Gender Differences in Outcomes of Ambulatory and Hospitalized Patients With Obesity Hypoventilation Syndrome

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BACKGROUND: Obesity hypoventilation syndrome (OHS) is associated with high morbidity and mortality. There are few data on whether there are gender differences in outcomes.

RESEARCH QUESTION: Is female gender associated with worse outcomes in ambulatory and hospitalized patients with OHS?

STUDY DESIGN AND METHODS: Post hoc analyses were performed on 2 separate OHS cohorts: (1) stable ambulatory patients from the 2 Pickwick randomized controlled trials; and (2) hospitalized patients with acute-on-chronic hypercapnic respiratory failure from a retrospective international cohort. We first conducted bivariate analyses of baseline characteristics and therapeutics between genders. Variables of interest from these analyses were then grouped into linear mixed effects models, Cox proportional hazards models, or logistic regression models to assess the association of gender on various clinical outcomes.

RESULTS: The ambulatory prospective cohort included 300 patients (64% female), and the hospitalized retrospective cohort included 1,162 patients (58% female). For both cohorts, women were significantly older and more obese than men. Compared with men, baseline $Paco_2$ was similar in ambulatory patients but higher in hospitalized women. In the ambulatory cohort, in unadjusted analysis, women had increased risk of emergency department visits. However, gender was not associated with the composite outcome of emergency department visit, hospitalization, or all-cause mortality in the fully adjusted model. In the hospitalized cohort, prescription of positive airway pressure was less prevalent in women at discharge. In unadjusted analysis, hospitalized women had a higher mortality at 3, 6, and 12 months following hospital discharge compared with men. However, after adjusting for age, gender was not associated with mortality.

INTERPRETATION: Although the diagnosis of OHS is established at a more advanced age in women, gender is not independently associated with worse clinical outcomes after adjusting for age. Future studies are needed to examine gender-related health disparities in diagnosis and treatment of OHS.

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KEY WORDS: gender differences; obesity hypoventilation syndrome; OSA; positive airway pressure

Take-Home Points

Study Question: Is female gender associated with worse outcomes in ambulatory and hospitalized patients with OHS?

Results: Women were on average 8 to 11 years older than men, had more comorbidities, and had worse outcomes. After adjusting for age, however, there were no gender differences in outcomes.

Interpretation: Our study shows significant gender differences in clinical presentation and prescription of PAP therapy in patients with OHS; additional research is needed to investigate the reasons behind disparities in diagnosis and treatment of OHS in women.

Obesity hypoventilation syndrome (OHS) is defined by the triad of obesity (BMI ≥ 30 kg/m^2), awake hypercapnia ($Paco_2$ ≥ 45 mm Hg), and sleep-disordered breathing, after excluding other causes of hypoventilation.[1] The most common form of sleep-disordered breathing in patients with OHS is OSA, which affects 90% of patients with OHS, including 73% with severe OSA.[2]

Patients with OHS have worse outcomes compared with patients with severe OSA or eucapnic severely obese patients.[1,3-5] Untreated OHS is associated with increased health care resource utilization and mortality compared with eucapnic OSA.[6-10] Moreover, patients with OHS have high short-term mortality following hospitalization for acute-on-chronic hypercapnic respiratory failure.[10] Discharging hospitalized patients with positive airway pressure (PAP) therapy is associated with reduced mortality.[11] Similarly, adherent PAP therapy is associated with better long-term outcomes in ambulatory patients.[12]

In contrast to OSA, in which there is a clear male predominance with an estimated 2:1 male-to-female ratio,[13,14] several studies have reported a higher prevalence of OHS in women.[9,15-18] In a large clinical sample of patients referred to a sleep center for suspicion of sleep-disordered breathing in Saudi Arabia, 144 (7.3%) of 1,973 patients were diagnosed with OHS; 67% were women.[16] In this cohort, women with OHS were older than men (61.5 ± 11.9 years vs 49.1 ± 12.5 years) and had a higher prevalence of comorbidities. Similarly, 3 studies of patients with OHS who were hospitalized with acute-on-chronic hypercapnic respiratory failure in Spain, France, and the United States reported a female prevalence of 77%, 77%, and 64%, respectively.[19-21] Furthermore, analysis of the Swedish national registry found that despite having worse hypoxemia and hypercapnia compared with men, there was a delay in prescribing home noninvasive ventilation (NIV) in women.[17] These findings suggest that gender disparity in OHS exists across various geographic regions with delays in diagnosis and initiation of appropriate long-term home PAP therapy. Gender bias may in part explain why nearly two-thirds of patients admitted to the hospital with acute-on-chronic hypercapnic respiratory failure are women.

Despite compelling evidence for gender disparities in OHS, there is a paucity of studies assessing clinical outcomes between genders. To our knowledge, there are no systematic large-scale studies examining the influence of gender on the most meaningful outcomes of exacerbations and mortality. We hypothesized that

ABBREVIATIONS: AHI = apnea hypopnea index; IQR = interquartile range; NIV = noninvasive ventilation; OHS = obesity hypoventilation syndrome; PAP = positive airway pressure; SF-36 = Short Form 36

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in patients with OHS, female gender is associated with increased health care resource utilization and mortality. To test our hypothesis, we conducted a post hoc analysis of health care resource utilization in ambulatory patients from the Pickwick randomized controlled trials[12,22] and postdischarge mortality in a large, international cohort of hospitalized patients with OHS.[10]

Study Design and Methods

Study Design and Data Collection

Post hoc analyses were conducted exploring the relationship between gender and clinical outcomes in 2 previously established cohorts of patients with OHS: (1) a prospective data set of stable ambulatory patients with OHS (Pickwick randomized controlled trials); and (2) a retrospective data set of patients hospitalized for acute-on-chronic hypercapnic respiratory failure due to suspected OHS assembled for the 2019 American Thoracic Society's clinical practice guidelines for OHS.

