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Predicting sleep disordered breathing in outpatients with suspected OSA

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Abstract

Background: Validated predictors of sleep disordered breathing (SDB) are required to streamline sleep services in the face of the obesity epidemic. Berlin, STOP and STOP-BANG questionnaires are useful in other settings, but their ability to predict obstructive sleep apnoea (OSA) in the sleep clinic population is unknown. We considered the utility of these questionnaires, other patient characteristics, co-morbidities, Epworth Sleepiness Scale (ESS), exhaled nitric oxide (F_ENO) and blood markers for the prediction of SDB on limited polygraphy.

Methods: Data was obtained on 129 patients referred with possible OSA. We selected cut-points of apnoea hypopnoea index (AHI) of ≥5 and ≥15 per hour from their home polygraphy and determined associations of these with individual symptoms, questionnaire scores and other results. ROC analysis, univariate and multivariate logistic regression were used to explore these.

Results: AHI was ≥5 in 97 and ≥15 in 56 patients. STOP and STOP-BANG scores were associated with both AHI cut-points but results with ESS and Berlin Questionnaire scores were negative. STOP-BANG had a negative predictive value 1.00 (0.77-1.00) for an AHI ≥15 with a score ≥3 predicting AHI≥5 with sensitivity 0.93 (95%CI 0.84-0.98) and accuracy 79%, whilst a score ≥6 predicted AHI≥15 with specificity 0.78 (0.65-0.88) and accuracy 72%. Neck circumference ≥17in and presence of witnessed apnoeas were independent predictors of SDB.

Conclusions: Both STOP and STOP-BANG questionnaires have utility for the prediction of SDB in the sleep clinic population. Modification of the STOP-BANG questionnaire merits further study in this and other patient groups.

(*Word count 246)*

Strengths and limitations of this study:

Strengths:

- This is the first study to prospectively evaluate the utility of the Berlin, STOP and STOP-BANG questionnaires in the prediction of sleep disordered breathing in the population referred to a sleep service for assessment of possible obstructive sleep apnoea.
- This results of this study show that the STOP and STOP-BANG, but not the Berlin questionnaire, have utility for prediction of sleep disordered breathing in the sleep clinic population.

Weaknesses:

- This study uses home unattended limited sleep studies rather than in-hospital attended full polysomnography, however this is considered standard clinical practice in the UK and is considered an acceptable method for diagnosis of OSA by the American Academy of Sleep Medicine.
- The sample size limits the conclusions that can be drawn from the multivariate analysis, however this was a secondary objective of the study.

Introduction

Obstructive sleep apnoea syndrome (OSAS) is common with prevalence of approximately 4% in middle-aged men and 2% in middle-aged women.(1) Frequent partial (hypopnoea) or complete (apnoea) upper airway collapse during sleep leads to oxygen desaturation, increased respiratory effort, arousal and sleep fragmentation.(2) Patients typically present with witnessed apnoeas, loud snoring and excessive daytime somnolence.(3) The syndrome is associated with impaired quality of life,(4) cognitive functioning and work performance,(5) and with increased risk of road traffic accidents.(6) OSAS is considered an independent risk factor for hypertension,(7) and has associations with coronary disease, stroke, heart failure, arrhythmias,(8) metabolic syndrome(9) and type 2 diabetes.(10)

Despite the substantial burden of this disease, it is under-recognised. One study estimated that 93% of females and 82% of males with moderate-severe OSAS were not clinically diagnosed,(11) and more recent data support this finding.(12) Sleep studies are required for OSAS diagnosis but are expensive and not widely available.(3) Given the recent increases in childhood(13) and adulthood obesity,(14) the workload for sleep clinics and sleep laboratories will increase. Predictors of sleep disordered breathing (SDB) are required to allow recognition of OSAS, and prioritisation of investigations.

Several questionnaires have been designed to screen for SDB in different populations. The Berlin Questionnaire was first validated in primary care against portable unattended sleep studies and a “high risk” score predicted a respiratory disturbance index >5 with sensitivity 0.86, specificity 0.77, positive predictive value 0.89 and likelihood ratio 3.79.(15) It’s utilisation in other populations has been assessed with variable success.(16-22) The STOP and STOP-BANG Questionnaires were originally validated in surgical patients using in-

hospital attended polysomnagraphy.(23) For prediction of apnoea hypopnoea index (AHI) greater than 5, 15 and 30, sensitivities for the STOP and STOP-BANG questionnaires were 65.6, 74.3 and 79.5%, and 83.9, 92.9 and 100%, respectively. The Berlin and STOP questionnaires have been compared in a cohort of surgical patients(24) and the STOP and STOP-BANG questionnaires have been compared in a large study involving several distinct cardiovascular and respiratory disease cohorts.(25) No study has, however, compared these screening tools in a sleep service-referred population. Also, along with changes in the population (i.e. rising obesity rates) there is increasing recognition in primary care, so it is necessary to update and re-evaluate established assessment tools in the face of the evolution in sleep clinic practice.

The objective of this study was, firstly, to compare utility of Berlin, STOP and STOP-BANG questionnaires for prediction of SDB in a population referred to the sleep clinic for assessment of possible OSA. Secondly, we sought to identify the most important variables from these questionnaires and routine sleep clinic assessment that might be utilised in the development of a composite predictive score for future use in this population.

Methods

This was a prospective observational study conducted May-December 2012. The protocol was approved by the West of Scotland Research Ethics Committee. Study participants received an information sheet and provided informed consent. .

Participants

Consecutive patients aged ≥16 years referred to the North Glasgow Sleep Service (a tertiary centre) for assessment of possible OSA were invited to participate.

Measurements

Height, weight, body mass index (BMI), neck circumference, blood pressure and Epworth Sleepiness Scale (ESS)(26) were completed at the Sleep Clinic. Participants attended the Sleep Laboratory on a separate day so that a Sleep Physiologist could provide, and instruct on fitting, a sleep study device. On that occasion, relevant symptoms and co-morbidities were recorded, Mallampatti score was assessed, and the Berlin and STOP-BANG Questionnaires were completed. Blood samples including non-fasting lipid profile, glycated haemoglobin (HbA1c) and C-reactive protein (CRP) were taken. Two fractional exhaled nitric oxide (F_ENO) measurements were taken using the NIOX MINO ® (Aerocrine, Solna, Sweden), and the mean calculated.

Sleep Studies

Unattended home limited polygraphy sleep studies were performed using the SOMNOmedics SOMNOscreen™ kit (Randersacker, Germany) with channels that recorded body position, thoraco-abdominal movements, oronasal airflow, heart rate, pulse oximetry and snoring. Sleep studies scoring by experienced Sleep Physiologists was in accordance with accepted guidelines.(27) An apnoea was defined as cessation of nasal flow for ≥10 seconds, whilst a hypnoea was defined as 50% reduction in nasal flow for ≥10 seconds, or lesser reduction in flow associated with oxygen desaturation of ≥4%.

The Epworth Sleepiness Scale (ESS), Berlin, STOP and STOP-BANG Questionnaires

The ESS is a validated measure of daytime sleepiness including eight questions, each with four possible responses, that assesses the likelihood of dozing in different situations; a score of ≥11/24 denotes excessive daytime somnolence.(26) The Berlin Questionnaire includes

questions in three categories that relate firstly to snoring and witnessed apnoeas, secondly, to tiredness, fatigue and sleepiness, and thirdly, to hypertension and obesity.(15) High risk of OSA is defined by scoring positively in ≥2 categories. The STOP Questionnaire includes four yes/no questions that relate to Snoring, Tiredness, Observed apnoeas and high blood Pressure.(23) High risk of OSA is defined as a score of ≥2. The STOP-BANG Questionnaire includes four additional questions relating to BMI, Age, Neck circumference and Gender, and high risk of OSA is defined as a score of ≥3.(23)

Statistical analyses

Statistical analyses were carried out using GraphPad Prism 5, IBM SPSS Statistics 19 and STATA 12. Normality of data was checked using D'Agostino & Pearson omnibus normality test. A priori, two cut-points were chosen for AHI: ≥5 events/hour (the standard cut-point for the diagnosis of OSA),(28) and ≥15 events/hour, to predict significant SDB (the standard cut-point for initiating continuous positive airway pressure [CPAP] therapy).(28) Groups were compared using unpaired t-tests, Mann-Whitney tests and Fisher's Exact tests as appropriate. Sensitivities, specificities, positive and negative predictive values, positive and negative likelihood ratios, and overall accuracies were calculated for each of the questionnaires for prediction of SDB as defined by AHI cut-points of ≥5 and ≥15. Associations between individual variables and each of the cut-points for AHI were explored using univariate and multivariate logistic regression. For multivariate analysis, in a few cases where BMI was known but neck circumference was not known, a value for the neck circumference was imputed using linear regression with BMI as the independent value. This allowed for a dataset of 116 cases with all of the variables known or imputed to be built to identify independent variables for inclusion in a composite score. Receiver operating characteristic (ROC) curve analysis was used to assess predictive value and an area under the

curve (AUC) >0.7 was considered clinically significant. Data are presented as mean (standard deviation), median (interquartile range) and proportion (percentage), unless stated otherwise. A p value <0.05 was considered statistically significant.

Results

150 subjects participated in this study, of which 129 had adequate sleep study data and were included in the analysis. AHI was ≥5 in 97/129 (75%) and ≥15 in 56/129 (43%). Overall, 82 (64%) were male, mean(SD) age was 49(11) years, and median(IQR) BMI was 32(29-39) kg/m^2.

Predicting SDB: Patient characteristics (See Table 1)

An AHI <5 ("rule-out measurement") was associated with female sex, younger age, lower weight and neck circumference, less frequently reported witnessed apnoeas, higher high density lipoprotein (HDL) cholesterol, and lower triglycerides, cholesterol/HDL and HbA1c. An AHI ≥15 ("rule-in measurement") was associated with male sex, obesity, higher weight, BMI and neck circumference, more frequently reported hypertension and witnessed apnoeas, lower HDL cholesterol, and higher triglycerides, cholesterol/HDL and HbA1c.

Predicting SDB: ESS, Berlin, STOP and STOP-BANG (See Tables 2, 3 and 4)

The ESS and Berlin questionnaire outcomes were not associated with either AHI cut-point. An AHI<5 was associated with lower STOP and STOP-BANG scores, and fewer subjects being classified as "high risk" for OSA by both STOP and STOP-BANG questionnaires. An AHI≥15 was associated with higher STOP and STOP-BANG scores and more subjects being classified as "high risk" for OSA by the STOP-BANG questionnaire but not by the STOP questionnaire.

For the AHI cut-point of ≥5, the Berlin, STOP, and STOP-BANG questionnaires had high sensitivities, moderate positive predictive values (PPV) and poor specificities and negative predictive values (NPV), for prediction of SDB. The STOP-BANG questionnaire performed best with an overall accuracy of 79%. For the AHI cut-point of ≥15, the Berlin questionnaire had high sensitivity, but otherwise performed poorly. The STOP and STOP-BANG questionnaires had high sensitivities and NPVs. Again, the STOP-BANG questionnaire performed best, but with a low overall accuracy of 56%. The low negative likelihood ratios for the STOP and STOP-BANG questionnaires at both cut-points indicate that these questionnaires have value in excluding disease. As shown in table 4, the cut-points for STOP-BANG score that were associated with best overall accuracy were ≥3 and ≥6 for prediction of AHI ≥5 and ≥15, respectively.

SDB versus no SDB: Predictors and a composite score (See Tables 5 and 6 and Figure 1)

For the cut-point of AHI of ≥5, univariate logistic regression showed significant associations for age, gender, weight, neck circumference, witnessed apnoeas, triglycerides and cholesterol/HDL ($p<0.05$). For the cut-point of ≥15, significant associations were found for gender, weight, BMI, neck circumference, witnessed apnoeas, obesity, hypertension, FeNO and cholesterol/HDL ($p<0.05$). Multivariate logistic regression based on the significant variables from univariate logistic regression showed that for both cut-points neck circumference and witnessed apnoeas were independent predictors of SDB. For the cut-point of AHI of ≥5, in a model incorporating neck circumference and witnessed apnoeas, the probability of SDB was 0.94 for individuals with neck circumference ≥17in and witnessed apnoeas (sensitivity 84%, overall accuracy 77%, ROC AUC 0.768, $p<0.001$). For the cut-point of AHI ≥15, the probability of SDB was 0.69 for individuals with neck circumference

≥17in and witnessed apnoeas (specificity 80%, overall accuracy 69%, ROC AUC 0.722, p<0.001).

Discussion

This is the first study to prospectively evaluate the utility of the Berlin, STOP and STOP-BANG questionnaires in prediction of sleep disordered breathing in a population referred to a tertiary sleep service for assessment of possible OSA. We found that in this population the Berlin Questionnaire had no significant association with cut-points of ≥5 or ≥15 for AHI, but that both the STOP and STOP-BANG scores were significantly associated with both cut-points. The STOP-BANG Questionnaire had better performance for the prediction of OSA on home sleep study, and different cut-points for STOP-BANG score could be selected depending on preference to exclude SDB (score <3) or predict SDB (score ≥6). In addition, we found notable associations between sleep study results and several patient characteristics. In particular, neck circumference and witnessed apnoeas were found to be independent predictors of SDB in our population.

