# Correlation Analysis of Sleep Study Variables in Obese *v.* Non-obese Military Personnel Diagnosed with Obstructive Sleep Apnea

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## Abstract

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**Background:** Several epidemiologic studies have found an association between obesity and the risk of Obstructive Sleep Apnea (OSA). However, the exact mechanisms involved in OSA among obese individuals and the interactions between obesity and OSA are unknown. One way to identify possible mechanisms of OSA specific to obesity is to explore differences in the pathophysiology of OSA between obese and non-obese patients. The military presents a unique opportunity to study non-obese patients because of the high number of non-obese soldiers that undergo sleep studies. Therefore, military sleep study records offer a prime opportunity to differentiate how OSA behaves in patients with and without obesity.

**Methods:** Our cross-sectional study compared associations between diagnostic markers of OSA and selected physiologic sleep disturbances among obese (body mass index (BMI) $\geq$ 30 kg/ $m^2$) and non-obese (BMI < 30 kg/ $m^2$) patients with OSA. We reviewed and analyzed a database of

OSA cases (N = 342) comprised of soldiers diagnosed with OSA who underwent polysomnography (PSG) at a major military medical center in 2010. The cases were divided into obese (n = 176) and non-obese (n = 166). Pearson correlations (*r*) were calculated for Apnea Hypopnea Index (AHI) among patients with mild OSA ($5 \leq AHI < 15$), moderate/severe OSA ($AHI \geq 15$), and both groups combined. PSG variables (arousal index (AI), minimum oxygen saturation ($O_2$ Sat)) were compared between the obese and non-obese groups.

**Results:** A statistically significant correlation between AHI and AI was only seen in moderate-severe OSA for obese patients *(*$r = 0.55$, $p < 0.01$) while significant correlations were seen in both mild *(*$r = 0.20$, $p = 0.02$) and moderate-severe OSA ($r = 0.45$, $p < 0.01$) for non-obese patients. On the other hand, statistically significant correlations between AHI and min $O_2$ were found in both mild ($r = -0.37$, $p < 0.01$) and moderate-severe ($r = -0.38$, $p < 0.01$) OSA for obese patients while the correlation was only found in mild ($r = -0.26$, $p = 0.01$) OSA for non-obese patients. Furthermore, the correlation between AHI (≥ 5, without disease severity stratification) and min $O_2$ sat was significantly (more than twofold) stronger for obese ($r = -0.56$, $p < .01$) than for non-obese patients ($r = -0.27$, $p < 0.01$) and the difference was also statistically significant ($p < 0.01$).

**Conclusions:** Results suggest that obstructive events during sleep in non-obese and obese patients with OSA might involve different cascades of pathophysiologic events. For obese, the correlation between frequency of arousal (AI) and number of obstructive events (AHI) increases as the disease progresses. And the depth of hypoxia was consistently associated with the number of obstructive events throughout the disease severity. However, for non-obese, the correlations between frequency of arousal and number of obstructive events also increases as the disease gets more severe, but, the non-obese lost the association between the number of

obstructive events and the depth of hypoxia as disease gets worse. Given that physiologic disturbances from the primary pathologic event of OSA may differ as a function of obesity, future study should focus on clarifying the different clinical manifestations of OSA in obese and non-obese patients and may further consider comparing the efficacy of treatment(s) for OSA between obese and non-obese patient groups.

**TABLE OF CONTENTS**

**Page**

LIST OF TABLES AND FIGURES

**Table Number** **Page**

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## Chapter I: Introduction and Background

Obstructive sleep apnea (OSA) is most common form of sleep-disordered breathing, affecting 3-7% of the population and characterized by frequent episodes of partial or complete obstruction of the upper airway during sleeps.[1,2] OSA has been acknowledged as an independent risk factor for cardiovascular disease and all-cause mortality.[3,4] It also disrupts nocturnal sleep quality which contributes to daytime fatigue and sleepiness.[1] Patients with untreated obstructive sleep apnea present an increased risk to general public safety because of a two to sevenfold increased risk of motor vehicle crashes.[5] Because of the risk to public safety and health, government agencies have sought to take measures to address OSA.