Prospective Cohort of Ambulatory Patients From the Pickwick Randomized Controlled Trials: The Pickwick Project included 2 parallel randomized controlled trials completed in 2 phases.[12,22] Patients who were referred for pulmonary consultations for suspected OHS or OSA were screened from May 2009 to March 2013 at 16 tertiary hospitals in Spain. Patients were eligible for the study if they were between 15 and 80 years old, had a diagnosis of clinically stable OHS (BMI $ 30 kg/m^2, Pa_{CO_2} $ 45 mm Hg, pH $ 7.35, no clinical worsening during the previous 2 months, and no alternative etiology for hypercapnic respiratory failure such as COPD or neuromuscular disease), and could tolerate a 30-minute trial of CPAP/NIV. Exclusion criteria included history of narcolepsy or restless leg syndrome, inability to complete questionnaires, severe chronic debilitating illness, severe chronic nasal obstruction, and/or inability to provide informed consent. The Pickwick Project was approved by the ethics committees of the 16 centers, and written informed consent was obtained from all patients.

In the Pickwick study, enrolled participants underwent baseline polysomnography and arterial blood gas analysis. Those with severe OSA (apnea-hypopnea index [AHI] $ 30 events per hour) were initially randomized to an NIV, CPAP, or control (lifestyle modification)

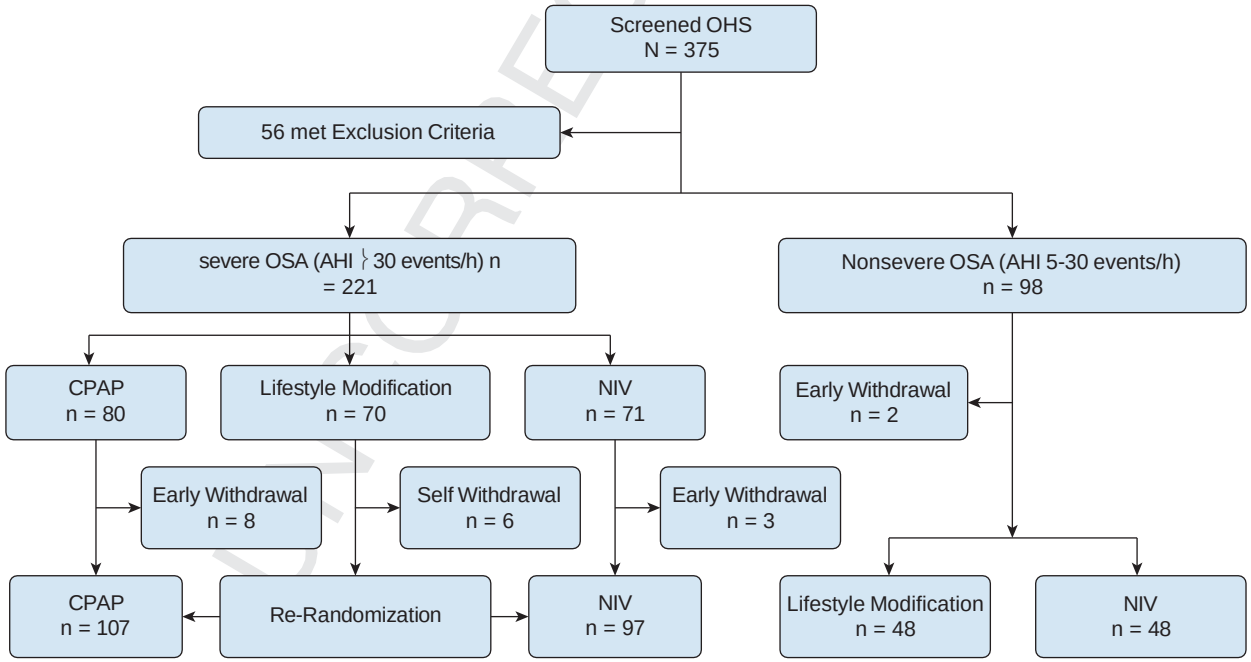

Figure 1 – *The Pickwick randomized clinical trials profile. Flowchart of the study protocol. Of selected patients, 56 were excluded due to exclusion criteria and 319 were randomized to treatment: 221 in the severe OSA trial and 98 in the nonsevere OSA trial. Of these 319 patients, an additional 6 from the lifestyle modification group of the severe OSA trial were excluded for disinterest in positive airway pressure and self-withdrew before re-randomization. The final cohort of 300 patients used for the current secondary analysis includes all participants from both trials who underwent intention-to-treat analyses at a minimum of 36-month follow-up. AHI ¼ apnea-hypopnea index; NIV ¼ noninvasive ventilation; OHS ¼ obesity hypoventilation syndrome.*

TABLE 1] Pickwick Trials: Baseline Patient Characteristics Prior to Treatment Assignment

Characteristic	Women (n ¼ 192)	Men (n ¼ 108)	*P* Value	Total N
Sociodemographic and clinical data				
Age, y	68.0 (60.0-73.0)	57.0 (46.0-66.0)	< .001	300
BMI, kg/m^2	42.8 (37.9-48.0)	40.9 (36.6-45.4)	.029	289
Smoking history			< .001	300
Formerly smoked	31 (16.1%)	44 (40.7%)		
Does not smoke	136 (70.8%)	26 (24.1%)		
Smokes	25 (13.0%)	38 (35.2%)		
Pack-years[a]	0.00 (0.00-27.5)	15.0 (0.00-37.5)	< .001	236
Neck circumference, cm	42.0 (39.0-45.0)	47.0 (44.0-49.0)	< .001	295
Alcohol drinkers[b]	11 (5.73%)	39 (36.4%)	< .001	299
Systolic BP, mm Hg	140 (130-147)	135 (129-146)	.291	297
Diastolic BP, mm Hg	80.0 (70.0-86.0)	80.0 (70.0-90.0)	.049	297
Dyspnea MRC scale $ 2	124 (64.6%)	49 (45.4%)	.002	300
6MWTD, m	306 ± 113	420 ± 106	< .001	256
FEV_1 (% of predicted)	77.0 (64.2-89.0)	77.0 (66.5-89.0)	.960	297
Need for 24-hour supplemental oxygen[c]	57 (29.7%)	21 (19.4%)	.071	300
Comorbidities at enrollment				
Hypertension	147 (76.6%)	66 (61.7%)	.010	299
Diabetes	87 (45.3%)	27 (25.0%)	.001	300
Diabetes treatment[a]	85 (44.5%)	25 (23.4%)	< .001	298
Dyslipidemia	90 (47.1%)	44 (40.7%)	.345	299
Dyslipidemia treatment[a]	77 (40.5%)	31 (29.0%)	.063	297
Ischemic heart disease	19 (9.95%)	7 (6.54%)	.432	298
Atrial fibrillation	18 (9.42%)	8 (7.41%)	.703	299
Chronic heart failure	36 (18.8%)	15 (13.9%)	.350	299
Peripheral arterial disease	17 (8.95%)	5 (4.63%)	.254	298
Pulmonary hypertension	20 (10.5%)	8 (7.48%)	.511	297
Quality of life				
Epworth Sleepiness Scale score	10.0 (6.00-14.0)	10.0 (7.00-14.0)	.693	289
FOSQ	69.0 (55.0-83.0)	85.5 (68.0-101)	< .001	294
SF-36 (Physical)	33.0 (26.9-39.8)	41.4 (32.6-46.9)	< .001	292
SF-36 (Mental)	42.8 (31.0-52.1)	46.6 (36.9-53.7)	.065	292

