Gender Differences in Obstructive Sleep Apnea with Comorbid Treatment-Resistant Depression

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Abstract

Background. A bidirectional relationship between major depression and obstructive sleep apnea has been established, suggesting the possibility of overlapping and compounding disease processes. Depression, however, while more prevalent in women, is a highly heterogeneous disorder and can be difficult to treat regardless of gender. A common overlapping symptom of depression and obstructive sleep apnea is fatigue. Gender differences in obstructive sleep apnea symptomatology (and fatigue in particular) are also consistently observed. Here, we investigate obstructive sleep apnea in specific relation to treatment-resistant depression.

Methods. A cross-sectional design was used to analyse data from 94 patients with treatment-resistant depression from a subspecialist mood disorders outpatient service who had no previous sleep assessment. Participants completed overnight polysomnography and a battery of rating scales assessing mood, sleep, and daytime functioning. Linear regression models determined whether presence of fatigue in treatment-resistant depression predicted sleep obstructive apnea severity.

Results. There was a high prevalence of previously undiagnosed obstructive sleep apnea in our sample of patients with treatment-resistant depression. Treatment-resistant depression closed the gap in obstructive sleep apnea prevalence between men and women.

Conclusions. We argue that typical symptoms of treatment-resistant depression may overshadow key symptoms of undetected obstructive sleep apnea. Specifically, we found that daytime fatigue masked a potentially significant underlying sleep disorder in women only. Comprehensive assessment and screening for sleep apnea in patients with treatment-resistant is encouraged, and the importance of investigating severity of fatigue in this population is emphasized.

Background

The heterogeneity of depression and its potential for recurrence lead some individuals to experience treatment-resistant depression (TRD). While there remains a lack of consensus on the concept and definition of TRD (1), it is most commonly defined as a major depressive episode which fails to respond to at least two antidepressant trials of adequate dose and duration (2). Up to 50–60% of patients do not achieve adequate response following antidepressant treatment (3). Often, inappropriate doses of medication or duration of treatment, non-adherence, and comorbid medical conditions including anxiety disorders, substance use disorder, personality disorders and other medical comorbidities contribute to pseudo-resistance and significantly interfere with treatment response (2,4). The high societal burden of depression underscores the need to better understand *all* factors contributing to episode onset, course, and treatment efficacy. One possible way to construe these factors is to examine common physical comorbidities of TRD, such as Obstructive Sleep Apnea (OSA). Nearly one fifth of individuals diagnosed with depression also show symptoms consistent with sleep-disordered breathing (SDB) such as OSA (5).

The longer OSA is left undiagnosed or untreated, the higher the risk of developing debilitating physical health complications that lead to increased morbidity, (e.g., cognitive decline) and mortality (6).

Findings from epidemiological and clinical studies suggest that OSA is underdiagnosed in women (7,8). Newer clinical studies confirm much lower men's vs. women's prevalence ratios in the range of 3:1–2:1, suggesting that variations in symptoms between men and women may lead to referral bias, misdiagnoses, and delay of treatment in women with OSA (7,8). It is necessary to investigate why women are disproportionately underdiagnosed if they experience OSA at a similar rate as men.

It is widely recognized that women often do not present with the "classic" symptoms of OSA such as excessive sleepiness and heavy snoring, but rather with less common or "atypical" symptoms such as daytime fatigue, unrestful sleep, insomnia, headaches, anxiety, depression, restless legs, nightmares, and palpitations (9, 10). A preeminent difference in the presentation of OSA between men and women may be the higher proportion of reported depressive symptoms, anxiety, and poorer quality of life in women (6, 11). Further, women with SDB may be more likely to develop cognitive impairment or dementia as compared to healthy women (12). Incidentally, women are diagnosed with major depression two-fold more than men and are more likely to be classified as having TRD (13).

Treatment Resistant Depression and OSA

The relationship between Major Depressive Disorder (MDD) and OSA appears to be bidirectional. Several studies show that patients with OSA experience more symptoms of depression than individuals without OSA. In a sample of 703 individuals with MDD, 13.94% met criteria for moderate to severe OSA (14). Moreover, a similar study demonstrated higher levels of SDB in MDD after excluding individuals with clinically significant SDB, suggesting that screening for OSA should be a standard practice in patients with MDD (15). Despite this evidence, the association between comorbid depression and OSA remains poorly understood.