In our study, the Berlin Questionnaire was almost ubiquitously positive (116 of 125 participants had a positive result) and the positivity rate did not differ between those with and without SDB. This was expected as this questionnaire was designed for primary care assessment and our study population consisted of individuals referred from primary care with symptoms suggestive of SDB. Our results indicate that the Berlin Questionnaire is not useful in the prediction of SDB in the sleep clinic referral population and this is consistent with previous reports.(19) However, the high sensitivities obtained for both AHI cut-points support previous findings that the Berlin Questionnaire may have a role as a "rule-out"

measurement in the primary care or screening setting(15, 17, 20, 24), though there have been some conflicting results, suggesting it does not have adequate discriminatory power.(16, 22)

In our study Epworth Sleepiness Scale data indicated that two thirds of participants had excessive daytime somnolence (ESS ≥11), however scores were similar in individuals with or without SDB. Therefore, at least in the sleep clinic population, the ESS does not have utility in the prediction of SDB. Nevertheless, it may be clinically useful in other respects - perhaps modified and/or combined with other structured questions, including those highlighted in this study - in prediction of compliance with and benefit from OSA treatment in patients with any degree of SDB. Exhaled nitric oxide levels were not significantly different between individuals with or without SDB whether defined by an AHI cut-point of ≥5 or ≥15. There is conflicting data in the literature regarding whether F_ENO is associated with SDB,(29-32) however our results suggest that it does not have utility in prediction of SDB; further work is required to clarify this.

We found that both the STOP and STOP-BANG questionnaires have utility in the prediction of SDB in the sleep clinic population, and that STOP-BANG was superior, with higher overall predictive accuracy. The STOP and STOP-BANG Questionnaires were developed and validated in a surgical population using in-laboratory polysomnagraphy(23) and have subsequently been studied in a cardiovascular disease population.(25) Our results are in agreement with these two earlier studies as regards the increased predictive value of STOP-BANG over STOP. In contrast to these earlier studies, however, we found sensitivities to be higher and specificities to be lower for both cut-points of AHI. This is as expected given that we were studying a symptomatic cohort referred to a sleep clinic, rather than a screening population, and this is also a desirable outcome for these questionnaires in situations where

missing even mild OSA would be undesirable. The negative likelihood ratios of <0.2 obtained for STOP and STOP-BANG indicate that these questionnaires are likely most useful for predicting low risk of confirming SDB: these may be of future value in combination in the primary care setting, perhaps combined with screening sleep studies, to determine requirement for sleep clinic review and detailed polygraphy.

At the AHI cut-point of ≥15, STOP-BANG had sensitivity and negative predictive value of 100%, and since this is the standard cut-point conventionally used to determine need for CPAP,(28) we suggest that the STOP-BANG questionnaire is the preferred tool for prediction of SDB in the sleep clinic setting of those currently available. STOP-BANG, perhaps with modifications, seems worthwhile for further exploration for the prediction of sleep study findings in a larger cohort and, more importantly, prediction of clinical outcomes including treatment success in symptomatic and screening populations.

The original STOP-BANG questionnaire uses a cut-point of ≥3 to predict SDB.(23) However, in our study we show that different cut-points can be selected depending on the preference to rule-in or rule-out SDB. A score of ≥3 had the highest overall accuracy and a sensitivity of 0.93 for the AHI cut-point of ≥5, whereas a score of ≥6 had the highest overall accuracy and a specificity of 0.78 for the AHI cut-point of ≥15. Two other studies have examined the usefulness of different cut-points for STOP-BANG score.(33-34) In the obese, a score of ≥3 was associated with a sensitivity of 0.90 for predicting an AHI >5, whilst, a score of ≥6 had a specificity of 0.88 for predicting an AHI >15 and similar results were obtained in the morbidly obese(33) and in another surgical population.(34) Thus, in the sleep clinic setting where the ultimate goal is to identify patients requiring CPAP, a higher cut-point

for STOP-BANG may be preferred whereas in a primary care setting where the priority is not to miss disease a lower cut-point may be chosen.

The STOP-BANG questionnaire is, however, still an imperfect tool for prediction of results on home polygraphy. Accordingly, the secondary objective of our study was to identify those variables for inclusion, and how they should be weighted in a locally developed composite score for future validation in the sleep clinic and potentially wider population. Univariate analysis showed several significant, expected associations for both cut-points of AHI. Using multivariate analysis, neck circumference ≥17in and the presence of witnessed apnoeas were independent predictors of SDB. Particularly when SDB was defined by an AHI cut-point of ≥5, the regression model derived indicated a high probability of SDB of 0.94 if both factors were present. The STOP-BANG questionnaire, of course, includes both of these variables, and it is possible that adjustment of the inclusion variables, or their weighting, might improve its performance. In future work, we aim to validate a simple composite score based on these two variables in a modification of the STOP-BANG Questionnaire, to determine utility for predicting sleep study data and outcomes with treatment.

A possible limitation of our study was that SDB was characterised using home unattended limited sleep studies rather that in-hospital attended full polysomnography. The latter is considered the gold standard for diagnosis of SDB but is more expensive, less easily accessed and potentially unrepresentative with sleep in an unfamiliar environment. Home unattended and in-hospital attended sleep studies have previously been shown to produce similar results. (35) Accordingly home testing with portable monitors is standard clinical practice in the UK, and is now considered an acceptable method for diagnosis of OSA by the American Academy of Sleep Medicine.(28) The sample size limits the conclusions that can be drawn from

multivariate analysis, however this was a secondary objective of the current study. It is possible that variables predictive of SDB on univariate analysis in this cohort would have been identified as independently predictive in multivariate models in a larger population. The results of this study allow us, and potentially others, to focus future work to validate more extensively the results obtained to date.

In conclusion, the Berlin Questionnaire was not useful in the prediction of SDB within our sleep clinic population. The STOP-BANG questionnaire had superior predictive performance to the STOP questionnaire at both cut-points of AHI (≥5 and ≥15). A STOP-BANG score of ≥3 had the highest overall accuracy and a sensitivity of 0.93 for the prediction of an AHI≥5, whilst a score of ≥6 had the highest overall accuracy and a specificity of 0.78 for the prediction of an AHI ≥15. Future work will validate a composite score including neck circumference ≥17in and the presence of witnessed apnoeas for the prediction of SDB in the sleep clinic referral population, with possibility then of evaluating in primary care and against treatment outcomes, with our overall aim to provide required tools for use in expanded and consolidated sleep services, given the obesity and OSA epidemics.

Contributorship Statement:

Douglas Cowan took a leading role in study protocol development, study document development, application for ethics approval, data collection, statistical analysis and paper writing.

Gwen Allardice provided statistical support and performed part of the statistical analysis.

Duncan MacFarlane, Darren Ramsay and Heather Ambler contributed to data collection, and carried out and scored sleep studies.

Stephen Banham contributed to study protocol development.

Eric Livingston contributed to study protocol development, study document development, application for ethics approval and paper writing.

Christopher Carlin contributed to study protocol development, data collection, statistical analysis and paper writing.

All authors approved the final draft before submission.

Christopher Carlin is responsible for the overall content as guarantor.

Competing Interest: None to declare.

Additional unpublished data from this study is available on request by email.

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This study was approved by the West of Scotland Regional Ethics Committee.

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Table 1: Comparison of patient characteristics including anthropometric measurements, co-morbidities, symptoms, inflammatory markers, lipid profile and oximetry between groups without and with SDB as defined by AHI <5 events/hour and ≥15 events/hour.

	AHI<5	*AHI≥5*	*p*	*AHI<15*	*AHI≥15*	*P*
Male gender	**15/32 (47%)**	**67/97 (69%)**	**0.034**	**38/73 (52%)**	**44/56 (79%)**	**0.003**
Age (yrs)	**44 (12)**	**51 (11)**	**0.004**	48 (13)	51 (9)	0.103
Weight (kg)	**89 (19)**	**101 (22)**	**0.022**	**92 (21)**	**107 (20)**	**0.001**
BMI (kg/m^2)	31 (28-36)	33 (29-40)	0.118	**31 (27-36)**	**34 (31-41)**	**0.009**
Obesity (BMI≥30 kg/m^2)	18/28 (64%)	61/85 (72%)	0.482	**38/63 (60%)**	**41/50 (82%)**	**0.014**
Neck circumference (in)	**15 (2)**	**17(2)**	**<0.001**	**16 (2)**	**17 (1)**	**<0.001**
Neck circumference ≥17in	**4/22 (18%)**	**45/76 (59%)**	**0.001**	**18/54 (33%)**	**31/44 (70%)**	**<0.001**
Mallampatti	2 (1)	2 (1)	0.192	2 (1)	2 (1)	0.900
SBP (mmHg)	134 (17)	136 (16)	0.480	134 (15)	138 (18)	0.194
DBP (mmHg)	82 (11)	83 (9)	0.528	81 (10)	85 (10)	0.086
Diabetes	2/32 (6%)	6/97 (6%)	1.000	4/73 (5%)	4/56 (7%)	0.727
Hypertension	7/32 (22%)	36/97 (37%)	0.134	**18/73 (25%)**	**25/56 (45%)**	**0.024**
Hyperlipidaemia	2/32 (6%)	18/97 (19%)	0.156	10/73 (14%)	10/56 (18%)	0.625
Loud snorer	28/32 (88%)	92/97 (95%)	0.224	65/73 (89%)	55/56 (98%)	0.077
Witnessed apnoeas	**15/32 (47%)**	**72/97 (74%)**	**0.008**	**40/73 (55%)**	**47/56 (84%)**	**<0.001**
*Nocturia**	11/32 (34%)	38/97 (39%)	0.679	26/73 (36%)	23/56 (41%)	0.585
*Nocturnal wakenings**	18/32 (56%)	65/97 (67%)	0.293	46/73 (63%)	37/56 (66%)	0.853
Nocturnal choking	15/32 (47%)	35/97 (36%)	0.301	28/73 (38%)	22/56 (39%)	1.000
Nocturnal gasping	11/32 (34%)	38/97 (39%)	0.679	26/73 (36%)	23/56 (41%)	0.585
F_eNO (ppb)	15 (12-25)	18 (12-26)	0.595	15 (11-24)	19 (12-27)	0.050
Cholesterol (mmol/L)	5.2 (1.1)	5.4 (1.0)	0.431	5.3 (1.1)	5.4 (0.9)	0.674
HDL cholesterol (mmol/L)	**1.3 (1.0-1.5)**	**1.1 (1.0-1.3)**	**0.008**	**1.2 (1.0-1.4)**	**1.1 (1.0-1.2)**	**0.016**
Triglycerides (mmol/L)	**1.9 (1.0-2.5)**	**2.2 (1.5-3.2)**	**0.015**	**1.9 (1.3-2.9)**	**2.3 (1.6-3.2)**	**0.042**
Cholesterol/HDL	**4.1 (3.3-5.0)**	**4.7 (3.8-5.7)**	**0.011**	**4.3 (3.5-5.6)**	**4.8 (4.0-5.8)**	**0.022**
HbA1c (mmol/mol)	**34 (32-37)**	**38 (36-41)**	**0.001**	**36 (33-39)**	**38 (36-42)**	**0.002**
CRP	3.0 (1.2-8.5)	3.8 (1.4-7.5)	0.608	3.0 (1.3-7.6)	4.3 (1.4-8.6)	0.173

Legend for Table 1: Data presented as mean (standard deviation), median (interquartile range) or proportion (percentage) as appropriate. Significant differences in bold. * ≥2/night. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; F_ENO, fraction of exhaled nitric oxide; HDL, high density lipoprotein; HbA1c, glycated haemoglobin; CRP, C-reactive protein; ODI, oxygen desaturation index; SpO_2, oxygen saturation; SpO_2 t<90, duration of time for which oxygen saturation less than 90%.

Table 2: Comparison of results of Epworth Sleepiness Scale (ESS) and Berlin, STOP and STOP-BANG Questionnaires between groups without and with SDB as defined by AHI <5 events/hour and ≥15 events/hour.

	AHI<5	***AHI≥5***	***p***	***AHI<15***	***AHI≥15***	***p***
ESS score	13 (8-16)	13 (7-17)	0.845	13 (7-16)	13 (9-18)	0.476
ESS +ve (≥11/24)	17/28 (61%)	63/92 (68%)	0.496	42/66 (64%)	38/54 (70%)	0.560
Berlin +ve	29/31 (94%)	87/94 (93%)	1.000	65/71 (92%)	51/54 (94%)	0.731
STOP score	**2.5 (2-3)**	**3 (2-3)**	**0.011**	**3 (2-3)**	**3 (3-3.5)**	**<0.001**
STOP +ve (≥2/4)	**27/32 (84%)**	**93/96 (97%)**	**0.023**	66/73 (90%)	54/55 (98%)	0.137
STOP-BANG score	**4 (2-5)**	**5 (5-6)**	**<0.001**	**5 (2-5)**	**6 (5-6)**	**<0.001**
STOP-BANG +ve (≥3/8)	**21/30 (70%)**	**88/93 (95%)**	**<0.001**	**54/68 (79%)**	**55/55 (100%)**	**<0.001**

Legend for Table 2: Data presented as median (interquartile range) or proportion (percentage) as appropriate. Significant differences in bold.

Table 3: Sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), likelihood ratios positive (LR+), likelihood ratios negative (LR-), and overall accuracies of the Berlin, STOP and STOP-BANG Questionnaires for prediction of significant SDB as defined by: A: AHI ≥5 events/hour; B: AHI ≥15 events/hour.

A: Cut-point = AHI ≥5 events/hour

	Sensitivity	***Specificity***	***PPV***	***NPV***	***LR+***	***LR-***	***Accuracy***
Berlin	0.93 (0.85-0.97)	0.06 (0.01-0.21)	0.75 (0.66-0.83)	0.22 (0.03-0.60)	0.99	1.15	71%
STOP	0.97 (0.91-0.99)	0.16 (0.05-0.33)	0.78 (0.69-0.85)	0.62 (0.24-0.91)	1.15	0.20	77%
STOP-BANG	0.95 (0.88-0.98)	0.30 (0.15-0.49)	0.81 (0.72-0.88)	0.64 (0.35-0.87)	1.35	0.18	79%

B: Cut-point = AHI ≥15 events/hour

	Sensitivity	***Specificity***	***PPV***	***NPV***	***LR+***	***LR-***	***Accuracy***
Berlin	0.94 (0.85-0.99)	0.08 (0.03-0.17)	0.44 (0.35-0.53)	0.67 (0.30-0.92)	1.03	0.66	46%
STOP	0.98 (0.90-1.00)	0.10 (0.04-0.19)	0.45 (0.36-0.54)	0.88 (0.47-1.00)	1.09	0.19	48%
STOP-BANG	1.00 (0.94-1.00)	0.21 (0.12-0.32)	0.50 (0.41-0.60)	1.00 (0.77-1.00)	1.26	0.00	56%

Legend for Table 3: Data presented with 95% confidence intervals.

