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Sleep Apnea In Veterans With Schizophrenia: Estimating Prevalence And Impact On Cognition

Stephen Edward Ghazikhanian

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SLEEP APNEA IN VETERANS WITH SCHIZOPHRENIA: ESTIMATING PREVALENCE AND IMPACT ON COGNITION

Stephen Ghazikhanian and Toral Surti. Department of Psychiatry, Yale University, School of Medicine, New Haven, CT.

Abstract:

The cognitive impairments of schizophrenia drive the functional disability of the illness but are difficult to treat. One barrier to effective cognitive interventions may be medical illnesses that compromise cognition and are over-represented in people with schizophrenia. Obstructive sleep apnea (OSA) is treatable, causes reversible impairments in many cognitive domains also affected by schizophrenia, and is likely under-diagnosed in people with schizophrenia. We have estimated the prevalence of OSA in schizophrenia, both by self-report and with a predictive model, and characterized the associations between OSA and cognition and functional capacity in schizophrenia, using a large dataset of 3942 patients with schizophrenia collected by the Veterans Administration Cooperative Studies Program (CSP) #572 “Genetics of Functional Disability in Schizophrenia and Bipolar Illness”. Neuropsychological tests included TMT-A, BACS Symbol Coding, Category Fluency, verbal learning, working memory and NAB Mazes. Functional capacity measures were the UCSD Performance Skills Assessment Battery (UPSA-B) and the Everyday Functioning Battery- Advanced Finances (EFB-AF). Phi correlations were used to assess associations of self-reported OSA (R-OSA) with demographic and clinical factors. Self-reported diagnosis may underestimate prevalence of OSA in this sample, so a clinical prediction model was also used to calculate predicted prevalence of OSA (P-OSA). Each participant’s composite cognitive score (CCS) was calculated by averaging their age- and gender-corrected T-

scores for each cognitive test, with higher scores indicative of better performance. T-tests compared assessments between reported and non-reported OSA (R-OSA v. nR-OSA) and predicted and non-predicted OSA (P-OSA v. nP-OSA). ANOVAs were used to examine differences in CCS, UPSA-B, and EFB-AF among R-OSA, predicted-and-not-reported OSA (PnR-OSA), and No-OSA. Binary logistic regression models of PnR-OSA with sociodemographic and clinical variables were used to characterize this vulnerable subgroup. The reported prevalence of OSA was 14.4% (n=566). R-OSA patients were more likely to have a college education, be married, and be functionally independent. The predicted prevalence of OSA was 71.9% (n=2834). R-OSA patients had higher CCS than nR-OSA, whereas P-OSA patients had lower CCS than nP-OSA (*p's*<0.0002). R-OSA patients performed better than nR-OSA in speed of processing assessments, whereas P-OSA individuals performed worse than nP-OSA in speed of processing, verbal learning, and working memory (*p's*<0.0005). R-OSA had higher UPSA-B and EFB-AF than nR-OSA (*p's*<0.0001). P-OSA patients had a lower EFB-AF than those with nP-OSA (*p*=0. 003). PnR-OSA patients performed worse than both R-OSA and No-OSA on CCS and EFB-AF, and worse than R-OSA on UPSA-B (*p's* <0.05). Veterans with PnR-OSA tended to be older, male, smokers, unmarried, and have higher BMI and less education that the rest of the sample. Our analyses suggest only 20% of OSA in schizophrenia is diagnosed. Self-reported OSA was associated with better performance on cognitive and functional measures, whereas predicted OSA was associated with worse performance on these measures. People with higher cognitive capacity may be more likely to seek medical care, while those with less cognitive capacity are at greater risk for having co-

occurring medical conditions that further compromise cognition. Patients vulnerable to under-diagnosis likely have the most to gain from treatment of their OSA.

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TABLE OF CONTENTS

INTRODUCTION

Cognitive Impairments and Resulting Disability in Schizophrenia

Schizophrenia, though only prevalent in under 1% of the population[1], ranks among the top 15 most disabling diseases in the world[2]. Adults with schizophrenia are estimated to lose an average of 28.5 years of life compared to their healthy peers[3] and are significantly less likely to be employed (73-85% unemployed)[4,5]. These high rates of disability and impairments in social and occupational functioning are marked by persisting positive, negative, and affective symptoms, including suicidal ideation, and cognitive impairments[6,7]. While psychotropic medications can treat positive symptoms (such as delusions, hallucinations and thought disorganization), cognitive impairments associated with schizophrenia (CIAS) have only shown small, if any, improvement with these medications[8,9] and have largely remained refractory to pharmacologic treatment[10]. CIAS have also been shown to be detrimental to functional capacity[11-13]. Furthermore, they are more strongly predictive of functional outcome than any other measurable symptom, including psychotic symptoms[11,14,15]. CIAS are thus the primary cause of disability in schizophrenia[16].

CIAS are present in 70-75% of patients with schizophrenia[17-19] and include deficits in attention, working memory, episodic memory, processing speed and executive function[20-23]. The 'Measurement and Treatment Research to Improve Cognition in Schizophrenia' (MATRICS) initiative, a collaboration between experts in schizophrenia and cognitive trials, led to the creation of the MATRICS Consensus Cognitive Battery (MCCB), which measures performance with specific cognitive tests across the following

seven domains: speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition[24-27], which is marked with difficulties in identifying emotions, feeling connected to others, inferring people's thoughts, and reacting emotionally to other[28] . Dysfunction across these domains in patients with schizophrenia is typically "moderately severe" to "severe", with patients performing 1.5–2.5 standard deviations below neurotypical controls[29,30].

The most striking CIAS are in speed of processing and working memory. Two separate studies found these domains were most impaired in patients with schizophrenia and associated with worse functioning[30,31]. One of the aforementioned studies found that speed of processing and social cognition best distinguished patients with schizophrenia from neurotypical controls[29]. The other showed that in addition to speed of processing and working memory, attention/vigilance are distinctly worse in unemployed patients with schizophrenia than patients who are able to maintain vocation[30,31]. A recent meta-analysis[32] comparing 942 patients with schizophrenia to 899 healthy controls corroborated deficits in all of these domains, highlighting more severe impairments in patients with 'deficit schizophrenia', which is marked by primary, enduring negative symptoms [32,33].

Cognitive Remediation Therapy (CRT), consisting of cognitive exercises and training, remains the most effective treatment of CIAS, though it provides modest improvements in cognition[34,35]. The most recent meta-analyses studying changes in CIAS after CRT found effect sizes ranging between 0.18-0.28[34], with no improvement noted in visual memory, the smallest significant effect size in social cognition, and the largest

significant effect in working memory. Known impairments in neuroplasticity of schizophrenia[36] may limit the efficacy of CRT; however, there likely remain other factors that impair cognition and learning in schizophrenia. One set of relatively under-studied and potentially modifiable such targets for treating CIAS are co-occurring non-psychiatric illnesses that also impair cognition.

Obstructive Sleep Apnea: A Co-Morbidity with Common Cognitive Impairments

Several medical illnesses that compromise cognition are more prevalent in schizophrenia than in the general population, including ischemic heart disease, stroke, hypertension, obesity, diabetes, influenza/pneumonia, COPD and cancer[37,38]. These illnesses reduce life-expectancy and quality of life and may also amplify and hinder treatment of CIAS. Obstructive sleep apnea (OSA), a condition of sleep-disordered breathing due to obstruction of upper airways and subsequent hypoxemia, is another such co-occurring disorder that may be exacerbating the poor health outcomes, psychiatric symptoms, cognitive deficits, and disability in schizophrenia[39]. OSA has been associated with increased symptoms of depression and anxiety,[40-42] hypothesized to be driven by a multifactorial feedback pathways stemming from apneic episodes including sleep fragmentation, pro-inflammatory and oxidative pathways resulting in neurotransmitter imbalance, and sympathetic hyperactivity[43]. These same pathways may result in cognitive impairments also seen in OSA.

Like schizophrenia, OSA is associated with cognitive impairments in the domains of attention, verbal memory, executive function, psychomotor function, and visuospatial memory[44-47]. The most recent and thorough analysis of cognition in OSA was a meta-

review that considered seven studies (5 meta-analyses and 2 systematic reviews) with a total of 6461 adults with OSA and 4932 healthy controls[44]. Their findings suggested significant impairments in the following domains (with effect sizes reported in parentheses): attention (0.58), memory (0.53), executive function (0.69), psychomotor function (0.96) visuospatial/constructional function (0.69), and language function (0.38)[44]. In this meta-review, speed of processing was a sub-domain of attention, and executive functioning included assessments from the previously mentioned MCCB (cognitive battery commonly used in schizophrenia) that assessed for working memory, reasoning, and problem solving (i.e., Neuropsychological Assessment Battery (NAB) Mazes & letter-number sequencing tests). Compared to healthy controls, patients with schizophrenia had similar to more marked impairment across these domains: attention (0.68-1.19), verbal memory (1.19-1.43), executive function (1.0-1.23), verbal fluency (0.79-1.53), visual memory (0.78-1.17), processing speed (0.8-1.26), working memory (1.0-1.04), and social cognition (0.84-1.44)[32]. A recent observational study found that social cognition may also be impaired in patients with OSA, particularly those patients with more prominent hypoxemia[48]. The significant similarities in cognitive dysfunction are also associated with comparable neural changes in both diseases.

Neurobiological Changes Common to OSA And Schizophrenia

Patients with OSA and schizophrenia have common neurostructural and neurofunctional abnormalities which have been associated with cognitive impairments. In OSA, the neurobiological abnormalities and cognitive impairments are prominently reversible when treated with positive airway pressure (PAP) during sleep.

General gray matter volume (GMV) loss is common to both OSA and schizophrenia. In OSA, decreased GMV in the anterior cingulate cortex (ACC), hippocampus, frontal, parietal, and temporal lobes is associated with worse OSA severity [45]. Furthermore, reduced GMV in left hippocampus, left posterior parietal cortex, and right superior frontal gyrus correlated with impairment in short-and long-term verbal memory, constructional ability, attention, and executive function[45]. In schizophrenia, similar regional reduction in gray matter and cortical thickness has been noted, particularly in the hippocampus, frontal and temporal lobes; this has been negatively correlated with improved cognition after CRT [49].

Brain structure is further changed by similar differences in white matter tract integrity (WMI) in both OSA and schizophrenia. Diffuse reduction of WMI involving the bilateral parietal and frontal lobes has been noted in OSA, and has been associated with neurocognitive deficits involving attention, executive function, and memory [45]. WMI connecting prefrontal and temporal lobes has also been reduced in schizophrenia[49], although a recent large study (n=1963 patients with schizophrenia) showed similar microstructural abnormalities throughout most major white matter regions in the brain[50].

Functional connectivity is similarly changed in the aforementioned regions in both diseases. For example, the default mode network (DMN), a large-scale brain network primarily comprised of connections between the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC) and angular gyrus, has been shown to have reduced functional connectivity in both disorders[51-54]. Meta-analyses of resting state connectivity of several brain networks noted widespread hypoconnectivity across key hubs including the dorsolateral prefrontal cortex (DLPFC), ACC, cerebellum, MPFC,

superior temporal gyrus (STG), hippocampus, PCC, amygdala, frontal pole (FP), nucleus accumbens (NAcc), and postcentral gyrus (PCG) in schizophrenia [54]. These global reductions have been associated with worse processing speed, working memory, episodic memory, attention, and verbal learning[55]. While this has been less thoroughly studied in OSA, the existing evidence implicates common changes to these regions of interest and their association with cognitive impairment. Most notably, a meta-analysis considering functional changes of the brain in OSA similarly noted hypoactivation of the DLPFC compared to healthy controls[56]. Furthermore, studies in OSA have shown negative correlations between verbal memory and the connectivity of the PCC and hippocampus, executive function and activation in the ACC and middle and inferior frontal gyri (M/IFG), and overall cognition and functional connectivity in bilateral frontal poles, middle temporal gyri, and hippocampi[45,52,57-59].

Treating OSA and schizophrenia with continuous PAP (CPAP) and CRT, respectively, does result in improvements and even normalization of these structural and functional neural changes, though with varied effects. Cognitive impairments and mood disturbances from OSA are treatable with CPAP, particularly in attention and vigilance [60-63]. A recent meta-analysis corroborated past work showing an improvement in attention and speed of processing with an effect size of 0.17[64]. Others have also found improvements in memory and executive function and tied it to neuroplastic changes in the brain in as short as one month of treatment, specifically with hypertrophy and increase in GMV of the thalamus, hippocampus, and frontal structures [62,65-67]. With long-term use of CPAP, widespread changes in microstructural integrity of WM fiber tracts have been noted; specifically, previous abnormalities appear reversible[62,68,69]. These

changes appear far more robust than what has been studied in schizophrenia, especially with regards to structural change. Many studies have provided evidence of increased activation in the DLPFC, FP, ACC, PCG, M/IFG, and occipital regions during working memory or executive function tasks after CRT [70-75]. However, only two studies have shown alterations in resting state functional connectivity between the frontal and temporal lobes[70,76,77]. Furthermore, only two studies have reported CRT inducing structural changes, specifically with GMV increases in the hippocampus, and only one study has noted improved microstructural integrity in the genu and body of the corpus callosum[70,76,78,79]. CPAP is shown to have a more robust impact on structural normalization; this is important to note as studies have indicated that increased GMV, specifically in frontal structures, are associated with better cognitive functioning after CRT[49]. Thus, the use of CPAP may help enhance the outcomes of CRT in treating CIAS. The under-utilization of CPAP is further emphasized when we consider prevalence of OSA in patients with schizophrenia.