Although a vast body of literature exists on the general link between OSA and depression, the impact of OSA in patients with chronic, treatment resistant depression has not received much attention. Given the high prevalence and symptom overlap of OSA and TRD in community and clinical populations, our aim is to investigate the comorbidity of OSA in TRD, explore potential gender differences, and characterize the particular importance of this comorbidity in women.

Current Study

The current study used a cross-sectional sample of adults with treatment resistant depression to probe the relation between OSA and TRD. We used an exploratory approach to examine the prevalence of previously undiagnosed OSA in men and women with OSA, and to elucidate any gender differences surrounding "atypical" symptoms such as fatigue on the clinical presentation and severity of OSA in TRD.

Methods

Participants

Individuals who participated in one of two studies examining the interface between sleep and mood disorders in the outpatient Mood Disorders Research and Treatment Service at Providence Care Hospital in Kingston Ontario, Canada were included in the current study. Ethical clearance was granted by the hospital's affiliated university Health Sciences Research Ethics Board. Patients undergoing treatment for depression who had inadequate response to two or more antidepressants and never undergone a sleep study were asked if they would like to participate. Individuals were excluded if they experienced current manic symptoms, symptoms of psychosis, acquired brain injury, personality disorders, or poorly controlled co-morbid medical conditions. Participants were included even if they presented with comorbid dysthymic disorder, generalized anxiety disorder, or social anxiety disorder.

Depressive Symptoms.

Diagnosis of TRD was made by an experienced psychiatrist in a subspecialist Mood Disorders service and confirmed using electronic patient records. Depression severity was assessed with The Montgomery Åsberg Depression Rating Scale (MADRS;16) and the Hamilton Depression Rating Scale (HAM-D; 17).

Anxiety Symptoms.

Anxiety severity was measured using the Beck Anxiety Inventory (BAI; 18).

Non-Specific Psychiatric Morbidity and Quality of Life.

The 12 item General Health Questionnaire (GHQ;19) was used to measure non-specific psychiatric morbidity and daily functioning. Higher scores represent higher levels of psychiatric morbidity. Area under the curve (AUC) analyses demonstrate acceptable specificity (78.5-91.0) and sensitivity (71.4-93.5) in detecting psychiatric illness (20).

Self-Reported Sleep Quality, Daytime Sleepiness and Fatigue.

The Pittsburgh Sleep Quality Index (PSQI) was used to measure self-reported sleep quality and disturbances in the past month (21). The PSQI includes 10 questions in various formats. A systematic review and meta-analysis of the PSQI's performance in a range of clinical and community samples describes a median internal consistency reliability score of 0.73 (22).

The Epworth Sleepiness Scale (ESS; 23) was used to measure subjective daytime sleepiness. It is often chosen for use in clinical practice and research because of its ease of use, short response time, and acceptable internal consistency (Cronbach's alpha .73 to .86; 24).

Finally, the fatigue subscale of the Profile of Mood States (POMS-f; 25) was used as a measure of fatigue. The POMS-f subscale demonstrates excellent internal consistency (Cronbach's alpha = .92; 26).

Sleep-Related Breathing.

Level 2 (full, in-home) polysomnography (PSG) was conducted by a certified sleep technologist using the MediPalm MP-22 from Braebon Medical Corporation (Kanata, Ontario). Participants were set up with the recording device in their own home by the sleep technologist and were asked to go to sleep at their regular time. The next morning the sleep technologist returned to collect the data and equipment. All reports were scored by a trained sleep technologist, and apneas/hypopneas were scored according to the current American Academy of Sleep Medicine standards (27). The criterion for a hypopnea was a drop in nasal pressure signal ≥50 % of baseline associated with either ≥3 % desaturation from pre-event baseline or arousal. The criterion for an apnea was a drop in peak thermal sensor airflow excursion by ≥90 % of baseline.

