Values for Optimal Sensitivity and Specificity

Cutoff values were chosen from the ROC curves for ocular variables that were moderate to good discriminators for detecting 4 consecutive missed signals and 4 overall missed signals on the OSLEP per minute (**Tables 4 and 5**). Three cutoff values were selected for the variables of IED, BTD, %TEC, +AVR,

**Table 1**—Summary of OSLEP measures (sleep latency, misses) and PVT measures (reaction time, lapses)

|                          | OSLEP         |                 |             |           |
|--------------------------|---------------|-----------------|-------------|-----------|
|                          | Sleep latency |                 | Misses      |           |
|                          | M ± SD (min)  | Mdn (IQR) (min) | M ± SD      | Mdn (IQR) |
| <b>Baseline</b> (n = 17) | 37.5 ± 5.1    | 40 (40-40)      | 0.05 ± 0.22 | 0 (0-0)   |
| <b>SR-AM</b> (n = 27)    | 32.5 ± 10.5   | 40 (23-40)      | 0.10 ± 0.30 | 0 (0-0)   |
| <b>SR-PM</b> (n = 27)    | 30.5 ± 11.2   | 39 (23-40)      | 0.14 ± 0.35 | 0 (0-0)   |
| <b>Overall*</b> (n = 71) | 32.3 ± 10.7   | 40 (25-40)      | 0.12 ± 0.32 | 0 (0-0)   |

|                          | PVT           |                     |             |           |
|--------------------------|---------------|---------------------|-------------|-----------|
|                          | Reaction Time |                     | Lapses      |           |
|                          | M ± SD (ms)   | Mdn (IQR) (ms)      | M ± SD      | Mdn (IQR) |
| <b>Baseline</b> (n = 21) | 244.4 ± 41.7  | 236.8 (215.7-265.1) | 0.28 ± 0.60 | 0 (0-0)   |
| <b>SR-AM</b> (n = 26)    | 234.4 ± 45.9  | 228.8 (211.3-249.1) | 0.22 ± 0.54 | 0 (0-0)   |
| <b>SR-PM</b> (n = 27)    | 286.1 ± 203.3 | 231.9 (208.0-280.9) | 0.63 ± 1.29 | 0 (0-1)   |
| <b>Overall*</b> (n = 75) | 263.7 ± 156.1 | 231.3 (210.2-265.1) | 0.45 ± 1.04 | 0 (0-0)   |

\*Overall analysis used clustering to account for multiple measures per participant. M, mean; Mdn, median; SR-AM, sleep restriction: morning; SR-PM, sleep restriction: afternoon.

**Table 2**—Summary of ocular variables during OSLEP and PVT tasks

|              | Ocular measures – OSLEP |                |                |                   | Ocular measures – PVT |                |                |                   |
|--------------|-------------------------|----------------|----------------|-------------------|-----------------------|----------------|----------------|-------------------|
|              | Baseline (n = 17)       | SR-AM (n = 27) | SR-PM (n = 27) | Overall* (n = 71) | Baseline (n = 21)     | SR-AM (n = 26) | SR-PM (n = 27) | Overall* (n = 75) |
| <b>IED</b>   |                         |                |                |                   |                       |                |                |                   |
| M ± SD       | 0.22 ± 0.36             | 0.34 ± 0.59    | 0.46 ± 1.12    | 0.39 ± 0.88       | 0.14 ± 0.06           | 0.16 ± 0.37    | 0.18 ± 0.16    | 0.17 ± 0.26       |
| Mdn          | 0.13                    | 0.17           | 0.17           | 0.17              | 0.13                  | 0.12           | 0.14           | 0.13              |
| (IQR)        | (0.10-0.20)             | (0.12-0.28)    | (0.10-0.37)    | (0.10-0.30)       | (0.09-0.16)           | (0.09-0.15)    | (0.10-0.18)    | (0.10-0.16)       |
| <b>BTB</b>   |                         |                |                |                   |                       |                |                |                   |
| M ± SD       | 0.48 ± 0.53             | 0.63 ± 1.44    | 1.10 ± 7.22    | 0.84 ± 5.13       | 0.39 ± 0.15           | 0.38 ± 0.43    | 0.43 ± 0.24    | 0.41 ± 0.33       |
| Mdn          | 0.36                    | 0.45           | 0.40           | 0.42              | 0.34                  | 0.34           | 0.36           | 0.35              |
| (IQR)        | (0.28-0.49)             | (0.32-0.61)    | (0.32-0.68)    | (0.32-0.61)       | (0.29-0.46)           | (0.27-0.40)    | (0.29-0.46)    | (0.29-0.44)       |
| <b>% TEC</b> |                         |                |                |                   |                       |                |                |                   |
| M ± SD       | 3.12 ± 7.74             | 3.94 ± 10.10   | 6.67 ± 19.29   | 5.18 ± 15.20      | 1.35 ± 2.83           | 1.44 ± 6.69    | 2.26 ± 4.98    | 1.89 ± 5.64       |
| Mdn          | 0.39                    | 0.62           | 0.91           | 0.70              | 0.08                  | 0.19           | 0.56           | 0.35              |
| (IQR)        | (0.05-1.87)             | (0.07-2.40)    | (0.15-4.92)    | (0.09-3.20)       | (0.02-1.12)           | (0.05-0.97)    | (0.09-1.67)    | (0.06-1.44)       |
| <b>+AVR</b>  |                         |                |                |                   |                       |                |                |                   |
| M ± SD       | 1.5 ± 0.4               | 1.64 ± 0.60    | 1.68 ± 0.74    | 1.64 ± 0.66       | 1.33 ± 0.35           | 1.23 ± 0.23    | 1.38 ± 0.42    | 1.33 ± 0.36       |
| Mdn          | 1.4                     | 1.45           | 1.44           | 1.43              | 1.20                  | 1.19           | 1.24           | 1.21              |
| (IQR)        | (1.2-1.6)               | (1.26-1.93)    | (1.23-1.89)    | (1.24-1.86)       | (1.10-1.42)           | (1.08-1.34)    | (1.08-1.49)    | (1.08-1.43)       |
| <b>JDS</b>   |                         |                |                |                   |                       |                |                |                   |
| M ± SD       | 4.1 ± 1.7               | 4.9 ± 1.9      | 4.7 ± 2.2      | 4.7 ± 2.0         | 3.3 ± 1.7             | 3.5 ± 1.4      | 4.2 ± 1.5      | 3.9 ± 1.5         |
| Mdn          | 3.8                     | 5.0            | 5.0            | 4.8               | 3.2                   | 3.3            | 3.9            | 3.7               |
| (IQR)        | (2.8-5.1)               | (3.6-6.4)      | (3.2-6.5)      | (3.3-6.4)         | (1.8-4.8)             | (2.4-4.4)      | (3.0-5.5)      | (2.7-5.1)         |

\*Overall analysis used clustering to account for multiple measures per participant. IED, inter-event duration; BTB, blink total duration; %TEC, percent time with eyes closed; +AVR, positive amplitude-velocity ratio; JDS, Johns Drowsiness Scale; M, mean; Mdn, median; SR-AM, sleep restriction: morning; SR-PM, sleep restriction: afternoon.



and JDS to demonstrate high sensitivity, high specificity, and intermediate cutoff options for detecting frequent drowsiness-related errors.

### PVT Lapses and Ocular Variables

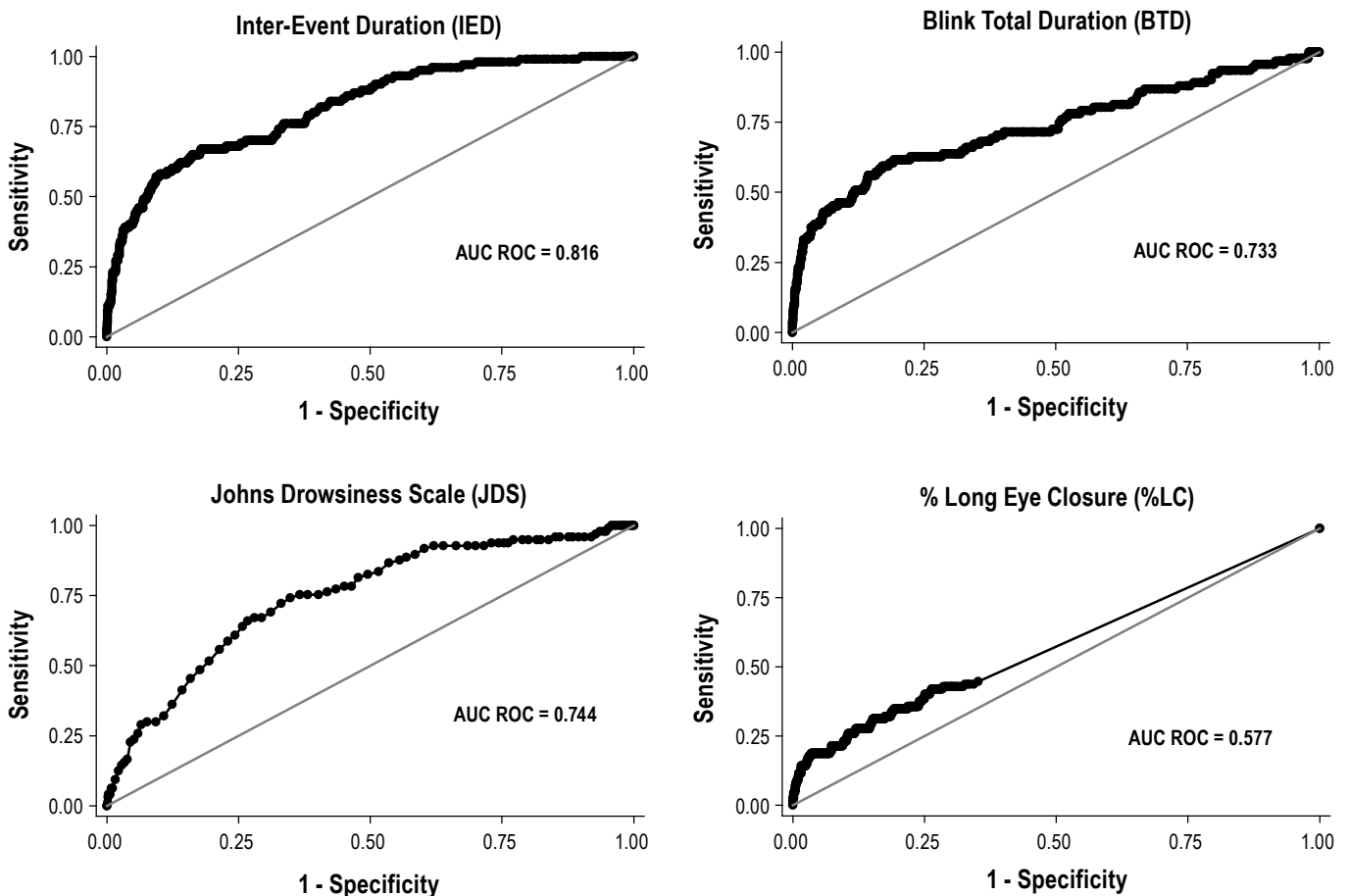
The sensitivity and specificity of detecting lapses at the selected cutoff values was determined (**Figure 4**). At cutoff

**Table 3**—ROC area under the curve analysis of missed signals on the OSLEP and ocular variables

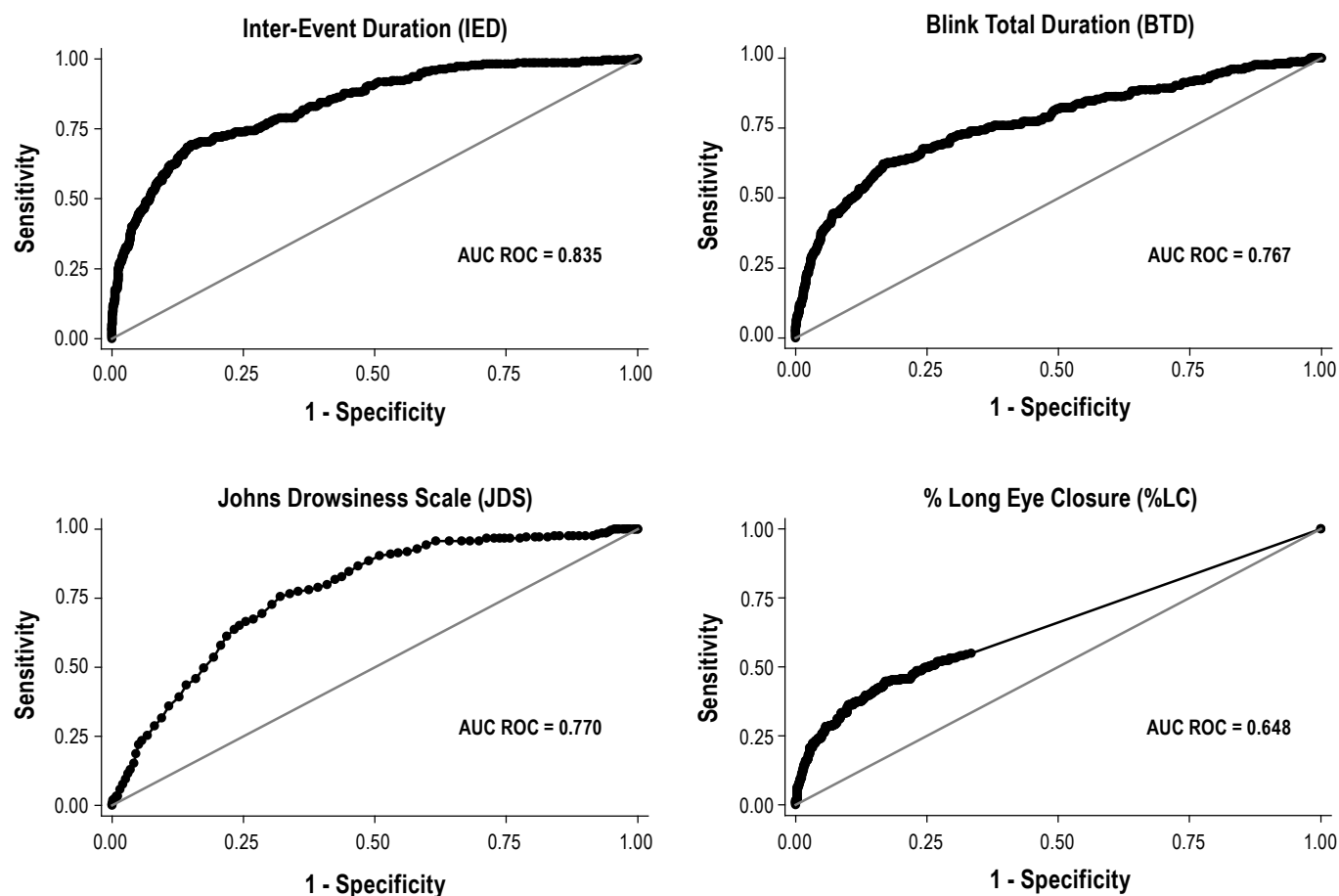
|                                 | Four or more consecutive missed signals by minute |              | Four or more missed signals overall in one minute |             |
|---------------------------------|---------------------------------------------------|--------------|---------------------------------------------------|-------------|
|                                 | AUC                                               | 95% CI       | AUC                                               | 95% CI      |
| <b>Blink duration variables</b> |                                                   |              |                                                   |             |
| IED                             | 0.816                                             | 0.729-0.892  | 0.835                                             | 0.758-0.897 |
| BTD                             | 0.733                                             | 0.625-0.839  | 0.767                                             | 0.687-0.849 |
| <b>Eyelid closure variables</b> |                                                   |              |                                                   |             |
| % TEC                           | 0.684                                             | 0.574-0.802  | 0.722                                             | 0.642-0.806 |
| %LC                             | 0.577                                             | 0.530-0.635* | 0.648                                             | 0.573-0.737 |
| <b>AVR variables</b>            |                                                   |              |                                                   |             |
| +AVR                            | 0.743                                             | 0.647-0.832  | 0.760                                             | 0.686-0.826 |
| –AVR                            | 0.669                                             | 0.561-0.767  | 0.641                                             | 0.529-0.732 |
| <b>Other</b>                    |                                                   |              |                                                   |             |
| DOQ                             | 0.652                                             | 0.545-0.735  | 0.582                                             | 0.477-0.671 |
| JDS                             | 0.744                                             | 0.615-0.850  | 0.770                                             | 0.686-0.851 |

\*Unadjusted 95% CIs are presented for %LC (consecutive missed signals). The variable %LC includes a high incidence of 0 values resulting in tied values due to bootstrap sampling procedures. This has been corrected for ties in the variable %LC (overall missed signals) but is unable to be corrected for %LC (consecutive missed signals). 95% CIs for all other variables have been adjusted to account for repeated measures on the participant. IED, inter-event duration; BTD, blink total duration; %TEC, percent time with eyes closed; %LC, percent long closures; +AVR, positive amplitude-velocity ratio; –AVR, negative amplitude-velocity ratio; DOQ, duration of ocular quiescence; JDS, Johns Drowsiness Scale; AUC, area under the curve.

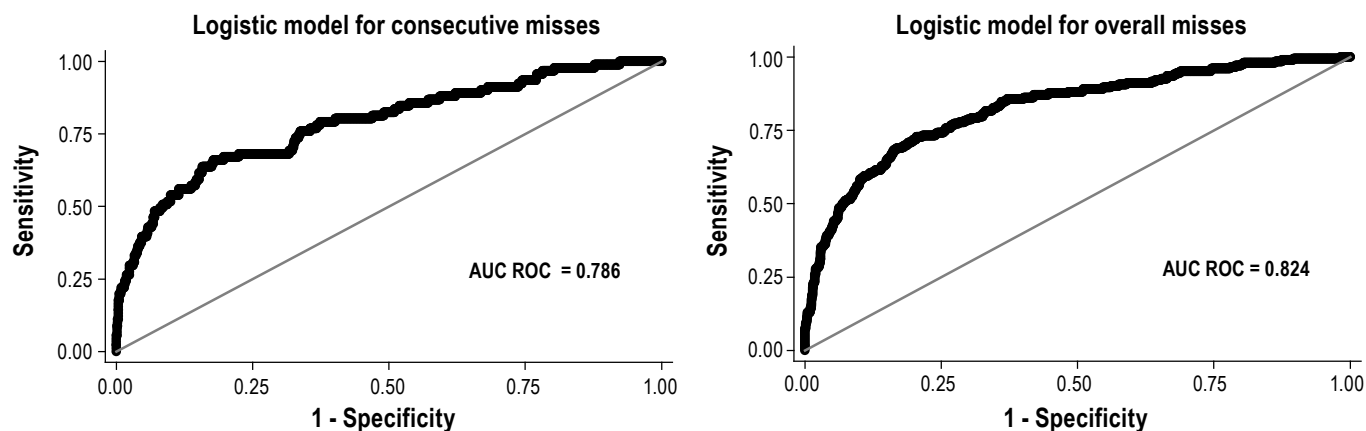
**Figure 1**—ROC curves of ocular variables for discrimination of consecutive missed signals using inter-event duration (IED), blink total duration (BTD), Johns Drowsiness Score (JDS), and percent long closures (%LC)



**Figure 2**—ROC curves of ocular variables for discrimination of overall missed signals using inter-event duration (IED), blink total duration (BTD), Johns Drowsiness Score, (JDS) and percent long closures (%LC)



**Figure 3**—Logistic models using the ocular variables IED (inter-event duration), BTD (blink total duration), %TEC (percent time with eyes closed), and +AVR (positive amplitude-velocity ratio) for four consecutive and overall misses on the OSLEP per minute



levels with an optimal balance between sensitivity and specificity (**Table 4**), identification of one lapse had low sensitivity, with increasing sensitivity with increasing number of lapses. IED, BTD, and JDS had good discrimination for  $\geq 3$  lapses in a minute on the PVT, with a sensitivity and specificity of 71% and 88% for the IED (100% and 86%, respectively, for  $\geq 5$  lapses). The JDS provided sensitivities of 77% and 100% for detecting

3 and  $\geq 5$  lapses in a minute, with specificities of 85% and 83%, respectively; +AVR was not sensitive to detecting lapses on the PVT. All 4 variables had high specificity in detecting any number of lapses on the PVT, and specificity did not decrease greatly with increasing number of lapses. Sensitivity of the identification of PVT lapses increased with lower cutoff levels (high sensitivity cutoff); however, this also resulted in a lowering of

**Table 4**—ROC cutoff values for each ocular variable for four or more consecutive missed signals by minute (including alternative high sensitivity and high specificity cutoff options)

|       | Optimal sensitivity/specificity |          |          | High sensitivity |          |          | High specificity |          |          |
|-------|---------------------------------|----------|----------|------------------|----------|----------|------------------|----------|----------|
|       | Cut-off                         | Sens (%) | Spec (%) | Cut-off          | Sens (%) | Spec (%) | Cut-off          | Sens (%) | Spec (%) |
| IED   | 0.203                           | 76.00    | 66.36    | 0.160            | 88.00    | 51.58    | 0.634            | 51.00    | 92.09    |
| BTD   | 0.462                           | 71.43    | 59.79    | 0.412            | 72.53    | 50.58    | 0.804            | 50.55    | 87.68    |
| % TEC | 0.660                           | 70.33    | 52.58    | 0.283            | 81.32    | 39.21    | 3.727            | 48.35    | 80.47    |
| +AVR  | 1.515                           | 76.84    | 60.21    | 1.407            | 80.00    | 50.13    | 2.010            | 50.53    | 84.08    |
| JDS   | 5.4                             | 75.26    | 63.40    | 4.6              | 82.47    | 50.47    | 6.5              | 51.55    | 80.61    |

IED, inter-event duration; BTD, blink total duration; %TEC, percent time with eyes closed; +AVR, positive amplitude-velocity ratio; JDS, Johns Drowsiness Scale; Sens, sensitivity; Spec, specificity.

**Table 5**—ROC cutoff values for each ocular variable for four overall missed signals by minute (including alternative high sensitivity and high specificity cutoff options)

|       | Optimal sensitivity/specificity |          |          | High sensitivity |          |          | High specificity |          |          |
|-------|---------------------------------|----------|----------|------------------|----------|----------|------------------|----------|----------|
|       | Cut-off                         | Sens (%) | Spec (%) | Cut-off          | Sens (%) | Spec (%) | Cut-off          | Sens (%) | Spec (%) |
| IED   | 0.209                           | 77.06    | 70.45    | 0.152            | 90.37    | 51.13    | 0.542            | 51.38    | 92.57    |
| BTD   | 0.468                           | 75.37    | 63.20    | 0.398            | 81.77    | 50.28    | 0.753            | 50.74    | 88.37    |
| % TEC | 0.617                           | 74.88    | 53.24    | 0.520            | 77.34    | 50.34    | 3.853            | 50.25    | 82.94    |
| +AVR  | 1.567                           | 78.30    | 66.34    | 1.402            | 83.02    | 50.88    | 1.990            | 50.47    | 85.31    |
| JDS   | 5.5                             | 75.60    | 67.97    | 4.5              | 88.52    | 51.16    | 6.4              | 53.59    | 80.63    |

IED, inter-event duration; BTD, blink total duration; %TEC, percent time with eyes closed; +AVR, positive amplitude-velocity ratio; JDS, Johns Drowsiness Scale; Sens, sensitivity; Spec, specificity.

specificity with the potential to erroneously classify individuals as unacceptably drowsy when they were not actually impaired. Raising cutoff levels to increase specificity (high specificity cutoff) resulted in extremely poor sensitivity in detecting PVT lapses for all variables other than JDS.

## DISCUSSION

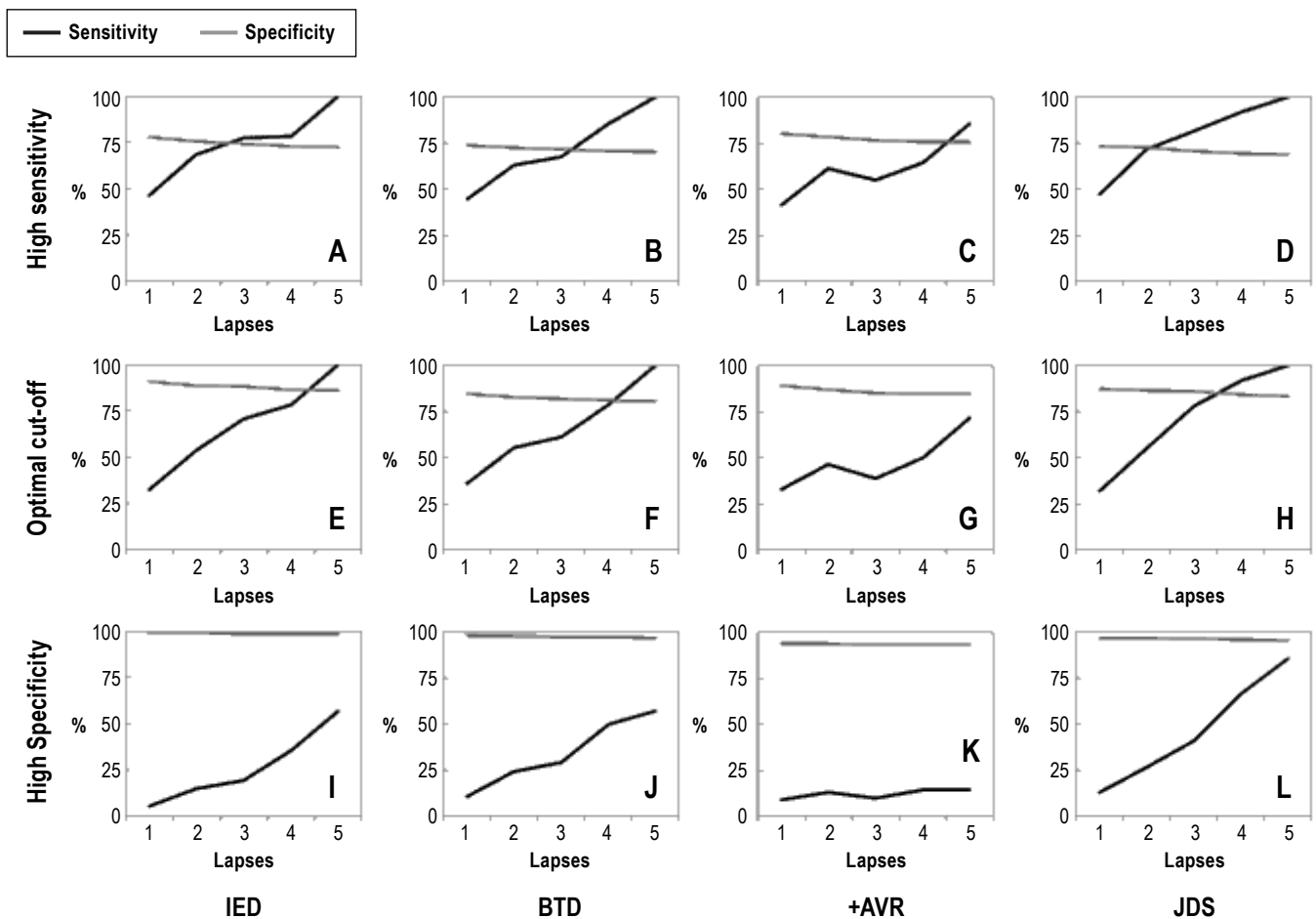
In this sleep restriction paradigm, measurement of eyelid movements accurately detected frequent episodes of failure to respond to visual signals during vigilance tasks. The average duration of episodes of eye closure (IED and BTD) provided the best discrimination from the primary measures, with the ratio of the amplitude to the velocity of eyelid movement during eyelid closure also providing good discrimination. These results support the use of ocular measures for identifying people who are impaired as a result of drowsiness.