Co-occurring OSA in Schizophrenia Deserves Further Study

OSA in schizophrenia is not well-studied, and findings indicate it may be under-recognized and under-treated. Recent estimates of OSA prevalence in schizophrenia range from 14.9&-40%[80-82], though past studies have found prevalence is as wide as 0.7-57.1%[83-85]. This range extends above the estimated 9-38% prevalence of OSA seen in the general population[86]. The largest population-based study of association between OSA and patients with serious mental illness was done by extracting diagnoses from electronic medical records of the Veteran population; it found a prevalence of OSA of 2.9% in the

general population and 4.52% in patients with psychosis[87]. A meta-analysis of OSA in serious mental illness did not have sufficient data to compare prevalence of OSA in schizophrenia to the general population[88]. Thus, more work is needed to further elucidate prevalence of OSA in schizophrenia.

Studies have shown that patients with schizophrenia may be at higher risk of developing OSA, and that OSA may be underrecognized. A Taiwanese national cohort study (n=5092) found a nearly two-fold increased risk of developing OSA amongst people with schizophrenia compared to age-matched control participants even after controlling for gender, age, comorbidities and duration of antipsychotic use [89]. A cross-sectional cohort study found that 57% of their sample of patients with schizophrenia were at high-risk for OSA based on symptom-related screening, though less than a quarter of these patients had received a prior diagnosis[80]. The true rate of OSA in schizophrenia is likely under-estimated due to under-diagnosis and increased risk of OSA development.

Though the effects of treating OSA on CIAS are grossly under-studied, the theoretical considerations above and one small study suggest that cognition can improve with OSA treatment in patients with co-occurring OSA. One study of 6 patients with schizophrenia has shown that treatment of OSA with CPAP improves CIAS[90]. In this sample, OSA treatment with CPAP resulted in a 0.59 Z score improvement in global cognition, with the most notable improvements in working memory (0.71 Z score improvement on digit sequencing) and motor speed (0.66 Z score improvement on token motor task)[90]. Thus, untreated OSA may be limiting the full potential improvements of CIAS, though many questions remain as to how these two disorders synergistically affect cognitive functioning and cognitive recovery.

Our study aims to understand the role of OSA in contributing to cognitive deficits and functional impairments in schizophrenia. To do this, we analyzed a data-set of 3942 Veterans with schizophrenia collected through the Veterans Affairs Cooperative Studies Program (CSP)# 572[91]. This dataset includes clinical ratings, cognitive assessments, measures of community functioning, and thorough medical histories. In this study, we describe the prevalence of reported OSA in this sample and use a clinical prediction model developed by Ustun et al.,[92] to calculate the predicted prevalence of OSA in the cohort. Then we studied the associations of reported and predicted OSA with cognition and functioning based on performance on a subset of the MCCB and standardized assessments of community functioning. Exploratory analyses included analyzing performance and predicting characteristics of patients who have predicted-but-unreported (and thus untreated) OSA. This work aims to characterize the contribution of OSA, a treatable condition, to CIAS and disability in schizophrenia.

STATEMENT OF PURPOSE

The cognitive impairments in schizophrenia have been nearly refractory to treatment, though they are largely responsible for the functional disability of the illness. In this study, we examined a pre-existing dataset to explore whether a co-occurring and treatable medical condition, obstructive sleep apnea (OSA), may be contributing to these cognitive and functional impairments, suggesting a strategy to improve community functioning in schizophrenia. The goal of this thesis is to estimate: 1) the prevalence of obstructive sleep apnea (OSA) in schizophrenia, and 2) the effects of OSA on cognition and functioning in schizophrenia, specifically within the Veteran population. This is accomplished through the following aims and, when appropriate, hypotheses.

Specific Aims:

1. Prevalence of OSA in Schizophrenia:
    a. Describe the prevalence of self-reported OSA diagnosis in this sample of Veterans with schizophrenia.
    b. Characterize associations of reported OSA diagnosis with significant sociodemographic and clinical measures.
    c. Use a clinical prediction model of OSA to estimate the prevalence of OSA in Veterans with schizophrenia and compare this estimated prevalence to that determined by patient report.

       Hypothesis: OSA will be under-diagnosed in this sample i.e., the clinical prediction model will identify significantly more patients with predicted OSA than those who reported OSA diagnosis.

2. Association of OSA and Cognition in Schizophrenia:
    a. Compare global cognitive function in those with reported OSA (R-OSA) to those who did not report OSA (nR-OSA).

       Hypothesis: Patients with R-OSA will have poorer cognitive functioning than those with nR-OSA.
    b. Compare global cognitive function in those with predicted OSA (P-OSA) to those without predicted OSA (nP-OSA).

       Hypothesis: Patients with P-OSA will have poorer cognitive functioning than those with nP-OSA.
    c. Examine the association of OSA on specific cognitive domains in Veterans with schizophrenia.

       Hypothesis: Cognitive functioning will be poorer in patients with R-OSA and P-OSA in the following domains: speed of learning, verbal learning, and reasoning and problem-solving.

3. Association of OSA and Functional Capacity in Schizophrenia:
    a. Compare performance on functional measures in those with R-OSA to those with nR-OSA.

       Hypothesis: Patients with R-OSA will have poorer performance on functional measures than those with nR-OSA.
    b. Compare performance on functional measures in those with P-OSA to those with nP-OSA.

Hypothesis: Patients with P-OSA will have poorer performance on functional measures than those with nP-OSA.

Exploratory Aims:

1. Examine differences in cognition and functioning in patients with R-OSA and undiagnosed OSA (i.e., predicted-and-not-reported OSA or PnR-OSA).
2. Describe differences in sociodemographic and clinical characteristics of patients with PnR-OSA and R-OSA.
3. Estimate the effect of treated versus untreated OSA on cognition and functioning in the subsample of Veterans with schizophrenia that reported OSA.

METHODS

Student Contributions:

All data, including demographic and clinical characteristics and cognitive and functional measure performance, were previously collected as part of the Cooperative Studies Program (CSP) #572 study[91] and were provided to TS and SG de-identified. The study was conceived by TS. SG was responsible for further data processing by creating binary variables from the following ordinal or nominal variables: "marital status" to "married", "level of education" to "college education", "income" to "low-income" (i.e., <$20,000 annual income), "residential status" to "independent living", and "employment status" to "employed". SG converted raw performance on various normed neuropsychological assessments to age-and-gender-corrected T-scores with the MATRICS software. Data processing included creating the following new variables from this dataset: "BMI" based on height and weight[93], a binary "predicted-OSA" variable based on calculation from a clinical prediction model[92], "Completeness" based on each participants rate of completing the required components of questionnaires, and a "Composite Cognitive Score (CCS)" which was an average of T-scores from each cognitive assessment per participant. An additional variable marking those patients who were predicted to have OSA but did not report having OSA (PnR-OSA) was also created. All statistical analyses, described below, were designed and completed by SG with some feedback from a consulting statistician and TS. All initial manuscript and figure authorship was completed by SG with editing and feedback provided by TS.

Ethics Statement:

This study was supported by Yale School of Medicine Fellowship for Medical Student Research and Richard K. Gershon Endowed Medical Student Research Fellowship awarded to SG. There are no conflicts of interest to report. This study does not contain any studies involving animals performed nor does it involve direct work with human participants. Data was initially collected with human participants and as such all procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants involved in the study[91].

Human Subjects Research:

Veterans Affairs Connecticut Healthcare System Research & Development Committee and the Cooperative Studies Program (CSP) #572 Executive Committee approved use of this de-identified data. All research participants provided informed consent to both immediate and long-term goals of the CSP#572 repository at the time of data collection and provided written consent for use of de-identified data for future studies related to schizophrenia and bipolar disorder, such as the present study.

Methods Description: *Participants, Measures, & Procedures*

Data Processing and data analysis were performed on de-identified data that was initially collected from Veterans who participated in the CSP#572: *Genetics of Functional Disability in Schizophrenia and Bipolar Illness* study [91].

Participants:

Veterans with schizophrenia and bipolar disorder were recruited for the multicenter CSP#572 study between 2011-2014. Patients of VA medical centers were identified with medical record information or referred by their clinicians. Potential participants were then sent an invitational mailing from local site investigators to assess their interest in participating in a VA research study. Diagnosis of schizophrenia or bipolar disorder was confirmed with the Structured Clinical Interview for DSM-IV (SCID)[94]. Participants completed questionnaires to provide demographic information and medical history, including the presence of other medical or psychiatric diagnoses. Neuropsychological testing and assessments of functional capacity were administered in person. The data from the 3942 Veterans with confirmed schizophrenia were included in these analyses.

Measures & Procedures:

Demographic Data: The following variables were included in our analyses: age, gender (male or female), race (White, Black, American Indian, Other), marital status (married or non-married), education level (no college or any college), low-income (<$20,000 or not), employment status (employed or unemployed), and residential status (independently living or not, e.g., unsupervised residential facility or supervised residential facility)

Clinical Characteristics: The following variables were included in our analyses: body-mass index (BMI), self-reported medical history (including diseases related to circulatory system, mental health, musculoskeletal health, hearing/vision problems, infectious disease, cancer, gastrointestinal disorders, renal issues, nervous system problems, endocrine disorders, pulmonary disorders, substance use including tobacco and alcohol, and other conditions, like OSA), self-reported number of prescription medications, and hospitalizations. Specific conditions per organ system were listed and Veterans were

asked to fill in a circle if they had the condition, write out the year in which they were diagnosed, and fill in a circle if they took any medications for the condition. The conditions were presented under subheadings as such: Circulatory Problems ("High Blood Pressure (Hypertension)," "Stroke," "Transient Ischemic Attack (TIA)," "Heart Attack," "Coronary Artery Disease/Coronary Heart Disease (includes angina)," "Peripheral Vascular Disease," "High Cholesterol," "Pulmonary Embolism or Deep Vein Thrombosis (DVT)," "Congestive Heart Failure," "Other Circulatory Problem"), Mental Health Disorders ("Anxiety reaction/Panic disorder," "Attention deficit hyperactivity disorder (ADHD)," "Bipolar disorder," "Post-traumatic stress disorder (PTSD)," "Depression," "Eating disorder," "Personality disorder," "Schizophrenia," "Social Phobia," "Other mental health disorder"), Skeletal/Muscular Problems ("Osteoarthritis," "Rheumatoid arthritis," "Other arthritis," "Gout," "Osteoporosis," "Other skeletal/muscular problem"), Hearing/Vision ("Cataracts," "Glaucoma," "Macular degeneration," "Blindness, all causes," "Tinnitus or ringing in the ears," "Severe hearing loss or partial deafness in one or both ears"), Infectious Diseases ("Tuberculosis," "Hepatitis C," "HIV/AIDS," "Other infectious disease"), Cancer ("Breast cancer," "Colon cancer/rectal cancer," "Lung cancer," "Prostate cancer," "Skin cancer," "Other cancer"), Kidney Disease ("Kidney disease without dialysis," "Kidney disease with dialysis," "Acute kidney disease with no dialysis"), Digestive System Problems ("Acid reflux/GERD," "Peptic ulcers," "Bowel obstruction," "Colon polyps," "Irritable Bowel Syndrome (IBS)," "Ulcerative colitis," "Crohn's disease," "Celiac disease/ sprue," "Other digestive system disorder") Nervous System Problems ("Migraine headaches," "other headaches," "Memory loss or impairment," "Dementia (includes Alzheimer's,

vascular, etc.)," "Concussion or other loss of consciousness," "Traumatic brain injury," "Spinal cord injury or impairment," "Epilepsy/seizures," "Parkinson's disease," "Amyotrophic lateral sclerosis (Lou Gehrig's disease)," "Multiple sclerosis," "Other nervous system problem"), and Other Conditions ("Asthma," "Chronic lung disease (COPD, Emphysema or Bronchitis)," "Diabetes/ 'sugar'," "Enlarged prostate (Benign prostatic hyperplasia)," "Liver condition (e.g., cirrhosis)," "Skin condition (e.g., eczema, psoriasis)," "Sleep apnea," "Thyroid problems," "Other disease/disorder"). Number of prescriptions and number of hospitalizations were ordinal variables represented by the following ranges: 0, 1-3, 4-6, 7-9, 10-15, 15 or more.

Neuropsychological (NP) assessment: The following assessments, which are well-normed, validated and included in the MATRICS Consensus Cognitive Battery[25], were used as measures of cognitive functioning in the following domains: speed of processing (Trail-making part A, the Brief Assessment of Cognition in Schizophrenia, BACS, Symbol Coding subtest, Category Fluency-animal naming), verbal learning (the Hopkins Verbal Learning Test, HVLT), working memory (Weschler Adult Intelligence Scale -III WAIS-III Letter-Number Sequencing,) and reasoning and problem-solving (Neuropsychological Assessment Battery, NAB, mazes test). Trail-making part A[95] is a timed paper-and-pencil test in which the respondent draws a line to connect consecutively numbered circles placed irregularly on a sheet of paper. BACS symbol coding[96] is a timed paper-and-pencil test in which the respondent uses a key to write digits that correspond to nonsense symbols. The category fluency[97] task is an oral test in which the respondent names as many animals as she/he can in 1 minute. The HVLT[98] is an orally administered assessment of verbal memory in which a list of 12 words from three

taxonomic categories is presented and the respondent is asked to recall as many as possible after each of three learning trials. The WAIS-III Letter-Number Sequencing assessment[99] is an orally administered test in which the respondent mentally reorders strings of number and letters and repeats them to the administrator. The NAB mazes test[100] includes seven timed paper-and-pencil mazes of increasing difficulty that measure foresight and planning. Raw scores for each assessment were age-and-gender corrected to T-scores, ranging from 0 to 100. A composite cognitive score (CCS) was calculated by averaging the age-and-gender corrected t-scores of each neuropsychological assessment for each participant.

