Obstructive Sleep Apnea
Pathophysiology, Comorbidities, and Consequences
Edited by Clete A. Kushida
Obstructive Sleep Apnea

Pathophysiology, Comorbidities, and Consequences
SLEEP DISORDERS

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Obstructive Sleep Apnea
Pathophysiology, Comorbidities, and Consequences

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Preface

When in doubt, pressurize the snout.

attributed to Philip R. Westbrook

I often thought of this mantra during my on-call nights when, as a Stanford sleep medicine fellow, I was awakened from sleep by a technologist informing me that one of the clinic patients had repetitive obstructive apneas with significant oxygen desaturations. The technologist would typically ask, can I start the patient on CPAP? Invariably, I would mutter a drowsy “yes,” often chiding myself that on the previous day I should have clearly written the respiratory thresholds for starting continuous positive airway pressure on the patient’s sleep-study order sheet. This anecdote illustrates the fact that continuous positive airway pressure has become such an important and ubiquitous treatment for obstructive sleep apnea since its development over a quarter century ago. The modern sleep specialist has new diagnostic tools and other treatments, such as upper airway surgery and oral appliances, for patients with obstructive sleep apnea; nevertheless, our field is still in its adolescence with respect to the diagnosis and treatment of obstructive sleep apnea and other sleep disorders.

The reader might wonder why a neurologist is editing a two-volume set of books on obstructive sleep apnea, since it is a sleep-related breathing disorder and would therefore appear to be within the domain of pulmonary physicians. However, besides pulmonologists, neurologists, psychiatrists, internists, pediatricians, and otolaryngologists have entered the field of sleep medicine. Many clinicians now treat patients with sleep disorders on a full-time basis. Sleep medicine has truly become multidisciplinary, and a sleep clinician is expected to diagnose and treat a wide range of sleep disorders, from insomnia to restless legs syndrome, that were previously referred by internists to other specialists.

It is indeed a testament to the ever-increasing knowledge base on obstructive sleep apnea that there is a need for a two-volume set of books on this topic. This book covers the pathophysiology, comorbidities, and consequences of obstructive sleep apnea, with sections exploring the features, factors, and characteristics of this disorder as well as its associations and consequences. The second volume, Obstructive Sleep Apnea: Diagnosis and Treatment, focuses on the diagnosis and treatment of obstructive sleep apnea, and includes a section on special conditions, disorders, and clinical issues. The authors and I have tried to conform the conditions and disorders described in this book to the second edition of the International Classification of Sleep Disorders: Diagnostic & Coding Manual published by the American Academy of Sleep Medicine in 2006, although some terms, such as obstructive sleep apnea syndrome and sleep-disordered breathing, have been retained in a few statements when appropriate. We have also tried to discuss new entities and findings such as complex sleep apnea, oxidative stress, cyclic alternating pattern, and adaptive servo-ventilation. However, given the rapidity with which the area of sleep medicine is advancing, it is highly conceivable that two volumes might not be sufficient to cover the topic of obstructive sleep apnea in just a few short years!
These books could not exist without the excellent contributions of a talented group of international authors; their detailed and comprehensive works are greatly appreciated. I am deeply indebted to the renowned and true pioneers of our field of sleep, William Dement, Christian Guilleminault, Sonia Ancoli-Israel, Chris Gillin, and Allan Rechtschaffen, who served as my mentors through various stages of my career. In all of my endeavors, I can always count on my parents, Samiko and Hiroshi Kushida, to assist me; these books were no exception. I have been very fortunate to serve, along with Dr. Dement, as Principal Investigator of the multicenter, randomized, double-blind, placebo-controlled Apnea Positive Pressure Long-Term Efficacy Study, sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health. To date, this is the largest controlled trial funded by the National Institutes of Health in the field of sleep.