Quantitative variables are described as median (interquartile range) or mean ± SD depending on the normality of the variable. Qualitative variables are described as absolute frequency (relative frequency). 6MWTD ¼ 6-min walk test distance; FOSQ ¼ Functional Outcomes of Sleep Questionnaire; MRC ¼ Medical Research Council; SF 36 ¼ Short Form 36.

[a]Includes only patients who reported to actively smoke or patients with diabetes or hyperlipidemia.

[b]People who drink > 30 g/d of alcohol in men and 20 g/d of alcohol in women.

[c]Oxygen therapy was prescribed during the baseline visit if clinically indicated.

group. After 2 months, the participants in the control (lifestyle modification) group were re-randomized to the NIV or CPAP group. Those without severe OSA (AHI < 30 events per hour) were initially randomized to an NIV or control (lifestyle modification) group. After 2 months, these participants remained in their original group (Fig 1).

All patients were followed up for a minimum of 3 years. These outcomes included arterial blood gas analysis, spirometry, 6-minute walk distance, dyspnea (using the Medical Research Council scale), sleepiness (according to the Epworth Sleepiness Scale), quality of life (using the Functional Outcomes of Sleep Questionnaire) and health-related quality of life (by Physical and Mental

TABLE 2] Pickwick Trials: Baseline Diagnostic Studies Prior to Treatment Assignment

	Women (n ¼ 192)	Men (n ¼ 108)	*P* Value	Total N
Polysomnographic parameters[a]				
Total sleep time, h	5.40 (4.50-6.15)	5.30 (4.42-6.18)	.937	293
Apnea-hypopnea index, events/h[b]	32.4 (17.9-69.3)	69.8 (36.4-94.9)	< .001	288
3% Oxygen desaturation index, events/h	40.6 (18.0-74.5)	70.1 (32.4-93.2)	< .001	281
Arousal index, events/h	32.7 (20.4-58.5)	59.5 (28.0-84.7)	< .001	272
Non-REM stages 1 and 2 sleep, %	77.2 (65.0-88.8)	85.9 (77.2-92.0)	< .001	279
Non-REM stage 3 sleep, %	12.9 (2.80-22.6)	3.18 (0.00-10.0)	< .001	276
REM sleep, %	8.90 (3.67-14.1)	9.45 (5.03-14.5)	.441	278
Mean Spo_2 during sleep	86.8 (83.0-90.0)	85.0 (81.0-89.0)	.039	286
Percentage of total sleep time below Spo_2 90%	75.9 (43.9-95.5)	75.0 (49.8,93.0)	.811	290
Arterial blood gases				
pH	7.40 (7.39-7.43)	7.39 (7.38-7.42)	.045	298
HCO_3, mEq/L	30.0 (28.0-32.0)	28.9 (27.8-31.2)	.031	292
HCO_3 $ 27, mEq/L	163 (87.2%)	91 (86.7%)	.999	292
$Paco_2$, mm Hg	49.8 (47.2-53.0)	49.0 (47.9-51.5)	.311	299
Pao_2, mm Hg	62.9 (56.5-70.0)	61.0 (56.3-68.0)	.725	299
Blood chemistry				
Fasting blood glucose, mg/dL	109 (94.0-135)	104 (93.0-123)	.250	285
Triglycerides, mg/dL	133 (101-166)	137 (109-165)	.610	213
Cholesterol, mg/dL	186 (165-216)	188 (167-205)	.521	283
HDL, mg/dL	48.0 (42.0-56.0)	42.0 (37.0-47.5)	< .001	271
LDL, mg/dL	110 (94.0-135)	112 (97.0-132)	.646	269
Creatinine, mg/dL	0.75 (0.62-0.96)	0.89 (0.79-1.00)	< .001	284
C-reactive protein, mg/L	1.80 (0.70-7.50)	1.30 (0.60-5.60)	.193	258
Echocardiographic parameters				
Pulmonary artery systolic pressure, mm Hg	39.0 (34.0-46.6)	40.0 (33.0-46.0)	.714	249
Pulmonary artery systolic pressure $40 mm Hg	78 (47.9%)	43 (51.2%)	.717	247
Right ventricular index performance (Tei index), ms	0.39 (0.28-0.54)	0.33 (0.26-0.48)	.012	262
E/A ratio	0.84 (0.68-1.01)	0.89 (0.77-1.10)	.009	268
Deceleration time, ms	236 (200-265)	211 (180-255)	.029	267
Left atrial diameter, mm	41.3 (36.0-46.0)	45.0 (39.9-49.0)	.023	270
Left ventricular ejection fraction, %	63.0 (60.0-70.0)	61.9 (58.0-68.0)	.112	279
Left ventricular mass index, g/m^2	109 (89.7-125)	107 (85.6-124)	.731	270

Quantitative variables are described as median (interquartile range) depending on the normality of the variable. Qualitative variables are described as absolute frequency (relative frequency). HCO_3 ¼ calculated bicarbonate from the arterial blood gases; REM ¼ rapid eye movement; Spo_2 ¼ oxygen saturation.