Although blink duration and the proportion of time with eyes closed increase during circumstances designed to increase drowsiness, there is only limited work attempting to relate these physiological metrics to the behavioral changes that occur with restricted sleep. Reliable automated measures of blink duration suitable for on-road driving have previously not been available and manual determination of blink duration has been measured from EEG/electrooculography signals, video recordings, or stationary infrared recordings.<sup>13,30,31</sup> Mean blink duration and proportion of blinks of prolonged duration increase during monotonous tasks and are related to subjectively reported drowsiness.<sup>13</sup> Blink duration is also increased in untreated obstructive sleep apnea patients and reduces following treatment both in the laboratory and during on road driving.<sup>32,33</sup> The variable IED, a measure of eyelid closure

duration between the points of maximum closing and re-opening velocity of the eyelid, has previously only recently been reported. This is a measure similar to blink duration, and proved to be most accurate at detecting drowsiness-related errors. Both blink duration and IED were recently shown to increase in duration after more than 24 hours of wakefulness and during the circadian nadir but the effect of milder sleep restriction, as used in our study, has not been described.<sup>34</sup>

The variable IED accurately identified drowsiness-related errors with an ROC curve area under the curve (AUC) of over 0.8 for detecting frequent missed signals during the OSLE task (AUC = 0.816, 95% CI 0.715-0.886, in the analysis of four consecutive missed signals and 0.834, 95% CI 0.757-0.896, in the analysis of four overall missed signals per minute). Total blink duration (BTD), the ratio of the amplitude to velocity of eyelid movements during eyelid closure (+AVR) and the Johns Drowsiness Score (JDS) were all moderately accurate at detecting frequent missed signals, with AUC of 0.733 to 0.767 for four or more consecutive missed signals and four or more overall missed signals per minute. The percentage of time with eyes closed (%TEC) had a moderate ability to identify frequent missed signals (AUC = 0.683 and 0.721), while other individual measures of eyelid movements (-AVR, %LC, and DOQ) had fair to poor ability to detect frequent drowsiness-related errors in both analyses of OSLE data. Several of these variables have recently been reported to have moderate ability to predict increased lapse frequency and slowing of reaction time, with AUC on ROC curves of between 0.62 to 0.74 for BTD, IED, %LC, AVR, and JDS.<sup>34</sup> These values are slightly lower than those identified in our study, perhaps due to the comparison utilizing ocular data collected prior to the vigilance

**Figure 4**—Sensitivity and specificity of the ocular variables correctly identifying increasing numbers of drowsiness-related PVT lapses (1–5) using OSLER-derived cutoff values at high sensitivity (A) IED, (B) BTd, (C) +AVR and (D) JDS; optimal cutoff values (E) IED, (F) BTd, (G) +AVR, (H) JDS; and high specificity cutoff values (I) IED, (J) BTd, (K) +AVR (L) JDS



Sensitivity = black, specificity = gray. IED, inter-event duration; BTd, blink total duration; %TEC, percent time with eyes closed; +AVR, positive amplitude-velocity ratio; JDS, Johns Drowsiness Scale.

testing rather than during the testing, and the comparison being over a longer time frame.

The percentage long eye closure and percentage of time with eyes closed variables are similar to PERCLOS (the proportion of time eyes are > 80% closed) that has been found to be good at discriminating between alert and drowsy states in some previous studies. The current analysis found that these variables had a moderate discriminatory power for detecting frequent drowsiness-related errors. %LC was poor at detecting sequential drowsiness-related errors, with a maximum sensitivity of 44.64% for detecting four consecutive missed signals on the OSLER, a strong indicator of brief sleep periods on EEG.<sup>21</sup> It proved to be more accurate at detecting four misses in total and %TEC, which includes all episodes of eye closure irrespective of duration, was more accurate than %LC. The proportion of time with eyes closed (PERCLOS) was moderately accurate at identifying behavioral lapses in drowsy participants in previous studies with improved accuracy when averaged over longer time periods.<sup>5,7</sup> It has been considered as a potential measure for real-time monitoring of drowsiness, although some laboratory

studies have also found other drowsiness detection methods more reliable than PERCLOS.<sup>35</sup>

In this study we found measures of eyelid closure duration, such as IED and BTd, and the ratio of amplitude to velocity of eyelid movements, to be better predictors of behavioral lapses than the percentage of time with eyes closed, producing the highest sensitivities and specificities. For example, the optimal cutoff value for IED, derived from the OSLER data, achieve a sensitivity of 71% for detecting three behavioral lapses on the PVT task, increasing to 100% for detecting five lapses while maintaining good specificity (88% and 86% respectively). Increasing sensitivity at the expense of lowering specificity results in a higher false positive rate, but also a higher likelihood of identifying episodes of drowsiness-related impairment. In applied settings such as on-road driving, it may be deemed more important to have a low rate of false negatives (high sensitivity), despite a greater false positive rate, to reduce the risk of missing episodes of drowsiness.

Sensitivity of accurately detecting PVT lapses at the selected cutoff values for IED, BTd, +AVR, and JDS increased with



increasing number of lapses, without a large decrease in specificity. Single instances of PVT lapse could be due to non-drowsiness-related events such as distraction. This is supported by the low sensitivity but high specificity found when testing all ocular variables at this number of lapses. The frequency of PVT lapses has been studied under a variety of circumstances, which can help in considering clinically relevant levels of drowsiness. For example, participants averaged five lapses in ten minutes at a blood alcohol level of 0.05% in one study.<sup>36</sup> Lapse frequencies of 8 and 16 in 10 minutes have been described for 24 and 72 hours of wakefulness, respectively.<sup>37</sup> Hence, lapse frequencies of two and certainly three or more in a minute would indicate marked drowsiness. IED, BTM, and JDS were all able to detect this frequency of lapses with high sensitivity and specificity. The selected lower cutoff levels for these variables provided sensitivities of 67% to 81% for detecting three lapses in a minute, increasing to 100% for detecting five or more lapses. The specificities were reasonable at 70% to 74% for detecting three or more lapses at this high sensitivity cutoff. Higher cutoff levels resulted in a higher specificity but low sensitivity which would indicate a high rate of false negatives. Monitoring drowsiness in an applied setting would require an appropriate balance, however the fact some of these metrics can achieve a good sensitivity for detecting a moderate frequency of drowsiness-related errors increasing to a very high sensitivity with very frequent errors, while maintaining a low false positive rate suggests that they have the potential to be used for drowsiness monitoring.

AVR for eyelid movements is a measure of the velocity of eyelid movements relative to the amplitude of the upper eyelid movement. AVR increases with drowsiness,<sup>17</sup> particularly for the eyelid re-opening phase. These ratios have been reported to have low inter-subject variability, and hence potentially reduce the need for individual calibration.<sup>17,38</sup> In the current study the +AVR (eyelid closure phase), had an ROC area under the curve that was similar to the measures of eyelid closure duration (IED and BTM) and the JDS. However, it tended to have a lower sensitivity than the other measures for detecting behavioral lapses at a range of cutoffs while maintaining a good specificity.

The use of logistic models to fit a more accurate measure of drowsiness using several of the recorded ocular variables, although producing good discriminatory ability, did not improve detection of missed OSLER signals beyond the use of individual ocular variables. IED was found to have more accurate discrimination alone than a logistic model using a combination of ocular measures.

The protocol allowed for a mixture of rested and moderate sleep restriction conditions and demonstrated that several ocular variables have good ability to detect drowsiness-related errors on two psychophysiological tasks. A number of factors might alter these outcomes in different settings. While four hours sleep restriction is a relatively realistic level of sleep loss experienced in the real world, a greater level of sleep restriction and associated drowsiness might alter the discriminatory power of different ocular variables in detecting behavioral lapses. For example the speed of eyelid movements or blink duration might increase prior to appreciable increases in the percent of time with eyes closed. While we found that blink duration measures were better predictors of performance within this paradigm of mild sleep restriction; others with more severe sleep deprivation have found that

percent of time with eyes closed is a better predictor.<sup>34</sup> There was some individual variability in ocular measures despite the same level of sleep restriction. This may be due to individual variability in responses to sleep loss and may also be due to baseline variability in psychophysiological measures, such as differences in ocular muscle responses. The applicability of results from the current study may be limited to the study tasks and the laboratory setting. In our study, participants were instructed to look directly ahead and sit still while performing the tasks. Although our findings suggest that ocular measurements may be a useful indicator of drowsiness during driving-related performance some caution needs to be exercised in extrapolating these results to other tasks and settings such as on-road driving where factors such as head and vehicle movement may affect eyelid measures. Of the vigilance tasks utilized in this study, the PVT, at 10-min duration, could be used in practical situations to assess driver drowsiness,<sup>39</sup> such as at a roadside testing stop. However, it is not suitable for the continuous monitoring of drowsiness as can be achieved with ocular measures.

To be functional in monitoring driver drowsiness, a device must be portable and able to acquire, process, and produce feedback to the driver before drowsiness reaches a level when deterioration in attention may lead to accidents. In this study, several ocular variables were reliable indicators of drowsiness-related deterioration in vigilance in the laboratory setting. Ocular variables which measured the duration of ocular events; IED (duration of eyelid events) and BTM (duration of blinks) were the most reliable in detecting drowsiness and lapses, with the ratio of velocity to amplitude of eyelid closure also a reliable indicator. These are promising measures for real-time drowsiness monitoring. Further research should evaluate their utility during a variety of tasks, in different environments (including on-road in vehicle validation) and under a variety of sleep restriction conditions.

## ABBREVIATIONS

- AVR, negative amplitude-velocity ratio
- +AVR, positive amplitude-velocity ratio
- %LC, percent long closures
- %TEC, percent time with eyes closed
- AUC, area under the curve
- BTM, blink total duration
- CI, confidence interval
- DOQ, duration of ocular quiescence
- EEG, electroencephalography
- ESS, Epworth Sleepiness Scale
- IED, inter-event duration
- JDS, Johns Drowsiness Scale
- MWT, maintenance of wakefulness test
- M, mean
- Mdn, median
- ODMS, Optalert Drowsiness Measurement System
- OSLER, Oxford Sleep Resistance Test
- PERCLOS, proportion of time eyes are more than 80% closed
- PVT, psychomotor vigilance task
- ROC, receiver operating characteristic
- SR-AM, sleep restriction: morning
- SR-PM, sleep restriction: afternoon

## REFERENCES

- Barger LK, Lockley SW, Rajaratnam SMW, Lanrigan CP. Neurobehavioral, health, and safety consequences associated with shift work in safety-sensitive professions. *Curr Neurol Neurosci Rep* 2009;9:155-64.
- Connor J, Norton R, Ameratunga S, Robinson E, Wigmore B, Jackson R. Prevalence of driver sleepiness in a random population-based sample of car driving. *Sleep* 2001;24:688-94.
- Johns MW, Chapman R, Crowley K, Tucker A. A new method for assessing the risks of drowsiness while driving. *Somnologie (Berl)* 2008;12:66-74.
- Schleicher R, Galley N, Briest S, Galley L. Blinks and saccades as indicators of fatigue in sleepiness warnings: looking tired? *Ergonomics* 2008;51:982-1010.
- Wierwille WW, Ellsworth LA. Evaluation of driver drowsiness by trained raters. *Accid Anal Prev* 1994;28:571-81.
- Strijkstra AM, Beersma DG, Drayer B, Halbesma N, Daan S. Subjective sleepiness correlates negatively with global alpha (8–12 Hz) and positively with central frontal theta (4–8Hz) frequencies in the human resting awake electroencephalogram. *Neurosci Lett* 2003;340:17-20.
- Dinges DF, Mallis M, Maislin G, Powell JW. *Evaluation of techniques for ocular measurements as an index of fatigue and the basis for alertness management*. U.S. Department of Transportation, National Highway Traffic Safety Administration, Contract No. DTNH22-93-D-07007, 1998.
- Akerstedt T, Peters B, Anund A, Kecklund G. Impaired alertness and performance driving home from the night shift: a driving simulator study. *J Sleep Res* 2005;14:17-20.
- Barbato G, De Padova V, Paolillo AR, Russo E, Ficcia G. Increased spontaneous eye blink rate following prolonged wakefulness. *Physiol Behav* 2007;90:151-4.
- Morris TL, Miller JC. Electrooculographic and performance indices of fatigue during simulated flight. *Biol Psychol* 1996;42:343-60.
- Tucker A, Johns M. The duration of eyelid movements during blinks: Changes with drowsiness. *Sleep* 2005;28(Abstract Supplement):A122.
- Sirevaag EJ, Stern JA. Ocular measures of fatigue and cognitive factors. In: Backs RW, Boucsein W, eds. *Engineering psychophysiology: issues and applications*. Hillsdale, NJ: Lawrence Erlbaum Associates, 2000:269-86.
- Caffier PP, Erdmann U, Ullsperger P. Experimental evaluation of eye-blink parameters as a drowsiness measure. *Eur J Appl Physiol* 2003;89:319-25.
- Johns M. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep* 1991;14:540-5.
- Maislin G, Pack AI, Kribbs NB, et al. A survey screen for prediction of apnea. *Sleep* 1995;18:158-66.
- Littner MR, Kushida C, Wise M, et al. Practice parameters for clinical use of the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test. *Sleep* 2005;28:113-21.
- Johns M, Tucker A, Chapman R, Crowley K, Michael N. Monitoring eye and eyelid movements by infrared reflectance oculography to measure drowsiness in drivers. *Somnologie (Berl)* 2007;11:234-42.
- Johns M, Tucker A. The amplitude-velocity ratios of eyelid movements during blinks: Changes with drowsiness. *Sleep* 2005;28(Abstract Supplement):A122.
- Bennett LS, Stradling JR, Davies RJ. A behavioural test to assess daytime sleepiness in obstructive sleep apnoea. *J Sleep Res* 1997;6:142-5.
- Banks S, Catchside P, Lack LC, Grunstein RR, McEvoy RD. The Maintenance of Wakefulness Test and driving simulator performance. *Sleep* 2007;28:1381-5.
- Mitler MM, Gujavarty KS, Browman CP. Maintenance of wakefulness test: a polysomnographic technique for evaluation treatment efficacy in patients with excessive somnolence. *Electroencephalogr Clin Neurophysiol* 1982;53:658-61.
- Priest B, Brichard C, Aubert G, Liistro G, Rodenstein DO. Microsleep during a simplified maintenance of wakefulness test. A validation study of the OSLER test. *Am J Respir Crit Care Med* 2001;163:1619-25.
- Janes H, Longton G, Pepe M. Accommodating covariates in ROC analysis. *Stata J* 2009;9:17-39.
- Pepe MS, Longton G, Janes H. Estimation and comparison of receiver operating characteristic curves. *Stata J* 2009;9:1-16.
- Dinges DF, Powell JW. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behav Res Methods Instrum Comput* 1985;17:652-5.
- Goel N, Rao H, Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. *Semin Neurol* 2009;29:320-39.
- Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. *J Clin Sleep Med* 2007;3:519-28.
- Dorrian J, Rogers NL, Dinges D. Psychomotor vigilance performance: Neurocognitive assay sensitive to sleep loss. In: Kushida CA, ed. *Sleep deprivation: clinical issues, pharmacology and sleep loss effects*. New York: Marcel Dekker, 2005:39-70.
- Basner M, Dinges DF. Maximizing sensitivity of the psychomotor vigilance test (PVT) to sleep loss. *Sleep* 2011;34:581-91.
- Ingre M, Akerstedt T, Peters B, Anund A, Kecklund G. Subjective sleepiness, simulated driving performance and blink duration: Examining individual differences. *J Sleep Res* 2006;15:47-53.
- Papadelis C, Chen Z, Kourtidou-Papadeli C, et al. Monitoring sleepiness with on-board electrophysiological recordings for preventing sleep-deprived traffic accidents. *Clin Neurophysiol* 2007;118:1906-22.
- Caffier PP, Erdmann U, Ullsperger P. The spontaneous eye-blink as sleepiness indicator in patients with obstructive sleep apnoea syndrome - A pilot study. *Sleep Med* 2005;6:155-62.
- Hakkanen H, Summala H, Partinen M, Tihonen M, Silvo J. Blink duration as an indicator of driver sleepiness in professional bus drivers. *Sleep* 1999;22:798-802.
- Anderson C, Chang AM, Sullivan JP, Ronda JM, Czeisler CA. Assessment of drowsiness based on ocular parameters detected by infra-red reflectance oculography. *J Clin Sleep Med* 2013;9:907-20.
- Sommer D, Golz M. Evaluation of PERCLOS based current fatigue monitoring technologies. *Conf Proc IEEE Eng Med Biol Soc* 2012;2010:4456-9.
- Howard ME, Jackson ML, Kennedy GA, Swann P, Barnes M, Pierce RJ. The interactive effects of extended wakefulness and low-dose alcohol on simulated driving and vigilance. *Sleep* 2007;30:1334-40.
- Van Dongen HP, Maislin G. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 2003;26:117-26.
- Johns MW. The amplitude-velocity ratio of blinks: A new method for monitoring drowsiness. *Sleep* 2003;26(Abstract Supplement):A51-2.
- Jackson ML, Croft RJ, Kennedy GA, Owens K, Howard ME. Cognitive components of simulated driving performance: Sleep loss effects and predictors. *Accid Anal Prev* 2013;50:438-44.

## SUBMISSION &amp; CORRESPONDENCE INFORMATION

Submitted for publication January, 2013

Submitted in final revised form September, 2013

Accepted for publication September, 2013

Address correspondence to: Dr. Vanessa Wilkinson, Institute for Breathing & Sleep, Austin Health, PO Box 5555, Heidelberg, Victoria, Australia 3084; Tel: (613) 94965390; Fax: (613) 9496 5124; Email: vanessa.wilkinson@austin.org.au

## DISCLOSURE STATEMENT

This was not an industry supported study. This project was supported by VicRoads, the state road and traffic authority in the state of Victoria, Australia. Dr. Howard has received research support from ResMed Foundation, Prevention Express, and Mining CRC. Part of Dr. Barnes salary is paid by involvement in sponsored clinical trial for Apnex Medical. Dr. Rajaratnam has served as a consultant (through service agreements with Monash University) to Vanda Pharmaceuticals, Philips Respironics, Edan-Safe, The Australian Workers' Union, and National Transport Commission, and has received research grants and/or unrestricted educational grants from Vanda Pharmaceuticals, Takeda Pharmaceuticals North America, Philips Lighting, Philips Respironics, Cephalon, and ResMed Foundation, and reimbursements for conference travel expenses from Vanda Pharmaceuticals. His institution has received equipment donations or other support from Optalert, Compumedics, and Tyco Healthcare. He has also served as an expert witness and/or consultant to shift work organizations. Dr. Rajaratnam presently serves on the Board of Directors of the Australasian Sleep Association, and has previously served on the Board of Directors of the Sleep Health Foundation. The other authors have indicated no financial conflicts of interest.

# Salivary Biomarkers of Physical Fatigue as Markers of Sleep Deprivation

Darren J. Michael, Ph.D.<sup>1</sup>; Bianca Valle, B.S.<sup>1</sup>; Jennifer Cox, B.S.<sup>1</sup>; John E. Kalns, Ph.D.<sup>1</sup>; Donovan L. Fogt, Ph.D.<sup>2</sup>

<sup>1</sup>Hyperion Biotechnology, San Antonio, TX; <sup>2</sup>University of Texas-San Antonio, San Antonio, TX

**Study Objective:** Determine whether a salivary biomarker of physical fatigue, referred to as the fatigue biomarker index (FBI), can discriminate a control group from a sleep deprived group when saliva is collected under controlled conditions. The study expands on previous work examining changes in the composition of saliva during periods of prolonged exercise.

**Methods:** Thirty (30) young adults (14 Control [CON]; 16 Sleep Deprived [SDEP]) were monitored for mood state (Profile of Mood States [POMS]), cognitive performance (Stroop Color-Conflict Tests), and salivary biomarkers of physical fatigue over a 48-h period with sampling at 3-h intervals. Trials lasted from 06:00 on day 1 (time = -3 h) to 09:00 on day 3 (time = 48 h). Levels of salivary biomarkers were calculated from liquid chromatography-mass spectrometry (LC-MS) data. Statistical comparisons were made using Wilcoxon rank sum tests with a Bonferroni correction to limit type 1 error. Receiver-operator characteristic (ROC) analysis was used to evaluate the ability of the various parameters to distinguish the SDEP population from the CON population.

**Results:** Longitudinal analysis demonstrated significant between-group differences in all three parameters. ROC analysis demonstrated that cognitive performance tests and salivary biomarkers of physical fatigue distinguish the SDEP population from the CON population.

**Conclusions:** A previously identified salivary biomarker of physical fatigue may provide an alternative method for discriminating sleep deprived from rested individuals. The salivary biomarker of physical fatigue holds promise as an objective measure of sleep deprivation, perhaps eventually removing the reliance on self-reported sleep diaries and/or repeated polysomnographs for longitudinal tracking of sleep quality and/or diagnosis of sleep disorders.

**Keywords:** Sleep deprivation, fatigue, biomarkers, mass spectrometry, chromatography, liquid, analytical chemistry methods

**Citation:** Michael DJ; Valle B; Cox J; Kalns JE; Fogt DL. Salivary biomarkers of physical fatigue as markers of sleep deprivation. *J Clin Sleep Med* 2013;9(12):1325-1331.

There are relatively few objective methods for the diagnosis and longitudinal monitoring of sleep disorders.<sup>1,2</sup> At present, clinicians rely primarily on patients' self-reported levels of sleepiness, as well as expensive, time-consuming, and relatively intrusive overnight polysomnographs (PSG).<sup>3</sup> Other objective methods proposed for use in sleep medicine include actigraphy, electroencephalography (EEG), multiple sleep latency test (MSLT), reaction times, pupillography, melatonin levels, metabolic rate, body temperature, heart rate, and heart rate variability.<sup>2,4-6</sup> While each of these techniques has proven promising, none has yet been adopted for the routine diagnosis and monitoring of all sleep disorders. Given the wide range of sleep disorders and the large number of other diseases which also alter sleep,<sup>2,7</sup> it is clear that there is a need for additional objective measures of sleep health.

Insufficient sleep impairs a number of specific functions, as well as an individual's general quality of life. Symptoms arising from sleep loss include increased propensity to fall asleep in inappropriate settings, inability to concentrate, impaired cognitive ability, slowed reaction time, reduced vigilance, headache, mood changes, and fatigue.<sup>8,9</sup> Numerous studies have demonstrated that the levels of impairment arising from acute and chronic sleep deprivation are similar to those observed in individuals with elevated blood alcohol content.<sup>10-14</sup> The social and

## BRIEF SUMMARY

**Current Knowledge/Study Rationale:** Previously, we described changes in the peptide composition of saliva during periods of prolonged physical exertion. Here, we determined whether similar changes in the peptide composition of saliva are associated with sleep and/or sleep deprivation.

**Study Impact:** At present, daytime sleepiness is assessed either by self-report, e.g. Epworth Sleepiness Scale, or by expensive and time-consuming clinical tests, e.g., multiple sleep latency test. An inexpensive and objective method to measure sleepiness would significantly improve a clinician's ability to diagnose and/or treat sleep disorders.

economic consequences associated with untreated or improperly treated sleep disorders are significant.<sup>15,16</sup>

The need for objective methods to diagnose and/or track sleep disorders is especially important in circumstances when individuals are motivated not to report truthfully either their amount of sleep or their level of fatigue. For example, financial pressure might motivate an individual to misreport sleep and/or fatigue, such as in a career field where pay is dependent upon hours worked, e.g., an airline pilot or long-haul truck driver. Alternatively, social pressure might motivate an individual to misreport sleep and/or fatigue, such as for an individual who is part of team, e.g., a member of an elite military unit or sports team. In these circumstances, self-reported values of sleep and/



or fatigue might differ significantly from true levels, thereby endangering the individual and others around them.

Recently, we have reported that physical fatigue changes the composition of saliva. Specifically, we found that the ratio of two endogenous salivary peptides changed significantly as individuals became more fatigued due to prolonged physical exercise.<sup>17</sup> The amino acid sequences of both heptapeptides were determined in our previous work. One peptide had the sequence GGHPPPP (657.7 Da), while the other peptide had the sequence ESPSLIA (715.8 Da). Both of these peptides arise naturally from the family of proteins known as the salivary proline-rich proteins (PRPs).<sup>18</sup> The specific ratio of peptides we reported, termed the fatigue biomarker index or FBI, was calculated as the abundance of GGHPPPP divided by the abundance of ESPSLIA. When the ratio is constructed in this way, the value of the FBI decreases as fatigue increases, much like pH levels decrease as the concentration of protons in solution increases. Our primary interest in developing this technology was to provide the US military with an objective measure of fatigue arising from physical activity. The value of this technology in military settings was highlighted by a previous study showing that an individual's FBI value at the start of training is useful as part of a model for predicting the outcome of training for candidates entering Special Forces training within the United States Air Force.<sup>19</sup>

Here, we report findings from a preliminary investigation of changes in FBI values during periods of sleep deprivation. Previously, we used data from the same study to investigate changes in cognitive performance<sup>20,21</sup> and heart rate variability.<sup>20</sup> While this study was designed to mimic typical conditions experienced in a military, rather than civilian, setting and included only a relatively small group of young, healthy adults, the results are promising and suggest that the small peptide composition of saliva can be used to monitor an individual's sleep.

## METHODS

### Selection Criteria

We recruited men between the ages of 18 and 35 years for inclusion in the study. Potential subjects included healthy (asymptomatic) college students, ROTC cadet trainees, and recreational (non-varsity) athletes self-reporting as healthy and fit enough to enter basic military or first responder training, non-smoking, free of disease, and not taking any psychotropic medications or dietary supplements that would alter neural or metabolic function. Subjects meeting our eligibility criteria were asked to read and sign an informed consent document approved by the Committee for the Protection of Human Subjects in Research of the University of Texas at San Antonio. This committee approved this study and provided oversight of all human research procedures.

### Experimental Design

All protocols were conducted in the Exercise Biochemistry and Metabolism Laboratory of the Department of Health and Kinesiology at The University of Texas at San Antonio. Consented subjects completed a basic medical history screening form, a standard physical examination, skinfold body fat analysis, and a clinical graded treadmill stress test with electrocardiogram

to identify preexisting heart conditions that could compromise safe participation and determine aerobic fitness level via indirect calorimetry (TrueMax 2400, ParvoMedics Sandy, UT). Final selection of subjects was dependent upon normal clinical results and history as determined by a participating physician indicating eligibility for safe inclusion in the study. During the health screening session consented subjects were familiarized with all testing planned for the subsequent 48-h protocol.

Eligible subjects ( $n = 35$ ) were randomly assigned to 1 of 2 experimental groups: (1) control (CON;  $n = 16$ ) or (2) sleep deprived (SDEP;  $n = 19$ ). (Note: Analysis of saliva samples was limited to subjects who completed the entire study [CON = 14; SDEP = 16]). The 48-h protocol took place  $\geq 1$  week following the health screening and familiarization session. The aim of the protocol was to increase fatigue gradually and safely over the course of 48 h. In the present study, we employed a modified version of a 24-h protocol we developed in which participants experienced sleep deprivation and were evaluated for cognitive performance and fatigue level every 3 h.<sup>21</sup>

All participants reported to the laboratory at 06:00 following an 8-h fast that excluded caffeine or other stimulants. They immediately received a small standardized breakfast (375 kcal) with water. For the purpose of analyzing data in this study, we define 06:00 as Time = -3 h. Data for the 48-h period were collected every 3 h from 09:00 on day one to 09:00 on day 3 (17 data collection points total). Every data collection point was 2 h post-prandial and post-fluid ingestion. Total dietary food and fluid intakes were controlled and provided at levels considered normal for the subject's age, weight, and daily activity level, allowing subjects to remain hydrated (data not shown).