OSA has only been recognized as a disease for about 50 years.[6,7] It was first characterized in obese individuals in the mid-1960s and the scientific link between obesity and pathogenesis of OSA has been extensively studied since then.[8] Because of early observations associating OSA with obesity, almost all of the earlier OSA studies focused on obese subjects. However, despite numerous studies, the pathogenesis of OSA and the link between OSA and obesity are not completely understood.[9-11]

Uncertainty regarding the pathogenesis of OSA has created policy development confusion in the public health arena. In 2013, the Federal Aviation Administration (FAA) proposed a policy requiring a mandatory sleep study for any pilot or pilot candidate found to have a BMI of 40 or greater during their flight physical. Shortly after publishing this guidance, FAA withdrew the proposal and clarified that they will not disqualify any pilot or candidate based on Body Mass Index (BMI) alone. [12] Similarly, the Federal Motor Carrier Safety Administration (FMCSA) has withheld any official BMI specific recommendation for mandatory OSA testing for commercial drivers due to conflicting research data.[13]

Obesity is clinically defined as excessive body fat accumulation to the extent that it may have a negative effect on health. Obesity is diagnosed with BMI ≥30. BMI ≥40 is considered morbidly obese. Obesity is understood to pre-dispose for OSA because of mechanical pressure to the upper airway. Excessive accumulation of fatty pharyngeal tissue is thought to cause greater upper airway collapsibility during sleep. [14-18] Upper airway collapsibility can be measured in passive critical closing pressure (Pcrit) and the Pcrit is considered to reflect the contribution of anatomical determinants to the pathogenesis of OSA.[19] Increase Pcrit is known to be significantly associated with obesity and male gender.[20] Several studies have shown successful reduction of Pcrit during sleep with weight loss. [21,22]

Even though anatomical predisposition is a key determinant of OSA susceptibility, there is growing evidence that non-anatomical factors contribute to the pathogenesis of OSA.[10,23] For example, substantial overlap of Pcrit has been found between patients with OSA and healthy controls.[24] Pcrit, by itself, is only minimally correlated with the primary disease severity index for OSA in a recent correlation analysis.[25] This suggests a greater role for non-anatomic determinants. The overall understanding of non-anatomical phenotypic traits that contribute to sleep apnea pathogenesis has accelerated in the past several years with increased knowledge of sleep physiology itself.[10]

Evidence suggesting the importance of non-anatomical determinants in the pathogenesis of OSA is growing and centers on a developing understanding of chemoreflex feedback and the autonomic nervous system, peripheral and central chemoreceptors. We know that humans are heavily reliant on chemoreflex feedback and arousal modulation during normal sleep to maintain appropriate cardiopulmonary function.[26] Peripheral chemoreceptors, located in the carotid bodies, respond primarily to hypoxia and central chemoreceptors, located on the ventral surface

of the medulla, respond primarily to hypercapnia.[27,28] In exploring the importance of chemoreceptors involvement in OSA pathogenesis, Somers and colleagues found potentiation of peripheral chemoreflex response to hypoxia with preservation of central chemoreflex activation among OSA patients compared to healthy subject.[29] During hypoxic breathing, ventilation and blood pressure were substantially increased in OSA patients compared with healthy subjects due to exaggerated peripheral chemoreceptor-mediated sympathetic response in OSA patients.