[a]Polysomnography was performed in baseline conditions without CPAP, noninvasive ventilation, or oxygen supplementation.

[b]Hypopneas were defined as a 30% reduction in the amplitude on nasal pressure signal lasting $ 10 seconds, leading to a cortical microarousal and/or a 3% arousal.

Short Form 36), echocardiography, adherence to PAP therapy, and side effects. Participants in the nonsevere OSA group who were randomized to lifestyle modification were assigned PAP adherence of 0 hours per day for the purposes of data analysis. Other clinically important outcomes were visits to the emergency department, hospital admissions, and all-cause mortality. The composite outcome for exacerbation included visits to the emergency department, hospital admissions, and all-cause mortality.

Retrospective Cohort of Hospitalized Patients: A systemic review was originally performed to inform a panel of experts developing clinical practice guidelines on

TABLE 3] Pickwick Trials: Therapeutics and Outcomes

	Women	Men	*P* Value	Total N
Adherence to CPAP or NIV at 3 years				
Adherence to PAP, h/night (CPAP or NIV)[a]	5.52 (0.27-7.00)	5.90 (1.48-7.00)	.584	252
Adherence to PAP therapy[b]	94/152 (61.8%)	62/100 (62.0%)	.999	252
Adherence to PAP, h/night (CPAP or NIV)[c]	3.83 (0.00-6.61)	5.28 (0.00-7.00)	.054	300
Adherence to PAP therapy[b]	94/192 (48.9%)	62/108 (57.4%)	.199	300
Outcomes at 3 years				
Pa_{CO_2}, mm Hg	44.2 (41.3-47.0)	44.0 (40.0-46.0)	.107	227
Pa_{O_2}, mm Hg	68.0 (62.8-75.0)	70.0 (61.0-78.5)	.433	227
Epworth Sleepiness Scale	4.00 (2.00-7.00)	4.00 (2.00-8.00)	.896	192
SF-36 (Physical)	36.3 (27.7-45.2)	46.3 (37.0-52.0)	< .001	180
SF-36 (Mental)	49.5 (39.2-56.0)	52.6 (43.8-57.3)	.070	180
Systolic BP, mm Hg	130 (120-140)	130 (120-143)	.885	208
Dyspnea MRC scale $2	43 (36.4%)	14 (21.9%)	.063	182
Need for 24-hour supplemental oxygen	33 (20.6%)	16 (18.0%)	.736	249
Pulmonary artery systolic pressure $40 mm Hg	11 (36.7%)	5 (20.8%)	.334	54
Exacerbation or death until last available follow up				
Emergency visit				300
Event (yes)	140 (72.9%)	52 (48.1%)	< .001	
Time to first event (mo)	27.31 (9.7-50.05)	36.71 (13.14- 63.54)		
Hospital admission				299
Event (yes)	105 (54.7%)	49 (45.4%)	.153	
Time to first event (mo)	34.04 (5.38-66.57)	40.77 (3.28-63.54)		
Death				300
Event (yes)	26 (13.5%)	19 (17.6%)	.438	
Time to first event (mo)	68.00 (49.26-80.01)	63.90 (47.75-75.00)		
Total				299
Event (yes)	153 (58.3%)	70 (48.1%)	.007	
Time to first event (mo)	12.41 (3.86-38.86)	22.29 (3.18-60.66)		

Quantitative variables are described as median (interquartile range). Qualitative variables are described as absolute frequency (percentage). MRC ¼ Medical Research Council; NIV ¼ noninvasive ventilation; SF 36 ¼ Short Form 36.

[a]Includes only patients who were allocated to either CPAP or NIV (n ¼ 252). Given the lower prevalence of severe OSA in women, more were randomized to lifestyle intervention (ie, no PAP therapy) compared with men. This analysis excludes women who were randomized to lifestyle changes (ie, no PAP therapy) and compares men and women who received PAP therapy.

[b]Adherence to PAP therapy defined as > 4 hours per night average PAP use.

[c]Comprises the entire cohort, including patients without severe OSA who were allocated to lifestyle intervention (ie, no PAP therapy). These patients were assigned a PAP adherence of 0 hours per day for purposes of analysis.

OHS for the American Thoracic Society.[10,11] The guideline panel asked whether hospitalized adult patients with acute-on-chronic hypercapnic respiratory failure suspected of having OHS should be discharged with or without empiric PAP treatment until the diagnosis of OHS is confirmed or excluded. To address the paucity of data in this area, the guideline panel completed a systematic review of previously published studies of hospitalized cohorts or if the study included a subgroup of hospitalized patients. From a search of 2,994 relevant articles, 9 articles from 6 different countries were identified. All studies were nonrandomized, comparative studies.

Following this review, a meta-analysis of individual patient data was performed by requesting data from the investigators to inform the guideline panel's recommendation. Participants included in this individual patient data meta-analysis were hospitalized patients with confirmed or suspected OHS. Patients were divided into 2 groups: those who were discharged on any mode of PAP and those who were not discharged on PAP. Severity of