Participants assigned to the CON group were allowed to sleep between the hours of 22:00-09:00, although they were awoken at 00:00, 03:00, and 06:00 and remained awake for approximately 1 h for data collection. Participants assigned to the SDEP group were monitored throughout the 48-h period and were not allowed to sleep. Schedules for data collection, as well as food and water intake, were identical for both groups. During non-sleep hours between data collection periods, all participants maintained a controlled but fixed daily schedule of very light activities (e.g., watching movies, studying, or reading).

Every 3 h during the 48-h period, subjects were weighed (in shorts and shirt, sans shoes). Before the subsequent collection of data, subjects then sat quietly for 20 min.

After the quiet period, subjects completed the Profile of Mood States<sup>22</sup> (POMS) survey for assessment of fatigue level and Stroop Color-Conflict Test<sup>23</sup> (Stroop tests) for assessment of cognitive performance. While the Stroop tests are known to be influenced by learning effects, they were selected for their ease of administration to groups of the size used in this study. The most relevant POMS factor for our investigation was that of "fatigue." This factor is determined by the sum of Likert-style scoring of seven subjective feelings ("worn out," "listless," "fatigued," "exhausted," "sluggish," "weary," "bushed"). No time limit was given to complete the POMS survey. No performance feedback was provided to subjects for the survey. For the Stroop tests, subjects were instructed to read aloud as many items as possible in 45 s during each of 3 conditions (word, color, incongruent color-word pairs). Instructions for the Stroop tests were repeated at every data collection point. The



number of correct responses for each 45-s test was recorded and no performance feedback was provided to subjects for the tests. The Stroop tests comprise 3 separate tests: color, word, and color-word. We added results from the 3 Stroop tests to calculate a “cumulative cognitive performance” score. We have previously demonstrated that the POMS fatigue factor tracks the decline in Stroop test cognitive performance during a 24-h fatiguing protocol including combinations of sleep deprivation, exercise, caloric restriction, and dehydration.<sup>21</sup>

Immediately after each data collection period, subjects were fed a small sandwich, raw vegetables, and cookies (300 kcal) with 0.4 L of water. The same meal was provided every 3 h to avoid possible digestion-related fluctuations in vagal tone following a large meal.

## Saliva

Saliva samples (~10 mL) were collected by passive drooling of clear saliva. Samples were placed on ice after collection and transferred to a -80°C freezer for storage until time of analysis. The salivary analyses have been published in detail.<sup>17</sup> Briefly, raw saliva was processed through a series of molecular-weight-cutoff filters selected to remove components of saliva greater than ~10 kDa. The amount of protein in the remaining solution was quantified (bicinchoninic acid [BCA] assay), so that a fixed amount of protein could be injected per sample (4 µg). To target the peptide components, we used a mass-specific tagging approach to label free amines in solution. Specifically, samples were labeled with light and heavy isotopes of acetic anhydride. The difference in mass of the 2 isotopes arises from the presence of protons or deuterons in all positions of both methyl groups in the acetic anhydride. By labeling 2 different aliquots of the same sample separately with the light and heavy variants of acetic anhydride, it was possible to identify those components of saliva with a free amine. These components appeared as pairs of ions separated by predictable masses in a mixture of the differently labeled samples. Once samples were labeled and analyzed by liquid chromatography with mass spectrometric detection, we quantified levels of a previously identified biomarker of physical fatigue,<sup>17</sup> referred to as the fatigue biomarker index (FBI). As a ratio of ion intensities for 2 different salivary peptides, the FBI is resistant to trivial sources of change, e.g., the amount of material injected.

## Statistical Analysis

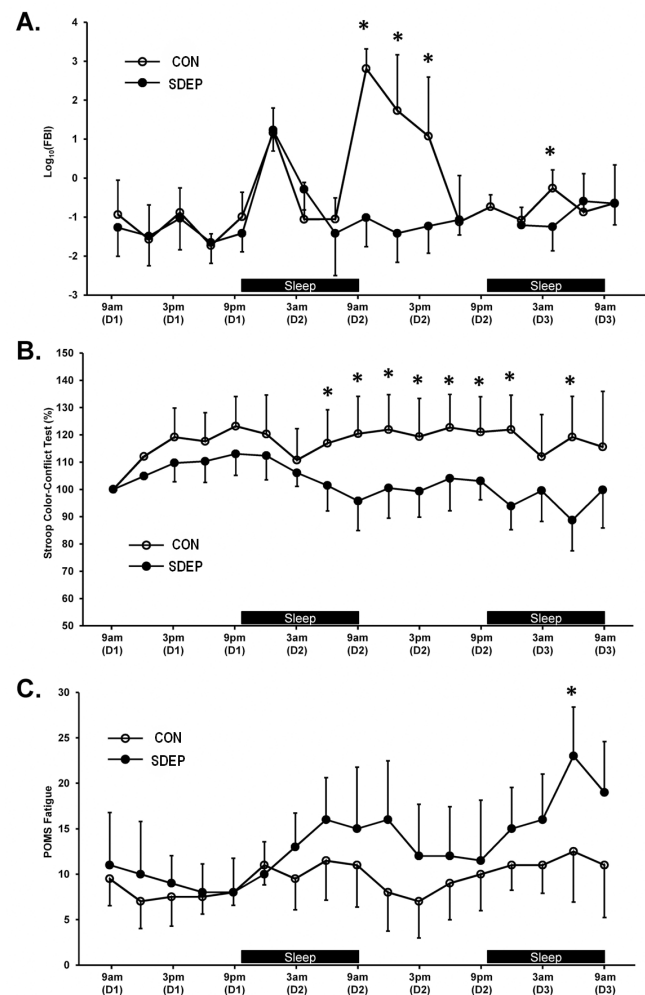
All statistical analyses were completed using R (R<sup>24</sup>; version 2.9.0; cran.r-project.org). Wilcoxon rank sum tests were used for pairwise comparisons between groups at each time point (Figure 1) and across averaged data (Figure 2), with a Bonferroni correction applied to limit the risk of committing type 1 error. Receiver-operator characteristic (ROC) curves were also used to assess cross-sectional data using the pROC package for R.<sup>25</sup> Our a priori significance level was  $p < 0.05$ .

## RESULTS

### Longitudinal Analysis

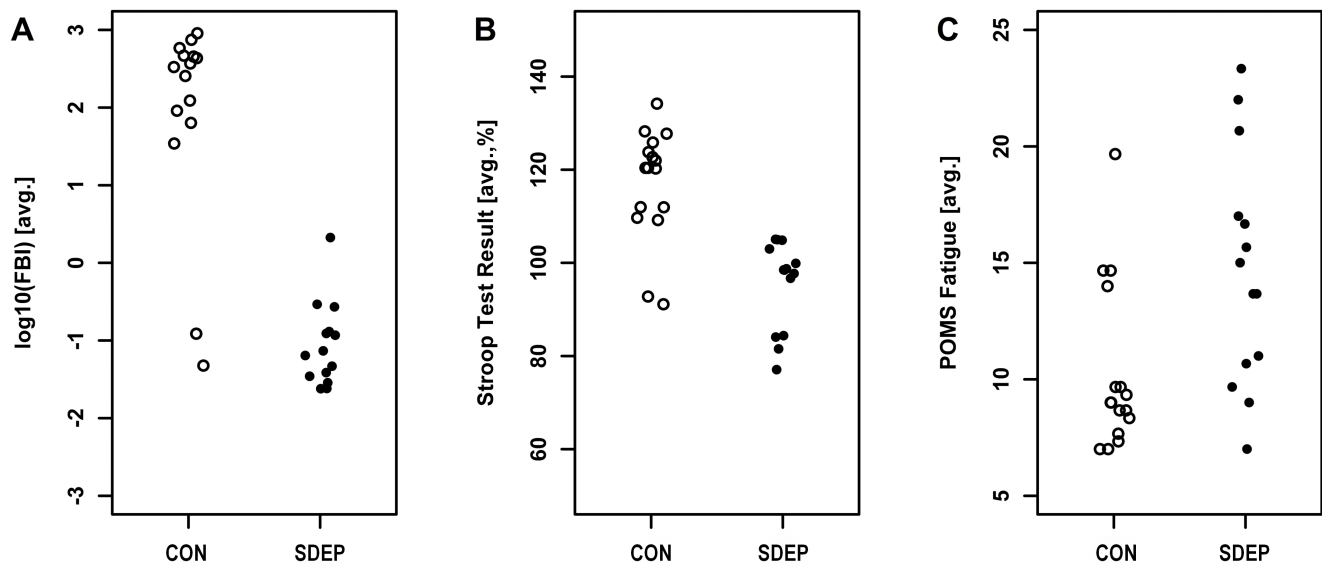
By using a 3-h sampling interval, this study provided relatively high resolution temporal data to evaluate changes in

**Figure 1**—Sleep deprivation led to significant changes in self-reported fatigue level, cognitive performance, and salivary biomarkers of physical fatigue



Subjects were evaluated every 3 h during the course of the study. (A) Levels of the salivary biomarker of physical fatigue remained similar across groups through the first hours of the study, and then changed significantly during the hours after the first night of sleep. Both groups showed a significant increase around midnight on the first day of the study, while only the CON group showed a similar, though muted, increase on the second day of the study. (B) Cumulative scores on the Stroop tests, shown as percentages relative to the subject's initial scores, remained similar across groups until the early morning hours of the second day. Scores for individuals in the SDEP group dropped significantly after the first evening, whereas scores for individuals in the CON group remained relatively constant. The initial upward slope seen in both groups is likely to do a learning effect. The absence of significant differences during these early time points suggests that the size of the learning effect was similar for both groups. (C) Self-reported fatigue levels drifted higher with time in both groups. Previous analysis using linear mixed-effects modeling showed a significant positive slope for both groups. With the statistical approach used here, groups did not differ significantly until late on the second day. \*indicates significant difference between groups.

parameters of interest, namely self-reported fatigue level, cognitive performance, and salivary biomarkers of physical fatigue. Self-reported fatigue levels were derived from the profile of mood states (POMS) survey; cognitive data came from the Stroop color-conflict tests; and salivary biomarkers of physical

**Figure 2**—Salivary biomarkers of physical fatigue efficiently detected the effects of sleep deprivation

Values for self-reported fatigue level, cognitive performance and salivary biomarkers of physical fatigue are shown by group for the data collected between 09:00 and 15:00 on the second day of the study. Each point represents average data for one individual. Receiver-operator characteristic (ROC) analysis suggested that salivary biomarkers of physical fatigue can identify sleep-deprived patients with reasonable specificity and selectivity (area under curve, 92%). Self-reported fatigue levels and cognitive performance tests also performed reasonably (area under curve, 77% and 88%, respectively).

fatigue were measured according to the previously described fatigue biomarker index (FBI). Longitudinal data are shown for all 3 parameters and both groups in **Figure 1**. While significant group differences were observed for all 3 parameters, the patterns of change differed. Significant between-group differences appeared first in the Stroop tests in the early morning hours after the first overnight period. Significant changes in the FBI followed soon after, while significant differences in POMS fatigue level were not observed until the early morning hours of the second overnight period. Whereas the significant difference in cognitive performance remained relatively stable after the first overnight period, differences in salivary biomarkers of physical fatigue were transient, lasting 6 to 9 h after the first overnight period of sleep deprivation. A significant difference in salivary biomarkers of fatigue reoccurred during the second overnight period.

### Cross-Sectional Analysis

In addition to analyzing changes in parameters as a function of time, we also evaluated the ability of each of the parameters to discriminate the sleep deprived population from the control population. To make the plots shown in **Figure 2**, data from the window just after the first overnight period (D2-09:00 through D2-15:00) were averaged for each subject, and then plotted by group. We used this window because it is the most relevant testing window for a future clinical test, assuming testing during traditional U.S. business hours (09:00-17:00). Significant between-group differences were observed for 2 (FBI and Stroop) of the 3 parameters. Receiver-operator characteristic (ROC) analysis suggested that cognitive performance tests and salivary biomarkers of physical fatigue performed well when trying to distinguish members of the SDEP and CON groups.

## DISCUSSION

### Summary

Here, we have compared the impact of sleep deprivation on three different parameters: self-reported fatigue level, cognitive performance, and salivary biomarkers of physical fatigue. The effects of sleep deprivation on the first two parameters have been described extensively elsewhere by us<sup>20,21</sup> and by others,<sup>9</sup> while salivary biomarkers of physical fatigue have been described only recently,<sup>17,19</sup> and it was not yet known how they would be affected by sleep deprivation. We observed significant longitudinal changes in all three parameters, and two of the parameters, cognitive performance tests and salivary biomarkers of physical fatigue, also performed well in cross-sectional tests.

### Possible Influence of Circadian Rhythms on the Fatigue Biomarker Index

During the initial part of the trial, the pattern of change for the FBI was similar for both the control and sleep deprived arms of the study. Unexpectedly, both traces included a significant increase in FBI values, suggesting a significant decrease in fatigue level, near midnight during the transition from day 1 to day 2 (**Figure 1A**). A similar, but blunted, increase is seen in the control arm at close to the same time in the second night (day 2-day 3 transition). These unexpected results suggest that the FBI may be affected by circadian rhythms, the hierarchy of oscillators that regulates a wide range of human behavior and physiology.<sup>26</sup> In humans, the circadian system includes both a central pacemaker, the suprachiasmatic nucleus (SCN), and a series of peripheral components.<sup>26</sup> The operation of these oscillators has been described at the cellular and molecular

level, and a number of studies have demonstrated the tight relationship between the circadian clock, hormone secretion, and metabolism.<sup>26-29</sup> In saliva, there is evidence of large-amplitude circadian rhythms for concentrations of several inorganic ions.<sup>30</sup> Other components of saliva including cortisol,<sup>31</sup> melatonin,<sup>32,33</sup> and a variety of metabolites<sup>29,34</sup> also follow circadian rhythms. In contrast, the circadian rhythms for salivary proteins in unstimulated saliva appear to be smaller in amplitude with a wide spread in acrophases, thereby removing significant oscillations from population data.<sup>30</sup>

Of the salivary components examined to date, melatonin has proven most promising as a direct measure of circadian rhythm.<sup>33</sup> Specifically, the dim light melatonin onset (DLMO) marker appears to be a robust measure of circadian rhythm even in the presence of confounding factors,<sup>32</sup> perhaps leading to its eventual use in clinical settings for the identification of circadian rhythm sleep disorders.<sup>35</sup> In contrast, levels of cortisol in serum and saliva are known to be influenced by a number of factors in addition to circadian rhythms, including a variety of acute and chronic stressors such as insomnia, obstructive sleep apnea, depression, and chronic fatigue.<sup>36,37</sup> While the exact relationship between measures of salivary cortisol and measures of sleep remains unclear,<sup>38</sup> there have been a number of intriguing findings. Of particular note is a previous report describing an association between cortisol and fatigue/physical symptoms.<sup>39</sup> Specifically, a population study of older adults identified significant associations of fatigue/physical symptoms with two different measures of cortisol, wakeup cortisol and cortisol awakening response (CAR). The reported association between low wakeup cortisol levels and increased fatigue/physical symptoms<sup>39</sup> later the same day agrees with observations of diminished morning cortisol levels in studies of individuals with chronic fatigue syndrome (CFS).<sup>40,41</sup> In the case of some sleep disorders, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis has even been suggested to have a causative role.<sup>36</sup> For example, nocturnal salivary cortisol levels are consistently elevated in insomnia,<sup>42</sup> providing support for the hypothesis that insomnia arises from hyperarousal of the HPA axis. In other sleep disorders, such as obstructive sleep apnea,<sup>36</sup> changes in cortisol are believed to be secondary. However, the wide range of external factors influencing salivary cortisol levels may limit their utility in the diagnosis of sleep disorders.

At present, the mechanism(s) regulating the generation of the peptides of the FBI remains unknown, and it remains unclear whether levels of these peptides might also change in response to other stressors besides sleep deprivation. Given the potential presence of circadian rhythms and the lack of understanding about other potential influences affecting levels of these peptides, FBI measurements should be interpreted carefully.

## Other Measures of Sleepiness

Given the increasing and varying needs of researchers, clinicians, patients, regulators, lawmakers, and insurers, several other approaches to quantifying sleepiness are also under development.<sup>43-45</sup> Methods to quantify sleepiness have arisen from various behavioral, electrophysiological, genetic, proteomic, and metabolomic studies of sleep and sleep deprivation. Methods of quantifying sleepiness have been proposed based on changes in behavioral factors such as response time<sup>6,46</sup> and

other measures of attention, as well as various electrophysiological factors such as changes in the power for a particular type of electroencephalographic wave.<sup>47</sup> Other methods for measuring sleepiness have focused on changes in the composition of serum,<sup>48</sup> saliva,<sup>49</sup> cerebrospinal fluid,<sup>50,51</sup> exhaled breath, and exhaled breath condensate.<sup>52</sup> Inflammatory factors such as IL-6, TNF- $\alpha$ , von Willebrand factor, and C-reactive protein<sup>53,54</sup> have drawn considerable attention. A gene expression study identified salivary amylase as a biomarker of sleep drive in both fruit flies (*Drosophila melanogaster*) and humans.<sup>49</sup> Indeed, heterozygote individuals with a single copy of the c.22G > A (rs73598374) polymorphism for adenosine deaminase differ significantly from homozygote individuals with respect to vulnerability to sleep loss, exhibiting both a reduction in sustained attention and an elevation in salivary  $\alpha$ -amylase activity during periods of prolonged waking.<sup>55</sup> Although many of these measures of sleepiness appear promising, the lack of specificity among many, if not all, of the sleep reporter and regulatory substances identified to date has led some to suggest that proper measurement of sleepiness will ultimately require simultaneous monitoring of numerous analytes.<sup>54</sup> While the peptide components of the FBI are more likely to be sleep reporter than sleep regulatory molecules, they might still be well-suited for inclusion in a multi-analyte approach to measuring sleepiness.

## Potential Clinical Applications for Salivary Biomarkers of Physical Fatigue

Despite the limitations discussed above, the promising results presented here suggest that salivary biomarkers of physical fatigue might provide useful clinical information with respect to patient sleep health. Potential uses include diagnosing sleep disorders and/or longitudinally monitoring fatigue arising from sleep deprivation. The former would help clinicians make diagnoses based on objective measures, and the latter would allow physicians to select the most effective treatment strategy for various sleep disorders. Salivary biomarkers of physical fatigue might be especially well-suited for diagnosing specific types of sleep disorder. For example, diagnosis of paradoxical insomnia, which is characterized by a significant mismatch between self-reported sleep data and objective measures of sleep obtained from polysomnographs,<sup>4</sup> would be much easier if clinicians had a rapid, inexpensive method to evaluate a patient's sleep history. In other sleep disorders, such as periodic limb movement, arousals from sleep are not perceived by patients suggesting that self-reported sleep data will not be accurate,<sup>56</sup> highlighting the need for objective measures of sleep. The technology described here might also be well-suited to phenotype patients with various polymorphisms associated with enhanced vulnerability to sleep loss, much like the use of sAA described above.<sup>55</sup> Overall, the FBI provides clinicians with an additional objective measure to guide the diagnosis and/or treatment of sleep disorders.

## Limitations, Future Studies, and Conclusion

The present study aimed to examine changes in salivary biomarkers of physical fatigue during a period of sleep deprivation. While the data are promising and suggest that salivary biomarkers of physical fatigue may be a useful and objective method to monitor sleep deprivation, the study also has



a number of limitations. For example, the sample size is relatively small, and the participants were young and relatively healthy. While subjects were asked about their sleep history, the study did not include a comprehensive evaluation of subjects to exclude all sleep disorders. In addition, our choices of instruments to evaluate cognitive performance and self-reported fatigue level—Stroop tests and POMS survey, respectively—may not represent the most sensitive tools for detecting changes related to sleep loss. Future studies will aim to study salivary changes related to sleep in subjects of much more varied demographic background and health condition.

In conclusion, we report here that the loss of sleep leads to significant changes in levels of a salivary biomarker of physical fatigue. If these preliminary findings are confirmed in future studies, salivary biomarkers of physical fatigue hold promise of providing clinicians, regulators, and patients with a fast, convenient, and relatively inexpensive method to diagnose and/or monitor sleep disorders.

## REFERENCES

- Carney CE, Buysse DJ, Ancoli-Israel S, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. *Sleep* 2012;35:287-302.
- American Academy of Sleep Medicine. *The international classification of sleep disorders, revised: diagnostic and coding manual*. Chicago, IL: American Academy of Sleep Medicine, 2001.
- Cooke JR, Ancoli-Israel S. Normal and abnormal sleep in the elderly. *Handb Clin Neurol* 2011;98:653-65.
- Edinger JD, Bonnet MH, Bootzin RR, et al. Derivation of research diagnostic criteria for insomnia: Report of an American Academy of Sleep Medicine work group. *Sleep* 2004;27:1567-96.
- Mittler MM, Miller JC. Methods of testing for sleepiness. *Behav Med* 1996;21:171-83.
- Dinges DF, Powell JW. Microcomputer analysis of performance on a portable, simple visual RT task sustained operations. *Behav Res Methods Instrum Comput* 1985;17:652-55.
- Mahowald MW, Schenck CH. Insights from studying human sleep disorders. *Nature* 2005;437:1279-85.
- National Highway Traffic Safety Administration. Drowsy driving and automobile crashes; report and recommendations from the national center on sleep disorders research/NHTSA expert panel on driver fatigue and sleepiness. DOT HS 808 707, 1998.
- Orzel-Gryglewska J. Consequences of sleep deprivation. *Int J Occup Med Environ Health* 2010;23:95-114.
- Arndt JT, Wilde GJ, Munt PW, MacLean AW. How do prolonged wakefulness and alcohol compare in the decrements they produce on a simulated driving task? *Accid Anal Prev* 2001;33:337-44.
- Dawson D, Reid K. Fatigue, alcohol and performance impairment. *Nature* 1997;388:235.
- Lamond N, Dawson D. Quantifying the performance impairment associated with fatigue. *J Sleep Res* 1999;8:255-62.
- Williamson AM, Feyer AM. Moderate sleep deprivation produces impairments in cognitive and motor performance equivalent to legally prescribed levels of alcohol intoxication. *Occup Environ Med* 2000;57:649-55.
- Falletti MG, Maruff P, Collie A, Darby DG, McStephen M. Qualitative similarities in cognitive impairment associated with 24 h of sustained wakefulness and a blood alcohol concentration of 0.05%. *J Sleep Res* 2003;12:265-74.
- Daley M, Morin CM, LeBlanc M, Gergoire JP, Savard J. The economic burden of insomnia: Direct and indirect costs for individuals with insomnia syndrome, insomnia symptoms, and good sleepers. *Sleep* 2009;32:55-64.
- Ozminkowski RJ, Wang S, Walsh JK. The direct and indirect costs of untreated insomnia in adults in the united states. *Sleep* 2007;30:263-73.
- Michael DJ, Daugherty S, Santos A, Ruby BC, Kalns JE. Fatigue biomarker index: An objective salivary measure of fatigue level. *Accid Anal Prev* 2012;45 Suppl:68-73.
- Carlson DM. Salivary proline-rich proteins: biochemistry, molecular biology and regulation of expression. *Crit Rev Oral Biol Med* 1993;4:495-502.
- Kalns J, Baskin J, Reinert A, et al. Predicting success in the tactical air combat party training pipeline. *Mil Med* 2011;176:431-7.
- Fogt DL, Cooke WH, Kalns JE, Michael DJ. Linear mixed-effects modeling of the relationship between heart rate variability and fatigue arising from sleep deprivation. *Aviat Space Environ Med* 2011;82:1104-9.
- Fogt DL, Kalns JE, Michael DJ. A comparison of cognitive performance decreases during acute, progressive fatigue arising from different concurrent stressors. *Mil Med* 2010;175:939-44.
- Manual for the profile of mood states. San Diego, CA: Educational and Industrial Testing Services, 1971.
- Frankenhaeuser M. Behavior and circulating catecholamines. *Brain Res* 1971;31:241-62.
- R development core team. R: A language and environment for statistical computing. <http://www.R-project.org> R Foundation for Statistical Computing, 2010.
- Robin X, Turck N, Hainard A, et al. pROC: An open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* 2011;12:77.
- Ko CH, Takahashi JS. Molecular components of the mammalian circadian clock. *Hum Mol Genet* 2006;15 Spec No 2:R271-7.
- Sahar S, Sassone-Corsi P. Regulation of metabolism: The circadian clock dictates the time. *Trends Endocrinol Metab* 2012;23:1-8.
- Minami Y, Kasukawa T, Kakazu Y, et al. Measurement of internal body time by blood metabolomics. *Proc Natl Acad Sci U S A* 2009;106:9890-5.
- Dallmann R, Viola AU, Tarokh L, Cajochen C, Brown SA. The human circadian metabolome. *Proc Natl Acad Sci U S A* 2012;109:2625-9.
- Dawes C. Circadian rhythms in the flow rate and composition of unstimulated and stimulated human submandibular saliva. *J Physiol* 1975;244:535-48.
- Weitzman ED, Fukushima D, Nogeire C, Roffwarg H, Gallagher TF, Hellman L. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. *J Clin Endocrinol Metab* 1971;33:14-22.
- Pandi-Perumal SR, Smits M, Spence W, et al. Dim light melatonin onset (DLMO): A tool for the analysis of circadian phase in human sleep and chronobiological disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;31:1-11.
- Mirick DK, Davis S. Melatonin as a biomarker of circadian dysregulation. *Cancer Epidemiol Biomarkers Prev* 2008;17:3306-13.
- Bertram HC, Eggers N, Eller N. Potential of human saliva for nuclear magnetic resonance-based metabolomics and for health-related biomarker identification. *Anal Chem* 2009;81:9188-93.
- Sack RL, Auckley D, Auger RR, et al. Circadian rhythm sleep disorders: Part I, basic principles, shift work and jet lag disorders. An American Academy of Sleep Medicine review. *Sleep* 2007;30:1460-83.
- Buckley TM, Schatzberg AF. On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: Normal HPA axis activity and circadian rhythm, exemplary sleep disorders. *J Clin Endocrinol Metab* 2005;90:3106-14.
- Adam EK, Kumari M. Assessing salivary cortisol in large-scale, epidemiological research. *Psychoneuroendocrinology* 2009;34:1423-36.
- Garde AH, Karlsson B, Hansen AM, Persson R, Akerstedt T. Sleep and salivary cortisol In: Kristenson M, Garvin P, Lundberg U, eds. The role of saliva cortisol measurement in health and disease. Oak Park, IL: Bentham Science Publishers, 2012:116-28. <http://dx.doi.org/10.2174/97816080534211120101>.
- Adam EK, Hawkey LC, Kudielka BM, Cacioppo JT. Day-to-day dynamics of experience—cortisol associations in a population-based sample of older adults. *Proc Natl Acad Sci U S A* 2006;103:17058-63.
- Nater UM, Maloney E, Boneva RS, et al. Attenuated morning salivary cortisol concentrations in a population-based study of persons with chronic fatigue syndrome and well controls. *J Clin Endocrinol Metab* 2008;93:703-9.
- Roberts AD, Wessely S, Chalder T, Papadopoulos A, Cleare AJ. Salivary cortisol response to awakening in chronic fatigue syndrome. *Br J Psychiatry* 2004;184:136-41.
- Bonnet MH, Arand DL. Hyperarousal and insomnia: State of the science. *Sleep Med Rev* 2010;14:9-15.
- Quan SF. Finding a research path for the identification of biomarkers of sleepiness. *J Clin Sleep Med* 2011;7(5 Suppl):S4-5.
- Quan SF, Shaw PJ, Naidoo N, Haeggstrom E, Krueger JM, Church GM. Panel discussion: Can there be a biomarker for sleepiness? *J Clin Sleep Med* 2011;7(5 Suppl):S45-8.
- Czeisler CA. Impact of sleepiness and sleep deficiency on public health—utility of biomarkers. *J Clin Sleep Med* 2011;7(5 Suppl):S6-8.
- Balkin TJ. Behavioral biomarkers of sleepiness. *J Clin Sleep Med* 2011;7(5 Suppl):S12-5.
- Davis CJ, Clinton JM, Jewett KA, Zielinski MR, Krueger JM. Delta wave power: An independent sleep phenotype or epiphenomenon? *J Clin Sleep Med* 2011;7(5 Suppl):S16-8.