Typically, an apnea-hypopnea index (AHI; number of apneas and hypopneas per hour) of greater than 5 is needed for diagnosis of OSA in addition to daytime symptoms. Patients with an AHI between 5 and 15 are considered to have mild OSA, patients with an AHI between 15 and 30 are considered to have moderate OSA, and patients with an AHI greater than 30 have severe OSA. The current study used the American Academy of Sleep Medicine's Sleep Apnea Definitions Task Force's definition (28) of respiratory disturbance index (RDI), which is the sum of the AHI plus the respiratory effort related arousals index (a sequence of breaths lasting 10 or more seconds leading to an arousal from sleep that does not meet criteria for an apnea or hypopnea) (27).

Procedure

Following the informed consent process, participants completed 3 appointments: Time 1 visit, PSG assessment, and Time 2 visit. At Time 1, basic demographics and health data were collected (e.g. age, Body Mass Index; BMI). Participants completed a battery of self-report assessments including the BAI, GHQ-12, SF-36, ESS, and the POMS (including POMS-f). Finally, the MADRS and HAM-D were completed by a study clinician. Following the Time 1 appointment, participants were scheduled for a PSG, which took place at their home on a night of their choosing. Once complete, participants returned for their Time 2 appointment to review the results of their PSG with a physician. Participants who were diagnosed with OSA were referred for further treatment to a sleep disorders clinic in Kingston, Ontario, Canada.

Data Analyses

Data were analyzed using IBM SPSS, Version 27 (Chicago, IL, USA). RDI and AHI scores were determined from PSG recordings. RDI and AHI are reported as mean number of arousals per hour during sleep. Participants were excluded from any analysis for missing data. Demographic and outcome variables were compared across gender using a one-way ANOVA or independent-samples Mann-Whitney U Test if variables were not normally distributed. Menopause was defined as age 55 or older. In general, non-parametric statistical tests were conducted when variables violated assumptions of normality. Parametric (Pearson Correlation) and non-parametric (Spearman's rho) correlations examined the strength of relationships between variables. To evaluate the role of fatigue (measured by POMS-f; dependent variable) in OSA severity (measured by AHI; independent variable) across genders (men x women), a

linear regression model was built for each gender. Statistical significance for all analysis was set at p = 0.05.

Results

One hundred and fourteen patients were entered into the study but only 94 (Table 1; 73% female; mean age ± SD: 48 ± 9 years) underwent PSG to determine sleep disorder comorbidity. The majority of the participants were in a current depressive episode (N = 82) with a small subset in a euthymic state (N = 11). On average, participants reported a mean score (± SD) of 22 ± 7.1 (N = 55) on the GHQ, out of a possible 48, with higher scores indicating poorer general health.

Table 1. Preliminary Gender Differences on Clinical Variables

	Men (*n* = 25)		**Women (*n* = 69)**		
	M(±*SD*)	*n*	M(±*SD*)	*n*	*p*
Age	46 (11)	25	48 (8.6)	69	.21
BMI	32 (6.2)	17	33 (7.4)	40	.40
MADRS	26 (9.2)	25	23 (8.4)	68	.13
HAM-D	22 (8.6)	25	20 (7.3)	68	.26
RDI	40 (43)	25	39 (44)	69	*.95
AHI	22 (24)	25	16 (21)	69	.28
ESS	9.6 (4.8)	24	9.4 (6.2)	66	.90
POMS	87 (47)	13	71 (44)	31	.28
POMSf	16 (7.7)	15	16 (7.1)	35	86
BAI	17 (12)	22	22 (13)	63	.10

Note *Mann-Whitney U Test

Undiagnosed OSA in both men and women with TRD

OSA was identified in up to 79% of patients with a chronic, treatment-resistant course of depression (RDI = 79%; AHI = 65%). Presence of OSA was not associated with episode state (depressed versus euthymic), with 100% of euthymic patients (N = 11, 82% female) scoring > 5 on RDI and AHI indices (RDI [mean ± SD] = 71 ± 40; AHI [mean ± SD] = 24 ± 18).

