

Gender and Age Disparity in Co-Morbidities Associated with OSA

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ABSTRACT

Introduction: Obstructive sleep apnea (OSA) is a known risk factor for metabolic disturbances, cardiovascular diseases, dyslipidemia, depression, and anxiety. A high comorbidity burden worsens the prognosis of OSA and the distribution of comorbidities is known to differ between men and women with a prognostic impact. Careful assessment of comorbidities should become standard clinical practice for OSA patients, for better phenotypic characterization to help provide individualized care in their management.

Method: This was a retrospective analysis of over 1000 charts which included patients with a first time clinical and polysomnography diagnosis of obstructive sleep apnea at the center. Data was compiled from 851 patients with OSA out of which 487 were men and 358 women with an age range of 19-85 years old. There were 212 males of age <55yrs and 275 males of >55yrs of age. There were 158 females of age <55yrs and 200 females >55yrs of age. Descriptive analysis was performed to compare gender and age group for co-morbidities associated with OSA at a cut-of age of 55years.

Results: The percentage of males newly diagnosed with OSA by PSG was approximately 60%, and demonstrated high AHI value representing a severe case of OSA compared to females. Prevalence of comorbidities in females of all ages was depression (36.2%), anxiety (21.7%), hypertension (37.7%), hyperlipidemia (23.9%), CAD (3.6%), afib (2.9%) and other heart conditions (9.4%). The prevalence of comorbidities in males of all ages was depression (17.9%), anxiety (17.9%), hypertension (42.3%), hyperlipidemia (31.6%), CAD (13.7%), afib (4.8%), and other heart conditions (13.7%). Age was a predictive factor in gender related comorbidities associated with OSA. Female subjects at age <55yrs with OSA presented with higher trends of anxiety, fatigue, and headache compared to the males. For both females and males at age >55yrs, dementia became a concerning comorbidity, which was predominant in males. Chief complaints for male subjects at age >55yrs diagnosed with OSA were dementia, numbness, and pain. There were more males diagnosed with OSA with diagnosis of hyperlipidemia, coronary artery disease (CAD), hypertension (HTN) and atrial-fibrillation compared to women of this age with OSA who had more depression.

Conclusion: Differences in gender and age-related co-morbidities associated with OSA exist and may have a prognostic impact on disease progression. 55yrs is a good cut off to delineate the effect of age on co-morbidities associated with OSA. More studies with a larger and diverse population are needed to validate these findings and generalize the conclusions.

Keywords

Obstructive Sleep Apnea, Apnea-hypopnea index, Fatigue, Depression, Coronary Artery Disease, Hypertension.

Introduction

Obstructive sleep apnea affects a majority of the population and is associated with hypertension [1], obesity [2], diabetes [3], heart attack [4] and stroke [5]. OSA is an independent risk factor for cardiologic impairment with comorbidities that include cerebrovascular diseases and metabolic syndrome [6]. Other known comorbidities associated with OSA include psychiatric disorders, such as depression [7] and anxiety [8].

The significance of comorbidities in OSA patients has emerged and is recently increasingly reported. A high comorbidity burden worsens the prognosis of OSA [9]. The distribution of comorbidities is known to differ between men and women with a prognostic impact [10]. There are also differences in pathophysiology and clinical presentation of comorbidities in elderly women when compared to the usual model of middle-aged men that dominates the current literature [11]. Careful assessment of comorbidities should become standard clinical practice for OSA patients, for better phenotypic characterization to help provide individualized care in their management.

Reports have consistently confirmed that OSA is more common in men than women [12]. OSA is underdiagnosed in females due to differences in clinical presentation and female-specific symptoms, as well as increased medical comorbidities [13].

Some studies have shown that OSA increases all-cause and cardiovascular related mortality predominantly in the middle-aged group (40-65), followed by a plateau or a reduction in mortality in older ages [14]. Other studies show a positive linear correlation between OSA and mortality, up to the age of 80. It is thought that the frequency of OSA rises with age, and, notably, OSA severity increases with age in the range 45–53 years [15]. However, the effect of age on the prevalence of sleep apnea in the general population remains unclear. It has been suggested that the sleep laboratory criteria used for diagnosis of sleep apnea should be adjusted for age [16]. This current data, showing increased OSA with age, can be controversial as mortality due to OSA and cardiovascular comorbidities can affect OSA prevalence at advanced ages [17].