48. Miller MA, Kandala NB, Kivimaki M, et al. Gender differences in the cross-sectional relationships between sleep duration and markers of inflammation: Whitehall II study. *Sleep* 2009;32:857-64.
49. Seugnet L, Boero J, Gottschalk L, Duntley SP, Shaw PJ. Identification of a biomarker for sleep drive in flies and humans. *Proc Natl Acad Sci U S A* 2006;103:19913-8.
50. Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Arch Neurol* 2002;59:1553-62.
51. Martinez-Rodriguez JE, Lin L, Iranzo A, et al. Decreased hypocretin-1 (orexin-a) levels in the cerebrospinal fluid of patients with myotonic dystrophy and excessive daytime sleepiness. *Sleep* 2003;26:287-90.
52. Carpagnano GE. Exhaled breath analysis and sleep. *J Clin Sleep Med* 2011;7(5 Suppl):S34-7.
53. Miller MA. Association of inflammatory markers with cardiovascular risk and sleepiness. *J Clin Sleep Med* 2011;7(5 Suppl):S31-3.
54. Clinton JM, Davis CJ, Zielinski MR, Jewett KA, Krueger JM. Biochemical regulation of sleep and sleep biomarkers. *J Clin Sleep Med* 2011;7(5 Suppl):S38-42.
55. Bachmann V, Klaus F, Bodenmann S, et al. Functional ada polymorphism increases sleep depth and reduces vigilant attention in humans. *Cereb Cortex* 2012;22:962-70.
56. Goldstein MZ. Practical geriatrics: Insomnia in late life. *Psychiatr Serv* 2001;52:1573-5.

## ACKNOWLEDGMENTS

Funding for this study was provided by the U.S. Army through a Phase-II STTR grant to Hyperion Biotechnology and the University of Texas San Antonio (RDE-COM, STTR W911SR-07-C-006).

## SUBMISSION & CORRESPONDENCE INFORMATION

**Submitted for publication April, 2013**

**Submitted in final revised form August, 2013**

**Accepted for publication August, 2013**

Address correspondence to: Darren J. Michael, Ph.D., 12002 Warfield St., Suite 101, San Antonio, TX 78216; Tel: (210) 493-7452; Fax: (210) 342-2005; E-mail: darrenmichael@hyperionbiotechnology.com

## DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.



# A Twin Study of Genetic Influences on Diurnal Preference and Risk for Alcohol Use Outcomes

Nathaniel F. Watson, M.D., M.Sc., F.A.A.S.M.<sup>1,3,4</sup>; Dedra Buchwald, M.D.<sup>2,4</sup>; Kathryn Paige Harden, Ph.D.<sup>5</sup>

<sup>1</sup>Department of Neurology, School of Medicine, University of Washington, Seattle, WA; <sup>2</sup>Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA; <sup>3</sup>University of Washington Medicine Sleep Center, Seattle, WA;

<sup>4</sup>University of Washington Twin Registry, Seattle, WA; <sup>5</sup>Department of Psychology, University of Texas, Austin, TX

**Objective:** The population-based University of Washington Twin Registry (UWTR) was used to examine (1) genetic influences on chronobiology and (2) whether these genetic factors influence alcohol-use phenotypes.

**Methods:** We used a reduced Horne-Östberg Morningness-Eveningness Questionnaire (rMEQ) to survey UWTR participants for diurnal preference. Frequency and quantity of alcohol use, as well as binge drinking (6+ drinks per occasion), were assessed on a 5-point Likert scale. Both diurnal preference and alcohol use were self-reported. Twin data were analyzed by using structural equation models.

**Results:** The sample consisted of 2,945 participants (mean age = 36.4 years), including 1,127 same-sex and opposite-sex twin pairs and 691 individual twins. The rMEQ range was 4-25, with a mean score of 15.3 (SD 4.0). Diurnal "morning types" comprised 30.7% (N = 903) of participants, while 17.4% (N = 513) were "evening types." Regarding alcohol use, 21.2% (N = 624) reported never drinking. Among drinkers, 35.7% (N = 829) reported ≥ 3 drinks per occasion and 48.1%

(N = 1,116) reported at least one instance of binge drinking. Genetic influences accounted for 37% of the variance in diurnal preference, with the remaining 63% due to non-shared environmental influences. Genetic propensities toward diurnal eveningness were significantly associated with increased alcohol quantity ( $\beta = -0.17$ ; SE = 0.05,  $p < 0.001$ ) and increased binge drinking ( $\beta = -0.19$ ; SE = 0.04,  $p < 0.001$ ), but not with frequency of alcohol use. Environmental paths between diurnal preference and alcohol use phenotypes were not significant.

**Conclusions:** Genetic influences on diurnal preference confer elevated risk for problematic alcohol use, including increased quantity and binge drinking. Differences in circadian rhythm may be an important and understudied pathway of risk for genetic influences on alcohol use.

**Keywords:** Twins, monozygotic, dizygotic, alcohol, circadian, diurnal

**Citation:** Watson NF; Buchwald D; Harden KP. A twin study of genetic influences on diurnal preference and risk for alcohol use outcomes. *J Clin Sleep Med* 2013;9(12):1333-1339.

## BRIEF SUMMARY

**Current Knowledge/Study Rationale:** Preliminary evidence suggests that diurnal preference is a contributing psychological factor in a multi-causal model of alcohol consumption. The extent to which the relationship between diurnal preference and alcohol use is driven by common underlying genetic variants is unknown.

**Study Impact:** This study shows that genetic factors favoring evening-type diurnal preference confer increased risk of binge drinking and increased alcohol consumption. This finding suggests that biological differences in circadian rhythm may be an important pathway of risk for genetic factors that promote alcohol use.

Circadian rhythms are biological processes, such as the human sleep-wake cycle, with an endogenous, entrainable oscillation of roughly 24 hours. The hypothalamic suprachiasmatic nucleus is the primary circadian pacemaker, ensuring a proper duration and consistent timing of sleep. Healthy sleep arises from an effective interaction between the sleep homeostat, which increases sleep propensity as a function of prior wakefulness, and the 24-hour circadian alerting signal generated by the suprachiasmatic nucleus.<sup>1</sup> In practical terms, this interaction results in a wide range of circadian functioning (also known as "diurnal preference" or "chronotype"), from morning types to evening types. Morning types go to bed early and function best in the early daytime hours, whereas evening types go to bed in the early morning hours and function best at later times in the day or evening.<sup>2</sup> Twin and molecular genetic studies consistently show that diurnal preference is influenced by genetic factors, with heritability between 40% and 54%.<sup>3-12</sup>

Recent research has focused on the role of circadian rhythms in health and disease. Circadian clock disruptions, often observed in shift work disorder, are associated with numerous medical conditions, including cardiovascular disease,<sup>13-15</sup> cancer,<sup>16-18</sup> and untoward pregnancy outcomes.<sup>19,20</sup> It is less clear whether

diurnal preference alone portends specific health outcomes. Preliminary evidence suggests that evening-type diurnal preference is associated with poor diet<sup>21</sup> and depression<sup>22</sup> and has adverse effects on measures of quality of life in adolescents.<sup>23</sup> We previously showed an association between evening type and habitual short and long sleep duration in a twin sample.<sup>12</sup> Since both short and long sleep are associated with adverse health outcomes,<sup>24-34</sup> these findings suggest that the evening type may represent an endophenotype for poor health.

Preliminary evidence also suggests that diurnal preference influences alcohol use, such that evening types consume more

alcohol than morning types.<sup>35-37</sup> Alcohol consumption is associated with a single-nucleotide polymorphism in NPAS2, a gene involved in the autoregulatory transcription/translation feedback loop that drives circadian rhythmicity.<sup>38</sup> Evening type is also correlated with novelty-seeking, which is thought to be associated with behavior activation by low basal dopaminergic activity in the brain.<sup>39,40</sup> This may lead to addictive behaviors, such as alcohol abuse or dependence, in an effort to enhance dopamine levels.<sup>41</sup> These preliminary studies suggest that diurnal preference is a contributing psychological factor in a multi-causal model of alcohol consumption. The extent to which the relationship between diurnal preference and alcohol use is driven by common underlying genetic variants has yet to be determined. Therefore, the goals of this twin study were to (1) determine the magnitude of genetic and environmental influences on diurnal preference and (2) evaluate the extent to which genetic influences on diurnal preference confer risk for alcohol use. We hypothesized that genetic predispositions toward eveningness would be associated with more problematic alcohol use, although the dearth of previous behavioral genetic research on this topic made our hypotheses necessarily speculative.

## METHODS

### University of Washington Twin Registry

The University of Washington Twin Registry is a community-based sample of twins constructed with data provided by the Washington State Department of Licensing. All data collection procedures were approved by the University of Washington Institutional Review Board. The minimum age for participation is 18, and < 5% of participants are older than age 66. As of April 2013, the Registry contained more than 7,500 twin pairs. Participants' zygosity is determined by using validated self-report methods, with an accuracy  $\geq 95\%$ .<sup>42,43</sup> Every participant completes a recruitment survey. In 2006 and 2008, an additional health survey that included items on diurnal preference and alcohol use was mailed to more than 4,000 enrolled twins. Further details on the characteristics of Registry participants are available elsewhere.<sup>44,45</sup>

Our study sample consisted of 2,945 individuals, including 1,127 twin pairs (200 monozygotic [MZ] male [17.7%], 82 dizygotic [DZ] male [7.3%], 432 MZ female [38.3%], 215 DZ female [19.1%], and 198 DZ opposite-sex [17.6%]), as well as 691 individual twins who participated without their co-twins. All twin pairs were raised together. Data from incomplete twin pairs were retained because they inform the within-person correlations between diurnal preference and alcohol use. Data collection procedures were approved by the University of Washington Institutional Review Board. The sex of individual twins closely mirrored that observed in complete twin pairs.

## Measures

### Diurnal Preference

Diurnal preference was measured by using the reduced Morningness-Eveningness Questionnaire (rMEQ),<sup>46</sup> a shortened version of the Horne and Östberg Morningness-Eveningness Questionnaire.<sup>47</sup> The rMEQ contains 5 items that assess

aspects of the morning-eveningness dimension (for example, "at what time in the evening do you feel tired and in need of sleep?"), rated on a 5-point Likert scale. Responses to each question are summed to give a total rMEQ score between 4 and 25, with higher scores indicating stronger morningness preference. We defined morning types as those with a score  $\geq 18$ , and evening types as those with a score  $\leq 11$ . The rMEQ has demonstrated good internal reliability and validity compared to the full Morningness-Eveningness Questionnaire.<sup>48</sup>

### Alcohol Use Phenotypes

Aspects of alcohol use were determined by using the Registry questionnaire. Alcohol frequency was ascertained by asking, "How often do you have a drink containing alcohol?" Potential responses were never, monthly or less, 2-4 times a month, 2-3 times a week, and  $\geq 4$  times a week. Alcohol quantity was ascertained by asking, "How many drinks of alcohol do you have on a typical day when you are drinking?" Potential responses were 1 or 2, 3 or 4, 5 or 6, 7 to 9, and 10 or more. Binge drinking was ascertained by asking, "How often do you have 6 or more drinks on one occasion?" Potential responses were never, less than monthly, monthly, weekly, daily, or almost daily. Responses to each of the three alcohol-related questions were scored on a scale of 1 to 5.

### Sociodemographics

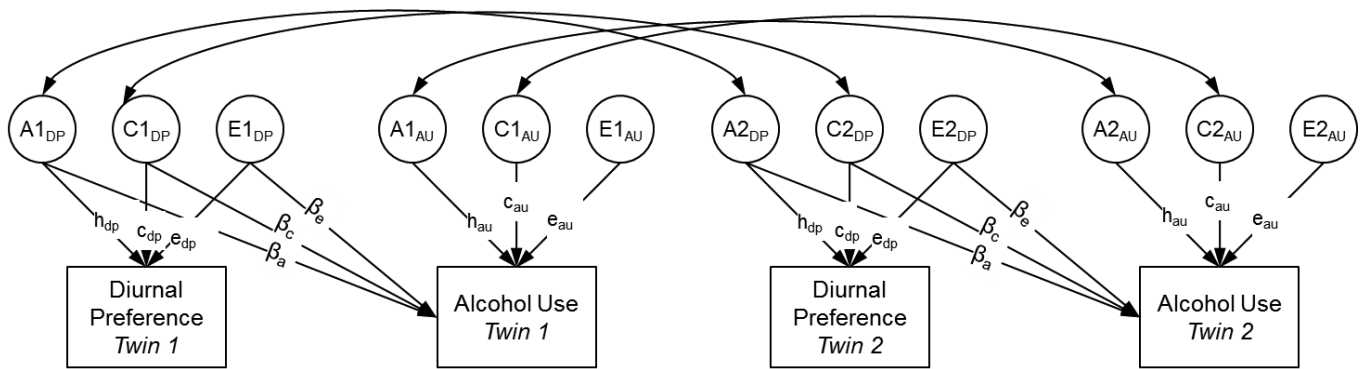
Age, sex, and race were self-reported. Race was dichotomized into White and non-white (American Indian, Alaska Native, Native Hawaiian, Pacific Islander, Asian, black or African American, or other) categories. Education was ascertained by the question, "What is the highest level of school you have completed?" A total of 7 responses were possible, ranging from "eighth grade or less" to "graduate or professional degree." The midpoint was "some college, but no degree or certificate."

### Statistical Analysis

We began by examining zygosity-specific twin pair correlations for diurnal preference and each of the 3 alcohol use phenotypes (alcohol frequency, alcohol quantity, and binge drinking). Within-trait, cross-twin correlations (e.g., the correlation between diurnal preference in Twin A and diurnal preference in Twin B) can be used to evaluate the magnitude of genetic and environmental influences on a given phenotype. Cross-trait, cross-twin correlations (e.g., the correlation between diurnal preference in Twin A and alcohol use frequency in Twin B) can be used to evaluate the contribution of genes to the association between the phenotypes.

Next, we evaluated these questions more formally by using the software program *Mplus* (Muthén & Muthén, 1998-2012, Los Angeles, CA) to fit quantitative genetic models. Specifically, we fit the bivariate twin model shown in **Figure 1**. Total variance in each of the observed phenotypes (boxes labeled "Diurnal Preference" and "Alcohol Use") was decomposed into 3 latent factors: additive genetic influences (A), shared environmental influences (C, meaning common environmental influences that make siblings similar to one another), and non-shared environmental influences (E, meaning environmental influences that are unique to each twin, plus measurement



**Figure 1**—Structural equation model of diurnal preference and alcohol use in adult twins

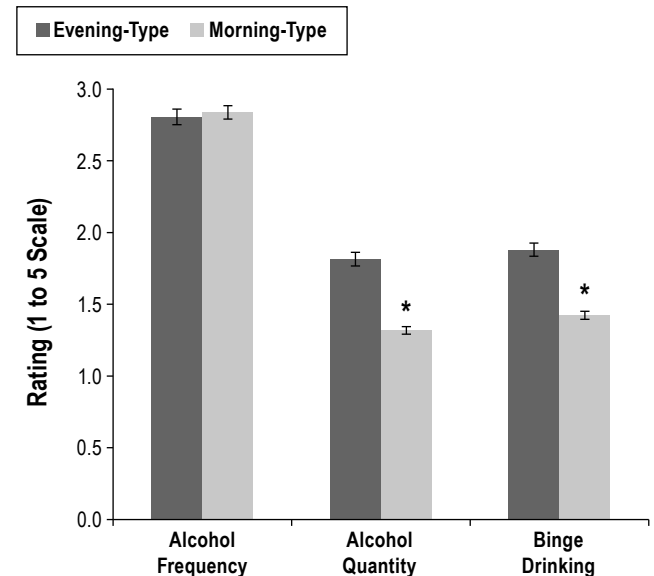
A, additive genetic variance; C, shared environmental variance; E, nonshared environmental variance. A, C, and E components standardized (mean = 0, standard deviation = 1). Correlation between A components fixed at 1.0 in monozygotic twins and 0.5 in dizygotic twins. Correlation between C components fixed to 1.0 in all twins. Correlation between E components fixed to 0 in all twins.  $\beta_a$ ,  $\beta_c$ , and  $\beta_e$  represent cross-paths estimating the extent to which genetic and environmental influences on diurnal preference also influence alcohol use. au, alcohol use; dp, diurnal preference.

**Table 1**—Sample characteristics

| Demographic Characteristics        | N (%)         |
|------------------------------------|---------------|
| Female                             | 1,891 (64.2%) |
| White                              | 2,607 (88.5%) |
| No high school degree              | 233 (7.9%)    |
| ≥ College degree                   | 1,890 (64.2%) |
| Study Variables                    | Mean (SD)     |
| Age (years)                        | 36.4 (15.7)   |
| Diurnal preference <sup>a</sup>    | 15.3 (4.02)   |
| Alcohol use frequency <sup>b</sup> | 2.77 (1.32)   |
| Alcohol quantity <sup>b</sup>      | 1.49 (0.83)   |
| Binge drinking <sup>b</sup>        | 1.59 (0.90)   |

MZ, monozygotic; DZ, dizygotic; SD, standard deviation. <sup>a</sup>The diurnal preference scale ranged from 5 to 25, with higher scores indicating more morning preference. <sup>b</sup>Alcohol use scales ranged from 1 to 5.

error). The ACE components for each phenotype were standardized (mean = 0, standard deviation = 1) and the paths from these components to the phenotype were estimated. The correlation between additive genetic influences (A) in the first and second member of each twin pair was fixed at 1.0 in MZ twins and 0.5 in DZ twins, consistent with genetic theory. The correlation between common environmental (C) factors was fixed at 1.0 in all pair types, whereas the correlation between unique environmental (E) factors was fixed at 0 in all pair types. Finally, alcohol use was regressed on the ACE components of diurnal preference (labeled  $\beta_a$ ,  $\beta_c$ ,  $\beta_e$  in **Figure 1**). These cross-paths estimate the extent to which genetic and environmental influences on diurnal preference also influence alcohol use. Note that the boxes labeled “Alcohol Use” in **Figure 1** refer to each of the 3 alcohol use phenotypes, which were modeled individually. Previous authors have described the logic and parameterization of twin models in great detail.<sup>49</sup> All models were estimated by using full information maximum likelihood to account for missing data from incomplete twin pairs.<sup>50</sup> All models controlled for age, white race, and educational attainment by regressing both diurnal preference and alcohol use phenotypes on these covariates

**Figure 2**—Alcohol use phenotypes by morning-type versus evening-type diurnal preference

Bars represent standard error around the mean. \*Significant difference.

## RESULTS

Sample characteristics and descriptive statistics for all study variables are summarized in **Table 1**. Overall, the sample was composed of predominantly younger adults (mean = 36.4 years; standard deviation = 15.7; range 19-93) who were well-educated (64.2% with a college degree or higher) and predominantly white (88.5%) and female (64.2%). Morning types comprised 30.7% of participants, while evening types comprised 17.4%. Never drinking was reported by 21.2%. Among drinkers, 35.7% reported typically drinking ≥ 3 drinks, and 48.1% reported ≥ 1 occasion of binge drinking. **Figure 2** illustrates the mean levels of alcohol frequency, alcohol quantity, and binge drinking reported by morning and evening types. Morning and evening types did not significantly differ in alcohol use frequency ( $p = 0.66$ ), but

**Table 2**—Twin correlations for diurnal preference and alcohol use phenotypes

|                                                           | MZ Twin Correlations |                    |                    | DZ Twin Correlations |                     |                     |                    |
|-----------------------------------------------------------|----------------------|--------------------|--------------------|----------------------|---------------------|---------------------|--------------------|
|                                                           | All                  | Male               | Female             | All                  | Male                | Female              | OS                 |
| <b>Within-Trait Correlations</b>                          |                      |                    |                    |                      |                     |                     |                    |
| Diurnal preference                                        | 0.50                 | 0.57               | 0.46               | 0.30                 | 0.27                | 0.18                | 0.44               |
| Alcohol frequency                                         | 0.60                 | 0.59               | 0.60               | 0.31                 | 0.34                | 0.34                | 0.24               |
| Alcohol quantity                                          | 0.51                 | 0.50               | 0.49               | 0.30                 | 0.17 <sup>ns</sup>  | 0.23                | 0.34               |
| Binge drinking                                            | 0.61                 | 0.63               | 0.55               | 0.26                 | 0.42                | 0.28                | 0.13 <sup>ns</sup> |
| <b>Cross-Trait Correlations (with Diurnal Preference)</b> |                      |                    |                    |                      |                     |                     |                    |
| Alcohol frequency                                         | 0.04 <sup>ns</sup>   | 0.05 <sup>ns</sup> | 0.04 <sup>ns</sup> | -0.01 <sup>ns</sup>  | -0.04 <sup>ns</sup> | 0.02 <sup>ns</sup>  | -0.03              |
| Alcohol quantity                                          | -0.20                | -0.28              | -0.13              | -0.16                | -0.18 <sup>ns</sup> | -0.05 <sup>ns</sup> | -0.22              |
| Binge drinking                                            | -0.17                | -0.23              | -0.13              | -0.17                | -0.19 <sup>ns</sup> | -0.08 <sup>ns</sup> | -0.23              |

All correlations are significantly different from zero at  $p < 0.05$  unless noted (ns).

**Table 3**—Comparisons between quantitative genetic models

| Model                                      | Fit of ACE Model ( $\chi^2$ ) | Fit of AE Model ( $\chi^2$ ) | Change in Model Fit ( $\Delta\chi^2$ ) |
|--------------------------------------------|-------------------------------|------------------------------|----------------------------------------|
| Diurnal Preference → Alcohol Use Frequency | 49.90<br>$df = 39, p = 0.11$  | 49.90<br>$df = 42, p = 0.19$ | < 0.001<br>$df = 3, p = 0.99$          |
| Diurnal Preference → Alcohol Quantity      | 50.69<br>$df = 39, p = 0.10$  | 51.03<br>$df = 42, p = 0.16$ | 0.34<br>$df = 3, p = 0.95$             |
| Diurnal Preference → Binge Drinking        | 52.84<br>$df = 39, p = 0.07$  | 52.84<br>$df = 42, p = 0.12$ | < 0.001<br>$df = 3, p = 0.99$          |

ACE = full model shown in Figure 1. AE = model in which paths from shared environmental factors (C) to phenotypes are fixed at zero.

**Table 4**—Results from bivariate behavioral genetic models of diurnal preference and alcohol use outcomes

| Parameter                                                  | Frequency of Alcohol Use | Quantity of Alcohol Use   | Binge Drinking            |
|------------------------------------------------------------|--------------------------|---------------------------|---------------------------|
| Genetic and Environmental Influences on Diurnal Preference |                          |                           |                           |
| Additive genetic ( $h_{dp}$ )                              | 0.55 (0.03) <sup>a</sup> | 0.55 (0.03) <sup>a</sup>  | 0.55 (0.03) <sup>a</sup>  |
| Non-shared environment ( $e_{dp}$ )                        | 0.72 (0.02) <sup>a</sup> | 0.72 (0.02) <sup>a</sup>  | 0.72 (0.02) <sup>a</sup>  |
| Diurnal Preference → Alcohol                               |                          |                           |                           |
| Genetic Path ( $\beta_a$ )                                 | -0.06 (0.04)             | -0.17 (0.05) <sup>a</sup> | -0.19 (0.04) <sup>a</sup> |
| Non-shared environmental path ( $\beta_e$ )                | -0.01 (0.02)             | -0.02 (0.03)              | -0.01 (0.02)              |
| Genetic and Environmental Influences Unique to Alcohol     |                          |                           |                           |
| Additive genetic ( $h_{au}$ )                              | 0.75 (0.02) <sup>a</sup> | 0.61 (0.03) <sup>a</sup>  | 0.72 (0.02) <sup>a</sup>  |
| Non-shared environment ( $e_{au}$ )                        | 0.63 (0.02) <sup>a</sup> | 0.73 (0.02) <sup>a</sup>  | 0.63 (0.02) <sup>a</sup>  |

Standardized parameter estimates are reported. SEs in parentheses. <sup>a</sup>Parameters are significantly different from zero at  $p < 0.05$ .

evening types consumed larger quantities ( $p < 0.001$ ) and were more likely to report binge drinking ( $p < 0.001$ ).

**Table 2** summarizes the within-trait, cross-twin correlations for diurnal preference and alcohol use phenotypes, as well as the cross-trait, cross-twin correlations between diurnal preference and each alcohol use phenotype. Overall, the MZ correlations for each trait exceeded the DZ correlations, consistent with the presence of heritable influences on each phenotype. More specifically, descriptive heritability estimates can be calculated as  $h^2 = 2*(r_{MZ} - r_{DZ})$ , yielding heritabilities of 40% for diurnal preference, 58% for alcohol use frequency, 42% for alcohol quantity, and 70% for binge drinking. Similarly, the cross-trait correlations (i.e., the correlation between alcohol use in Twin A and diurnal preference in Twin B) suggest that diurnal preference is more strongly related to our measures of alcohol quantity and binge drinking than to our measures of

frequency of alcohol use. These initial descriptive results are formally assessed with the structural equation models.

Model fit comparisons for the quantitative genetic models are summarized in **Table 3**. For all alcohol use outcomes, the full “ACE” model (as illustrated in **Figure 1**) did not fit the data significantly better than a trimmed “AE” model, in which all paths from the shared environmental factors (C) to the phenotypes ( $c_{dp}$ ,  $c_{au}$ , and  $\beta_c$ ) were fixed at zero. In other words, shared environmental influences on alcohol use phenotypes, diurnal preference, and their associations were not significant. Consequently, we report standardized parameter estimates from the AE models in **Table 4**. Root mean square error of approximation (RMSEA), comparative fit index (CFI), and Tucker-Lewis Index (TLI) are alternate indices of model fit, with RMSEA values  $< 0.06$  and CFI and TLI values  $> 0.95$  indicating good fit.<sup>51</sup> The overall fit for each of the 3 AE models

was good (alcohol use frequency: RMSEA = 0.018, CFI = 0.99, TLI = 0.99; alcohol quantity: RMSEA = 0.020, CFI = 0.99, TLI = 0.99; binge drinking: RMSEA = 0.021, CFI = 0.99, TLI = 0.99).