This book is dedicated not only to my parents but also to the marvelous core team of the Apnea Positive Pressure Long-Term Efficacy Study, consisting of William Dement, Pamela Hyde, Deborah Nichols, Eileen Leary, Tyson Holmes, Dan Bloch, as well as National Heart, Lung, and Blood Institute officials (Michael Twery and Gail Weinmann), site directors, co-ordinators, consultants, committee members, key Stanford site personnel (Chia-Yu Cardell, Rhonda Wong, Pete Silva, Jennifer Blair), Data and Safety Monitoring Board members, and other personnel without whom this project could not have functioned in such a meticulous and efficient manner.

It is my sincere hope that the reader will strive to become expert in the field of sleep. Although there is always room for improvement, awareness of sleep disorders by patients, physicians, and the general public is at an all-time high. However, available funding for sleep research and the number of young investigators interested in a career in basic or clinical sleep research are areas that need enhancement. The interested reader can directly contribute to this field in several ways: applying for membership in the American Academy of Sleep Medicine or Sleep Research Society, serving on committees in these organizations, becoming board certified in sleep medicine, submitting a sleep-related grant proposal to the National Institutes of Health, and/or just simply learning more about sleep and its disorders.

Lastly, etched forever in my memory is a sticker posted on the door of Mary Carskadon’s former office at Stanford that contained words to live by: “Be alert. The world needs more lerts.”

Clete A. Kushida
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There are more than a few primary, fundamental questions in the field of sleep that remain unanswered. Research into our field is still in its infancy, with only a little over 50 years since the discovery of rapid eye movement (REM) sleep that initiated the systematic, scientific exploration of sleep and its disorders. Any list of the most important questions to resolve in sleep would probably contain the following:

- Why do we sleep (i.e., what is the function of sleep)?
- Where is sleep controlled in the brain?
- What determines the onset of sleep?
- How can we cure obstructive sleep apnea?

Of these content areas, the question that has direct clinical relevance is the one regarding obstructive sleep apnea (OSA). Sleep apnea is also arguably the most important disorder of sleep, since it is the one sleep disorder that the majority of sleep clinicians spend the bulk of their time diagnosing and treating and it has serious consequences to the affected individual and society as well. Unfortunately, the current therapies either do not effectively treat this disorder or enable high patient adherence in a large proportion of patients. However, there is hope as technology and molecular procedures, such as those involving stem cells, advance and improve over time.

Since Terry Young’s landmark epidemiology study published in 1993 (1) showed that a quarter of men and about 10% of women between the ages of 30 and 60 years have polysomnographic evidence of OSA, we know that it is one of the more highly prevalent diseases in the world. Although the pathogenesis of this disorder has not been conclusively demonstrated, risk factors for the development of OSA, such as obesity, craniofacial disproportion, and ventilatory control abnormalities, have been identified. The first-line treatment modality for OSA is nasal continuous positive airway pressure (CPAP), which was invented a little over 25 years ago. This consists of a portable device that provides a fan-generated continuous flow of air into the upper airway via a mask fitted over the nose; this airflow splints open the airway, thereby preventing its collapse. CPAP does have its limitations, particularly in terms of patient adherence that often stems from discomfort due to the mask. Randomized controlled clinical trials (Table 1) that evaluated adherence to both sham and active CPAP interventions and reported hours of use, have demonstrated that the mean nightly active CPAP use was 4.46 hours (2). Surprisingly, OSA patients on sham CPAP were slightly better in their mean nightly sham CPAP use (4.85 hours) (2). Despite the limitations of CPAP, it is the most commonly prescribed treatment for OSA.

