National Institute for Health and Care Excellence

Final

Obstructive sleep apnoea/hypopnoea syndrome and obesity hypoventilation syndrome in over 16s

Evidence review A: When to suspect OSAHS, OHS and COPD–OSAHS overlap syndrome

NICE Guideline NG202

Diagnostic association/prediction evidence review

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Final

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

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1.1. Review question: In whom should obstructive sleep apnoea/hypopnoea syndrome (OSAHS), obesity hypoventilation syndrome (OHS) or COPD-OSAHS overlap syndrome be suspected (for example, based on symptoms or coexisting conditions)?

1.2. Introduction

People with obstructive sleep apnoea experience frequent episodes of complete or partial upper airway obstruction which disrupt sleep and lead to a range of symptoms. Typically, these relate to sleepiness and upper airway side effects, such as choking. More recently it has been recognised that some people experience sleep disruption and insomnia rather than hypersomnolence. As the condition is common, primary care practitioners and pre-operative assessment teams should have awareness of symptoms, and that sleep disturbance may be a presenting feature. Obese people (BMI over 30 kg/m^2) may develop OSAHS or hypoventilation during sleep. Obesity hypoventilation is defined as BMI over 30 kg/m^2 and with PaCO2 greater than 6.0kPa during wakefulness plus sleep disordered breathing. COPD-OSAHS overlap syndrome in seen in people with COPD and OSAHS, so eliciting sleep related symptoms in a COPD patient is important.

1.3. PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People without a diagnosis of OSAHS/OHS/ COPD-OSAHS overlap syndrome Stratification by setting – primary care vs specialist care
Prognostic variables under consideration	Predictors: Symptoms & signs • snoring • witnessed apnoea • unrefreshing sleep • somnolence during waking hours • nocturia • tiredness • insomnia • headaches • sleep fragmentation • ankle swelling • unexplained elevated Hb • cognitive dysfunction/memory impairment Co-existing conditions • treatment resistant hypertension • nocturnal non-dipping hypertension • treatment resistant arrhythmias

	• atrial fibrillation • T2DM • diabetic macular oedema • aortic aneurysms • chronic heart failure • cardiovascular events • stroke • down's syndrome • acromegaly • BMI over 30 kg/m^2 Any of the above, alone or in combination
Comparator	Any of the above vs an absence of risk factors
Confounding factors	age, sex, BMI, co-morbidities

Outcomes	• association data
	  ○ adjusted RR or OR (adjusted for key confounders of age, sex, BMI, co-morbidities)
	• accuracy data
	  ○ sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)
	
	Stratified by prediction of OSAHS or OHS or COPD OSAHS overlap syndrome

Study design	• prospective cohort studies • retrospective cohort studies will be included only if no sufficient prospective cohort studies are identified • including studies with cross-sectional assessment of presence or absence of the relevant diagnosis (i.e. all participants must be tested for presence or absence of OSAHS/OHS/ COPD OSAHS overlap syndrome) Studies will only be included if all the key confounders have been accounted for in a multivariate analysis

1.4. Clinical evidence

1.4.1. Included studies

OSAHS

A search was conducted for cohort studies investigating the association of the following factors: snoring, witnessed apnoea, unrefreshing sleep, somnolence during waking hours, nocturia, tiredness, insomnia, headaches, sleep fragmentation, ankle swelling, unexplained elevated Hb, cognitive dysfunction/memory impairment, co-existing conditions, treatment resistant hypertension, nocturnal non-dipping hypertension, treatment resistant arrhythmias, atrial fibrillation, type 2 diabetes, diabetic macular oedema, aortic aneurysms, chronic heart failure, cardiovascular events, stroke, Down's syndrome, acromegaly and BMI over 30 kg/m^2 with suspected OSAHS.

Seventeen studies were included in the review:[15, 22, 45, 69, 74, 88, 104, 113, 114, 179, 182, 201, 216, 222, 224, 229, 250]

Evidence from these studies is summarised in the clinical evidence summary below.

The included studies investigated the effects of following risk factors: non-arteritic anterior ischaemic optic neuropathy (NAION) (sudden loss of vision in one eye due to decreased blood flow to the optic nerve), polycystic ovary syndrome (PCOS), bipolar disorder, essential hypertension, end-stage renal disease (ESRD), acute cerebral infarction (ACI) and transient ischemic attack (TIA), asthma, severe aortic stenosis (AS), thoracic aortic aneurysm (TAA), obesity, asthma, type 2 diabetes, mild cognitive impairment (MCI), Down's syndrome (DS), type 1 diabetes and primary headache disorders (PHD).

Some risk factors such as non-arteritic anterior ischaemic optic neuropathy (NAION), polycystic ovary syndrome (PCOS), bipolar disorder, end-stage renal disease (ESRD) were not specified in the protocol but were included as the committee considered these were risk factors to be associated with high risk for OSAHS.

No relevant clinical studies investigating the effects of snoring, witnessed apnoea, unrefreshing sleep, somnolence during waking hours, nocturia, tiredness, insomnia, sleep fragmentation, ankle swelling, unexplained elevated Hb, treatment resistant arrhythmias, atrial fibrillation, diabetic macular oedema, aortic aneurysms, chronic heart failure, acromegaly on risk of OSA were identified.

All studies were conducted in secondary care.

Only 3 studies matched controls for all key confounders (age, sex, BMI, co-morbidities) and the rest of the studies adjusted for 2 or 3 confounders.

Most studies reported incidence/prevalence of OSAHS as the outcome; however, a few studies reported AHI which was also considered as an association outcome.

Some studies reported results as adjusted odds ratio/hazards ratio for the outcomes, and these have been reported as in the studies. Some studies had matched controls but did not report adjusted measures of effect in such cases data has been analysed using prevalence/incidence data of OSAHS reported in the studies.

OHS

No studies were identified assessing the risk of OHS.

COPD-OSAHS overlap syndrome

No studies were identified assessing the risk of COPD-OSAHS overlap syndrome.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.4.1.1. Excluded studies

See the excluded studies list in Appendix D.

