Contents lists available at ScienceDirect

# **Respiratory Medicine**

journal homepage: www.elsevier.com/locate/rmed



**Original Research** 

# Clinical information predicting severe obstructive sleep apnea: A cross-sectional study of patients waiting for sleep diagnostics

Trygve M. Jonassen<sup>a,b,\*</sup>, Bjørn Bjorvatn<sup>a,b,d</sup>, Ingvild W. Saxvig<sup>a,d</sup>, Tomas ML. Eagan<sup>a,c</sup>, Sverre Lehmann<sup>a, c, d</sup>

<sup>a</sup> Centre for Sleep Medicine, Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway

<sup>b</sup> Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

<sup>2</sup> Department of Clinical Science, University of Bergen, Norway

<sup>d</sup> Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen, Norway

ARTICLE INFO ABSTRACT Keywords: Introduction: Obstructive sleep apnea (OSA) is highly prevalent with serious health consequences. Demand for Obstructive sleep apnea diagnostic studies is high, in many countries exceeding capacity. Patient prioritization tools Purpose: The objective of this cross-sectional study was to identify predictors of severe OSA among patients on Age differences waiting lists for sleep studies, to better prioritize time to examinations. Comorbidities in OSA Methods: The sample comprised 3646 patients (30.3% women) referred to a university clinic in Western Norway with suspected OSA. All patients underwent respiratory polygraphy. Severe OSA was defined by an apneahypopnea index  $\geq$ 30. Information on symptoms (snoring, breathing cessations, daytime sleepiness) and medical history was collected with questionnaires, including prior diagnosis of angina, myocardial infarction, stroke, hypertension, depression or diabetes. Blood pressure was measured with thresholds of 90 and 140 mmHg defining diastolic and systolic hypertension. Results: 15.7% had severe OSA. In multivariate logistic regression analysis, factors positively associated with severe OSA were increasing age, male sex, snoring, breathing cessations, BMI  $\geq$  30, diastolic hypertension, selfreported history of hypertension, and self-reported myocardial infarction. A prediction score (range 0-5) devised from 5 of these items (age  $\geq$ 50, snoring, breathing cessations, BMI  $\geq$ 30, and self-reported hypertension) had a sensitivity of 96.2% and a negative predictive value of 97.1% for severe OSA, when a score  $\geq$ 2 was set as cut-off. Conclusions: Based on a prediction score derived from simple, easily available data, patients unlikely to suffer from severe OSA can be identified, and thus facilitate more urgent consideration of patients more likely to have severe OSA.

# 1. Introduction

Obstructive sleep apnea (OSA) is a major public health challenge, affecting a large proportion of the European population. According to recent publications, the prevalence in adults of moderate-to-severe OSA, defined by an apnea-hypopnea index (AHI)  $\geq$  15, is as high as 20–50% [1-3].

Although the diagnostic capacity for OSA in many countries has increased by utilizing home portable respiratory polygraphy (PG) as the diagnostic tool rather than the more time-consuming polysomnography (PSG), many reference centers have long waiting lists, reflecting the increased public health burden of OSA. In Norway, the waiting time for evaluation at a specialist center varies from two to 52 weeks [4]. Adding to this, several Norwegian centers report of waiting times of more than 100 weeks for continuous positive airway pressure (CPAP) titration [5], meaning some patients will have to wait more than two years from referral until treatment is initiated. This is of major concern, since postponed diagnosis and treatment may lead to poorer outcomes, especially in severe OSA patients [6]. Consequently, the prioritizing of referred patients for a diagnostic study should be based on probability of severe OSA rather than a first-come-first-serve routine.

Unfortunately, studies of general populations have found that the relationships between objective indices of disease severity from sleep recordings and the cardinal symptoms of OSA (snoring, observed

https://doi.org/10.1016/j.rmed.2022.106860

Received 2 December 2021; Received in revised form 15 March 2022; Accepted 22 April 2022 Available online 26 April 2022

0954-6111/© 2022 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).



<sup>\*</sup> Corresponding author. Haukeland universitetssykehus, Lungeavdelingen, Postboks 1400, 5021, Bergen, Norway. E-mail address: jotm@helse-bergen.no (T.M. Jonassen).

breathing cessations and excessive daytime sleepiness) are poor [3]. Thus, there is a need for better characterization of factors increasing the pretest likelihood of having OSA for better prioritizing the health services. Patients referred to a specialist center for a sleep study under suspicion of OSA are usually symptomatic and/or have other risk factors, such as morbid obesity, cardiovascular disease, hypertension, depression, or diabetes mellitus [7]. OSA prevalence increases with older age [6,8]. However, several studies have described a very low or non-existent association between OSA, morbidity and mortality in older subjects, indicating that sleep apnea represents a particular entity in seniors compared with the middle-aged [9]. Furthermore, symptoms of sleep apnea, such as snoring and daytime sleepiness, also seem to decline after the age of about 60 years in both women and men [10,11], complicating the selection of patients from primary health care to specialist centers for objective sleep studies. OSA prevalence also varies significantly by sex. Population-based studies have reported male to female ratios ranging from 3:1 to 5:1, whereas in clinical populations it is substantially higher, ranging from 8:1 to 10:1 [12]. This discrepancy indicates considerable under-diagnosis of OSA in women. Women are more likely than men to complain of daytime fatigue, lack of energy, insomnia symptoms, morning headaches, mood disturbances and nightmares, and are less likely to report snoring or witnessed apneas [13]. This "atypical" presentation might explain why sleep apnea often remains undiagnosed in women [14]. Even though standardized screening check lists and questionnaires may be useful to identify high-risk patients [15], most GPs use their clinical experience, otherwise unaided, in deciding when to refer for a diagnostic procedure [16].