Functional capacity: Two tests were administered to assess functional capacity: University of California San Diego (UCSD) Performance Skills Assessment -Brief (UPSA-B) and the Everyday Functioning Battery- Advanced Finances (EFB-AF). The UPSA-B[101] asks patients to perform everyday tasks related to communication and finances. During the Communication subtest, participants role-play exercises using an unplugged telephone (e.g., emergency call; dialing a number from memory; calling to reschedule a doctor's appointment). For the Finance subtest, participants count change, read a utility bill, and write a check for the bill. Raw scores were reported on a scale of 0 to 20. The EFB-AF[102] requires individuals to prepare bank deposits, write checks to pay bills, maintain a checkbook balance, and organize payments such that a pre-specified amount of money is left available at the end of the task. Raw scores were reported on a scale of 0 to 13. Both these tests have high correlation to cognitive performance and everyday functional disability in schizophrenia [103,104].

Negative symptoms: Avolition (reduced motivation and activity), alogia (reduced verbal output), and affective flattening were assessed by trained research staff at the time of the diagnostic assessment with the use of SCID items, rated based on present/absent criteria.

Posttraumatic stress disorder (PTSD): The PTSD module from the MINI International Diagnostic interview[105] was used as the assessment instrument, examining the presence of current (i.e., last 6 months) of PTSD.

Major depression: SCID was used to examine the lifetime history of a major depressive episode.

Assessment of suicidality: The Columbia Suicide Severity Rating Scale[106] was administered to assess suicidal ideation, suicide attempts, and severity of suicidality.

Clinical Prediction Model: We used a model published by Ustun et al., 2016[92] that was generated using Supersparse Linear Integer Models (SLIM) machine learning method for creating a medical scoring system. This scoring system relied on ten extractable features based on age, BMI, gender, smoking status, and history of hypertension and diabetes Those who scored greater than 29 points were predicted to have OSA with a false positive rate of approximately 20%. Age comprised two greater than or equal to 30 scored 16 points and greater than or equal to 60 scored an additional 16 points. BMI greater than or equal to 25 scored 12 points, greater than or equal to 30 scored 2 additional points, greater than or equal to 35 an addition 10 points, and greater than or equal to 40 an additional 4 points. History of diabetes scored 6 points, history of hypertension scored 4 points, current smoking status scored 2 points. Female gender scored a reduction of 14 points.

The True Positive Rate (TPR) or sensitivity for this model was 64.2% (58.6-69.1% range) and False Positive Rate (FPR) was 23.0% (15-30.6% range).

Statistical Methods:

Specific Aim #1: Descriptive statistics were used to determine the prevalence of self-reported OSA (R-OSA) in the CSP#572 dataset of Veterans with schizophrenia, in addition to exploring the demographic and clinical characteristics of Veterans with both diseases. To further describe R-OSA in this population, multiple Chi-Square tests and Phi correlations with Bonferroni's correction were performed to assess the association of OSA with the following variables: age, gender, race, marital status, education level, income, body-mass index (BMI), medical and psychiatric comorbidities, independent living/residential status, polypharmacy, and hospitalization frequency. Use of the clinical prediction model identified Veterans predicted to have OSA and descriptive statistics were used to estimate prevalence. A Mcnemar's test was used to compare proportion of predicted OSA (P-OSA) and R-OSA. All comparisons between R-OSA and not-reported OSA (nR-OSA) were corrected for multiple comparisons (n=100) with Bonferroni's correction and evaluated with a $p<0.0005$ accordingly; this includes the aforementioned Phi correlation, chi-square tests, and subsequent T-tests.

Specific Aim #2: Composite Cognitive Scores (CCS) were examined for normal distribution by visualization and the Shapiro-Wilk test. Two-sided T-tests compared mean CCS in participants with reported and not-reported OSA (R-OSAv. nR-OSA) and predicted and not-predicted OSA (P-OSA v. nP-OSA), followed by calculation of effect sizes (Cohen's d). All comparisons between P-OSA and nP-OSA were corrected for

multiple comparisons (n=10) with Bonferroni's correction and evaluated at a $p<0.005$. Then, to determine the unique association between reported OSA and cognition, a univariate linear regression predicting CCS with the study variable of OSA (e.g., R-OSA) and multivariate models with additional independent variables were performed. These additional variates included pre-identified variables associated with cognitive performance and OSA, including age, gender, education, income, race, number of prescriptions and hospitalizations, cardiovascular, neurological, and psychiatric comorbidities. 'Completeness', a measure of completeness of required sections for each participant's questionnaire, was also included to serve as an adjustment for limitations with self-report and possible confounder in measures of cognition and functioning. Additionally, variables that had a statistically significant Phi Coefficients > 0.1 with R-OSA from specific aim #1 were included as independent variables. The same series of analyses, including two-sided T-tests and linear regressions, were performed to study the associations of P-OSA with cognition. Finally, two-sided T-tests were used to compare mean scores of each neuropsychological test between R-OSA v. nR-OSA and P-OSA v. nP-OSA, with subsequent calculation of effect sizes (Cohen's d).

Specific Aim #3: UPSA-B and EFB-AF scores were both be examined for normality in the same manner as above. Two-sided Mann-Whitney U tests were used to compare means between the groups R-OSA v. nR-OSA as well as P-OSA v. nP-OSA. Univariate and multivariate linear regressions predicting performance on each functional capacity measure (i.e., UPSA-B and EFB-AF) were performed with the aforementioned independent variables from specific aim #2 to estimate the unique association between OSA (i.e., R-OSA and P-OSA) and functional capacity.

Exploratory Aims: ANOVA was used to compare means of CCS, UPSA-B, and EBF-AF across three groups: R-OSA, those with predicted and unreported OSA (PnR-OSA), and those without predicted or reported OSA (No-OSA), at $p<0.016$; Tukey HSD post-hoc tests were used to compare mean differences between these three groups (R-OSA v. PnR-OSA v. No-OSA), with a $p<0.0028$. Binary Logistic Regression was used to model PnR-OSA and R-OSA with sociodemographic and diagnostically verified clinical characteristics as the independent variables; statistically significant predictors of PnR-OSA and R-OSA were reported as adjusted Odds-Ratio (aOR). Finally, CCS and functional assessments scores of the subsample of Veterans with R-OSA were compared with two-sided T-tests ($p <0.016$) with reported treatment as the independent variable.

RESULTS:

Specific Aim # 1: Prevalence of OSA in Schizophrenia

A total of 566 patients (14.4%) from our sample of 3942 Veterans with schizophrenia reported OSA (R-OSA). Table 1a describes sociodemographic data for this sample compared to Veterans who did not report OSA (nR-OSA). R-OSA patients were more likely to have gone to college, be married, and live independently.

Table 1a: Sociodemographic Characteristics of Participants with Reported OSA

	Reported OSA (R-OSA)	**Did Not Report OSA (nR-OSA)**	**p-values (only <0.05)**
Male (%)	527 (93.3%)	3117 (92.6%)	
Mean age (SD)	56 (8.45)	54.95 (10.33)	0.009
Race-White (%)	230 (40.6%)	1323 (39.2%)	
Race-Black/African-American (%)	296 (52.3%)	1862 (55.2%)	
American-Indian (%)	32 (5.7%)	139 (4.1%)	
Race-Other	40 (7.1%)	160 (4.7%)	0.02
No College	187 (33.2%)	1522 (45.3%)	9.6105E-8*
Married	146 (25.9%)	546 (16.3%)	2.8067E-8*
Employed	51 (9.0%)	321 (9.5%)	
Living Independently	408 (72.1%)	2116 (63.0%)	0.000028*
Low Income	224 (39.8%)	1542 (46.2%)	0.004

* denotes p<0.0005, adjusting for multiple comparisons; SD-Standard Deviation

Table 1b describes clinical information gathered from a diagnostic interview in R-OSA and nR-OSA patients. Veterans with R-OSA were more likely to have PTSD, a history of MDD, and a history of suicidal ideation and suicide attempt.

Table 1b: Diagnostic Characteristics of R-OSA and nR-OSA

	R-OSA	**nR-OSA**	**p-values (only <0.05)**
PTSD-MINI (%)	187(33.1%)	682 (20.2%)	9.1333E-12*
MDD-SCID (%)	308 (54.6%)	1318 (39.2%)	5.7704E-12*
Avolition-SCID (%)	251 (44.6%)	1479 (43.9%)	
Alogia- SCID (%)	167 (29.6%)	1203 (35.7%)	0.005
Flat Affect- SCID (%)	256 (45.4%)	1600 (47.5%)	
Suicidal Ideation- CSS (%)	419 (74%)	2079 (61.7%)	1.865E-8*
Past Suicide Attempt (%)	261 (46.6%)	1296 (38.7%)	0.000410*

* denotes p<0.0005, adjusting for multiple comparisons
Abbreviations: R-OSA – Reported OSA; nR-OSA- did not report OSA; PTSD- Post Traumatic Stress Disorder; MINI- Mini International Neuropsychiatric Interview; MDD- Major Depressive Disorder; SCID- Structured Clinical Interview for DSM-IV;

Table 1c describes those variables that are a part of the clinical prediction model developed by Ustun et al (2016)[92] in R-OSA and nR-OSA. Veterans with R-OSA were more likely to have higher BMI, hypertension, diabetes, and be non-smokers.

Table 1c: Medical Characteristics of R-OSA

	R-OSA	nR-OSA	p-values (only <0.05)
Age (SD)	56.00 (8.45)	54.95 (10.33)	0.009
BMI (SD)	33.11 (7.21)	28.63 (5.74)	6.1452E-39*
Male (%)	527 (93.3%)	3117 (92.6%)	
Hypertension (%)	412 (72.8%)	1732 (51.3%)	6.0046E-22*
Diabetes (%)	237 (41.9%)	770 (22.8%)	4.2422E-20*
Smoker (%)	273 (48.9%)	1971 (58.7%)	0.000017*

* denotes p<0.0005, adjusting for multiple comparisons
Abbreviations: R-OSA – Reported OSA; nR-OSA- did not report OSA, SD-Standard Deviation

Strong correlations (Phi's Coefficient >0.15) were found between R-OSA and number of prescription medications (Phi's Coefficient = 0.207), depression (0.166), GERD (0.163), anxiety and panic disorders (0.162), memory loss (0.158), type 2 diabetes (0.153), hypertension (0.151), p<0.0005. Moderate correlations were found between R-OSA and tinnitus (0.141), migraines (0.125), COPD (0.125), benign prostatic hyperplasia (0.124), PTSD (0.123), high cholesterol (0.121), osteoarthritis (0.118), hearing loss (0.115), rheumatoid arthritis (0.113), other arthritises (0.108), and gout (0.107), p<0.0005. Weak correlations (Phi's Coefficient >0.05, *p*<0.0005) were found between R-OSA and personality disorder (0.097), bowel obstruction (0.097), irritable bowel syndrome (0.097), TBI (0.097), coronary artery disease (0.096), loss of consciousness(0.094), asthma(0.092), heart attack (0.090), bipolar disorder (0.082),

eating disorder(0.082), polyps (0.080), spinal cord injury or impairment (0.075), peripheral vascular disease (0.074), gastrointestinal ulcers(0.074), current smoker (-0.069), social anxiety disorder (0.065), cataracts (0.065), acute renal failure (0.063), macular degeneration(0.063), kidney disease not requiring dialysis(0.062), stroke (0.062), frequency of hospitalizations(0.062), and pulmonary embolism/deep venous thrombosis (DVT) (0.061).

Using the clinical prediction model developed by Ustun et al.[92], we identified Veterans predicted to have OSA versus those unlikely to have OSA. 138 Veterans, including 27 Veterans with R-OSA, were excluded from this and future analyses involving predicted v. unpredicted OSA due to missing data-points needed for this prediction. The estimated prevalence of OSA in this sample was 71.9% (n=2834). A Mcnemar's test to compare proportions of P-OSA and R-OSA found a statistically significant difference (Z=46.51, p=0.0E0) in these rates, such that 60.3% of the sample had predicted and not reported OSA, 95% confidence interval (CI) [58.7%, 62.0%]. Figure 1 demonstrates the number of Veterans with P-OSA v. nP-OSA split by whether they reported or did not report OSA. This highlights that 83.5% of patients with P-OSA did not in fact report having the condition. However, 87% of patients with R-OSA also had P-OSA.