Gender differences have also been reported to be significant for recognizing obstructive sleep apnea mechanisms and responses to therapy [18]. These reports have been described as inconsistent, in part due to clustering of age groups and/or genders. For example, even though high comorbidity of OSA and depression may suggest that both disorders share a common neurobiological risk factor, i.e. on the neurotransmitter level such as via the serotonergic system [19], the prevalence of more women having depression with a diagnosis of OSA [20] suggest a higher complexity of the pathophysiology associated with the female gender. Additionally, more males with cardiovascular diseases have OSA, which has

significant association with resistant hypertension [21]. More studies are required to address any confounding factors and endpoints, with a significant number of women and men who have similar OSA severity to justify the differences in comorbidities associated with OSA [22].

EENA's point-of-care specialty practice offers a unique opportunity to perform retrospective analysis to assess comorbidities associated with OSA and the prevalence disparity between gender and age.

The overall objective of this study was to conduct a 2-year review and analysis of electronic medical records in order to evaluate comorbid conditions that may be influenced by gender and age with the diagnosis of obstructive sleep apnea.

Material and Methods

The steps for the screening and evaluation are delineated as follows: A self-referred or referred patient by the primary physician is registered into the Center's EMR system. All consent forms and educational materials on proposed research are made available at the first visit. Volunteers were required to review and acknowledge acceptance of the informed consent. Once consent is obtained, volunteers received information regarding patient portal registration and had a week to complete the registration process before the first sleep disorder consultation appointment is made with the provider. Routine assessment and evaluation were performed per practice guidelines and protocols. For sleep assessment, a board-certified sleep specialist evaluated, diagnosed and requested PSG studies as needed. Patients received an in-lab PSG diagnostic study and treatment as prescribed, with CPAP, per regular management protocol. Participants of specific trials all provided informed consent per IRB and approved guidelines. PSG data were scored by a certified registered polysomnography technologist (RPSGT) using American Academy of Sleep Medicine (AASM) criteria. Apnea-hypopnea index (AHI) was used in the diagnosis and assessment of severity according to approved guidelines. Clinical evaluation included a sleep history, physical examination, and routine laboratory investigational analysis under the supervision of the board-certified Neurology/Psychiatry/Sleep medicine specialist.

All studies were approved by the institutional review board at participating center and carried out in accordance with The Code of Ethics of the Declaration of Helsinki.

Study Population (Subjects)

This was a retrospective analysis of over 1000 charts which included patients with a first time clinical and polysomnography diagnosis of obstructive sleep apnea at the center. Data was compiled from 851 patients with OSA out of which 487 were men and 358 women with an age range of 19-85 years old. There were 212 males of age <55yrs and 275 males of >55yrs of age. There were 158 females of age <55yrs and 200 females >55yrs of age. Descriptive analysis was performed to compare gender and age groups with OSA at a cut of age of 55years.

Polysomnography & Apnea-Hypopnea Index (AHI)

The apnea-hypopnea index (AHI), used in the diagnosis and assessment of severity of OSA, is obtained via polysomnography. The average number of apneas and hypopneas per hour of sleep is based on recommendation by the American Academy of Sleep Medicine. Apnea Criteria is defined as the drop in the peak thermal sensor excursion >90% of baseline; duration of the event lasts at least 10 seconds; and at least 90% of the event's duration meets the amplitude reduction for apnea.

For Hypopnea Criteria, the nasal pressure signal excursion drops by >30% of baseline; the duration of this drop occurs for a period lasting at least 10 seconds; and there is a >4% desaturation from pre-event baseline.

At least 90% of the event's distribution must meet the amplitude reduction criteria for hypopnea. In addition to AHI, polysomnography diagnosis results include measurement of other hypoxia-related parameters, such as oxygen saturation— defined as the percentage of available hemoglobin that is saturated with oxygen.

Clinical Diagnosis

Clinical diagnoses were derived from CPT codes as indicated in the EMR which were submitted for coding and billing purposes.

Results

The pie-chart of figure 1a shows a break-down of diagnosis via CPT codes from the EMR of this point-of-care specialized Neurology & Sleep outpatient clinic and accredited Sleep Center. More than 75-85% of the patients that were seen at the center had varying diagnoses of neuropathy and paresthesia, consistent with the specialization of the physician. Obstructive sleep apnea was the second largest presentation to the center at about 10%, followed by fatigue and Alzheimer's dementia.

