Influence of Exercise, Weight Loss, and Exercise Plus Weight Loss on Sleep Apnea

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3. Background and Significance

Obstructive sleep apnea (OSA) is characterized by repeated episodes of upper airway obstruction during sleep, resulting in a reduction in (hypopnea) or complete pause (an apnea) of airflow despite continued attempts at inspiration. These obstructions are often terminated by arousal from sleep and are accompanied by surges in sympathetic activity. In severe OSA, these events can occur hundreds of times per night.

3.1. Prevalence and Risk Factors. The primary criterion for OSA is the apnea-hypopnea index (AHI), defined as the number of apneas (i.e., complete cessation of airflow for at least 10 sec) or hypopneas (i.e., > 50% reduction in airflow, accompanied by an arousal or an oxygen desaturation > 4%) per hour of sleep. Current estimates indicate that 15-25% of U.S. adults have at least mild OSA (AHI 5-10) and 5-15% of U.S. adults have at least moderate OSA (AHI ≥ 15).[28-30] However, because OSA is commonly undiagnosed, these are probably underestimates of the prevalence rates.[29] Indeed, a recent study indicated that 26% of adults were at high risk for OSA,[31] and with increased obesity rates, the prevalence of OSA will likely increase.[32,33]

There are numerous risk factors for OSA. OSA is more common among blacks, Hispanics, and Pacific Islanders than whites,[34] more common in men,[35] and more common with advanced age.[36] Excess body weight is a key risk.[32] A body mass index (BMI) > 28 is found in 60-90% of people with OSA.[32] Distribution of the excess weight is important; increased neck girth and high waist-to-hip circumference ratio are better predictors of OSA than BMI.[37] Schwartz et al. describe how central obesity leads OSA.[38] As fat accumulates around the torso, a mechanical load is imposed on the upper airway, resulting in decreased lung volume and increased upper-airway collapsibility.[38] Central obesity, in particular, has been associated with defects in neuromuscular control of the upper airway. These defects are probably partly due to elevations in inflammatory cytokines, which negatively influence upper airway neuromuscular function. Pharyngeal muscle abnormalities, family history, sleeping in the supine position, alcohol use, smoking, and menopause are also OSA risk factors.[39,40]

Studies suggest that the prevalence of OSA is approximately twice as high in veterans as in non-veterans.[2,3] This higher prevalence can be partly explained by a relatively high prevalence of many risk factors, including obesity and smoking. Stress-related sleep disturbance, noted especially in combat veterans,[41] also likely contributes to OSA, as apnea episodes are commonly precipitated by fragmented sleep patterns.[42]

3.2. Pathogenesis. Probably both anatomic and neural factors cause OSA.[43,44] The anatomic hypothesis is that OSA is due to a structural abnormality of the pharynx resulting from fat deposition, craniofacial abnormalities, or enlargement of the tongue, tonsils, or soft tissue. Research supports this hypothesis,[43] as increased volume of pharyngeal walls and tongue size have been associated with increased risk of OSA.[45]

The neural hypothesis is that apneics have impaired pharyngeal dilator muscle function at sleep onset.[43] Some evidence indicates that while awake, apneics have a relatively narrow pharyngeal airway lumen[46] and increased pharyngeal muscle activity,[47] presumably to protect against collapse.[47] Withdrawal of this muscle activity during sleep might cause upper airway collapse, but it is unknown whether the pharyngeal dilator activity at sleep onset is abnormally reduced in apneics or whether this occurs normally during sleep.[43]

3.3. Treatment Options.

3.3.1. PAP and Surgery. The two most common treatments for OSA are nasal positive airway pressure (PAP) and surgery. In severe OSA, PAP has been shown to effectively reverse upper airway obstructions during sleep,[48] though sleep impairment, daytime sleepiness, and some apnea often persist.[49] However, in mild to moderate OSA, PAP has not been as consistently efficacious.[50] Furthermore, there is equivocal evidence whether PAP causes improvements in cardiovascular and metabolic health,[12-14,51] neurobehavioral performance,[52,53] mood,[54] or quality of life.[55]

PAP also has low adherence. Its inconvenience and side effects (e.g., dry mouth, rash) possibly explain why adherence is only 50% in some studies, even with a liberal criterion of 4 hr of PAP use per night.[56]

One of the most disconcerting side effects of PAP is that it commonly elicits weight gain,[15,16] though some research has shown that PAP can elicit weight loss[57] or facilitate other weight loss treatment.[58] The potential for weight gain is a serious drawback for a disorder that is so clearly linked with obesity.

Surgical interventions target anatomical obstructions,[59] but there is little overall evidence to support the efficacy of surgery for OSA.[60] Furthermore, severe pain and post-operative infection commonly accompany the surgeries, and many surgical patients are dissatisfied.[60] There have been limited randomized trials of other strategies, e.g., upper airway dilator muscle stimulation,[61] upper airway muscle training,[62] and acupuncture.[63,64]

3.3.2. Weight Loss is a common first treatment for OSA. Estimates indicate that AHI is reduced by about 3% for every 1% drop in weight.[17,18] In a recent meta-analysis, interventions of similar duration and weight loss as proposed resulted in 34% decrease of AHI.[18] Weight loss likely promotes increased upper airway caliber by decreasing upper airway fat deposition and increasing lung volume by decreasing the mechanical load on the chest wall. Upper airway collapsibility has been shown to decrease substantially following weight reduction.

Behavioral weight loss studies typically involve weekly or twice monthly behavioral meetings with weight loss staff[65,66] and can elicit weight loss of 0.5-1.0 kg/week.[67-69] The structure of this treatment[69-72] focuses on the following: (1) Goal setting allows participants to establish measurable goals that they can track; study counselors use these goals to assess progress and provide tailored feedback about the rate of weight loss. (2) Self-monitoring[70] requires daily recording of foods and the kcal and macronutrients (g) in each food item; counselors review the journals to assess adherence to recommendations.[72] (3) Teaching stimulus control concepts involve creating home and work environments that, for example, are free of cues to overeat.[69]

Within the framework of these three components is information on nutrition and physical activity, including setting a goal (based on weight and height) of usually 1,200-1,500 kcal/day (≤ 20% of kcal from fat), and a goal of 150 minutes of moderate physical activity/week.[73] A meta-analysis of 37 intervention studies concluded that a 10% decrease in percentage of calories from fat was associated with 3 kg decrease in body weight,[74] and another meta-analysis of 33 RCTs and 10 cohort studies found consistent evidence of clinically meaningful weight loss elicited by lower fat intake.[75] Considering that the average percentage of calories from fat is approximately 50% in the US, reduction of fat intake to ≤20% (as proposed) could be highly beneficial.

In addition, several successful studies have used meal replacements (e.g., SlimFast™) to facilitate weight loss.[76-78] At 6 months, Look AHEAD participants who were in the highest quartile of meal replacement use were four times more likely to achieve a 10% weight loss.[76] Likewise, a 12-week RCT of obese subjects (N=100) randomized to a prescribed diet of 1,200-1,500 calories vs. a diet with the same caloric goal but with meal replacement found body weight reductions of 1.5%±0.4 SE and 7.8%±0.9, respectively.[77]

3.3.3. Evidence for Exercise as an OSA Treatment. Studies from our lab are reviewed in **4.1**.

3.3.3.1. Epidemiologic Evidence. Peppard and Young used data from the Wisconsin Sleep Cohort Study.[24] Following control for BMI, body fat, age, and sex, mean AHI for non-exercisers was 5.3, but AHI was 3.9, 3.2, and 2.8 for those reporting 1-2 h/wk, 3-6 h/wk, and > 7 h/wk of exercise respectively. As the weekly exercise duration increased, odds of having mild or moderate OSA decreased linearly. Compared with non-exercisers, those who exercised ≥ 7 h/wk had 0.33 and 0.31 the odds of having mild or moderate OSA.

Likewise, in the Sleep Heart Health Study, ≥ 3 h/wk of vigorous exercise significantly reduced the odds of having moderate OSA (OR = 0.68), even after control for daytime sleepiness and obesity.[25] A similar relationship was discovered between moderate exercise and OSA (OR = 0.80).