1.4.2. Summary of clinical studies included in the evidence review

Study	Risk factor	Population	Outcomes	Comments
Arda 2013[15] Turkey Prospective cohort study	Non-arteritic anterior ischaemic optic neuropathy (NAION).	N= 20 patients with a newly diagnosed NAION were included in this study. N= 20 age and sex matched subjects with similar risk factors for NAION, such as DM and HT, constituted the control group.	Diagnosis of sleep apnoea	The aim of this study was to show the prevalence of obstructive sleep apnoea (OSA) in non-arteritic anterior ischaemic optic neuropathy (NAION). Controls matched for age and sex. Not matched for BMI and co-morbidities. Duration of study- 4 years
Balachandran 2019[22] UK Population-based retrospective cohort study	Polycystic ovary syndrome (PCOS).	N= 76 978 women with PCOS and N=143 077 matched control women without PCOS. Matched for age-, BMI- and location. Inclusion criteria: All women who were aged 18–50 years at the index date (study entry) and had a documentation of PCOS at any time during the study period were included in the exposed group. Patients with any documentation of OSA prior to the index date were excluded. Women without documented PCOS at any time during the study period were included in the unexposed (control) arm. The index date was defined as the date of first documentation of PCOS for newly diagnosed cases and from the date patient became eligible if the first documentation of PCOS was prior to the eligibility date Each exposed patient was randomly matched to two unexposed patients (1:2 ratio) for general practice, age at index date and BMI	Incidence of OSA	Objective was to assess the risk of OSA in women with vs without PCOS Controls matched for age at index date and BMI Duration of study- 7 years

Study	Risk factor	Population	Outcomes	Comments
Chang 2019[45] Taiwan Prospective cohort study	Bipolar disorder	N=3650 patients with bipolar disorder and who had no history of OSA prior to enrolment Only patients who were prescribed lithium, valproate, carbamazepine, lamotrigine, aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone for at least 28 cumulative days after the date of BD diagnosis were included in the BD cohort. N=18250 without bipolar disorder matched by sex and age	Incidence of OSA follow-up 7.49 years	Matched by age and sex Participants enrolled between 2000 and 2010 and followed until end of 2013
Fletcher 1985[69] USA Prospective cohort study	Essential hypertension	N=46 hypertensive men N=34 normotensive men	Apnoea index Hypopnoea index	Matched only for age and weight Duration of study-NR
Gaisl 2020[74] Prospective cohort study Switzerland	Patients with thoracic aortic aneurysm (TAA).	N=208 TAA N=104 control Patients with TAA were recruited from an ongoing cohort study. Matched controls were recruited form the outpatient clinic of the University Hospital Zurich between Jan and November 2018 82% male; age: 62 (11) years; BMI 27 (4) Kg/m2	Prevalence of OSA	Confounding variables: Age, sex, height, weight and left ventricular ejection fraction Duration of study-NR
Hachul 2019[88] Prospective cohort study Brazil	Women with polycystic ovary syndrome (PCOS).	N=30 PCOS N=14 healthy control A total of 55 subjects were selected to participate in the study. The volunteers, ranging in age from 16 to 45 years, were recruited from the Endocrinology Division of the Federal University of São Paulo, Brazil.11 individuals were excluded because of missing data (8 related to the PSQI and 3 to BMI).	High risk of OSA	Confounding variables: Age, BMI Duration of study-NR
Huang 2018[104]	end-stage renal disease	Dialysis patients.	Risk of OSA	Confounding variables: age, sex,

Study	Risk factor	Population	Outcomes	Comments
	(ESRD)	90,353 patients with newly diagnosed ESRD from 1 January 2000 to 31 December 2011. After excluding patients who were under 20 years of age, and those who had an OSA history), kidney transplantation, or a follow-up period of less than 90 days, 88,801 ESRD patients were enrolled, including 78,814 HD and 9987 PD (including continuous ambulatory peritoneal dialysis and automated peritoneal dialysis) patients. Next haemodialysis (HD) with peritoneal dialysis (PD) patients were matched by age and sex in a 2:1 ratio and generated an ESRD cohort including a HD cohort consisting of 19,574 patients and a PD cohort with 9987 patients. 118,244 individuals were selected in the database who did not have a history of CKD or ESRD as the non-ESRD control cohort matched with the ESRD cohort by age, sex, and index-year in a 1:4 ratio. Men: control 55,092 (46.6 %); total ESRD 13,773 (46.6%) Mean age (SD): control- 54.0 (14.9); 54.1 (14.8)		and index-year. Duration: Between 2010 and 2011
Joo 2011[113] Korea Prospective cohort study	acute cerebral infarction (ACI) and transient ischemic attack (TIA)	N=61 patients with acute cerebral infarction (ACI) N=13 patients with transient ischemic attack (TIA); N= 64 control Consecutive patients (aged 45 to 80 years) admitted to the Department of Neurology at the Korea University Medical Center for an ACI or transient ischemic attacks (TIA), with 48 h of onset, were enrolled in the present study. Patients with any of the following were excluded: (1) a decreased level of consciousness on admission;	Prevalence of sleep disordered breathing	Controls matched for age- not matched for all sex, BMI and co-morbidities. SDB at 48 h following ACI or TIA

Study	Risk factor	Population	Outcomes	Comments
		(2) a seizure at stroke onset; (3) a baseline oxygen saturation of <95%; (4) chronic obstructive pulmonary disease; (5) a neuromuscular junction disorder (e.g., myasthenia gravis); or (6) a neurodegenerative disorder, such as, Parkinson's disease, progressive supra nuclear palsy, or Alzheimer's disease. Age-matched patient's spouses or family members with no history of physician diagnosed stroke were enrolled as controls		
Julien 2009[114] Canada Prospective cohort study	Asthma	N= 26 patients with severe asthma consecutively recruited to a difficult asthma program N= 26 patients with moderate asthma, N= 26 controls without asthma of similar age and body mass index. Subjects with asthma were recruited from the Difficult Asthma Programme.2 Recruitment to the programme was solely on the basis of asthma history. Severe asthma was defined according to American Thoracic Society criteria1 and required at least 1 major criterion: daily oral steroids for >50% of the previous 12 months, or high-dose inhaled steroid: fluticasone 1000 mg/d or equivalent, and at least 1 other add-on therapy continuously for 12 months; and 2 minor criteria: daily short-acting b-agonist persistent FEV1 <70% and FEV1/forced vital capacity <80% predicted, urgent visits or steroid bursts in the last 12 months, prompt deterioration with <25% steroid dose reduction, or previous near-fatal asthma within 3 years. Moderate asthma was defined as well controlled asthma symptoms (Juniper asthma control score13 <1), use of long acting b-agonist and	Prevalence of OSA	Control group matched for age, BMI and sex Duration of study-NR

Study	Risk factor	Population	Outcomes	Comments
		fluticasone (or equivalent) 200 mg/d and 1000 mg/d, 2 steroid bursts in the past year and none within 3 months, total days on oral steroids <30 in the previous 12 months, FEV1 >70% predicted, and 1 unscheduled clinical visit in the previous 12 months. Exclusion criteria for both groups included current smoking and other conditions which could lead to cardiorespiratory symptomatology. No sleep related information was obtained from subjects before recruitment into the Difficult Asthma Program or the current study. Consecutive patients enrolled in the program were approached to participate in this study. Of the patients approached during the recruitment period, 26 of 27 patients with severe asthma and 26 of 31 patients with moderate asthma consented to participate. Control subjects were recruited through community advertisements, which referred to a clinical study on ‘‘breathing patterns and asthma.’’ Subjects were required to be generally healthy, to be non- smoking for at least 1 year, and to have no previous history of asthma, respiratory problems, or prescription of inhalers. No sleep-related information was used in the recruitment or screening process. Potential recruits meeting eligibility criteria were included based on age, body mass index (BMI), and sex to match the asthmatic groups. Epworth sleepiness scores were obtained only after informed consent.		
Prinz 2011[179] Germany Prospective cohort	Severe aortic stenosis (AS).	N=67	Prevalence of sleep apnoea	Study objective to assess the occurrence, severity and clinical correlates of sleep apnoea in