Figure 1b demonstrates the percentage of male and female patients newly diagnosed with OSA by PSG, with approximately 60% males, i.e. predominant.

AHI is the number of apneas or hypopneas recorded during the study per hour of sleep. This is generally expressed as the number of events per hour and based on the AHI. The severity of OSA is classified as follows: None/Minimal: AHI < 5 per hour; Mild: AHI ≥ 5, but < 15 per hour; Moderate: AHI ≥ 15, but < 30 per hour; Severe: AHI ≥ 30 per hour. In figure 2a we show a trend towards higher AHI values in male subjects, exceeding the 30 per hour threshold compared to the females. This suggests that males presented with more severe cases of OSA compared to females.

Epworth Sleepiness Scale (ESS) was not a good predictive of OSA in patients (data not shown), even though males diagnosed with OSA demonstrated high AHI values, representing a severe case compared to females.

Reductions in blood oxygen levels (desaturation) are recorded during polysomnography or limited channel monitoring. A normal blood oxygen level (saturation) is usually 96 - 97%. Reductions between 90-96% are usually considered mild. Dips into the 80 - 89% range can be considered moderate, and those below 80% are severe. Figure 2b represents the oxygen saturation levels of male and female subsets of OSA patients whose AHI values are presented in figure 2a. In contrast to the AHI values, the majority of both male and female oxygen saturation levels trended at ~ 80% (0.8), with a few severe cases trending more for males at between 60%-80% (0.6-0.8). These graphs support the idea that more males presented and were diagnosed with OSA at the center, and most of them were moderate to severe cases as indicated by the AHI values and levels of oxygen saturation.

Co-morbidities were extrapolated from the medical history of 138 females and 168 males diagnosed with OSA, with the prevalence of a co-morbidity occurring per subject. Overall more females diagnosed with OSA had at least a diagnosis of pain, headache, or fatigue compared to males, who trended towards more severe cases of OSA, Figure 3a. Furthermore, prevalence of comorbidities in females of all ages was depression (36.2%), anxiety (21.7%), hypertension (37.7%), hyperlipidemia (23.9%), CAD (3.6%), afib (2.9%), and other heart conditions (9.4%). The prevalence of comorbidities in males of all ages were depression (17.9%), anxiety (17.9%), hypertension (42.3%), hyperlipidemia (31.6%), CAD (13.7%), afib (4.8%), and other heart conditions (13.7%), as shown in Figure 3b.