The Centre for Sleep Medicine, Department of Thoracic Medicine, Haukeland University Hospital examines about 1000 new patients annually on suspicion of OSA. Since 2011, pre- and post-test data on all consenting patients referred with suspected OSA has been collected in a register. Taking advantage of this database, the aim of the current study was to use the pre-test information to identify predictors of severe OSA among patients on waiting lists. We hypothesized that all clinical predictors would have a weaker relationship with severe OSA in older compared to younger patients, and in women compared to men.

# 2. Methods

# 2.1. Study design

In this cross-sectional study, we examined data collected from patients referred to our sleep clinic between 2011 and 2016 with suspicion of OSA. All consenting patients (n = 3770) with suspected sleep apnea were recruited. Exclusion criteria were insufficient diagnostic data from polygraphy (n = 124), leaving 3646 patients for further analyses. Fewer than 10% of the referred patients refused to participate in the study.

# 2.2. Measurements

Information about prior medical history and symptoms suggestive of OSA was collected using questionnaires.

Questions included self-reported hypertension, myocardial infarction, stroke, angina pectoris, diabetes, and depression. All questions had the same phrasing: "Have you ever been diagnosed with (condition)?"

OSA symptoms were assessed by three items from the Karolinska Sleep Questionnaire: snoring, breathing cessations during sleep (as observed by others) and fatigue or sleepiness at work or during leisure time. For each item, there were five optional answers to describe how often one has experienced this symptom during the last three months ("never", "rarely", "sometimes", "mostly" or "always"). As "I do not know" is not among the predefined options on this questionnaire, it might be difficult for some patients to provide answers to all of these questions. This is particularly relevant to the questions about snoring and breathing cessations, as knowledge of this relies on observations made by others. Thus, data were only considered missing if all three of the questions on OSA symptoms were left unanswered. Missing answers to one or two of these questions were recoded to "never". Further, answers were dichotomized by recoding "mostly" and "always" to "yes", and "sometimes", "rarely" and "never" to "no".

All patients' height and weight were measured, from which the body mass index (BMI) was calculated. A trained nurse measured blood pressure (BP) with a machine reader after the patients had been sitting for 10 min. Two recordings were taken, and the second recording was selected. Diastolic hypertension was defined as a diastolic BP of at least 90 mmHg, and systolic hypertension was defined as a systolic BP of at least 140 mmHg.

All patients (n = 3646) included in our analyses successfully underwent a PG sleep recording, using a portable type 3 device (Embletta or Nox). These recordings were scored in accordance with the 2007 American Academy of Sleep guidelines, using desaturations of 4% or more to define hypopnea. OSA severity was determined from the apnea-hypopnea index (AHI); no OSA if AHI <5, mild if AHI between 5 and 14.9, moderate if AHI between 15 and 29.9, and severe if AHI  $\geq$ 30.

## 2.3. Statistical analyses

Bivariate analyses were performed for different categorical explanatory variables with OSA severity in three categories (AHI < 15 = no ormild OSA; AHI 15–29.9 = moderate OSA; AHI > 30 = severe OSA) as the outcome variable, using two-sided Chi square tests to determine significance. To further explore how symptoms and comorbidities were related to AHI cut-offs of 15 and 30, multiple logistic regression analyses were performed. Age, sex, BMI and symptoms of OSA were included as adjusting variables in all analyses, but due to possible collinearity between the different comorbidities, including diastolic and systolic hypertension, these were entered separately. To test the effects of age and sex on these relationships, interaction analyses were performed for all explanatory variables. Receiver-operator characteristic (ROC) curves were constructed from variables associated with severe OSA, to assess their combined predictive utility. Based on results from ROC analysis, a prediction scoring model was devised, and predictive parameters (sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV)) for different score cut-offs were calculated. Statistical analyses were done in SPSS 26, except for the interaction analyses which were performed using the *effmenu2* function in Stata 12. Statistical significance was set to 5% for all analyses.

## 3. Results

Characteristics of the study population stratified by sex are summarized in Table 1. In total, 69.7% of the patients were men (p < 0.001) and the mean age of the population was 49 years (SD = 13.4). Compared to men, women were older and less frequently reported snoring and breathing cessations, but more frequent daytime sleepiness. There was no sex difference in measured BMI, or in the occurrence of self-reported hypertension, stroke, angina pectoris, and diabetes. BP measurements consistent with hypertension (both diastolic and systolic), and a history of myocardial infarction were more common in men than in women, whereas women were more likely than men to report a history of depression. PG sleep recordings were within normal range (AHI <5) in 35.1% of the patients. 31.9% had mild OSA, 17.3% had moderate OSA, and 15.7% had severe OSA. Women had PG readings consistent with no OSA more often than men, whereas moderate/severe OSA was significantly more common in the male population.