Table 4: Sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), likelihood ratios positive (LR+), likelihood ratios negative (LR-), and overall accuracies of different cut-points of the STOP-BANG questionnaire for prediction of significant SDB as defined by: A: AHI ≥5 events/hour; B: AHI ≥15 events/hour.

A: Cut-point = AHI ≥5 events/hour

STOP-BANG cut-point (/8)	*Proportion +ve SB*	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*LR+*	*LR-*	*Accuracy*
≥2	92/96	0.99 (0.92-1.00)	0.12 (0.03-0.32)	0.77 (0.67-0.85)	0.75 (0.19-0.99)	1.13	0.11	77%
≥3	82/96	0.93 (0.84-0.98)	0.38 (0.19-0.59)	0.82 (0.72-0.89)	0.64 (0.35-0.87)	1.49	0.18	79%
≥4	79/96	0.90 (0.81-0.96)	0.42 (0.22-0.63)	0.82 (0.72-0.90)	0.59 (0.33-0.82)	1.55	0.23	78%
≥5	67/96	0.81 (0.70-0.89)	0.62 (0.41-0.81)	0.87 (0.76-0.94)	0.52 (0.32-0.71)	2.15	0.31	76%
≥6	38/96	0.46 (0.34-0.58)	0.79 (0.58-0.93)	0.87 (0.72-0.96)	0.33 (0.21-0.46)	2.20	0.68	54%
≥7	15/96	0.18 (0.10-0.29)	0.92 (0.73-0.99)	0.87 (0.60-0.98)	0.27 (0.18-0.38)	2.17	0.89	36%
8	5/96	0.07 (0.02-0.15)	1.00 (0.86-1.00)	1.00 0.48-1.00)	0.26 (0.18-0.37)	-	0.93	30%

B: Cut-point = AHI ≥15 events/hour

STOP-BANG cut-point (/8)	*Proportion +ve SB*	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*LR+*	*LR-*	*Accuracy*
≥2	92/96	1.00 (0.91-1.00)	0.07 (0.02-0.18)	0.45 (0.34-0.55)	1.00 (0.40-1.00)	1.08	0	47%
≥3	82/96	1.00 (0.91-1.00)	0.25 (0.15-0.39)	0.50 (0.39-0.61)	1.00 (0.77-1.00)	1.34	0	57%
≥4	79/96	1.00 (0.91-1.00)	0.31 (0.19-0.45)	0.52 (0.40-0.63)	1.00 (0.80-1.00)	1.45	0	60%
≥5	67/96	0.93 (0.80-0.98)	0.47 (0.34-0.61)	0.57 (0.44-0.69)	0.90 (0.73-0.98)	1.76	0.15	67%
≥6	38/96	0.63 (0.47-0.78)	0.78 (0.65-0.88)	0.68 (0.51-0.82)	0.74 (0.61-0.85)	2.91	0.47	72%
≥7	15/96	0.22 (0.11-0.38)	0.89 (0.78-0.96)	0.60 (0.32-0.84)	0.60 (0.49-0.71)	2.01	0.88	60%
8	5/96	0.10 (0.03-0.23)	0.98 (0.90-1.00)	0.80 (0.28-0.99)	0.59 (0.48-0.70)	5.36	0.92	60%

Legend for Table 4: Data presented with 95% confidence intervals. Abbreviations: SB, STOP-BANG.

Table 5: Probabilities of SDB using a composite score based on neck circumference (≥17in or <17in) and presence (1) or absence (0) of witnessed apnoeas derived from logistic regression models. SDB defined by: A: AHI ≥5 events/hour; B: AHI ≥15 events/hour.

A: Cut-point = AHI ≥5 events/hour

	Witnessed Apnoeas	
Neck Circumference (in)	***0***	***1***
<17	0.47	0.75
≥17	0.83	0.94

B: Cut-point = AHI ≥15 events/hour

	Witnessed Apnoeas	
Neck Circumference (in)	***0***	***1***
<17	0.17	0.40
≥17	0.40	0.69

Table 6: Sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), and overall accuracies of logistic models for prediction of SDB as defined by: A: AHI ≥5 events/hour; predict SDB *unless* neck <17in *and* witnessed apnoeas absent; B: AHI ≥15 events/hour; predict SDB *only if* neck ≥17in *and* witnessed apnoeas present.

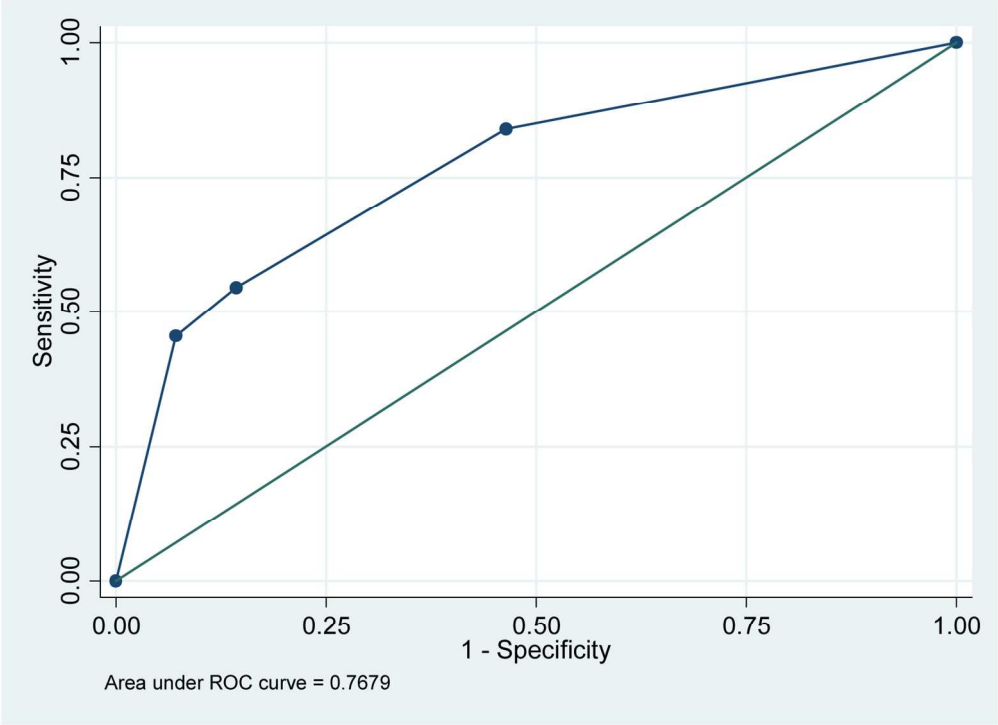
Model	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*Accuracy*
A	0.84 (0.75-0.91)	0.54 (0.34-0.72)	0.85 (0.76-0.92)	0.52 (0.32-0.71)	77%
B	0.56 (0.41-0.70)	0.80 (0.68-0.89)	0.69 (0.53-0.82)	0.69 (0.57-0.79)	69%

Legend for Table 6: Data presented with 95% confidence intervals.

Figure 1: ROC curves of logistic models for prediction of SDB as defined by: A: AHI ≥5 events/hour; predict SDB *unless* neck <17in *and* witnessed apnoeas absent; B: AHI ≥15 events/hour; predict SDB *only if* neck ≥17in *and* witnessed apnoeas present.

Model A:

Model B:



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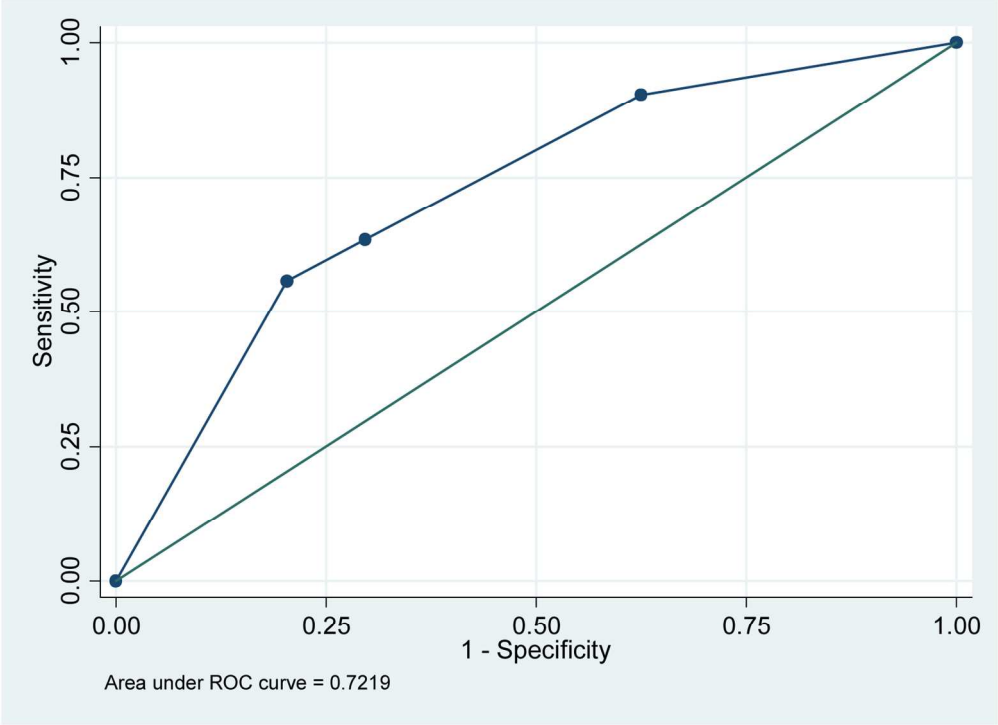

140x102mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7*
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	

Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,18
		(b) Indicate number of participants with missing data for each variable of interest	19
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*9,10,19-23*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	20-21
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10,22-23
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Predicting sleep disordered breathing in outpatients with suspected OSA

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Predicting sleep disordered breathing in outpatients with suspected OSA

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Competing Interest: None to declare.

Additional unpublished data from this study is available on request by email.

There was no funding for this study.

This study was approved by the West of Scotland Regional Ethics Committee.

Abstract

Background: Validated predictors of sleep disordered breathing (SDB) are required to streamline sleep services in the face of the obesity epidemic. Berlin, STOP and STOP-BANG questionnaires are useful in other settings, but their ability to predict obstructive sleep apnoea (OSA) in the sleep clinic population is unknown. We considered the utility of these questionnaires, other patient characteristics, co-morbidities, Epworth Sleepiness Scale (ESS), exhaled nitric oxide (F_ENO) and blood markers for the prediction of SDB on limited polygraphy.

Methods: Data was obtained on 129 patients referred with possible OSA. We selected cut-points of apnoea hypopnoea index (AHI) of ≥5 and ≥15 per hour from their home polygraphy and determined associations of these with individual symptoms, questionnaire scores and other results. ROC analysis, univariate and multivariate logistic regression were used to explore these.

Results: AHI was ≥5 in 97 and ≥15 in 56 patients. STOP and STOP-BANG scores were associated with both AHI cut-points but results with ESS and Berlin Questionnaire scores were negative. STOP-BANG had a negative predictive value 1.00 (0.77-1.00) for an AHI ≥15 with a score ≥3 predicting AHI≥5 with sensitivity 0.93 (95%CI 0.84-0.98) and accuracy 79%, whilst a score ≥6 predicted AHI≥15 with specificity 0.78 (0.65-0.88) and accuracy 72%. Neck circumference ≥17in and presence of witnessed apnoeas were independent predictors of SDB.

Conclusions: Both STOP and STOP-BANG questionnaires have utility for the prediction of SDB in the sleep clinic population. Modification of the STOP-BANG questionnaire merits further study in this and other patient groups.

(*Word count 246)*

Strengths and limitations of this study:

Strengths:

- This is the first study to prospectively evaluate the utility of the Berlin, STOP and STOP-BANG questionnaires in the prediction of sleep disordered breathing in the population referred to a sleep service for assessment of possible obstructive sleep apnoea.
- This results of this study show that the STOP and STOP-BANG, but not the Berlin questionnaire, have utility for prediction of sleep disordered breathing in the sleep clinic population.

Weaknesses:

- This study uses home unattended limited sleep studies rather than in-hospital attended full polysomnography, however this is considered standard clinical practice in the UK and is considered an acceptable method for diagnosis of OSA by the American Academy of Sleep Medicine.
- The sample size limits the conclusions that can be drawn from the multivariate analysis, however this was a secondary objective of the study.

Introduction

Obstructive sleep apnoea syndrome (OSAS) is common with prevalence of approximately 4% in middle-aged men and 2% in middle-aged women.(1) Frequent partial (hypopnoea) or complete (apnoea) upper airway collapse during sleep leads to oxygen desaturation, increased respiratory effort, arousal and sleep fragmentation.(2) Patients typically present with witnessed apnoeas, loud snoring and excessive daytime somnolence.(3) The syndrome is associated with impaired quality of life,(4) cognitive functioning and work performance,(5) and with increased risk of road traffic accidents.(6) OSAS is considered an independent risk factor for hypertension,(7) and has associations with coronary disease, stroke, heart failure, arrhythmias,(8) metabolic syndrome(9) and type 2 diabetes.(10)

Despite the substantial burden of this disease, it is under-recognised. One study estimated that 93% of females and 82% of males with moderate-severe OSAS were not clinically diagnosed,(11) and more recent data support this finding.(12) Sleep studies are required for OSAS diagnosis but are expensive and not widely available.(3) Given the recent increases in childhood(13) and adulthood obesity,(14) the workload for sleep clinics and sleep laboratories will increase. Predictors of sleep disordered breathing (SDB) are required to allow recognition of OSAS, and prioritisation of investigations.