One study found that 6.1% of truck drivers at high risk for OSA were regular exercisers, but 82.4% of those at high risk reported no exercise.[79] Vazquez et al. found that those with RDI ≥ 50 reported less physical activity than those with RDI < 50.[80] Smaller studies have reported similar exercise-OSA associations.[81,82] However, causality cannot be established from epidemiologic data.

3.3.3.2. Experimental Evidence. Several studies have found reductions in OSA severity following exercise interventions that elicited no weight loss. An uncontrolled study by Giebelhaus et al. examined exercise as an adjuvant treatment for N=11 apneics receiving PAP.[26] The exercise involved separate weekly 2-h sessions of aerobic exercise and weight training for 6 months. A 30% reduction in AHI (32.8 to 23.6) was achieved after exercise. Also, in a study of 20 adults with mild to moderate apnea, Sengul et al. randomized participants to a 12-week no-treatment control or an exercise training treatment.[83] The exercise involved aerobic activity for 45-60 min per bout at 60-70 % VO_{2peak} for three days/wk, in addition to breathing exercises to improve ventilatory muscle strength. Exercise training elicited a ~25 % reduction in AHI (15.2 to 11.0) and improvements in quality of life and functional outcomes of sleepiness. Aerobic fitness increased by 14%.

Exercise training has been shown to lessen OSA severity in patients with chronic heart failure, who have a high prevalence of OSA. For 10 adults, a 6-month cardiac rehabilitation program reduced AHI by 65%

without changing body weight; 8 control participants had no change in AHI.[84] Similarly, 4 months of exercise in N=8 with chronic heart failure resulted in a 36% decrease in AHI, and improvement in nocturnal O_2 saturation, but no change in body weight.[85] However, the generalizability of these data to other OSA patients is unclear.

Studies involving exercise combined with weight loss have been sparse, and most have not adequately documented that exercise had occurred.[86-88] For example, in a recent study by Barnes et al.,[86] 12 obese adults completed a 16-week program involving a very low energy diet, and exercise training (mostly unsupervised). Reductions in body weight (12 kg, 13%) and AHI (25%) were found. Exercise was not monitored. However, the results suggest that the participants did not exercise much since aerobic fitness increased by only 6%, though baseline levels of the participants were in the lowest 10th percentile for their age.

We are aware of only one study, a trial by Norman et al.,[27] that adequately documented exercise combined with weight loss. Individuals with OSA (N = 9) participated in a 6-month exercise program involving moderate aerobic exercise (50-80% VO_{2max}) for 30-45 min on 3 days/wk, supplemented by light resistance training and brief dietary counseling. The intervention elicited a 46% reduction in AHI (21.7 to 11.8), an 18% improvement in aerobic fitness, and a 6% decrease in body mass (-6.2 kg).

Clearly, there is a need to further establish the efficacy of carefully monitored exercise and weight loss for OSA. The exercise+weight loss intervention proposed could well elicit greater improvements in AHI, as it will involve a similar intensity but more prolonged and frequent aerobic exercise, more intensive resistance exercise, and more weight loss (10%).

In summary, converging data suggest that exercise training reduces severity of OSA. Experimental studies have had limitations (e.g., small sample sizes and no control). Consistently, studies have shown that well-documented chronic exercise lasting ≥ 12 weeks and improving fitness by 10% elicit reductions in OSA of 25-30% independent of body weight changes. Studies with weight loss of 10-15%, but without exercise, have elicited similar or greater reductions in OSA. The limited research involving both moderate exercise training and significant weight loss has revealed a reduction in OSA of almost 50%. These results suggest additive benefits of exercise and weight loss for reducing OSA. Large RCTs are needed to confirm these results.

3.4. Possible Mechanisms for Improved OSA with Exercise. Although exercise and weight loss have some overlapping mechanisms for reducing OSA, there are rationales for additive effects of exercise and weight loss. Both dependent and independent of body weight changes, exercise may reduce OSA by increasing ventilatory muscle strength, including upper airway musculature. Increased resting ventilatory muscle tone could reduce compliance of the upper airway and, thus, diminish collapsibility. Greater pressure developed by ventilatory muscles may also counteract a tendency for airway obstruction via a more efficient exchange of air.

Particularly in the obese, a decrease in chest wall compliance could reduce the force-generating capacity of inspiratory muscles and predispose one to upper airway collapse due to reduced pressure development. Also, low static lung volumes (e.g., expiratory reserve volume) are associated with apnea and nocturnal oxygen desaturation. Exercise training has been shown to improve respiratory muscle strength in people with respiratory muscle weakness and in sedentary adults.[89]

Chronic exercise may also reduce OSA severity by decreasing fatigability of ventilatory and upper airway muscles.[90,91] The upper airway (UA) dilator muscles of apneics consist of a greater proportion of fast-twitch muscle fibers compared with those who do not have OSA,[92] conferring greater fatigability (and possibly progressive loss of force generation during sleep).[93] In animals, chronic exercise elicits an oxidative fiber-type shift of the UA dilator muscles,[94] and chronic low-frequency electrical stimulation induces similar muscle fiber alterations of the genioglossus.[95] Activation of the UA dilator muscles increases in parallel with increasing exercise intensity.[96] Similarly, training the UA dilator muscles during wakefulness, either via wind instrument practice or electrical stimulation, has been shown to reduce AHI.[62,97]

Exercise-induced augmentation of serotonergic output could also plausibly reduce OSA severity. The “wakefulness stimulus” that supplies neural drive to the UA dilators while awake is primarily due to serotonergic input to the hypoglossal nerve.[98] Blunting the sleep-associated withdrawal of neural drive to the UA dilators by increasing serotonergic outflow could preserve UA patency and reduce OSA severity.[99] Serotonergic drugs have been mildly efficacious at reducing OSA severity.[100] Increases central serotonin synthesis after exercise training[101] could have a similar effect. Exercise could also reduce OSA via reduced sleep fragmentation,[102] thus reducing the frequency of respiratory events by promoting stable sleep and less ventilatory instability.[103]

Exercise may also reduce OSA by preventing fluid displacement from the lower extremities to the upper body during sleep. Conversely, Redolfi et al. found that duration of daytime sitting was strongly associated with AHI[104] and with lower body retention of fluid that was displaced to the upper body during sleep.

3.5. Safety Issues for Exercise in Individuals with OSA. Although individuals with sleep apnea are commonly sedentary and overweight with multiple cardiovascular disease (CVD) risk factors, studies have uniformly found vigorous acute exercise to be safe for these individuals.[105] In these studies, patients with moderate or worse OSA have been able to successfully complete cardiopulmonary exercise testing without adverse incidents (e.g., ischemia, chest pain). Experimental studies have reported no adverse effects of exercise training.[20] Thus, supervised exercise is still considered safe and recommended for this population.

3.6. Comorbidities of OSA and How Exercise May Modify Them. The effects of OSA are wide-ranging, negatively impacting cardiovascular, metabolic, cognitive, and psychological function. There are strong rationales for expecting that exercise would elicit positive changes in many of these consequences of OSA.