Morning preference was significantly predicted by white race ( $\beta = 0.10$ ,  $SE = 0.03$ ,  $p < 0.05$ ), higher educational attainment ( $\beta = 0.07$ ,  $SE = 0.03$ ,  $p < 0.05$ ), and older age ( $\beta = 0.39$ ,  $SE = 0.03$ ,  $p < 0.05$ ). Diurnal preference did not differ according to sex (males = 15.23,  $SD = 4.07$ ; females = 15.28,  $SD = 3.94$ ,  $p = 0.82$ ). Alcohol use frequency, alcohol quantity, and binge drinking were not significantly associated with white race. Alcohol frequency was unrelated to age, but older people reported lower alcohol quantity ( $\beta = -0.01$ ,  $SE = 0.002$ ,  $p < 0.05$ ) and less frequent binge drinking ( $\beta = -0.21$ ,  $SE = 0.04$ ,  $p < 0.05$ ). People with higher educational attainment drank more frequently ( $\beta = 0.11$ ,  $SE = 0.03$ ,  $p < 0.05$ ), but reported lower alcohol quantity per occasion ( $\beta = -0.124$ ,  $SE = 0.03$ ,  $p < 0.05$ ). Educational attainment was not significantly associated with binge drinking.

After controlling for covariates, the proportion of residual variation in diurnal preference attributable to genetic influences can be calculated as the square of the genetic path ( $h_{dp}$ ) divided by the sum of the squared paths ( $h_{dp}^2 + e_{dp}^2$ ). Thus, genetic influences accounted for 37% of the variance in diurnal preference that could not be attributed to covariates, with the remaining 63% due to non-shared environmental influences. Notably, this heritability estimate is similar to that obtained in a recent study by Kuna and colleagues (41%), even though they used a different self-report instrument to assess diurnal preference.<sup>52</sup>

Genetic propensities toward eveningness were significantly associated with increased alcohol quantity ( $\beta_a = -0.17$ ;  $SE = 0.05$ ,  $p < 0.001$ ) and increased frequency of binge drinking ( $\beta_a = -0.19$ ;  $SE = 0.04$ ,  $p < 0.001$ ), but not with frequency of alcohol use. The non-shared environmental paths between diurnal preference and alcohol use phenotypes were not significant. In other words, a common set of genes influences both evening preference and elevated alcohol use, and this genetic overlap entirely accounts for the associations between diurnal preference, alcohol quantity, and binge drinking.

After accounting for variance shared with diurnal preference and with covariates, the proportions of unique variance in alcohol use frequency, alcohol quantity, and binge drinking frequency attributable to genetic influences were 59%, 41%, and 57%, respectively. The remaining variation was attributable to environmental influences unique to each twin.

## DISCUSSION

We found that genetic influences on diurnal preference conferred increased risk of problematic alcohol use. Evening-type diurnal preference, alcohol quantity, and binge drinking frequency were linked by a common set of genes that entirely encompasses the association among these phenotypes. Common environmental influences were negligible, suggesting that behavior learned in early life with regard to chronotype is unrelated to familial attitudes about alcohol use—in other words, chronotype and attitudes about alcohol do not co-segregate.

Work schedules that start early in the day are most suitable for morning types. For evening types, the combination of late

bedtimes driven by the endogenous clock and early waking times dictated by social factors during the work week results in short sleep and sleep debt, for which they compensate by extending sleep duration on weekends.<sup>53-55</sup> This serves to reduce sleep quality and increase daytime sleepiness in evening types and drive associations between evening-type diurnal preference and untoward health outcomes, including psychological and psychosomatic disturbances.<sup>53,56-58</sup> We found that evening-type twins endorsed larger quantities of alcohol consumed and more frequent binge drinking than morning-type twins, a finding consistent with previous studies.<sup>35,56,59</sup> Alcohol consumption can represent behavioral manifestations of trouble coping with social demands,<sup>60</sup> such as the struggles experienced by evening types who are obliged to rise early. This social situation highlights the importance of our findings for the health of evening-type twins and suggests that evening-type diurnal preference in modern society may be innately unhealthy and lead to poor health choices.

Alcohol abuse in the US exacts over \$230 billion annually in costs related to crime, lost work productivity, and health-care, amounting to 2.7% of the US gross domestic product.<sup>61,62</sup> Alcohol consumption causes 3.8% of all global deaths and is responsible for 4.6% of global disability-adjusted life-years, a composite measure of total years of healthy life lost.<sup>62</sup> The damage to social relationships caused by alcohol abuse is harder to quantify, but no less substantial. In this context, our findings take on increased importance, as they have the potential to inform interventions to improve public and personal health. Social initiatives aimed at making work timing and other social activities more flexible for a broader range of chronotypes may reduce troublesome alcohol use. Also, elucidation of shared genetic pathways by future research may yield opportunities to develop targeted therapeutic agents that can reduce the risk of alcohol abuse in evening types.

The human circadian clock is maintained by a set of genes (CLOCK, BMAL1, PER 1, 2, and 3, CRY 1 and 2, TIM, and NPAS2) in the suprachiasmatic nucleus that control circadian rhythms, and thus diurnal preference, through a transcriptional, translational feedback loop.<sup>63</sup> Clock genes not only control circadian rhythms, but also rhythmically regulate nearly 10,000 mammalian genes in multiple tissues involving numerous biological processes.<sup>64</sup> NPAS2 is associated with average weekly alcohol intake,<sup>38</sup> and polymorphisms in the CLOCK, BMAL1, PER3, and TIM genes are associated with susceptibility to mood disorders such as depression,<sup>65-68</sup> a common risk factor for alcohol abuse.<sup>69</sup> Polymorphisms in the serotonin transporter gene are associated with hazardous drinking in certain environmental circumstances,<sup>70</sup> and this monoamine neurotransmitter is a key component of sleep/wake REM/NREM brain physiology.<sup>71</sup> Evening-type diurnal preference is linked with novelty seeking, a potential signal of reduced dopaminergic activity,<sup>39,40</sup> while dopamine promotes wakefulness and influences sleep stages.<sup>72</sup> These are but a few of the many potential genes and pathways that may constitute the shared genetic influences on evening-type diurnal preference and alcohol use outcomes. Future twin studies have the potential to reveal these genes and pathways by inserting polymorphisms of interest into bivariate genetic models of circadian type and alcohol use and observing the effect on the shared genetic estimates in the model.

Several issues about our study warrant discussion. Our twins were predominantly younger adult white women, and therefore our results should be applied to the general population with caution. However, this limitation is tempered by the fact our sample was derived from the community and not from a clinical population seeking healthcare, thus increasing the generalizability of our results. Subjective measures that enable the extrapolation of circadian phase, such as sleep logs, can accurately predict self-reported circadian type,<sup>73</sup> although direct comparisons of rMEQ scores with objective measures, such as actigraphy, are lacking. Self-reported alcohol use phenotypes are, of course, subject to biases and errors in reporting; however, there is no clear alternative to self-report for measuring alcohol use in the “real world” in humans. It would be interesting for future research to examine the relation between sleep and alcohol using ecological momentary assessment technologies,<sup>74</sup> which can yield data less subject to retrospective recall biases. Increased frequency of alcohol use was not associated with genetic propensity toward diurnal eveningness. This suggests that frequency of alcohol use represents a different aspect of alcohol consumption than the potentially more problematic constructs of increased quantity and bingeing which imply a lack of control of alcohol use. Lastly, diurnal preference was assigned based on a single measure, but it may represent a developmental state more than a trait. However, our analysis was age adjusted to account for this issue.

## CONCLUSIONS

To our knowledge, this is the first study to show that genetic factors favoring evening-type diurnal preference confer increased risk of unhealthy phenotypes, namely binge drinking and increased alcohol consumption. This finding suggests that biological differences in circadian rhythm may be an important pathway of risk for genetic factors that promote alcohol use. It also provides further evidence that evening-type diurnal preference is an endophenotype of poor health. From a societal perspective, adjustment of school and work times to be more tolerant of evening-type diurnal preference may pay dividends at the public health level.

## REFERENCES

- Borbély AA. A two-process model of sleep regulation. *Human Neurobiol* 1982;1:195-204.
- Kleitman N. *Sleep and wakefulness*. Chicago: Chicago University Press, 1963.
- Barclay NL, Gregory AM. Quantitative genetic research on sleep: A review of normal sleep, sleep disturbances and associated emotional, behavioural, and health-related difficulties. *Sleep Med Rev* 2012;17:29-40.
- Archer SN, Robilliard DL, Skene DJ, et al. A length polymorphism in the circadian clock gene *per3* is linked to delayed sleep phase syndrome and extreme diurnal preference. *Sleep* 2003;26:413-5.
- Barclay NL, Eley TC, Buysse DJ, Archer SN, Gregory AM. Diurnal preference and sleep quality: Same genes? A study of young adult twins. *Chronobiol Int* 2010;27:278-96.
- Hur Y. Stability of genetic influence on morningness-eveningness: A cross-sectional examination of South Korean twins from preadolescence to young adulthood. *J Sleep Res* 2007;16:17-23.
- Hur Y, Bouchard TJ, Lykken DT. Genetic and environmental influence on morningness-eveningness. *Pers Individ Dif* 1998;25:917-25.
- Jones KHS, Ellis J, Von Schantz M, Skene DJ, Dijk DJ, Archer SN. Age-related change in the association between a polymorphism in the *per3* gene and preferred timing of sleep and waking activities. *J Sleep Res* 2007;16:12-6.
- Koskenvuo M, Hublin C, Partinen M, Heikkilä K, Kaprio J. Heritability of diurnal type: A nationwide study of 8753 adult twin pairs. *J Sleep Res* 2007;16:156-62.
- Pereira DS, Tufik S, Louzada FM. Association of the length polymorphism in the human *per3* gene with the delayed sleep-phase syndrome: Does latitude have an influence upon it? *Sleep* 2005;29:32.
- Vink JM, Groot AS, Kerkhof GA, Boomsma DI. Genetic analysis of morningness and eveningness. *Chronobiol Int* 2001;18:809-22.
- Watson NF, Buchwald D, Noonan C, Vitiello MV, Pack AI, Goldberg J. Is circadian type associated with sleep duration in twins? *Sleep Biol Rhythms* 2012;10:61-8.
- Portaluppi F, Tiseo R, Smolensky MH, Hermida RC, Ayala DE, Fabbian F. Circadian rhythms and cardiovascular health. *Sleep Med Rev* 2012;16:151-66.
- Puttonen S, Harma M, Hublin C. Shift work and cardiovascular disease - pathways from circadian stress to morbidity. *Scand J Work Environ Health* 2010;36:96-108.
- Vyas MV, Garg AX, Iansavichus AV, et al. Shift work and vascular events: Systematic review and meta-analysis. *BMJ* 2012;345:e4800.
- Menegaux F, Truong T, Anger A, et al. Night work and breast cancer: A population-based case-control study in France (the CECILE study). *Int J Cancer* 2012;132:924-31.
- Monsees GM, Kraft P, Hankinson SE, Hunter DJ, Schernhammer ES. Circadian genes and breast cancer susceptibility in rotating shift workers. *Int J Cancer* 2012;131:2547-52.
- Savvidis C, Koutsilieris M. Circadian rhythm disruption in cancer biology. *Mol Med* 2012;18:1249-60.
- Bonzini M, Palmer KT, Coggon D, Carugno M, Cromi A, Ferrario MM. Shift work and pregnancy outcomes: A systematic review with meta-analysis of currently available epidemiological studies. *BJOG* 2011;118:1429-37.
- Rocheleau CM, Lawson CC, Whelan EA, Rich-Edwards JW. Shift work and adverse pregnancy outcomes: Comments on a recent meta-analysis. *BJOG* 2012;119:378; author reply 379-80.
- Kanerva N, Kronholm E, Partonen T, et al. Tendency toward eveningness is associated with unhealthy dietary habits. *Chronobiol Int* 2012;29:920-7.
- Kitamura S, Hida A, Watanabe M, et al. Evening preference is related to the incidence of depressive states independent of sleep-wake conditions. *Chronobiol Int* 2010;27:1797-812.
- Delgado Prieto P, Diaz-Morales JF, Escibano BC, Collado Mateo MJ, Randler C. Morningness-eveningness and health-related quality of life among adolescents. *Span J Psychol* 2012;15:613-23.
- Ayas NT, White DP, Al-Delaimy WK, et al. A prospective study of self-reported sleep duration and incident diabetes in women. *Diabetes Care* 2003;26:380-4.
- Ayas NT, White DP, Manson JE, et al. A prospective study of sleep duration and coronary heart disease in women. *Arch Intern Med* 2003;163:205-9.
- Eguchi K, Hoshida S, Ishikawa S, Shimada K, Kario K. Short sleep duration is an independent predictor of stroke events in elderly hypertensive patients. *J Am Soc Hypertens* 2010;4:255-62.
- Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Short sleep duration as a risk factor for hypertension: Analyses of the first national health and nutrition examination survey. *Hypertension* 2006;47:833-9.
- Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Sleep duration as a risk factor for diabetes incidence in a large U.S. sample. *Sleep* 2007;30:1667-73.
- Gottlieb DJ, Redline S, Nieto FJ, et al. Association of usual sleep duration with hypertension: The sleep heart health study. *Sleep* 2006;29:1009-14.
- Hublin C, Partinen M, Koskenvuo M, Kaprio J. Sleep and mortality: A population-based 22-year follow-up study. *Sleep* 2007;30:1245-53.
- Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. *Arch Gen Psychiatry* 2002;59:131-6.
- Mullington JM, Simpson NS, Meier-Ewert HK, Haack M. Sleep loss and inflammation. *Best Pract Res Clin Endocrinol Metab* 2010;24:775-84.
- Watson NF, Buchwald D, Vitiello MV, Noonan C, Goldberg J. A twin study of sleep duration and body mass index. *J Clin Sleep Med* 2010;6:11-7.
- Zizi F, Jean-Louis G, Brown CD, Ogedegbe G, Boutin-Foster C, McFarlane SI. Sleep duration and the risk of diabetes mellitus: Epidemiologic evidence and pathophysiologic insights. *Curr Diab Rep* 2010;10:43-7.
- Adan A. Chronotype and personality factors in the daily consumption of alcohol and psychostimulants. *Addiction* 1994;89:455-62.
- Onyper SV, Thacher PV, Gilbert JW, Graddess SG. Class start times, sleep, and academic performance in college: A path analysis. *Chronobiol Int* 2012;29:318-35.
- Urban R, Magyarodi T, Rigo A. Morningness-eveningness, chronotypes and health-impairing behaviors in adolescents. *Chronobiol Int* 2011;28:238-47.
- Gamble KL, Motesinger-Reif AA, Hida A, et al. Shift work in nurses: Contribution of phenotypes and genotypes to adaptation. *PLoS One* 2011;6:e18395.



39. Gurpegui M, Jurado D, Luna JD, Fernandez-Molina C, Moreno-Abril O, Galvez R. Personality traits associated with caffeine intake and smoking. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;31:997-1005.
40. Hsu CY, Gau SS, Shang CY, Chiu YN, Lee MB. Associations between chronotypes, psychopathology, and personality among incoming college students. *Chronobiol Int* 2012;29:491-501.
41. Le Bon O, Basiaux P, Streel E, et al. Personality profile and drug of choice: a multivariate analysis using cloninger's tci on heroin addicts, alcoholics, and a random population group. *Drug Alcohol Depend* 2004;73:175-82.
42. Torgersen S. The determination of twin zygosity by means of a mailed questionnaire. *Acta Genet Med Gemellol (Roma)* 1979;28:225-36.
43. Eisen S, Neuman R, Goldberg J, Rice J, True W. Determining zygosity in the vietnam era twin registry: An approach using questionnaires. *Clin Genet* 1989;35:423-32.
44. Watson NF, Goldberg J, Arguelles L, Buchwald D. Genetic and environmental influences on insomnia, daytime sleepiness, and obesity in twins. *Sleep* 2006;29:645-9.
45. Strachan E, Hunt C, Afari N, et al. University of Washington Twin Registry: Poised for the next generation of twin research. *Twin Res Hum Genet* 2013;16:455-62.
46. Adan A, Almirall H. Horne and ostberg morningness-eveningness questionnaire: A reduced scale. *Pers Individ Dif* 1991;12:241-53.
47. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol* 1976;4:97-110.
48. Chelminski I, Petros TV, Plaud JJ, Ferraro R. Psychometric properties of the reduced horne and ostberg questionnaire. *Pers Individ Dif* 2000;29:469-78.
49. Neale MC, Maes HHM. *Methodology for genetics studies of twins and families*. Dordrecht, The Netherlands: Kluwer Academic, 2004.
50. Schafer JL, Graham JW. Missing data: Our view of the state of the art. *Psychol Methods* 2002;7:147.
51. Hu LT, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Struct Equ Modeling* 1999;6:1-55.
52. Kuna ST, Maislin G, Pack FM, Staley B, Hachadoorian R, Coccato EF, Pack AL. Heritability of performance deficit accumulation during acute sleep deprivation in twins. *Sleep* 2012;35:1223-33.
53. Giannotti F, Cortesi F, Sebastiani T, Ottaviano S. Circadian preference, sleep and daytime behaviour in adolescence. *J Sleep Res* 2002;11:191-9.
54. Roenneberg T, Wirz-Justice A, Merrow M. Life between clocks: Daily temporal patterns of human chronotypes. *J Biol Rhythms* 2003;18:80-90.
55. Taillard J, Philip P, Coste O, Sagaspe P, Bioulac B. The circadian and homeostatic modulation of sleep pressure during wakefulness differs between morning and evening chronotypes. *J Sleep Res* 2003;12:275-82.
56. Mecacci L, Rocchetti G. Morning and evening types: Stress-related personality aspects. *Personal Individ Dif* 1998;25:537-42.
57. Chelminski I, Ferraro FR, Petros TV, Plaud JJ. An analysis of the "eveningness-morningness" dimension in "depressive" college students. *J Affect Disord* 1999;52:19-29.
58. Takeuchi H, Morisane H, Iwanaga A, Hino N, Matsuoka A, Harada T. Morningness-eveningness preference and mood in japanese junior high school students. *Psychiatry Clin Neurosci* 2002;56:227-8.
59. Taillard J, Philip P, Bioulac B. Morningness/eveningness and the need for sleep. *J Sleep Res* 1999;8:291-5.
60. Steinhausen HC, Metzke CW. Frequency and correlates of substance use among preadolescents and adolescents in a swiss epidemiological study. *J Child Psychol Psychiatry* 1998;39:387-97.
61. National Institute on Drug Abuse. <http://www.drugabuse.gov/related-topics/trends-statistics#costs>. Accessed 3/11/2013.
62. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 2009;373:2223-33.
63. Albrecht U. Invited review: Regulation of mammalian circadian clock genes. *J Appl Physiol* 2002;92:1348-55.
64. Yan J, Wang H, Liu Y, Shao C. Analysis of gene regulatory networks in the mammalian circadian rhythm. *PLoS Comput Biol* 2008;4:e1000193.
65. Mendlewicz J. Disruption of the circadian timing systems: Molecular mechanisms in mood disorders. *CNS Drugs* 2009;23 Suppl 2:15-26.
66. Artoli P, Lorenzi C, Pirovano A, Serretti A, Benedetti F, Catalano M, Smeraldi E. How do genes exert their role? Period 3 gene variants and possible influences on mood disorder phenotypes. *Eur Neuropsychopharmacol* 2007;17:587-94.
67. Partonen T, Treutlein J, Alpmann A, et al. Three circadian clock genes *per2*, *arntl*, and *npas2* contribute to winter depression. *Ann Med* 2007;39:229-38.
68. Takao T, Tachikawa H, Kawanishi Y, Mizukami K, Asada T. Clock gene *t3111c* polymorphism is associated with japanese schizophrenics: A preliminary study. *Eur Neuropsychopharmacol* 2007;17:273-6.
69. Pettinati HM, O'Brien CP, Dundon WD. Current status of co-occurring mood and substance use disorders: A new therapeutic target. *Am J Psychiatry* 2013;170:23-30.
70. Laucht M, Treutlein J, Schmid B, et al. Impact of psychosocial adversity on alcohol intake in young adults: Moderation by the *ll* genotype of the serotonin transporter polymorphism. *Biol Psychiatry* 2009;66:102-9.
71. Monti JM. Serotonin control of sleep-wake behavior. *Sleep Med Rev* 2011;15:269-81.
72. Lu BS, Zee PC. Neurobiology of sleep. *Clin Chest Med* 2010;31:309-18.
73. Martin SK, Eastman CI. Sleep logs of young adults with self-selected sleep times predict the dim light melatonin onset. *Chronobiol Int* 2002;19:695-707.
74. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. *Annu Rev Clin Psychol* 2008;4:1-32.

## SUBMISSION & CORRESPONDENCE INFORMATION

**Submitted for publication April, 2013**

**Submitted in final revised form June, 2013**

**Accepted for publication August, 2013**

Address correspondence to: Nathaniel F. Watson, M.D., M.Sc., University of Washington Medicine Sleep Center, Box 359803, 325 Ninth Avenue, Seattle, WA 98104-2499; Tel: (206) 744-4337; Fax (206) 744-5657; E-mail: [nwatson@uw.edu](mailto:nwatson@uw.edu)

## DISCLOSURE STATEMENT

This was not an industry supported study. This study was funded by K23 HL083350 and RC2 HL103416 from the National Heart, Lung, and Blood Institute and by a University of Washington General Clinical Research Center Pilot Grant. This work was performed at the University of Washington and the University of Texas. The authors have indicated no financial conflicts of interest.



# Treatment of Cataplexy in a Three-Year-Old Using Venlafaxine

Michelle Ratkiewicz, D.O.; Mark Splaingard, M.D., F.A.A.S.M.

*Division of Pulmonary Medicine, Nationwide Children's Hospital, Columbus, OH*

Narcolepsy with cataplexy is rare in children under 5 years of age. There is limited information on safe and effective treatment of cataplexy in young children. We describe successful treatment of cataplexy in a 3-year-old using venlafaxine and subsequently followed for over 2 years.

**Keywords:** Cataplexy, toddler, venlafaxine

**Citation:** Ratkiewicz M; Splaingard M. Treatment of cataplexy in a three-year-old using venlafaxine. *J Clin Sleep Med* 2013;9(12):1341-1342.

Narcolepsy with cataplexy is an uncommon disorder in the general population, but is exceedingly rare in children under 5 years of age. In a database review of over 1200 cases, only 2.1% of patients had onset of symptoms of narcolepsy prior to 5 years of age, and even fewer (1.1%) had cataplexy.<sup>1</sup> Venlafaxine, a serotonin and noradrenaline reuptake inhibitor, has been used to treat a variety of disorders including cataplexy in older children and adults, ADHD and autism spectrum disorders.<sup>2,3</sup> We report the successful use of venlafaxine to treat cataplexy in a 3-year-old boy.

## REPORT OF CASE

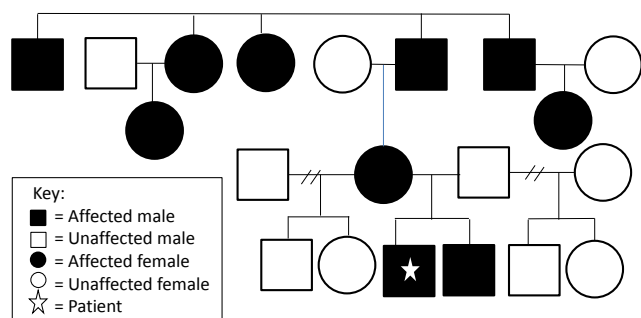
This 6-year-old boy was first evaluated at 7 months of age for suspected cataplexy. His mother, who has narcolepsy with cataplexy diagnosed at 10 years of age, reported that he developed a "head drop" only when he was tickled by his father. Several attempts to elicit a cataplexy event in the clinic were unsuccessful. Observation was recommended due to limited symptoms and age. As a toddler, he slept a minimum of 12 hours each night. Family history (see **Figure 1**) was remarkable for numerous family members with narcolepsy with cataplexy. His evaluation at 2 years of age included a brain MRI, which showed enlarged symmetric ventricles without evidence of obstruction, and an otherwise structurally normal brain. Polysomnogram and an extended montage video electroencephalogram (EEG) done with tickling was normal. By age 3, daily episodes of "head nodding" occurred when he laughed on the playground at preschool. Subsequently, an episode of cataplexy was precipitated with tickling in the clinic that was videotaped. Initial therapy was venlafaxine 5 mg (0.34 mg/kg) daily in the morning. A compounded liquid suspension was used to provide accurate dosing. One week later symptoms were unchanged, so his dose was increased to 6 mg daily (0.41 mg/kg/day). The frequency of cataplexy was then reduced to only 2 episodes over a 3-week period, and no adverse effects were observed. His dosage was then increased to 7 mg daily (0.47 mg/kg) and at a clinic visit 1 month later, he had not had any episodes

of cataplexy. At subsequent clinic visits over the following 2 years, he continued to do well without any episodes of cataplexy and no adverse effects of the medication. His dose was adjusted for weight to maintain a dose of 0.4 mg/kg/day. His growth remained at the 25<sup>th</sup> percentile for weight and length with normal developmental milestones, normal blood pressures, and no evidence of precocious puberty. Modified Epworth Sleepiness Scale score remains 11-13 and he continues to nap periodically without excessive daytime sleepiness. He was found to be HLA DQB1\*0602 positive. Mother refused lumbar puncture for hypocretin analysis. On his first MSLT, done recently at 6 years of age, while on venlafaxine, he slept during 5 out of 5 naps with a mean sleep onset latency of 8.3 minutes with 1 SOREM.

## DISCUSSION

This case demonstrates that venlafaxine is a well-tolerated and effective treatment for cataplexy in a young child. Similar findings in a group of six children between the ages of 7 and 12 have been reported. They all had a good response to therapy without significant adverse effects at doses between 37.5 mg and 150 mg per day, which are considerably higher than the dose required to achieve relief of symptoms in our patient, even when accounting for the difference in weight.<sup>5</sup> Aran and colleagues looked retrospectively at a variety of medications, including venlafaxine, to treat narcolepsy. In their study, continuation of venlafaxine was moderate and higher than fluoxetine, tricyclic antidepressants, or other selective serotonin reuptake inhibitors. They also found venlafaxine to be primarily helpful for cataplexy,<sup>1</sup> which is consistent with the effects experienced by our patient. Accurate dosing in a small child can be a challenge, as there is not a commercially available liquid suspension and the smallest tablet is 37.5 mg. A compounded liquid formulation is currently being prescribed for our patient, which has previously been shown to chemically stable for 15 days when refrigerated.<sup>4</sup> Based on our experience, venlafaxine can be used safely and efficaciously in young children with narcolepsy with cataplexy.

**Figure 1—Family pedigree of narcolepsy with cataplexy**



## REFERENCES

1. Aran A, Einen M, Lin L, et al. Clinical and therapeutic aspects of childhood narcolepsy-cataplexy: a retrospective study of 51 children. *Sleep* 2010;33:1457-64.
2. Hollander E, Kaplan A, Cartwright C, Reichman D. Venlafaxine in children, adolescents, and young adults with autism spectrum disorders: an open retrospective clinical report. *J Child Neurol* 2000;15:132-5.

3. Findling R, Greenhill L, McNamara N, et al. Venlafaxine in the treatment of children and adolescents with attention-deficit/ hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2007;17:433-45.
4. Kervela J, Castagnet S, Chiadmi F, et al. Assessment of stability in extemporaneously prepared venlafaxine solutions. *Eur J Hosp Pharm* 2009;15:30-2.
5. Moller L, Ostergaard J. Treatment with venlafaxine in six cases of children with narcolepsy with cataplexy and hypnagogic hallucinations. *J Child Adolesc Psychopharmacol* 2009;19:197-201.

## SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication July, 2013

Submitted in final revised form July, 2013

Accepted for publication July, 2013

Address correspondence to: Michelle Ratkiewicz, D.O., Nationwide Children's Hospital, Division of Pulmonary Medicine, 700 Children's Drive, Columbus, Ohio 43205; Tel: (614) 722-4766; Fax: (614) 722-4755; E-mail: Michelle.ratkiewicz@nationwidechildrens.org

## DISCLOSURE STATEMENT

This was not an industry supported study. The child described in the case was evaluated in the Sleep Clinic at Nationwide Children's Hospital. The authors have indicated no financial conflicts of interest.