Several questionnaires have been designed to screen for SDB in different populations. The Berlin Questionnaire was first validated in primary care against portable unattended sleep studies and a “high risk” score predicted a respiratory disturbance index >5 with sensitivity 0.86, specificity 0.77, positive predictive value 0.89 and likelihood ratio 3.79.(15) It’s utilisation in other populations has been assessed with variable success.(16-22) The STOP and STOP-BANG Questionnaires were originally validated in surgical patients using in-

hospital attended polysomnagraphy.(23) For prediction of apnoea hypopnoea index (AHI) greater than 5, 15 and 30, sensitivities for the STOP and STOP-BANG questionnaires were 65.6, 74.3 and 79.5%, and 83.9, 92.9 and 100%, respectively. The Berlin and STOP questionnaires have been compared in a cohort of surgical patients (24) and the STOP and STOP-BANG questionnaires have been compared in a large study involving several distinct cardiovascular and respiratory disease cohorts.(25) No study has, however, compared these screening tools in a sleep service-referred population. Finally, because of rising obesity rates, there is the potential for increasing recognition of SDB in primary care and in the face of this evolution in sleep clinic practice it is therefore necessary to update and re-evaluate established assessment tools.

The objective of this study was, firstly, to compare utility of Berlin, STOP and STOP-BANG questionnaires for prediction of SDB in a population referred to the sleep clinic for assessment of possible OSA. Secondly, we sought to identify the most important variables from these questionnaires and routine sleep clinic assessment that might be utilised in the development of a composite predictive score for future use in this population.

Methods

This was a prospective observational study conducted May-December 2012. The protocol was approved by the West of Scotland Research Ethics Committee. Study participants received an information sheet and provided informed consent. .

Participants

Consecutive patients aged ≥16 years referred to the North Glasgow Sleep Service (a tertiary centre) for assessment of possible OSA were invited to participate.

Measurements

Height, weight, body mass index (BMI), neck circumference, blood pressure and Epworth Sleepiness Scale (ESS)(26) were completed at the Sleep Clinic. Participants attended the Sleep Laboratory on a separate day so that a Sleep Physiologist could provide, and instruct on fitting, a sleep study device. On that occasion, relevant symptoms and co-morbidities were recorded, Mallampatti score was assessed, and the Berlin and STOP-BANG Questionnaires were completed. Blood samples including non-fasting lipid profile, glycated haemoglobin (HbA1c) and C-reactive protein (CRP) were taken. Two fractional exhaled nitric oxide (F_ENO) measurements were taken using the NIOX MINO ® (Aerocrine, Solna, Sweden), and the mean calculated.

Sleep Studies

Unattended home limited polygraphy sleep studies were performed using the SOMNOmedics SOMNOscreen™ kit (Randersacker, Germany) with channels that recorded body position, thoraco-abdominal movements, oronasal airflow, heart rate, pulse oximetry and snoring. Sleep study scoring by experienced Sleep Physiologists was in accordance with accepted guidelines.(27) An apnoea was defined as cessation of nasal flow for ≥10 seconds, whilst a hypnoea was defined as 50% reduction in nasal flow for ≥10 seconds, or lesser reduction in flow associated with oxygen desaturation of ≥4%.

The Epworth Sleepiness Scale (ESS), Berlin, STOP and STOP-BANG Questionnaires

The ESS is a validated measure of daytime sleepiness including eight questions, each with four possible responses, that assesses the likelihood of dozing in different situations; a score of ≥11/24 denotes excessive daytime somnolence.(26) The Berlin Questionnaire includes

questions in three categories that relate firstly to snoring and witnessed apnoeas, secondly, to tiredness, fatigue and sleepiness, and thirdly, to hypertension and obesity.(15) High risk of OSA is defined by scoring positively in ≥2 categories. The STOP Questionnaire includes four yes/no questions that relate to Snoring, Tiredness, Observed apnoeas and high blood Pressure.(23) High risk of OSA is defined as a score of ≥2. The STOP-BANG Questionnaire includes four additional questions relating to BMI, Age, Neck circumference and Gender, and high risk of OSA is defined as a score of ≥3.(23)

Statistical analyses

Statistical analyses were carried out using GraphPad Prism 5, IBM SPSS Statistics 19 and STATA 12. Normality of data was checked using D'Agostino & Pearson omnibus normality test. A priori, two cut-points were chosen for AHI: ≥5 events/hour (the standard cut-point for the diagnosis of OSA),(28) and ≥15 events/hour, to predict significant SDB (the standard cut-point for initiating continuous positive airway pressure [CPAP] therapy).(28) Groups were compared using unpaired t-tests, Mann-Whitney tests and Fisher's Exact tests as appropriate. Sensitivities, specificities, positive and negative predictive values, positive and negative likelihood ratios, and overall accuracies were calculated for each of the questionnaires for prediction of SDB as defined by AHI cut-points of ≥5 and ≥15. Associations between individual variables and each of the cut-points for AHI were explored using univariate and multivariate logistic regression. For multivariate analysis, in a few cases where BMI was known but neck circumference was not known, a value for the neck circumference was imputed using linear regression with BMI as the independent value. This allowed for a dataset of 116 cases with all of the variables known or imputed to be built to identify independent variables for inclusion in a composite score. Receiver operating characteristic (ROC) curve analysis was used to assess predictive value and an area under the

curve (AUC) >0.7 was considered clinically significant. Data are presented as mean (standard deviation), median (interquartile range) and proportion (percentage), unless stated otherwise. A p value <0.05 was considered statistically significant.

Results

150 subjects participated in this study, of which 129 had adequate sleep study data and were included in the analysis. AHI was ≥5 in 97/129 (75%) and ≥15 in 56/129 (43%). Overall, 82 (64%) were male, mean(SD) age was 49(11) years, and median(IQR) BMI was 32(29-39) kg/m^2.

Predicting SDB: Patient characteristics (See Table 1)

An AHI <5 ("rule-out measurement") was associated with female sex, younger age, lower weight and neck circumference, less frequently reported witnessed apnoeas, higher high density lipoprotein (HDL) cholesterol, and lower triglycerides, cholesterol/HDL and HbA1c. An AHI ≥15 ("rule-in measurement") was associated with male sex, obesity, higher weight, BMI and neck circumference, more frequently reported hypertension and witnessed apnoeas, lower HDL cholesterol, and higher triglycerides, cholesterol/HDL and HbA1c.

Predicting SDB: ESS, Berlin, STOP and STOP-BANG (See Tables 2, 3 and 4)

The ESS and Berlin questionnaire outcomes were not associated with either AHI cut-point. An AHI<5 was associated with lower STOP and STOP-BANG scores, and fewer subjects being classified as "high risk" for OSA by both STOP and STOP-BANG questionnaires. An AHI≥15 was associated with higher STOP and STOP-BANG scores and more subjects being classified as "high risk" for OSA by the STOP-BANG questionnaire but not by the STOP questionnaire.

For the AHI cut-point of ≥5, the Berlin, STOP, and STOP-BANG questionnaires had high sensitivities, moderate positive predictive values (PPV) and poor specificities and negative predictive values (NPV), for prediction of SDB. The STOP-BANG questionnaire performed best with an overall accuracy of 79%. For the AHI cut-point of ≥15, the Berlin questionnaire had high sensitivity, but otherwise performed poorly. The STOP and STOP-BANG questionnaires had high sensitivities and NPVs. Again, the STOP-BANG questionnaire performed best, but with a low overall accuracy of 56%. The low negative likelihood ratios for the STOP and STOP-BANG questionnaires at both cut-points indicate that these questionnaires have value in excluding disease. As shown in table 4, the cut-points for STOP-BANG score that were associated with best overall accuracy were ≥3 and ≥6 for prediction of AHI ≥5 and ≥15, respectively.

SDB versus no SDB: Predictors and a composite score (See Tables 5 and 6 and Figure 1)

For the cut-point of AHI of ≥5, univariate logistic regression showed significant associations for age, gender, weight, neck circumference, witnessed apnoeas, triglycerides and cholesterol/HDL ($p<0.05$). For the cut-point of ≥15, significant associations were found for gender, weight, BMI, neck circumference, witnessed apnoeas, obesity, hypertension, FeNO and cholesterol/HDL ($p<0.05$). Multivariate logistic regression based on the significant variables from univariate logistic regression showed that for both cut-points neck circumference and witnessed apnoeas were independent predictors of SDB. For the cut-point of AHI of ≥5, in a model incorporating neck circumference and witnessed apnoeas, the probability of SDB was 0.94 for individuals with neck circumference ≥17in and witnessed apnoeas (sensitivity 84%, overall accuracy 77%, ROC AUC 0.768, $p<0.001$). For the cut-point of AHI ≥15, the probability of SDB was 0.69 for individuals with neck circumference

≥17in and witnessed apnoeas (specificity 80%, overall accuracy 69%, ROC AUC 0.722, p<0.001).

Discussion

This is the first study to prospectively evaluate the utility of the Berlin, STOP and STOP-BANG questionnaires in prediction of sleep disordered breathing in a population referred to a tertiary sleep service for assessment of possible OSA. We found that in this population the Berlin Questionnaire had no significant association with cut-points of ≥5 or ≥15 for AHI, but that both the STOP and STOP-BANG scores were significantly associated with both cut-points. The STOP-BANG Questionnaire had better performance for the prediction of OSA on home sleep study, and different cut-points for STOP-BANG score could be selected depending on preference to exclude SDB (score <3) or predict SDB (score ≥6). In addition, we found notable associations between sleep study results and several patient characteristics. In particular, neck circumference and witnessed apnoeas were found to be independent predictors of SDB in our population.

In our study, the Berlin Questionnaire was almost ubiquitously positive (116 of 125 participants had a positive result) and the positivity rate did not differ between those with and without SDB. This was expected as this questionnaire was designed for primary care assessment and our study population consisted of individuals referred from primary care with symptoms suggestive of SDB. Our results indicate that the Berlin Questionnaire is not useful in the prediction of SDB in the sleep clinic referral population and this is consistent with previous reports.(19) The high sensitivities obtained for both AHI cut-points support previous findings that the Berlin Questionnaire may have a role as a "rule-out" measurement

in the primary care or screening setting(15, 17, 20, 24), though there have been some conflicting results, suggesting it does not have adequate discriminatory power.(16, 22)

In our study Epworth Sleepiness Scale data indicated that two thirds of participants had excessive daytime somnolence (ESS ≥11), however scores were similar in individuals with or without SDB. Therefore, at least in the sleep clinic population, the ESS is not useful for the prediction of SDB. It may be of value,perhaps combined with other measures, including those highlighted in this study, in prediction of compliance with and benefit from OSA treatment. Further research is required to address this question. Exhaled nitric oxide levels were not significantly different between individuals with or without SDB whether defined by an AHI cut-point of ≥5 or ≥15. There is conflicting data in the literature regarding whether F_ENO is associated with SDB,(29-32) however our results suggest that it does not have utility in prediction of SDB; further work is required to clarify this.

We found that both the STOP and STOP-BANG questionnaires have utility in the prediction of SDB in the sleep clinic population, and that STOP-BANG was superior, with higher overall predictive accuracy. The STOP and STOP-BANG Questionnaires were developed and validated in a surgical population using in-laboratory polysomnagraphy(23) and have subsequently been studied in a cardiovascular disease population.(25) Our results are in agreement with these two earlier studies as regards the increased predictive value of STOP-BANG over STOP. In contrast to these earlier studies, however, we found sensitivities to be higher and specificities to be lower for both cut-points of AHI. We suggest that of the two AHI cut-points, ≥15 events/hr is the more important, being diagnostic of at least moderate SDB and also an indication for CPAP treatment. At this cut-point, STOP and STOP-BANG performed with high sensitivities and negative predictive values (STOP-BANG superior to

STOP) indicating that these questionnaires are more useful in excluding significant SDB. This is further corroborated by the negative likelihood ratios of <0.2 obtained for STOP and STOP-BANG that also indicate that these questionnaires are most useful in ruling out SDB. The STOP-BANG may be of value in the primary care setting, perhaps combined with type IV portable monitoring sleep studies, to determine requirement for sleep clinic review and more detailed polygraphy.

At the AHI cut-point of ≥15, STOP-BANG had sensitivity and negative predictive value of 100%, and since this is the standard cut-point conventionally used to determine need for CPAP,(28) we suggest that the STOP-BANG questionnaire is the preferred tool for prediction of SDB in the sleep clinic setting of those currently available. STOP-BANG, perhaps with modifications, meritsfurther evaluation for the prediction of SDB in the sleep clinic population and, more importantly, its utility in prediction of clinical outcomes including treatment success should be assessed.

The original STOP-BANG questionnaire uses a cut-point of ≥3 to predict SDB.(23) However, in our study we show that different cut-points can be selected depending on the preference to rule-in or rule-out SDB. A score of ≥3 had the highest overall accuracy and a sensitivity of 0.93 for the AHI cut-point of ≥5, whereas a score of ≥6 had the highest overall accuracy and a specificity of 0.78 for the AHI cut-point of ≥15. Two other studies have examined the usefulness of different cut-points for STOP-BANG score.(33-34) In the obese, a score of ≥3 was associated with a sensitivity of 0.90 for predicting an AHI >5, whilst, a score of ≥6 had a specificity of 0.88 for predicting an AHI >15 and similar results have been obtained in the morbidly obese(33) and in a surgical population.(34) Thus, in the sleep clinic setting where the ultimate goal is to identify patients requiring CPAP, a higher cut-point for

STOP-BANG may be preferred whereas in a primary care setting where the priority is not to miss disease a lower cut-point may be chosen.