Bivariate analyses are presented in Table 2. Moderate and severe OSA was more common with increasing age and among male patients. Two of the symptoms (snoring, breathing cessations), all measurements (diastolic and systolic hypertension, BMI), and four of the self-reported comorbidities (hypertension, myocardial infarction, angina, diabetes) were more common in more severe OSA. Self-reported depression correlated negatively to OSA severity, whereas no relationship was

#### Table 1

	Women $n = 1103$	$Men \; n = 2543$	$p^*$
Age – yrs	$50.6 \pm 14.0$	$\textbf{48.5} \pm \textbf{13.1}$	< 0.01
Symptoms of OSA - no. (%)			
Snoring	793 (73.2)	2153 (85.6)	< 0.01
Breathing cessations	353 (32.6)	1291 (51.3)	< 0.01
Daytime sleepiness	827 (76.4)	1806 (71.8)	< 0.01
Measurements			
BMI - Median (Range)	28.7 (16.7-64.2)	28.7	0.38
		(17.4–70.3)	
Diastolic hypertension - no.	169 (16.8)	634 (27.1)	< 0.01
(%)			
Systolic hypertension - no. (%)	273 (27.1)	854 (36.5)	< 0.01
AHI - no. (%)			
<5	514 (46.6)	766 (30.1)	< 0.01
5–14.9	364 (33.0)	799 (31.4)	
15–29.9	137 (12.4)	494 (19.4)	
$\geq$ 30	88 (8.0)	484 (19.0)	
Comorbidities - no. (%)			
Hypertension	358 (33.9)	870 (35.3)	0.42
Myocardial infarction	27 (2.5)	159 (6.5)	< 0.01
Stroke	22 (2.1)	66 (2.7)	0.26
Angina pectoris	35 (3.4)	95 (4.0)	0.44
Diabetes	99 (9.3)	209 (8.5)	0.42
Depression	378 (36.2)	493 (20.2)	< 0.01

BMI, body mass index; AHI, apnea hypopnea index.

\*Chi-Square test for all variables except Age (independent samples T-test) and BMI (Mood's median test).

#### Table 2

Polygraphy results by age, sex, symptoms, clinical measurements or comorbidities in 3646 patients with suspicion of OSA.

	AHI <15		$\begin{array}{c} 15 \leq \\ < 30 \end{array}$	AHI	AHI ≥30		<i>p</i> *
	n	% <sup>a</sup>	n	% <sup>a</sup>	n	% <sup>a</sup>	
Age							
<40 yrs.	736	85.6	56	6.5	68	7.9	$<\!0.01$
40–59 yrs.	1259	65.5	364	19.0	297	15.5	
$\geq$ 60 yrs.	448	51.7	211	24.4	207	23.9	
Sex							
Women	878	79.6	137	12.4	88	8.0	$<\!0.01$
Men	1565	61.5	494	19.4	484	19.0	
Symptoms of OSA							
Snoring	1886	78.3	540	86.5	520	91.9	$<\!0.01$
Breathing cessations	926	38.5	321	51.4	397	70.1	$<\!0.01$
Daytime sleepiness	1792	74.4	439	70.4	402	71.0	0.06
Measurements							
BMI $\geq$ 30	817	34.3	247	40.2	359	64.2	$<\!0.01$
DBP $\geq$ 90 mmHg	440	19.8	165	28.1	198	36.8	$<\!0.01$
SBP $\geq 140 \text{ mmHg}$	659	29.6	235	40.0	233	43.2	< 0.01
Comorbidities							
Hypertension	692	29.4	251	40.9	285	51.4	< 0.01
Myocardial infarction	90	3.8	39	6.4	57	10.3	< 0.01
Stroke	50	2.1	20	3.3	18	3.4	0.10
Angina	71	3.1	28	4.7	31	5.7	< 0.01
Diabetes	171	7.3	69	11.2	68	12.3	< 0.01
Depression	636	27.3	126	20.9	109	19.7	< 0.01

\*Chi-Square test.

BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

<sup>a</sup> Column percentages presented for all explanatory variables except Age and Sex, presented by row percentages.

### found between OSA and a history of stroke.

In the multivariate analyses, older age, male sex, two of the OSA symptoms (snoring, breathing cessations during sleep), and clinical measurements of BMI  $\geq$ 30 and diastolic BP  $\geq$  90 mmHg were all associated with OSA for AHI cut-offs of both 15 and 30 (Table 3). Systolic hypertension was only associated with OSA for an AHI cut-off of 15. Of the self-reported co-morbidities, only hypertension correlated positively

with OSA when an AHI cut-off of 15 was applied; for an AHI cut-off of 30 both hypertension and a history of myocardial infarction were associated with OSA. Depression remained negatively correlated with OSA for an AHI cut-off of 15, but not for an AHI cut-off of 30 (Table 3).

Interaction analyses between age and all other explanatory variables were statistically significant for sex, breathing cessations, measurements of a BMI  $\geq$ 30 and a systolic BP  $\geq$  140 mmHg, and self-reported hypertension, when an AHI  $\geq$ 15 was the outcome variable (Table 4). For AHI  $\geq$ 30 as an outcome, statistically significant interactions were found between age and breathing cessations and BMI, with both variables conferring more than a two-fold risk of OSA in patients below 40 years of age, compared to in patients aged 60 years and higher (Table 4). Interaction analyses between sex and explanatory variables other than age returned statistically insignificant results.