CPAP has been shown to decrease abnormal respiratory events and arousals; however, there is some controversy whether sleep architecture is significantly improved (3,4). Nevertheless, untreated OSA has been associated with hypertension,
<table>
<thead>
<tr>
<th>Primary author (year) (ref)</th>
<th>n</th>
<th>Duration</th>
<th>Adherence (hr)</th>
<th>Diff</th>
<th>Type of control and OSA criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engleman (1994) (44)</td>
<td>32</td>
<td>4 wk</td>
<td>3.7 ± 0.4</td>
<td>N/A</td>
<td>Placebo tablet, AHI = 49 ± 1.5, crossover</td>
</tr>
<tr>
<td>Jenkinson (1999) (35)</td>
<td>52/49</td>
<td>4 wk</td>
<td>5.4</td>
<td>4.6</td>
<td>0.035 Sham (1 cmH₂O), O₂ desaturations for OSA diagnosis</td>
</tr>
<tr>
<td>Loredo (1999) (3)</td>
<td>23/18</td>
<td>1 wk</td>
<td>&gt;5</td>
<td>&gt;5</td>
<td>— Sham (2 cmH₂O), AHI 56.4 vs. 44.2</td>
</tr>
<tr>
<td>Yu (1999) (38)</td>
<td>20/14</td>
<td>1 wk</td>
<td>5.6 ± 1.1</td>
<td>5.2 ± 1.2</td>
<td>n.s. Sham (2 cmH₂O), AHI 45.9 vs. 35.2</td>
</tr>
<tr>
<td>Dimsdale (2000) (53)</td>
<td>21/18</td>
<td>1 wk</td>
<td>&gt;5</td>
<td>&gt;5</td>
<td>— Sham (2 cmH₂O), AHI 53.6 vs. 41.7</td>
</tr>
<tr>
<td>Hack (2000) (51)</td>
<td>32/37</td>
<td>4 wk</td>
<td>5.6</td>
<td>5.0</td>
<td>n.s. Sham (1 cmH₂O), O₂ desaturations for OSA diagnosis</td>
</tr>
<tr>
<td>Bardwell (2001) (54)</td>
<td>20/16</td>
<td>1 wk</td>
<td>5.5 ± 0.3</td>
<td>4.9 ± 0.3</td>
<td>n.s. Sham (2 cmH₂O), AHI 4.36 vs. 56.8</td>
</tr>
<tr>
<td>Barbe (2001) (52)</td>
<td>29/25</td>
<td>6 wk</td>
<td>5 ± 0.4</td>
<td>4 ± 0.5</td>
<td>n.s. Sham, AHI ≥ 30, ESS &lt; 10</td>
</tr>
<tr>
<td>Henke (2001) (55)</td>
<td>27/18</td>
<td>35 days</td>
<td>5.8–5.9</td>
<td>4.9–5.2</td>
<td>n.s. Sham (0–1 cmH₂O), AHI 62.1 vs. 68.1</td>
</tr>
<tr>
<td>Monasterio (2001) (56)</td>
<td>68/59</td>
<td>6 mo</td>
<td>4.8 ± 2.2</td>
<td>—</td>
<td>N/A Sleep hygiene + weight loss, AHI 20 vs. 21</td>
</tr>
<tr>
<td>Montserrat (2001) (57)</td>
<td>24/23</td>
<td>6 wk</td>
<td>4.25 ± 2</td>
<td>4.5 ± 2</td>
<td>N/A Sham, AHI 50.5 vs. 57.1</td>
</tr>
<tr>
<td>Ziegler (2001) (58)</td>
<td>20/18</td>
<td>10 days</td>
<td>Unknown</td>
<td>Unknown</td>
<td>n.s. Sham (2 cmH₂O), AHI 54 vs. 39</td>
</tr>
<tr>
<td>Barnes (2002) (59)</td>
<td>15/13</td>
<td>8 wk</td>
<td>3.5 ± 2.1</td>
<td>—</td>
<td>N/A Placebo tablet, AHI 12.9 ± 6.3</td>
</tr>
<tr>
<td>Pepperell (2002) (60)</td>
<td>53/51</td>
<td>4 wk</td>
<td>4.9 ± 2.0</td>
<td>4.5 ± 2.4</td>
<td>n.s. Sham (1 cmH₂O), O₂ desaturations for OSA diagnosis</td>
</tr>
<tr>
<td>Becker (2003) (61)</td>
<td>16/16</td>
<td>9 wk</td>
<td>5.5 ± 2.0</td>
<td>5.4 ± 2.2</td>
<td>n.s. Sham (3–4 cmH₂O), AHI 62.5 vs. 65</td>
</tr>
<tr>
<td>Profant (2003) (62)</td>
<td>21/18</td>
<td>1 wk</td>
<td>&gt;5</td>
<td>&gt;5</td>
<td>— Sham (2 cmH₂O), AHI 53.6 vs. 41.7</td>
</tr>
</tbody>
</table>