TRD closes the gap in OSA prevalence between men and women

Men and women had similar diagnostic frequencies of OSA (RDI: men, 80% and women, 78%; AHI: men, 64% and women, 65%; RDI, $X^2[1, N = 94] = 0.01$, $p = 0.55$; AHI, $X^2[1, N = 94] = 0.01$, $p = 0.55$). Additionally, men and women experienced similar amount of arousals (Table 1, Fig. 1; One-way ANOVA for gender, RDI: $F[1] = 0.005$, $p = 0.95$; AHI: $F[1] = 1.2$, $p = 0.28$) Reported symptoms of depression did not differ between men and women (Table 1; one-way ANOVA for gender, HAMD: $F[1] = 1.3$, $p = 0.26$; MADRS: $F[1] = 2.3$ $p = 0.13$). However, severity of OSA (RDI and AHI) was negatively correlated with depressive symptoms as measured by HAM-D (RDI: $r[94]=-0.30$, $p = 0.003$; AHI: $r[94]=-0.26$, $p = 0.012$). When analysed by gender, the negative association between OSA and symptoms of depression only existed in men, but not in women (men: RDI, $r[25]=-0.46$, $p = 0.021$ and ADI, $r[25]=-0.52$, $p = 0.008$; women: RDI, $r[68]=-0.22$, $p = 0.08$ and AHI, $r[68]=-0.16$, $p = 0.18$).

Co-morbid TRD Masks OSA Symptoms in Women Only

Subjective sleep quality, as measured by PSQI, suggests that the group reported clinical insomnia of moderate severity (mean ± SD: 17 ± 16 [N = 73]). Overall daytime sleepiness scores as measured by ESS scores were mean ± SD, 9.5 ± 6.0 (N = 73), indicating higher than normal daytime sleepiness. Men and women in our study reported similar amounts of fatigue as measured by POMS-f, respectively (Table 1). However, daytime fatigue but not sleepiness was significantly associated with symptoms of depression in women only (Table 1; daytime fatigue, POMS-f and HAM-D: $r[35] = 0.35$, $p = 0.04$; ESS and HAM-D: $r[65] = 0.14$, $p = 0.25$). Daytime fatigue and sleepiness were not associated with OSA in men or women. However, in a linear regression model, daytime fatigue (but not sleepiness) as measured by POMS-f significantly predicts OSA severity (AHI) in women only ($R^2 = 0.33 \pm 0.12$; $p = 0.05$) or more specifically, in women, for every one unit increase in fatigue on the POMS-f, there is a 0.33 increase in AHI mean hourly arousals. Therefore, in women, daytime fatigue associated with chronic depression may mask a potentially significant underlying sleep disorder.

OSA Worsens with Age in Women

In our sample, age was not correlated with OSA (RDI, $r[94] = 0.12$, $p = 0.25$; AHI, $r[94] = 0.07$,$p = 0.52$). However, 75% of participants were under the age of 55 yrs (range: 22–63). We split the group into over and under 55 years of age to reflect the fact that the majority of women will have achieved menopause by age 55. The severity of OSA was significantly higher in women over the age of 55 (one way between subjects ANOVA, AHI comparing women over and under 55 yrs, $F[1,67] = 5.3$, $p = 0.02$). On average, younger women had ‘mild’ OSA (mean ± SD, 13 ± 14 SA events) while women over 55 yrs had ‘moderate’ or more severe OSA (mean ± SD, 25 ± 32 SA events). BMI and depressive symptoms were not statistically different between women over and under the age of 55 (one-way between subjects ANOVA for BMI and HAM-D comparing women over and under 55 yrs, BMI: $F[1, 38]: 0.77$, $p = 0.38$; HAM-D: $F[1,66] = 0.01$, $p = 0.9$). This association was not observed in men (one way between subjects ANOVA, AHI comparing men over and under 55 yrs, $F[1, 23] = 0.35$, $p = 0.56$

Discussion

The goal of this study was to determine the prevalence of OSA in a sample of individuals with TRD, and to elucidate the roles of gender and fatigue on the clinical presentation and severity of OSA in TRD. First, our results showed a surprisingly high (79%) prevalence of previously undiagnosed OSA in TRD. Second, we found that typical symptoms reported in TRD (fatigue, sleepiness), can overshadow key symptoms of undetected OSA—noting that fatigue significantly predicted the severity of OSA in women, but not in men. Our results also showed that OSA severity increased in women over 55, demonstrating a positive relation between OSA severity and age in women only. To our knowledge, this is the first study to investigate gender differences in TRD with co-morbid OSA.