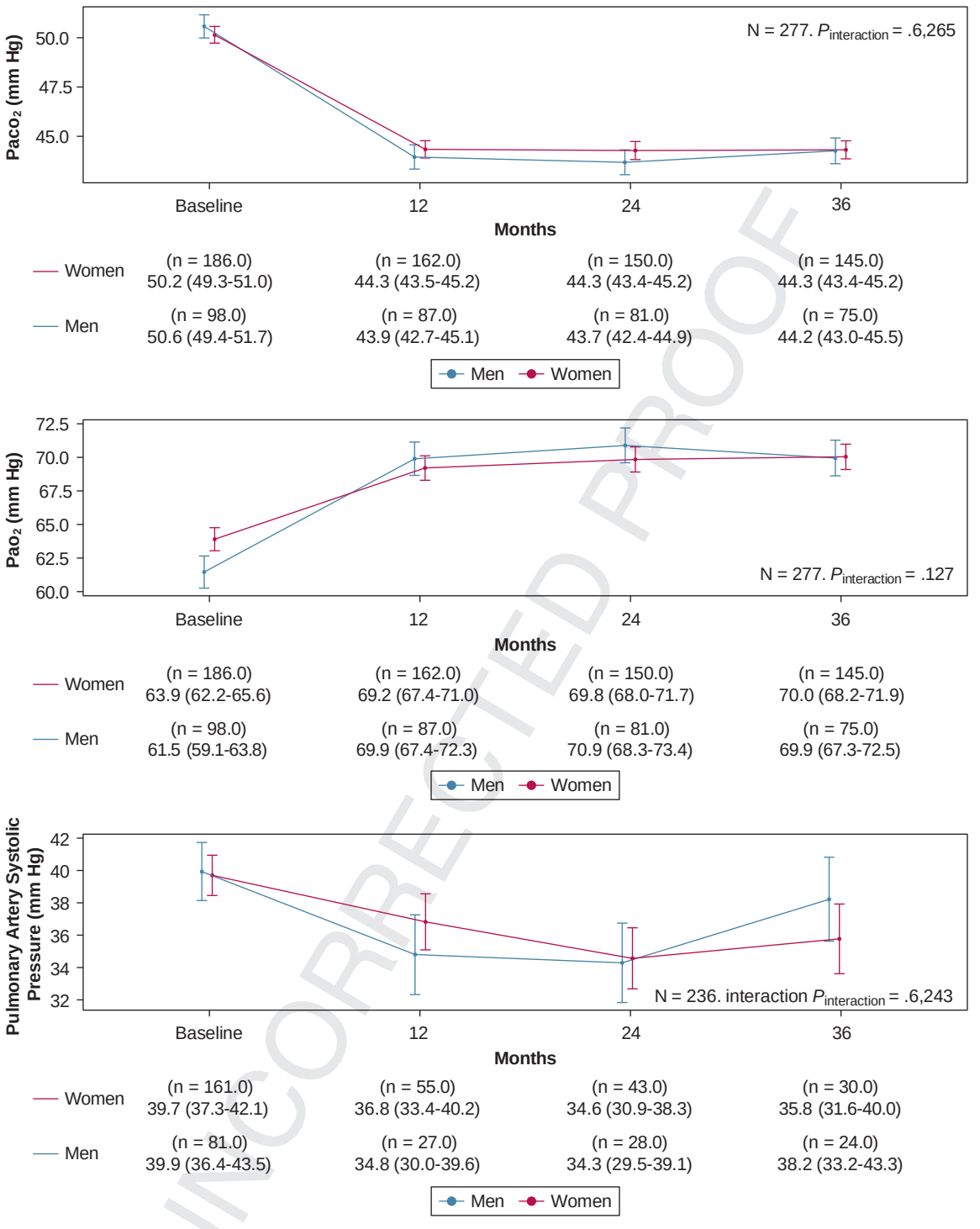

Figure 2 – *Adjusted longitudinal changes in $Paco_2$, Pao_2, and pulmonary artery systolic pressure after 36 months of follow-up. Longitudinal models are adjusted for age, BMI, positive airway pressure adherence, apnea-hypopnea index, diabetes, hypertension, and smoking status. There was no significant interaction between visit date and gender.*

OHS (defined by baseline $Paco_2$), age, and BMI were determined a priori to be covariates of interest. Outcomes included all-cause mortality at 3, 6, 9, and 12 months. This data set was limited by not having any information on comorbidities, PAP adherence, or cause of death.

Given the retrospective nature of this analysis, the Institutional Review Board (IRB) determined the study was exempt from further IRB review (University of Chicago IRB 19-1563). The study was approved by the University of Chicago's IRB (IRB 19-1563).

TABLE 4] Cox Proportional Hazards Models of the Composite Outcome in the Pickwick Trials

Predictor	Model 1			Model 2			Model 3			Model 4			Model 5		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Gender (female)	1.36	1.02-1.81	.034	1.10	0.80-1.52	.564	1.11	0.79-1.54	.553	1.19	0.85-1.68	.310	1.25	0.86-1.80	.243
Age (per 1 year)				1.02	1.01-1.03	.003	1.02	1.01-1.03	.004	1.02	1.01-1.04	.002	1.03	1.01-1.04	.001
BMI (per 1 unit)				1.02	1.00-1.04	.070	1.02	1.00-1.04	.072	1.01	0.99-1.04	.149	1.02	1.00-1.04	.092
PAP adherent[a]							1.02	0.77-1.34	.888	0.98	0.73-1.32	.903	0.97	0.72-1.30	.849
AHI (per 1 unit)										1.00	1.00-1.01	.160	1.00	1.00-1.01	.177
Diabetes													1.18	0.89-1.58	.247
Hypertension													0.78	0.56-1.10	.154
Smoking													1.13	0.82-1.55	.455
Observations	299			288			288			284			283		
Nagelkerke R^2	0.016			0.050			0.050			0.058			0.074		

AHI ¼ apnea-hypopnea index; HR ¼ hazard ratio; PAP ¼ positive airway pressure (noninvasive ventilation or CPAP).
[a]Adherence to PAP therapy defined as > 4 hours per night average PAP use.

Data Analysis

Bivariate analyses of baseline characteristics and therapeutics between genders were performed. Continuous variables are described as mean ± SD or median (interquartile range [IQR]) depending on the normality of the variable, and they were compared by using *t* tests or nonparametric tests, respectively. Categorical variables are described as proportions and were compared by using the C^2 test. Statistical significance was defined as *P* values < .05, and statistical analysis was performed by using R Project for Statistical Computing and Stata 16.0 (Stata Corp). Given the differences in sample size and available variables in the 2 groups, a different analytic approach was performed for ambulatory and hospitalized cohorts.

Prospective Cohort of Ambulatory Patients From the Pickwick Randomized Controlled Trials: Outcomes of repeated measures such as $Paco_2$, Pao_2, and pulmonary artery systolic pressure during 3 years of follow-up were compared between genders using adjusted linear mixed effects models. The models included subject as random effects and time (as a categorical variable), sex-time interaction, and confounders such as age, BMI, PAP adherence, AHI, diabetes, hypertension, and smoking status as fixed effects. Survival analysis using Cox proportional hazards was performed to estimate the association of gender with the composite outcome of exacerbations (emergency department visits, hospitalizations, and all-cause mortality until last available follow-up) in both unadjusted and adjusted models. The models adjusted for age, BMI, PAP adherence, AHI, diabetes, hypertension, and smoking status. Confounders included in the linear mixed effects model and the Cox proportional hazards were sociodemographic variables and comorbidities that were significantly different between genders at baseline (age, BMI, AHI, diabetes, hypertension, and smoking) or relevant to the outcome of interest (ie, PAP adherence). To avoid collinearity, certain covariates were not included in the models despite being significantly different between the 2 genders (eg, neck circumference, oxygen desaturation index, arousal index).