Abbreviations: AHI, apnea-hypopnea index; ESS, Epworth sleepiness scale; N/A, not applicable; n.s., not significant; OSA, obstructive sleep apnea; ref, reference.
myocardial infarction, cardiac failure, stroke, cardiac dysrhythmias, increased risk for industrial and motor vehicle accidents, and sudden death (5,6). In fact, data from the Sleep Heart Health Study, a multi-center observational project funded by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH), showed a linear relationship between severity of sleep-disordered breathing (SDB) and hypertension (7,8). There is also an emerging body of evidence (9,10) that neurocognitive abilities, especially in the domains of attention, working memory, and executive function, may be impaired with OSA.

The major studies on the effects of OSA on neurocognitive function are summarized in Table 2. The neurocognitive function tests administered to the OSA subjects are typically segregated into the domains of attention and psychomotor (A/P) function, learning and memory (L/M), and executive and frontal-lobe (E/F) function. Engleman et al. (10) reviewed some of the case-control studies in Table 2; review of these studies indicated that community-acquired subjects with mild average indices of SDB showed slight attentional and executive function impairment. Those studies with moderate and severe SDB indices revealed moderate and large impairment in all three areas of neurocognitive function. However, relatively small sample sizes and inadequate control groups handicapped these earlier studies. In addition, newer technologies, such as the Sustained Attention Metric (11–18) and functional magnetic resonance imaging (MRI) have not been used to systematically evaluate neurocognitive function in OSA patients.

The etiology of the decline in neurocognitive function with OSA is unknown. The theory that the hypoxemia of OSA is responsible for this decline is controversial; prior research on OSA patients (19) and hypoxemic chronic obstructive pulmonary disease (COPD) patients (20,21) failed to find a relationship between measures of hypoxemia and neurocognitive function. However, other investigators (22) have found that OSA patients with hypoxemia were significantly more cognitively impaired than OSA patients without hypoxemia. Another theory is that the decline in neurocognitive function with OSA is related to sleepiness. This does not appear to be completely true; OSA patients performed worse in neuropsychological tests than both healthy volunteers and patients with other disorders of excessive sleepiness (19). Perhaps the most parsimonious explanation is that these OSA-related neurocognitive deficits are the result of a combination of both hypoxemia and decreased vigilance; some investigators (23,24) found that these deficits in OSA patients were associated with both of these variables.

CPAP has been shown to improve neurocognitive function in a few studies with limited sample sizes. These studies have demonstrated improvements in tests of A/P function (25,26), tests of L/M (25), as well as in tests of E/F function (27). However, other investigators have detected persistent deficits in similar measures of psychomotor, short-term memory, and executive function with CPAP use, indicating that some deficits may be due to irreversible anoxic central nervous system damage (28–31).