There are several reasons to explain why patients with MDD have an increased prevalence of co-morbid OSA as compared to the general population. For instance, respiratory related sleep fragmentation and/or the effect of hypoxia on the prefrontal cortex were identified more in depressed as compared to healthy individuals during sleep (29). Chronic inflammation (increased CRP and ferritin levels) found in a subpopulation of individuals with MDD is identified as a risk factor for moderate to severe OSA (15). General Health Questionnaire scores showed impaired general health in our TRD sample, with no differences between genders. Subjective sleep quality as measured by PSQI showed clinical insomnia of moderate severity in our group, with no differences between the sexes. Depression is known to exacerbate poor sleep quality as measured by PSQI (30) contributing to the complex relationship between insomnia, depressive symptoms and SDB. However, the exact biological/physiological mechanism explaining comorbid MDD and OSA has yet to be identified.

Although men and women had similar diagnostic frequencies of OSA in our sample, we demonstrate that TRD closes the gap in OSA prevalence between men and women with MDD. A possible explanation for this diagnostic disparity comes from previous research highlighting that women often fail to acknowledge OSA symptoms and subsequently do not seek medical help. Existing literature identifies possible explanations for this phenomenon: [1] women may perceive snoring as “un lady-like” and avoid seeking care (31), and [2] a large proportion of women with OSA do not report any of the “classic” symptoms such as snoring or apneas and endorse insomnia, headaches, and tiredness (32). Our study further confirms that typical OSA presentation in women is masked in a population of treatment resistant MDD patients.

Men and women experienced similar severity of OSA across our group, in contrast to the general population where the severity of OSA is found to be higher in male patients (33). Interestingly, women tend to be symptomatic at lower AHI scores due to long-term effects of REM sleep disruption or more episodes of upper airway resistance during sleep producing symptoms such as daytime fatigue (31). We found an inverse association between depressive symptoms and severity of OSA in men, as previously reported (34). Conflicting views exist regarding the association between OSA severity and mental disorders (35); in general, women have a later onset of OSA and a positive correlation between AHI and the severity of depression, indicating a possibility of a causal relationship (36). Thus, depression co-morbidity in women is an important confounding factor that may affect severity of OSA.

Men and women in our study reported similar amounts of fatigue as measured by POMS-f (Table 1). Our results point out the challenges in parsing the separate effects of depressive severity and fatigue in those with MDD and co-morbid OSA. We found that a specific measure of fatigue (POMS-f) significantly predicted OSA severity in women but not in men. Therefore, daytime fatigue in TRD may mask a potentially significant underlying sleep disorder *only in women*. This is an important finding given that we confirmed that women with TRD are unlikely to be recognized and treated for co-morbid OSA. Fatigue, at least in part caused by SDB, may be related to the treatment resistance and assessment of fatigue may aid in recognizing co-morbid OSA in depressed women. Thus, simple and reliable measure such as POMS in TRD could aid in identifying and predicting the severity of co-morbid OSA.

Epworth Sleepiness Scores overall showed higher than normal daytime sleepiness in the entire group with no differences between genders: Complaints of fatigue, tiredness, and lack of energy are equally if not more common in OSA as compared to excessive daytime sleepiness (EDS) and fatigue is associated with more severe dysfunction than EDS in patients with OSA (37). Presence of EDS is associated with a greater risk of depression in OSA (38), and patients reporting higher levels of EDS are more likely to report higher levels of depression (39). Interestingly, fatigue in OSA is more strongly associated with depressive symptoms than measures of OSA severity (35).

Limitations And Future Considerations

There are several limitations of this study. Our results are based on retrospective data and analysis in a population of patients with TRD with missing data in some assessments. Given the nature of our population, we had more females in our group and thus our sample size was biased toward females. We did not have data available on additional medical co-morbidities, smoking status or alcohol consumption that could have contributed to the high prevalence of OSA in this population. It is reasonable to assume that psychotropic medications lead to weight gain over years of depression treatment in a significant number of our subjects, further contributing to a surprisingly high OSA prevalence.

Perhaps the most impactful finding from this study is the demonstration that daytime fatigue masked a potentially significant underlying sleep disorder in women only. We emphasize the importance of investigating severity of fatigue in this sub-set of individuals as it could be associated to undiagnosed OSA. Additionally, we propose comprehensive assessment and screening for OSA in both men and women with TRD, and suggest that quantification of SDB should be standard practice in depression research and clinical care.