Retrospective Cohort of Hospitalized Patients: Logistic regression models were fitted to assess the relationship between gender and 12-month mortality in the hospitalized retrospective international cohort. Covariates introduced in the models were age, BMI, PAP prescription on discharge, and OHS severity (baseline $Paco_2$). A 2-way interaction term evaluating the moderating effect of age on gender was included in the separate main effects model.

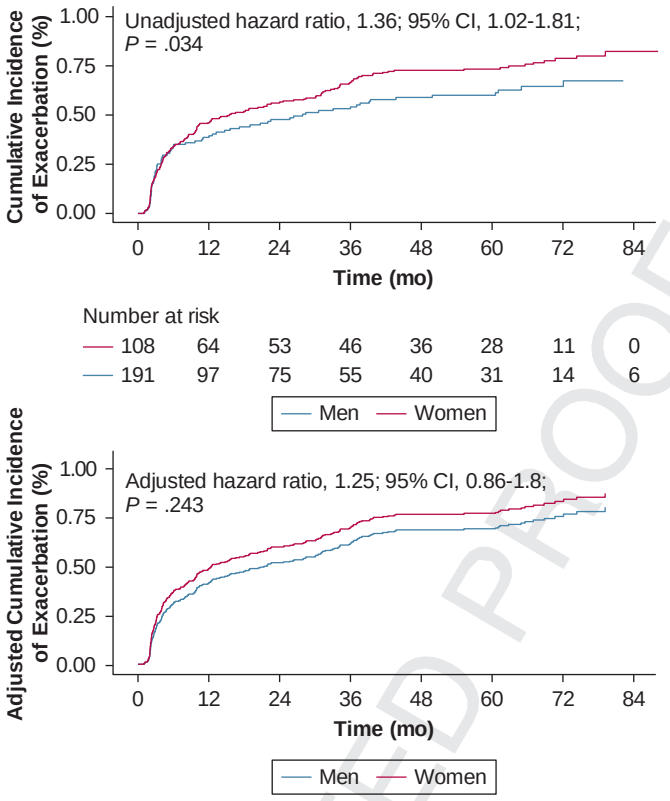

Figure 3 – *Cumulative incidence of exacerbation based on gender until the last available follow-up. Adjusted cumulative incidence of exacerbation is adjusted for age, BMI, positive airway pressure adherence, apnea-hypopnea index, diabetes, hypertension, and smoking status. HR ¼ hazard ratio.*

Results

Prospective Cohort of the Pickwick Study's Ambulatory Patients

Of the 375 patients who met inclusion criteria, 56 were excluded and 19 were early withdrawals (Fig 1), and the remainder were followed up within their respective treatment arms for a minimum of 36 months. This final cohort consisted of 300 patients, of whom 192 (64.0%) were female. Tables 1 and 2 summarize the baseline characteristics and echocardiographic and polysomnographic parameters prior to treatment assignment. Results of the bivariate analysis show that women were older, more obese, and had worse exercise tolerance and worse quality of life, in addition to having a higher prevalence of diabetes and hypertension. Regarding hemodynamics and echocardiographic data, no baseline difference was found between genders for systolic BP, pulmonary hypertension, pulmonary

TABLE 5] International Hospitalized Cohort: Baseline Patient Characteristics, Therapeutics, and Outcomes

	Women (n ¼ 676)	Men (n ¼ 486)	Total (N ¼ 1,162)	*P* Value
			66 (56.2-74.9)	< .001
BMI, kg/m²	43.3 (38.6-46.9)	41.6 (37-46.4)	42.5 (37.8-46.7)	.051
PAP therapy at discharge[a]	581 (85.9%)	462 (95.1%)	1043 (89.8%)	< .001
			44 (3.8%)	.009
6-month mortality	58 (8.9%)	18 (3.9%)	76 (6.8%)	.001
			106 (9.5%)	.013
12-month mortality	101 (15.4%)	38 (8.2%)	139 (12.4%)	< .001

Quantitative variables are described as median (interquartile range) depending on the normality of the variable. Qualitative variables are described as absolute frequency (relative frequency). PAP ¼ positive airway pressure (noninvasive ventilation [NIV] or CPAP).
[a]Overall, 91% of patients were discharged on NIV. The final home NIV settings were not available.

TABLE 6] International Hospitalized Cohort: Gender Stratified According to PAP

Mortality	Women (n ¼ 676)			Men (n ¼ 486)		
	Discharged on PAP (n ¼ 581)	Discharged Not on PAP (n ¼ 95)	Relative Risk Ratio (95% CI)	Discharged on PAP (n ¼ 462)	Discharged Not on PAP (n ¼ 24)	Relative Risk Ratio (95% CI)
3 months	15 (2.58%)	19 (20%)	0.13 (0.07-0.25)[a]	9 (1.95%)	1 (4.17%)	0.47 (0.62-3.54)
6 months	33 (5.68%)	25 (26.3%)	0.22 (0.13-0.35)[a]	16 (3.46%)	2 (8.33%)	0.42 (0.10-1.70)
9 months	45 (7.75%)	29 (30.5%)	0.25 (0.17-0.38)[a]	30 (6.50%)	2 (8.33%)	0.78 (0.20-3.07)
12 months	66 (11.4%)	35 (36.8%)	0.31 (0.22-0.44)[a]	35 (7.58%)	3 (12.5%)	0.61 (0.20-1.83)

PAP ¼ positive airway pressure (noninvasive ventilation or CPAP).
[a]Indicates significance at 99% level.

systolic artery pressure, or left ventricular ejection fraction. However, women had worse right ventricular function based on a longer right ventricular index performance (Tei index). The worse right ventricular function was likely due to worse left ventricular diastolic function (ie, lower E/A ratio, higher deceleration time). On baseline polysomnograms, men had more severe OSA (median AHI, 69.8 events per hour vs 32.4 events per hour) and, consequently, a higher arousal index and more hypoxemia during sleep. The duration of non-rapid eye movement stage 3 (N3 or slow wave sleep) was higher in women. However, women expressed worse sleep quality according to responses on the Functional Outcomes of Sleep Questionnaire.