The STOP-BANG questionnaire is, however, still an imperfect tool for prediction of results on home polygraphy. Accordingly, the secondary objective of our study was to identify variables for inclusion in a locally developed composite score for future validation in the sleep clinic and potentially wider population. Univariate analysis showed several significant, expected associations for both cut-points of AHI. Using multivariate analysis, neck circumference ≥17in and the presence of witnessed apnoeas were independent predictors of SDB. This is not a novel finding, but does support the robustness of our data. Particularly when SDB was defined by an AHI cut-point of ≥5, the regression model derived indicated a high probability of SDB of 0.94 if both factors were present. The STOP-BANG questionnaire, of course, includes both of these variables, and it is possible that adjustment of the inclusion variables, or their weighting, might improve its performance. In future work, we aim to validate a simple composite score based on these two variables in a modification of STOP-BANG, to determine utility for predicting sleep study data and outcomes with treatment.

Ultimately, a predictive tool that can be utilised in primary care is the goal. Our results indicate low specificity of STOP-BANG, and therefore in its current form, if used in primary care to identify patients requiring referral for further assessment, it is likely to result in a significant percentage of patients being referred unnecessarily (false positives). It is hoped that a modified STOP-BANG with improved specificity, while not compromising sensitivity, may be developed that can be used safely in primary care for identification of patients requiring referral to sleep services. Of upmost importance too is the prediction of treatment

outcome. Non-adherence to CPAP treatment occurs in between 46 and 83%.(35-36) Prediction of poor adherence by STOP-BANG or other similar tools would allow greater attention to interventions to improve adherence in patients more likely to default from treatment. The authors are not aware of any studies investigating this question and future research should explore this important issue.

A possible limitation of our study was that SDB was characterised using home unattended limited sleep studies rather that in-hospital attended full polysomnography. The latter is considered the gold standard for diagnosis of SDB but is more expensive, less easily accessed and potentially unrepresentative with sleep in an unfamiliar environment. Home unattended and in-hospital attended sleep studies have previously been shown to produce similar results.(37) Accordingly home testing with portable monitors is standard clinical practice in the UK, and is now considered an acceptable method for diagnosis of OSA by the American Academy of Sleep Medicine.(28) The sample size limits the conclusions that can be drawn from multivariate analysis, however this was a secondary objective of the current study. It is possible that variables predictive of SDB on univariate analysis in this cohort would have been identified as independently predictive in multivariate models in a larger population. The results of this study allow us, and potentially others, to focus future work to validate more extensively the results obtained to date. We chose AHI cut-points of ≥5 and ≥15 to define significant SDB. This was based on the consensus guideline produced by the Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine that states that diagnosis of OSA is based on a cut-point of >15 events/hr or >5 events/hr with relevant symptoms, and that CPAP is indicated for treatment of moderate to severe OSA with ≥15 events/hr.(28) Although the cut-point of >30 events/hr is consistent with severe OSA we suggest that this cut-point is less clinically relevant from a diagnostic perspective or from that

of determining treatment. Finally, due to the prospective design of our study, we cannot comment on the relative value of other tools developed for prediction of OSA such as the Sleep Apnea Clinical Score (38) and American Society of Anesthesiologists Checklist. (39) To compare their utility with that of the Berlin, STOP and STOP-BANG questionnaires in the population referred to the sleep service would require a further study.

In conclusion, the Berlin Questionnaire was not useful in the prediction of SDB within our sleep clinic population. The STOP-BANG questionnaire had superior predictive performance to the STOP questionnaire at both cut-points of AHI (≥5 and ≥15). A STOP-BANG score of ≥3 had the highest overall accuracy and a sensitivity of 0.93 for the prediction of an AHI≥5, whilst a score of ≥6 had the highest overall accuracy and a specificity of 0.78 for the prediction of an AHI ≥15. Future work will validate a composite score including neck circumference ≥17in and the presence of witnessed apnoeas for the prediction of SDB in the sleep clinic referral population. An optimised composite score could then beevaluated in primary care and against treatment outcomes, with our overall aim being to provide required tools for use in the expanded and consolidated sleep services that are now necessary given the current obesity and OSA epidemics.

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This study was approved by the West of Scotland Regional Ethics Committee.

Contributorship Statement:

Douglas Cowan took a leading role in study protocol development, study document development, application for ethics approval, data collection, statistical analysis and paper writing.

Gwen Allardice provided statistical support and performed part of the statistical analysis.

Duncan MacFarlane, Darren Ramsay and Heather Ambler contributed to data collection, and carried out and scored sleep studies.

Stephen Banham contributed to study protocol development.

Eric Livingston contributed to study protocol development, study document development, application for ethics approval and paper writing.

Christopher Carlin contributed to study protocol development, data collection, statistical analysis and paper writing.

All authors approved the final draft before submission.

Christopher Carlin is responsible for the overall content as guarantor.

Competing Interest: None to declare.

Data Sharing Statement: Additional unpublished data from this study is available on request by email.

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Table 1: Comparison of patient characteristics including anthropometric measurements, co-morbidities, symptoms, inflammatory markers, lipid profile and oximetry between groups without and with SDB as defined by AHI <5 events/hour and ≥15 events/hour.

	AHI<5	*AHI≥5*	*p*	*AHI<15*	*AHI≥15*	*P*
Male gender	**15/32 (47%)**	**67/97 (69%)**	**0.034**	**38/73 (52%)**	**44/56 (79%)**	**0.003**
Age (yrs)	**44 (12)**	**51 (11)**	**0.004**	48 (13)	51 (9)	0.103
Weight (kg)	**89 (19)**	**101 (22)**	**0.022**	**92 (21)**	**107 (20)**	**0.001**
BMI (kg/m^2)	31 (28-36)	33 (29-40)	0.118	**31 (27-36)**	**34 (31-41)**	**0.009**
Obesity (BMI≥30 kg/m^2)	18/28 (64%)	61/85 (72%)	0.482	**38/63 (60%)**	**41/50 (82%)**	**0.014**
Neck circumference (in)	**15 (2)**	**17(2)**	**<0.001**	**16 (2)**	**17 (1)**	**<0.001**
Neck circumference ≥17in	**4/22 (18%)**	**45/76 (59%)**	**0.001**	**18/54 (33%)**	**31/44 (70%)**	**<0.001**
Mallampatti	2 (1)	2 (1)	0.192	2 (1)	2 (1)	0.900
SBP (mmHg)	134 (17)	136 (16)	0.480	134 (15)	138 (18)	0.194
DBP (mmHg)	82 (11)	83 (9)	0.528	81 (10)	85 (10)	0.086
Diabetes	2/32 (6%)	6/97 (6%)	1.000	4/73 (5%)	4/56 (7%)	0.727
Hypertension	7/32 (22%)	36/97 (37%)	0.134	**18/73 (25%)**	**25/56 (45%)**	**0.024**
Hyperlipidaemia	2/32 (6%)	18/97 (19%)	0.156	10/73 (14%)	10/56 (18%)	0.625
Loud snorer	28/32 (88%)	92/97 (95%)	0.224	65/73 (89%)	55/56 (98%)	0.077
Witnessed apnoeas	**15/32 (47%)**	**72/97 (74%)**	**0.008**	**40/73 (55%)**	**47/56 (84%)**	**<0.001**
*Nocturia**	11/32 (34%)	38/97 (39%)	0.679	26/73 (36%)	23/56 (41%)	0.585
*Nocturnal wakenings**	18/32 (56%)	65/97 (67%)	0.293	46/73 (63%)	37/56 (66%)	0.853
Nocturnal choking	15/32 (47%)	35/97 (36%)	0.301	28/73 (38%)	22/56 (39%)	1.000
Nocturnal gasping	11/32 (34%)	38/97 (39%)	0.679	26/73 (36%)	23/56 (41%)	0.585
F_eNO (ppb)	15 (12-25)	18 (12-26)	0.595	15 (11-24)	19 (12-27)	0.050
Cholesterol (mmol/L)	5.2 (1.1)	5.4 (1.0)	0.431	5.3 (1.1)	5.4 (0.9)	0.674
HDL cholesterol (mmol/L)	**1.3 (1.0-1.5)**	**1.1 (1.0-1.3)**	**0.008**	**1.2 (1.0-1.4)**	**1.1 (1.0-1.2)**	**0.016**
Triglycerides (mmol/L)	**1.9 (1.0-2.5)**	**2.2 (1.5-3.2)**	**0.015**	**1.9 (1.3-2.9)**	**2.3 (1.6-3.2)**	**0.042**
Cholesterol/HDL	**4.1 (3.3-5.0)**	**4.7 (3.8-5.7)**	**0.011**	**4.3 (3.5-5.6)**	**4.8 (4.0-5.8)**	**0.022**
HbA1c (mmol/mol)	**34 (32-37)**	**38 (36-41)**	**0.001**	**36 (33-39)**	**38 (36-42)**	**0.002**
CRP	3.0 (1.2-8.5)	3.8 (1.4-7.5)	0.608	3.0 (1.3-7.6)	4.3 (1.4-8.6)	0.173

Legend for Table 1: Data presented as mean (standard deviation), median (interquartile range) or proportion (percentage) as appropriate. Significant differences in bold. * ≥2/night. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; F_ENO, fraction of exhaled nitric oxide; HDL, high density lipoprotein; HbA1c, glycated haemoglobin; CRP, C-reactive protein; ODI, oxygen desaturation index; SpO_2, oxygen saturation; SpO_2 t<90, duration of time for which oxygen saturation less than 90%.

Table 2: Comparison of results of Epworth Sleepiness Scale (ESS) and Berlin, STOP and STOP-BANG Questionnaires between groups without and with SDB as defined by AHI <5 events/hour and ≥15 events/hour.

	AHI<5	***AHI≥5***	***p***	***AHI<15***	***AHI≥15***	***p***
ESS score	13 (8-16)	13 (7-17)	0.845	13 (7-16)	13 (9-18)	0.476
ESS +ve (≥11/24)	17/28 (61%)	63/92 (68%)	0.496	42/66 (64%)	38/54 (70%)	0.560
Berlin +ve	29/31 (94%)	87/94 (93%)	1.000	65/71 (92%)	51/54 (94%)	0.731
STOP score	**2.5 (2-3)**	**3 (2-3)**	**0.011**	**3 (2-3)**	**3 (3-3.5)**	**<0.001**
STOP +ve (≥2/4)	**27/32 (84%)**	**93/96 (97%)**	**0.023**	66/73 (90%)	54/55 (98%)	0.137
STOP-BANG score	**4 (2-5)**	**5 (5-6)**	**<0.001**	**5 (2-5)**	**6 (5-6)**	**<0.001**
STOP-BANG +ve (≥3/8)	**21/30 (70%)**	**88/93 (95%)**	**<0.001**	**54/68 (79%)**	**55/55 (100%)**	**<0.001**

Legend for Table 2: Data presented as median (interquartile range) or proportion (percentage) as appropriate. Significant differences in bold.

Table 3: Sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), likelihood ratios positive (LR+), likelihood ratios negative (LR-), and overall accuracies of the Berlin, STOP and STOP-BANG Questionnaires for prediction of significant SDB as defined by: A: AHI ≥5 events/hour; B: AHI ≥15 events/hour.

A: Cut-point = AHI ≥5 events/hour

	Sensitivity	***Specificity***	***PPV***	***NPV***	***LR+***	***LR-***	***Accuracy***
Berlin	0.93 (0.85-0.97)	0.06 (0.01-0.21)	0.75 (0.66-0.83)	0.22 (0.03-0.60)	0.99	1.15	71%
STOP	0.97 (0.91-0.99)	0.16 (0.05-0.33)	0.78 (0.69-0.85)	0.62 (0.24-0.91)	1.15	0.20	77%
STOP-BANG	0.95 (0.88-0.98)	0.30 (0.15-0.49)	0.81 (0.72-0.88)	0.64 (0.35-0.87)	1.35	0.18	79%

B: Cut-point = AHI ≥15 events/hour

	Sensitivity	***Specificity***	***PPV***	***NPV***	***LR+***	***LR-***	***Accuracy***
Berlin	0.94 (0.85-0.99)	0.08 (0.03-0.17)	0.44 (0.35-0.53)	0.67 (0.30-0.92)	1.03	0.66	46%
STOP	0.98 (0.90-1.00)	0.10 (0.04-0.19)	0.45 (0.36-0.54)	0.88 (0.47-1.00)	1.09	0.19	48%
STOP-BANG	1.00 (0.94-1.00)	0.21 (0.12-0.32)	0.50 (0.41-0.60)	1.00 (0.77-1.00)	1.26	0.00	56%

Legend for Table 3: Data presented with 95% confidence intervals.

Table 4: Sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), likelihood ratios positive (LR+), likelihood ratios negative (LR-), and overall accuracies of different cut-points of the STOP-BANG questionnaire for prediction of significant SDB as defined by: A: AHI ≥5 events/hour; B: AHI ≥15 events/hour.