The etiology of the daytime sleepiness associated with OSA is unknown. It is widely believed that the SDB of OSA results in brief arousals from sleep, which, in turn, fragments sleep and produces daytime sleepiness. However, this hypothesis has not been adequately tested, and there is controversy regarding whether it is accurate (26,32,33). Regardless of the etiology of this sleepiness, this symptom is a primary criterion for the diagnosis of OSA. CPAP has been demonstrated to improve the sleepiness associated with OSA both in long-term
<table>
<thead>
<tr>
<th>Primary author (year)</th>
<th>Study type</th>
<th>n</th>
<th>OSA severity</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Findley (1986) (22)</td>
<td>CS</td>
<td>26</td>
<td>Severe</td>
<td>Improved&lt;sup&gt;a&lt;/sup&gt; in 4/8 A/P, L/M, and E/F tests for hypoxemic vs. non-hypoxemic OSA subjects</td>
</tr>
<tr>
<td>Greenberg (1987) (19)</td>
<td>CC</td>
<td>14/14</td>
<td>Severe</td>
<td>Improved&lt;sup&gt;a&lt;/sup&gt; in 7/14 A/P and E/F tests vs. controls</td>
</tr>
<tr>
<td>Bédard (1991) (23)</td>
<td>CC</td>
<td>20/10</td>
<td>Mod–severe</td>
<td>Improved&lt;sup&gt;a&lt;/sup&gt; in 7/9 A/P and 2/4 E/F tests; decrease&lt;sup&gt;a&lt;/sup&gt; in 5/6 L/M tests (only severe cases)</td>
</tr>
<tr>
<td>Presty (1991) (63)</td>
<td>CS</td>
<td>119</td>
<td>Mild–severe</td>
<td>Improved&lt;sup&gt;a&lt;/sup&gt; in A/P and L/M tests for those OSA patients with severe hypoxia</td>
</tr>
<tr>
<td>Presty (1992) (64)</td>
<td>CS</td>
<td>29</td>
<td>Mod–severe</td>
<td>Correlation&lt;sup&gt;a&lt;/sup&gt; between AH1 and 1/2 EF tests and IQ decrease; no correlation in 3 A/P or 1 L/M tests</td>
</tr>
<tr>
<td>Telakivi (1993) (65)</td>
<td>CS</td>
<td>31</td>
<td>Mild–severe</td>
<td>No correlation between hypoxia or sleepiness and 7 A/P, L/M, and E/F tests</td>
</tr>
<tr>
<td>Ingram (1994) (66)</td>
<td>CC</td>
<td>16/43</td>
<td>Mild–severe</td>
<td>No difference in OSA vs. controls subjects ≥ 54 yrs for 1 A/P test</td>
</tr>
<tr>
<td>Naëguelé (1995) (67)</td>
<td>CC</td>
<td>17/17</td>
<td>Severe</td>
<td>Improved&lt;sup&gt;a&lt;/sup&gt; in 1/4 A/P tests, 8/10 L/M tests, and 3/9 E/F tests vs. controls</td>
</tr>
<tr>
<td>Verstraeten (1996) (68)</td>
<td>CC</td>
<td>26/22</td>
<td>Mild–severe</td>
<td>No differences in OSA vs. insomnia subjects for 6 A/P, L/M, or E/F tests</td>
</tr>
<tr>
<td>Kim (1997) (69)</td>
<td>CH</td>
<td>199/642</td>
<td>Mild–severe</td>
<td>Negative association&lt;sup&gt;a&lt;/sup&gt; between log AH1 and psychomotor efficiency in 8 A/P, L/M, or E/F tests</td>
</tr>
<tr>
<td>Redline (1997) (70)</td>
<td>CC</td>
<td>32/20</td>
<td>Mild–mod</td>
<td>Improved&lt;sup&gt;a&lt;/sup&gt; in 1/4 A/P tests, 0/3 L/M tests, and 1/5 E/F tests vs. controls</td>
</tr>
<tr>
<td>Engleman (1997) (71)</td>
<td>RCT</td>
<td>16</td>
<td>Mild</td>
<td>Improved&lt;sup&gt;a&lt;/sup&gt; mental flexibility</td>
</tr>
<tr>
<td>Engleman (1998) (45)</td>
<td>RCT</td>
<td>23</td>
<td>Mod–severe</td>
<td>Improved&lt;sup&gt;a&lt;/sup&gt; in 2/3 A/P tests, 0/2 L/M tests, and 0/4 E/F tests vs. controls</td>
</tr>
<tr>
<td>Engleman (1999) (40)</td>
<td>RCT</td>
<td>34</td>
<td>Mild</td>
<td>Improved&lt;sup&gt;a&lt;/sup&gt; in 1/3 A/P tests and 1/3 E/F tests vs. controls</td>
</tr>
<tr>
<td>Hack (2000) (51)</td>
<td>RCT</td>
<td>59</td>
<td>Mild–severe</td>
<td>Improved driving simulation</td>
</tr>
<tr>
<td>Barbé (2001) (52)</td>
<td>RCT</td>
<td>29/25</td>
<td>Severe</td>
<td>No difference in active vs. sham CPAP groups for 8 A/P, L/M, and E/F tests</td>
</tr>
<tr>
<td>Bardwell (2001) (54)</td>
<td>RCT</td>
<td>36</td>
<td>Mod–severe</td>
<td>Improved&lt;sup&gt;a&lt;/sup&gt; in 1/2 A/P tests, 0/4 L/M tests, and 0/2 E/F tests vs. controls</td>
</tr>
<tr>
<td>Henke (2001) (55)</td>
<td>RCT</td>
<td>46</td>
<td>Mod–severe</td>
<td>Improved&lt;sup&gt;a&lt;/sup&gt; in 2/3 A/P tests, 3/3 L/M tests, and 2/3 E/F tests vs. controls</td>
</tr>
<tr>
<td>Monasterio (2001) (56)</td>
<td>RCT</td>
<td>42</td>
<td>Mild–mod</td>
<td>Improved&lt;sup&gt;a&lt;/sup&gt; in 0/4 A/P tests, 0/2 L/M tests, and 0/8 E/F tests vs. controls</td>
</tr>
<tr>
<td>Barnes (2002) (59)</td>
<td>RCT</td>
<td>42</td>
<td>Mild–mod</td>
<td>Improved&lt;sup&gt;a&lt;/sup&gt; in 0/3 A/P tests, 0/2 L/M tests, and 0/8 E/F tests vs. controls</td>
</tr>
<tr>
<td>Barnes (2004) (72)</td>
<td>RCT</td>
<td>80</td>
<td>Mild–mod</td>
<td>Improved&lt;sup&gt;a&lt;/sup&gt; in 0/2 A/P and 2/5 E/F tests vs. controls</td>
</tr>
</tbody>
</table>