3.6.1. Cardiovascular and Metabolic Health. Repeated episodes of hypoxia, increased sympathetic control, and increased arterial pressure resulting from OSA all contribute to the development of CVD.[4,5] These effects stimulate an inflammatory response, as documented by chronically elevated levels of inflammatory cytokines (e.g., tumor necrosis factor α [TNF-α], interleukin-6 [IL-6]) and the systemic inflammation marker C-reactive protein (CRP).[106,107] As a result of chronic inflammation, a progressive cascade of endothelial dysfunction, atherosclerosis, and CVD eventually develops. A consistent association of OSA with hypertension has been shown, as an AHI ≥ 15 has been associated with a 3-fold increased risk of developing hypertension.[108] The risk of myocardial infarction, mortality from CVD, and stroke are also greater in individuals with OSA.[4,109]

OSA is also associated with lower heart rate variability (HRV),[110] which is predictive of cardiovascular disease and mortality.[111] Conversely, OSA treatment results in improved HRV.[110] Metabolic dysfunction is prominent in OSA, as insulin resistance, impaired glucose tolerance, and increased visceral fat are all associated with OSA.[6,106] Much of the metabolic dysfunction can be attributed to excess body weight.[112] Exercise has well-documented effects of reducing blood pressure, increasing HRV,[113] and lowering the risk of CVD. Exercise elicits dramatic improvements in metabolic function; both acute and chronic exercise have elicited improved insulin sensitivity, glucose tolerance, and glycemic control.[114] **This study will assess changes in resting heart rate (HR), HRV, blood pressure, multiple markers of inflammation (e.g., CRP, IL-6, TNF-α), body weight/composition, insulin, glucose, lipids, and hemoglobin a1c.**

3.6.2. Daytime Sleepiness and Fatigue. Exercise reduces daytime sleepiness in individuals with OSA,[81,115] and is well known for its ability to reduce fatigue and increase energy, including in apneics.[81] **This study will include the Functional Outcomes of Sleepiness Questionnaire to measure this.**[116]

3.6.3. Depression, Anxiety, Quality of Life. Depression and anxiety are commonly associated with OSA, as approximately 25-45% of apneics have an affective disorder.[117] OSA has also been clearly associated with impaired quality of life. Exercise training has consistently elicited improvements in all of these variables

3.6.4. Sleep Quality. Due to airway obstructions and resulting arousals, apneics experience highly fragmented sleep. The sleep fragmentation, in turn, is associated with increased daytime sleepiness. Epidemiological and experimental evidence has indicated that exercise improves sleep quality.[118] Moreover, exercise interventions in populations with greater sleep problems have consistently reported significant improvements in sleep quality. Improved sleep was also found in an experimental study of apnea patients.[19] **This study will assess both actigraphic and subjective sleep quality (sleep diary, Pittsburgh Sleep Quality Index[119]).**

3.7. Significance. OSA is a dangerous disorder affecting ~10-20% of adults and 20-40% of veterans. OSA will likely become more common as obesity prevalence has increased. Successful treatments remain elusive. Exercise and weight loss could be uniquely helpful for preventing/reversing sequelae of OSA. If exercise + weight loss elicited a chronic OSA reduction of ≥50%, this could be a very important treatment alternative.

4. Work Accomplished

4.1 Shawn D. Youngstedt, PhD

4.1.1. Studies of Veterans. Dr. Youngstedt has substantial experience studying veterans. He was the PI of a recent VA Merit-funded RCT that demonstrated significant benefit of bright-light treatment for PTSD, depression, and sleep in OIF/OIF veterans (N=65). He was also the PI of a DoD study of exercise treatment of combat-related PTSD (n=40). Many of the these studies' procedures were similar to those proposed here.

4.1.2. RCT of the Effects Exercise Training on OSA and Sleep. In our recent 2-year study,[19-21] for Chris Kline's PhD dissertation, we randomized 43 OSA patients to an exercise or stretching control that involved many of the same procedures as proposed here. However, herein we are proposing several changes in the recruitment methods and inclusion criteria that should enhance recruitment (described in **5.3**).

4.1.2.1. Initial Screening. One thousand individuals underwent phone screening. Four hundred underwent further screening with questionnaires sent in the mail, among whom ~10% participated in the study. Considering the large number of OSA cases at the Phoenix VA (~30,000) and the number of new cases per week (n=30), we are confident that we will be able to recruit a sufficient number of subjects. Other methods, including a run-in period with three visits to the laboratory over a week, were similar to those proposed. .

Many (n=104) of the candidates were excluded at the stage of screening because they were no longer interested, and a primary disincentive was that they were to avoid trying to lose weight. The potential for weight loss will likely make the proposed study relatively more attractive to candidates. About 200 other candidates were excluded for reporting that they were trying to lose weight. For the present study, we propose a less conservative approach based on this criterion, in which we will exclude only those individuals who have lost ≥5% in the previous 6 months weight or who are involved with an experimental weight loss program or another structured weight loss regimen, such as Weight-Watchers (**5.3.3.1**).

4.1.2.2. Retention and Adherence. Of the N=43 participants who were randomized to the treatments, 5 dropped out of the study at an average of 4.6±0.2 weeks into the intervention. Four participants in the exercise training intervention needed to switch from the treadmill to cycle ergometer training due to temporary development of shin splints. Based on this finding, as well as the goals of customizing the exercise to participants' preferences and being more inclusive in participant selection, participants in the proposed study will perform treadmill, cycle ergometer, or elliptical trainer exercise (or some combination). The participants who completed all 12 weeks of the exercise training intervention attended 93.1±1.7% of the prescribed sessions and completed 88.6±2.1% and 84.4±2.9% of the prescribed aerobic and resistance exercise doses, respectively. The participants who completed the 12-week stretching intervention attended 86.9±2.0% of the prescribed sessions. This high adherence results can be attributed to the screening and personal attention paid to the participants, as proposed here. Participants also adhered to the requests to maintain their usual physical activity and dietary habits, as assessed with an odometer and questionnaire, respectively.

4.1.2.3. Influence of Treatment on OSA Severity. Compared with the stretching control (24.4±5.6 to 28.9±6.4), exercise training elicited a significant reduction (32.2±5.6 to 24.6±4.4) in AHI ($F_{1,40}$ = 9.54, P < 0.01).[19] The magnitude of effect for supine AHI (g = -0.46) was similar to that for total AHI (g = -0.45), and the amount of time spent supine did not change from pre- to post-intervention. Treatment success, defined as post-intervention apnea-hypopnea index < 20 and reduction ≥ 50% from baseline, was noted in 25% and 7% of the exercise and stretching participants, respectively. Treatment response (≥20% reduction in AHI) was found in 63% and 21% of the exercise and stretching participants, respectively (Fisher exact test, p=0.02).

4.1.2.4. Psychometic Variables.[20] Compared with the stretching treatment, exercise elicited significant improvements in depressive symptoms, fatigue, and vigor, and several aspects of health-related quality of life (P < .05). Scores on the Epworth Sleepiness Scale and the Functional Outcomes of Sleepiness Questionnaire (FOSQ) also improved following exercise versus control to a similar degree in terms of effect sizes (d > 0.5), though these changes were not statistically significant with the sample size tested. The proposed sample of N=90 has adequate power for showing statistically significant changes in the FOSQ.

4.1.2.5. Cardiovascular Measures.[21] For the previous study, we also recruited a control group (n=9) of individuals who had an AHI of < 15, but were otherwise similar to the experimental group, in terms of age, BMI, etc. Baseline assessments of heart rate recovery from maximal exercise were compared between the experimental subjects (who had AHI of ≥15) and the control subjects, who did not undergo the intervention. Heart rate recovery following maximal exercise, a well-established marker of parasympathetic reactivation and SNS withdrawal following exercise, was significantly blunted in the OSA participants compared with the control participants, as assessed at 1 min (P=.03), 3 min (P=.02), and 5 min post-exercise (P=.03). Moreover, impaired heart rate recovery was significantly correlated with OSA severity. Following exercise training, the OSA subjects had a significant improvement in heart rate recovery, indicating improved autonomic regulation. In the proposed study, we will assess the effects of the treatments on blood pressure and heart rate variability.

4.2. Lilibeth A. Pineda, MD, director of Sleep Medicine at the Phoenix VA, will refer subjects to the study, help diagnose and screen new cases, and supervise the assessment and scoring of the PSG recordings.