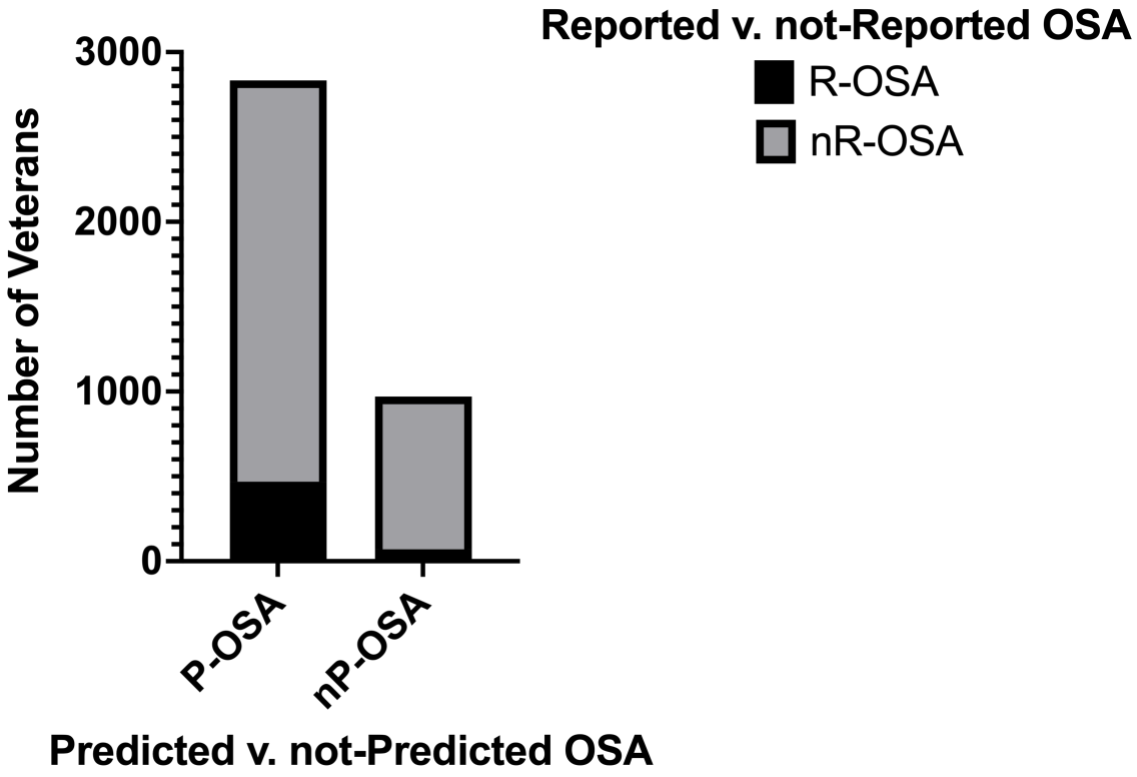

Figure 1: Predicted v. Reported OSA Contingency Graph
There were 469 Veterans with R-OSA and P-OSA from a total of 2,834 Veterans with P-OSA. Only 70 Veterans with R-OSA also had nP-OSA with a total of 970 Veterans with nP-OSA.

Specific Aim #2: *Association of OSA and Cognition in Schizophrenia*

We next sought to determine whether cognitive performance differed in R-OSA versus nR-OSA and P-OSA versus nP-OSA. The mean age- and gender- adjusted global composite cognitive scores (CCS) were significantly higher in R-OSA (mean = 37.61; standard deviation SD = 7.21) than in nR-OSA (mean = 36.27, SD = 7.77; p= 0.000159). The difference between R-OSA and nR-OSA GCC means was 1.33 T-Scores, 95% CI [0.64, 2.03]). The *Cohen's d* effect size was 0.174, 95% CI [0.084, 0. 264]. Figure 2 shows the distribution of CCS in R-OSA and nR-OSA.

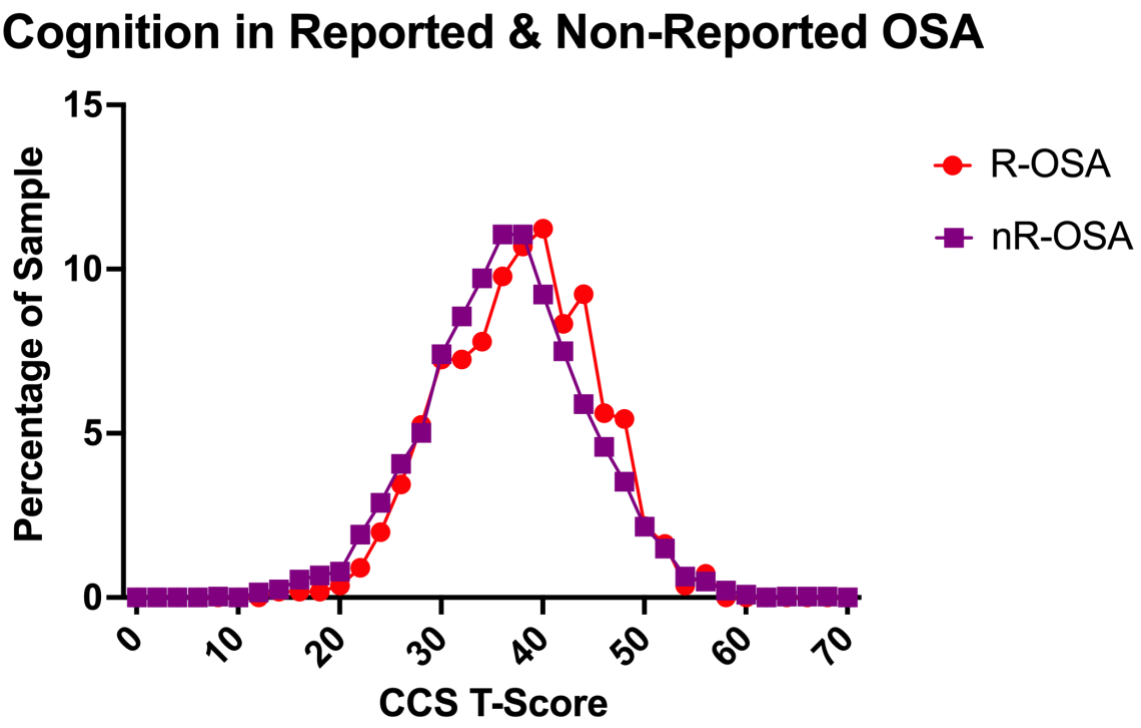

Figure 2: Distribution of Composite Cognitive Score in Reported & Non-Reported OSA
In R-OSA, the median was 36.33 with an interquartile range of 10.17. The minimum score was 8.67 and the maximum was 67.33. In nR-OSA, the median was 37.83 with an interquartile range of 10.46. The minimum score was 13.00 and the maximum was 56.50.

While cognitive performance was better in R-OSA than in nR-OSA, CCS in P-OSA was lower than in nP-OSA (p= 0. 000010; *Cohen's d* = -0.171, 95% CI [-0.244, -0.098]). The mean and standard deviation of CCS for P-OSA and nP-OSA were 36.15 (7.74) and 37.46 (8.04), respectively. The mean difference between P-OSA and nP-OSA CCS was -1.31, 95% CI [-1.89, -0.73]. Figures 3 depicts the distribution of CCS for P-OSA and nP-OSA Veterans.

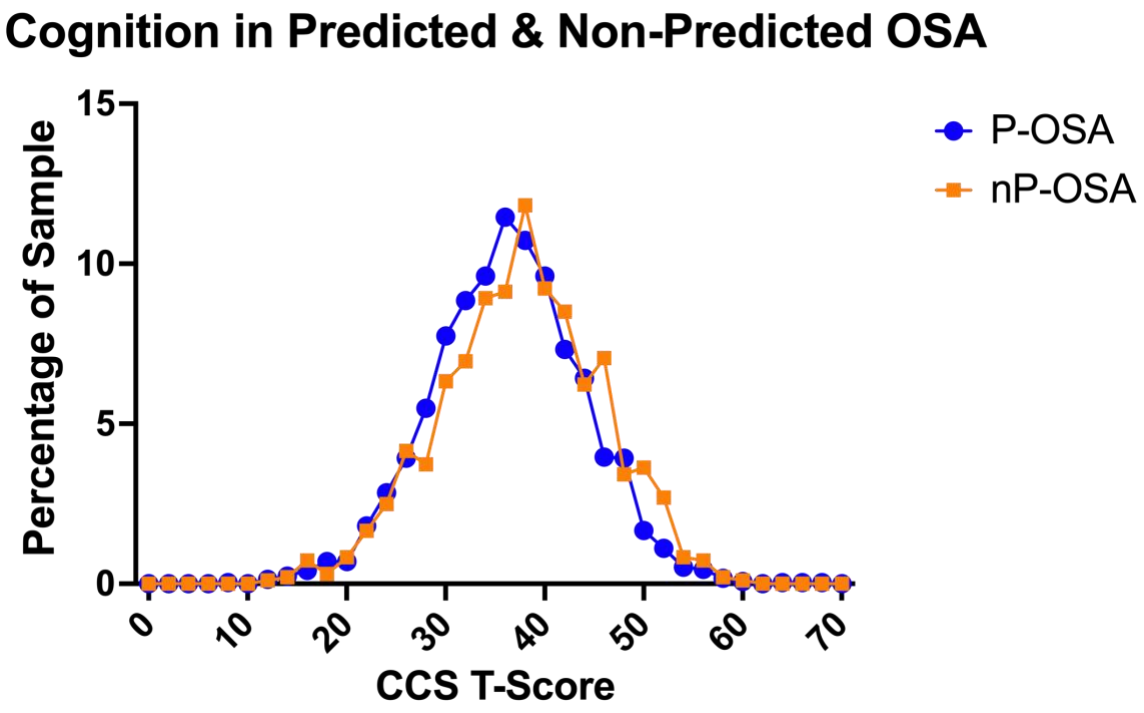

Figure 3: Distribution of Composite Cognitive Score in Predicted & Non-Predicted OSA
In P-OSA, the median was 36.17 with an interquartile range of 10.00. The minimum score was 8.67 and the maximum was 65.00. In nP-OSA, the median was 37.67 with an interquartile range of 10.67. The minimum score was 12.17 and the maximum was 59.33.

Linear regression analyses were then performed to study the relationship between OSA and CCS. R-OSA had a standardized coefficient (or Beta) of 0.061 (p= 0.000159) in association with CCS in univariate analyses, while P-OSA had a standardized coefficient (or Beta) of -0.074 (p=0.000005) in association with CCS. R-OSA maintained a significant association with CCS (B= 0.037, p=0.02) even after controlling for sociodemographic and medical variables; P-OSA did not maintain a statistically significant relationship in multivariate analyses. Table 3 reports multivariate linear regressions predicting CCS with R-OSA and P-OSA as the study variables in addition to statistically significant covariates.

Table 3: Linear Regression of CCS with Reported & Predicted OSA as Study Variable

	Beta in Univariate Model with R-OSA	*Beta in Multivariate Model With R-OSA*	*Beta in Univariate Model with P-OSA*	*Beta in Multivariate Model with P-OSA*
R-OSA	0.061**	0.036		
P-OSA			-0.074**	----
Age		-0.144**		-0.150**
BMI		0.034		----
Completeness		0.036		0.036
Female		0.041		0.044
White		0.045		0.044
College		0.188**		0.189**
Living Independently		0.140**		0.141**
Employed		0.063**		0.064**
Suicidal Ideation		0.070**		0.071**
Alogia		-0.094**		-0.094**
Flat Affect		-0.060**		-0.061**
Number of Hospitalizations		-0.030		---
Number of Prescriptions		-0.141**		-0.140**
Hypertension		-0.033		-0.035
Rheumatoid Arthritis		-0.032		-0.031
Memory Loss		-0.060**		-0.059**
Benign Prostatic Hyperplasia		0.043		0.045
Depression		---		0.033
Bipolar Disorder		0.052**		0.052**
Personality Disorder		0.043		0.043
Social Phobia		0.032		0.032
Stroke		-0.034		-0.034
Skin Cancer		0.043		0.042
Loss of Consciousness		0.050		0.051
Epilepsy		-0.033		-0.033
Drinks Alcohol		0.032		0.033

Italicized variables are medical variables based on self-report by patient.
Only statically significant variables are listed above*;* other variables included in multivariate model include: Married, MINI-PTSD, SCID-MDD, Suicide Attempts, Avolition, Current Smoker, Dementia, TBI, High Cholesterol, TIA, Osteoarthritis, Other arthritises, Gout, Anxiety, self-reported PTSD, Eating Disorder, ADHD, GERD, Tinnitus, Hearing Loss, Blindness, Glaucoma, Macular Degeneration, COPD, Diabetes, Colon Cancer, Lung Cancer, Breast Cancer, Prostate Cancer, Other Cancers, Parkinson's Disease, Non-Migraine Headaches, Migraines, Amyotrophic Lateral Sclerosis, Multiple Sclerosis,HIV.
** denotes a p-value <0.001

In considering specific neuropsychological tests, Table 4 compares the mean T-scores and standard deviations between R-OSA and nR-OSA for each assessment.

Table 4: Specific Neuropsychological Test Performance in R-OSA v. nR-OSA

	R-OSA	**nR-OSA**	**p-value (only <0.05)**
TMT-A (SD)	36.27 (12.46)	35.20 (13.11)	---
BACS SC (SD)	35.69 (11.29)	33.76 (11.74)	0.000345*
Category Fluency (SD)	41.51 (9.77)	39.89 (10.14)	0.000470*
HVLT (SD)	35.10 (7.08)	34.39 (7.49)	0.037
LNS (SD)	35.28 (11.91)	33.36 (12.63)	0.000511
NAB Mazes (SD)	42.19 (7.98)	41.53 (8.26)	----

* denotes p<0.0005, adjusting for multiple comparisons
Abbreviations: R-OSA – Reported OSA; nR-OSA – did not report OSA; TMT-A – Trail-making test part A; BACS SC- Brief Assessment of Cognition in Schizophrenia Symbol Coding Subtest; HVLT- Hopkins Verbal Learning Test; LNS- Letter-Number Sequencing; NAB – Neuropsychological Assessment Battery;

The mean difference between R-OSA & nR-OSA BACS SC T-score was 1.92 (95% CI [0.87, 2.98]), with T-scores in R-OSA being statistically significantly higher than in nR-OSA (p=0.000345); *Cohen's d* was 0.165, 95% CI [0.074, 0.255]. The mean difference between R-OSA & nR-OSA Category Fluency T score was 1.62 (95% CI [0.71, 2.53]), with T-scores in R-OSA being statistically significantly higher than in nR-OSA (p=0. 000470); *Cohen's d* was 0.161, 95% CI [0.071, 0.251]. Figure 4 illustrates average T-

scores for each test, denoting statistically significant differences between the groups (p <0.0005).