<sup>a</sup>Significance level, p < 0.05. OSA severity by average apnea-hypopnea index (AH1), with mild = 5–15 events/hr, moderate = 15–30 events/hr, and severe >30 events/hr.

Abbreviations: A/P, tests of attention and psychomotor function; CC, case-control; CH, cohort; CPAP, continuous positive airway pressure; CS, case series; E/F, tests of executive and frontal lobe function; IQ, intelligence quotient; L/M, tests of learning and memory; OSA, obstructive sleep apnea; RCT, randomized control trial; ref, reference.
studies (34) and in comparisons with subtherapeutic CPAP (35); however, in the former limited studies, this improvement did not approach the baseline levels of controls without OSA.

The effects of CPAP on mood states in OSA patients are largely unknown. The results have been mixed, with some studies reporting improvement (36,37), others revealing significant improvement in both active CPAP and placebo groups (38), or finally others showing no significant effects (25,39). However, these studies were limited by their use of small sample sizes, standard and nonstandard indices of mood state, and different types of controls.

Quality of life assessment has become an integral component of health outcomes research. This assessment is still in its infancy for the evaluation of sleep apnea patients. Nevertheless, a few studies with small sample sizes have documented significant improvement in quality of life indices following CPAP treatment in OSA patients (26,35,40,41).

Up to the present time, there has never been a multicenter, randomized, double-blind, placebo-controlled, long-term study to systematically investigate the therapeutic effectiveness of CPAP, despite its widespread use as the primary treatment for OSA (42) and the perception by the majority of patients with OSA that it is a successful treatment for this disorder (43). To date, the efficacy of CPAP has generally been evaluated against control groups that do not meet the requirements of placebo groups since the controls are not subjected to the same instrumental constraints (44–47) as the experimental group. This lack of adequate placebo-controlled studies combined with the patient costs of CPAP, has called into question the usefulness of CPAP as a primary therapy for OSA (48,49).

The NHLBI-funded, multicenter Apnea Positive Pressure Long-term Efficacy Study (APPLES), under the leadership of Dr. William C. Dement and Dr. Clete A. Kushida is designed to examine this question. Although there is some evidence as described above that OSA affects these areas of human function and that these effects may be reversed with CPAP, it has never been evaluated in a comprehensive, systematic, and well-controlled manner. The primary goal of APPLES is to test the hypothesis that CPAP therapy results in significant, stable, and long-term benefits to neurocognitive function, mood, sleepiness, and quality of life in patients with OSA.