A: Cut-point = AHI ≥5 events/hour

STOP-BANG cut-point (/8)	*Proportion +ve SB*	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*LR+*	*LR-*	*Accuracy*
≥2	92/96	0.99 (0.92-1.00)	0.12 (0.03-0.32)	0.77 (0.67-0.85)	0.75 (0.19-0.99)	1.13	0.11	77%
≥3	82/96	0.93 (0.84-0.98)	0.38 (0.19-0.59)	0.82 (0.72-0.89)	0.64 (0.35-0.87)	1.49	0.18	79%
≥4	79/96	0.90 (0.81-0.96)	0.42 (0.22-0.63)	0.82 (0.72-0.90)	0.59 (0.33-0.82)	1.55	0.23	78%
≥5	67/96	0.81 (0.70-0.89)	0.62 (0.41-0.81)	0.87 (0.76-0.94)	0.52 (0.32-0.71)	2.15	0.31	76%
≥6	38/96	0.46 (0.34-0.58)	0.79 (0.58-0.93)	0.87 (0.72-0.96)	0.33 (0.21-0.46)	2.20	0.68	54%
≥7	15/96	0.18 (0.10-0.29)	0.92 (0.73-0.99)	0.87 (0.60-0.98)	0.27 (0.18-0.38)	2.17	0.89	36%
8	5/96	0.07 (0.02-0.15)	1.00 (0.86-1.00)	1.00 0.48-1.00)	0.26 (0.18-0.37)	-	0.93	30%

B: Cut-point = AHI ≥15 events/hour

STOP-BANG cut-point (/8)	*Proportion +ve SB*	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*LR+*	*LR-*	*Accuracy*
≥2	92/96	1.00 (0.91-1.00)	0.07 (0.02-0.18)	0.45 (0.34-0.55)	1.00 (0.40-1.00)	1.08	0	47%
≥3	82/96	1.00 (0.91-1.00)	0.25 (0.15-0.39)	0.50 (0.39-0.61)	1.00 (0.77-1.00)	1.34	0	57%
≥4	79/96	1.00 (0.91-1.00)	0.31 (0.19-0.45)	0.52 (0.40-0.63)	1.00 (0.80-1.00)	1.45	0	60%
≥5	67/96	0.93 (0.80-0.98)	0.47 (0.34-0.61)	0.57 (0.44-0.69)	0.90 (0.73-0.98)	1.76	0.15	67%
≥6	38/96	0.63 (0.47-0.78)	0.78 (0.65-0.88)	0.68 (0.51-0.82)	0.74 (0.61-0.85)	2.91	0.47	72%
≥7	15/96	0.22 (0.11-0.38)	0.89 (0.78-0.96)	0.60 (0.32-0.84)	0.60 (0.49-0.71)	2.01	0.88	60%
8	5/96	0.10 (0.03-0.23)	0.98 (0.90-1.00)	0.80 (0.28-0.99)	0.59 (0.48-0.70)	5.36	0.92	60%

Legend for Table 4: Data presented with 95% confidence intervals. Abbreviations: SB, STOP-BANG.

Table 5: Probabilities of SDB using a composite score based on neck circumference (≥17in or <17in) and presence (1) or absence (0) of witnessed apnoeas derived from logistic regression models. SDB defined by: A: AHI ≥5 events/hour; B: AHI ≥15 events/hour.

A: Cut-point = AHI ≥5 events/hour

	Witnessed Apnoeas	
Neck Circumference (in)	***0***	***1***
<17	0.47	0.75
≥17	0.83	0.94

B: Cut-point = AHI ≥15 events/hour

	Witnessed Apnoeas	
Neck Circumference (in)	***0***	***1***
<17	0.17	0.40
≥17	0.40	0.69

Table 6: Sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), and overall accuracies of logistic models for prediction of SDB as defined by: A: AHI ≥5 events/hour; predict SDB *unless* neck <17in *and* witnessed apnoeas absent; B: AHI ≥15 events/hour; predict SDB *only if* neck ≥17in *and* witnessed apnoeas present.

Model	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*Accuracy*
A	0.84 (0.75-0.91)	0.54 (0.34-0.72)	0.85 (0.76-0.92)	0.52 (0.32-0.71)	77%
B	0.56 (0.41-0.70)	0.80 (0.68-0.89)	0.69 (0.53-0.82)	0.69 (0.57-0.79)	69%

Legend for Table 6: Data presented with 95% confidence intervals.

Figure 1: ROC curves of logistic models for prediction of SDB as defined by: Model A: AHI ≥5 events/hour; predict SDB *unless* neck <17in *and* witnessed apnoeas absent; Model B: AHI ≥15 events/hour; predict SDB *only if* neck ≥17in *and* witnessed apnoeas present.

Predicting sleep disordered breathing in outpatients with suspected OSA

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This study was approved by the West of Scotland Regional Ethics Committee.

Abstract

Background: Validated predictors of sleep disordered breathing (SDB) are required to streamline sleep services in the face of the obesity epidemic. Berlin, STOP and STOP-BANG questionnaires are useful in other settings, but their ability to predict obstructive sleep apnoea (OSA) in the sleep clinic population is unknown. We considered the utility of these questionnaires, other patient characteristics, co-morbidities, Epworth Sleepiness Scale (ESS), exhaled nitric oxide (F_ENO) and blood markers for the prediction of SDB on limited polygraphy.

Methods: Data was obtained on 129 patients referred with possible OSA. We selected cut-points of apnoea hypopnoea index (AHI) of ≥5 and ≥15 per hour from their home polygraphy and determined associations of these with individual symptoms, questionnaire scores and other results. ROC analysis, univariate and multivariate logistic regression were used to explore these.

Results: AHI was ≥5 in 97 and ≥15 in 56 patients. STOP and STOP-BANG scores were associated with both AHI cut-points but results with ESS and Berlin Questionnaire scores were negative. STOP-BANG had a negative predictive value 1.00 (0.77-1.00) for an AHI ≥15 with a score ≥3 predicting AHI≥5 with sensitivity 0.93 (95%CI 0.84-0.98) and accuracy 79%, whilst a score ≥6 predicted AHI≥15 with specificity 0.78 (0.65-0.88) and accuracy 72%. Neck circumference ≥17in and presence of witnessed apnoeas were independent predictors of SDB.

Conclusions: Both STOP and STOP-BANG questionnaires have utility for the prediction of SDB in the sleep clinic population. Modification of the STOP-BANG questionnaire merits further study in this and other patient groups.

(*Word count 246)*

Strengths and limitations of this study:

Strengths:

- This is the first study to prospectively evaluate the utility of the Berlin, STOP and STOP-BANG questionnaires in the prediction of sleep disordered breathing in the population referred to a sleep service for assessment of possible obstructive sleep apnoea.
- This results of this study show that the STOP and STOP-BANG, but not the Berlin questionnaire, have utility for prediction of sleep disordered breathing in the sleep clinic population.

Weaknesses:

- This study uses home unattended limited sleep studies rather than in-hospital attended full polysomnography, however this is considered standard clinical practice in the UK and is considered an acceptable method for diagnosis of OSA by the American Academy of Sleep Medicine.
- The sample size limits the conclusions that can be drawn from the multivariate analysis, however this was a secondary objective of the study.

Introduction

Obstructive sleep apnoea syndrome (OSAS) is common with prevalence of approximately 4% in middle-aged men and 2% in middle-aged women.(1) Frequent partial (hypopnoea) or complete (apnoea) upper airway collapse during sleep leads to oxygen desaturation, increased respiratory effort, arousal and sleep fragmentation.(2) Patients typically present with witnessed apnoeas, loud snoring and excessive daytime somnolence.(3) The syndrome is associated with impaired quality of life,(4) cognitive functioning and work performance,(5) and with increased risk of road traffic accidents.(6) OSAS is considered an independent risk factor for hypertension,(7) and has associations with coronary disease, stroke, heart failure, arrhythmias,(8) metabolic syndrome(9) and type 2 diabetes.(10)

Despite the substantial burden of this disease, it is under-recognised. One study estimated that 93% of females and 82% of males with moderate-severe OSAS were not clinically diagnosed,(11) and more recent data support this finding.(12) Sleep studies are required for OSAS diagnosis but are expensive and not widely available.(3) Given the recent increases in childhood(13) and adulthood obesity,(14) the workload for sleep clinics and sleep laboratories will increase. Predictors of sleep disordered breathing (SDB) are required to allow recognition of OSAS, and prioritisation of investigations.

Several questionnaires have been designed to screen for SDB in different populations. The Berlin Questionnaire was first validated in primary care against portable unattended sleep studies and a "high risk" score predicted a respiratory disturbance index >5 with sensitivity 0.86, specificity 0.77, positive predictive value 0.89 and likelihood ratio 3.79.(15) It's utilisation in other populations has been assessed with variable success.(16-22) The STOP and STOP-BANG Questionnaires were originally validated in surgical patients using in-

hospital attended polysomnagraphy.(23) For prediction of apnoea hypopnoea index (AHI) greater than 5, 15 and 30, sensitivities for the STOP and STOP-BANG questionnaires were 65.6, 74.3 and 79.5%, and 83.9, 92.9 and 100%, respectively. The Berlin and STOP questionnaires have been compared in a cohort of surgical patients (24) and the STOP and STOP-BANG questionnaires have been compared in a large study involving several distinct cardiovascular and respiratory disease cohorts.(25) No study has, however, compared these screening tools in a sleep service-referred population. Finally, because of ~~Also, along with changes in the population (i.e.~~ rising obesity rates, ~~)~~there is the potential for increasing recognition of SDB in primary care~~, so~~ and in the face of this evolution in sleep clinic practice it is therefore necessary to update and re-evaluate established assessment tools ~~in the face of the evolution in sleep clinic practice~~.

The objective of this study was, firstly, to compare utility of Berlin, STOP and STOP-BANG questionnaires for prediction of SDB in a population referred to the sleep clinic for assessment of possible OSA. Secondly, we sought to identify the most important variables from these questionnaires and routine sleep clinic assessment that might be utilised in the development of a composite predictive score for future use in this population.

Methods

This was a prospective observational study conducted May-December 2012. The protocol was approved by the West of Scotland Research Ethics Committee. Study participants received an information sheet and provided informed consent. .

Participants

Consecutive patients aged ≥16 years referred to the North Glasgow Sleep Service (a tertiary centre) for assessment of possible OSA were invited to participate.

Measurements

Height, weight, body mass index (BMI), neck circumference, blood pressure and Epworth Sleepiness Scale (ESS)(26) were completed at the Sleep Clinic. Participants attended the Sleep Laboratory on a separate day so that a Sleep Physiologist could provide, and instruct on fitting, a sleep study device. On that occasion, relevant symptoms and co-morbidities were recorded, Mallampatti score was assessed, and the Berlin and STOP-BANG Questionnaires were completed. Blood samples including non-fasting lipid profile, glycated haemoglobin (HbA1c) and C-reactive protein (CRP) were taken. Two fractional exhaled nitric oxide (F_ENO) measurements were taken using the NIOX MINO ® (Aerocrine, Solna, Sweden), and the mean calculated.

Sleep Studies

Unattended home limited polygraphy sleep studies were performed using the SOMNOmedics SOMNOscreen™ kit (Randersacker, Germany) with channels that recorded body position, thoraco-abdominal movements, oronasal airflow, heart rate, pulse oximetry and snoring. Sleep ~~studies~~ study scoring by experienced Sleep Physiologists was in accordance with accepted guidelines.(27) An apnoea was defined as cessation of nasal flow for ≥10 seconds, whilst a hypnoea was defined as 50% reduction in nasal flow for ≥10 seconds, or lesser reduction in flow associated with oxygen desaturation of ≥4%.

The Epworth Sleepiness Scale (ESS), Berlin, STOP and STOP-BANG Questionnaires

The ESS is a validated measure of daytime sleepiness including eight questions, each with four possible responses, that assesses the likelihood of dozing in different situations; a score of ≥11/24 denotes excessive daytime somnolence.(26) The Berlin Questionnaire includes questions in three categories that relate firstly to snoring and witnessed apnoeas, secondly, to tiredness, fatigue and sleepiness, and thirdly, to hypertension and obesity.(15) High risk of OSA is defined by scoring positively in ≥2 categories. The STOP Questionnaire includes four yes/no questions that relate to Snoring, Tiredness, Observed apnoeas and high blood Pressure.(23) High risk of OSA is defined as a score of ≥2. The STOP-BANG Questionnaire includes four additional questions relating to BMI, Age, Neck circumference and Gender, and high risk of OSA is defined as a score of ≥3.(23)

Statistical analyses

Statistical analyses were carried out using GraphPad Prism 5, IBM SPSS Statistics 19 and STATA 12. Normality of data was checked using D'Agostino & Pearson omnibus normality test. A priori, two cut-points were chosen for AHI: ≥5 events/hour (the standard cut-point for the diagnosis of OSA),(28) and ≥15 events/hour, to predict significant SDB (the standard cut-point for initiating continuous positive airway pressure [CPAP] therapy).(28) Groups were compared using unpaired t-tests, Mann-Whitney tests and Fisher's Exact tests as appropriate. Sensitivities, specificities, positive and negative predictive values, positive and negative likelihood ratios, and overall accuracies were calculated for each of the questionnaires for prediction of SDB as defined by AHI cut-points of ≥5 and ≥15. Associations between individual variables and each of the cut-points for AHI were explored using univariate and multivariate logistic regression. For multivariate analysis, in a few cases where BMI was known but neck circumference was not known, a value for the neck circumference was imputed using linear regression with BMI as the independent value. This

allowed for a dataset of 116 cases with all of the variables known or imputed to be built to identify independent variables for inclusion in a composite score. Receiver operating characteristic (ROC) curve analysis was used to assess predictive value and an area under the curve (AUC) >0.7 was considered clinically significant. Data are presented as mean (standard deviation), median (interquartile range) and proportion (percentage), unless stated otherwise. A p value <0.05 was considered statistically significant.

Results

150 subjects participated in this study, of which 129 had adequate sleep study data and were included in the analysis. AHI was ≥5 in 97/129 (75%) and ≥15 in 56/129 (43%). Overall, 82 (64%) were male, mean(SD) age was 49(11) years, and median(IQR) BMI was 32(29-39) kg/m^2.

Predicting SDB: Patient characteristics (See Table 1)

An AHI <5 ("rule-out measurement") was associated with female sex, younger age, lower weight and neck circumference, less frequently reported witnessed apnoeas, higher high density lipoprotein (HDL) cholesterol, and lower triglycerides, cholesterol/HDL and HbA1c. An AHI ≥15 ("rule-in measurement") was associated with male sex, obesity, higher weight, BMI and neck circumference, more frequently reported hypertension and witnessed apnoeas, lower HDL cholesterol, and higher triglycerides, cholesterol/HDL and HbA1c.

Predicting SDB: ESS, Berlin, STOP and STOP-BANG (See Tables 2, 3 and 4)

The ESS and Berlin questionnaire outcomes were not associated with either AHI cut-point. An AHI<5 was associated with lower STOP and STOP-BANG scores, and fewer subjects being classified as "high risk" for OSA by both STOP and STOP-BANG questionnaires. An

AHI≥15 was associated with higher STOP and STOP-BANG scores and more subjects being classified as "high risk" for OSA by the STOP-BANG questionnaire but not by the STOP questionnaire.