4.3. Ashley Bremer, BS, RD, is director of the Move! program at the Phoenix VA. In pioneering research of obese veterans (n=20) by Bremer et al. (Food and Nutrition Conference & Expo, Houston, October 20, 2013),

a 6-16 week intervention involving behavioral counseling (as proposed here) and strict meal replacement elicited an average body weight reduction of 16%, and >20% for veterans who were in the program for over 6 weeks. Moreover, the intervention resulted in dramatic improvements in glucose regulation, lipids, and blood pressure; a decreased use of medicines; and postponement of knee surgery in some patients due to lowered pain. Ms. Bremer will lead the weight loss interventions for the study. Moreover, Dr. Gabrielle Turner-McGrievy, who also has extensive experience accomplishing weight loss, will serve as a consultant for the weight loss.
4.4. Michael Todd, PhD, is a biostatistician with expertise in statistical analysis of health behavior data. He will be working with Dr. Youngstedt on an R01 project examining effects of chronic moderate sleep restriction in older long sleepers and average sleepers for which similar analyses of repeated measures data will be conducted. For the proposed project, Dr. Todd will provide guidance on data analyses and interpretation.
4.5. Megan Petrov, PhD, a clinical psychologist (license pending) and sleep scientist, will provide counseling and/or immediate referral to participants who experience psychological difficulties during the experiment; assess potential disparities in OSA and in responses to the treatments; and facilitate minority recruitment.

5. Work Proposed

5.1. Timeline. The proposed 4-year randomized controlled trial will assess N=90 veterans (ages 18-60 years) with OSA. Each year, 22-23 participants will be assessed in 18-week cycles, including screening, baseline, and a 16-week intervention. Follow-up assessments will continue for 3 months after the intervention.

5.2. Design Overview. Following extensive screening and baseline assessment, overweight/obese veterans with OSA (N=90) will be randomized to one of three 16-week treatments: (1) **Exercise Alone,** consisting of aerobic and resistance exercise (n=30); (2) **Weight Loss Alone** (n=30), with a goal of 10% reduction of body weight; or (3) **Exercise + Weight Loss** (n=30). Before and after the treatments, participants will undergo 5 days/nights of home-based actigraphic and diary-assessed sleep, and 1 night of laboratory polysomnographic (PSG) recording to assess OSA severity. Secondary co-morbidity measures will include body weight/ composition, blood pressure, heart rate variability, glucose, insulin, hemoglobin A1c, lipids, and inflammation.

5.3. Volunteer Recruitment and Screening. The study sample will be drawn primarily from the Phoenix VA. There are over 30,000 Phoenix VA veterans who have been diagnosed with OSA. Approximately 50% of patients referred to the Phoenix VA sleep laboratory are cases of suspected OSA who must wait an average of 20 weeks between referral and treatment (usually PAP). Each week, there are about 25 new cases of Phoenix VA vetearans. As observed elsewhere,[11,17] PAP adherence is very low in these patients.

For the present study, several steps will be taken to recruit participants. First, other VA physicians and nurses will be informed about the prevalence, predictors, and consequences of OSA and asked to refer suspected cases to the VA Sleep Laboratory. Second, patients who have been referred to the sleep laboratory for suspected OSA and who appear to meet other inclusion criteria (based on VA medical records) will be sent a letter inviting participant by Dr. Lilibeth Pineda (**Appendix 3**). If deemed necessary by the IRB, we will acquire HIPAA waiver to review the records and contact these patients, as we have done for other VA studies. Third, once patients are diagnosed with OSA, they will be informed/reminded about the study and that they may still enter the study in the future. We will also recruit veterans by notifying non-VA sleep clinics about the study and via advertisements in VA, ASU, military media, newspapers,,and flyers posted throughout the VA and on TV. Recruitment efforts will be structured to reflect the demographics of Phoenix VA veterans.

5.3.1. Screening Process. Participant recruitment will follow a multistage process of describing the study, obtaining consent, and screening for eligibility. Inclusion and exclusion criteria are shown in **Table 1**; they were developed to maximize participation of veterans with OSA while minimizing the risks of adverse outcomes.

5.3.1.1. Initial Screening. Prospective participants will contact the lab for further details and take a 10-min phone screen to determine initial eligibility. Individuals who remain eligible will be mailed a packet with further study information and additional screening questionnaires, including questions about personal health history, medication use, sleep history, OSA-specific symptoms, and the Berlin Questionnaire,[120] which can predict AHI of > 5 with a sensitivity of 0.86, specificity of 0.77, and a positive predictive value of 0.89. Also included will be a letter detailing the risks of OSA (e.g, sleepiness, accidents); a warning that treatments might increase sleepiness; advice about how to recognize sleepiness and steps to prevent/counteract it; advice that there are better-established treatments for OSA, which subjects might receive more rapidly outside the VA.

Our previous study excluded hundreds of individuals based on the criterion that that they reported that they were trying to lose weight. Considering the high percentage of overweight individuals who try and fail to

lose weight, we believe and such a criterion is too restrictive. Consistent with successful weight loss studies, our proposed screening should reduce the number of "false positive" exclusions based on this criterion.

Many exercise studies (including our OSA trial) have involved very strict exclusion criteria. We recognize that safety is of utmost importance, but guidelines of the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) suggest that such restrictive criteria are not necessary, particularly not for moderate exercise. Indeed, moderate exercise is one of the healthiest interventions for many conditions and is annually recommended for thousands of patients who are less healthy than the proposed sample. Moreover, considering the high prevalence of many of these conditions among veterans with OSA, adhering to such stringent criteria would limit our ability to recruit an adequate sample size or a representative sample of veterans with OSA. Following ACSM/AHA guidelines, we propose steps that will allow inclusion of a sample with some disease, but without significant risk associated with the study.

Table 1. Study inclusion and exclusion criteria.

Inclusion criteria:	
Age	18-60 years of age
Moderate-severity OSA	AHI ≥ 10 at screening
Overweight/obese	BMI ≥28
Physically inactive	Sedentary lifestyle (planned activity for purpose of health < 2 days/week)
Stable weight	Not engaged in weight loss study or program
Stable medications	Medications for thyroid, cholesterol, blood pressure, and other conditions at same dose for ≥ 2 months
Informed consent and acceptance of randomization	Must be capable and willing to provide informed consent and accept randomization assignment
Exclusion criteria:	
Current OSA treatment	Current use of PAP, dental devices, etc. for OSA treatment. Past PAP or oral appliances are not exclusions if discontinued ≥2 months before study
Significant disease	Known or signs/symptoms* of cardiovascular,** metabolic,† or pulmonary†† disease
Uncontrolled hypertension	Blood pressure > 159/99 mmHg
Unable to exercise	Musculoskeletal, orthopedic, neuromuscular, or other conditions that do not allow exercise or where exercise is contraindicated
Accident	Any accident attributable to sleepiness in previous 3 years
Pregnancy	Current pregnancy/planning to become pregnant
Clinically judged unsuitable	As evaluated by supervising medical physician

* Signs or symptoms include angina, dyspnea, dizziness, orthopnea, ankle edema, intermittent claudication, heart murmur, or shortness of breath with usual activities. ** Includes cardiac, peripheral vascular, renal, chronic heart failure, or cerebrovascular disease. † Includes Type 1 and Type 2 diabetes mellitus or liver disease. †† Includes chronic obstructive pulmonary disease, interstitial lung disease, or cystic fibrosis.

5.3.1.2. Laboratory Visit 1. Individuals who have previously been diagnosed with OSA, or who were classified as "high risk" for OSA by the Berlin Questionnaire and are otherwise eligible, will be invited to the lab for further study orientation and screening. They will sign an informed consent approved by the Phoenix VA and ASU IRBs. Participants will then be screened for minimal cognitive function, i.e., scores >26 on the Min-Mental State Examination. The medical records will be searched for screening criteria, and the participants' primary care physicians will be contacted and given an opportunity to recommend against study participation.

5.3.1.3. Home OSA Screening. All prospective subjects will undergo screening for OSA in their homes. Each participant will be assessed with the Apnea Risk Evaluation System (ARES) (Watermark, West Palm Beach, FL). The device is relatively noninvasive, with probes on the forehead, oxygen desaturation from the finger, a respiratory effort sensor belt, and nasal cannula. The ARES has been well validated against PSG. An AHI of ≥10 recorded with the ARES will be the criterion for advancing to subsequent screening steps.