Study	Risk factor	Population	Outcomes	Comments
study		Severe aortic stenosis (AS). N=42 consecutive patients (19 male; mean age 72 years), who came for further evaluation of isolated severe aortic stenosis (aortic valve opening area #1.0 cm2); all patients with diabetes mellitus and concomitant pulmonary disease, particularly those with forced expiratory volume in 1s <50%, were excluded. Further exclusion criteria included a diagnosis of acute coronary syndrome or change of stable medication within the preceding 2 weeks. All patients had standard preoperative diagnostics, including echocardiography and left and right heart catheterisation. Right heart catheterisation was carried out to assess mean pulmonary artery pressure (mPAP) and pulmonary capillary wedge pressure (PCWP).13 In-hospital unattended cardiorespiratory polygraphy was performed after informed consent had been obtained from each patient before participation. Control group N=25 patients (14 male; 70 years), who had cardiac catheterisation based on a pathological stress test and individual risk stratification. Coronary artery disease was angiographically excluded in each of these patients. The entire control group had preserved left ventricular ejection fraction (>55%) and no valve disease. The control group was matched for age, gender and body mass index (BMI).		patients with AS. Control group was matched for age, gender and body mass index (BMI). Not matched for co-morbidities. Study period: 4 months
Subramanian 2019[216]	Type 2 diabetes	N= 360,250 exposed cohorts	Incidence of OSA	Objective to compare incidence of OSA in patients with and without

Study	Risk factor	Population	Outcomes	Comments
Retrospective cohort study UK		N=1,296,489 unexposed patient cohorts Adult patients aged 16 years and above registered for at least 12 months with any of the eligible general practices prior to study entry formed the source population. The exposed cohort consisted of adult patients with type 2 diabetes. Type 2 diabetes diagnosis was ascertained by the presence of any type 2 diabetes clinical code in the patient's medical record and the absence of any record of type 1 diabetes. The Read code list used to define exposure has previously been used to study type 2 diabetes. Unexposed cohort For every exposed patient, up to 4 controls were randomly selected from an age-, sex- and BMI-matched pool of eligible patients without a record of type 2 diabetes at any time point before or during the study period. Age and BMI were matched to within 1 year and 2 kg/m2 respectively. Patients with a prevalent OSA diagnosis were excluded. The study cohort was derived from The Health Improvement Network (THIN), a UK primary care database, from 01/01/2005 to 31/12/2017.		type 2 diabetes and to investigate risk factors for OSA in patients with type 2 diabetes. Follow-up period- 15 months. Control group matched for age, sex and BMI.
Rice 2015[182] USA prospective cohort study	Obesity	N=573 lean women (BMI of less than 25 kg/m^2) N=459 obese women (BMI total of 1032 pregnant women	High risk for OSA	Analysis adjusted for maternal age, education, marital status and parity. Adjusted odds ratio reported.

Study	Risk factor	Population	Outcomes	Comments
		between the ages of 18 and 45 years (mean age = 28.6 years, standard deviation = 6.2 years) participated in the study. This study was conducted among pregnant women attending prenatal care clinics at the Instituto Nacional Materno Perinatal (INMP) in the city of Lima, Peru between February 2013 and March 2014. Eligible women were 18 years of age or older, could speak and read Spanish, and with a gestational age between 24 to 28 weeks. Women were weighed in light clothing using the WHO standard guidelines.		Duration of study-2013-2014
Shen 2015[201] Taiwan retrospective cohort study	Asthma	N = 155347 without asthma N = 38840 with asthma Patients above 20 years, who had been diagnosed with asthma, as the asthma cohort. Exclusion criteria included those diagnosed before index date, and with incomplete gender or age information. The index date was defined as the date of asthma diagnosis. The comparison cohort was randomly selected from all NHI beneficiaries, no asthma, above 20 years, and were frequency-matched for gender, age (every five years), and Index year with a 1:4 ratio. The diagnosis of asthma was made based on a target history, and a comprehensive pulmonary function evaluation.	Incidence of OSA	Model adjusted for age, sex and comorbidities of hypertension, diabetes, hyperlipidaemia, COPD, CAD, stroke, rhinitis, chronic sinusitis, GERD and obesity. The mean follow-up period was 6.95 years (SD = 3.33) for the asthma cohort, and 6.51 years (SD = 3.44) for the comparison cohort.
Terpening 2015[222] Australia Prospective cohort	Mild cognitive impairment (MCI)	N=46 patients with MCI N=40 age matched controls	Sleep disordered breathing	Control group matched for age Duration of study-NR

Study	Risk factor	Population	Outcomes	Comments
study				
Trois 2009[224] USA Retrospective cohort study	Down's syndrome (DS)	N= 16 with Down's syndrome (DS) N= 48 without Down's syndrome (DS). 16 adults with DS underwent evaluation for sleep disordered breathing. Interventions: Polysomnographic results were compared to a retrospective sample of adult patients referred for clinically suspected OSAS.	Diagnosis of sleep apnoea	Controls matched for age, sex and BMI Duration of study-NR
Van dijk 2011[229] The Netherlands Retrospective cohort study	type 1 diabetes	N= 99 adult patients with type 1 diabetes (55 men, 44 women, duration of diabetes 26.9±1.2 years) N= 99 age-, sex- and BMI-matched non-diabetic controls. 99 consecutive patients with type 1 diabetes mellitus (55 men, 44 women) attending the outpatient clinic of the Leiden University Medical Center, and 99 age-, sex- and BMI-matched non-diabetic controls recruited by advertisement. Every patient with type 1 diabetes was individually matched with one non-diabetic healthy control for age, sex and BMI	High risk OSA	Matched for age, sex and BMI. Duration of study-NR
Yin 2019[250] Taiwan Retrospective cohort study	Primary headache disorders (PHD)	N=1346 Primary headache disorders (PHD) cohort N=5384 Comparison cohort. All patients in longitudinal health insurance database (LHID) who were diagnosed for PHDs for the first time from 2000 to 2005 were identified according to the International Classification of Headache Disorders, Second Edition criteria (N=1346). Patients diagnosed of	Incidence of OSA	Adjusted for confounding variables: age, sex, index date and comorbidities (chronic obstructive pulmonary disease [COPD], hypertension, diabetes, hyperlipidaemia, stroke, obesity and depression). Duration of study-NR

Study	Risk factor	Population	Outcomes	Comments
		PHDs before 2000 were excluded to increase the likelihood of identifying new cases. From the beginning of 2000 to the end of 2005 during which a patient was first diagnosed with PHDs was set as the index date. randomly selected 5384 subjects (a sample size fourfold that of the PHDs group) from LHID, frequency matched with the study cohort in terms of age, sex, index date and comorbidities (chronic obstructive pulmonary disease [COPD], hypertension, diabetes, hyperlipidaemia, stroke, obesity and depression). Each patient was then followed up from the index date until the occurrence of SA.		