Based on the above findings, we wanted to create a simple-to-use prediction score for clinical practice.

A predicted probability variable generated from age, sex, symptoms of snoring and breathing cessations, BMI, and self-reported hypertension discriminated well between patients with an AHI  $\geq$ 30 and patients with an AHI <30 (Fig. 1). Adding self-reported myocardial infarction to the regression model did not significantly improve the area under the curve (AUC) of the ROC curve. Diastolic hypertension, although associated with severe OSA, was not included, as the purpose of this analysis was to examine the predictive properties of easily available data usually included in referrals for sleep studies.

A clinical prediction model for severe OSA was developed, based on the presence or absence of six items associated with severe OSA, with each item assigned a score of either 0 or 1, making a total score ranging from 0 (no items present) to 6 (all items present). The items included in the model were age  $\geq$ 50 years, male sex, snoring, breathing cessations, BMI  $\geq$ 30, and self-reported hypertension. Overall, this model had a sensitivity of 94.0% and NPV of 96.8% for severe OSA when a score  $\geq$ 3 was set as cut-off, but analyses stratified by sex revealed sensitivities of 82.7% and 95.9% in women and men, respectively. By removing male sex from the items included in the score, and thus ending up with a score ranging from 0 to 5, the sensitivity for severe OSA in women improved to 97.5%, with a score  $\geq$ 2 as cut-off. The predictive properties of this model are presented in Table 5.

## 4. Discussion

The main findings of this study were that older age, male sex, symptoms of snoring and breathing cessations, an elevated BMI, and hypertension (both reported and measured) were all strong predictors of severe OSA in a sleep clinic population. A score calculated from five of these variables (age  $\geq$ 50 years, snoring, breathing cessations, BMI  $\geq$ 30 and self-reported hypertension) had a high sensitivity and NPV for severe OSA, when a score  $\geq$ 2 was set as cut-off. Consequently, a diagnosis of severe OSA is unlikely in patients positive for less than two of the aforementioned predictors. Breathing cessations and elevated BMI had weaker associations with severe OSA in patients aged 60 or higher, compared to the younger segment of the study population. Sex, however, did not significantly impact any of the predictors' relationships to severe OSA. For self-reported daytime sleepiness and co-morbid depression, trends for negative associations to severe OSA were found.

The major strength of the study was a large sample size, allowing for precision in estimates. Another asset was the ample collection of objectively measured data, such as height and weight, blood pressure, and PG sleep recordings.

There were some limitations to the study. Firstly, OSA was diagnosed by PG and not PSG, leading to underestimation of the AHI. Secondly, former guidelines were applied in PG scoring, using desaturations of 4% to define hypopneas. Consequently, the occurrence of severe OSA probably was significantly lower than it would have been if PGs had been scored according to current guidelines. Thirdly, information about comorbidities was not collected from health records, but obtained via

#### Table 3

Crude and adjusted<sup>a</sup> odds ratios for having OSA as defined by AHI cut-offs of 15 and 30.

	$AHI \geq \!\! 15$				$AHI \geq \!\! 30$			
	Crude OR	95% CI	Adjusted OR	95% CI	Crude OR	95% CI	Adjusted OR	95% CI
Age								
<40	1		1		1		1	
40-59	3.12	2.52 - 3.85	2.96	2.36 - 3.71	2.13	1.62 - 2.81	1.89	1.41-2.55
$\geq 60$	5.54	4.39-6.99	6.81	5.28-8.78	3.66	2.73-4.90	4.31	3.13-5.95
Sex								
Women	1		1		1		1	
Men	2.44	2.06 - 2.88	2.61	2.16-3.14	2.71	2.13-3.44	2.64	2.03-3.44
Symptoms of OSA								
Snoring	2.26	1.84 - 2.77	1.76	1.39-2.23	2.82	2.06-3.87	1.86	1.31-2.65
Breathing cessations	2.44	2.11 - 2.81	1.97	1.67 - 2.31	3.36	2.77-4.08	2.71	2.19-3.36
Daytime sleepiness	0.83	0.71-0.97	0.85	0.72 - 1.01	0.88	0.72 - 1.07	0.84	0.67-1.04
Measurements								
BMI $\geq$ 30	2.04	1.77 - 2.36	2.24	1.92 - 2.62	3.26	2.70-3.94	3.65	2.98-4.47
DBP $\geq$ 90 mmHg	1.93	1.64-2.27	1.58	1.32 - 1.89	2.12	1.74-2.58	1.72	1.39-2.15
SBP $\geq 140 \text{ mmHg}$	1.69	1.45-1.96	1.20	1.01 - 1.42	1.63	1.35-1.97	1.13	0.92-1.40
Comorbidities								
Hypertension	2.03	1.76 - 2.35	1.28	1.09 - 1.52	2.27	1.89 - 2.72	1.46	1.18 - 1.80
Myocardial infarction	2.26	1.68-3.04	1.23	0.89-1.71	2.51	1.81 - 3.48	1.54	1.07 - 2.22
Stroke	1.59	1.03-2.43	0.98	0.61 - 1.57	1.43	0.85-2.42	0.95	0.53 - 1.68
Angina	1.71	1.20-2.43	0.98	0.66-1.45	1.70	1.12 - 2.57	1.08	0.68 - 1.71
Diabetes	1.70	1.34-2.15	1.14	0.87-1.49	1.60	1.20-2.13	1.06	0.76-1.46
Depression	0.68	0.57-0.81	0.78	0.65-0.95	0.70	0.56-0.88	0.83	0.65 - 1.07

BMI = body mass index, DBP = diastolic blood pressure, SBP = systolic blood pressure.