5.3.1.4. Laboratory Visit 2: Physical Exam. A comprehensive medical history and physical examination will further insure the safety of the study. Exclusion criteria will include signs/symptoms of cardiovascular disease, including angina, dyspnea, dizziness, orthopnea, ankle edema, heart palpitations, intermittent claudication, heart murmur, or shortness of breath with usual activities; chronic heart failure;

uncontrolled hypertension (>159/99 mm Hg); cerebrovascular disease; chronic heart failure; Type I or Type II diabetes; liver disease; chronic obstructive pulmonary disease; interstitial lung disease; and cystic fibrosis. In a departure from many previous exercise studies, the following will **not** necessarily be exclusions (depending on severity and approval of the subjects' physicians): thyroid disorders, smoking; use of beta-blocker drugs; and musculoskeletal problems (if participants can perform cycling or elliptical training in lieu of treadmill exercise).

The participant's resting EKG will be assessed by a physician or nurse (NP) who is certified to diagnose abnormalities and ascertain the safety of moderate exercise. The participant will then perform a MD- or NP-supervised maximal treadmill or cycle ergometer test, excluding for ischemia and EKG abnormalities.

5.3.1.5. Run-in Period. Following initial acceptance into the study and before baseline testing, participants will be required to visit the laboratory on three separate occasions within a one-week period. During each visit, participants will view 30-min video programs developed by the research team that will include lifestyle recommendations for improving sleep and reducing sleep apnea severity. Each visit will last approximately 45 min, with the last 15 min allowed for discussing any issues with a trained research staff member. Prior studies involving similar lifestyle recommendations have not resulted in significant changes in diet or physical activity. These run-in sessions will be scheduled at times convenient for each participant, but it will be clearly conveyed that attendance at these sessions is required for study eligibility. This run-in will help insure that participants are willing to make a commitment to study participation. Similar run-in protocols have resulted in excellent adherence to our previous study of exercise for sleep apnea[19] and in other clinical trials.

5.4. Baseline. During a 1-week baseline period, participants will follow their usual sleep and activity habits.

5.5. Treatment Randomization, Instructions, Adherence Strategies. Following baseline, participants will be randomized to one of three 16-wk treatments: (1) **Exercise Alone** (n=30) (**5.5.1**); (2) **Weight Loss Alone** (n=30) (**5.5.2**); or (3) **Exercise + Weight Loss** (n=30) (**5.5.3**). Randomization will be stratified by age (< vs. ≥ 40), sex, and severity of screening AHI (10-25 or > 25) in blocks of 6, using a computer-generated list.

The duration of the intervention was chosen so that there would be sufficient time to detect chronic adaptations to the interventions without placing undue burden on the participants. Sixteen weeks is sufficient time to detect chronic exercise benefits[114] and to achieve the targeted weight loss using the moderately challenging proposed procedures. Following randomization, treatment expectancy for changes in OSA severity, sleep quality, daytime sleepiness, mood, and health will be assessed via 5-point Likert scales.

Lifestyle Activity and Eating. Because lifestyle changes could mask the effects of the experimental exercise and weight loss, participants will be asked to maintain their normal activity and eating habits, except as prescribed for the study. In our previous trial, such requests were followed, as evidenced by the lack of weight loss[19] and the proposed monitoring methods.

To monitor changes in unsupervised physical activity, participants will wear a waist accelerometer from baseline through the post-intervention assessment (except during experimental exercise). This device has been validated against energy expenditure estimated with oxygen consumption and doubly labeled water. It records daily steps and time spent in light, moderate, and vigorous activity. Data will be analyzed in 2-wk bins.

Food intake will be assessed with the Automated Self-Administered 24-hr diet recall (ASA24) (http://riskfactor.cancer.gov/tools/instruments/asa24/), to be completed twice during baseline and during Weeks 8 and 16 of treatment. The recall is among the highest quality with the least bias and subject burden.

Adherence Strategies. Adherence will be promoted with a personalized approach to the intervention. One staff member will serve as the principal contact for each participant. In our experience, participants prefer to work with one person to make appointments, etc. Staff will be trained to develop rapport with the participant by discussing expectations of the participant's and staff's roles. We have found that personalizing this relationship in a professional context enables participants to be more direct about problems, thus enabling a strong foundation for problem solving. Prior to randomization, staff will share expectations regarding study attendance requirements and will ask participants about their expectations regarding randomization. During pre-randomization visits, we will ask participants whether they can make this type of commitment. If they cannot, we will exclude them. If they believe they can, we will ask them to sign a contract that affirms their commitment to attend their scheduled exercise and diet counseling. If participants are nonetheless unable to attend scheduled appointments, we will ask them to call as far as possible ahead of time to reschedule. If a participant misses an exercise session, his/her assigned staff will call to check-in, encourage attendance, and help

troubleshoot barriers. The VA Exercise Center (EC) will be open 7 days per week for 15 h/day to accommodate a variety of schedules. Because it is unrealistic to expect 100% adherence to the exercise protocol, unforeseen circumstances (e.g., an unexpected trip out of town) might prevent an individual from coming to the EC but might still allow him/her to continue to exercise. In these situations, we will provide the participant with a Polar HR monitor and instruct him/her how to keep his/her HR at the desired level for the required number of minutes. We will have precise data from the participant's laboratory exercise sessions and can use this information to develop a specific and accurate exercise prescription. In these situations, we will also ask participants to keep a diary of the frequency/duration of these sessions. We will download data from the HR monitor to confirm the diary data. Similar accommodation for missing the nutritional counseling will be arranged. If necessary, up to two counseling sessions will occur via telephone. We will allow four unsupervised exercise sessions throughout the trial. In addition, the run-in and incentives will help ensure adherence.

5.5.1. Exercise Alone. Participants in the Exercise Alone treatment (n=30) will report to the VA EC 4 times per week for 16 consecutive weeks. To increase adherence to this treatment, participants will be free to choose the dates and times that they exercise (between 0600 and 2100 hr), provided that they remain consistent throughout the intervention. Adherence to the intervention will be defined by attendance and performance of the prescribed exercise. After obtaining resting measures of HR and BP, most of the subjects (75%) will exercise under the direct supervision of a certified clinical exercise physiologist, indicating significant training in emergency procedures. The relatively healthy subjects will be monitored by a trained research associate.

The Aerobic Exercise Component will be performed on treadmills, cycle ergometers, or elliptical trainers. Allowing any/all of these exercise modes will allow inclusion of participants who might be unable to safely or comfortably perform treadmill exercise due to musculoskeletal problems; customization of the exercise to participants' preferences; and reduction of the risk of muscle soreness and injuries. The duration of the aerobic exercise per session will progressively increase from 15 min during Week 1 to 30 min during Week 4. Thereafter, the duration of the aerobic exercise on the days that include resistance training will remain at 30 min. On the two days/week that do not include resistance training, the duration of treadmill exercise will continue to progressively increase by 5 min/wk until 45 min is reached in Week 7. This gradual ramping of exercise minimizes muscle soreness and the risk of injury. Each exercise bout will be preceded and followed by a warm-up and cool-down, not included in the exercise bout. The frequency of aerobic exercise was chosen because improvement in aerobic fitness greatly diminishes beyond 4 days/wk. Intensity of the exercise for most participants will be 55-70% of each participant's estimated maximum HR, a range considered to be of moderate intensity and consistent with ACSM recommendations. For participants taking medications that alter HR responses, intensity will be prescribed at moderate intensity levels on the Borg Ratings of Perceived Exertion (RPE) scale, on which they will be educated regarding judgment of intensity. HR will be continuously assessed with a telemetric monitor, and blood pressure will be intermittently evaluated with manual sphygmomanometry. Treadmill speed/grade and cycle ergometer speed will be manipulated to keep each participant within his/her prescribed HR or RPE range. Total weekly aerobic exercise will be 150 min, the amount recommended by the ACSM and AHA. The increase from Week 1 to Week 16 in the speed of the treadmill or cycle ergometer required to elicit this HR will be recorded as an index of fitness improvement.