1.4.3. Quality assessment of clinical studies included in the evidence review

Table 2: Clinical evidence summary: People with primary headache disorder vs control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	HR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Primary headache disorder (95% CI)
Incidence of sleep apnoea	6730 (1 study)	⨁⨁⊖⊖ LOW[2,] due to risk of bias	HR 2.17 (1.26 to 3.7)[1]	7 per 1000	8 more per 1000 (from 2 more to 19 more)[3]

1 multivariate cox proportional hazards regression analysis measured HR
2 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
3 GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.

Table 3: Clinical evidence summary: People with asthma vs control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	HR (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Asthma (95% CI)
Incidence of OSA	194187 (1 study)	⨁⨁⊖⊖ LOW [2] due to risk of bias	HR 1.87 (1.61 to 2.17)[1]	3 per 1000	3 more per 1000 (from 2 more to 4 more)[3]

1 Model adjusted for age, sex and comorbidities of hypertension, diabetes, hyperlipidaemia, COPD, CAD, stroke, rhinitis, chronic sinusitis, GERD and obesity
2 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
3 GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.

Table 4: Clinical evidence summary: People with moderate asthma vs People without asthma

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No asthma	Risk difference with Moderate asthma (95% CI)
prevalence of OSA -total AHI >15 events/hour	52 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.88 (0.97 to 3.64)	Moderate	
				308 per 1000	271 more per 1000 (from 9 fewer to 813 more)

1 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Default MID (0.5XSD) used to assess imprecision. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.

Table 5: Clinical evidence summary: People with severe asthma vs People without asthma

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No asthma	Risk difference with Severe asthma (95% CI)
prevalence of OSA -total AHI >15 events/hour	52 (1 study)	⨁⊖⊖⊖ VERY LOW[1] due to risk of bias	RR 2.88 (1.59 to 5.2)	Moderate	
				308 per 1000	579 more per 1000 (from 182 more to 1000 more)[2]

1 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.

Table 6: Clinical evidence summary: People with bipolar disorder vs control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Bipolar disorder (95% CI)
Incidence of OSA	21900 (1 study)	⨁⊖⊖⊖ VERY LOW[2,3] due to risk of bias, imprecision	HR 1.54 (0.99 to 2.37)[1]	5 per 1000	3 more per 1000 (from 0 fewer to 7 more)

1 Adjusted for demographics and baseline co-morbidities.
2 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
3 Default MID (0.5XSD) used to assess imprecision. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.

Table 7: Clinical evidence summary: People with hypertension (essential hypertension) vs control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Hypertensives (95% CI)
apnoea index	80 (1 study)	⨁⊖⊖⊖ VERY LOW due to risk of bias[1]		The mean apnoea index in the control groups was 3.3	The mean apnoea index in the intervention groups was 6.7 higher (5.99 to 7.41 higher)
hypopnoea index	80 (1 study)	⨁⊖⊖⊖ VERY LOW due to risk of bias[1]		The mean hypopnoea index	The mean hypopnoea index in the intervention groups was 2.5 higher (1.95 to 3.05 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Hypertensives (95% CI)
				in the control groups was 5.6	
1 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias					

Table 8: Clinical evidence summary: People with type I diabetes vs control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Type I diabetes (95% CI)
Increased risk of OSA	198 (1 study)	⨁⊖⊖⊖ VERY LOW[1] due to risk of bias	RR 3.4 (1.31 to 8.86)	Moderate	
				51 per 1000	122 more per 1000 (from 16 more to 401 more) [2]
1 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.					

Table 9:Clinical evidence summary: People with non-arteritic anterior ischaemic optic neuropathy (NAION) vs control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Patients with non-arteritic anterior ischaemic optic neuropathy (95% CI)
Prevalence of OSA				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Patients with non-arteritic anterior ischaemic optic neuropathy (95% CI)
	40 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.31 (0.9 to 1.89)	650 per 1000	201 more per 1000 (from 65 fewer to 578 more)

1 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Default MID (0.5XSD) used to assess imprecision. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.

Table 10: Clinical evidence summary: People with PCOS vs people without PCOS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Without PCOS	Risk difference with PCOS (95% CI)
Incident OSA	220,055 (1 study)	⨁⊖⊖⊖ VERY LOW[1] due to risk of bias	RR 2.49 (2.10 to 2.97)	Moderate	
				2 per 1000	3 more per 1000 (from 2 more to 4 more)[2]
High risk for OSA (Berlin questionnaire)	44 (1 study)	⨁⨁⊖⊖ LOW[1] due to risk of bias	RR 8.87 (1.32 to 59.77)	Moderate	
				71 per 1000	559 more per 1000 (from 23 more to 1000 more)[2]

1 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2. Default MID (0.5XSD) used to assess imprecision. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.

Table 11: Clinical evidence summary: obese pregnant women vs lean pregnant women

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Lean pregnant women	Risk difference with Obese pregnant women (95% CI)
Incidence of OSA	682 (1 study)	⨁⨁⨀⨀ LOW[2] due to risk of bias	OR 13.2 (6.27 to 27.79)[1]	21 per 1000	199 more per 1000 (from 97 more to 352 more) [3]

1 adjusted odds ratio

2 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

3 GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.

Table 12: Clinical evidence summary: overweight pregnant women vs lean pregnant women

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Lean pregnant women	Risk difference with Overweight pregnant women (95% CI)
Incidence OSA	682 (1 study)	⨁⨁⨀⨀ LOW[2] due to risk of bias	OR 3.69 (1.82 to 7.48)[1]	21 per 1000	52 more per 1000 (from 17 more to 117 more)[3]

1 adjusted odds ratio

2 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

3 GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.

Table 13: Clinical evidence summary: People with acute cerebral infarction vs control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Acute cerebral infarction (95% CI)
prevalence of OSA	125 (1 study)	⨁⨁⊖⊖ LOW[1] due to risk of bias	RR 1.55 (1.01 to 2.38)	Moderate	
				328 per 1000	180 more per 1000 (from 3 more to 453 more)[2]

1 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

2. Default MID used to assess imprecision. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.

Table 14: Clinical evidence summary: People with transient ischaemic attack vs control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Transient ischaemic attack (95% CI)
prevalence of OSA	77 (1 study)	⨁⊖⊖⊖ VERY LOW[1] due to risk of bias	RR 2.11 (1.27 to 3.49)	Moderate	
				328 per 1000	364 more per 1000 (from 89 more to 817 more) [2]

1 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

2 Default MID (0.5XSD) used to assess imprecision. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.

Table 15: Clinical evidence summary: People with mild cognitive impairment vs control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Mild cognitive impairment (95% CI)
AHI	86 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean AHI in control group was 12.6	The mean ahi in the intervention groups was 2.3 higher (3.2 lower to 7.8 higher)

1 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Default MID (0.5XSD) used to assess imprecision.

Table 16: Clinical evidence summary: People with severe aortic stenosis vs control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Severe aortic stenosis (95% CI)
prevalence OSA[2]	67 (1 study)	⨁⊖⊖⊖ VERY LOW[1] due to risk of bias	RR 0.56 (0.34 to 0.92)	Moderate	
				640 per 1000	282 fewer per 1000 (from 51 fewer to 422 fewer)2

1 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2 GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.