<sup>a</sup> Adjusting variables were age, sex, symptoms of OSA, and BMI. The other explanatory variables were added separately.

#### Table 4

Interaction analyses by age: Adjusted<sup>a</sup> odds ratios for having OSA as defined by AHI cut-offs of 15 and 30.

	$AHI \ge 1$	5					AHI≥30							
	<40 yrs.		40-59yrs.		$\geq$ 60yrs.		<40yrs.		40-59yrs.		$\geq$ 60yrs.			
	OR	95% CI	OR	95%CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI		
Sex														
Women	1 1 1							No significant interaction						
Men	3.29	1.76-6.16	3.24	2.49-4.21	1.79 1.32-2.43									
Symptoms of OSA														
No breathing cessations	No sigi	No significant interaction							1		1			
Breathing cessations							3.34	1.98-5.86	3.53	2.61-4.76	1.63	1.14 - 2.34		
Measurements														
BMI<30	1		1		1		1		1		1			
BMI≥30	4.11	2.71-6.24	2.15	1.76 - 2.63	1.76	1.30 - 2.39	6.18	3.41 - 11.20	3.94	2.98 - 5.20	2.66	1.88 - 3.76		
SBP<140 mmHg	1		1		1		No significant interaction							
SBP≥140 mmHg	1.58	1.00-2.49	1.32	1.06 - 1.65	0.88	0.65 - 1.20	-							
Comorbidities														
No hypertension	1		1		1		No significant interaction							
Hypertension	2.45	1.46-4.09	1.31	1.06-1.62	1.14	0.85–1.53								

BMI, body mass index; SBP, systolic blood pressure.

<sup>a</sup> Adjusting variables were age, sex, symptoms of OSA and BMI.

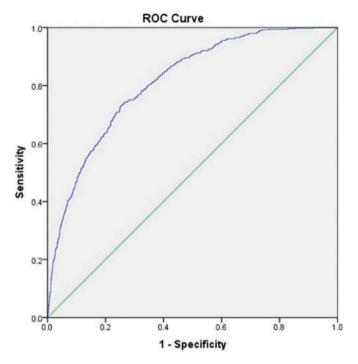
self-reports, thereby introducing possible recall bias.

The predictors of severe OSA in this study are in line with previously published reports as multiple studies have found OSA to be associated with increasing age, male sex, symptoms of snoring and breathing cessations, elevated BMI, and hypertension [17].

The score calculated from the presence or absence of these items performed well in identifying patients unlikely to suffer from severe OSA. No previous study on exactly this prediction model has been published, but our results are comparable and non-inferior to data published on other clinical prediction tools. A recent meta-analysis, comparing four commonly used screening tools for OSA, the Berlin questionnaire, STOP-BANG questionnaire (SB), STOP questionnaire and Epworth sleepiness scale (ESS), found the SB to be the most accurate tool for detecting OSA, with sensitivity and specificity levels of 93% and 35% for severe OSA [18]. SB consists of eight dichotomous items (snoring (S), tiredness (T), observed apneas (O), high blood pressure (P), BMI (B), age (A), neck circumference (N), gender (G)) and was originally validated for use by anesthetists to screen surgical patients preoperatively [19],

but has since also been widely used in sleep clinics. In a meta-analysis of nine studies from sleep clinic populations, the pooled sensitivity of a SB score  $\geq$ 3 to predict severe OSA was 96%, and the corresponding NPV was 90% [20]. In fact, a recent study of a sleep clinic population in South Korea found that excluding tiredness and neck circumference, and thus only assessing six items, of which five were the same as the items constituting the prediction tool developed in our study, did not affect the screening performance of the questionnaire [21]. In our opinion, the prediction score developed in our study offers a clear advantage over the SB in that it consist of only five items, and information on these is usually provided in referrals for diagnostic evaluation of OSA.

Finding no association between self-reported daytime sleepiness and severe OSA will perhaps be surprising to many, as daytime sleepiness is a common symptom in patients with OSA. Of note, in the present study sleepiness/tiredness was only assessed with a single question, and not by use of a more elaborate questionnaire. An earlier investigation of sleepiness in a subset of the same study population found a positive relationship between OSA severity and sleepiness, when sleepiness was



**Fig. 1.** Receiver operator curve: A predicted probability variable discriminating between patients with and without severe OSA, as defined by an apneahypopnea index above and below 30. Predicted probability variable calculated from regression model including age, sex, snoring, breathing cessations, BMI and self-reported hypertension. AUC 0.81.

assessed using ESS [22]. The ESS was not utilized in the present study, as the main purpose was to identify easily available information predictive of OSA, and a questionnaire like the ESS was considered too cumbersome for use by GPs. The results from the present study are, nevertheless, supported by several earlier reports, with sleepiness being neither specific nor sensitive to the diagnosis of OSA. Firstly, in a large community sample, Bixler et al. [23] identified the following risk factors for sleepiness in descending order: depression, obesity, increasing age, sleep duration, diabetes, smoking, and severity of OSA. Secondly, in developing a simplified screening questionnaire for OSA, Chai-Coetzer et al. [24] found no relationship between excessive daytime sleepiness and OSA. Although daytime sleepiness might not be predictive of severe OSA, it is an important factor to take into account when making treatment decisions, as sleepy OSA patients are more likely than non-sleepy patients to respond and adhere to CPAP [25].