Table 3 presents therapeutics and unadjusted outcomes at either 36 months or until last follow-up, stratified according to gender. There were no gender differences in adherence to PAP (CPAP or NIV) therapy when the data were limited to the 252 patients who were allocated to CPAP or NIV (ie, after excluding 48 patients allocated to lifestyle intervention). However, adherence to PAP therapy was lower in women when the entire cohort of 300 patients were included and patients without severe OSA (40 women and 8 men) who were allocated to lifestyle intervention (ie, no PAP therapy) were assigned a PAP adherence of 0 hours per day. The degree of improvements in Pa_{O_2}, Pa_{CO_2}, systolic BP, proportion with pulmonary hypertension, and sleepiness according to the Epworth Sleepiness Scale were similar between genders at 3 years. Adjusted proportion of women in the unadjusted analysis reached the composite outcome of exacerbations (58.3% vs 48.1%; *P* ¼ .007); the median time to first event in woman was 9.4 months earlier than in men (Table 3). The main driver of the worse composite outcome in women was higher rates of emergency department visits (72.9% vs 48.1%; *P* < .001); the median time to first emergency department visit in woman was 9.4 months earlier than in men. There was trend toward higher rate of hospitalization in women (54.7% vs 45.4%; *P* ¼ .153). However, there was no difference in all-cause mortality.

In the unadjusted model, female gender was associated with a higher risk of the composite outcome of exacerbations (hazard ratio, 1.36; 95% CI, 1.02-1.81). However, there was no significant difference in the composite outcome of exacerbations in the fully adjusted model (Model 5 of Table 4). Figure 3 illustrates the cumulative risk of the composite outcome until the last available follow-up from a fully adjusted model.

Retrospective Cohort of Hospitalized Patients:

Individual patient data were collected for 1,162 patients hospitalized with acute-on-chronic hypercapnic respiratory failure and carrying a diagnosis of known or suspected OHS. For the entire retrospective cohort, the majority of patients were women (58.2%). Table 5 summarizes the results of bivariate analysis for patient characteristics and outcomes according to gender. At baseline, women were older, more obese, and had more severe OHS

longitudinal changes in Pa_{O_2}, Pa_{CO_2}, and pulmonary artery systolic pressure over 3 years were not different between men and women (Fig 2).

Regarding the composite outcome of exacerbations (emergency department visits, hospitalizations, and all-cause mortality until last available follow-up), a higher

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Hg)	2.07[a] (1.40-3.07)	1.32 (0.87-2.02)	1.30 (0.85-2.00)	1.20 (0.77-1.85)	1.17 (0.75-1.82)	0.02[a] (0.002-0.29)
		1.06[a] (1.04-1.08)	1.05[a] (1.03-1.07)	1.05[a] (1.03-1.07)	1.04[a] (1.02-1.06)	1.00 (0.97-1.03)
			1.00 (0.97-1.03)	1.00 (0.97-1.03)	1.00 (0.97-1.03)	1.00 (0.97-1.03)
				0.37[a] (0.23-0.58)	0.45[a] (0.28-0.73)	0.46[a] (0.28-0.75)
					1.02[a] (1.01-1.03)	1.02[a] (1.01-1.03)
						1.06[a] (1.02-1.10)
	1,162	1,162	1,157	1,157	1,157	1,157

based on higher baseline Pa_{CO_2}. On discharge, women were less likely to receive PAP therapy. Women had a higher mortality at 3, 6, 9, and 12 months. Discharge without PAP was associated with an overall increased risk of mortality. The association of PAP prescription with reduced mortality was more evident in women at each time point. In men, however, PAP prescription at discharge was not associated with reduced mortality (Table 6).

Table 7 presents the results of logistic regression models exploring the association between gender and 12-month mortality after controlling for covariates of interest. By univariate regression (Model 1), female gender was associated with a two-fold increase in the odds of death at 12 months' postdischarge (OR, 2.07; 95% CI, 1.40-3.07). However, after controlling for age, there was no association between gender and mortality (Model 2). The covariates of age, Pa_{CO_2}, and PAP prescription were significantly associated with mortality (Model 5). A statistically significant interaction was detected between gender and age (Model 6), suggesting that age moderates the effect of gender on 12-month mortality.

The largest contributor to the pooled cohort was derived from a Swedish national database, accounting for 49.3% of the patient-level data.[17] To acknowledge this disproportionate contribution, additional sensitivity analyses were performed. All logistic regression models were reanalyzed without this subgroup and only on this subgroup (data not shown). No change was found in the significance or direction of coefficients after excluding data from the Swedish registry.

Discussion

This is the first and largest study examining the association of gender on clinically important outcomes, including health care resource utilization, in 2 large cohorts of patients with OHS. Our main findings were: (1) for both cohorts, women were older and more obese at the time of presentation; (2) hospitalized women received less prescription for PAP therapy than men upon hospital discharge; and (3) after adjusting for age, no association was found between gender and hospitalizations or death for ambulatory patients or short-term mortality following discharge of hospitalized patients.

Despite geographic differences, our prospective cohort of ambulatory patients from Spain (Pickwick studies) resembles the prospective ambulatory cohort from Saudi Arabia.[16] In both studies, women outnumbered men

higher prevalence of comorbidities such as hypertension and diabetes. Although women with OHS in both

cohorts had a median AHI within the severe OSA range, he prevalence of mild to moderate OSA was much higher in women. 1209

Findings of the international hospitalized cohort were comparable to prior hospitalized OHS cohorts for some patient characteristics. The female prevalence of 58% among the current hospitalized patients with OHS was less than the female prevalence rates of 77% and 64% reported in French and US cohorts, respectively.[20,21] The US cohort was younger (average, 58.4 ± 15.2 years) than our international cohort (median, 66 years [IQR, 56.2-74.9 years]) but had similar BMI and severity of OHS (baseline $Paco_2$ level). The French cohort was similar in age and BMI but had less severe OHS (baseline $Paco_2$, 49 mm Hg [IQR, 47-53 mm Hg]) compared with our cohort (baseline $Paco_2$, 61.5 mm Hg [IQR, 52-72 mm Hg]).