For the AHI cut-point of ≥5, the Berlin, STOP, and STOP-BANG questionnaires had high sensitivities, moderate positive predictive values (PPV) and poor specificities and negative predictive values (NPV), for prediction of SDB. The STOP-BANG questionnaire performed best with an overall accuracy of 79%. For the AHI cut-point of ≥15, the Berlin questionnaire had high sensitivity, but otherwise performed poorly. The STOP and STOP-BANG questionnaires had high sensitivities and NPVs. Again, the STOP-BANG questionnaire performed best, but with a low overall accuracy of 56%. The low negative likelihood ratios for the STOP and STOP-BANG questionnaires at both cut-points indicate that these questionnaires have value in excluding disease. As shown in table 4, the cut-points for STOP-BANG score that were associated with best overall accuracy were ≥3 and ≥6 for prediction of AHI ≥5 and ≥15, respectively.

SDB versus no SDB: Predictors and a composite score (See Tables 5 and 6 and Figure 1)

For the cut-point of AHI of ≥5, univariate logistic regression showed significant associations for age, gender, weight, neck circumference, witnessed apnoeas, triglycerides and cholesterol/HDL ($p<0.05$). For the cut-point of ≥15, significant associations were found for gender, weight, BMI, neck circumference, witnessed apnoeas, obesity, hypertension, FeNO and cholesterol/HDL ($p<0.05$). Multivariate logistic regression based on the significant variables from univariate logistic regression showed that for both cut-points neck circumference and witnessed apnoeas were independent predictors of SDB. For the cut-point of AHI of ≥5, in a model incorporating neck circumference and witnessed apnoeas, the

probability of SDB was 0.94 for individuals with neck circumference ≥17in and witnessed apnoeas (sensitivity 84%, overall accuracy 77%, ROC AUC 0.768, p<0.001). For the cut-point of AHI ≥15, the probability of SDB was 0.69 for individuals with neck circumference ≥17in and witnessed apnoeas (specificity 80%, overall accuracy 69%, ROC AUC 0.722, p<0.001).

Discussion

This is the first study to prospectively evaluate the utility of the Berlin, STOP and STOP-BANG questionnaires in prediction of sleep disordered breathing in a population referred to a tertiary sleep service for assessment of possible OSA. We found that in this population the Berlin Questionnaire had no significant association with cut-points of ≥5 or ≥15 for AHI, but that both the STOP and STOP-BANG scores were significantly associated with both cut-points. The STOP-BANG Questionnaire had better performance for the prediction of OSA on home sleep study, and different cut-points for STOP-BANG score could be selected depending on preference to exclude SDB (score <3) or predict SDB (score ≥6). In addition, we found notable associations between sleep study results and several patient characteristics. In particular, neck circumference and witnessed apnoeas were found to be independent predictors of SDB in our population.

In our study, the Berlin Questionnaire was almost ubiquitously positive (116 of 125 participants had a positive result) and the positivity rate did not differ between those with and without SDB. This was expected as this questionnaire was designed for primary care assessment and our study population consisted of individuals referred from primary care with symptoms suggestive of SDB. Our results indicate that the Berlin Questionnaire is not useful in the prediction of SDB in the sleep clinic referral population and this is consistent with

previous reports.(19) ~~However, t~~The high sensitivities obtained for both AHI cut-points support previous findings that the Berlin Questionnaire may have a role as a "rule-out" measurement in the primary care or screening setting(15, 17, 20, 24), though there have been some conflicting results, suggesting it does not have adequate discriminatory power.(16, 22)

In our study Epworth Sleepiness Scale data indicated that two thirds of participants had excessive daytime somnolence (ESS ≥11), however scores were similar in individuals with or without SDB. Therefore, at least in the sleep clinic population, the ESS ~~does not have utility in~~ is not useful for the prediction of SDB. ~~Nevertheless, i~~It may be of value, ~~be clinically useful in other respects –~~ perhaps ~~modified and/or~~ combined with other ~~structured questions~~measures, including those highlighted in this study, ~~–~~ in prediction of compliance with and benefit from OSA treatment ~~in patients with any degree of SDB~~. Further research is required to address this question. Exhaled nitric oxide levels were not significantly different between individuals with or without SDB whether defined by an AHI cut-point of ≥5 or ≥15. There is conflicting data in the literature regarding whether F_ENO is associated with SDB,(29-32) however our results suggest that it does not have utility in prediction of SDB; further work is required to clarify this.

We found that both the STOP and STOP-BANG questionnaires have utility in the prediction of SDB in the sleep clinic population, and that STOP-BANG was superior, with higher overall predictive accuracy. The STOP and STOP-BANG Questionnaires were developed and validated in a surgical population using in-laboratory polysomnagraphy(23) and have subsequently been studied in a cardiovascular disease population.(25) Our results are in agreement with these two earlier studies as regards the increased predictive value of STOP-BANG over STOP. In contrast to these earlier studies, however, we found sensitivities to be

higher and specificities to be lower for both cut-points of AHI. ~~This is as expected given that we were studying a symptomatic cohort referred to a sleep clinic, rather than a screening population, and this is also a desirable outcome for these questionnaires in situations where missing even mild OSA would be undesirable.~~ We suggest that of the two AHI cut-points, ≥15 events/hr is the more important, being diagnostic of at least moderate SDB and also an indication for CPAP treatment. At this cut-point, STOP and STOP-BANG performed with high sensitivities and negative predictive values (STOP-BANG superior to STOP) indicating that these questionnaires are more useful in excluding significant SDB. This is further corroborated by the negative likelihood ratios of <0.2 obtained for STOP and STOP-BANG that also indicate that these questionnaires are ~~likely~~ most useful ~~for~~ in ~~predicting low risk of confirming~~ruling out SDB. The STOP-BANG ~~: these~~ may be of ~~future~~ value in ~~combination in~~ the primary care setting, perhaps combined with type IV portable monitoring~~screening~~ sleep studies, to determine requirement for sleep clinic review and more detailed polygraphy.

At the AHI cut-point of ≥15, STOP-BANG had sensitivity and negative predictive value of 100%, and since this is the standard cut-point conventionally used to determine need for CPAP,(28) we suggest that the STOP-BANG questionnaire is the preferred tool for prediction of SDB in the sleep clinic setting of those currently available. STOP-BANG, perhaps with modifications, merits~~seems worthwhile for~~ further ~~exploration~~ evaluation for the prediction of ~~sleep study findings~~SDB in ~~a larger~~the sleep clinic ~~cohort~~ population and, more importantly, its utility in prediction of clinical outcomes including treatment success ~~in symptomatic and screening populations~~should be assessed.

The original STOP-BANG questionnaire uses a cut-point of ≥3 to predict SDB.(23) However, in our study we show that different cut-points can be selected depending on the

preference to rule-in or rule-out SDB. A score of ≥3 had the highest overall accuracy and a sensitivity of 0.93 for the AHI cut-point of ≥5, whereas a score of ≥6 had the highest overall accuracy and a specificity of 0.78 for the AHI cut-point of ≥15. Two other studies have examined the usefulness of different cut-points for STOP-BANG score.(33-34) In the obese, a score of ≥3 was associated with a sensitivity of 0.90 for predicting an AHI >5, whilst, a score of ≥6 had a specificity of 0.88 for predicting an AHI >15 and similar results ~~were~~ have been obtained in the morbidly obese(33) and in a~~nother~~ surgical population.(34) Thus, in the sleep clinic setting where the ultimate goal is to identify patients requiring CPAP, a higher cut-point for STOP-BANG may be preferred whereas in a primary care setting where the priority is not to miss disease a lower cut-point may be chosen.

The STOP-BANG questionnaire is, however, still an imperfect tool for prediction of results on home polygraphy. Accordingly, the secondary objective of our study was to identify ~~those~~ variables for inclusion~~, and how they should be weighted~~ in a locally developed composite score for future validation in the sleep clinic and potentially wider population. Univariate analysis showed several significant, expected associations for both cut-points of AHI. Using multivariate analysis, neck circumference ≥17in and the presence of witnessed apnoeas were independent predictors of SDB. This is not a novel finding, but does support the robustness of our data. Particularly when SDB was defined by an AHI cut-point of ≥5, the regression model derived indicated a high probability of SDB of 0.94 if both factors were present. The STOP-BANG questionnaire, of course, includes both of these variables, and it is possible that adjustment of the inclusion variables, or their weighting, might improve its performance. In future work, we aim to validate a simple composite score based on these two variables in a modification of ~~the~~ STOP-BANG ~~Questionnaire~~, to determine utility for predicting sleep study data and outcomes with treatment.

Ultimately, a predictive tool that can be utilised in primary care is the goal. Our results indicate low specificity of STOP-BANG, and therefore in its current form, if used in primary care to identify patients requiring referral for further assessment, it is likely to result in a significant percentage of patients being referred unnecessarily (false positives). It is hoped that a modified STOP-BANG with improved specificity, while not compromising sensitivity, may be developed that can be used safely in primary care for identification of patients requiring referral to sleep services. Of upmost importance too is the prediction of treatment outcome. Non-adherence to CPAP treatment occurs in between 46 and 83%.(35-36) Prediction of poor adherence by STOP-BANG or other similar tools would allow greater attention to interventions to improve adherence in patients more likely to default from treatment. The authors are not aware of any studies investigating this question and future research should explore this important issue.

A possible limitation of our study was that SDB was characterised using home unattended limited sleep studies rather that in-hospital attended full polysomnography. The latter is considered the gold standard for diagnosis of SDB but is more expensive, less easily accessed and potentially unrepresentative with sleep in an unfamiliar environment. Home unattended and in-hospital attended sleep studies have previously been shown to produce similar results. (37) Accordingly home testing with portable monitors is standard clinical practice in the UK, and is now considered an acceptable method for diagnosis of OSA by the American Academy of Sleep Medicine.(28) The sample size limits the conclusions that can be drawn from multivariate analysis, however this was a secondary objective of the current study. It is possible that variables predictive of SDB on univariate analysis in this cohort would have been identified as independently predictive in multivariate models in a larger population. The

results of this study allow us, and potentially others, to focus future work to validate more extensively the results obtained to date. We chose AHI cut-points of ≥5 and ≥15 to define significant SDB. This was based on the consensus guideline produced by the Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine that states that diagnosis of OSA is based on a cut-point of >15 events/hr or >5 events/hr with relevant symptoms, and that CPAP is indicated for treatment of moderate to severe OSA with ≥15 events/hr.(28) Although the cut-point of >30 events/hr is consistent with severe OSA we suggest that this cut-point is less clinically relevant from a diagnostic perspective or from that of determining treatment. Finally, due to the prospective design of our study, we cannot comment on the relative value of other tools developed for prediction of OSA such as the Sleep Apnea Clinical Score (38) and American Society of Anesthesiologists Checklist. (39) To compare their utility with that of the Berlin, STOP and STOP-BANG questionnaires in the population referred to the sleep service would require a further study.

In conclusion, the Berlin Questionnaire was not useful in the prediction of SDB within our sleep clinic population. The STOP-BANG questionnaire had superior predictive performance to the STOP questionnaire at both cut-points of AHI (≥5 and ≥15). A STOP-BANG score of ≥3 had the highest overall accuracy and a sensitivity of 0.93 for the prediction of an AHI≥5, whilst a score of ≥6 had the highest overall accuracy and a specificity of 0.78 for the prediction of an AHI ≥15. Future work will validate a composite score including neck circumference ≥17in and the presence of witnessed apnoeas for the prediction of SDB in the sleep clinic referral population. An optimised composite score could then be~~, with possibility then of evaluating~~ evaluated in primary care and against treatment outcomes, with our overall aim being to provide required tools for use in the expanded and consolidated sleep services that are now necessary~~,~~ given the current obesity and OSA epidemics.

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Table 1: Comparison of patient characteristics including anthropometric measurements, co-morbidities, symptoms, inflammatory markers, lipid profile and oximetry between groups without and with SDB as defined by AHI <5 events/hour and ≥15 events/hour.