## Does the Clinical Phenotype of Fatal Familial Insomnia Depend on *PRNP* codon 129 Methionine-Valine Polymorphism?

Sven Rupperecht, M.D.<sup>1,2</sup>; Alexander Grimm, M.D.<sup>1</sup>; Torsten Schultze, B.A.<sup>1</sup>; Jan Zinke, M.D.<sup>1</sup>; Panagiota Karvouniari, M.D.<sup>1</sup>; Hubertus Axer, M.D., Ph.D.<sup>1</sup>; Otto W. Witte, M.D., Ph.D.<sup>1,2</sup>; Matthias Schwab, M.D., Ph.D.<sup>1</sup>

<sup>1</sup>Hans-Berger-Department of Neurology, Jena University Hospital, Germany;

<sup>2</sup>Center for Sepsis Control and Care, Jena University Hospital, Germany

CASE REPORTS

Fatal familial insomnia (FFI) is a rare, hereditary prion-protein disease. Methionine-valine polymorphism at codon 129 of the prion-protein gene (*PRNP*) determines the phenotype in other hereditary prion-protein diseases, but association with the clinical phenotype in FFI remains uncertain.

Early clinical findings in FFI comprise disturbances of the sleep-wake cycle and mild neuropsychiatric changes which typically emerge during middle to late adulthood. Here we describe an unusually early onset and rapid progression of FFI associated with dorsal midbrain involvement in a female patient with *PRNP* mutation at codon 178 and homozygote methionine polymorphism at codon 129. Early dorsal midbrain involvement became apparent by total loss of REM sleep and isolated bilateral trochlear nerve palsy.

Early onset and rapid progression disease type associated with dorsal midbrain involvement may indicate a different spatiotemporal distribution of the neurodegenerative process in FFI patients with *PRNP* mutation and codon 129 methionine homozygosity compared to methionine-valine heterozygosity.

**Keywords:** Fatal familial insomnia, methionine-valine polymorphism, trochlear palsy, thalamic degeneration, sleep regulation

**Citation:** Rupperecht S; Grimm A; Schultze T; Zinke J; Karvouniari P; Axer H; Witte OW; Schwab M. Does the clinical phenotype of fatal familial insomnia depend on *PRNP* codon 129 methionine-valine polymorphism? *J Clin Sleep Med* 2013;9(12):1343-1345.

Fatal familial insomnia (FFI) is a rare, autosomal-dominant inherited prion-protein (PrP) disease, which has been documented in 27 pedigrees worldwide. It is attributable to a *PRNP* missense-mutation at codon 178 and methionine-valine polymorphism at codon 129 on chromosome 20. FFI is always fatal and affects both sexes equally. Mean age at onset of disease is around 50 years, while the duration of the disease varies from 8 to 72 months. Early clinical features in FFI combine subtle disturbances of the sleep-wake cycle, sleep abnormalities such as loss of sleep spindles plus mild neuropsychiatric changes.<sup>1</sup>

*PRNP* codon 129 polymorphism determines clinical phenotype in other hereditary prion diseases such as familial Creutzfeldt-Jakob disease (fCJD) by modifying PrP conformation and protein-protein interaction. Genetic analysis for *PRNP* codon 129 polymorphism, however, were only carried out in less than the half of the published FFI cases.<sup>1</sup> Therefore it remains uncertain to which degree *PRNP* codon 129 polymorphism influences the clinical phenotype of FFI.

To contribute to elucidating the influence of methionine-valine polymorphism on clinical phenotype, we report a case with unusual early onset and rapid progression of FFI associated with early dorsal midbrain involvement in a patient with *PRNP* missense-mutation at codon 178 and homozygote methionine polymorphism at codon 129, indicating a different clinical phenotype in FFI patients with *PRNP* mutation and codon 129 methionine homozygosity compared to methionine-valine heterozygosity.

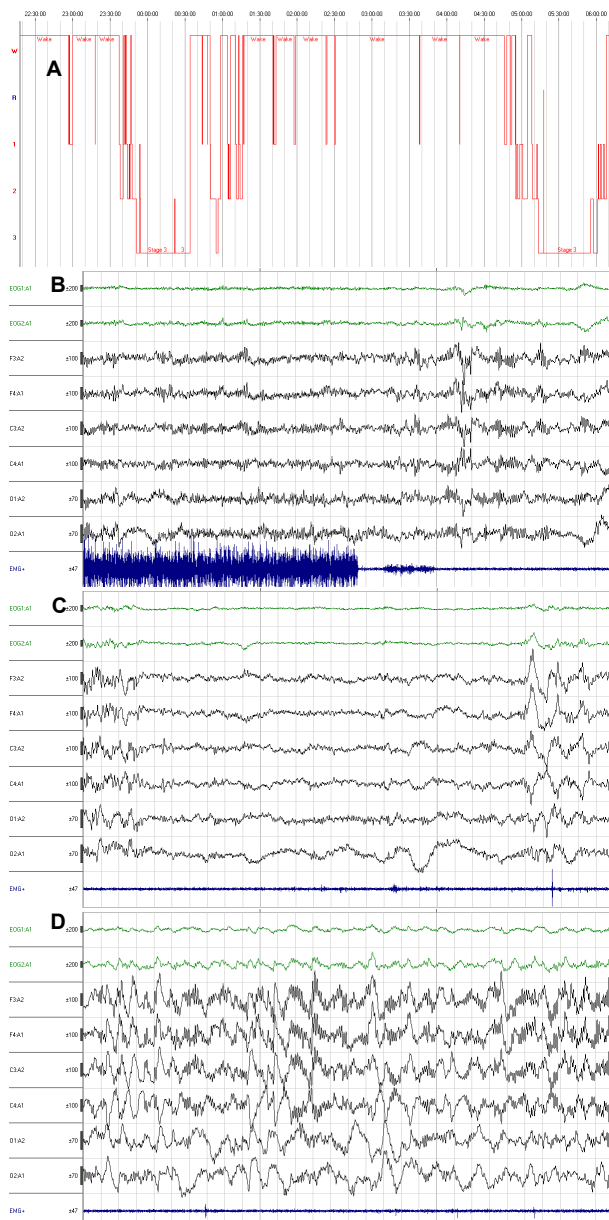
### REPORT OF CASE

A 23-year-old female, presented with double vision emerging when looking down and to the left and right. Neuroophthalmological examination showed superior oblique motility deficits on both sides indicative of bilateral trochlear nerve palsy. Apart from that neurological and neuropsychological examination was normal. Neurological work-up excluded neuromuscular, inflammatory, metabolic, or vascular disturbances. MRI scan of the brain was normal.

The patient's history revealed that the maternal grandfather and his brother died from suspected prion disease. Genetic analysis confirmed *PRNP* mutation at codon 178 and homozygote methionine polymorphism at codon 129 in our patient.

Polysomnographically, cyclic sleep organisation was replaced by rapid alternations between wakefulness and sleep stage NREM 1/2 interrupted delta sleep (**Figure 1**). REM sleep and sleep spindles were not detectable at all (**Figure 1**). Within 3 months, the patient developed the typical FFI features, including pronounced disturbances in sleep-wake cycle, cognitive decline, autonomic hyperactivity, and extrapyramidal motor symptoms. <sup>18</sup>F-FDG-PET revealed now bilateral thalamic and frontoparietal accentuated cortical hypometabolism (**Figure 2**) accompanied by frontoparietal cortical atrophy on the corresponding CT. Cerebrospinal fluid analysis was normal including normal levels of 14-3-3 protein. The patient died 5 months later due to respiratory failure. Autopsy was not performed.

**Figure 1**—Overnight sleep profile (A) and representative polysomnographic 30-sec epochs including wake-sleep transition (B), NREM 2 (C) and delta sleep (D)

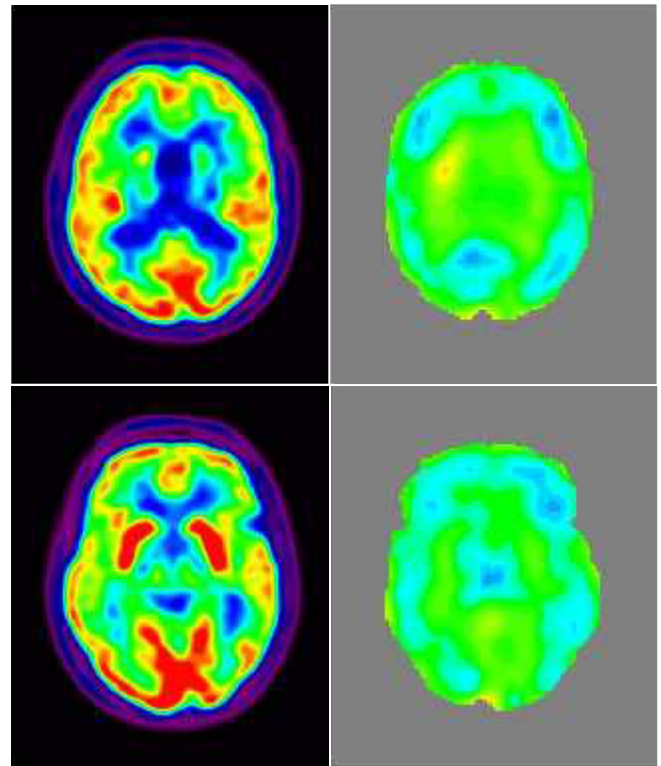


Sleep profile: Absence of cyclic sleep organization replaced by rapid alternations between wakefulness and sleep stage NREM 1/2 interrupted by preserved episodes of delta sleep. Wake-sleep transition: Initial awake EEG patterns characterized by symmetrical diffuse alpha activity replaced by low voltage mixed frequency theta activity in the second half of the epoch. NREM 2: Low voltage theta and superimposed alpha activity followed by a series of K-complexes. Sleep-spindles are not detectable. Delta Sleep: Diffuse polymorphic delta activity superimposed by alpha activity.

## DISCUSSION

Bilateral trochlear nerve palsy and loss of REM sleep are unusual early findings in FFI, highly indicative for dorsal midbrain involvement. Together with early onset and rapid disease

**Figure 2**— $^{18}\text{F}$ -FDG-PET of the brain



Reduced bilateral thalamic metabolism and widespread cortical hypometabolism with frontoparietal and left-hemispheric accentuation.

progression, this indicates a distinct FFI phenotype in patients with *PRNP* codon 129 homozygote methionine polymorphism.

Trochlear nuclei are located in the tegmental midbrain, and only dorsal midbrain lesions can affect trochlear nerves bilaterally.<sup>2</sup> REM sleep generating areas such as pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei are closely located to the trochlear nuclei. Lesions of the PPT and LDT nuclei reduce or even eliminate REM sleep without affecting NREM sleep in animal studies.<sup>3,4</sup>

Early neurodegenerative manifestation in FFI seems to be predominantly restricted to the thalamus and adjacent regions.<sup>1</sup> Loss of sleep spindles, indicative for thalamic involvement, was also present early in our patient. Presence of bilateral trochlear palsy combined with loss of REM sleep indicates concomitant affection of dorsal midbrain structures. Histopathological changes have also been described for dorsal midbrain structures in FFI, particularly in patients with short disease duration.<sup>1</sup> However, neuropathological midbrain involvement has not yet been linked to *PRNP* codon 129 polymorphism.<sup>1</sup>

In addition to midbrain manifestation, early onset and rapid disease progression were prominent features in our patient. In fCJD *PRNP* codon 129, polymorphism determines age of onset and progression of disease.<sup>5</sup> An association between *PRNP* codon 129 methionine homozygosity and short disease duration could also be demonstrated in FFI.<sup>1</sup>

FFI primarily manifest in middle to late adulthood. However, several FFI cases with onset of disease in early adulthood have recently been reported.<sup>6</sup> Together with our findings, this

indicates an association between early disease onset and *PRNP* codon 129 methionine homozygosity.

In agreement with previous studies detection of 14-3-3 protein in CSF, which is highly predictive in the diagnosis of other prion diseases, was negative in our patient. In fCJD, 14-3-3 protein levels depend on *PRNP* codon 129 polymorphism.<sup>7</sup> Such a linkage between 14-3-3 protein levels and *PRNP* codon 129 polymorphism has, however, not been systematically addressed in FFI.<sup>7</sup>

Taken together, our case supports the assumption of a distinct clinical phenotype in patients with *PRNP* codon 129 methionine homozygosity. Since FFI is a diagnostic challenge, clinicians should be aware of unusual clinical features and FFI needs to be considered in young patients with unclear neuropsychiatric symptoms.

## REFERENCES

1. Montagna P. Fatal familial insomnia and the role of the thalamus in sleep regulation. *Handb Clin Neurol* 2011;99:981-96.
2. Barr DB, McFadzean RM, Hadley D, Ramsay A, Houston CA, Russell D. Acquired bilateral superior oblique palsy: a localising sign in the dorsal midbrain. *Eur J Ophthalmol* 1997;7:271-6.
3. Shouse MN, Siegel JM. Pontine regulation of REM sleep components in cats: integrity of the pedunculopontine tegmentum (PPT) is important for phasic events but unnecessary for atonia during REM sleep. *Brain Res* 1992;571:50-63.

4. Webster HH, Jones BE. Neurotoxic lesions of the dorsolateral pontomesencephalic tegmentum-cholinergic cell area in the cat. II. Effects upon sleep-waking states. *Brain Res* 1988;458:285-302.
5. Gambetti P, Parchi P, Petersen RB, Chen SG, Lugaresi E. Fatal familial insomnia and familial Creutzfeldt-Jakob disease: clinical, pathological and molecular features. *Brain Pathol* 1995;5:43-51.
6. Harder A, Gregor A, Wirth T, et al. Early age of onset in fatal familial insomnia. Two novel cases and review of the literature. *J Neurol* 2004;251:715-24.
7. Ladogana A, Sanchez-Juan P, Mitrova E, et al. Cerebrospinal fluid biomarkers in human genetic transmissible spongiform encephalopathies. *J Neurol* 2009;256:1620-8.

## SUBMISSION & CORRESPONDENCE INFORMATION

**Submitted for publication April, 2013**

**Submitted in final revised form July, 2013**

**Accepted for publication July, 2013**

Address correspondence to: Sven Rupperecht, M.D., Hans-Berger-Department of Neurology, Jena University Hospital, Erlanger Alle 101, 07740 Jena, Germany; Tel: +49-3641-9-323480; Fax: +49-3641-9-323402; E-mail: Sven.Rupperecht@med.uni-jena.de

## DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.





## Alternobaric Vertigo in a Patient on Positive Airway Pressure Therapy

Andres Endara-Bravo, M.D.; Daniel Ahoubim, M.D.; Edward Mezerhane, M.D.; R. Alexandre Abreu, M.D., F.A.A.S.M.

*Sleep Medicine Program, University of Miami – Miller School of Medicine, Miami, FL*

Continuous positive airway pressure (CPAP) is a safe therapy for the management of obstructive sleep apnea (OSA). Complications such as sinus infection, bronchitis, ear pain, nasal congestion, and dryness of mucous membranes secondary to CPAP use have been reported. To follow, we describe a rare case of alternobaric vertigo secondary to CPAP therapy. To date, there has been only one reported case of hearing loss

and vertigo during CPAP treatment with complete resolution of symptoms after cessation of PAP. However, re-challenging the patient with CPAP at gradual increments was never reported.

**Keywords:** Alternobaric vertigo, CPAP, OSA

**Citation:** Endara-Bravo A; Ahoubim D; Mezerhane E; Abreu RA. Alternobaric vertigo in a patient on positive airway pressure therapy. *J Clin Sleep Med* 2013;9(12):1347-1348.

Continuous positive airway pressure (CPAP) is a safe therapy for the management of obstructive sleep apnea (OSA). Complications such as sinus infection, bronchitis, ear pain, nasal congestion, and dryness of mucous membranes secondary to CPAP use have been reported.<sup>1</sup> To follow, we describe a rare case of alternobaric vertigo secondary to CPAP therapy. To date, there has been only one reported case of hearing loss and vertigo during CPAP treatment with complete resolution of symptoms after cessation of PAP.<sup>2</sup> However, re-challenging the patient with CPAP at gradual increments was never reported.

### REPORT OF CASE

A 64-year-old Caucasian male with significant history of Parkinson disease and hypertension was diagnosed with moderate OSA, requiring CPAP at 12 cm H<sub>2</sub>O. During the initial night of PAP therapy, the patient complained of vertigo of short duration, which, associated with nausea and vomiting, caused him to wake up. Within a few minutes of discontinuing CPAP therapy, the patient experienced complete resolution of symptoms. He denied any history of similar symptoms in the past, including hearing loss and tinnitus, and his medical history was negative for allergic rhinitis or any recent incidence of upper airway respiratory infection. Physical examination revealed normal vital signs along with a body mass index of 31 kg/m<sup>2</sup>. Otologic examination showed normal tympanic membranes. Other than resting tremor, the physical exam was unremarkable, and magnetic resonance imaging of the inner auditory canals was normal. When CPAP at 12 cm H<sub>2</sub>O was re-commenced with the patient, vertigo once again returned, this time with greater duration. In an attempt to desensitize the effect of CPAP it was started at a lower pressure of 6 cm H<sub>2</sub>O, followed by slow increments of 1 cm H<sub>2</sub>O pressure at weekly intervals until the recommended pressure was reached without sequelae.

### DISCUSSION

Alternobaric vertigo is a frequently experienced sensation witnessed in the areas of aviation and diving. It occurs from the expansion of trapped air within the middle ear space due to the inability of the Eustachian tubes to equalize the middle ear pressure with ambient pressure. The positive middle ear pressure results in the sudden movement of the stapes at the oval window causing excess vestibular stimulation. The onset of vertigo is rapid and can have duration of between several seconds to a number of minutes. Symptoms resolve when the pressures in both ears reach ambient levels.<sup>3</sup> Precipitant factors for alternobaric vertigo include history of allergic rhinitis or recent upper airway infection, both of which conditions can affect the patency of the Eustachian tube.

The pathophysiology of alternobaric vertigo in PAP therapy is similar to the cases evidenced in aviation and diving. Vertigo occurs after interruption of PAP where the increased air pressure in the middle ear does not equalize to the ambient air, resulting in the presenting symptoms as described in the case above.

New-onset vertigo during initiation of PAP therapy should raise the suspicion of alternobaric vertigo. Starting PAP at lower pressures, with slow increments up to the desired pressure, was seen to be effective in relieving symptoms of vertigo secondary to PAP therapy.

### REFERENCES

1. Nino-Murcia G, McCann CC, Bliwise DL, Guilleminault C, Dement WC. Compliance and side effects in sleep apnea patients treated with nasal continuous positive airway pressure. *West J Med* 1989;150:165-9.
2. De Vega Gomez A, Corrales Zazuza M, Payo Losa F. Hypoacusis and vertigo as a side effect of the use continuous positive airway pressure (nasal CPAP) in obstructive sleep apnea syndrome (OSAS). *Arch Bronconeumol* 1998;34:228.
3. Brandt T. Vertigo, its multisensory syndromes, 2nd ed. London: Springer, 2003: 351-2.

## SUBMISSION & CORRESPONDENCE INFORMATION

**Submitted for publication May, 2013**

**Submitted in final revised form July, 2013**

**Accepted for publication July, 2013**

Address correspondence to: Andres S. Endara-Bravo, M.D.; Tel: (662) 415-5286;

E-mail: asendara@yahoo.com

## DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest. There was no investigational or off label use.

## Sleep and Pregnancy-Induced Hypertension: A Possible Target for Intervention?

Alyssa Haney, M.S.; Daniel J. Buysse, M.D., F.A.A.S.M.; Michele Okun, Ph.D.

University of Pittsburgh, Pittsburgh, PA

Sleep disturbances in the general population are associated with elevated blood pressure. This may be due to several mechanisms, including sympathetic activation and hypothalamic-pituitary-adrenal (HPA) axis disturbance. Elevated blood pressure in pregnancy can have devastating effects on both maternal and fetal health and is associated with increased risk for preeclampsia and poor delivery outcomes. Preliminary evidence suggests that mechanisms linking sleep and blood pressure in the general population may also hold in the pregnant population. However, the effects of disturbed sleep on physiologic mechanisms that may directly influence

blood pressure in pregnancy have not been well studied. The role that sleep disturbance plays in gestational blood pressure elevation and its subsequent consequences warrant further investigation. This review evaluates the current literature on sleep disturbance and elevated blood pressure in pregnancy and proposes possible treatment interventions.

**Keywords:** Sleep disturbance, blood pressure, pregnancy, hypertension, weight

**Citation:** Haney A; Buysse DJ; Okun M. Sleep and pregnancy-induced hypertension: a possible target for intervention? *J Clin Sleep Med* 2013;9(12):1349-1356.

The association between sleep disturbances and elevated blood pressure has been extensively studied in the general population. However, relatively few studies have investigated this relationship in the pregnant population. Pregnancy predisposes women to a variety of sleep disturbances.<sup>1,2</sup> Similar to non-pregnant individuals, sleep disturbance in pregnancy may be a risk factor for elevated blood pressure, which can lead to maternal and fetal morbidity.<sup>3,4</sup> Gestational hypertension, defined as a blood pressure higher than 140/90 diagnosed after 20 weeks of gestation, is associated with fetal growth restriction and abruptio placentae and can predispose to preeclampsia, as well as cardiovascular disease later in life.<sup>1,4-6</sup> There are few studies evaluating the link between sleep and blood pressure during pregnancy. In this paper, we first review the relationship between sleep and blood pressure in non-pregnant adults. We then outline factors that predispose pregnant women to poor sleep. We conclude with a review of the emerging literature on the associations between sleep and blood pressure in pregnancy.

### SLEEP AND BLOOD PRESSURE IN THE NON-PREGNANT POPULATION

In the U.S. the average sleep duration has decreased by 1.5-2 h/night, with > 30% of Americans sleeping < 6 h/night.<sup>7</sup> This phenomenon and the concurrent increase in hypertension intimated a possible link between sleep duration and blood pressure. Recently, a series of epidemiological papers have noted an association between sleep duration (both short and long) and elevated blood pressure<sup>8-11</sup>; for example, the Sleep Heart Health Study reported that participants who slept < 5 or ≥ 9 h/night had a greater frequency of hypertension than individuals sleeping

7 to 8 h/night.<sup>12</sup> Buxton et al. analyzed the 2004-2005 US National Health Interview Survey data (n = 56,507 observations, adults 18-85 years) and found those with short (< 7 h) and long (> 8 h) sleep were more likely to have elevated blood pressure than those sleeping 7 to 8 h/night.<sup>13</sup> These studies underscore the potential consequences of obtaining too little or too much sleep.

Similar to sleep duration, sleep quality is commonly evaluated. It can be ascertained directly with subjective methods or inferred from objective measures. Fiorentini et al., for instance, evaluated sleep quality in a cohort of hypertensive and type 2 diabetic participants. They found that poor sleep quality, defined by a Pittsburgh Sleep Quality Index score > 5, was more frequent among those with hypertension.<sup>14</sup> Knutson et al. examined the association between sleep quality, measured by actigraphy, and blood pressure in mid-life adults. They found that lower sleep quality, as indicated by sleep duration and sleep maintenance, was associated with higher systolic and diastolic blood pressure levels both cross-sectionally and longitudinally over 5 years.<sup>11</sup>

Hypertension is commonly thought to occur in mid-life or aging individuals. However, pre-hypertension and hypertension are rapidly rising in adolescents. It is possible that several health behaviors that originate in adolescence, including poor diet, smoking, and poor sleep, may increase the risk for prehypertension and an earlier development of hypertension.<sup>15,16</sup> This phenomenon could partly explain why adverse pregnancy outcomes, such as preeclampsia and gestational diabetes, are increasing despite advances in medical technology. Support for this hypothesis comes from Javaheri et al. who studied the sleep of 238 adolescents using actigraphy. They found that poor quality sleep, defined as sleep efficiency ≤ 85% or short

sleep duration ( $\leq 6.5$  h), was associated with elevated blood pressure. Specifically, they found that the odds of prehypertension increased 4.5-fold in adolescents who had low sleep efficiency and 2.8-fold for those with short sleep.<sup>17</sup> Taken together, these studies support the hypothesis that poor sleep quality, beginning much earlier in life than previously recognized, is associated with increased risk of developing hypertension and associated morbidities. They also suggest that early intervention may prove beneficial in reducing adverse health outcomes.<sup>15-17</sup>

In addition to associations with quantitative aspects of blood pressure, sleep disturbance has been associated with impaired nocturnal blood pressure dipping.<sup>18-20</sup> During normal sleep, blood pressure dips by 10% to 20%, in part due to a decrease in sympathetic output.<sup>21</sup> A nocturnal blood pressure dip  $< 10\%$  defines non-dipping. Several studies have shown that reduced blood pressure dipping during sleep is an indicator of cardiovascular disease.<sup>22-24</sup> Ohkubo and colleagues, for instance, studied 24-h ambulatory blood pressure in 1,542 Japanese adults  $> 40$  years of age, and followed them for an average 9.2 years. They found that for each 5% deficit in normal nocturnal dipping values, there was an associated 20% greater risk of developing cardiovascular disease.<sup>25</sup> This study highlights emerging evidence which indicates that nocturnal blood pressure may be a better predictor for cardiovascular risk than daytime blood pressure readings.<sup>26-28</sup> Reduced nocturnal blood pressure dipping can have significant immediate and future cardiovascular implications, including cognitive impairment and cerebrovascular disease.<sup>18-20,29,30</sup> Furthermore, since sleep disturbances, such as poor sleep quality, have been associated with blunted nocturnal blood pressure dipping, the clinical importance of assessing sleep as a potential risk factor for cardiovascular disease is substantially strengthened.<sup>19,20</sup>

Sleep disordered breathing (SDB), also referred to as obstructive sleep apnea (OSA), has a prevalence of up to 15% in the general population, and is even greater in obese (40%) and morbidly obese (70% to 90%) patients.<sup>31</sup> It is strongly associated with elevated blood pressure. In OSA, repeated episodes of partial or complete upper airway collapse lead to apneas (cessation of airflow for  $\geq 10$  sec, usually followed by an electroencephalographically measured arousal) or hypopneas (discernible reduction in airflow for 10 sec associated with an oxyhemoglobin desaturation of 4%). The apnea-hypopnea index (AHI), defined by the number of apneas or hypopneas per hour of sleep, describes disease severity. Mild OSA is defined as AHI of 5 to 15, moderate disease as AHI of 15 to 30, and severe disease as AHI  $> 30$ .<sup>31</sup> Episodes of apnea or hypopnea can cause hypoxia and result in frequent arousals, and thus sleep fragmentation. Repeated episodes of hypoxia and reoxygenation have also been shown to be associated with endocrine and metabolic disturbance, as well as elevated risk for metabolic syndrome and cardiovascular disease in OSA patients.<sup>5,6,32,33</sup> SDB has also been shown to be an independent risk factor for hypertension.<sup>34-36</sup> Indeed, treatment of SDB using positive airway pressure is associated with a reduction in incident hypertension and a significant improvement in hypertensive patients.<sup>37,38</sup> However, these relationships have not been observed universally.<sup>39</sup>

## PSYCHOSOCIAL CORRELATES OF SLEEP AND ELEVATED BLOOD PRESSURE

In addition to sleep disturbance, several psychosocial factors are recognized correlates of increased blood pressure. These factors may also exacerbate the occurrence and the negative consequences of sleep disturbance in pregnancy, similar to what has been observed in non-pregnant individuals.<sup>40,41</sup> Psychosocial stress, including occupational stress, social isolation, marital stress, and low socioeconomic status, have been associated with elevated blood pressure in the non-pregnant population.<sup>42-50</sup> The most commonly evaluated, however, is acute psychological stress. It has been postulated that stress and sleep disturbance interact to compound cardiovascular vulnerability.<sup>51</sup> A detailed examination of the role of psychosocial factors on sleep and blood pressure is beyond the scope of this review (see reviews<sup>20,52,53</sup>). Here, we merely highlight the importance of appreciating the complex relationships among these factors that may be particularly relevant during pregnancy.