Depression, like OSA, is a common disorder with a prevalence in the adult Norwegian population of about 10% [26]. The prevalence of depression in the study population was substantially higher than in the general population, as 23% of the patients reported ever having been diagnosed with depression. Analyses revealed no positive correlations between depression and OSA, but rather the contrary in that increasing OSA severity was associated with reduced prevalence of depression. In a previous study from our research group, the negative correlation between depression and OSA severity in these patients was also evident when depression was assessed using the Hospital Anxiety and Depression Scale questionnaire [27]. Although a positive association between depression and OSA has been suspected, most studies have failed to demonstrate its existence [28,29]. A possible explanation to the high prevalence of depression in sleep clinic populations could be the aforementioned strong association between depression and daytime sleepiness [23].

According to the study hypothesis, we expected to find that predictors of severe OSA would have weaker relationships in older compared to younger adults, and in women compared to men. However, only two of the predictors (breathing cessations and BMI) had an agedependent relationship to severe OSA, and none of the predictors were found to interact with sex and severe OSA. A possible explanation to the finding that breathing cessations confer a larger risk of severe OSA in younger compared to older adults, could be that older people are more likely to live alone, something that was not adjusted for in the analysis. The finding of obesity being more common in middle-aged than in older OSA patients, confirmed the results of a recent study [30]. As to the reason why age- and sex-dependent relationships to severe OSA were not found for more of the predictors, this probably relies on the selection of the study population, which consisted of patients referred mainly by GPs on the basis of classic symptoms of OSA. Thus, women with atypical symptoms and older adults with little or no symptoms were probably under-considered for referral.

Past studies have reported that long waiting times for evaluation of sleep apnea is an international problem [31]. More recent statistics from Norway show considerable delay both from referral to diagnostic evaluation for OSA, and from a diagnosis of OSA is made until CPAP treatment is initiated [4,5]. Further increases to these waiting times can be

### Table 5

The predictive properties of an OSA score\* in detecting severe OSA in 3456 patients referred for diagnostic respiratory polygraphy: The absence or presence of severe OSA for OSA score cut-offs of 1, 2, 3 and 4 in different age strata and in total study population.

	<40 yrs.				40–59 yrs.			$\geq$ 60 yrs.				Total				
	AHI<30		0 AHI≥30		AHI<30 AHI≥3		30 AHI<30		30	AHI≥30		AHI<30		AHI≥30		
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
OSA score <1	90	12.2	1	1.6	52	3.3	0	0.0	0	0.0	0	0.0	142	4.9	1	0.2
OSA score $\geq 1$	650	87.8	60	98.4	1504	96.7	288	100.0	613	100.0	198	100.0	2767	95.1	546	99.8
PPV (%)	8.5				16.1				24.4				16.5			
NPV (%)	98.9				100.0				no val	ue			99.3			
OSA score <2	371	50.1	4	6.6	301	19.3	10	3.5	43	7.0	7	3.5	715	24.6	21	3.8
OSA score $\geq 2$	369	49.9	57	93.4	1255	80.7	278	96.5	570	93.0	191	96.5	2194	75.4	526	96.2
PPV (%)	13.4				18.1				25.1				19.3			
NPV (%)	98.9				96.8				86.0				97.1			
OSA score <3	620	83.8	25	41.0	799	51.3	55	19.1	180	29.4	25	12.6	1599	55.0	105	19.2
OSA score $\geq 3$	120	16.2	36	59.0	757	48.7	233	80.9	433	70.6	173	87.4	1310	45.0	442	80.8
PPV (%)	23.1				23.5				28.5				25.2			
NPV (%)	96.1				93.6				87.8				93.8			
OSA score <4	725	98.0	51	83.6	1270	81.6	159	55.2	422	68.8	77	38.9	2417	83.1	287	52.5
OSA score $\geq 4$	15	2.0	10	16.4	286	18.4	129	44.8	191	31.2	121	61.1	492	16.9	260	47.5
PPV (%)	40.0				31.1				38.8				34.6			
NPV (%)	93.4				88.9				84.6				89.4			

PPV, positive predictive value; NPV, negative predictive value.

\*OSA score calculated from the presence or absence of age  $\geq$ 50 yrs, snoring, observed apneas, BMI  $\geq$ 30, and hypertension, range 0–5.

expected as a consequence of the ongoing Covid-19 pandemic, underscoring the need for improved health prioritization.

To conclude, by applying the prediction score devised from pretest data in this study, patients referred under suspicion of OSA with a negative score are unlikely to have severe OSA and thus should be considered for less urgent diagnostic evaluation than patients with a positive score. However, we would advise this score to be used as a supplement to, rather than a replacement for, clinical judgement, when prioritizing referrals for sleep diagnostics, as OSA is a multidimensional disorder and its severity is dependent on several factors, not just the AHI.

## Funding

This study received no funding.