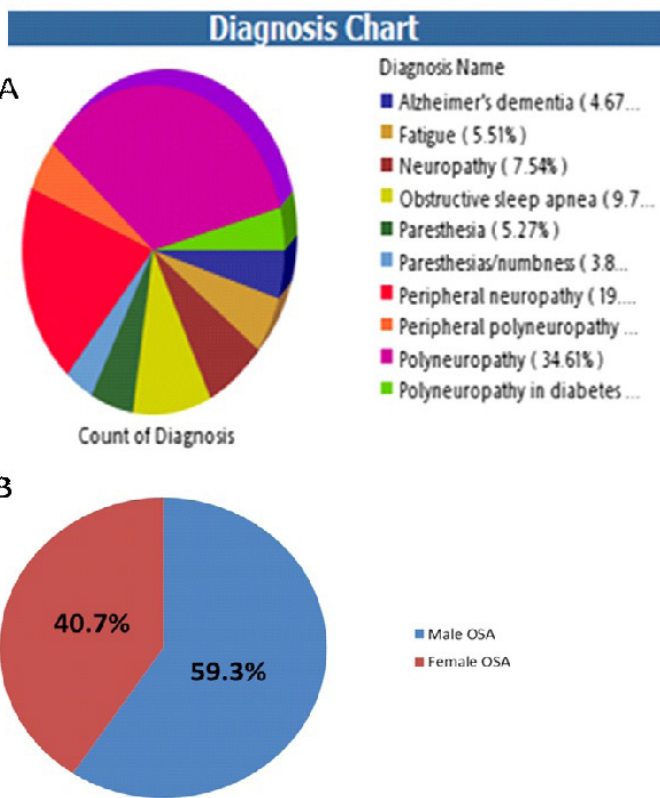


Figure 1

A. Chart showing the % of new patients with different diagnoses including OSA in 2014.

B. Out of the 851 OSA patients 59.3% were males and 40.7% females.

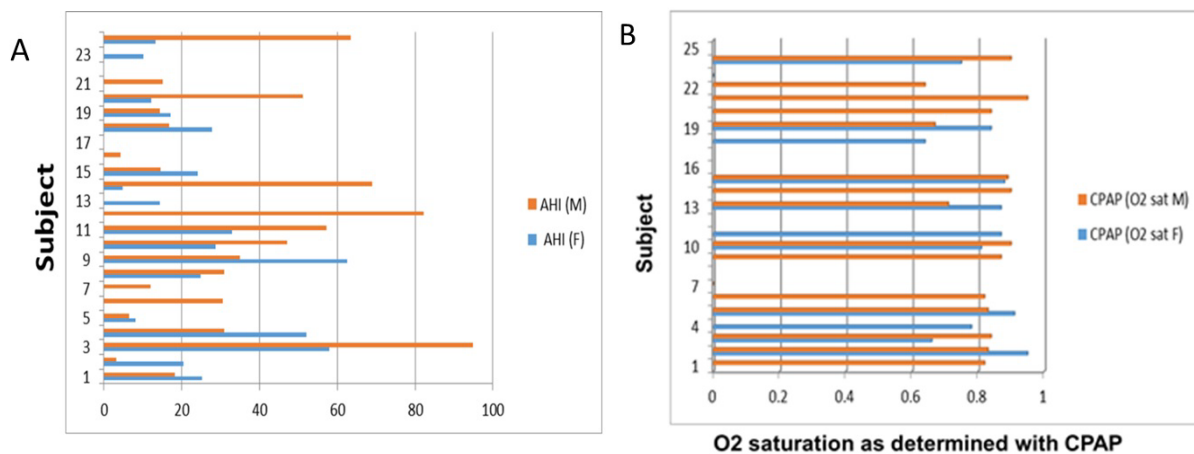


Figure 2

- A. Males with OSA have higher AHI levels compared to females. The X-axis represents the number of events per hour. Minimal: AHI <5 per hour; Mild: AHI>5, but <15 per hour; Moderate: AHI >15 but < 30 per hour; Severe AHI >30 per hour.
- B. Reductions in blood oxygen levels (desaturation) recorded during the CPAP-polysomnography titration phase. Blue bars represent oxygen saturation for female subjects. Red bars represent oxygen saturation for male subjects.

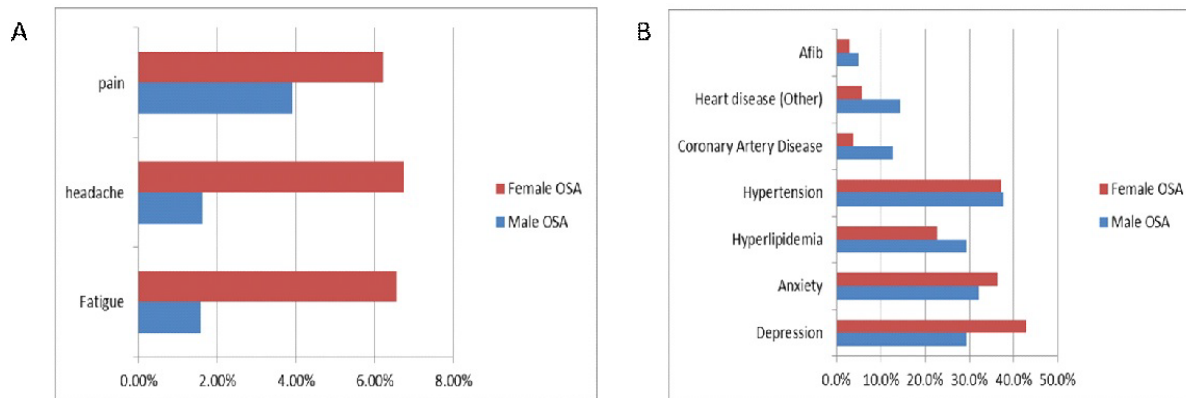


Figure 3

- A. Co-morbidities associated with new diagnosis of OSA in female subjects (red) and male subjects (blue). Y-axis represents the comorbidities. X-axis represents arbitrary percentages to demonstrate the number of OSA subjects with pain, headache and fatigue.
- B. Co-morbidities associated with new diagnosis of OSA in female subjects (red) and male subjects (blue). Y-axis represents the comorbidities. X-axis represents arbitrary percentages to demonstrate the number of OSA subjects with comorbidities and OSA. Depression and anxiety are major comorbid conditions associated with OSA in females.