The mechanisms that link sleep disturbances and elevated blood pressure are complex and involve several pathways. In OSA for example, nocturnal hypoxemia induces oxidative stress, inflammatory responses, and reduction in nitric oxide, which mediates vascular functions including dilatation and anticoagulation and has antioxidant properties.<sup>54</sup> Sleep disturbances have also been shown to increase sympathetic tone and hypothalamic-pituitary-adrenal axis function in experimental studies. Spiegel et al. found that experimentally induced short sleep (4 h) is associated with alterations in sympathovagal balance and 24-h salivary cortisol levels when compared to normal sleep (7-8 h).<sup>55</sup> Similar findings have been found in other experimental studies.<sup>56,57</sup> Sleep quality measures, including sleep latency and non-restorative sleep, have also been linked to metabolic and autonomic changes which have been associated with cardiovascular disease and hypertension.<sup>17,58</sup>

The relationship among cardiovascular changes, neuroendocrine changes, and sleep disturbance is not as clear. Tochikubo et al. found that in overtime workers, blood pressure, urinary norepinephrine levels, and sympathovagal disturbance (measured by heart rate variability) were higher on days after sleep restriction. However, sympathovagal disturbance was measured the evening after sleep restriction. Hence, this finding could have been due to increased stress due to sleepiness after a work day.<sup>59</sup> Additionally, Kato et al. described elevated blood pressure after sleep restriction, although they did not find significant changes in heart rate, forearm vascular resistance, or plasma catecholamines with sleep deprivation.<sup>60</sup> These studies show that although blood pressure appears to be directly influenced by sleep restriction, the exact mechanisms remain unclear.

## SLEEP DISTURBANCE IN PREGNANCY

Sleep disturbances are distinctly more common in pregnant than in non-pregnant women assessed from the general population. Okun and Coussons-Read examined sleep data collected at 12, 24, and 36 weeks' gestation from 35 pregnant and once from 43 comparable non-pregnant women. As early as 12 weeks, pregnant women reported an increased number of



**Table 1**—Physical and hormonal changes in pregnancy, subsequent symptoms, and effect on sleep

| Physical Changes                             | Symptom                                                                                          | Effect on Sleep                                                                               |
|----------------------------------------------|--------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Increasing uterine Size                      | Difficulty laying supine                                                                         | Sleep disruption; poor sleep quality                                                          |
| Hormone increases or Iron deficiency         | Restless legs syndrome (RLS)                                                                     | Difficulty falling asleep                                                                     |
| Decreased tone of lower esophageal sphincter | Predisposes to gastric reflux symptoms                                                           | Sleep disruption due to discomfort                                                            |
| Increased rate of micturition                | Increased renal blood flow; Dilation of ureters and renal pelvis; Uterine pressure on bladder    | Frequent nocturnal awakenings                                                                 |
| Hormonal Changes                             | Symptom                                                                                          | Effect on Sleep                                                                               |
| Increased estrogen                           | Decrease nasopharyngeal airway patency: Potential predisposition to OSA<br>Increase RLS symptoms | Sleep disruption via breathing occlusions. Changes in sleep architecture; decreases REM sleep |
| Increased progesterone                       | Increase minute ventilation; Increase nasopharyngeal muscle tone                                 | Altered sleep architecture Increases NREM sleep                                               |

References: 53, 65, 68, 72, 79

naps, nocturnal awakenings, time spent awake during the night, and poorer sleep quality than non-pregnant women.<sup>61</sup> Sleep in the pregnant women progressively worsened, with over 50% of the women meeting sleep criteria for insomnia by the end of pregnancy. Suzuki et al. found that among 192 pregnant women surveyed retrospectively, 88% had alterations in sleep compared with their usual experience.<sup>62</sup> The reported changes included insomnia, parasomnias (nightmares and night terrors), restless leg syndrome (RLS), snoring, and sleep apnea. Among the most frequent self-reported causes of sleep disturbance during pregnancy were urinary frequency, back or hip ache, and heartburn. Facco et al. investigated sleep during pregnancy in a prospective cohort of 189 women assessed at 2 points during pregnancy, with a mean baseline assessment of 13.8 ( $\pm$  3.8) weeks and a mean second assessment of 30.0 ( $\pm$  2.2) weeks. At the second assessment, sleep duration significantly decreased compared to baseline (7.4  $\pm$  1.2 h vs. 7.0  $\pm$  1.3), the number of participants who reported snoring increased (11% vs. 16.4%), incidence of restless leg syndrome increased (17.5% vs. 31.2%), and there was an increase of poor sleep quality as measured by Pittsburgh Sleep Quality Index > 5 (39.0% vs. 53.5%).<sup>36</sup>

In pregnancy, hormonal changes occur to ensure the survival of the fetus. However, these hormonal changes may result in substantial sleep disturbances.<sup>1</sup> By the last few weeks of pregnancy, daily estrogen production is one thousand times premenopausal ovulatory levels, and progesterone levels increase from 25 ng/mL at 6 weeks to 150 ng/mL at 37 weeks.<sup>64</sup> Estrogen reduces rapid eye movement sleep (REM) and progesterone reduces NREM sleep.<sup>1,65,66</sup> Estrogen can also cause physical changes that can affect sleep, including hyperemia, mucosal edema, hypersecretion, and increased friability in the upper airways. These changes result in reduction of nasopharyngeal airway patency, which can cause a sensation of nasal stuffiness and may exacerbate sleep disordered breathing in women with elevated body mass index.<sup>67</sup> Progesterone is thought to act via peripheral chemoreceptors and centrally in the medulla to increase respiratory drive.<sup>68</sup> This, in conjunction with greater metabolic carbon dioxide production and increased minute ventilation, can cause respiratory alkalosis, which can reduce

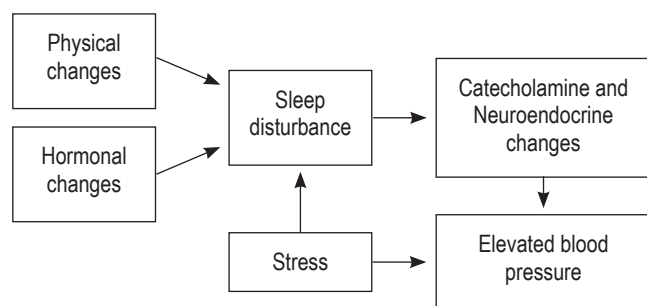
respiratory drive and predispose to central sleep apnea.<sup>1</sup> Furthermore, oxygen consumption is increased by approximately 20% to 33% by the third trimester due to fetal demands and changes in maternal metabolism. Increased oxygen consumption, along with a reduced functional residual capacity due to an enlarging uterus, results in a lowered oxygen reserve and can affect oxygen homeostasis more than in the non-pregnant state.<sup>1,69</sup> **Table 1** illustrates the major physical and hormonal changes in pregnancy that can affect sleep.

The dramatic physical changes unique to pregnancy can further affect sleep. The enlarging uterus can upwardly displace the diaphragm, further compromising functional residual capacity, which decreases by 10% to 25% at term. This, together with reduction in chest wall and total respiratory compliance, may lead many pregnant women to experience shortness of breath while lying supine. The inability to assume a comfortable sleeping position, especially during the third trimester of pregnancy, may have a significant impact on a pregnant woman's ability to initiate and maintain sleep.<sup>36</sup> Discomfort from back and leg cramps may also disrupt sleep. Lower esophageal sphincter tone decreases throughout pregnancy, reaching its lowest point in late pregnancy. Resulting gastroesophageal reflux can cause discomfort and sleep disruptions.<sup>70</sup> Additionally, renal blood flow increases in pregnancy throughout first and second trimester, along with dilation of the ureters and renal pelvises. These changes and the pressure of an enlarged uterus on the bladder cause pregnant women to wake several times per night to urinate.<sup>36</sup>

## SLEEP AND HYPERTENSION IN PREGNANCY

Elevated maternal blood pressure during pregnancy poses great risk for both mother and fetus. Approximately 10% of pregnancies are affected by hypertension. Consequences of pregnancy-related hypertension include increased risk of abruptio placentae, disseminated intravascular coagulation, cerebral hemorrhage, hepatic failure, and acute renal failure.<sup>5</sup> Furthermore, elevated blood pressure in pregnancy can be part of preeclampsia and eclampsia, which carry maternal mortality rates of 10% to 15%, and future risk for cardiovascular disease.<sup>4,71</sup>

**Figure 1**—Proposed model of how physical and hormonal changes in pregnancy coupled with stress result in disturbed sleep which can result in elevated blood pressure



Normative physical changes, such as changes in body habitus, and hormonal changes, including dramatic increases in estrogen and progesterone, are recognized contributors to sleep disturbance in pregnancy. Subsequent to the sleep disturbance are various catecholamine and neuroendocrine changes which can negatively impact blood pressure. Concurrent stress, whether daily hassles or serious life events, is both an independent and dependent modifier of blood pressure. These associations are critical throughout pregnancy as elevated blood pressure is linked with increased risk of preeclampsia and preterm birth.

Systolic and diastolic blood pressure normally fall in early pregnancy by 5–10 mm Hg, reaching a mean nadir of 105/60 mm Hg, and then gradually rise to pre-pregnancy values by term.<sup>72</sup> However, emerging evidence indicates that sleep disturbance may disrupt the normal course of gestational blood pressure changes. Williams et al. found that self-reported short ( $\leq 6$  h) and long ( $\geq 10$  h) sleep durations in early pregnancy (mean 14 weeks) were associated with elevated blood pressure, particularly mean third trimester blood pressures, in 1,272 women. Mean third trimester systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressure (MAP) for women who reported short early pregnancy sleep durations ( $\leq 6$  h) compared to normal sleep duration (9 h) were 3.72, 3.04, and 3.18 mm Hg higher, respectively, after adjustment for maternal age, race/ethnicity, parity, educational status, and pre-pregnancy body mass index. The differences in third trimester SBP, DBP, and MAP for women who reported long sleep durations ( $\geq 10$  h), compared with those reporting sleeping 9 h nightly, were 4.21, 3.43, and 3.65 mm Hg higher, respectively.<sup>3</sup> A similar conclusion was reached by Reid and colleagues who reported that women with gestational hypertension has less total sleep time, lower sleep efficiency, and a lower percentage of REM sleep than healthy pregnant women.<sup>73</sup> Although the mechanisms behind these differences are not clear, they may be similar to those that link short and long sleep durations with increased BP in the non-pregnant population.

Furthermore, as in the non-pregnant population, psychological stress may play a role in both sleep disturbance and blood pressure elevation.<sup>74</sup> Pregnancy can be a mentally taxing time for women, especially in those with concurrent stressful life events or psychosocial stress. Stress may further elevate blood pressure in pregnant women, similar to what has been observed in non-pregnant cohorts.<sup>40,41,74</sup> We propose that the hormonal and physical changes, as well as stress of pregnancy, induce

sleep disturbance and may result in blood pressure perturbations. **Figure 1** illustrates this model.

## SLEEP RELATED BREATHING DISORDERS IN PREGNANCY

SDB is characterized by abnormal respiratory patterns (e.g., apneas, hypopneas) or abnormal gas exchange (e.g., hypoxia). Sleep related breathing disorders like snoring and obstructive sleep apnea occur in pregnancy; however, there is little data detailing their incidence or prevalence. Most investigators agree that sleep related breathing disorders are more prevalent in pregnant women than non-pregnant women. As previously noted, estimates in non-pregnant women range from 2% to 5%, whereas estimates in pregnancy range from ~10% in early pregnancy to upwards of 30% in late pregnancy.<sup>67,75–78</sup> There is currently a paucity of objective data on the incidence of sleep related breathing disorders in pregnancy. Our current knowledge relies primarily on self-reported symptoms, including excessive daytime sleepiness, snoring, or breathing cessations, which suggest but do not confirm the presence of OSA. The development of SDB in pregnancy is considered a consequence of necessary physiologic adaptations that occur in pregnancy,<sup>79</sup> such as dramatic hormonal and subsequent physical changes. Estrogen, for instance, can cause upper airway narrowing and could predispose pregnant women to snore and develop SDB. Progesterone, on the other hand, increases minute ventilation, and the resulting respiratory alkalosis enhances sensitivity of the respiratory center to carbon dioxide in pregnancy, which may predispose to central sleep apnea.<sup>1</sup>

SDB, independent of maternal BMI, is associated with an increased risk of hypertension in pregnancy, as well as maternal morbidity.<sup>73,78,80–86</sup> In one study, preeclampsia, a hypertensive syndrome in pregnancy, was significantly more common among snorers than non-snorers (10% versus 4%,  $p < 0.05$ ), as was gestational hypertension (14% versus 6%,  $p < 0.01$ ).<sup>87</sup> This was recently corroborated in a report by O'Brien and colleagues, who found that pregnancy-onset snoring was independently associated with gestational hypertension (OR 2.36 [1.48–3.77],  $p < 0.001$ ) and preeclampsia (OR 1.59 [1.06–2.37],  $p = 0.024$ ) in 1,719 third-trimester pregnant women.<sup>78</sup> Another study reported that snoring and “excessive daytime sleepiness,” which could indicate poor sleep, were reported more commonly in later pregnancy in women with preeclampsia than those without preeclampsia or non-pregnant controls.<sup>88</sup> In a large cross-sectional study of immediately postpartum women, Perez-Chada et al. reported an increase in gestational hypertension and preeclampsia among those with symptoms of SDB even after adjusting for potential confounders such as BMI.<sup>89</sup> In a similar study, Bourjeily et al. adjusted for comorbid conditions and reported an increase in preeclampsia and gestational hypertension in women with SDB.<sup>90</sup> **Table 2** summarizes a series of studies that have examined the frequency and consequences of SDB in pregnancy.

## SIGNIFICANCE

Hypertensive disorders in pregnancy are prevalent and pose risk to both mother and child. Additionally, they can carry risk

**Table 2**—Selected listing of sleep disordered breathing (SDB) in pregnancy studies

| First Author               | Study Design                                                                                                                                                                    | Outcome Measures                                                                                                                              | Major Findings                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ayrim A <sup>83</sup>      | Cross sectional study of 200 pregnant and 200 age-matched controls. Epworth Sleepiness Scale (ESS) were assessed to determine excessive daytime sleepiness.                     | Gestational hypertension and snoring                                                                                                          | Excessive daytime sleepiness or snoring was associated with GH or other fetal outcomes.                                                                                                                                                                                                                                                                                       |
| Bourjeily G <sup>97</sup>  | Retrospective study with 1,000 postpartum women. SDB assessed by the Multivariable Apnoea Prediction Index Questionnaire.                                                       | Pregnancy and fetal outcomes in women with SDB                                                                                                | SDB symptoms were found to have higher likelihood of pregnancy-induced hypertension and preeclampsia (adjusted OR 2.3, 95% CI 1.4-4.0)                                                                                                                                                                                                                                        |
| Chen <sup>98</sup>         | Retrospective study of 791 pregnant women with OSA assessed by PSG, compared to 3,955 controls.                                                                                 | Birth outcome by OSA status                                                                                                                   | Women with OSA were more likely than controls to have preeclampsia (OR 1.60 [95% CI, 2.16-11.26]), low birth weight (OR 1.76 (95% CI, 1.28-2.40), preterm birth 2.31 (95% CI, 1.77-3.01), small for gestational age infants 1.34 (95% CI, 1.09-1.66), CS1.74 (95% CI, 1.48-2.04)                                                                                              |
| Connolly G <sup>99</sup>   | Case control prospective study of 15 women with preeclampsia and 15 without preeclampsia in each trimester. Both groups compared to 15 non-pregnant women                       | Inspiratory flow measured by nasal canula, pulse oximetry and abdominal belt based on pregnancy and preeclampsia status                       | Women with preeclampsia had more time with inspiratory flow limitation in the third trimester subjects than the other 2 groups (31% ± 8.4% of sleep period time vs. 15.5% ± 2.3% vs. < 5%) (p = 0.001)                                                                                                                                                                        |
| Facco F <sup>77</sup>      | Retrospective cohort study of 143 postpartum women. PSG assessed mild SDB in 34 and moderate to severe SDB in 26.                                                               | The association between SDB and adverse pregnancy outcome (pregnancy-related hypertension, gestational diabetes, or preterm birth ≤ 34 weeks) | Increasing severity of SDB was associated with increasing risk of adverse pregnancy outcome: AHI < 5, 18.1%; AHI 5 to 14.9, 23.5%; AHI ≥ 15, 38.5% (p = 0.038)                                                                                                                                                                                                                |
| Champagne K <sup>100</sup> | Case-control study comparing 17 pregnant women with GH and 33 without GH on frequency of PSG-assessed OSA.                                                                      | OSA defined by apnea/hypopnea index (AHI) ≥ 15 events per hour, without requirement for desaturation.                                         | Women with GH had greater AHI (38.6 ± 36.7) compared to normotensive women (18.2 ± 12.2).                                                                                                                                                                                                                                                                                     |
| Izci B <sup>67</sup>       | Prospective study of 100 third trimester women and 100 non-pregnant women. Upper airway dimensions and SDB symptoms were measured using acoustic reflection                     | Upper airway dimensions and SDB symptoms (snoring) in pregnant women versus non-pregnant women                                                | Snoring was more common in pregnant women (41%) versus non-pregnant women (17%) and then returned back to non pregnant levels (18%) post partum. Upper airway dimensions were also smaller in pregnant women as compared to non-pregnant and post-partum women.                                                                                                               |
| Louis JM <sup>84</sup>     | Retrospective study of 57 women with OSA and 114 healthy controls.                                                                                                              | Maternal morbidity and preterm birth                                                                                                          | OSA patient had more preeclampsia (19.3% vs 7.0%, p = 0.02) and preterm birth (29.8% vs 12.3%, p = 0.007). OSA was associated with increased risk for maternal morbidity as well (OR 4.6 (1.5-13.7).                                                                                                                                                                          |
| Maasilta P <sup>75</sup>   | Case control study of PSG-assessed SDB in obese pregnant women. Participants were 11 obese women (BMI, 34 kg/m <sup>2</sup> ) and 11 control women (BMI, 23 kg/m <sup>2</sup> ) | Occurrence of SDB in obese women during pregnancy                                                                                             | More SDB symptoms occurred in obese women compared to non-obese women. Apnea-hypopnea indexes (1.7 events/h vs 0.2 events/h; p < 0.05), 4% oxygen desaturations (5.3 events/h vs 0.3 events/h; p < 0.005), and snoring times (32% vs 1%, p < 0.001) were significantly different between the 2 groups.                                                                        |
| O'Brien L <sup>78</sup>    | Prospective study of 1,719 pregnant women in late pregnancy. Screening for presence and duration of habitual snoring                                                            | Clinical diagnosis of gestational hypertension, preeclampsia, and gestational diabetes                                                        | New-onset snoring during pregnancy is quite frequent (25%) and is associated with an increased risk of gestational hypertension (OR 2.36 [1.48-3.77, p < 0.001]) and preeclampsia (OR 1.59 [1.06-2.37], p = 0.024). There was no effect on gestational diabetes.                                                                                                              |
| Reid J <sup>73</sup>       | Cross-sectional comparison of self-reported sleep and PSG-assessed SDB in pregnant women with (34) and without (26) GH.                                                         | Presence of SDB in late pregnancy. Secondly reported on PSG-assessed sleep                                                                    | Women with GH have a higher frequency of SDB (53%) than healthy pregnant women (12%). This finding is confounded by obesity, which was significantly more frequent among women with GH. Women with GH also had less total sleep time (252 ± 81 min vs 311 ± 54 min, p = 0.003 and lower sleep efficiency (62% ± 19.5% vs 71.9% ± 10.3%, p = 0.003) compared to healthy women. |



for maternal morbidity later in life. Preeclampsia, especially if complicated by HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), predisposes to future cardiovascular disease.<sup>31</sup> A meta-analysis by Bellamy et al. found that women who developed gestational hypertension or preeclampsia had an increased risk of developing hypertension later in life. The relative risk of ischemic heart disease, stroke, and venous thromboembolism were also increased later in life in women with prior diagnoses of preeclampsia. Furthermore, Bellamy et al. found that women who developed preeclampsia had greater all-cause mortality risk compared to women who had normal blood pressure during pregnancy. This risk was even greater for women who developed preeclampsia before 37 weeks.<sup>71</sup> Kestenbaum et al. also found that gestational hypertension, mild and severe preeclampsia were associated with 2.8-fold higher risk of cardiovascular events, and that severe preeclampsia was associated with 2.3-fold higher risk of thromboembolic events.<sup>4</sup> Furthermore, hypertensive disorders in pregnancy are associated with poor fetal outcomes including preterm birth, small for gestational age infants, and abruptio placentae.<sup>5</sup> The delayed morbidity risk of hypertensive disorders, as well as the immediate risk to mother and fetus risk, only amplifies the need for better understanding and prevention.

## CONCLUSION

Elevated blood pressure in pregnancy can have devastating effects on both maternal and fetal health during the perinatal period and beyond. The causes of hypertensive syndromes in pregnancy like preeclampsia and gestational hypertension appear to be multifactorial. However, numerous studies demonstrate a strong link between sleep duration, quality or sleep related breathing disorders and blood pressure in non-pregnant adults; emerging studies suggest a similar relationship in the pregnant population. This link represents a possible source of preventative measures for gestational hypertension and preeclampsia. However, more complete understanding of the association between sleep and blood pressure in pregnancy is needed. Well-controlled, longitudinal studies with large cohorts and both objective and subjective sleep measurements are needed to better assess sleep in pregnancy and how it relates to blood pressure. These studies should include blood pressure measurements throughout pregnancy, as well as pregnancy outcomes, to assess the effect of sleep on both maternal and fetal health. Currently, screening for sleep disruption in pregnant women is not common practice. More knowledge and widespread understanding of the effects that sleep has on pregnancy may improve upon the obstetrician's ability to screen for those with sleep disruption and who may be at risk for hypertensive disorders. Utilization of short questionnaires, such as the Insomnia Symptom Questionnaire (ISQ),<sup>91</sup> could be incorporated into prenatal care to assist in the identification of those women at-risk for sleep problems. Emerging data suggests that a modest number of pregnant women have difficulty initiating sleep (DIS).<sup>92</sup> Given the associations between DIS and adverse health outcomes,<sup>93-95</sup> this may be an appropriate target for intervention. Early identification of at-risk women may allow for simple interventions, including counseling on the impacts of sleep on maternal and fetal health and prescribing behavioral

sleep regimens to not only improve sleep but potentially blood pressure as well. While there is currently a paucity of studies that have examined the impact of interventions on sleep in pregnant women, there is some evidence from a study of postpartum mothers that a behavioral-education intervention could be applied in pregnancy.<sup>96</sup> In this randomized controlled trial, women received intervention, which consisted of an in-person meeting with a nurse for sleep strategies, a booklet, and phone contacts, or usual care. Although there was no difference in the primary outcome of maternal nocturnal sleep, it is possible that the length of data collection or the measures used in the study were unable to capture the benefits of the intervention. It is probable, for instance, that improving sleep in the early postpartum is not feasible. Assessing the women further post-delivery may indicate otherwise.

## REFERENCES

1. Sahota PK, Jain SS, Dhand R. Sleep disorders in pregnancy. *Curr Opin Pulm Med* 2003;9:477-83.
2. Balserak BI, Lee K. Sleep Disturbances and sleep-related disorders in pregnancy. In: Kryger MH, Roth T, Dement WC, eds. *Principles and practice of sleep medicine*. 5th ed. St. Louis: Elsevier, 2011:1572-86.
3. Williams MA, Miller RS, Qiu C, Cripe SM, Gelaye B, Enquobahrie D. Associations of early pregnancy sleep duration with trimester-specific blood pressures and hypertensive disorders in pregnancy. *Sleep* 2010;33:1363-71.
4. Kestenbaum B, Seliger SL, Easterling TR, et al. Cardiovascular and thromboembolic events following hypertensive pregnancy. *Am J Kidney Dis* 2003;42:982-9.
5. Liu CM, Cheng PJ, Chang SD. Maternal complications and perinatal outcomes associated with gestational hypertension and severe preeclampsia in Taiwanese women. *J Formos Med Assoc* 2008;107:129-38.
6. Srinivas SK, Edlow AG, Neff PM, Sammel MD, Andrela CM, Elovitz MA. Rethinking IUGR in preeclampsia: dependent or independent of maternal hypertension? *J Perinatol* 2009;29:680-4.
7. Luckhaupt SE. Short sleep duration among workers- United States, 2010. 2012.
8. Cappuccio FP, Stranges S, Kandala NB, et al. Gender-specific associations of short sleep duration with prevalent and incident hypertension: the Whitehall II Study. *Hypertension* 2007;50:693-700.
9. Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. *Hypertension* 2006;47:833-9.
10. Kim J, Jo I. Age-dependent association between sleep duration and hypertension in the adult Korean population. *Am J Hypertens* 2010;23:1286-91.
11. Knutson KL, Van CE, Rathouz PJ, et al. Association between sleep and blood pressure in midlife: the CARDIA sleep study. *Arch Intern Med* 2009;169:1055-61.
12. Gottlieb DJ, Redline S, Nieto FJ, et al. Association of usual sleep duration with hypertension: the Sleep Heart Health Study. *Sleep* 2006;29:1009-14.
13. Buxton OM, Marcelli E. Short and long sleep are positively associated with obesity, diabetes, hypertension, and cardiovascular disease among adults in the United States. *Soc Sci Med* 2010;71:1027-36.
14. Fiorentini A, Valente R, Perciaccante A, Tubani L. Sleep's quality disorders in patients with hypertension and type 2 diabetes mellitus. *Int J Cardiol* 2007;114:E50-2.
15. Countryman AJ, Saab PG, Llabre MM, Penedo FJ, McCalla JR, Schneiderman N. Cardiometabolic risk in adolescents: associations with physical activity, fitness, and sleep. *Ann Behav Med* 2013;45:121-31.
16. Narang I, Manhiot C, Davies-Shaw J, et al. Sleep disturbance and cardiovascular risk in adolescents. *CMAJ* 2012;184:E913-20.
17. Javaheri S, Storer-Isser A, Rosen CL, Redline S. Sleep quality and elevated blood pressure in adolescents. *Circulation* 2008;118:1034-40.
18. Sherwood A, Routledge FS, Wohlgemuth WK, Hinderliter AL, Kuhn CM, Blumenthal JA. Blood pressure dipping: ethnicity, sleep quality, and sympathetic nervous system activity. *Am J Hypertens* 2011;24:982-8.
19. Loreda JS, Nelesen R, Ancoli-Israel S, Dimsdale JE. Sleep quality and blood pressure dipping in normal adults. *Sleep* 2004;27:1097-103.
20. Matthews KA, Kamarck TW, Hall H, et al. Blood pressure dipping and sleep disturbance in African-American and Caucasian men and women. *Am J Hypertens* 2008;21:826-31.