Resistance Training Component. Resistance exercise (30 min) will be performed immediately following the aerobic exercise on two nonconsecutive days/wk. Eight exercises (separated by 90-sec rest) targeting the chest, upper back, shoulders, biceps, triceps, quadriceps, hamstrings, and calves will be performed. One set of each exercise for 8-12 repetitions will be prescribed. Similar muscle groups will not be stressed in consecutive exercises. For the bench press and leg press, participants will initially set the training intensity to 60% of their baseline 3-repetition maximum. For the remaining exercises, staff will help establish optimal weight, and weight will be increased once 12 repetitions can be performed while maintaining proper form. This prescription is consistent with ACSM's definition of moderate-intensity. We chose two sessions/wk to reduce the risk of injury and because it produces ≥75% of the strength benefits seen from ≥3 sessions/week. One set per exercise was chosen to reduce time burden, and because research shows minimal strength improvements with more sets. Consistent with ACSM guidelines, weekly resistance exercise will be 60 min.

5.5.2. Weight Loss Alone. Participants in the Weight Loss Alone treatment will attend 16 weekly diet counseling sessions. Prior to the intervention, participants will meet with a weight loss counselor who will calculate energy and fat gram goals for the participant to produce a 500 kcal/day deficit in energy intake. Energy from fat will be ≤20% of total energy intake. Participants will be provided with structured meal plans, which will provide them with caloric goals for meals and snacks, along with meal ideas. Additionally,

participants will be asked to replace one meal with a meal replacement bar or shake (e.g., SlimFast™ or Special K™ shakes or bars) each day. Participants will also be provided with a pocket-sized journal to record dietary intake activity each week and a book of calorie and fat gram amounts. The goal of the intervention is to induce a 10% weight loss within 16 weeks. Previous studies with similar methods have shown an average loss of 0.5-1.0 kg/week, which would produce a weight loss range of approximately 8-16%. The plan would be less aggressive than that of co-investigator, Bremer et al., but we are aiming for half the weight loss that they found.

At the beginning of each week, participants will be e-mailed or mailed a lesson covering a new topic that they will be asked to read prior to meeting with a counselor. These lessons will include calculating energy needs for weight loss; importance of self-monitoring of calories and how to do it; portion control tips; dining out and grocery shopping tips; dealing with friends and family support; dealing with temptations and special occasions; emotional eating; understanding behavior chains; ; relapse prevention; keeping progress going; etc. Each lesson will include an interactive worksheet that participants can complete prior to their weekly meeting with the weight loss counselor. In each session, a trained weight loss counselor will go over the brief behavioral weight loss lesson. The counselor will then review the weekly calorie and fat gram journals and provide feedback on dietary intake and weight loss pattern. Participants will be provided with a weekly supply of bars and/or shakes at each visit in flavors that they choose (1 meal replacement per day).

Each weekly nutrition session (30 minutes) will include the following: (1) review of the previous week's goal, (2) overview of the previous week's diet journal, (3) recommended tips for improving or maintaining current diet behaviors, (4) overview of the behavioral lesson topic for the week, (5) and a goal-setting activity. Participants who do not arrive for their counseling session will be offered an alternate day and time to complete their meeting that week. If they are unable to attend a meeting that week, participants will be offered a phone counseling session. Participants who are not losing at the expected rate of 0.5-1.0 kg/week will receive additional information on strategies that may help them to increase the rate of weight loss.

5.5.3. Exercise + Weight Loss. Participants in the Exercise + Weight Loss treatment will perform the same exercise and weight loss protocol described for Exercise Alone and Weight Loss Alone, respectively.

5.6. Measurements. A timeline for the study measurements is displayed in **Table 2**.

Table 2. Experimental Measures during the 2-Week Baseline and 12-Week Intervention.

Pre-Treatment	Treatment Weeks 1-16	Post-Treatment
	(1) Exercise Alone (2)Weight Loss Alone (3) Exercise + Weight Loss	
1. 5-Day home sleep (actigraphy/diary) 2.1-Night PSG-Apnea, HRV 3. Weight/DEXA 4.Blood pressure 5. Insulin, glucose, hemoglobin A1c, lipids 6. Inflammation 7. ASA24-Diet Recall 8. FOSQ, PSQI, snoring	Wks 4, 8, 12, 16: FOSQ, PSQI, snoring End of Wk 8: ASA24 Wks 5, 10: Physical: blood pressure, insulin, glucose, and hemoglobin a1c	1. 5-Day home sleep (actigraphy/diary) 2.1-Night PSG-Apnea, HRV 3. Weight/DEXA 4.Blood pressure 5. Insulin, glucose, hemoglobin A1c, lipids 6. Inflammation 7. ASA24 8. FOSQ, PSQI, snoring
Waist Actigraphic Assessment of Activity		
Key. PSG-Polysomnography, DEXA-Body Composition, FOSQ-Functional Outcomes of Sleepiness; PSQI-Pittsburgh Sleep Quality Inventory, ASA24-Dietary Recall		

5.6.1. Sleep and OSA Assessment. Both at baseline and following completion of the 16-week intervention, sleep will be assessed objectively for 5 days/nights in the home and for 1 night in the sleep laboratory.

Home Recording. Participants will be asked to maintain their sleep habits. Sleep will be assessed with wrist actigraphs, which are used to estimate sleep/wakefulness based upon validated algorithms associating wrist movement with PSG. Actigraphy probably provides the best measure of daytime napping, an indication of sleepiness. Measures will include sleep onset latency, wakefulness after sleep onset, time in bed (TIB), total sleep time (TST), sleep efficiency (SE), and daytime napping. Sleep apnea will be assessed with the ARES on the last night of assessment at the end of the intervention and then compared with screening and follow-up.

Actigraphic data will be supplemented with a daily sleep diary, which will assess subjective perceptions of sleep onset latency, wake time after sleep onset, time in bed, total sleep time, insomnia, and sleep quality.

Self-reported sleep measures are also deemed important indications of treatment effects. Actigraphic and sleep diary data will be averaged over the 5 days of assessment by an investigator blinded to treatment. Subjective sleep will also be assessed with the Pittsburgh Sleep Quality Inventory,[119] as described in **5.6.3**.

Laboratory PSG. Following actigraphic recording, sleep will be assessed for one night in the laboratory. Note that whereas screening for OSA will occur at home with the ARES, experimental PSG measurement before and after the treatment will occur in the VA Sleep Laboratory. Participants will arrive in the laboratory approximately 2 h before their usual bedtimes. A fixed 8-hr sleep schedule, coinciding with each participant's usual schedule, will be used. Standard PSG preparation will occur beginning 1 h prior to bedtime. Assessments will include EEG, EOG (eye movement), EMG from the chin and legs, ECG, thoracic and abdominal belts to monitor respiratory effort, a nasal thermistor to measure airflow, and a pulse oximeter to monitor oxygen desaturation. Blinded measures of sleep onset latency, wake time after sleep onset, total sleep time (TST), sleep efficiency (% time asleep), percentage of TST spent in stage 1-3 NREM and REM sleep, SaO_2 (i.e., minimum SaO_2 and the percentage of TST spent with SaO_2 < 90%), oxygen desaturation index (ODI; i.e., the number of SaO_2 desaturations ≥ 4% per hour of sleep), arousal index (i.e., the number of arousals per hr of sleep) and AHI will recorded. AHI will also be summarized by sleep stage and body position. A microphone will quantify the percentage of sleep time spent snoring and the intensity of the snoring (in dB). At the baseline recording, having an AHI of < 10 will result in study exclusion.

PSG will include the measurement of heart rate variability (HRV) with the Firstbeat Bodyguard device (Firstbeat Technologies). OSA has been associated with reductions in HRV during sleep, and, conversely, improvement in OSA has been associated with increases in HRV. Software in the monitoring device will be used to calculate the Fast Fourier Transformed power spectrum of HRV for each participant, providing data on very low frequency (VLF), low frequency (LF), and high frequency (HF) power; peak frequency; peak frequency power) and time-domain variables (heart rate mean and standard deviation). HRV coherences is defined as the highest HRV in the LF band (0.04-0.15 Hz) of HR frequency spectrum. It is calculated as the ratio of HRV variance (power) in the LF peak to the remainder of variance in the HRV frequency spectrum. HRV coherence represents parasympathetic tone and will be the metric used for the present study.