Table 17: Clinical evidence summary: People with Down's syndrome vs control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Median and range	Anticipated absolute effects	
				Risk with Control	Risk difference with Downs syndrome (95% CI)
Mean AHI	64 (1 study)	VERY LOW[1] due to risk of bias	Down's syndrome: 37 (0-118) Control: 16 (0-148)		Not estimable[2]

1 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias; no indirectness

2 Data not in an analysable format. Reported as in the paper.

Table 18: Clinical evidence summary: People with type 2 diabetes vs without type 2 diabetes

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	IRR[2] (95% CI) [fully adjusted]	Anticipated absolute effects	
				Risk with Control	Risk difference with patients with type 2 diabetes (95% CI)
risk of OSA	N= 360,250 exposed and 1,296,489 unexposed patient cohorts [1]	VERY LOW[3] due to risk of bias	1.36 (1.30-1.42) [5] Type 2 diabetes: 3110/360250 (0.88%) Without type 2 diabetes: 1296489/5968 (0.46%)	-	Not estimable [4]

1Methods: multivariable analysis. Key covariates included: age, sex, BMI, Townsend deprivation quintile, smoking status and ethnicity.

2adjusted incidence rate ratio

3 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias; no indirectness

4 Data as reported as in the paper

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	IRR[2] (95% CI) [fully adjusted]	Anticipated absolute effects	
				Risk with Control	Risk difference with patients with type 2 diabetes (95% CI)
5 Default MID (0.5XSD) used to assess imprecision. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.					

Table 19: Clinical evidence summary: People with end stage renal disease (ESRD) haemodialysis and peritoneal dialysis vs control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	aSHR (95% CI)[1]	Anticipated absolute effects	
				Risk with Control	Risk difference with End stage renal disease (ESRD) haemodialysis (95% CI)
risk of OSA	N = 29561 (1 study)	⨁⊖⊖⊖ VERY LOW[2] due to imprecision	aSHR 1.31 (0.7 to 2.45)1	-	
1 adjusted sub hazard ratio, multivariable analysis including age, gender, CAD, stroke, hyperlipidaemia, COPD, hypertension, CHF, and obesity 2 Default MID used to assess imprecision. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.					

Table 20: Clinical evidence summary: People with thoracic aortic aneurysm vs matched control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Adjusted odds ratio	Anticipated absolute effects	
				Risk with Control	Risk difference with End stage renal disease (ESRD) haemodialysis (95% CI)
Prevalence of OSA	N = 312 (1 study)	⨁⊖⊖⊖ LOW[2] due to imprecision	1.87 [95% 1.05-3.34]	47% (n=104)	Not estimable[3]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Adjusted odds ratio	Anticipated absolute effects	
				Risk with Control	Risk difference with End stage renal disease (ESRD) haemodialysis (95% CI)
(Defined as AHI≥/5)			Risk with TAA group- 63% (n=208)		

1 adjusted for the matching variables age, sex, height, weight and left ventricular ejection fraction.
2 Default MID used to assess imprecision. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.

See Appendix F for full GRADE tables.

1.5. Economic evidence

1.5.1. Included studies

No health economic studies were included.

1.5.2. Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.5.3. Health economic modelling

Original modelling was not conducted for this question.

1.5.4. Health economic evidence statements

No relevant economic evaluations were identified.

1.6. The committee's discussion of the evidence

1.6.1. Interpreting the evidence

1.6.1.1. The outcomes that matter most

The committee considered assessment of presence or absence of OSAHS, OHS or COPD OSAHS overlap syndrome for decision making.

Most studies reported incidence/prevalence of sleep apnoea as the outcome; however, a few studies reported AHI which was also considered as a direct association for OSAHS.

OSAHS

There was evidence from eighteen cohort studies investigating the effects of following risk factors in people with OSAHS: essential hypertension, acute cerebral infraction, transient ischaemic attack (TIA), thoracic aortic aneurysm, non-arteritic anterior ischaemic optic neuropathy (NAION), obesity, type 2 diabetes, type 1 diabetes, end stage renal disease (ESRD), polycystic ovary syndrome (PCOS), moderate and severe asthma, overweight and obese pregnant women, Down's syndrome, bipolar disorder, primary headache disorders. The majority of the studies were small, however, a few studies (those assessing the risk of Polycystic ovary syndrome (PCOS), Type 2 diabetes and asthma) were very large with more than 100,000 participants.

Some risk factors such as NAION, PCOS, bipolar disorder, ESRD were not specified in the protocol but were included as the committee considered these conditions to be associated with high risk for OSAHS.

No relevant clinical studies investigating the effects of snoring, witnessed apnoea, unrefreshing sleep, somnolence during waking hours, nocturia, tiredness, insomnia, sleep fragmentation, ankle swelling, unexplained elevated haemoglobin (Hb)/ unexplained polycythaemia, treatment resistant arrhythmias, atrial fibrillation, diabetic macular oedema, aortic aneurysms, chronic heart failure, acromegaly on risk of OSAHS were identified.

The quality of the evidence varied from low to very low quality; majority of the evidence was downgraded due to risk of bias, and imprecision. Some of the outcomes were at high risk of bias as some studies did not adjust for all of the confounding factors identified by the committee. Only 3 studies matched controls for all key confounders (age, sex, BMI, co-morbidities) and the rest of the studies adjusted for 2 or 3 key confounders. The committee also acknowledged that some uncertainty existed across the effect sizes seen within the evidence, with some confidence intervals crossing the MID thresholds or line of no effect. The committee took into account the low quality including the uncertainty in their interpretation of the evidence.

OHS

There was no evidence assessing the risk of OHS.

COPD -OSAHS overlap syndrome

There was no evidence assessing the risk of COPD-OSAHS overlap syndrome.

The committee acknowledged the limited quality and number of studies included in this review.

1.6.1.2. Benefits and harms

OSAHS

The evidence suggested that there was higher risk of OSAHS compared to control in people with primary headache disorders, asthma, essential hypertension, type I diabetes, non-arteritic anterior ischaemic optic neuropathy (NAION), polycystic ovary syndrome (PCOS), obesity in pregnancy, acute cerebral infarction, transient ischaemic attack (TIA), Down's syndrome, type 2 diabetes, end stage renal disease (ESRD) haemodialysis and peritoneal dialysis and thoracic aortic aneurysm. The evidence suggested that there was no increased risk for OSAHS with mild cognitive impairment and bipolar disorder when compared to controls.

The evidence suggested that there was lower risk of OSAHS in people with severe aortic stenosis. The evidence was from small low-quality studies hence the committee were uncertain about association of aortic stenosis with OSAHS.

The committee considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study. Due to the low quality of the evidence, small number of studies and small population in some studies, the committee also took their clinical experiences into account when making their recommendations. The committee discussed that not all risk factors in the review were strongly associated with OSAHS. Based on the available evidence and the committee's experience they made recommendations only for those risk factors which they considered to be associated with a high risk of OSAHS.