The sympathetic activities can be also markedly increased by cortical arousal during sleep. Much is already known about the dual roles of arousals in the pathogenesis of OSA. For example, it is known that the arousal response provides a critical physiologic role to terminate some apneas. However, arousal is not required for the termination of all apneas.[30,31] Gradually increasing activity of the pharyngeal dilator muscle as a response to the collapse of the pharyngeal airway during sleep is often sufficient to restore airflow without cortical arousal.[32] Some individuals with high airway collapsibility can even maintain airway patency for significant periods of time during sleep without any obstructions or arousals.[33] However, if an obstructive event continues during sleep despite increased contraction of airway dilator muscles, transient cortical arousal will usually help to urgently terminate a prolonged obstructive event.[32] On the other hand, these dramatic compensatory responses recruited by arousals may further destabilize ventilatory control system and contributing next obstructive events if it occurs too frequently.[30]

Involvement of non-anatomical factors in the pathogenesis of OSA associated with obesity has been suggested.[18] This is largely due to accumulating evidence of non-anatomical mechanisms involved in OSA. Neuromuscular effects of obesity were studied and demonstrated a marked blunting of upper airway neuromuscular responses.[18] Also, putative cytokines from

excessively accumulated fat in adipose tissues may have been contributed to the pathogenesis of OSA in obese indiviudals.[22] Recently, increased pro-inflammatory cytokines including tumor necrosis factor (TNF)-*a* and interleukin (IL)-6 secretions were found in patients with OSA compared to healthy subjects.[34] Interestingly, this specific variation in immune parameter in OSA is also found in individuals with obesity.[35] The relationship between the elevated proinflamatory cytokine and OSA is unclear. It is not known whether this may be a cause or a consequence of the disease.

OSA has special importance in military. The incidence rate of OSA in the military increased almost 6 times from 2001 to 2009 and the rate of "complex OSA" or "comorbid OSA" is suggested to be higher in the military than among civilians.[36] Complex OSA is generally considered a form of mixed sleep apnea with persistence of underlying central apneas upon exposure to Continuous Positive Airway Pressure (CPAP) or other positive airway devices when obstructive events have disappeared.[37] It is important to know that 58.1% of military personnel undergoing a sleep study have one or more medical comorbidities and most of them are service related.[36] According to Collen et al., OSA was also found 34.5% of 116 soldiers with diagnosed Traumatic Brain Injury (TBI) in their study and most of the participants were non-obese male.[38] The link between service related psychological or neurological comorbidity and the development of OSA for military personnel is unclear at this stage.

Understanding the scientific link between obesity and OSA also has an economic importance, and this is especially true in military populations. According to one of the military press, separated members with an in-service diagnosis of OSA can file claims with Veteran Affairs (VA), and 88 % are rated 50 % disabled.[39] Also, 13 % of approximately 427,000 veterans who served after 9/11 draw VA disability compensation due to service-connected OSA and it

costs more than $500 million per year.[39,40] The rating level of service connected OSA is assured once a CPAP machine is prescribed to keep the patent airway during sleep to prevent apneas, which lead to daytime drowsiness and cognitive impairment. This rating was set years ago based on studies that estimated "average impairment in earnings loss" and "need for a CPAP" interpreted as "continuous use of an external agent to maintain health."[39] The briefer from VA Advisory Committee on Disability Compensation, stated during their recent committee meeting, "The most common path to a VA sleep apnea disability rating is to be overweight and have this common sleep disorder diagnosed as they separate or retire from service".[41] Also, Todd Harrison, a military budget expert at the Center for Strategic and Budgetary Assessments said, "Sleep apnea is not a combat injury, especially if it's caused by obesity."[42]

In the military, a Soldier with self-reported sleep issues may refer themselves for a sleep assessment. This assessment will often lead to a sleep study. Commanders who witness excessive somnolence or anything else they believe to be a sleep issue may also refer Soldiers for a sleep assessment. Given the physically demanding jobs and associated physical fitness requirements in the military, a high number of young non-obese males may self-select or be selected for PSG providing a rare opportunity to investigate the different physiologic parameters of OSA in obese and non-obese patient groups.