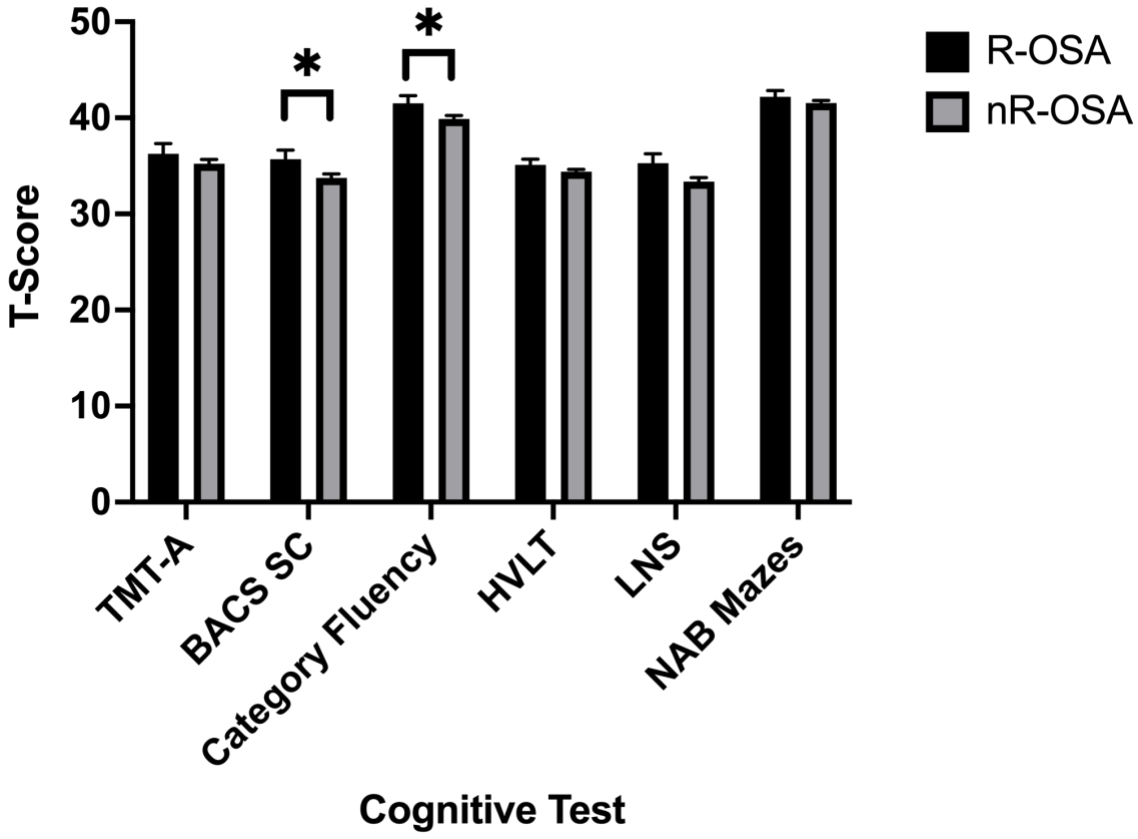

Figure 4: Performance on Neuropsychological Tests in Reported v. Non-Reported OSA
Bars represent 95% CI; * denotes those with p-value <0.0005, based on Bonferroni's correction.
Abbreviations: R-OSA – Reported OSA; nR-OSA – did not report OSA; TMT-A – Trail-making test part A; BACS SC- Brief Assessment of Cognition in Schizophrenia Symbol Coding Subtest; HVLT- Hopkins Verbal Learning Test; LNS- Letter-Number Sequencing; NAB – Neuropsychological Assessment Battery

In considering specific neuropsychological tests, Table 5 compares the mean T-scores and standard deviations between P-OSAv. nP-OSA for each assessment.

Table 5: Specific Neuropsychological Test Performance in R-OSA v. nP-OSA

	P-OSA	**nP-OSA**	**p-value (only <0.05)**
TMT-A (SD)	34.76 (12.94)	37.13 (13.23)	0. 000001*
BACS SC (SD)	33.70 (11.46)	35.07 (12.24)	0.002*
Category Fluency (SD)	39.97 (10.05)	40.71 (10.29)	0.049
HVLT (SD)	34.23 (7.24)	35.32 (7.89)	0.000173*
LNS (SD)	33.07 (12.43)	35.27 (12.74)	0.000002*
NAB Mazes (SD)	41.52 (7.86)	42.00 (9.25)	

* denotes p<0.005, adjusting for multiple comparisons
Abbreviations: P-OSA – Predicted OSA; nP-OSA – did not predict OSA; TMT-A – Trail-making test part A; BACS SC- Brief Assessment of Cognition in Schizophrenia Symbol Coding Subtest; HVLT- Hopkins Verbal Learning Test; LNS- Letter-Number Sequencing; NAB – Neuropsychological Assessment Battery;

The mean difference between P-OSA & nP-OSA TMT-A T score was -2.37 (95% CI [-3.33, -1.41], with T score in P-OSA being statistically significantly lower than in nP-OSA (*p*= 0. 000001); *Cohen's d* was -0.182 (95% CI [-0.256, -0.108]). The mean difference between P-OSA & nP-OSA BACS SC T score was -1.37, 95% CI [-2.25, -0.49], with T score in P-OSA being statistically significantly lower than in nP-OSA (*p*=0.002); *Cohen's d* was -0.117 (95% CI [-0.191, -0.044]). The mean difference P-OSA & nP-OSA HVLT T score was -1.08, 95% CI [-1.65, -0.52], with T score in P-OSA being statistically significantly lower than in nP-OSA (p= 0.000173); *Cohen's d* was -0.146 (95% CI [-0.219, -0.073]). The mean difference P-OSA & nP-OSA LNS T score was -2.20, 95% CI [-3.12, -1.29], with T score in P-OSA being statistically significantly lower than in nP-OSA (*p*= 0.000002); *Cohen's d* was -0.176 (95% [-0.249, -0.103]). Figure 5

illustrates average T-scores for each test, denoting statistically significant differences between the groups (p<0.005).

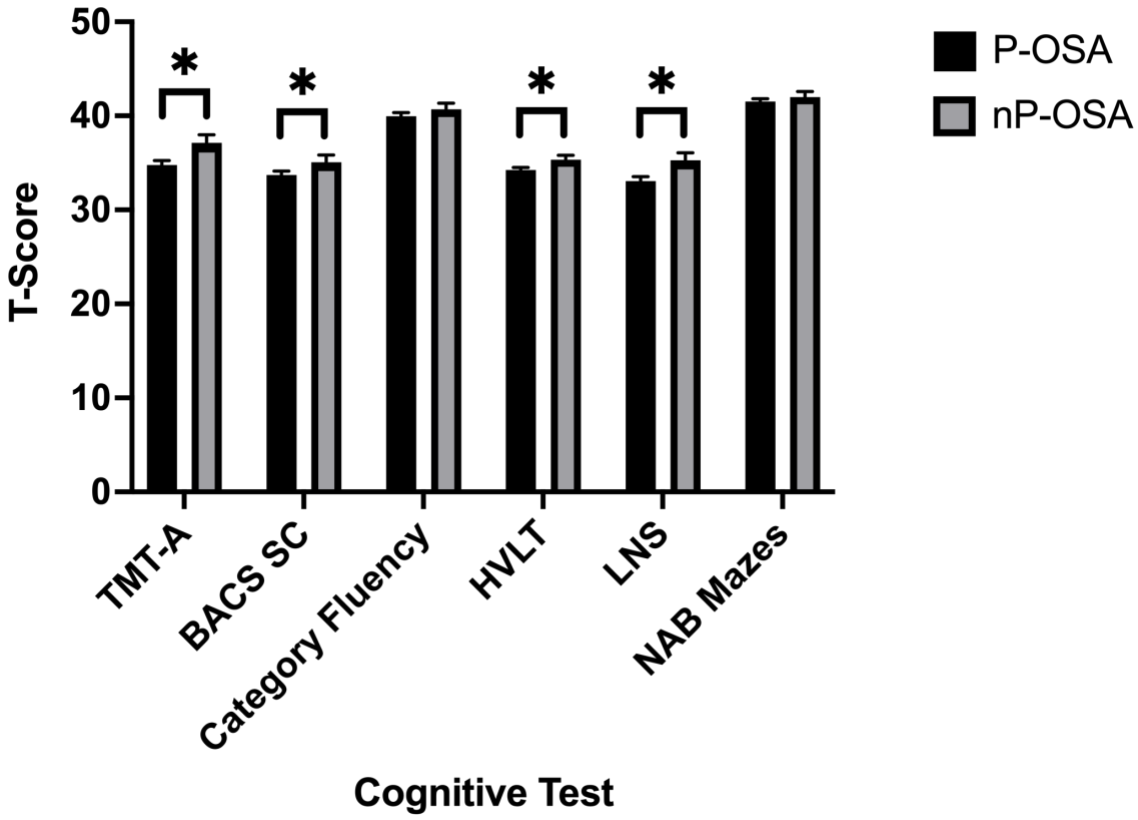

Figure 5: Performance on Neuropsychological Tests in Predicted v. Non-Predicted OSA
Bars represent 95% CI; * denotes those with p-value <0.005, based on Bonferroni's correction.
Abbreviations: P-OSA – Predicted OSA; nP-OSA – did not predict OSA; TMT-A – Trail-making test part A; BACS SC- Brief Assessment of Cognition in Schizophrenia Symbol Coding Subtest; HVLT- Hopkins Verbal Learning Test; LNS- Letter-Number Sequencing; NAB – Neuropsychological Assessment Battery

Specific Aim #3: Association of OSA and Functioning in Schizophrenia

After examining measures of cognition, we sought to study functional capacity measures, specifically the UPSA-B & EFB-AF, as they related to reported and predicted OSA. Table 6 describes performance of both measures in R-OSA v. nR-OSA and P-OSA v. nP-OSA.

Table 6: Functional Capacity Assessments in Reported and Predicted OSA

	R-OSA	**nR-OSA**	**p-value**
UPSA-B (SD)	15.32 (2.95)	14.81 (3.17)	0.000056 **
EFB-AF (SD)	8.71 (3.7)	8.00 (4.01)	0. 000037**

	P-OSA	**nP-OSA**	**p-value**
UPSA-B (SD)	14.88(3.12)	14.96 (3.10)	0.499
EFB-AF (SD)	8.02(3.99)	8.46(3.89)	0.003*

*denotes p-value < 0.005, based on Bonferroni's correction for multiple comparisons in P-OSA. **denotes p-value < 0.0005, based on Bonferroni's correction for multiple comparisons in R-OSA.
Abbreviations:R-OSA—Reported OSA; nR-OSA- not reported OSA; P-OSA – Predicted OSA; np-OSA – model did not predict OSA; UPSA-B: UCSD Performance Skills Assessment Battery- Brief ; EFB-AF – Everyday Functioning Battery- Advanced Finances.

UPSA-B in R-OSA was statistically significantly higher than in nR-OSA (p= 0.000056). The mean difference UPSA-B score in R-OSA and nR-OSA was 0.55, 95% CI [0.27, 0.82], *Cohen's d* = 0.173 95% CI = [0.084, 0. 262]. There was no statistically significant difference in UPSA-B between P-OSA and nP-OSA (p= 0.499). EFB-AF in R-OSA was statistically significantly higher than in nR-OSA (p= 0. 000037). The mean difference in EFB-AF between R-OSA and nR-OSA was 0.71, 95% CI [0.36, 1.07], *Cohen's d* =0.179, 95% CI [0.090, 0.269]. EFB-AF in P-OSA was statistically significantly lower than in nP-OSA (p= 0.003). The mean difference in EFB-AF between P-OSA and nP-OSA EFB-AF was -0.45, 95% CI [-0.74, -0.16], *Cohen's d* = -0.112, 95% CI [-0.186, -0.038].

Figures 6 demonstrates the frequency distribution of UPSA-B in R-OSA v. nR-OSA and P-OSA v. nP-OSA. Figures 7 demonstrate the frequency distribution of EFB-AF for R-OSA v. nR-OSA and P-OSA v. nP-OSA.