Age was a predictive factor in gender related comorbidities associated with OSA. Figure 4a shows that female subjects at age <55yrs with OSA presented with higher trends of anxiety, fatigue, and headache compared to the males with OSA at <55yrs. There were equal numbers of OSA patients with insomnia in both male and female at <55yrs.

The chief complaints of female subjects at age >55yrs with OSA continued to persist as fatigue, anxiety, headache, and increasing insomnia. Interesting for both females and males at age >55yrs, dementia became a concerning comorbidity, which was predominant in males, as well as pain. Chief complaints of male subjects at age >55yrs diagnosed with OSA are dementia, numbness, and pain, Figure 4b. Patients diagnosed with OSA had anxiety as a co-morbid condition in their medical history for both sexes and across all age groups.

Age was a predictive factor in associating heart conditions as a comorbid condition with OSA in males and females particularly over 55 years of age. In male subjects at age <55yrs, hypertension and hyperlipidemia trended higher than in females, who had more depression & anxiety associated with their OSA, Figure 5A.

For males at >55yrs with OSA, co-morbidities related to heart disease became predominant. There were more males diagnosed with OSA who also had the additional diagnosis of hyperlipidemia, coronary artery disease (CAD), hypertension (HTN), Atrial-fibrillation, and other heart conditions compared to women of this age with OSA who had more depression, Figure 5b.

With regards to adherence and compliance for OSA treatment, 67% of the male patients at <55 years with at least 1 month of clinical management including follow-up reported using their

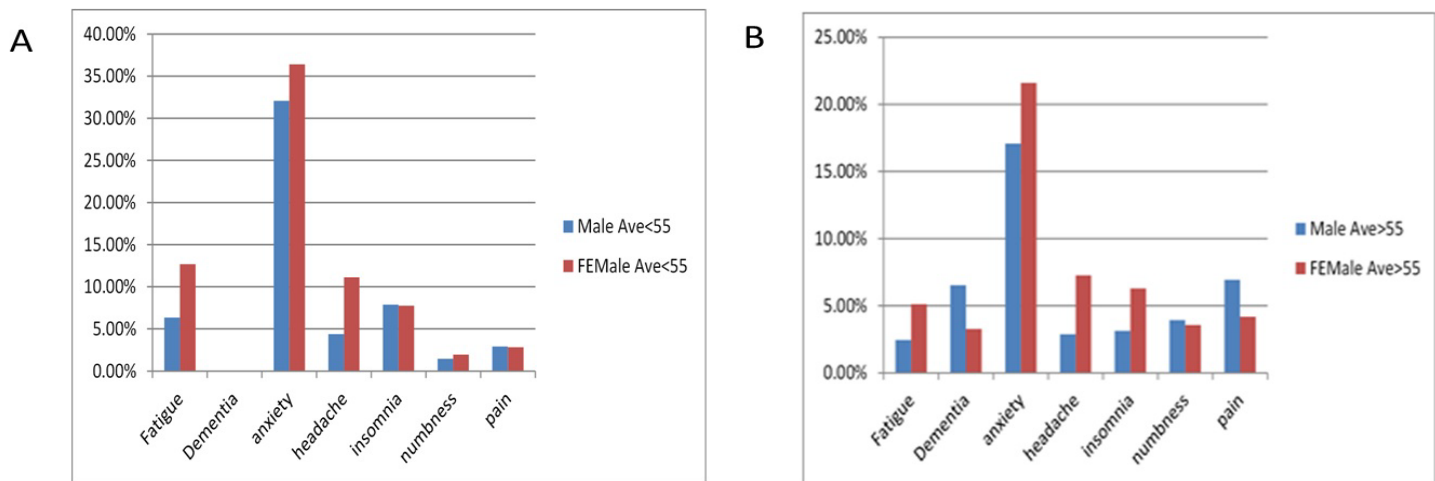


Figure 4

A. Co-morbidities associated with new diagnosis of OSA in female subjects (red) and male subjects (blue). Y- Axis represent arbitrary percentages. X-axis represents the comorbidities. For subjects at age <55yrs with OSA.