## Chapter II: Methods

Subjects

We conducted a cross-sectional study of tri-service military personnel with a confirmed diagnosis of OSA after PSG. All PSG were performed in 2010 at a major military medical treatment facility in the Pacific Northwest. Military personnel underwent a sleep medicine evaluation upon referral from their primary care or behavioral medicine provider or as directed by command when sleep difficulties hinder duty performance or as part of a service-connected disability evaluation. It is military specific clinical practice to perform PSG on almost all active duty personnel who have a sleep medicine evaluation because they are in a high-risk profession. PSG performed for continuous positive airway pressure titration, postsurgical evaluation, or if the patient had previously undergone PSG were excluded.

Data elements were recorded in a de-identified database prior to statistical analysis. A total of 761 active duties military personnel from the US Army, Air Force, Navy, who met the inclusion criteria underwent PSG at Madigan Army Medical Center in 2010 and 390 of them had a confirmed diagnosis of OSA. However, 48 of those 390 were also excluded because their heights and/or weights were not recorded. Therefore, a total of 342 patients with confirmed diagnosis of OSA participated in this study. Baseline biometric parameters of age, gender, and BMI were obtained. Pertinent PSG variables (AHI, AI, and minimum O2 sat., Total Sleep Time (TST), % Rapid Eye Movement (REM) sleep) were also included.

Study Aim

The primary aim of this study was to examine any differences in correlation of primary disease index with objective pathophysiologic measures in PSG between obese and non-obese active duty soldiers.

Data Analyses

Data was analyzed with IBM SPSS for Windows (Version 22, Inc., Chicago, IL). Means of subject's characteristics for each patient group (non-obese and obese) in terms of demographics (age, gender, BMI), and PSG variables(AI, AHI, minimum oxygen saturation, Total Sleep Time, % REM sleep) were calculated with standard deviations. The significance of mean differences between two patient groups in each term were also determined by using Chi-square test, independent-sample T test, or Fisher's exact test based on the type and size of the selected variable. Chi-square test for nominal or categorical variables and independent sample T test for continuous variables were used to examine differences between them. In case of sample size less than 5 with nominal or categorical variables, Fisher's exact test was used instead of Chi-square test.

Data were sorted out to include only positive OSA patients in the study pool by using an AHI cutoff of equal or greater than 5. As a preliminary descriptive analysis, correlations of primary disease index, AHI with other chosen surrogate measures including BMI, AI, and Minimum $O_2$ saturation were explored to validate the associations for the study population ($AHI \geq 5$). In our main analysis, the participants were split into obese and non-obese patient group and Pearson's correlation coefficients of primary disease index, AHI with surrogate measures of objective pathophysiologic measures (AI and Minimum O2 sat.) for each patient group. Then the participants were further stratified by disease severity, mild ($5 \leq AHI \leq 15$) and

moderate to severe (AHI≥15) within the obese and non-obese subgroups, and Pearson's correlation coefficients of AHI with AI and Minimum O2 sat. were calculated for each category for the comparison. Spearman's correlations were also calculated for each category to assess the effect of outliers. The significance of differences in each correlation coefficient between obese and non-obese patient groups were evaluated by using r to z transformation. The significance of all the correlation coefficients was determined with p-value with use of an alpha level of 0.05 including the difference in correlations between two patient groups.

## Chapter III: Results

The mean age and gender distribution of the study participants were comparable between non-obese and obese patient groups. Both patient groups were almost equally male predominant (97.2%, 97.6%), and the mean age of both patient groups was early-mid 30's (32.37, 35.87). The mean difference of BMI between obese and non-obese patient group was about 7 (27.57 for non-obese patient group, 34.42 for obese patient group). The disease severity was higher in the obese patient group, indicated by higher mean on the Apnea Hypopnea Index. (20.15 vs.25.87) The mean Total Sleep Time (TST) for each patient group was similar (428 min, 419 min). Portion of REM stage of sleep was slightly higher in the non-obese patient group (16.42 vs 15.10) even with lower AHI compared to the obese patient group (20.15 vs 25.87). The sample means of each category between obese and non-obese were independent except minimum O2 sat. and % REM sleep. Although, the mean differences of minimum O2 sat. and % REM sleep were small, the differences were statistically significant.