The study evaluates this hypothesis by administering a comprehensive yet novel test battery containing measures of neurocognitive function, mood, sleepiness, and quality of life on over a thousand OSA subjects in the United States assigned to either active or sham (subtherapeutic) CPAP therapy in a double-blinded and randomized manner (50). Subtherapeutic CPAP has been used successfully as a placebo in a few studies (3,35,51,52). For APPLES, the use of the active vs. sham CPAP devices will evaluate the long-term benefits of CPAP therapy for a six-month period. The major risk of the study is that the subjects randomized to the sham CPAP condition are without effective treatment for a seven-month period from the time of enrollment into the study. However, this period of subtherapeutic treatment for OSA appears brief considering that OSA remains largely undiagnosed and untreated by physicians, there is a significant delay from appearance of symptoms to seeking treatment on the part of the patient, and the majority of sleep clinics and laboratories have very lengthy waiting lists. We are also incorporating functional magnetic resonance imaging (fMRI) in APPLES, because the use of these technologies will assist us in determining if OSA-related neurocognitive deficits are associated with changes in cortical activation, and whether CPAP can reverse these changes.
If, as anticipated, we find that CPAP usage results in improved daily function for OSA patients, the most important benefit of the study includes advancing the knowledge that CPAP can effectively treat the debilitating consequences of OSA in the areas of neurocognitive function, mood, sleepiness, and quality of life. We further anticipate providing the necessary evidence to symptomatic individuals and health care providers that CPAP has a lasting positive impact on the nature of this sleep-related breathing disorder.

APPLES is designed to evaluate neurocognitive function, mood, sleepiness, and quality-of-life in OSA patients; however, there are other known consequences of OSA, which impact the cardiac, cardiovascular, and endocrine systems, as well as affecting a patient’s alertness, mental state, and driving ability. These individual and societal domains of human existence that are affected by OSA are described in this two-volume set of books on obstructive sleep apnea. In addition, these books also discuss upper airway surgery, oral appliances, and adjunctive and alternative treatments, all of which constitute the other major therapeutic approaches for OSA. It is the sincere hope of this author that these books will stimulate further research into the effects and consequences of OSA as well as its treatment, so that we can successfully diagnose and cure the majority of patients with this debilitating disease.

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12 Chapter 12. Risk Factors


TABLE 1 Risk Factors and Possible Risk Factors for OSA

<table>
<thead>
<tr>
<th>Risk factors for OSA</th>
<th>Possible risk factors for OSA</th>
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<tr>
<td>Specific diseases that are risk factors for OSA</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>Age</td>
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<td>Conditions causing macroglossia</td>
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<td>Fat distribution</td>
<td>Smoking</td>
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<td>Polycystic ovarian syndrome</td>
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<td>Neck circumference</td>
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<td>Craniofacial features</td>
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<td>Nasal resistance</td>
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<td>Gender</td>
<td>Alcohol</td>
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<td>Snoring</td>
<td>Body position</td>
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<tr>
<td>Neurological conditions (stroke, neuromuscular diseases, etc.)</td>
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<tr>
<td>Congenital abnormalities that cause retrognathia</td>
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<td>Menopause</td>
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<td>Ethnicity</td>
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Abbreviation: OSA, obstructive sleep apnea.


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Chapter 19. Endocrine Function and Glucose Metabolism


Obstructive Sleep Apnea Corticotropic (ACTH, Cortisol) – ?

Somatotropic (GH / IGF-1) Thyrotropic (TSH, T4, T3) –

Lactotropic

(Prolactin) – ? Gonadotropic (LH, FSH) – Glucose metabolism (glucose intolerance insulin resistance) –

FIGURE 1 Effects of obstructive sleep apnea on endocrine function and glucose metabolism. (–)

indicates an established negative effect whereas (?) indicates lack of conclusive evidence on the relationship between obstructive sleep apnea and a specific endocrine axis. Abbreviations: ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin like growth factor-1; LH, luteinizing hormone; T3,
triiodothyronine; T₄, thyroxine; TSH, thyroid-stimulating hormone.


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