Similar to a prior report,[16] women with OHS in the current study were significantly older than men. It remains unclear whether this finding is due to clinician bias leading to delays in diagnosing OHS in women or gender differences in the pathophysiology of OHS. Gender bias in diagnosis of sleep-disordered breathing has been previously reported in OSA. Epidemiologic data from population-based studies from various countries have reported a 2:1 ratio of OSA in men and women.[13,14,23-28] However, studies enrolling patients from clinics consistently show a higher ratio of men-to-women compared with epidemiologic data, suggesting a gender bias in clinically diagnosing OSA.[15,29,30]

Gender bias in timely diagnosis of OHS is clinically relevant because in contrast to OSA, in which there is a clear male predominance, several studies have reported a higher prevalence of OHS in women.[16,17] Gender differences are even more pronounced in patients with OHS hospitalized for acute-on-chronic hypercapnic respiratory failure, with nearly two-thirds of patients being women.[19-21] Our data also confirmed a higher prevalence of OHS in women in both ambulatory and hospitalized cohorts. Gender bias extends beyond timely diagnosis. In the Swedish national registry, prescription of home NIV was delayed in women despite having worse hypoxemia and hypercapnia compared with men.[17] Our findings confirm that in hospitalized women, despite having a higher baseline $Paco_2$, fewer women were discharged on PAP therapy.

Alternative explanations beyond gender bias may be related to the pathophysiology of OHS. Hormonal theories, centered on leptin and progesterone, are consistently reported in the literature. Leptin resistance has been implicated in the development of OHS.[31,32]

Adipocytes release leptin to reduce appetite, and experimental animal models have also shown that this hormone plays a significant role in upper airway patency, ventilatory function, and hypercapnic ventilatory response. Leptin stimulates respiratory drive and may also protect against airway collapsibility. Hypercapnic patients with obesity have higher serum leptin levels than eucapnic patients with obesity.[32,33] At any level of obesity, serum leptin levels are nearly twice as high in women compared with men ($P < 0.001$).[34,35] As such, it is plausible that leptin resistance with resultant central hypoventilation is more prevalent in women, leading to a higher prevalence of OHS.

Similar to leptin, the hormone progesterone can act as a respiratory simulant and upper airway muscle dilator. These effects of progesterone are so well established that the hormone has even been attempted as a therapeutic in both OSA and OHS.[36-38] An association between OSA and menopause is strongly recognized through large cohort analyses showing an increased odds of OSA with menopause (OR, 2.6; 95% CI, 1.4-4.8) and a 40% to 50% reduction in OSA when using hormone replacement therapy in postmenopausal women.[39,40] This increased risk for OSA, present in 90% of patients with OHS, and loss of progesterone's respiratory stimulation following menopause are hypothesized explanations for the older presentation of OHS in women compared with men.[41] Although we did not collect data on menopause status, the majority of women were older than 60 years (75% in the ambulatory cohort and 76.5% in the hospitalized cohort). These findings are consistent with the Saudi ambulatory study that assessed for menopause status according to patient history and found that menopause was highly prevalent among women with OHS.[16]

On univariate analysis, our data suggest that women with OHS have higher risks for increased health care resource utilization and increased mortality following hospital discharge. However, after adjusting for important covariates, gender was not independently associated with worse outcomes. Among ambulatory patients with OHS in stable chronic hypercapnic respiratory failure, age was a significant predictor of increased risk of exacerbations. In patients with OHS hospitalized for acute-on-chronic hypercapnic respiratory failure, age, baseline $Paco_2$, and discharge without PAP significantly increased 12-month mortality following hospitalization. Age exhibited a particularly strong association with outcomes in both cohorts and is worthy of further examination. In the hospitalized

cohort, age seems to moderate the relationship between gender and 12-month mortality following hospital discharge. This finding suggests an underlying mechanism that may explain the increased short- to medium-term mortality in older women with OHS compared with men.

The current study has several limitations. Both ambulatory and international cohorts include predominantly European and Australian patients, which may limit generalizability to other patient populations. The analysis of ambulatory patients with OHS was performed on a cohort of participants enrolled in 2 randomized clinical trials designed to assess treatment options for patients with OHS. Trial exclusion and inclusion criteria may have resulted in selection bias. For example, patients with OHS with nonsevere OSA (AHI < 30 events per hour) were assigned to either NIV or lifestyle modification. This AHI cutoff was based on the Pickwick study protocol. Consistent with a prior study,[16] women with OHS had significantly lower AHI than men (median AHI, 32.4 events per hour vs 69.8 events per hour); thus, globally, women were disproportionately assigned to lifestyle modification (40 women vs 8 men). Although our analyses controlled for both PAP prescription and adherence, such protocols for treatment assignment can affect generalizability to patients in clinical practice.

The greatest limitations in the analysis of hospitalized patients with OHS pertains to the quality of the original studies that contributed to this cohort. There is concern for selection bias, with few studies enrolling consecutive patients. Similarly, there was great variability in exclusion and inclusion criteria across the studies. The cause of mortality was not well established in most studies. Important covariates that may confound the relationship between gender and mortality in OHS were missing from multiple studies. These include cardiovascular comorbidities, OSA severity, and PAP adherence.

Interpretation

We examined patients with OHS from 2 large cohorts representing complementary clinical contexts: ambulatory and hospitalized patients. Our results show significant gender differences in the presentation and use of PAP therapy for OHS. Despite these findings, in adjusted analyses, gender was not independently associated with health care resource utilization or all-cause mortality. This work represents the first study examining gender effects on important patient-centered long-term clinical outcomes in OHS. Future longitudinal studies are needed to investigate the disparities in diagnosis and treatment of OHS in women.

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