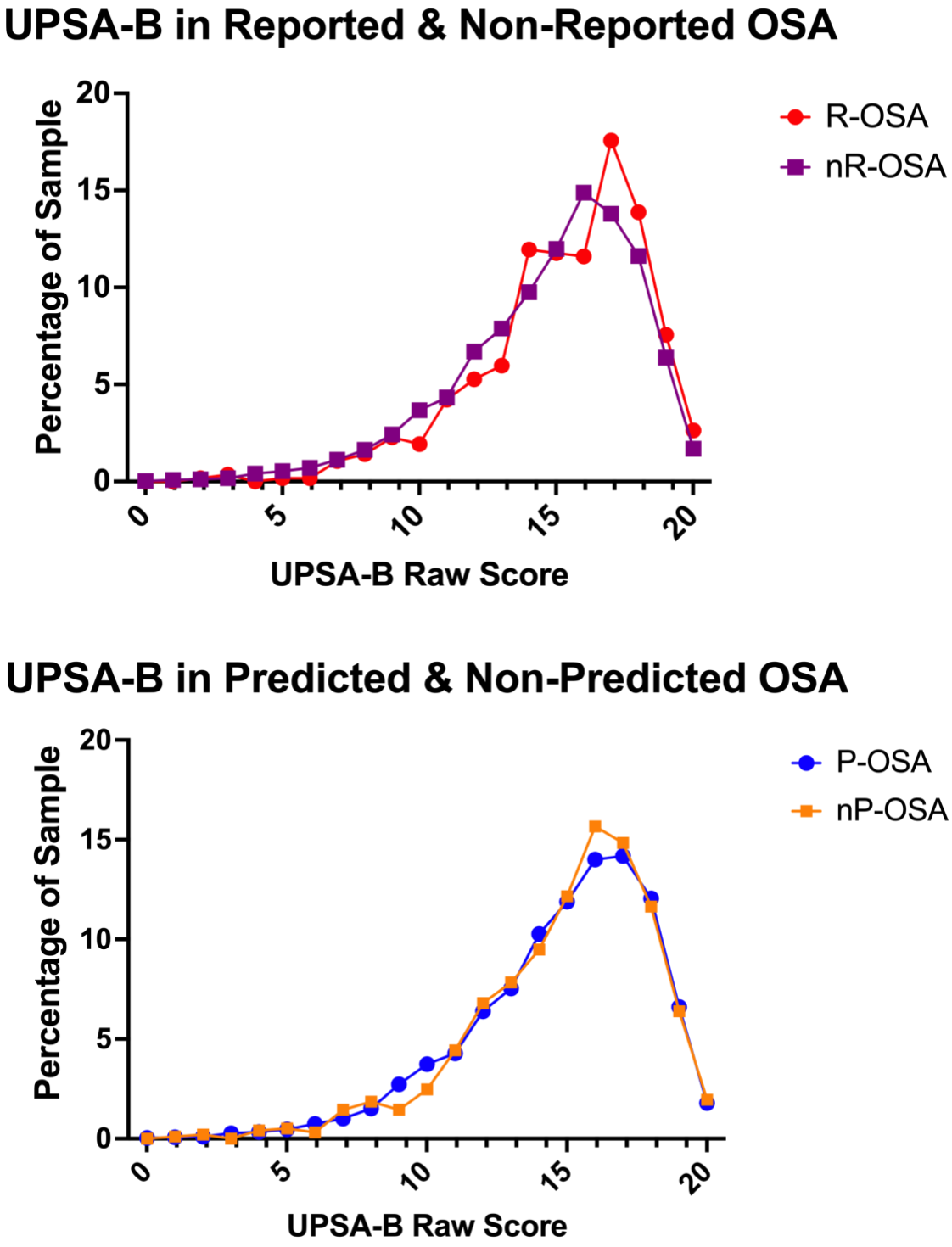

Figure 6 Frequency Distribution of UPSA-B in OSA

The top graph depicts the distribution of UPSA-B in R-OSA and nR-OSA. In R-OSA, the median was 16.00 with an interquartile range of 3.00. The minimum score was 2.00 and the maximum was 20.00. In nR-OSA, the median was 15.00 with an interquartile range of 4.00. The minimum score was 1.00 and the maximum was 20.00. The bottom graph depicts the distribution of UPSA-B in P-OSA and nP-OSA. In P-OSA, the median was 15.00 with an interquartile range of 4.00. The minimum score was 1.00 and the

maximum was 20.00. In nP-OSA, the median was 16.00 with an interquartile range of 4.00. The minimum score was 1.00 and the maximum was 20.00.

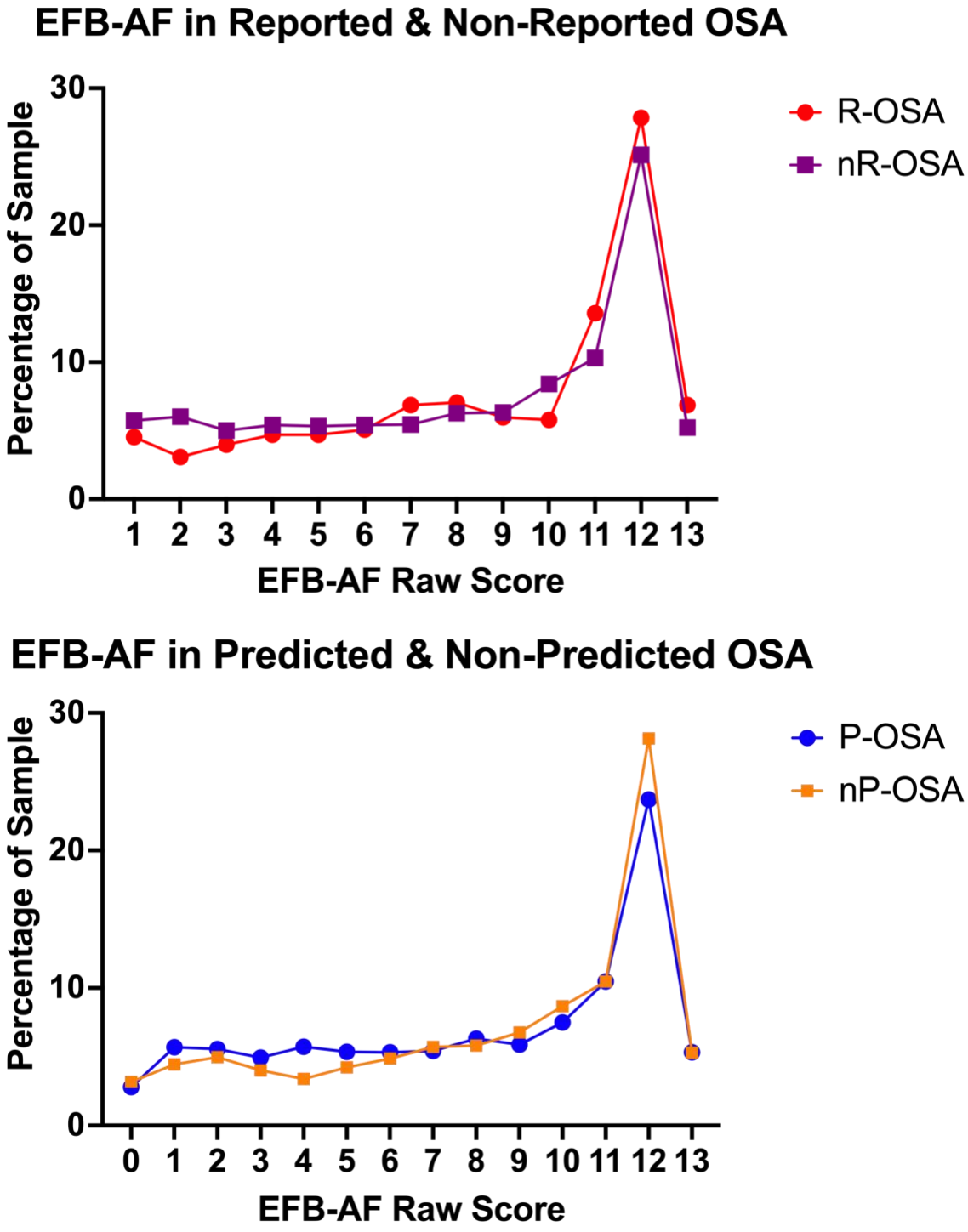

Figure 7 Frequency Distribution of EFB-AF in OSA

The top graph depicts the distribution of EFB-AF in R-OSA and nR-OSA. In R-OSA, the median was 10.00 with an interquartile range of 6.00. The minimum score was 0.00 and the maximum was 13.00. In nR-OSA, the median was 9.00 with an interquartile range of 7.00. The minimum score was 0.00 and the maximum was 13.00. The bottom graph depicts the distribution of UPSA-B in P-OSA and nP-OSA. In P-OSA, the median was 9.00 with an interquartile range of 7.00. The minimum score was 0.00 and the maximum was 13.00. In nP-OSA, the median was 10.00 with an interquartile range of 6.00. The minimum score was 0.00 and the maximum was 13.00.

Linear regression analyses were then performed to study the relationship between OSA and each functional capacity measure (i.e., UPSA-B and EFB-AF). R-OSA had a standardized coefficient (or Beta) of 0.061 (p= 0.000146) in association with UPSA-B in univariate analyses; it did not maintain a statistically significant association after controlling for sociodemographic and medical variables. P-OSA had a statistically insignificant coefficient (or Beta) of -0.12 (p= 0.447) in association with UPSA-B in univariate analyses. Table 7 reports multivariate linear regressions predicting UPSA-B with R-OSA as the study variable.

Table 7: Linear Regression of UPSA-B with Reported OSA as Study Variable

	Beta in Univariate Model with R-OSA	*Beta in Multivariate Model With R-OSA*
R-OSA	0.061**	---
Age		-0.125**
BMI		0.074**
Completeness		0.050**
Female		0.035
White		0.073**
College		0.159**
Independent Residence		0.188**
Employed		0.055**
Suicidal Ideation		0.048
MDD-SCID		0.048
Alogia		-0.090**
Avolition		-0.063**

Number of Hospitalizations	-0.039
Number of Prescriptions	-0.039
Depression	0.051
Memory Loss	-0.034
Benign Prostatic Hyperplasia	0.055**
Eating Disorder	-0.041
Skin Cancer	0.032
MS	-0.037

Italicized variables are medical variables based on self-report by patient.
Only statically significant variables listed above; Other variables included in multivariate model include: Marital Status(Married), MINI-PTSD, Suicide Attempts, Flat Affect, Current Smoker, Current Drinker, Dementia, TBI, High Cholesterol, Hypertension, TIA, Stroke, Loss of Consciousness, Epilepsy, Osteoarthritis, Rheumatoid Arthritis, Other arthritises, Gout, Anxiety, self-reported PTSD, Bipolar Disorder, Personality Disorder, Social Phobia, ADHD, GERD, Tinnitus, Hearing Loss, Blindness, Glaucoma, Macular Degeneration COPD, Diabetes, Colon Cancer, Lung Cancer, Breast Cancer, Prostate Cancer, Other Cancers, Parkinson's Disease, Non-Migraine Headaches, Migraines, ALS,HIV.
** denotes a p-value <0.001

R-OSA had a standardized coefficient (or Beta) of 0.063 (p=0.000089) in association with EFB-AF in univariate analyses, while P-OSA had a standardized coefficient (or Beta) of -0.049 (p= 0.003) in association with EFB-AF. Neither R-OSA or P-OSA maintained a significant association with EFB-AF after controlling for sociodemographic and medical variables. Table 8 reports multivariate linear regressions predicting EFB-AF with R-OSA and P-OSA as the study variables, respectively.

Table 8: Linear Regression of EFB-AF with Reported & Predicted OSA as Study Variable

	Beta in Univariate Model with R-OSA	*Beta in Multivariate Model With R-OSA*	*Beta in Univariate Model with P-OSA*	*Beta in Multivariate Model with P-OSA*
R-OSA	0.063**	---		
P-OSA			-0.049	---
Age		-0.189**		-0.199**
BMI		0.040		---
Female		0.039		0.047
White		0.110**		0.110**

College	0.209**	0.210**
Independent Residence	0.174**	0.175**
Employed	0.050**	0.050**
Suicidal Ideation	0.051	0.051
SCID-Depression	0.033	0.034
Alogia	-0.069**	-0.068**
Avolition	-0.044	-0.044
Number of Hospitalizations	-0.044	-0.043
Number of Prescriptions	-0.038	-0.038
Depression	0.050	0.051
Eating Disorder	-0.067**	-0.066**
Glaucoma	-0.036	-0.037
BPH	0.050**	0.051**
Rheumatoid Arthritis	-0.053**	0.053**
Colorectal Cancer	----	-0.029
Other Cancer	-0.047	-0.047
Loss of Consciousness	0.030	0.031
Current Smoker	-0.035	-0.040

Italicized variables are medical variables based on self-report by patient.
Only statically significant variables listed above; Other variables included in multivariate model include: Marital Status(Married), MINI-PTSD, Suicide Attempts, Flat Affect, Current Drinker, Dementia, TBI, Epilepsy, Stroke, High Cholesterol, Hypertension, TIA, Osteoarthritis, Other arthritises, Gout, Anxiety, self-reported PTSD, Bipolar Disorder, Personality Disorder, Social Phobia , ADHD, GERD, Tinnitus, Hearing Loss, Blindness, Macular Degeneration COPD, Diabetes, Lung Cancer, Breast Cancer, Prostate Cancer, Parkinson's Disease, Non-Migraine Headaches, Migraines, ALS, MS,HIV.
** denotes a p-value <0.001

Exploratory Aims:

The first exploratory analyses aimed to specifically compare cognition and functional capacity in reported versus undiagnosed (i.e., predicted-and-not-reported) OSA in this sample. Table 9 describes CCS and performance on functional capacity measures in three groups: Reported OSA (R-OSA), Predicted-not-reported OSA (PnR-OSA), and neither-predicted-nor-reported OSA (No-OSA).