21. Calhoun DA, Harding SM. Sleep and hypertension. *Chest* 2010;138:434-43.
22. Dolan E, Stanton AV, Thom S, et al. Ambulatory blood pressure monitoring predicts cardiovascular events in treated hypertensive patients—an Anglo-Scandinavian cardiac outcomes trial substudy. *J Hypertens* 2009;27:876-85.
23. Kario K, Pickering TG, Matsuo T, Hoshida S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension* 2001;38:852-7.
24. Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Predictors of all-cause mortality in clinical ambulatory monitoring: unique aspects of blood pressure during sleep. *Hypertension* 2007;49:1235-41.
25. Ohkubo T, Hozawa A, Nagai K, et al. Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: the Ohasama study. *J Hypertens* 2000;18:847-54.
26. Dolan E, Stanton A, Thijs L, et al. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension* 2005;46:156-61.
27. Pedersen OL, Mancia G, Pickering T, et al. Ambulatory blood pressure monitoring after 1 year on valsartan or amlodipine-based treatment: a VALUE substudy. *J Hypertens* 2007;25:707-12.
28. Salles GF, Cardoso CR, Muxfeldt ES. Prognostic influence of office and ambulatory blood pressures in resistant hypertension. *Arch Intern Med* 2008;168:2340-6.
29. Barksdale DJ, Woods-Giscombe C, Logan JG. Stress, cortisol, and nighttime blood pressure dipping in nonhypertensive black American women. *Biol Res Nurs* 2013;15:330-7.
30. Yano Y, Kario K. Nocturnal blood pressure, morning blood pressure surge, and cerebrovascular events. *Curr Hypertens Rep* 2012;14:219-27.
31. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;342:1378-84.
32. Punjabi NM, Beamer BA. Alterations in glucose disposal in sleep-disordered breathing. *Am J Respir Crit Care Med* 2009;179:235-40.
33. Hu FB, Willett WC, Colditz GA, et al. Prospective study of snoring and risk of hypertension in women. *Am J Epidemiol* 1999;150:806-16.
34. Goncalves SC, Martinez D, Gus M, et al. Obstructive sleep apnea and resistant hypertension: a case-control study. *Chest* 2007;132:1858-62.
35. Logan AG, Perlikowski SM, Mente A, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *J Hypertens* 2001;19:2271-7.
36. Facco FL, Kramer J, Ho KH, Zee PC, Grobman WA. Sleep disturbances in pregnancy. *Obstet Gynecol* 2010;115:77-83.
37. Bottini P, Taranto-Montemurro L, Novali M, et al. Effects of CPAP on systemic hypertension in OSAH: a monocentric, observational, cohort study. *Respir Med* 2012;106:1329-34.
38. Marin JM, Agusti A, Villar I, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA* 2012;307:2169-76.
39. Kasiakogias A, Tsioufis C, Thomopoulos C, et al. Effects of continuous positive airway pressure on blood pressure in hypertensive patients with obstructive sleep apnea: a 3-year follow-up. *J Hypertens* 2013;31:352-60.
40. van Mill JG, Hoogendijk WJ, Vogelzangs N, van DR, Penninx BW. Insomnia and sleep duration in a large cohort of patients with major depressive disorder and anxiety disorders. *J Clin Psychiatry* 2010;71:239-46.
41. Hall MH, Matthews KA, Kravitz HM, et al. Race and financial strain are independent correlates of sleep in midlife women: the SWAN sleep study. *Sleep* 2009;32:73-82.
42. Vrijkotte TG, van Doornen LJ, de Geus EJ. Effects of work stress on ambulatory blood pressure, heart rate, and heart rate variability. *Hypertension* 2000;35:880-6.
43. Steptoe A, Siegrist J, Kirschbaum C, Marmot M. Effort-reward imbalance, overcommitment, and measures of cortisol and blood pressure over the working day. *Psychosom Med* 2004;66:323-9.
44. Steptoe A, Marmot M. Psychosocial, hemostatic, and inflammatory correlates of delayed poststress blood pressure recovery. *Psychosom Med* 2006;68:531-7.
45. Steptoe A, Owen N, Kunz-Ebrecht SR, Brydon L. Loneliness and neuroendocrine, cardiovascular, and inflammatory stress responses in middle-aged men and women. *Psychoneuroendocrinology* 2004;29:593-611.
46. Nealey-Moore JB, Smith TW, Uchino BN, Hawkins MW, Olson-Cerny C. Cardiovascular reactivity during positive and negative marital interactions. *J Behav Med* 2007;30:505-19.
47. Smith TW, Uchino BN, Berg CA, et al. Conflict and collaboration in middle-aged and older couples: II. Cardiovascular reactivity during marital interaction. *Psychol Aging* 2009;24:274-86.
48. Adler NE, Ostrove JM. Socioeconomic status and health: what we know and what we don't. *Ann N Y Acad Sci* 1999;896:3-15.
49. Albert MA, Glynn RJ, Buring J, Ridker PM. Impact of traditional and novel risk factors on the relationship between socioeconomic status and incident cardiovascular events. *Circulation* 2006;114:2619-26.
50. Conen D, Glynn RJ, Ridker PM, Buring JE, Albert MA. Socioeconomic status, blood pressure progression, and incident hypertension in a prospective cohort of female health professionals. *Eur Heart J* 2009;30:1378-84.
51. Franzen PL, Gianaros PJ, Marsland AL, et al. Cardiovascular reactivity to acute psychological stress following sleep deprivation. *Psychosom Med* 2011;73:679-82.
52. Chida Y, Hamer M. Chronic psychosocial factors and acute physiological responses to laboratory-induced stress in healthy populations: a quantitative review of 30 years of investigations. *Psychol Bull* 2008;134:829-85.
53. Jehn ML. Psychosocial factors and racial differences in blood pressure dipping. *Am J Hypertens* 2009;22:584.
54. Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. *Am J Respir Crit Care Med* 2002;166:159-65.
55. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999;354:1435-9.
56. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci U S A* 2009;106:4453-8.
57. Reynolds AC, Dorrian J, Liu PY, et al. Impact of five nights of sleep restriction on glucose metabolism, leptin and testosterone in young adult men. *PLoS One* 2012;7:e41218.
58. Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Sleep duration as a risk factor for diabetes incidence in a large U.S. sample. *Sleep* 2007;30:1667-73.
59. Tochikubo O, Ikeda A, Miyajima E, Ishii M. Effects of insufficient sleep on blood pressure monitored by a new multi biomedical recorder. *Hypertension* 1996;27:1318-24.
60. Kato M, Phillips BG, Sigurdsson G, Narkiewicz K, Pesek CA, Somers VK. Effects of sleep deprivation on neural circulatory control. *Hypertension* 2000;35:1173-5.
61. Okun ML, Coussons-Read ME. Sleep disruption during pregnancy: how does it influence serum cytokines? *J Reprod Immunol* 2007;73:158-65.
62. Suzuki S, Dennerstein L, Greenwood KM, Armstrong SM, Satohisa E. Sleeping patterns during pregnancy in Japanese women. *J Psychosom Obstet Gynaecol* 1994;15:19-26.
63. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193-213.
64. Challis JRG, Matthews SG, Gibb W, Lye SJ. Endocrine and paracrine regulation of birth at term and preterm. *Endocr Rev* 2000;21:514-50.
65. Baker FC, Mitchell D, Driver HS. Oral contraceptives alter sleep and raise body temperature in young women. *Pflugers Arch* 2001;442:729-37.
66. Driver HS, Dijk DJ, Werth E, Biedermann K, Borbély AA. Sleep and the sleep electroencephalogram across the menstrual cycle in young healthy women. *J Clin Endocrinol Metab* 1996;81:728-35.
67. Izzli B, Vennelle M, Liston WA, Dundas KC, Calder AA, Douglas NJ. Sleep-disordered breathing and upper airway size in pregnancy and post-partum. *Eur Respir J* 2006;27:321-7.
68. Saaresranta T, Polo O. Hormones and breathing. *Chest* 2002;122:2165-82.
69. Kambam JR, Handte RE, Brown WU, Smith BE. Effect of normal and pre-eclamptic pregnancies on the oxyhemoglobin dissociation curve. *Anesthesiology* 1986;65:426-7.
70. Van Thiel DH, Gavalier JS, Joshi SN, Sara RK, Stremple J. Heartburn of pregnancy. *Gastroenterology* 1977;72:666-8.
71. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ* 2007;335:974.
72. Grindheim G, Estensen ME, Langesaeter E, Rosseland LA, Toska K. Changes in blood pressure during healthy pregnancy: a longitudinal cohort study. *J Hypertens* 2012;30:342-50.
73. Reid J, Skomro R, Cotton D, et al. Pregnant women with gestational hypertension may have a high frequency of sleep disordered breathing. *Sleep* 2011;34:1033-8.
74. Lynn FA, Alderdice FA, Crealey GE, McElroy JC. Associations between maternal characteristics and pregnancy-related stress among low-risk mothers: an observational cross-sectional study. *Int J Nurs Stud* 2011;48:620-7.
75. Maasilta P, Bachour A, Teramo K, Polo O, Laitinen LA. Sleep-related disordered breathing during pregnancy in obese women. *Chest* 2001;120:1448-54.
76. Franklin KA, Holmgren PA, Jonsson F, Poromaa N, Stenlund H, Svanborg E. Snoring, pregnancy-induced hypertension, and growth retardation of the fetus. *Chest* 2000;117:137-41.

77. Facco FL, Liu CS, Cabello AA, Kick A, Grobman WA, Zee PC. Sleep-disordered breathing: a risk factor for adverse pregnancy outcomes? *Am J Perinatol* 2012;29:277-82.
78. O'Brien LM, Bullough AS, Owusu JT, et al. Pregnancy-onset habitual snoring, gestational hypertension, and preeclampsia: prospective cohort study. *Am J Obstet Gynecol* 2012;207:487-9.
79. Feinsilver SH, Hertz G. Respiration during sleep in pregnancy. *Clin Chest Med* 1992;13:637-44.
80. Guilleminault C, Kirsoglu C, Ohayon MM. C-reactive protein and sleep-disordered breathing. *Sleep* 2004;27:1507-11.
81. Guilleminault C, Kim YD, Palombini L, Li K, Powell N. Upper airway resistance syndrome and its treatment. *Sleep* 2000;23 Suppl 4:S197-S200.
82. Blyton DM, Skilton MR, Edwards N, Hennessy A, Celermajor DS, Sullivan CE. Treatment of sleep disordered breathing reverses low fetal activity levels in preeclampsia. *Sleep* 2013;36:15-21.
83. Ayrim A, Keskin EA, Ozol D, Onaran Y, Yidirim Z, Kafali H. Influence of self-reported snoring and witnessed sleep apnea on gestational hypertension and fetal outcome in pregnancy. *Arch Gynecol Obstet* 2011;283:195-9.
84. Louis JM, Auckley D, Sokol RJ, Mercer BM. Maternal and neonatal morbidities associated with obstructive sleep apnea complicating pregnancy. *Am J Obstet Gynecol* 2010;202:261-5.
85. Ursavas A, Karadag M, Nalci N, Ercan I, Gozu RO. Self-reported snoring, maternal obesity and neck circumference as risk factors for pregnancy-induced hypertension and preeclampsia. *Respiration* 2008;76:33-9.
86. Yinon D, Lowenstein L, Suraya S, et al. Pre-eclampsia is associated with sleep-disordered breathing and endothelial dysfunction. *Eur Respir J* 2006;27:328-33.
87. Edwards N, Blyton DM, Hennessy A, Sullivan CE. Severity of sleep-disordered breathing improves following parturition. *Sleep* 2005;28:737-41.
88. Izci B, Martin SE, Dundas KC, Liston WA, Calder AA, Douglas NJ. Sleep complaints: Snoring and daytime sleepiness in pregnant and pre-eclamptic women. *Sleep Med* 2005;6:163-9.
89. Perez-Chada D, Videla AJ, O'Flaherty ME, et al. Snoring, witnessed sleep apnoeas and pregnancy-induced hypertension. *Acta Obstet Gynecol Scand* 2007;86:788-92.
90. Bourjeily G, Raker CA, Chalhoub M, Miller MA. Pregnancy and fetal outcomes of symptoms of sleep-disordered breathing. *Eur Respir J* 2010;36:849-55.
91. Okun ML, Kravitz HM, Sowers MF, Moul DE, Buysse DJ, Hall M. Psychometric evaluation of the Insomnia Symptom Questionnaire: a self-report measure to identify chronic insomnia. *J Clin Sleep Med* 2009;5:41-51.
92. Okun ML, Luther JF, Wisniewski SR, Wisner KL. Disturbed sleep and inflammatory cytokine in depressed and nondepressed pregnant women: An exploratory analysis of pregnancy outcomes. *Psychosom Med* 2013;75:670-81.
93. Torre-Bouscoulet L, Garcia SC, Vazquez Garcia JC, et al. Perceptions of short and long sleep duration and comorbid conditions: the PLATINO study. *Sleep Med* 2013;14:850-7.
94. Troxel WM, Buysse DJ, Matthews KA, et al. Sleep symptoms predict the development of the metabolic syndrome. *Sleep* 2010;33:1633-40.
95. Grandner MA, Perlis ML. Insomnia as a cardiometabolic risk factor. *Sleep* 2013;36:11-2.
96. Stremmler R, Hodnett E, Kenton L, et al. Effect of behavioural-educational intervention on sleep for primiparous women and their infants in early postpartum: multisite randomised controlled trial. *BMJ* 2013;346:f1164.
97. Bourjeily G, Ankner G, Mohsenin V. Sleep-disordered breathing in pregnancy. *Clin Chest Med* 2011;32:175-89.
98. Chen YH, Kang JH, Lin CC, Wang IT, Keller JJ, Lin HC. Obstructive sleep apnea and the risk of adverse pregnancy outcomes. *Am J Obstet Gynecol* 2012;206:136-5.
99. Connolly G, Razak AR, Hayanga A, Russell A, McKenna P, McNicholas WT. Inspiratory flow limitation during sleep in pre-eclampsia: comparison with normal pregnant and nonpregnant women. *Eur Respir J* 2001;18:672-6.
100. Champagne K, Schwartzman K, Opatry L, et al. Obstructive sleep apnoea and its association with gestational hypertension. *Eur Respir J* 2009;33:559-65.

## ACKNOWLEDGMENTS

The authors thank Joann Broadus for her assistance with manuscript preparation

## SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication February, 2013

Submitted in final revised form July, 2013

Accepted for publication August, 2013

Address correspondence to: Michele Okun, Ph.D., University of Pittsburgh, Western Psychiatric Institute and Clinic, 3811 O'Hara St. E1124, Pittsburgh, PA 15213; Tel: (412) 586-9434; E-mail: okunml@upmc.edu

## DISCLOSURE STATEMENT

This was not an industry supported study. Funded by grants NIH RO010813 (P.I. Okun) and the NIMH Medical Student Fellowship Program in Mental Health Research through the Department of Psychiatry of the University of Pittsburgh School of Medicine. The authors have indicated no financial conflicts of interest.



## Nocturnal Oral Movements in a Patient with Schizophrenia

Justin K. Liegmann, M.D.; Lourdes M. DelRosso, M.D.; Romy Hoque, M.D.

Division of Sleep Medicine, Department of Neurology, Louisiana State University School of Medicine, Shreveport, LA

A 61-year-old man with history of schizophrenia, generalized tonic clonic seizure disorder, and hypertension who lives in a skilled nursing facility presented with snoring and gasping for air during the night. The patient's care staff reports no abnormal nocturnal behaviors, and no generalized seizures in the last 5 years. His medications include haloperidol, olanzapine, benzotropine, valproic acid, levetiracetam, trazodone, sertraline, lisinopril, and aspirin.

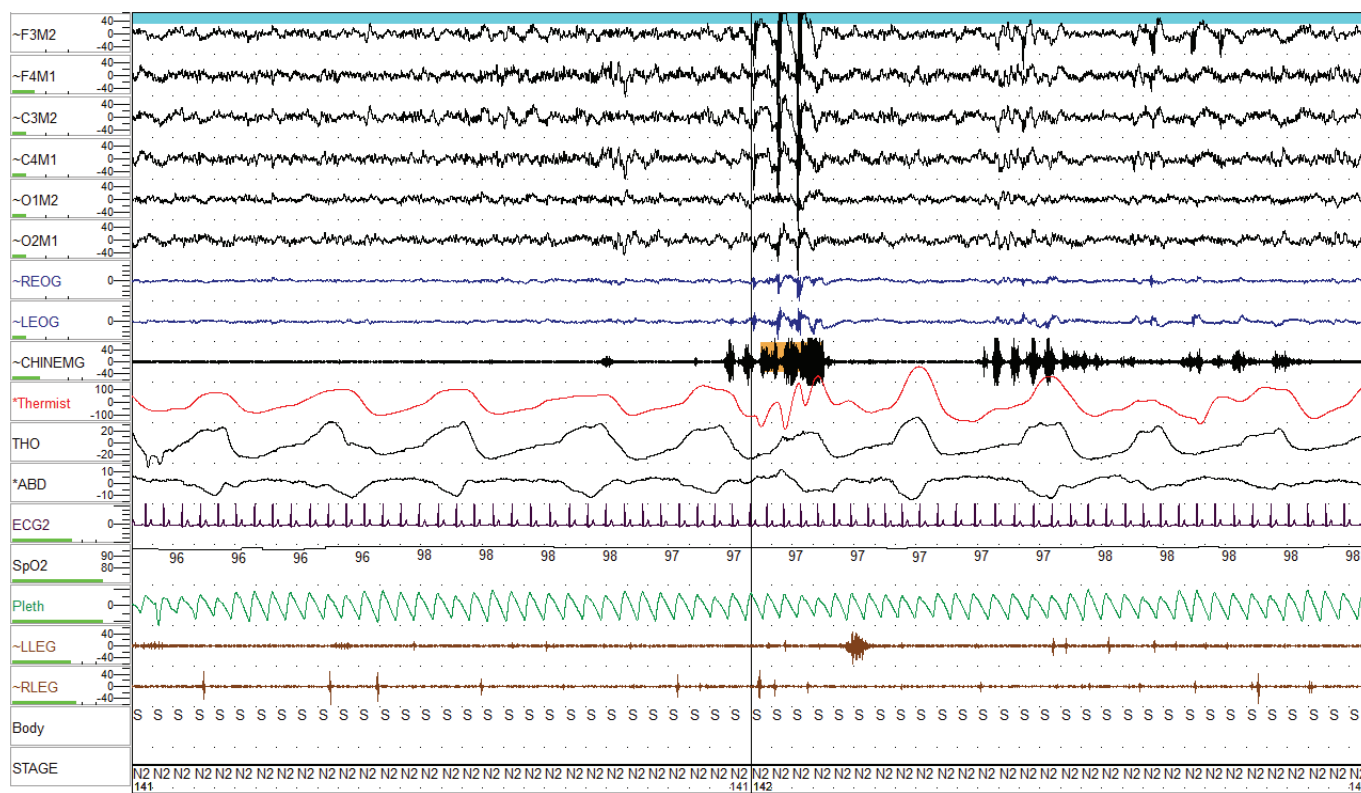
On physical examination, his body mass index was 22 kg/m<sup>2</sup>. Neither masseter muscle hypertrophy nor temporomandibular joint pain was noted. The patient was edentulous without gum lesions; he did not wear dentures. No movements of the tongue were noted

with the mouth open, and patient was able to sustain tongue protrusion for longer than one minute. Neither facial grimacing nor limb dyskinesia was noted. The oral airway was Mallampati IV.

Polysomnogram revealed an apnea-hypopnea index of 7 with a sleep efficiency of 98%. Unusual chewing movements were noted during NREM sleep (**Video 1**, **Figures 1, 2**). These movements were not associated with sleep disordered breathing. No audible grinding was noted on video.

**QUESTION:** What is the most likely diagnosis for the movements shown in Video 1?

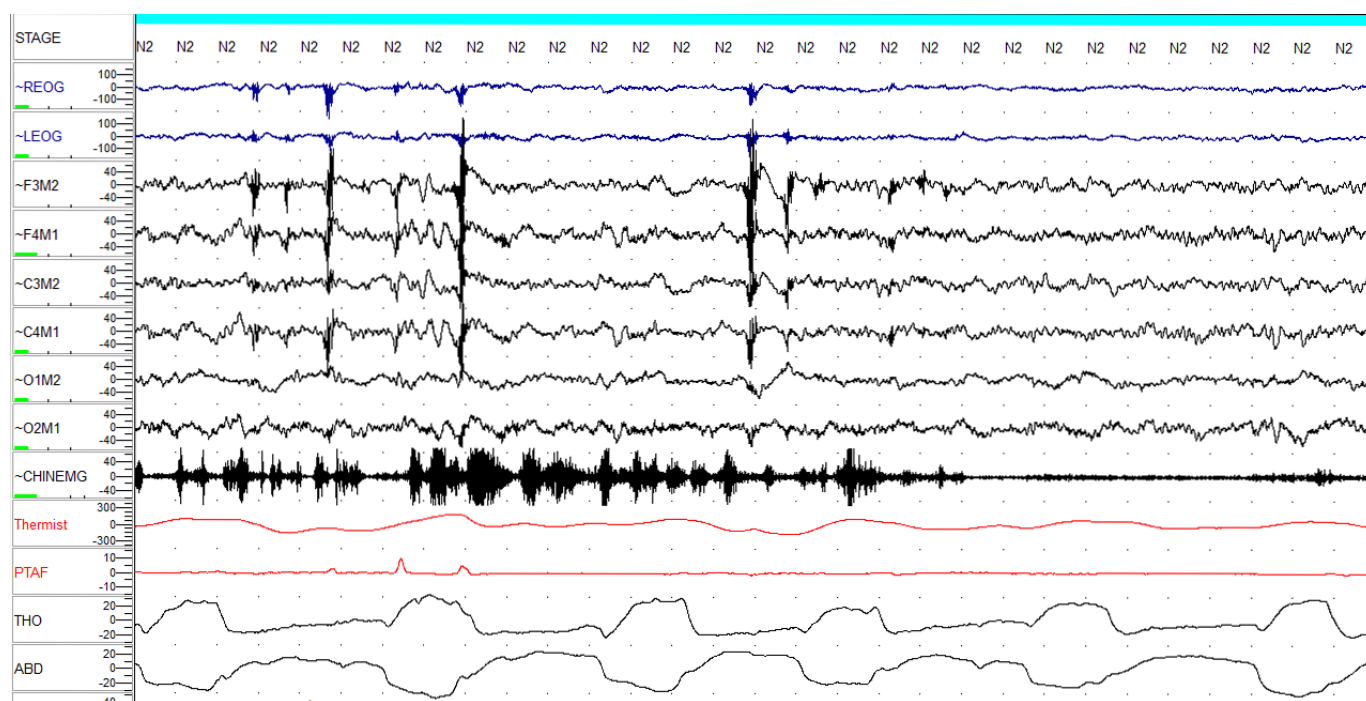
**Figure 1**—One-minute polysomnogram segment corresponding to Video 1



This image shows elevated chin electromyography tone associated with oral movements during sleep stage N2.



**Figure 2**—30-second polysomnogram epoch showing elevated chin electromyography (EMG) tone associated with oral movements during sleep stage N2



Note the relatively minor electroencephalography artifact in comparison to the prominent EMG changes, this may represent lack of scalp muscle involvement.

## ANSWER: Edentulous oral dyskinesia

### DISCUSSION

Oral dyskinesia consists of involuntary movements of the lips, tongue, and jaw. They are classified according to cause and movement description.<sup>1</sup> Oral dyskinesia has been reported in up to 16% of edentulous patients and is most commonly seen in those with poor oral health, oral pain, ill-fitting dentures, or without dentures.<sup>2</sup> Edentulous oral dyskinesia (EOD) is thought to be associated with loss of the tooth and periodontal ligament proprioceptive input.<sup>3</sup>

Oral dyskinesia is also associated with dopamine antagonist neuroleptic use (i.e., tardive dyskinesia), choreatic neurodegenerative diseases (e.g., Huntington disease), and basal ganglia lesions. Dyskinesia of EOD is limited to the oral area, while dyskinesia associated with the neuroleptic medications or neurodegenerative disorders are more widespread involving the face, trunk, and extremities. Tardive dyskinesia is an extrapyramidal movement secondary to neuroleptic medications that cross the blood brain barrier and inhibit central D2 receptors producing choreoathetoid movements in the oral-buccal-lingual muscles, face, limb, and trunk.

Similar to neuroleptic medication induced/tardive dyskinesia, EOD may have involuntary protrusion of the tongue. In contrast to EOD, those with tardive dyskinesia are usually unable to maintain voluntary prolonged tongue protrusion without involuntary retraction. Tardive dyskinesia movements are exacerbated by emotional arousal, decrease with relaxation, and disappear with sleep.<sup>4</sup>

Repetitive oral movements during sleep including lip smacking, mumbling, or chewing may also occur in seizure disorder. The lack of an electrographic correlate, the absence of daytime seizures, and the absence of generalized seizures for 5 years make the diagnosis of nocturnal seizures less likely in our patient.

**Figure 2** shows a 30-second epoch depicting the polysomnographic features of the oral movement, which meet many of the criteria for bruxism in the American Academy of Sleep Medicine Scoring Manual (rhythmic masticatory muscle activity form). Chin EMG amplitude is twice the background EMG amplitude, each event is between 0.25-2 seconds, and more than three EMG elevations occur in sequence. The last criterion of a minimum of two episodes of audible tooth grinding was not met.<sup>5</sup>

The movements do not meet International Classification of Sleep Disorders 2<sup>nd</sup> edition (ICSD-2) criteria for sleep related bruxism. Given that the patient is edentulous, tooth-grinding noises during sleep, tooth clenching during sleep, and abnormal tooth wear are not possible. The patient denies jaw muscle discomfort upon awakening, and no masseter muscle hypertrophy was noted with jaw clenching. In the elderly, the prevalence of bruxism may be as low as 3%.<sup>6</sup>

### SLEEP MEDICINE PEARLS

1. Tardive dyskinesia disappears with sleep.
2. The ICSD-2 criteria for bruxism technically require the presence of teeth.
3. Oral dyskinesia is common in edentulous elderly patients and may persist during sleep.

### CITATION

Liegmann JK; DelRosso LM; Hoque R. Nocturnal oral movements in a patient with schizophrenia. *J Clin Sleep Med* 2013;9(12):1358-1360.

### REFERENCES

1. Blanchet PJ, Rompre PH, Lavigne GJ, Lamarche C. Oral dyskinesia: a clinical overview. *Int J Prosthodont* 2005;18:10-9.
2. Koller WC. Edentulous orodyskinesia. *Ann Neurol* 1983;13:97-9.
3. Satcher HD, Underwood RB, Beatty RA, Sugar O. Orofacial dyskinesia. A dental dimension. *JAMA* 1971;216:1459-63.
4. American Psychiatric Association. Task Force on Tardive Dyskinesia. *Tardive dyskinesia: a task force report of the American Psychiatric Association*. Washington, DC: American Psychiatric Association, 1992.
5. American Academy of Sleep Medicine. *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications*. Version 2.0. Darien, IL: American Academy of Sleep Medicine, 2012.
6. American Academy of Sleep Medicine. *International classification of sleep disorders; diagnostic and coding manual*. 2nd ed. Westchester, IL: American Academy of Sleep Medicine, 2005.

### SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication June, 2013

Submitted in final revised form July, 2013

Accepted for publication July, 2013

Address correspondence to: Lourdes DelRosso, M.D., Assistant Professor of Sleep Medicine, Louisiana State University School of Medicine, Shreveport, LA; E-mail: lordydel@yahoo.com

### DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.



## Erratum

There is an error in the issue number in the citation of the editorial by Quan et al. on PubMed Central. The citation should read: Quan SF; Epstein LJ. A warning shot across the bow: the changing face of sleep medicine. *J Clin Sleep Med* 2013;9(4):301-302.

---