5.6.2. VA Laboratory Assessment. Following the home and laboratory sleep assessment at baseline and post-intervention, participants will undergo 90 min of VA laboratory assessments by technicians blinded to treatment. Following a 12 h fast and 24 h abstention from exercise, participants will arrive in the lab in the morning. Upon arrival, participants will change into hospital "scrubs" of predetermined size and weight.

Blood Pressure. After sitting for 10 min, blood pressure will be assessed with standard procedures.

Blood Draw and Measures. A phlebotomist will insert a catheter into the antecubital vein and draw a 20 ml sample. Blood for plasma (10 ml) will be drawn into EDTA vacutainers, placed on ice, centrifuged at 4°C within 30 min, and plasma aliquots will be stored at -80ºC. The assays for glucose, insulin, and hemoglobin a1c will be performed within 24 h and compared with values assessed during brief physical exams at Weeks 5 and 10 of the intervention (see **5.6.4**). Lipid levels (HDL, LDL, VLDL, triglyclerides) will also be assessed.

Markers of inflammation will be assessed at UCLA, where we have collaborators. Circulating markers of inflammation will include plasma levels of IL-6, TNF-a, and CRP. Molecular markers of inflammatory signaling will include the pro-inflammatory NF-κBκ/Rel 235 family, and the signal transducer and activators of transcription (STAT). These markers are elevated in OSA patients, and decreased with exercise training. Recent infections (e.g., URTI), will result in rescheduling of these measures. Also assessed and statistically controlled will be information about biobehavioral confounds of inflammation, including alcohol consumption, smoking history, BMI, physical activity; and use of medications (antidepressants, statins, and NSAID).

Body Weight and Composition. Height and weight will be assessed to the nearest 0.5 cm and 0.1 kg, respectively. Waist, hip, and neck circumference measures will follow ACSM guidelines. A certified tech will perform dual energy x-ray absorptiometry (DEXA) scan will assess lean tissue mass and fat mass for the entire body, as well as for the trunk only and neck only. Intra-instrument variability for DEXA is <5.2%.

Pulmonary Function. Pulmonary function will be tested with a spirometer. Maximal inspiratory and expiratory maneuvers will be performed three times, and average of the three inspiratory and expiratory flow-volume loops will be calculated. Variables will include forced vital capacity (FVC), forced expiratory volume in 1

s, peak inspiratory flow, peak expiratory flow. The ratio of forced expiratory flow to forced inspiratory flow at mid-vital capacity (FEF_{50}/FIF_{50}) will be used as a marker for upper airway obstruction.

Respiratory Muscle Strength. Maximum static inspiratory (MIP) and expiratory (MEP) mouth pressures will serve as markers of respiratory muscle strength. MIP and MEP assessments will be obtained with respiratory pressure gauges (VacuMed, Ventura, CA) while the subject is seated with nasal clips. For MIP, participants will be instructed to exhale completely to residual volume and then provide a maximal inspiratory effort against an occluded mouthpiece. For MEP, participants will be told to inhale slowly to total lung capacity and then exhale with maximal force. The highest maximum pressures developed over 3 consecutive efforts will be recorded for MIP and MEP. Respiratory muscle strength will be calculated as (MIP+MEP/2).

5.6.3. Experimental Questionnaires. The following questionnaires (10-15 minutes total) will be administered by staff blinded to treatment at baseline and following every 4 weeks of the intervention.

The **Functional Outcomes of Sleepiness Questionnaire (FOSQ-10)**[116] is a 10-item scale that measures how sleepiness affects daytime functioning; it has a 4-point scale ("extreme difficulty" to "no difficulty"). The FOSQ distinguishes between healthy adults and apnea patients and has a 1-week test-retest reliability of r >0.8. For some studies of OSA, the FOSQ has been the primary outcome measure.
The **Pittsburgh Sleep Quality Inventory (PSQI)**[119] is the most commonly used measure of subjective sleep quality. There are 21 questions, and a global score > 5 indicates poor sleep quality. The PSQI has high test-retest reliability (r = 0.85) and successfully distinguishes between diagnosed good and poor sleepers.

Snoring Symptoms Inventory. In our previous study, anecdotal reports indicated that exercise substantially reduced snoring, which could have significant health implications even in the absence of improvement in OSA. This 25-item scale has been sensitive to uvulopalatoplasty. Also, bed partners or housemates of participants will be asked to assess snoring changes (from 1=much better to 5=much worse).

5.6.4. Physical Examinations during the Intervention. At Weeks 5 and 10 of the intervention, participants' health will be monitored by a brief physical examination, including blood pressure and fasting assessment of glucose, insulin, and hemoglobin a1c. Physician judgment of significant health deterioration or significant impairments in these variables at these time points will result in exclusion from the study.

5.7. Follow-Up Assessments. Three months after completion of the intervention, participants will undergo another night of home OSA assessment with the ARES. Participants will also return to the laboratory to assess body weight and and completeseveral questionnaires, including the **PSQI, FOSQ, Snoring Symptoms Inventory, physical activity recall, involvement in PAP and other treatments, and 24-hr dietary recall.**

5.8. Compensation. Participants will receive $400 after the post-study measures. Pro-rated pay for drop-outs will be $40 for screening; $20 per week of the study; and $20 for follow-up. The Exercise Alone and Weight Loss Alone groups will have the opportunity to receive the other intervention free of charge following the study.

5.9. Sample Size and Power. The power calculations are based on our previous study and other published studies. We found an AHI reduction from 32.2±5.6 SD to 24.6±4.4 (7.6 or 24%) following a 12-week exercise protocol, and the attrition rate was 11%.[19] The standard deviation of the change in AHI was large (13), perhaps because of the relatively short intervention duration and small sample size compared with what are proposed. In a recent meta analysis of the effect of dietary weight loss on AHI, we find an average reduction of AHI of 34% in studies involving weight loss of approximately 10% over intervention durations of 12-20 weeks.[18] Based on this finding, we assume a reduction of total AHI from 32.2±5.6 to 21.25±5.2 following the Weight Loss Alone treatment (10.9 or ~34% reduction). A previous study indicated a 46% reduction in total AHI (from 21.7±9.0 to 11.8±6.8) following exercise and weight loss.[27] Based on these data, in calculating power, we assume decreases in AHI of increasing magnitude will be observed following exercise alone, weight loss alone, and exercise + weight loss. We assume a reduction of AHI from 32.2±5.6 to 17.3±5.2 (14.9 or 46% reduction) after exercise + weight loss, and we assume 10% attrition. In our power calculations, the overall significance level is set at α=0.05. To insure we will have sufficient testing power, order-restricted tests are not considered in power estimation, but this type of testing will be applied in our data analyses to test the hypothesized pattern.

To ensure power for the **Primary Hypothesis (*Compared with exercise alone and weight loss alone, exercise+weight loss will elicit significantly greater improvements in AHI)*** we consider weight loss alone vs. exercise+weight loss. We set the significance level at 0.025 to adjust for multiple testing. With n=30

per treatment, the power is 86% to detect an average difference of 4 (14.9 vs 10.9, or 46% vs 34%) in AHI reduction between the treatments assuming treatment standard deviations of 5. The power is 82.2% with a 10% attrition. We expect higher statistical power to compare exercise alone vs. exercise+weight loss.

For **Secondary Hypothesis 1**, ***Compared with exercise alone and weight loss alone, exercise + weight loss will elicit significantly greater improvements in OSA at 3-month follow-up***, we anticipate decreases in compliance, resulting in greater within-treatment variability and/or lower between-treatment differences, and less powerful between-treatment tests. As such, we consider 82% to be an upper bound power estimate of this hypothesis. If, for example, at follow-up, the magnitude of the effect of condition were only 80% of that anticipated at post-test, power to detect significant differences would be approximately 65%.