**Table 1- Subjects Characteristic (non-obese v. obese)**

| | Non-obese, Mean (SD) | Obese, Mean (SD) | p-value* |
|---|---|---|---|
| | N=166 | N=176 | |
| **Demographics** | | | |
| Age | 32.37 (8.5 6) | 35.87 (7.62) | 0.24 |
| Gender, male (%) | 97.6 | 97.2 | 0.80 |
| BMI | 27.57(1.85) | 34.44(2.98) | N/A |
| **PSG variables** | | | |
| Arousal Index | 24.90(12.41) | 27.04(16.80) | 0.12 |
| AHI | 20.15(20.40) | 25.87(23.37) | 0.65 |

| | | | |
|---|---|---|---|
| Min. O2 saturation | 84.69(4.99) | 81.79(7.09) | <.01* |
| Total Sleep Time ** | 428(57) | 419(61) | 0.09 |
| REM Sleep (%) | 16.42(6.60) | 15.10(6.88) | <.01* |

Definitions of abbreviations: SD=Standard Deviation; AHI=Apnea Hypopnea Index; AI=Arousal Index; Min. O2=minimum oxygen; ESS=Epworth Sleepiness Scale; Min. O2=minimum oxygen, * p-value is a test between the two groups, **: TST was measured in minutes

As a preliminary descriptive analysis, we tried to validate the association of each selected surrogate measures (BMI, arousal index, and minimum oxygen saturation) with primary disease severity index (AHI) in our entire study pool. Although, statistically significant correlations were found with each surrogate measures, the strength of association between AHI and BMI *(r=0.17, p<.01)* was much weaker compare to the strength of association between AI *(r=0.61, p<.01)* or minimum oxygen saturation *(r*=0.48, *p*<.01).

**Table 2- Preliminary descriptive analysis**

Pearson's coefficient

| | BMI (r, p) [CI] | Arousal Index (r, p) [CI] | Minimum O2 Sat (r, p) [CI] |
|---|---|---|---|
| Correlation of AHI with | 0.17 (<.01*) [0.07~0.27] | 0.61 (<.01*) [0.54~0.67] | -0.48(<0.1*) [-0.56~-0.40] |

Spearman's coefficient

| | BMI (r, p) [CI] | Arousal Index (r, p) [CI] | Minimum O2 Sat (r, p) [CI] |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Correlation of AHI with | 0.21 (<.01*)<br>[0.11~0.31] | 0.56 (<.01*)<br>[0.48~0.63] | -0.51(<0.1*)<br>[-0.58~-0.43] |

Minimum O2 sat. = Minimum oxygen saturation; BMI = Body Mass Index; AHI = Apnea Hypopnea Index; Corr. = Correlation; *r* = correlation coefficient; * statistically significant at $p \leq .05$

In our main analysis, correlations of AHI with arousal index and minimum oxygen saturations were compared by non-obese and obese patients groups. We found high correlations between arousal and AHI in both obese (*r*=.62) and non-obese (*r*=.58) groups, but did not find a statistically significant difference between these subgroups (*p*=.50). In contrast, the correlation between AHI and minimum oxygen saturation was significantly different between obese and non-obese patient groups (< *.01*) and obese participants had twice the reduced r values (.27 v .56).