The committee agreed that after taking a sleep history, further assessment for OSAHS should be carried out in people presenting with classical symptoms and features of OSAHS, such as unexplained excessive sleepiness, snoring, apnoea's observed during sleep and choking during sleep, but that a broader range of symptoms should also be recognised, such as sleep fragmentation, insomnia, and fatigue in people without excessive sleepiness. They agreed that a single symptom alone such as snoring is not sufficient for further investigation and that 2 or more of the above listed symptoms or features should be identified to warrant assessment.

The committee from their experience agreed that risk of OSAHS is increased in obesity and overweight individuals, it also causes problems in pregnancy too and prevalence increases across trimesters.

The committee from their experience discussed that there was high prevalence of OSAHS in people with acromegaly due to upper airway soft tissue and skeletal changes. The committee from their experience stated that there was a high prevalence of OSAHS in people with hypothyroidism as this can cause reduced upper airway muscle tone, blunted chemosensitivity, and upper airway obstruction related to thyroid enlargement, mucopolysaccharide deposition, and weight gain.

In people with Down's syndrome, macroglossia and mid facial hypoplasia, plus alterations in ventilatory drive, may contribute to OSAHS.

The committee from their experience noted that there was a strong association between treatment resistant hypertension and OSAHS and highlighted the need to identify these patients for further assessment on a case by case basis.

The committee from their experience stated that there was a higher risk of OSAHS in people with stroke and hence agreed that early diagnosis and management of OSAHS in such people may facilitate recovery and reduce long-term sequelae of untreated OSAHS.

The committee from the evidence and their experience stated that people with type 2 diabetes, cardiac arrhythmia (particularly atrial fibrillation), chronic heart failure, moderate or severe asthma, polycystic ovary syndrome (PCOS),obese/overweight, obese/overweight pregnant women, Down's syndrome and non-arteritic anterior ischaemic optic neuropathy (NAION) were at a higher risk of OSAHS and agreed that further assessment should be done on a case-by-case basis in such patients, as effective treatment of OSAHS may influence the outcome of these conditions. The committee also observed there seemed to be an association between atrial fibrillation and OSAHS in epidemiological and clinical cohorts, and a higher risk of recurrence of the arrhythmia in patients with untreated OSAHS patients.

The committee agreed that these recommendations aim to raise awareness of symptoms and associated conditions that should raise suspicion of OSAHS, as well as prompting assessment. The committee discussed that in current practice not all people with the listed symptoms and conditions are considered for further assessment for OSAHS, hence implementation of these recommendations could increase the number of people being assessed and referred to sleep centres.

The committee noted that initial assessment is made with questionnaires (see Evidence report B for questionnaires) and this is generally carried out in primary care. However, assessment is important in secondary and tertiary care where patients with conditions outlined are managed and in people being assessed by anaesthetic and surgical teams for surgery. The committee also cautioned that existing questionnaires focus on sleepiness, whereas some patients present with insomnia, fatigue or sleep fragmentation alone, hence clinicians need to have an awareness that these symptoms could be caused by sleep disordered breathing and thus refer to sleep centre for assessment.

OHS

There was no evidence on assessing risk factors for OHS. The committee took their clinical experiences into account when making their recommendations.

The committee agreed that further assessment for OHS should be carried out in people with obesity together with symptoms of OSAHS or features of nocturnal hypoventilation.

They agreed that in people with obesity (BMI of 30 kg/m^2 or more) and symptoms of OSAHS (snoring, witnessed apnoea, unrefreshing sleep, waking headaches, excessive sleepiness/tiredness/fatigue, nocturia, sleep fragmentation/insomnia, cognitive dysfunction/memory impairment), or features of nocturnal hypoventilation such as waking headaches, excessive sleepiness during waking hours poor quality sleep, peripheral oedema, low oxygen saturation < 94% on air and unexplained polycythemia, are at high risk of OHS and should be assessed appropriately. These criteria were chosen because some people with OHS have OSAHS, some have hypoventilation alone, and others have combination of both. A low arterial oxygen saturation value or polycythaemia may be indicative of OHS but raised $PaCO_2$ is needed for diagnosis (for more information see Evidence report D for diagnostic tests).

The committee discussed that in current practice not all people with the listed symptoms and features are considered for further assessment for OHS, hence implementation of these recommendations may change practice for the majority of providers leading to more testing and treatment. This will be magnified by the rising prevalence of obesity in the general population.

COPD-OSAHS overlap syndrome

There was no evidence on assessing risk factors for COPD-OSAHS overlap syndrome. The committee took their clinical experiences into account when making their recommendations.

COPD-OSAHS overlap syndrome describes the combination of COPD and OSAHS. These are two of the most prevalent pulmonary conditions and therefore the combination is likely to be common. Hypoxaemia due to COPD is exacerbated during sleep by OSAHS, which may worsen prognosis and symptom burden. Some people with COPD-OSAHS overlap syndrome may develop ventilatory failure. The committee agreed that symptoms of OSAHS, often alongside features of hypoventilation, in people with COPD should alert healthcare professionals to investigate for COPD-OSAHS overlap syndrome. The type of symptoms, nature of sleep disordered breathing and outcome will be affected by the relative severity of COPD and OSAHS.

The committee noted that people with symptoms of OSAHS (snoring, witnessed apnoea, unrefreshing sleep, waking headaches, excessive sleepiness, impairment), diagnosis of COPD and features of hypoventilation such as waking headaches, peripheral oedema, hypoxemia (low oxygen saturation < 94% on air) and unexplained polycythaemia have a high probability of COPD-OSAHS overlap syndrome and should be assessed appropriately. They noted that sleep fragmentation and/or insomnia is common in COPD patients related to breathlessness, cough, medication such as theophyllines and oral steroid therapy, and restless legs, and may worsen at times of an exacerbation, so a careful sleep history is required. Some symptoms of COPD-OSAHS overlap syndrome may be related to COPD itself rather than OSAHS, such as sleep disturbance and unrefreshing sleep due to breathlessness.

Sleepiness in COPD-OSAHS overlap syndrome may not be a feature in some patients, or conversely sleepiness may be caused by non-OSAHS factors such as cough, breathlessness, medication such as theophyllines and restless legs.

It is estimated that COPD-OSAHS overlap syndrome has a prevalence of approximately 1% and is currently under recognised. The committee discussed that in current practice not all people with the listed symptoms for OSAHS and features in the recommendation are considered for further assessment for COPD-OSAHS overlap syndrome, hence implementation of these recommendations may change practice for the majority of providers. The condition reflects an increased understanding of the impact of common comorbidities in the population, and a growth in referrals for sleep study is anticipated. As a result of

increased diagnosis, CPAP and NIV use may increase. Treatment in turn may reduce acute admissions and decrease long-term complications.

1.6.2. Cost effectiveness and resource use

There were no economic evaluations identified for this review question.