Table 9: Performance in Reported, Predicted-not-Reported, and No-OSA

	R-OSA	**PnR-OSA**	**No-OSA**
CCS (SD)	37.71 (7.14)	36.07 (7.53)	37.46 (7.92)
UPSA-B (SD)	15.31 (2.93)	14.78 (3.15)	14.97 (3.08)
EFB-AF (SD)	8.76 (3.70)	7.89 (4.03)	8.46 (3.88)

Abbreviations: R-OSA—Reported OSA; PnR-OSA- predicted not reported OSA; No-OSA – neither predicted nor reported OSA. CCS- Composite cognitive Score; UPSA-B: UCSD Performance Skills Assessment Battery- Brief ; EFB-AF – Everyday Functioning Battery- Advanced Finances

A one-way ANOVA found statistically significant mean differences in CCS (F(2,3788)= [18.12], p= 1.4794E-8), UPSA-B (F(2,3827)=[7.74], p= 0.000444), and EFB-AF (F,(2,3736)=[13.01], p= 0.000002) between at least two of these three groups.

Figure 8 shows the mean CCS and 95% CI for R-OSA, PnR-OSA, and No-OSA. Tukey's HSD Test for multiple comparisons found that mean CCS in PnR-OSA was 1.42 (95% CI [0.72, 2.13]) T scores lower than CCS in No-OSA (p= 0.000007) and 1.71 (95% CI [0.86, 2.56]) T scores lower than CCS in R-OSA (p= 0.000007). No statistically significant difference between mean CCS in R-OSA and No-OSA (p= 0.769).

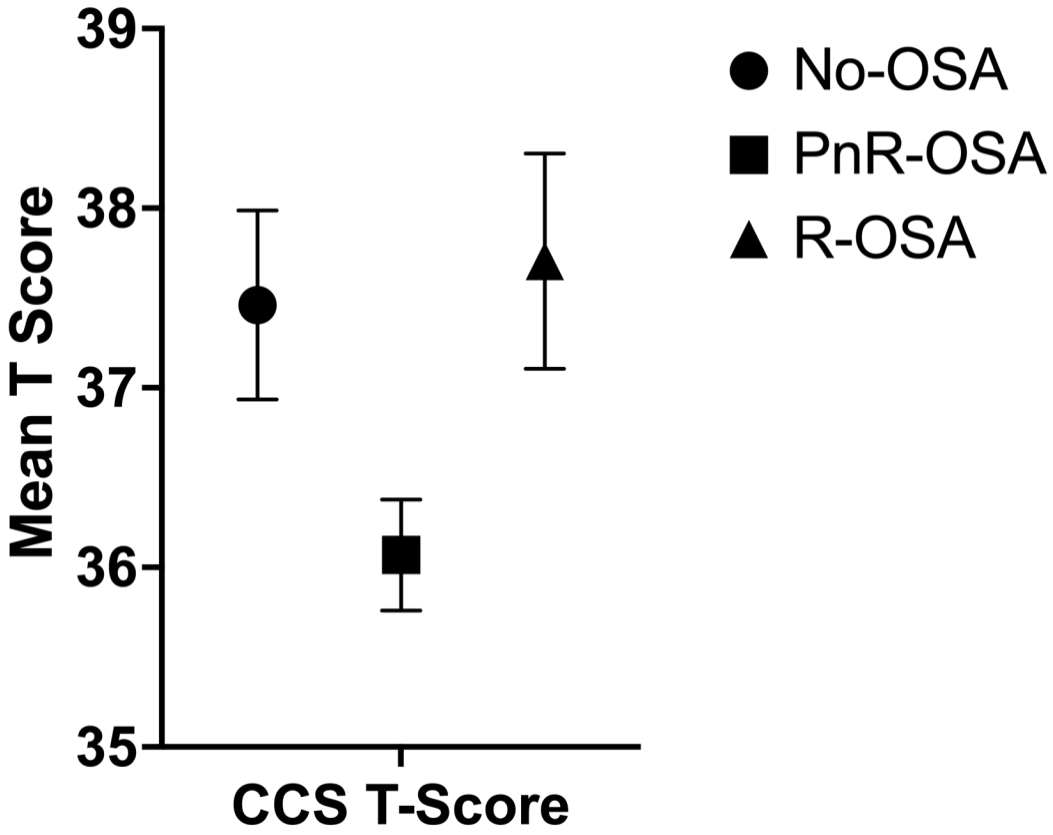

Figure 8 Composite cognitive Scores in Reported, Predicted-not-Reported, and No-OSA
Mean CCS in Veterans with predicted and not reported OSA (PnR-OSA) is statistically significantly lower than CCS in patients with reported OSA and no OSA. Error Bars represent 95% CI.

Figure 9 shows the mean UPSA-B and 95% CI for R-OSA, PnR-OSA, and No-OSA. Tukey's HSD Test for multiple comparisons found that mean UPSA-B in PnR-OSA was 0.57 (95% CI [0.23, 0.92]) points lower than UPSA-B in R-OSA (p= 0.000314). No statistically significant difference was found between mean UPSA-B in PnR-OSA and No-OSA (p= 0.277) or R-OSA and No-OSA (p=0.061).

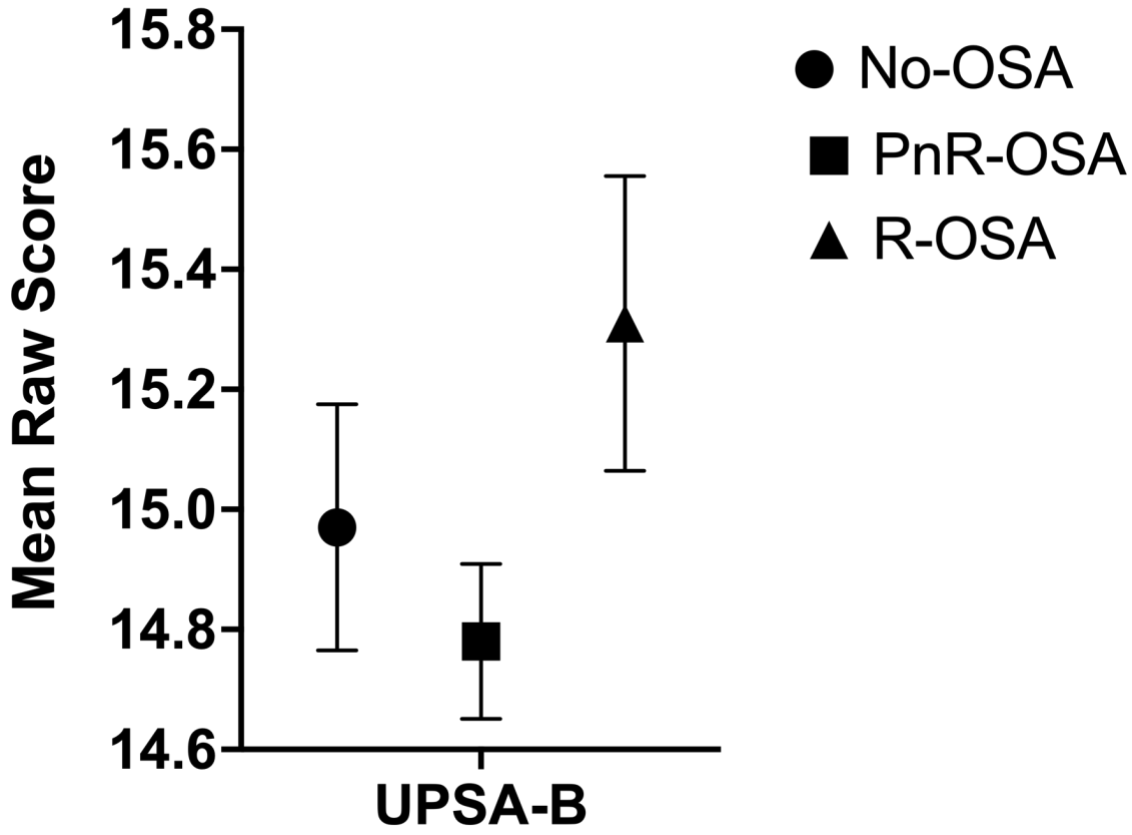

Figure 9 UPSA-B in Reported, Predicted-not-Reported, and No-OSA
Mean UPSA-B in Veterans with predicted and not reported OSA (PnR-OSA) is statistically significantly lower than UPSA-B in patients with reported OSA. Error Bars represent 95% CI.

Figure 10 shows the mean EFB-AF and 95% CI for R-OSA, PnR-OSA, and No-OSA. Tukey's HSD Test for multiple comparisons found that mean EFB-AF in PnR-OSA was 0.54 (95% CI [0.17, 0.91]) points lower than EFB-AF in No-OSA (p = 0.002) and 0.83 (95% CI [0.39, 1.27]) points lower than EFB-AF in R-OSA (p= 0.000025). No statistically significant difference was found between mean EFB-AF in R-OSA and No-OSA (p= 0.368).

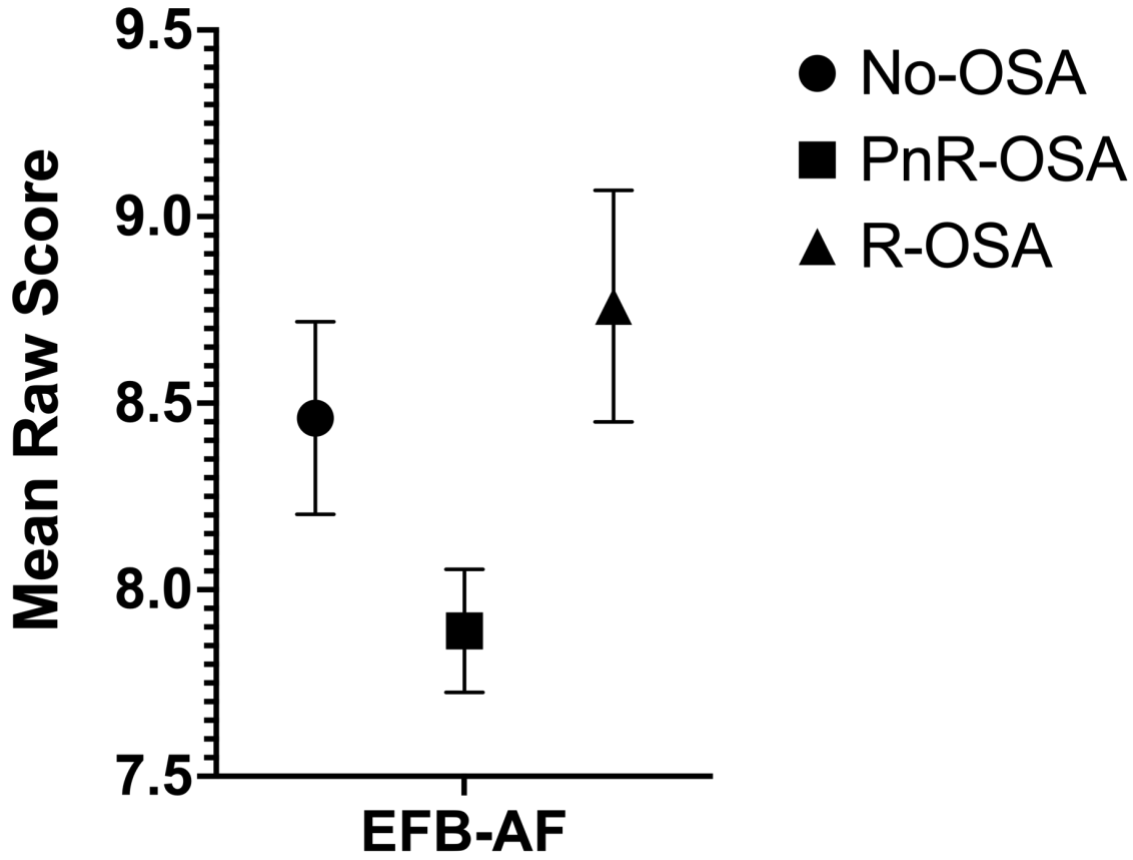

Figure 10 EFB-AF in Reported, Predicted-not-Reported, and No-OSA
Mean EFB-AF in Veterans with predicted and not reported OSA (PnR-OSA) is statistically significantly lower than EFB-AF in patients with reported OSA and no OSA. Error Bars represent 95% CI.

The next analyses were binomial logistical regressions that aimed to identify demographic and medical predictors of potentially undiagnosed (i.e., predicted-and-not-reported) OSA. Table 10 highlights the statistically significant adjusted odds-ratios that predict likelihood of being a Veteran with PnR-OSA or R-OSA. Overall, both groups were associated with older age and heavier BMI. Veterans were more likely to have reported OSA if they went to college, were married, employed, drink alcohol, had a history of depression and PTSD, and had a higher frequency of hospitalizations and number of prescription medications. Patients were more likely to have predicted and not

reported OSA if they were male, unmarried, had no college education, were current smokers, did not have history of depression, and had lower number of hospitalizations.

Table 10: Adjusted Odds-Ratios of Demographic and Medical Variables in Reported and Undiagnosed(PnR) OSA

	PnR-OSA	***R-OSA***
Age	1.067**	1.017
BMI	1.108**	1.107**
Completeness	---	0.841
Female	0.133**	--
College	0.844	1.458**
Married	0.785	1.394
Employed	--	1.417
Smoker	2.007**	---
Drinker	0.834	1.553**
SCID-Depression	0.833	1.423
MINI-PTSD	---	1.619**
Number of Prescriptions	---	1.398**
Number of Hospitalizations	0.873	1.189

** denotes a p-value <0.001

Only statically significant variables listed above;Other variables included: Race-White, low annual income, residential status (Living Independently), Alogia, Flat Affect, Avolition, Suicidal Ideation, Past Suicide Attempt.