Equal number of OSA patients with insomnia in both male and female under the age of 55yrs. Chief complaints of Female subjects at age <55yrs diagnosed with OSA are anxiety, fatigue and headache.

B. Co-morbidities associated with new diagnosis of OSA in female subjects (red) and male subjects (blue). Y- Axis represents arbitrary percentages. X-axis represents the comorbidities.

For subjects at age >55yrs with OSA. Higher number of OSA patients with insomnia in females compared to males above the age of 55yrs. Chief complaints of Male subjects at age >55yrs diagnosed with OSA are dementia, numbness and pain.

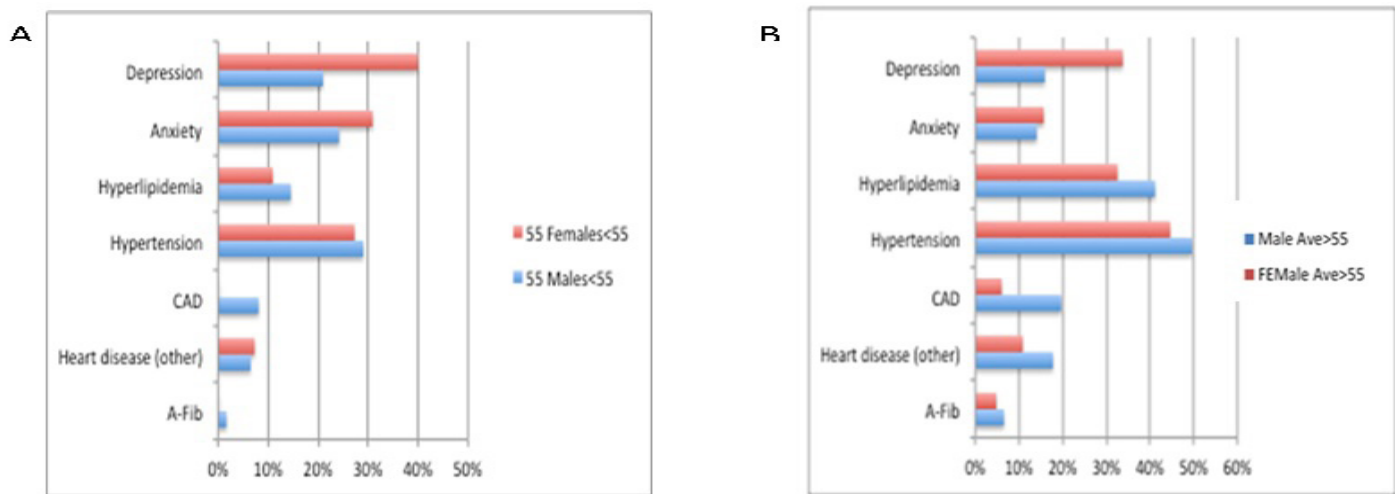


Figure 5

A. Co-morbidities associated with new diagnosis of OSA in female subjects (red) and male subjects (blue). X- axis represent arbitrary percentages. Y-axis represent the comorbidities. In female subjects at age <55yrs, depression & anxiety in comparison to hypertension in males are comorbid conditions associated with OSA.

B. In female subjects >55yrs with OSA, depression is the predominant comorbid condition compared to hyperlipidemia, CAD, HTN & other heart dx in men.

CPAP machines in compliance. A greater number i.e. 83% of male patients at >55 years with at least 1 month of clinical management including follow-up, reported using their CPAP machines in compliance. Female patients were less likely to have diagnostic PSG testing or use a CPAP machine regardless of age (data not shown).

Lastly, we determined other additional neurological conditions in this OSA population. Figure 6a shows that more female subjects at age <55yrs presented predominately with seizure followed by

neuropathy in addition to the diagnosis of OSA. At age >55yrs neuropathy was the major comorbid condition in addition to OSA in females and more in males Figure 6b. Other conditions such as Lyme disease and multiple sclerosis were also diagnosed in some of the subjects with OSA but without significant gender or age differences.