Based on their clinical experience and interpretation of the clinical evidence, the committee provided a list of conditions where there is potential for increased risk of OSAHS. In these cases, the committee explained that clinicians should ask relevant questions to enquire whether the person has relevant symptoms. Two or more of the symptoms would indicate a need for further assessment. The committee noted that in current practice not all people with the listed symptoms and conditions are currently considered for further assessment for OSAHS, hence implementation of these recommendations should lead to more people being diagnosed and treated. Although there is no evidence of cost effectiveness for assessment of people with individual signs and symptoms, there is plenty of evidence that treatment of mild, moderate and severe OSAHS is cost effective.

In the case of OHS and COPD-OSAHS overlap syndrome, the committee used a similar framework and identified a list of symptoms that would indicate the need for further assessment such as spirometry or blood gases. The committee discussed that in current practice not all people are being systematically considered for assessment of OHS or COPD-OSAHS overlap syndrome, hence implementation of these recommendations should lead to more people being diagnosed and treated. Although there is no evidence of cost effectiveness, there can be no treatment benefits for patients if they are not identified in the first place.

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Appendices

Appendix A: Review protocols

Table 21: Review protocol: When to suspect

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	When to suspect
2.	Review question	In whom should obstructive sleep apnoea/hypopnoea syndrome, obesity hypoventilation syndrome or COPD-OSAHS overlap syndrome be suspected (for example, based on symptoms or coexisting conditions)?
3.	Objective	To identify people who should be formally assessed for the presence or absence of OSAHS/OHS/ COPD-OSAHS overlap syndrome by finding markers (co-existing conditions or symptoms/signs) that are either strongly associated with OSAHS/OHS/ COPD-OSAHS overlap syndrome or that predict the presence of OSAHS/OHS/ COPD-OSAHS overlap syndrome.
4.	Searches	The following databases (from inception) will be searched: • Embase • MEDLINE Searches will be restricted by: • English language studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Obstructive sleep apnoea/hypopnoea syndrome is the most common form of sleep disordered breathing. The guideline will also cover obesity hypoventilation syndrome and COPD-OSAHS overlap syndrome (the coexistence of obstructive sleep apnoea/hypopnoea syndrome and chronic obstructive pulmonary disease).
6.	Population	Inclusion: • People without a diagnosis of OSAHS/OHS/ COPD-OSAHS overlap syndrome Stratification by setting – primary care vs specialist care

7.	Intervention/Exposure /Test	Predictors:
		• Symptoms & signs
		  ○ Snoring
		  ○ Witnessed apnoea
		  ○ Unrefreshing sleep
		  ○ Somnolence during waking hours

		○ Nocturia ○ Tiredness ○ Insomnia ○ Headaches ○ Sleep fragmentation ○ Ankle swelling ○ Unexplained elevated Hb ○ Cognitive dysfunction/memory impairment • Co-existing conditions ○ Treatment resistant hypertension ○ Nocturnal non-dipping hypertension ○ Treatment resistant arrhythmias ○ Atrial fibrillation ○ T2DM ○ Diabetic macular oedema ○ Aortic aneurysms ○ Chronic heart failure ○ Cardiovascular events ○ Stroke ○ Down's syndrome ○ Acromegaly ○ BMI over 30 kg/m^2 Any of the above, alone or in combination
8.	Comparator/Reference standard/Confounding factors	Any of the above vs an absence of risk factors
9.	Types of study to be included	• Prospective cohort studies • Retrospective cohort studies will be included only if no sufficient prospective cohort studies are identified • Including studies with cross-sectional assessment of presence or absence of the relevant diagnosis (i.e. all participants must be tested for presence or absence of OSAHS/OHS/OS) Studies will only be included if all the key confounders have been accounted for in a multivariate analysis
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts • Studies not adjusted for pre-specified key confounders.
11.	Context	-
12.	Primary outcomes (critical outcomes)	• Association data ○ Adjusted RR or OR (adjusted for key confounders of age, sex, BMI, co-morbidities) • Accuracy data ○ SN, SP, PPV, NPV Stratified by prediction of OSAHS or OHS or COPD-OSAHS overlap syndrome
13.	Secondary outcomes (important outcomes)	Not applicable
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the

		searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).	
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. The methodological quality of each study will be assessed using the QUIPS checklist. 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.	
16.	Strategy for data synthesis	• Meta-analyses will be performed if possible, using Cochrane Review Manager (RevMan5) depending on the appropriateness of data. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/	
17.	Analysis of sub-groups	Not applicable	
18.	Type and method of review	☐	Intervention
		☒	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☒	Diagnostic association/prediction review

19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	NA
22.	Anticipated completion date	NA
23.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail SleepApnoHypo@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
24.	Review team members	From the National Guideline Centre: Carlos Sharpin, Guideline lead Sharangini Rajesh, Senior systematic reviewer Audrius Stonkus, Systematic reviewer Emtiyaz Chowdhury (until January 2020), Health economist David Wonderling, Head of health economics Agnes Cuyas, Information specialist (till December 2019) Jill Cobb, , Information specialist
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website:

		https://www.nice.org.uk/guidance/indevelopment/gid-ng10098
28.	Other registration details	NA – not registered
29.	Reference/URL for published protocol	NA – not registered
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
31.	Keywords	-
32.	Details of existing review of same topic by same authors	NA
33.	Additional information	-
34.	Details of final publication	www.nice.org.uk

Table 22: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[166]

Inclusion and exclusion criteria

- If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.
- If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'.
- Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

Sleep apnoea search strategy 13 – when to suspect

This literature search strategy was used for the following review:

- In whom should obstructive sleep apnoea/hypopnoea syndrome, obesity hypoventilation syndrome or COPD-OSAHS overlap syndrome be suspected (for example, based on symptoms or coexisting conditions)?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[166]

For more information, please see the Methods Report published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using the following approaches:

- Population AND Prognostic/risk factor terms AND Study filter(s)

Table 23: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 7 July 2020	Exclusions Observational studies
Embase (OVID)	1974 – 7 July 2020	Exclusions Observational studies

Medline (Ovid) search terms

1.	exp Sleep Apnea Syndromes/
2.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
3.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
4.	(OSAHS or OSA or OSAS).ti,ab.
5.	(obes* adj3 hypoventil*).ti,ab.
6.	pickwick*.ti,ab.
7.	or/1-6
8.	limit 7 to English language
9.	letter/
10.	editorial/
11.	news/
12.	exp historical article/
13.	Anecdotes as Topic/
14.	comment/
15.	case report/
16.	(letter or comment*).ti.
17.	or/9-16
18.	randomized controlled trial/ or random*.ti,ab.
19.	17 not 18
20.	animals/ not humans/
21.	exp Animals, Laboratory/
22.	exp Animal Experimentation/
23.	exp Models, Animal/
24.	exp Rodentia/
25.	(rat or rats or mouse or mice).ti.
26.	or/19-25
27.	8 not 26
28.	exp "signs and symptoms"/
29.	symptom assessment/
30.	diagnosis/ or prognosis/
31.	(clinical adj3 (manifestation* or feature* or finding* or aspect* or marker*)).ti,ab.
32.	(presenting adj3 (feature* or finding* or factor*)).ti,ab.
33.	presentation*.ti,ab.
34.	(physical adj3 (manifestaion* or characteristic* or feature* or finding*)).ti,ab.