### No conflicts of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

## Ethical approval

The study was conducted in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments, and was approved by the regional ethics committee of Western Norway (REK-Vest) with case number 2014/1060.

## Informed consent

Written informed consent was obtained from all patients included in the study.

## CRediT authorship contribution statement

**Trygve M. Jonassen:** Formal analysis, Writing – original draft, Writing – review & editing. **Bjørn Bjorvatn:** Supervision, Writing – review & editing. **Ingvild W. Saxvig:** Data curation, Writing – review & editing. **Tomas ML. Eagan:** Supervision, Writing – review & editing. **Sverre Lehmann:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

We wish to confirm that there are no conflicts of interest associated with the enclosed manuscript and there has been no significant financial support for this work that could have influenced its outcome.

## References

- K.A. Franklin, C. Sahlin, H. Stenlund, E. Lindberg, Sleep apnoea is a common occurrence in females, Eur. Respir. J. 41 (3) (2013) 610–615, https://doi.org/ 10.1183/09031936.00212711.
- [2] R. Heinzer, S. Vat, P. Marques-Vidal, H. Marti-Soler, D. Andries, N. Tobback, V. Mooser, M. Preisig, A. Malhotra, G. Waeber, P. Vollenweider, M. Tafti, J. Haba-Rubio, Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study, Lancet Respir. Med. 3 (4) (2015) 310–318, https://doi.org/ 10.1016/S2213-2600(15)00043-0.
- [3] E.S. Arnardottir, E. Bjornsdottir, K.A. Olafsdottir, B. Benediktsdottir, T. Gislason, Obstructive sleep apnoea in the general population: highly prevalent but minimal symptoms, Eur. Respir. J. 47 (1) (2016) 194–202, https://doi.org/10.1183/ 13993003.01148-2015.