For **Secondary Hypothesis 2, *Compared with baseline, each treatment will elicit significant improvements in AHI***, the power calculation is based on paired one-sided t-tests to test the reduction of AHI. Since there are 3 treatments, multiple-testing Bonferroni-adjusted significance level is set at 0.05/3=0.017. For exercise alone, from our preliminary data, we set the mean±SD reduction in AHI (baseline minus post-treatment) at 7.6±12.5 (24% reduction) for the power calculation. The standard deviation is smaller than in our preliminary study because of the longer duration and larger sample size. With n=30, tests should have power of 86.0% to detect such a post-exercise difference. With 10% attrition, our tests should have power of 82% to detect this change. Also, we propose a 16 wk treatment, which is a longer than in our previous study and may result in larger reduction with smaller variance. We expect that the AHI reduction will be at least as great as seen in our previous study. Because we expect that weight loss alone and exercise+weight loss will elicit larger effects than exercise alone, the power to detect changes in AHI will be greater for these other treatments.

For **Secondary Hypothesis 3**, **Compared with exercise alone and weight loss alone, exercise + weight loss will elicit significantly greater improvements in measures of co-morbidity,** we use PSQI, systolic blood pressure, and hemoglobin a1c for power calculations. Power is estimated based on two-sample t-tests on the changes (post-treatment minus baseline) of each variable. Having repeated measures for some of these variables will further increase power. Similar treatment effects are assumed for weight loss alone and exercise alone. In this hypothesis, since the outcomes of interests were chosen based on previous studies instead of random selection, alpha for each test is set at 0.05. For Hypothesis 3, n=30 per treatment will result in power of ~80% on all the tests except for SBP with minimum detectable differences determined based on our preliminary data (**Table 3**). The power is close to 80% for PSQI and hemoglobin a1c, but 42-47% for systolic blood pressure, assuming 10% attrition. There is clearly sufficient power to detect baseline-to-post improvements for the co-morbidity variables following each individual treatment. Here we focus on effects of weight loss only and exercise only. At alpha of .05, for PSQI, the detectable average reduction is set at 1.5 with standard deviation of 1.8 (for both treatments). Estimated power is 99% with 30 subjects in each group and assuming 10% attrition. For SBP, power is 96% to detect a reduction of 6.7 with standard deviation of 10 with 30 subjects in the group and 10% attrition. Finally, for Ha1c, power is >.99 to detect an average reduction of 0.2% with standard deviation 0.1% assuming 10% attrition. In summary, with 30 subjects in each of the three treatment groups, we are confident that our tests will have power of 80% for most outcome variables.

Table 3. Statistical power under different reduction scenarios for Secondary Hypothesis 3.

PSQI *Reduction=1.5 SD_{diff} =1.8		**SBP** Reduction=6.7 SD_{diff} =10			**Ha1c** Reduction=0.2 (%) SD_{diff} =0.1 (%)	
#Diff	**Power**	Diff	Power		Diff (%)	Power
1.15	78.8%	3.8	42.5%		0.07	85.0%
1.26	85.0%	4.12	47.3%		0.077	90.4%

5.10. Statistical Analysis. We will first examine univariate and bivariate statistics to determine the distributional characteristics of study variables and to identify potentially relevant background covariates and confounders. For the **Primary Hypothesis and Secondary Hypotheses 1 and 3**, we will use an analysis of covariance (ANCOVA) approach to examine treatment effects on post-intervention (i.e., immediate post-test for Primary Hypothesis and Secondary Hypothesis 3; 3-month follow-up for Secondary Hypothesis 1) outcome values (i.e., AHI scores for Primary Hypothesis and Secondary Hypothesis 1; comorbidity measures for Secondary Hypothesis 3), with treatment as the primary independent variable, and adjusting for baseline outcome value, intervention dose (percentage of sessions attended), baseline outcome value, age, sex,

duration of OSA diagnosis, plus any other relevant covariates. We will test for ordering of treatment means (not adjusted for covariates) via order-restricted tests within the R package flexisoreg. Next, we will test for overall differences among treatment groups on post-treatment AHI values with order-restricted comparisons (isotonic contrasts) of covariate-adjusted means to test for the predicted ordered patterning of the three treatment means. For **Secondary Hypothesis 2**, we will examine the effect of time point (pre- vs. post-treatment) on AHI scores at each treatment level (i.e., test "simple main effects" of time) in the context of a repeated measures ANCOVA. Analyses will be based on an intent-to-treat plan. For each hypothesis, overall alpha will be set at .05, with a Bonferroni correction applied when multiple non-independent tests are conducted. **Missing data** due to dropout or other causes will be addressed with analyses of multiply-imputed datasets generated with SAS PROC MI based on models drawing on all available participant data.

Mediation Analysis. Possible mediating variables that could explain the reduction in OSA will be evaluated using MacKinnon's product of coefficients test. Pre-specified potential mediators will include percent of NREM-3 (deep sleep), body weight, trunk body fat percentage, respiratory muscle strength, and upper airway obstruction (FIF_{50}/FEF_{50}). Each potential mediator will be tested in a single mediator model, to include (1) estimating the effect of the intervention on the potential mediator (i.e., α coefficient) by regressing the mediator's post-intervention value on the intervention group while controlling for the potential mediator's baseline value; (2) estimating the effect of changes in the mediator on changes in AHI (i.e., β coefficient) by regressing post-intervention AHI on the mediator's post-intervention value, controlling for treatment group, baseline AHI, and the mediator's baseline value; and (3) calculating the product of coefficients by multiplying the α and β coefficients. Coefficients will be obtained through linear regression models using SAS PROC GLM. Asymmetric confidence limits based on the distribution of the product of coefficients will be created using the PRODCLIN program; confidence intervals that do not include zero will indicate a significant mediation effect.

5.11. Process evaluation. An independent observer will assess study feasibility, fidelity of protocol delivery, and subject adherence. Participants will also complete a survey of barriers and benefits to study participation.

5.12. Timeline. The study will take 4 years. Equipment purchases will occur in the initial 2 months. With rolling admission, we will strive to schedule waves of ≥ 5 participants. Baseline assessments should begin by the end of Month 2, and baseline assessments of new waves of participants will occur monthly. Data collection is expected to take 44 months. Final analyses and manuscripts preparation will occur during the final 2 months.

5.13. Potential Problems and Limitations of Methods. Excellent participant recruitment will be paramount. We previously assessed N=43 OSA subjects over 2 yr for consultant Chris Kline's dissertation. However, for the proposed study, we have a much closer association with Sleep Medicine at the VA. The director, co-investigator Dr. Pineda, interprets about 25 new cases of OSA per week. She and the staff can inform these patients about the study. We would need to recruit only 2% of these cases if this was our only source of subjects. We will also seek a HIPAA waiver to provide information about our study to the 30,000 Phoenix VA patients who have been diagnosed with OSA. Other factors that will benefit recruitment include an expanded subject age range (from 18-55 to 18-60 years of age); less stringent inclusion criteria; and having Dr. Kline as a consultant. If we still are unable to recruit enough veterans, we will request permission to include non-veterans.

Retention of participants will be critical for the success of the study, and sedentary and/or overweight individuals are high risk of drop-out or poor adherence to exercise. However, a run-in period will reduce the number of non-adherents, and personalized attention throughout the intervention should promote retention. For our previous study, only 5 of the 43 participants who began the intervention discontinued the study. Another ld benefit for retention is that the entire study will be conducted at the Phoenix VA, whereas in our previous proposal, the PSG, interventions, and laboratory measures were going to be conducted off-site at USC.

The intervention will be more conducive to exercise and weight loss than is typical, which will limit the study's generalizeability. Presently, we believe it is most imperative to establish efficacy. As exemplified by the VA "Move!" program, there is an accelerated focus on exercise and weight loss which could facilitate these behaviors among veterans with OSA at no cost. Subsequent studies could compare lab vs. home intervention.

Follow-up assessments will be influenced by uncontrolled factors, e.g., the extent to which participants maintain or initiate exercise, weight loss, or PAP. Ethics dictate allowing post-study treatments. Careful assessment of these should permit some conclusions regarding the chronicity of post-treatment improvements.