**Table 3-Correlation analysis of AHI with AI and Minimum Oxygen Saturation (Non-obese v. obese without disease severity stratification)**

Pearson's correlation

| | **Non-obese** (N=166)<br>r1(p)<br>[CI] | **Obese** (N=176)<br>r2(p)<br>[CI] | Significance of the difference (p) between r1 and r2 |
|---|---|---|---|
| Correlation AHI with Arousal Index | 0.58 (<.01*)<br>[0.47~0.67] | 0.62 (<.01*)<br>[0.49~0.73] | 0.50 |
| Correlation AHI with Minimum O2. Sat. | -0.27(<.01*)<br>[-0.41 ~ -0.12] | -0.56(<.01*)<br>[-0.65 ~ -0.45] | <.01* |

Spearman's correlation

| | **Non-obese** (N=166) r1(p) [CI] | **Obese** (N=176) r2(p) [CI] | Significance of the difference (p) between r1 and r2 |
|---|---|---|---|
| Correlation AHI with Arousal Index | 0.50 (<.01*) [0.38~0.61] | 0.57 (<.01*) [0.46~0.66] | 0.37 |
| Correlation AHI with Minimum O2. Sat. | -0.34(<.01*) [-0.47 ~ -0.20] | -0.63(<.01*) [-0.71 ~ -0.53] | <.01* |

Minimum O2 sat. = Minimum oxygen saturation; BMI = Body Mass Index; AHI = Apnea Hypopnea Index; Corr.= Correlation; *r* = correlation coefficient; *: statistically significant at $p \leq .05$

We further stratified the disease by severity and then split participants into obese and non-obese patient groups. For the obese patient group, correlations between frequency of arousal (AI) and number of obstructive events (AHI) increased as the disease progressed from mild to moderate-severe (*r*=0.14, *r*=0.55) and the depth of hypoxia (minimum O2 sat.) was consistently associated with the number of obstructive events throughout the disease severity (*r=-0.37, r=-0.38*). For the non-obese patient group, although, correlations between frequency of arousal and number of obstructive events also increased as the disease got more severe (*r*=0.20, *r*=0.45), they were losing association between the number of obstructive events and the depth of hypoxia as disease gets worse(*r*=-0.26, *r*=-0.08).

**Table 4-Correlation analysis of AHI with AI and Minimum Oxygen Saturation (Non-obese v. obese with disease severity stratification**

**Pearson's correlation**

| **Non-Obese** | Mild, N=100, r (p) [CI] | Moderate-severe N=66, r(p) [CI] | **Obese** | Mild, N=79, r (p) [CI] | Moderate-severe N=97, r(p) [CI] |
|---|---|---|---|---|---|
| Correlation AHI & Arousal index | 0.20 (0.02*) [0.01~0.38] | 0.45 (<.01*) [0.23~0.62] | Correlation AHI & Arousal index | 0.14 (0.12) [0.08~0.35] | 0.55 (<.01*) [0.39~0.68] |
| Correlation AHI & Min. O2 Sat. | -0.26 (0.01*) [-0.43~-0.07] | -0.08 (0.55) [-0.32~0.17] | Correlation AHI & Min. O2 Sat. | -0.37 (<.01*) [-0.55~-0.16] | -0.38 (<.01*) [-0.54~-0.20] |

**Spearman's correlation**

| **Non-Obese** | Mild, N=100, r (p) [CI] | Moderate-severe N=66, r(p) [CI] | **Obese** | Mild, N=79, r (p) [CI] | Moderate-severe N=97, r(p) [CI] |
|---|---|---|---|---|---|
| Correlation AHI & Arousal index | 0.16 (0.11) [0.04~0.35) | 0.44 (<.01*) [0.22~0.62] | Correlation AHI & Arousal index | 0.18 (0.12) [-0.04~0.39] | 0.55 (<.01*) [0.39~0.68] |
| Correlation AHI & Min. O2 Sat. | -0.25 (< .01*) [-0.43~-0.06] | -0.14 (0.24) [-0.37~0.18] | Correlation AHI & Min. O2 Sat. | -0.37 (<.01*) [-0.55~-0.16] | -0.39 (<.01*) [-0.55~ -0.21] |

Minimum O2 sat. = Minimum oxygen saturation; BMI = Body Mass Index; AHI = Apnea Hypopnea Index;

Corr.= Correlation; *r* = correlation coefficient; *: statistically significant at $p \leq .05$, Mild: $5 \leq AHI < 15$,