	AHI<5	*AHI≥5*	*p*	*AHI<15*	*AHI≥15*	*P*
Male gender	**15/32 (47%)**	**67/97 (69%)**	**0.034**	**38/73 (52%)**	**44/56 (79%)**	**0.003**
Age (yrs)	**44 (12)**	**51 (11)**	**0.004**	48 (13)	51 (9)	0.103
Weight (kg)	**89 (19)**	**101 (22)**	**0.022**	**92 (21)**	**107 (20)**	**0.001**
BMI (kg/m^2)	31 (28-36)	33 (29-40)	0.118	**31 (27-36)**	**34 (31-41)**	**0.009**
Obesity (BMI≥30 kg/m^2)	18/28 (64%)	61/85 (72%)	0.482	**38/63 (60%)**	**41/50 (82%)**	**0.014**
Neck circumference (in)	**15 (2)**	**17(2)**	**<0.001**	**16 (2)**	**17 (1)**	**<0.001**
Neck circumference ≥17in	**4/22 (18%)**	**45/76 (59%)**	**0.001**	**18/54 (33%)**	**31/44 (70%)**	**<0.001**
Mallampatti	2 (1)	2 (1)	0.192	2 (1)	2 (1)	0.900
SBP (mmHg)	134 (17)	136 (16)	0.480	134 (15)	138 (18)	0.194
DBP (mmHg)	82 (11)	83 (9)	0.528	81 (10)	85 (10)	0.086
Diabetes	2/32 (6%)	6/97 (6%)	1.000	4/73 (5%)	4/56 (7%)	0.727
Hypertension	7/32 (22%)	36/97 (37%)	0.134	**18/73 (25%)**	**25/56 (45%)**	**0.024**
Hyperlipidaemia	2/32 (6%)	18/97 (19%)	0.156	10/73 (14%)	10/56 (18%)	0.625
Loud snorer	28/32 (88%)	92/97 (95%)	0.224	65/73 (89%)	55/56 (98%)	0.077
Witnessed apnoeas	**15/32 (47%)**	**72/97 (74%)**	**0.008**	**40/73 (55%)**	**47/56 (84%)**	**<0.001**
*Nocturia**	11/32 (34%)	38/97 (39%)	0.679	26/73 (36%)	23/56 (41%)	0.585
*Nocturnal wakenings**	18/32 (56%)	65/97 (67%)	0.293	46/73 (63%)	37/56 (66%)	0.853
Nocturnal choking	15/32 (47%)	35/97 (36%)	0.301	28/73 (38%)	22/56 (39%)	1.000
Nocturnal gasping	11/32 (34%)	38/97 (39%)	0.679	26/73 (36%)	23/56 (41%)	0.585
F_eNO (ppb)	15 (12-25)	18 (12-26)	0.595	15 (11-24)	19 (12-27)	0.050
Cholesterol (mmol/L)	5.2 (1.1)	5.4 (1.0)	0.431	5.3 (1.1)	5.4 (0.9)	0.674
HDL cholesterol (mmol/L)	**1.3 (1.0-1.5)**	**1.1 (1.0-1.3)**	**0.008**	**1.2 (1.0-1.4)**	**1.1 (1.0-1.2)**	**0.016**
Triglycerides (mmol/L)	**1.9 (1.0-2.5)**	**2.2 (1.5-3.2)**	**0.015**	**1.9 (1.3-2.9)**	**2.3 (1.6-3.2)**	**0.042**
Cholesterol/HDL	**4.1 (3.3-5.0)**	**4.7 (3.8-5.7)**	**0.011**	**4.3 (3.5-5.6)**	**4.8 (4.0-5.8)**	**0.022**
HbA1c (mmol/mol)	**34 (32-37)**	**38 (36-41)**	**0.001**	**36 (33-39)**	**38 (36-42)**	**0.002**
CRP	3.0 (1.2-8.5)	3.8 (1.4-7.5)	0.608	3.0 (1.3-7.6)	4.3 (1.4-8.6)	0.173

Legend for Table 1: Data presented as mean (standard deviation), median (interquartile range) or proportion (percentage) as appropriate. Significant differences in bold. * ≥2/night. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; F_ENO, fraction of exhaled nitric oxide; HDL, high density lipoprotein; HbA1c, glycated haemoglobin; CRP, C-reactive protein; ODI, oxygen desaturation index; SpO_2, oxygen saturation; SpO_2 t<90, duration of time for which oxygen saturation less than 90%.

Table 2: Comparison of results of Epworth Sleepiness Scale (ESS) and Berlin, STOP and STOP-BANG Questionnaires between groups without and with SDB as defined by AHI <5 events/hour and ≥15 events/hour.

	AHI<5	***AHI≥5***	***p***	***AHI<15***	***AHI≥15***	***p***
ESS score	13 (8-16)	13 (7-17)	0.845	13 (7-16)	13 (9-18)	0.476
ESS +ve (≥11/24)	17/28 (61%)	63/92 (68%)	0.496	42/66 (64%)	38/54 (70%)	0.560
Berlin +ve	29/31 (94%)	87/94 (93%)	1.000	65/71 (92%)	51/54 (94%)	0.731
STOP score	**2.5 (2-3)**	**3 (2-3)**	**0.011**	**3 (2-3)**	**3 (3-3.5)**	**<0.001**
STOP +ve (≥2/4)	**27/32 (84%)**	**93/96 (97%)**	**0.023**	66/73 (90%)	54/55 (98%)	0.137
STOP-BANG score	**4 (2-5)**	**5 (5-6)**	**<0.001**	**5 (2-5)**	**6 (5-6)**	**<0.001**
STOP-BANG +ve (≥3/8)	**21/30 (70%)**	**88/93 (95%)**	**<0.001**	**54/68 (79%)**	**55/55 (100%)**	**<0.001**

Legend for Table 2: Data presented as median (interquartile range) or proportion (percentage) as appropriate. Significant differences in bold.

Table 3: Sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), likelihood ratios positive (LR+), likelihood ratios negative (LR-), and overall accuracies of the Berlin, STOP and STOP-BANG Questionnaires for prediction of significant SDB as defined by: A: AHI ≥5 events/hour; B: AHI ≥15 events/hour.

A: Cut-point = AHI ≥5 events/hour

	Sensitivity	***Specificity***	***PPV***	***NPV***	***LR+***	***LR-***	***Accuracy***
Berlin	0.93 (0.85-0.97)	0.06 (0.01-0.21)	0.75 (0.66-0.83)	0.22 (0.03-0.60)	0.99	1.15	71%
STOP	0.97 (0.91-0.99)	0.16 (0.05-0.33)	0.78 (0.69-0.85)	0.62 (0.24-0.91)	1.15	0.20	77%
STOP-BANG	0.95 (0.88-0.98)	0.30 (0.15-0.49)	0.81 (0.72-0.88)	0.64 (0.35-0.87)	1.35	0.18	79%

B: Cut-point = AHI ≥15 events/hour

	Sensitivity	***Specificity***	***PPV***	***NPV***	***LR+***	***LR-***	***Accuracy***
Berlin	0.94 (0.85-0.99)	0.08 (0.03-0.17)	0.44 (0.35-0.53)	0.67 (0.30-0.92)	1.03	0.66	46%
STOP	0.98 (0.90-1.00)	0.10 (0.04-0.19)	0.45 (0.36-0.54)	0.88 (0.47-1.00)	1.09	0.19	48%
STOP-BANG	1.00 (0.94-1.00)	0.21 (0.12-0.32)	0.50 (0.41-0.60)	1.00 (0.77-1.00)	1.26	0.00	56%

Legend for Table 3: Data presented with 95% confidence intervals.

Table 4: Sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), likelihood ratios positive (LR+), likelihood ratios negative (LR-), and overall accuracies of different cut-points of the STOP-BANG questionnaire for prediction of significant SDB as defined by: A: AHI ≥5 events/hour; B: AHI ≥15 events/hour.

A: Cut-point = AHI ≥5 events/hour

STOP-BANG cut-point (/8)	*Proportion +ve SB*	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*LR+*	*LR-*	*Accuracy*
≥2	92/96	0.99 (0.92-1.00)	0.12 (0.03-0.32)	0.77 (0.67-0.85)	0.75 (0.19-0.99)	1.13	0.11	77%
≥3	82/96	0.93 (0.84-0.98)	0.38 (0.19-0.59)	0.82 (0.72-0.89)	0.64 (0.35-0.87)	1.49	0.18	79%
≥4	79/96	0.90 (0.81-0.96)	0.42 (0.22-0.63)	0.82 (0.72-0.90)	0.59 (0.33-0.82)	1.55	0.23	78%
≥5	67/96	0.81 (0.70-0.89)	0.62 (0.41-0.81)	0.87 (0.76-0.94)	0.52 (0.32-0.71)	2.15	0.31	76%
≥6	38/96	0.46 (0.34-0.58)	0.79 (0.58-0.93)	0.87 (0.72-0.96)	0.33 (0.21-0.46)	2.20	0.68	54%
≥7	15/96	0.18 (0.10-0.29)	0.92 (0.73-0.99)	0.87 (0.60-0.98)	0.27 (0.18-0.38)	2.17	0.89	36%
8	5/96	0.07 (0.02-0.15)	1.00 (0.86-1.00)	1.00 0.48-1.00)	0.26 (0.18-0.37)	-	0.93	30%

B: Cut-point = AHI ≥15 events/hour

STOP-BANG cut-point (/8)	*Proportion +ve SB*	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*LR+*	*LR-*	*Accuracy*
≥2	92/96	1.00 (0.91-1.00)	0.07 (0.02-0.18)	0.45 (0.34-0.55)	1.00 (0.40-1.00)	1.08	0	47%
≥3	82/96	1.00 (0.91-1.00)	0.25 (0.15-0.39)	0.50 (0.39-0.61)	1.00 (0.77-1.00)	1.34	0	57%
≥4	79/96	1.00 (0.91-1.00)	0.31 (0.19-0.45)	0.52 (0.40-0.63)	1.00 (0.80-1.00)	1.45	0	60%
≥5	67/96	0.93 (0.80-0.98)	0.47 (0.34-0.61)	0.57 (0.44-0.69)	0.90 (0.73-0.98)	1.76	0.15	67%
≥6	38/96	0.63 (0.47-0.78)	0.78 (0.65-0.88)	0.68 (0.51-0.82)	0.74 (0.61-0.85)	2.91	0.47	72%
≥7	15/96	0.22 (0.11-0.38)	0.89 (0.78-0.96)	0.60 (0.32-0.84)	0.60 (0.49-0.71)	2.01	0.88	60%
8	5/96	0.10 (0.03-0.23)	0.98 (0.90-1.00)	0.80 (0.28-0.99)	0.59 (0.48-0.70)	5.36	0.92	60%

Legend for Table 4: Data presented with 95% confidence intervals. Abbreviations: SB, STOP-BANG.

Table 5: Probabilities of SDB using a composite score based on neck circumference (≥17in or <17in) and presence (1) or absence (0) of witnessed apnoeas derived from logistic regression models. SDB defined by: A: AHI ≥5 events/hour; B: AHI ≥15 events/hour.

A: Cut-point = AHI ≥5 events/hour

	Witnessed Apnoeas	
Neck Circumference (in)	***0***	***1***
<17	0.47	0.75
≥17	0.83	0.94

B: Cut-point = AHI ≥15 events/hour

	Witnessed Apnoeas	
Neck Circumference (in)	***0***	***1***
<17	0.17	0.40
≥17	0.40	0.69

Table 6: Sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), and overall accuracies of logistic models for prediction of SDB as defined by: A: AHI ≥5 events/hour; predict SDB *unless* neck <17in *and* witnessed apnoeas absent; B: AHI ≥15 events/hour; predict SDB *only if* neck ≥17in *and* witnessed apnoeas present.

Model	***Sensitivity***	***Specificity***	***PPV***	***NPV***	***Accuracy***
A	0.84 (0.75-0.91)	0.54 (0.34-0.72)	0.85 (0.76-0.92)	0.52 (0.32-0.71)	77%
B	0.56 (0.41-0.70)	0.80 (0.68-0.89)	0.69 (0.53-0.82)	0.69 (0.57-0.79)	69%

Legend for Table 6: Data presented with 95% confidence intervals.

Figure 1: ROC curves of logistic models for prediction of SDB as defined by: Model A: AHI ≥5 events/hour; predict SDB *unless* neck <17in *and* witnessed apnoeas absent; Model B: AHI ≥15 events/hour; predict SDB *only if* neck ≥17in *and* witnessed apnoeas present.

~~Model A:~~

~~Model B:~~

Contributorship Statement:

Douglas Cowan took a leading role in study protocol development, study document development, application for ethics approval, data collection, statistical analysis and paper writing.

Gwen Allardice provided statistical support and performed part of the statistical analysis.

Duncan MacFarlane, Darren Ramsay and Heather Ambler contributed to data collection, and carried out and scored sleep studies.

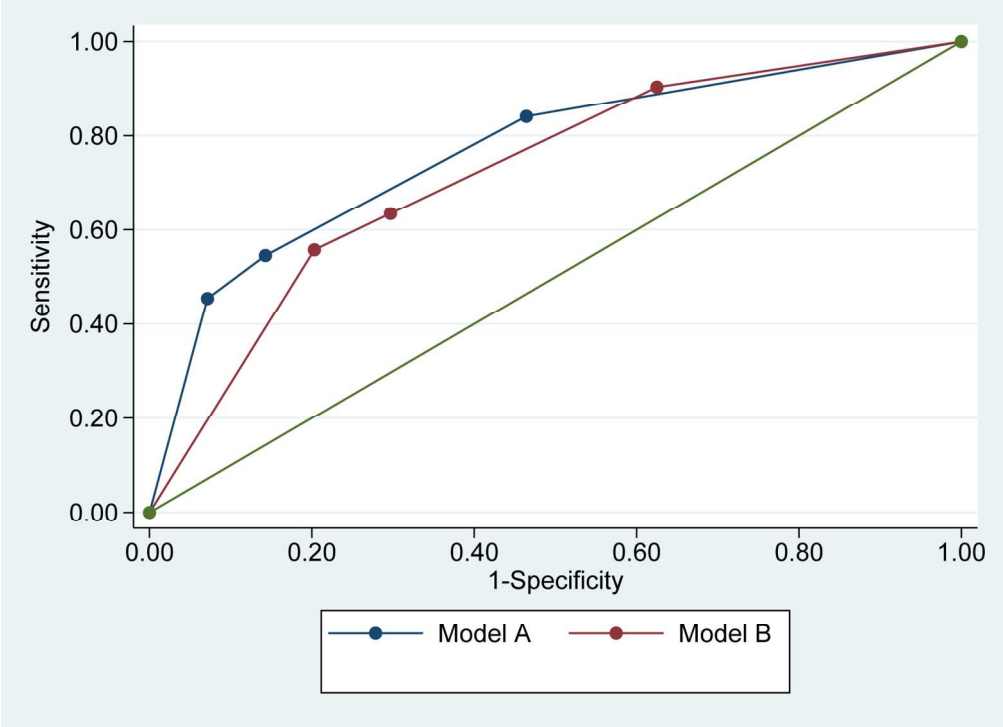
Stephen Banham contributed to study protocol development.

Eric Livingston contributed to study protocol development, study document development, application for ethics approval and paper writing.

Christopher Carlin contributed to study protocol development, data collection, statistical analysis and paper writing.

All authors approved the final draft before submission.

Christopher Carlin is responsible for the overall content as guarantor.



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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7*
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	

Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,18
		(b) Indicate number of participants with missing data for each variable of interest	19
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*9,10,19-23*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	20-21
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10,22-23
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.