Abbreviations: PnR-OSA—Predicted-and-not reported OSA; R-OSA—reported OSA; SCID- Structured Clinical Interview for DSM-IV

A final exploratory aim was to assess whether treatment for OSA in patients with reported OSA had any association with cognition and functional capacity. Table 11 describes performance on CCS, UPSA-B, and EFB-AF in self-reported treated and untreated OSA. No statistically significant differences were noted.

Table 11: Cognition and Functional Capacity in Treated and Untreated OSA

	Treated-OSA	**Untreated-OSA**	**p-value**
CCS (SD)	37.15 (6.85)	37.92 (7.44)	0.221

UPSA-B (SD)	15.36 (2.84)	15.23 (3.04)	0.600
EFB-AF (SD)	8.82 (3.56)	8.64 (3.80)	0.587

DISCUSSION:

Our study described the self-reported and predicted prevalence of OSA in schizophrenia and is the largest study to date to evaluate the association of OSA with cognition and functional capacity in this population. Our analyses suggest that more than 80% of OSA in schizophrenia is not diagnosed with 60% of patients with schizophrenia having undiagnosed OSA. Self-reported OSA was associated with better performance on cognitive and functional measures, whereas predicted OSA was associated with worse performance on these measures. This difference was likely driven by the large subsample of predicted-and-not-reported OSA who performed worse than reported-OSA on all measures, suggesting that the patients most vulnerable to missed OSA diagnosis have the most significant cognitive impairments. The extent that these cognitive impairments are caused by OSA cannot be determined from this study; however, it is notable that those with more significant cognitive impairment have an undiagnosed, treatable illness that could be contributing to their cognitive impairments and functional disability. Thus, the schizophrenia patients with greatest cognitive impairment may have the most to gain from more aggressive OSA screening, diagnosis, and treatment.

OSA is Prevalent and Highly Underdiagnosed in Schizophrenia

Our finding of self-reported OSA prevalence at 14.4% is comparable to previous reports of OSA in schizophrenia, which range from 15-48%,[7,107] and is notably higher than historical estimates in the general population[108]. Our predicted prevalence at 72.1% was outstandingly higher than reported OSA, with an estimated 60% of Veterans with schizophrenia having undiagnosed and untreated OSA. The model we used provides a

relatively conservative estimate of OSA as it had a specificity of 77% and sensitivity of 64.2%[92]; thus, there is approximately a net 10% of OSA-diagnosis that is not predicted by the model. The model did not predict 13% of R-OSA, which represents a portion of true OSA that was missed by the predictive model. Our findings demonstrate even more marked discrepancies in diagnosis and high-risk or predicted status of OSA in patients with mental illness than past work[80,109,110]. Our study is notably different from these past studies in relying on self-report and lack of polysomnography, while being able to consider a significantly larger sample size. These aforementioned studies relied on common screening questionnaires for OSA, like STOP-BANG[111], No-SAS[112], No-Apnea[113], and Berlin Questionnaire[114], which have not been validated in patients with schizophrenia. Furthermore, one group found that these symptom-based screenings have low specificity in patients with schizophrenia, as these symptoms often overlap with symptoms related to schizophrenia or psychotropic medications, and recommended using an objective metric based on BMI and neck circumference[115], with nearly identical specificity and sensitivity to the predictive model used in this study. Furthermore, the objective variables in this model are measures that can easily be identified from the electronic medical record and can allow for even easier screening of OSA. Symptom based screening may however be beneficial in identifying patients with OSA that the predictive model misses.

The high rates of predicted OSA are likely multifactorial. Known risk-factors for OSA, like cardiovascular disease and central obesity,[116] are more prevalent in patients with schizophrenia[37,38]. This can be due to genetic predispositions[117], adverse metabolic effects of second-generation antipsychotics[118], and higher likelihood of engaging in

behaviors that increase risk of OSA developing, including increased smoking, sedentary lifestyle, and poorer eating habits[119,120], many of which may be caused by negative symptoms of their serious mental illness[121]. Older age is a known risk factor for OSA[116] and our sample skewed older, with a mean age of approximately 55 years. Additionally, patients with schizophrenia may show signs of accelerated or exaggerated aging[122], which would further increase risk of OSA at younger chronologic ages. Our sample of Veterans was almost entirely male (93%), another known risk factor for OSA. Additionally, past work has shown that the prevalence of OSA in Veterans has been increasing over the past decade[123,124]. Our findings may therefore overestimate OSA prevalence in civilian populations of schizophrenia.

Under-diagnosis Impacts Patients with Worse Cognition & Disability

Our findings suggest that the under-diagnosis of OSA is likely non-random and impacts patients with worse cognition and functional capacity disproportionately. Patients with predicted OSA (P-OSA) performed worse on assessments of processing speed, verbal learning, and working memory, domains that are known to be affected by OSA[125]. Patients with P-OSA were also more likely to have no college education, be unmarried, and have less frequent hospitalizations. Being married can be a reflection of higher cognitive abilities[126] but also increases the likelihood of witnessed apneic events or snoring[127], facilitating the diagnosis of OSA. Patients with predicted and not reported OSA (PnR-OSA) had lower scores that those with reported-OSA (R-OSA) on CCS and both measures of functional capacity (UPSA-B and EFB-AF), and worse than those with No-OSA on CCS and EFB-AF. In contrast, those with R-OSA had higher composite

cognitive scores and performed better on functional capacity measures, showing no statistically significant difference than patients with no predicted or reported OSA. Patients with R-OSA even maintained a positive association with CCS after controlling for medical comorbidities and demographics, including education, employment status, marital status, independent living, higher rates of hospitalization and prescription medications (all of which were notably higher in patients with R-OSA) than the rest of the sample.

Overall, these findings suggest that those with those higher cognitive capacity are more likely to seek care and overcome the many barriers required to confirm diagnosis of OSA. Identified barriers to care include complex appointment schedules, transportation difficulties, lack of understanding amongst patients and caregivers about the severity of the problem, and the provider perception that patients cannot tolerate in-laboratory (in-lab) polysomnography or use CPAP[128,129]. Patients with R-OSA also had positive correlations with other diagnoses that require invasive testing and barrier, like macular degeneration and gastrointestinal polyps. Those with less cognitive capacity may be more likely to succumb to barriers to diagnosis and treatment, and as a result be impacted by co-occurring medical conditions that further compromise cognition and functioning.

Our findings of functional capacity mirrored cognitive performance in reported v. predicted OSA, though less drastically. Patients with R-OSA did better on the UPSA-B and EFB-AF than nR-OSA, and patients with P-OSA did worse on the EFB-AF; however, patients with P-OSA did not perform differently on the UPSA-B than nP-OSA. Both assessments have negatively skewed distributions, suggesting a ceiling effect. Past work have treated UPSA-B as dichotomous predictors of functioning and independent

living[101], and have found it does not predict real-word functional identifiers, like employment status, after controlling for other variables[130]. In our sample, however, employment status was not only associated with better performance on UPSA-B and EFB-AF, but was also a significant predictor of R-OSA. This further supports the idea that higher cognition and functioning may increase the likelihood of patients seeking and receiving care. Neurocognitive performance, which continues to correlate with debility from premorbid to chronic schizophrenia[131], may be a more sensitive detector of disability. Negative symptoms have been shown to mediate the relationship between cognition and functional outcome[132] and are key predictors of real-world functioning[133] in schizophrenia, rendering the UPSA-B a non-significant predictor[134].

Affective Symptoms in Schizophrenia: Marker of OSA or Higher Cognition

Presence of affective and negative symptoms in this sample also demonstrated a unique relationship with reported and predicted OSA. R-OSA was positively associated with history of affective disorders, including past major depression and PTSD, whereas PnR-OSA was negatively associated with a history of MDD. OSA is known to contribute to depressive symptoms[135] and past work has shown higher prevalence of OSA in MDD[88]. Depression in schizophrenia is also far more prevalent than in the general population[136], but there is evidence to suggest that depressive symptoms are associated with higher levels of cognition and functioning, and lower levels of co-occurring disease. For example, symptoms of depression and anxiety were associated with lower rates of metabolic syndrome, with a single point increase on the Beck Depression inventory associated with a 5.1% decreased probability of developing metabolic syndrome in

patients with schizophrenia[137]. Furthermore, expressive deficits and restrictions in affective and emotional ranges in schizophrenia are typically associated with less dysphoric symptoms but increased neurocognitive impairments and psychosocial functioning[32,138,139]. This is supported by some of our non-primary findings, including negative symptoms (i.e., avolition, alogia, and flat affect) having a significant negative association with CCS, UPSA, and EFB-AF in our multivariate models while diagnostically verified history of depression and self-reported suicidal ideation maintained a positive association with these measures. Additionally, there were lower rates of negative symptoms in R-OSA, particularly alogia ($p=0.005$), although they did not meet the conservative threshold of statistical significance used in our analyses.

The Importance of CPAP and OSA Treatment

Exploratory analyses did not reveal a difference in cognition or functional capacity between patients who did and did not report receiving treatment for OSA. A major limitation in this exploratory aim is the wording of the questionnaire patients completed. It asked the Veteran to check a box if they "take meds" for each illness; the main treatment for OSA does not involve 'taking meds' and thus may have been a source of unclarity for each participant. A small pilot study[90] and additional case report[140] have previously found improvement in cognition in patients with schizophrenia who were adherent to CPAP.

Treating OSA in schizophrenia could improve cognition, functioning, and ultimately mortality. Undertreatment of physical co-morbidities continues to drive the large life expectancy gap in schizophrenia[141]. Recent studies have shown patients with

psychosis have comparable rates of CPAP adherence (~65% 3 months after full CPAP trial) and improvements in apneic and hypoaneic events to the general population[142,143]. Patients with schizophrenia, thus, not only tolerate OSA treatment but may have more to gain.

CPAP adherence has been tied to improved cognition and prevention of cognitive decline in other populations[144]. The effect size of P-OSA in cognition and functional capacity from our study, ranging from -0.12 to -0.18, is small but comparable in magnitude to improvements that can be seen with CPAP[64] and CIAS[34]. Treating and reversing impairments in cognition is particularly important as lower cognitive functioning, in addition to cardiovascular disease, diabetes, and hypertension, is an independent risk factor of mortality in serious mental illness[145]. Treatment of OSA can also reduce the sympathetic activation, oxidative stress and pro-inflammatory reactions that are a result of intermittent hypoxia seen in OSA that worsen cardiovascular disease and psychiatric symptoms[146]. There is concern, however, that those that have the most to gain (i.e., those with more severely impaired cognition) may be less adherent as a result of being unable to identify the benefits of treatment[147]. Patient education, technological, and psychosocial intervention strategies can be used to promote adherence and ensure effective treatment.

Strengths, Limitations and Future Considerations

This thesis has many strengths and important limitations to consider. This is the largest study to date considering the relationship between OSA and cognition and functioning in patients with schizophrenia. This large sample size of nearly 4000

Veterans who had undergone questionnaires and neuropsychological and functional batteries was a very rich and robust dataset. The power afforded by working with such a large sample allowed for particularly conservative thresholds for statistical significance. Additionally, rigorous consideration and inclusion of co-variates in linear regression models may contribute to an under-estimation of the unique association of OSA with cognition and functioning. The main limitation of this study is its reliance on self-report for medical history and treatment. This in and of itself may be a barrier for those with worse cognition and functioning and may inaccurately reflect their medical history, which was integral to the predictive scoring system. To account for this, we used a 'completeness' variable that considered how thoroughly each Veteran completed the required portions of the questionnaires and controlled for this in our models. The completeness variable in fact maintained a significant positive association with CCS and UPSA-B. Additionally, It is important to note that this study was cross-sectional in nature, and thus temporal relationships with OSA treatment and cognitive and functional performance cannot be ascertained.

This study did not have data on Veteran sleep quantity, quality or other characteristics that are important for the diagnosis of sleep apnea, including apneic episodes. The clinical prediction model that we used, however, has a sensitivity and specificity that is comparable to, if not better[92] than, other symptom-driven models. The use of such a model is particularly important in patients whose negative symptoms can result in an inability to communicate such symptoms as excessive daytime sleepiness, snoring, changes in concentration and mood. Nevertheless, this study is limited in its lack of sleep symptom data; future work can explore how the presence or absence of these

symptoms impacts diagnostic rates in this population. Another important limitation to acknowledge is that this study was completed in the Veteran population. Veterans tend to be older than the civilian population, disproportionately male, and have higher rates of mental illness[148,149]. This may impact the generalizability of our findings to civilian populations of schizophrenia.

Future work can further elucidate associations between OSA diagnosis, cognition and functioning in schizophrenia. Use of polysomnography in future studies can verify apneic-hypoapneic events and work to correlate these events with performance on cognitive and functional capacity measures. Most importantly, future work can study the impact of CPAP on cognition by comparing performance on neuropsychological batteries before and after CPAP adherence in patients with schizophrenia. Additional research may explore whether CPAP treatment benefits patients with schizophrenia differently than others by conducting a case-control study with age- and gender-matched neurotypical controls.

Conclusions

OSA is likely very common in patients with schizophrenia. Most of these patients, particularly the most vulnerable with the worst cognition and functioning, may be unaware of their diagnosis and not receiving treatment. Use of a clinical prediction model based on quantitative measures and medical history can identify at-risk patients whose psychiatric illness reduces reliability of symptom-driven screening. Treatment of their OSA might improve their cognition, sleep, and physical health, which in turn could reduce disability and mortality.

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