Moderate-severe: AHI $\geq 15$

## Chapter IV: Discussion and Conclusion

Discussion:

To the best of our knowledge, this is the first study to correlate disease severity of OSA with selected objective pathophysiologic measures from PSG between obese and non-obese patients. According to our results, BMI was only weakly associated with OSA, supporting the premise that anatomical predisposition alone is inadequate to fully explain susceptibility to OSA. We found differences in non-anatomic PSG outcomes (e.g., arousal, oxygen desaturation) between obese and non-obese patients with OSA, suggesting the anatomical predisposition of OSA pathogenesis is not as well-explained by passive Pcrit or as dependent on BMI as previously believed.

As expected, arousals occurred more consistently to terminate obstructive events during sleep with increasing disease severity in both non-obese and obese patients, but frequency of arousals did not differ between groups. From a survival standpoint, arousal from sleep during an OSA event is critical. Increased airway collapsibility and ventilatory control system instability are the expected physiologic features of normal sleep.[31] Arousal is a complex protective response during sleep that is neurally-mediated through proprioceptive or chemo-receptor feedback loops, and requires coordination of the Autonomic and Central Nervous Systems.[43] Non-anatomic protective responses, such as arousal, are vital to counteract increasing upper airway collapse, which increases during OSA events. If airway collapsibility exceeds the capacity of intrinsic neuromuscular response, cortical arousal must occur to acutely boost the neural input to upper airway dilator muscles. However, although arousal may serve as an urgent rescue measure for a prolonged obstructive event, it is not required to terminate every obstructive event during sleep.

Furthermore arousal may destabilize the ventilatory control system and contribute to additional obstructive events, if it occurs too frequently.[30]

The boundary between protective and pathologic arousal during sleep could largely depend on the degree of blood gas disturbances at the time of obstructive events. For example, protective arousal response should occur without any delay if there is significant hypoxia caused by an obstructive event. Alternatively, arousal should not occur if there is only negligible amount of oxygen desaturation at the end of obstructive events during sleep.

One of the most important findings of our study was that the contribution of increased obstructive events to the depth of hypoxia was different between non-obese and obese patients groups. The maximum oxygen desaturation was a good indicator for OSA disease severity only among obese patients with OSA. There was no reliable association between AHI and minimum $O_2$ saturation in non-obese patients, while we observed a consistent association in obese patients. This result agrees with an earlier Australian study by Ling and colleagues who proposed that BMI influences accuracy of Oxygen Desaturation Index, and that OSA is more consistently associated with oxygen desaturation in obese patients.[44] Obese individuals suffered far greater hypoxia as the disease progressed in our study too. The depth of hypoxia was consistently associated with the number of obstructive events regardless of disease severity in obese patients. Some investigators speculate that the greater degree of oxygen desaturation among obese OSA patients is due to obese OSA patients' aggravated baseline oxygen saturation and obesity-related atelectasis.[44,45] However, the theory of a blunted upper airway neuromuscular response due to obesity has also been proposed as an explanation for the potentiation of oxygen desaturation in obese OSA patients. [18] Obesity is believed to be a disruptor of appropriate neuromuscular response to airways obstructions during sleep, but the linking mechanisms between obesity and

neural responses have not been delineated. Although, role of delayed necessary arousal to the greater hypoxemia from obstructive events for obese patients is unclear, it's possible this is due to an abnormally high arousal threshold as a result of obesity as a disease.

In contrast, we found evidence of obstructive events which caused arousals without oxygen desaturation as the disease progressed in non-obese patients. In comparison to obese patients, for the non-obese, a much weaker correlation was found between AHI and minimum $O_2$ saturation in mild OSA. The weak correlation completely disappeared as OSA progressed. It appears that the urgent arousal response for terminating obstructive events was not an issue for the non-obese. The non-obese did not demonstrate increased hypoxia as obstructive events accumulated. Since the obstructive events resulting in arousals without desaturations were selectively occurring in non-obese patients, this may indicate an abnormally low arousal threshold for non-obese OSA patients.