Conclusions

We demonstrated that screening, diagnosis, and treatments of OSA are often delayed in a chronically depressed population. Given the impact of untreated OSA on general health and quality of life, diagnosing and treating ‘silent’ OSA in TRD is paramount in improving patient outcomes. This study contributes an updated understanding of OSA and the best practices associated with diagnosis. AHI is

now considered an imperfect metric for the definition of OSA with respect to symptoms and outcomes (40). Given the specific presentation in women and the frequent co-morbidity of OSA in TRD, our results confirm the importance of comprehensive clinical sleep assessment and evaluation of symptoms while exploring “treatment resistance” in women with MDD. We suggest a personalized approach to the diagnosis and management of patients with OSA as most appropriate.

Abbreviations

TRD	Treatment-Resistant Depression
OSA	Obstructive Sleep Apnea
SDB	Sleep-Disordered Breathing
MDD	Major Depressive Disorder
MADRS	Montgomery Åsberg Depression Rating Scale
HAM-D	Hamilton Depression Rating Scale
BAI	Beck Anxiety Inventory
GHQ	General Health Questionnaire
AUC	Area Under the Curve
PSQI	Pittsburgh Sleep Quality Index
ESS	Epworth Sleepiness Scale
POMS-f	Profile of Mood States- fatigue subscale
PSG	Polysomnography
AHI	Apnea-Hypopnea Index
RDI	Respiratory Disturbance Index
BMI	Body Mass Index
EDS	Excessive daytime sleepiness

Declarations

Ethics approval and consent to participate: Ethics approval for this study was granted by the Queen’s University Health Sciences Research Ethics Board (IRB# 00001173). All participants reviewed and signed a letter of information and consent approved by the associated ethics board prior to participating in any study-related activities.

Consent for publication: Not applicable.

Availability of data and materials: Data is available upon request to the corresponding author.

Competing interests: The authors declare that they have no competing interests.