Discussion

Approximately 3 new patients presented daily at the center to be evaluated for OSA. Overall, there were a greater number of men

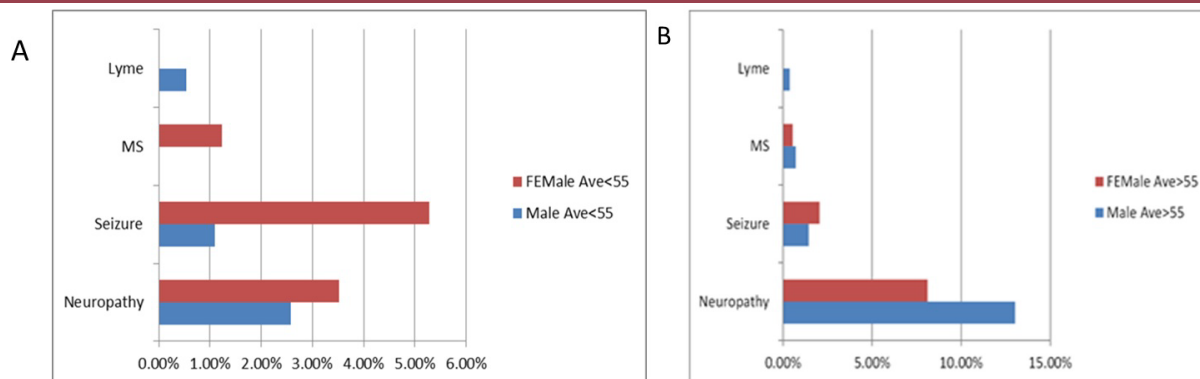


Figure 6

- A. Co-morbidities associated with new diagnosis of OSA in female subjects (red) and male subjects (blue). X-axis represent arbitrary percentages. Y-axis represent the comorbidities for subjects at age <55yrs with OSA. For female subjects at age <55yrs, seizure is the predominant comorbid condition associated with the diagnosis of OSA.
- B. Neuropathy is the major comorbid condition associated with OSA in men over 55yrs.

diagnosed with OSA compared to women. This is consistent with the report that men tend to be referred to sleep medicine centers more often than women [23]. The majority of the newly diagnosed OSA patients presented with secondary comorbid pathology.

While fatigue, headache and depression have previously been reported to be associated with OSA in women, we are the first to provide a clear distinction of these symptoms by age. Specifically, women at the age of <55yrs demonstrated more headache and fatigue in conjunction with their OSA, while older women of >55yrs had depression in conjunction with their OSA diagnosis. In women, depression and anxiety were associated with OSA, while men over 55 years of age presented with factors related to heart disease. Men over 55 years of age with a primary diagnosis of OSA also presented with neuropathy, albeit there was a greater variation in women of the same age group.

OSA was associated with psychological disorders in women whereas men presented with more cardiogenic comorbidities in addition to OSA. Further studies are needed to elucidate factors that may cause this predisposition in women compared to men. Additionally, age related factors need to be investigated to elucidate the link between the onset of OSA and depression in women.

Active management of insomnia in male patients diagnosed with OSA, which included regular follow-ups, showed improved compliance to CPAP use and better treatment success of OSA. Further studies and a larger cohort of patients will be needed to validate and understand the differences observed with women, who were less likely to have an in-lab polysomnography or to be compliant to the use of CPAP. Considering that fatigue, depression, and anxiety were predominant diagnoses in addition to OSA in women, we hypothesize that addressing those factors may facilitate and enhance the management of OSA. The associations of OSA and neuropathy have been described extensively in the literature. In this analysis we determined that OSA was co-morbid with neuropathy more in men >55yrs compared to women within the same age group. This will be the first report that defines an age

cut-off for these co-morbid conditions. Further studies should focus on gender and age-related factors that increase predisposition of men with OSA having neuropathy compared to women at >55yrs. We chose the age of 55yrs as a cut of point based on report in the literature that OSA occurrence showed 2 peaks at 0–4 years and 55–59 years “Clinical Patterns of Obstructive Sleep Apnea and Its Comorbid Conditions: A Data Mining Approach [24].

In summary, we describe differences in gender and age-related co-morbidities associated with OSA with prognostic impact and implications to management and compliance to CPAP.

More studies are needed that further defines age groups for the management of OSA. It is important for clinicians and scientists to determine an age cut-off point (e.g. 55yrs) and stay consistent to ensure uniformity and reproducibility of results across different groups.

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