- [4] Norsk Helsenett, Ventetider for Søvnregistrering, Utredning Av Pustestopp under Søvn (Polygrafi), 2020. May 19, https://minhelse.helsenorge.no/velg-behandlingss ted/behandlinger/ventetider-for?bid=211.
- [5] Norsk Helsenett, Ventetider for Tilpasning Av Cpap, 2020. May 19, https://minhe lse.helsenorge.no/velg-behandlingssted/behandlinger/ventetider-for?bid=285.
- [6] T. Young, L. Finn, P.E. Peppard, M. Szklo-Coxe, D. Austin, F.J. Nieto, R. Stubbs, K. M. Hla, Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort, Sleep 31 (8) (2008) 1071–1078.
- [7] L.J. Epstein, D. Kristo, P.J. Strollo Jr., N. Friedman, A. Malhotra, S.P. Patil, K. Ramar, R. Rogers, R.J. Schwab, E.M. Weaver, M.D. Weinstein, Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults, J. Clin. Sleep Med. 5 (3) (2009) 263–276. Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep M.
- [8] E.O. Bixler, A.N. Vgontzas, T. Ten Have, K. Tyson, A. Kales, Effects of age on sleep apnea in men: I. Prevalence and severity, Am. J. Respir. Crit. Care Med. 157 (1) (1998) 144–148, https://doi.org/10.1164/ajrccm.157.1.9706079.
- S.H. Launois, J.L. Pepin, P. Levy, Sleep apnea in the elderly: a specific entity? Sleep Med. Rev. 11 (2) (2007) 87–97, https://doi.org/10.1016/j.smrv.2006.08.005.
- [10] E. Lindberg, A. Taube, C. Janson, T. Gislason, K. Svardsudd, G. Boman, A 10-year follow-up of snoring in men, Chest 114 (4) (1998) 1048–1055.
- [11] M. Svensson, E. Lindberg, T. Naessen, C. Janson, Risk factors associated with snoring in women with special emphasis on body mass index: a population-based study, Chest 129 (4) (2006) 933–941, https://doi.org/10.1378/chest.129.4.933.
- [12] A. Wimms, H. Woehrle, S. Ketheeswaran, D. Ramanan, J. Armitstead, Obstructive sleep apnea in women: specific issues and interventions, BioMed Res. Int. 2016 (2016) 1764837, https://doi.org/10.1155/2016/1764837.
- [13] M.R. Bonsignore, T. Saaresranta, R.L. Riha, Sex differences in obstructive sleep apnoea, Eur. Respir. Rev. 28 (154) (2019), https://doi.org/10.1183/ 16000617.0030-2019.
- [14] J. Theorell-Haglow, C.B. Miller, D.J. Bartlett, B.J. Yee, H.D. Openshaw, R. R. Grunstein, Gender differences in obstructive sleep apnoea, insomnia and restless legs syndrome in adults - what do we know? A clinical update, Sleep Med. Rev. 38 (2018) 28–38, https://doi.org/10.1016/j.smrv.2017.03.003.
- [15] G.E. Silva, K.D. Vana, J.L. Goodwin, D.L. Sherrill, S.F. Quan, Identification of patients with sleep disordered breathing: comparing the four-variable screening tool, STOP, STOP-Bang, and Epworth Sleepiness Scales, J. Clin. Sleep Med. 7 (5) (2011) 467–472, https://doi.org/10.5664/JCSM.1308.
- [16] J.W. Mold, C. Quattlebaum, E. Schinnerer, L. Boeckman, W. Orr, K. Hollabaugh, Identification by primary care clinicians of patients with obstructive sleep apnea: a practice-based research network (PBRN) study, J. Am. Board Fam. Med. 24 (2) (2011) 138–145, https://doi.org/10.3122/jabfm.2011.02.100095.
- [17] K.A. Franklin, E. Lindberg, Obstructive sleep apnea is a common disorder in the population-a review on the epidemiology of sleep apnea, J. Thorac. Dis. 7 (8) (2015) 1311–1322, https://doi.org/10.3978/j.issn.2072-1439.2015.06.11.
- [18] H.Y. Chiu, P.Y. Chen, L.P. Chuang, N.H. Chen, Y.K. Tu, Y.J. Hsieh, Y.C. Wang, C. Guilleminault, Diagnostic accuracy of the Berlin questionnaire, STOP-BANG, STOP, and Epworth sleepiness scale in detecting obstructive sleep apnea: a bivariate meta-analysis, Sleep Med. Rev. 36 (2017) 57–70, https://doi.org/ 10.1016/j.smrv.2016.10.004.
- [19] F. Chung, B. Yegneswaran, P. Liao, S.A. Chung, S. Vairavanathan, S. Islam, A. Khajehdehi, C.M. Shapiro, STOP questionnaire: a tool to screen patients for obstructive sleep apnea, Anesthesiology 108 (5) (2008) 812–821, https://doi.org/ 10.1097/ALN.0b013e31816d83e4.
- [20] M. Nagappa, P. Liao, J. Wong, D. Auckley, S.K. Ramachandran, S. Memtsoudis, B. Mokhlesi, F. Chung, Validation of the STOP-bang questionnaire as a screening tool for obstructive sleep apnea among different populations: a systematic review and meta-analysis, PLoS One 10 (12) (2015), e0143697, https://doi.org/10.1371/ journal.pone.0143697.
- [21] K.T. Kim, Y.W. Cho, Real-world STOPBANG: how useful is STOPBANG for sleep clinics? Sleep Breath. 23 (4) (2019) 1219–1226, https://doi.org/10.1007/s11325 019-01806-6.
- [22] B. Bjorvatn, S. Lehmann, S. Gulati, H. Aurlien, S. Pallesen, I.W. Saxvig, Prevalence of excessive sleepiness is higher whereas insomnia is lower with greater severity of obstructive sleep apnea, Sleep Breath. 19 (4) (2015) 1387–1393, https://doi.org/ 10.1007/s11325-015-1155-5.
- [23] E.O. Bixler, A.N. Vgontzas, H.M. Lin, S.L. Calhoun, A. Vela-Bueno, A. Kales, Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression, J. Clin. Endocrinol. Metab. 90 (8) (2005) 4510–4515, https://doi.org/10.1210/jc.2005-0035.
- [24] C.L. Chai-Coetzer, N.A. Antic, L.S. Rowland, P.G. Catcheside, A. Esterman, R. L. Reed, H. Williams, S. Dunn, R.D. McEvoy, A simplified model of screening questionnaire and home monitoring for obstructive sleep apnoea in primary care, Thorax 66 (3) (2011) 213–219, https://doi.org/10.1136/thx.2010.152801.
- [25] N. Wolkove, M. Baltzan, H. Kamel, R. Dabrusin, M. Palayew, Long-term compliance with continuous positive airway pressure in patients with obstructive sleep apnea, Cancer Res. J. 15 (7) (2008) 365–369, https://doi.org/10.1155/2008/534372.
- [26] Oslo: Institute of Public Health, Mental Illness Among Adults in Norway, August 8, 2016. Public Health Report - Health Status in Norway [online document], https ://www.fhi.no/en/op/hin/mental-health/psykisk-helse-hos-voksne/.
- [27] B. Bjorvatn, N. Rajakulendren, S. Lehmann, S. Pallesen, Increased severity of obstructive sleep apnea is associated with less anxiety and depression, J. Sleep Res. 27 (6) (2018), e12647, https://doi.org/10.1111/jsr.12647.
- [28] A.S. BaHammam, T. Kendzerska, R. Gupta, C. Ramasubramanian, D.N. Neubauer, M. Narasimhan, S.R. Pandi-Perumal, A. Moscovitch, Comorbid depression in obstructive sleep apnea: an under-recognized association, Sleep Breath. 20 (2) (2016) 447–456, https://doi.org/10.1007/s11325-015-1223-x.

T.M. Jonassen et al.

- [29] S. Garbarino, W.A. Bardwell, O. Guglielmi, C. Chiorri, E. Bonanni, N. Magnavita, Association of anxiety and depression in obstructive sleep apnea patients: a systematic review and meta-analysis, Behav. Sleep Med. 18 (1) (2020) 35–57, https://doi.org/10.1080/15402002.2018.1545649.
- [30] Y.G. Lee, Y.J. Lee, D.U. Jeong, Differential effects of obesity on obstructive sleep apnea syndrome according to age, Psychiatry Investig. 14 (5) (2017) 656–661, https://doi.org/10.4306/pi.2017.14.5.656.
- [31] W.W. Flemons, N.J. Douglas, S.T. Kuna, D.O. Rodenstein, J. Wheatley, Access to diagnosis and treatment of patients with suspected sleep apnea, Am. J. Respir. Crit. Care Med. 169 (6) (2004) 668–672, https://doi.org/10.1164/rccm.200308-1124PP.