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Figures

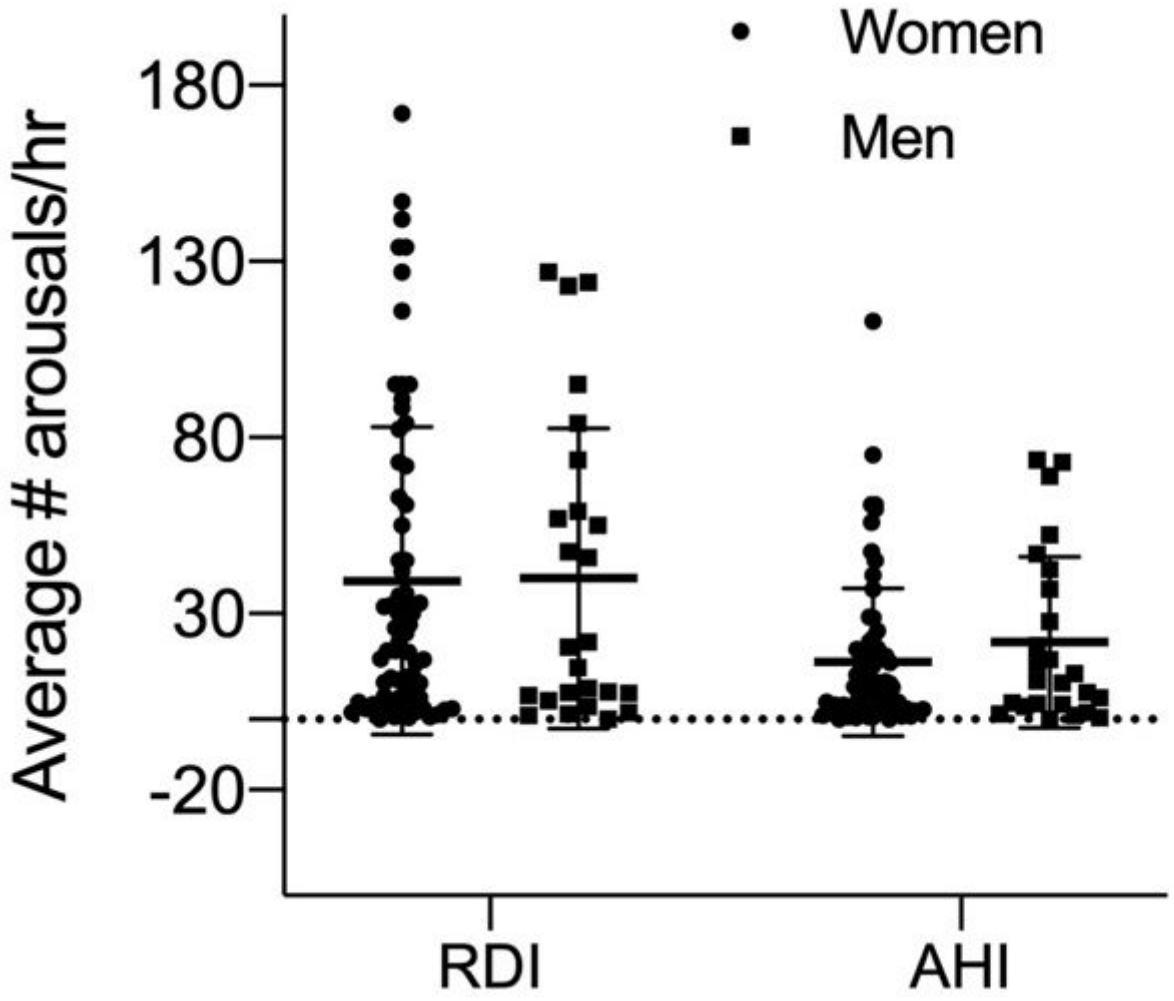

Figure 1

Men and Women with TRD have similar average number of arousals/hr as measured by RDI and AHI

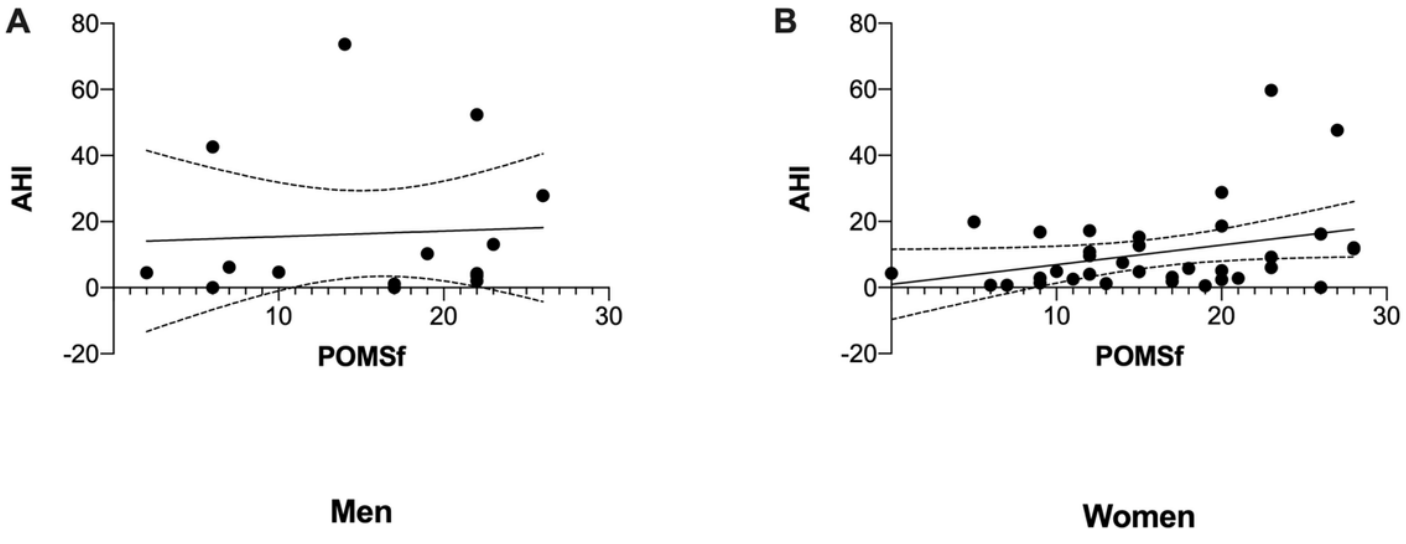

Figure 2

POMSf predicts the severity of sleep apnea as measured by AHI in Women (A) but not in Men (B) in TRD