Arousal threshold can be lowered by numerous endogenous or exogenous factors. For example, the REM stage of sleep is considered a "vulnerable" period for arousal during sleep. It has been shown that EMG activity of pharyngeal dilator muscles are progressively reduced from wakefulness to NREM to REM sleep.[46] Also, a study by Rees and his colleague demonstrated a significantly increased arousal response to an added inspiratory resistive load in REM sleep compared with non-REM sleep stages 2, 3 or 4 in healthy men.[31] Interestingly, the % REM sleep was slightly longer in the non-obese patient group even with their lower mean AHI compared to the obese patient group in our present study. Although, the mean difference of % REM sleep between non-obese and obese patients groups was small, the difference was still statistically significant. However, contribution of higher % REM sleep in non-obese patients to our finding of selective arousals without oxygen desaturation during obstructive event is inconclusive.

There are other known risk factors that increase anatomical predisposition to OSA, including male gender and increased age. We found no significant differences in mean age and male gender between patient groups in our sample. All the participants in our study were active duty military and the majority (97%) of participants was male. Therefore, there are some specific cohort effects that may explain or contribute to our findings. Chronic consumption of centrally acting medications including opioid pain medications, anti-depressants, and sleep promoting agents is common in military population.[47,48] Appropriate upper airway control during sleep requires fine calibration of neurochemical control system. Most of these medications act on neurotransmitters or receptors of certain neuromodulators. However, tailoring therapeutic effects of these medications is difficult due to non-specific effects on neurotransmitters throughout brain. The chronic consumption of certain centrally-acting medications may disrupt normal neurochemical control of upper airway motor neurons.

Also, military populations suffer from unique service-related medical comorbidities affecting their sleep, such as Traumatic Brain Injury (TBI).[47] The association between OSA and TBI suggests that the central nervous system has an important role in modulating OSA, particularly in events such as arousal. The increasing incidence of TBI is an emerging concern in military medicine.[49] There is a much higher prevalence of OSA among soldiers with TBI compared to the general population.[38] For individuals with TBI, a main concern is the disruption of major central endogenous neurochemical pathway that occurs after the primary mechanical insult. [50] During the secondary phase of TBI pathogenesis, neurochemical pathway of upper airway motor neurons can also be affected.

As a result of pathophysiologic variability between non-obese and obese OSA patients, patients may respond to different type of treatment based on the primary pathophysiologic

disturbances leading to the OSA. Although Continuous Positive Airway Pressure (CPAP) is a relatively efficacious treatment for OSA, there is still significant number OSA cases refractory to CPAP treatment.[51] Most of the CPAP refractory OSA is due to underlying or undiagnosed central sleep apnea. [51] According to our results, we anticipate there are higher rates of CPAP refractory OSA among non-obese patients compared to obese patients because it seems that the pathophysiology of OSA for non-obese patients has more central involvement. Comparisons of CPAP or other pharmacological treatment efficacy between obese and non-obese OSA patients are recommended.

Conclusion:

Findings from our research demonstrated that higher frequency of obstructive events consistently correlated with higher frequency of arousals for both obese and non-obese OSA patients. However, the degree of maximum oxygen desaturation was much more strongly associated with the primary disease severity index of OSA, AHI, for obese patients compared with non-obese patients and the gap widened as the disease worsened. From these findings, we concluded that arousals were occurring without oxygen desaturation during obstructive events for non-obese OSA patients.

Given that pathophysiology from the primary pathologic event of OSA may differ as a function of obesity, screening and treatment options for OSA may need to be optimized based on BMI. Therefore, future studies should focus on clarifying the different clinical manifestations of OSA in obese and non-obese patients and may further consider comparing the efficacy of treatment(s) for OSA between obese and non-obese patient groups.

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