35.	(sign or signs or symptom* or recogni* or identif* or complain*).ti,ab.
36.	(diagnos* or prognos* or assess* or criteria* or predict*).ti,ab.
37.	or/28-36
38.	Snoring/
39.	(snore* or snoring).ti,ab.
40.	((unrefresh* or un-refres* or daytime or day-time or fragment*) adj3 sleep*).ti,ab.
41.	(nocturia or tired* or insomnia* or headache* or somnolence or drows* or fatigue* or sleepiness).ti,ab.
42.	(ankle* adj3 (swell* or swollen)).ti,ab.
43.	((elevate* or high*) adj3 (hemoglobin or haemoglobin or hb or hgb)).ti,ab.
44.	(cognitive dysfunction* or brian fog or memor* impairment*).ti,ab.
45.	or/38-44
46.	((resistan* or nocturnal or nondipping or non-dipping) adj2 hypertension).ti,ab.
47.	(resistan* adj2 arrhythmia*).ti,ab.
48.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
49.	*Atrial Fibrillation/
50.	((diabet* adj2 (type 2 or type ii)) or T2D).ti.
51.	((diabetic macular adj (odema or edema)) or DME).ti,ab.
52.	*Aortic Aneurysm/
53.	aortic aneurysm*.ti,ab.
54.	((heart or cardiac or myocardial) adj2 (failure or decompensation)).ti,ab.
55.	*Heart Failure/
56.	*cardiovascular diseases/ or *cardiovascular abnormalities/ or *cardiovascular infections/ or *heart diseases/ or *vascular diseases/
57.	(cardiovascular adj2 event*).ti,ab.
58.	*Stroke/
59.	(stroke or strokes).ti,ab.
60.	*Down Syndrome/
61.	(down* syndrome* or mongolism or trisomy 21).ti,ab.
62.	*Acromegaly/
63.	acromegal*.ti,ab.
64.	((Body mass index or BMI) adj2 >30).ti,ab.
65.	exp *Obesity/ or exp *Overweight/
66.	(obesity or obese or overweight or over-weight or over weight).ti.
67.	or/46-66
68.	27 and (37 or 45 or 67)
69.	Epidemiologic studies/
70.	Observational study/
71.	exp Cohort studies/
72.	(cohort adj (study or studies or analys* or data)).ti,ab.
73.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
74.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
75.	Controlled Before-After Studies/
76.	Historically Controlled Study/

77.	Interrupted Time Series Analysis/
78.	(before adj2 after adj2 (study or studies or data)).ti,ab.
79.	or/69-78
80.	exp case control studies/
81.	case control*.ti,ab.
82.	or/80-81
83.	79 or 82
84.	Cross-sectional studies/
85.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
86.	or/84-85
87.	79 or 86
88.	79 or 82 or 86
89.	68 and 88

Embase (Ovid) search terms

1.	exp Sleep Disordered Breathing/
2.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
3.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
4.	(OSAHS or OSA or OSAS).ti,ab.
5.	(obes* adj3 hypoventil*).ti,ab.
6.	pickwick*.ti,ab.
7.	or/1-6
8.	limit 7 to English language
9.	letter.pt. or letter/
10.	note.pt.
11.	editorial.pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/9-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice).ti.
24.	or/16-23
25.	8 not 24
26.	symptom assessment/
27.	diagnosis/
28.	prognosis/
29.	(clinical adj3 (manifestation* or feature* or finding* or aspect* or marker*)).ti,ab.
30.	(presenting adj3 (feature* or finding* or factor*)).ti,ab.
31.	presentation*.ti,ab.

32.	(physical adj3 (manifestaion* or characteristic* or feature* or finding*)).ti,ab.
33.	(sign or signs or symptom* or recogni* or identif* or complain*).ti,ab.
34.	(diagnos* or prognos* or assess* or criteria* or predict*).ti,ab.
35.	symptomatology/
36.	or/26-35
37.	*snoring/
38.	(snore* or snoring).ti,ab.
39.	((unrefresh* or un-refres* or daytime or day-time or fragment*) adj3 sleep*).ti,ab.
40.	(nocturia or tired* or insomnia* or headache* or somnolence or drows* or fatigue* or sleepiness).ti,ab.
41.	(ankle* adj3 (swell* or swollen)).ti,ab.
42.	((elevate* or high*) adj3 (hemoglobin or haemoglobin or hb or hgb)).ti,ab.
43.	(cognitive dysfunction* or brian fog or memor* impairment*).ti,ab.
44.	or/37-43
45.	((resistan* or nocturnal or nondipping or non-dipping) adj2 hypertension).ti,ab.
46.	(resistan* adj2 arrhythmia*).ti,ab.
47.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
48.	*atrial fibrillation/
49.	((diabet* adj2 (type 2 or type ii)) or T2D).ti.
50.	((diabetic macular adj (odema or edema)) or DME).ti,ab.
51.	*aortic aneurysm/
52.	aortic aneurysm*.ti,ab.
53.	((heart or cardiac or myocardial) adj2 (failure or decompensation)).ti,ab.
54.	*heart failure/
55.	*cardiovascular disease/ or *cardiovascular malformation/ or *cardiovascular infection/ or *heart disease/ or *vascular disease/
56.	(cardiovascular adj2 event*).ti,ab.
57.	*cerebrovascular accident/
58.	(stroke or strokes).ti,ab.
59.	*Down syndrome/
60.	(down* syndrome* or mongolism or trisomy 21).ti,ab.
61.	*acromegaly/
62.	acromegal*.ti,ab.
63.	((Body mass index or BMI) adj2 >30).ti,ab.
64.	exp *obesity/
65.	(obesity or obese or overweight or over-weight or over weight).ti.
66.	or/45-65
67.	25 and (36 or 44 or 66)
68.	Clinical study/
69.	Observational study/
70.	family study/
71.	longitudinal study/
72.	retrospective study/
73.	prospective study/
74.	cohort analysis/
75.	follow-up/

76.	cohort*.ti,ab.
77.	75 and 76
78.	(cohort adj (study or studies or analys* or data)).ti,ab.
79.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
80.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
81.	(before adj2 after adj2 (study or studies or data)).ti,ab.
82.	or/68-74,77-81
83.	exp case control study/
84.	case control*.ti,ab.
85.	or/83-84
86.	82 or 85
87.	cross-sectional study/
88.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
89.	or/87-88
90.	82 or 89
91.	82 or 85 or 89
92.	67 and 91

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to sleep apnoea population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updated after March 2018) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies.

B.2.1 Health economic studies strategy

Table 24: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 6 July 2020	Exclusions Health economics studies
Embase	2014 – 6 July 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

	exp Sleep Apnea Syndromes/
1.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
2.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
3.	(OSAHS or OSA or OSAS).ti,ab.
4.	(obes* adj3 hypoventil*).ti,ab.

5.	pickwick*.ti,ab.
6.	or/1-6
7.	limit 7 to English language
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/9-16
17.	randomized controlled trial/ or random*.ti,ab.
18.	17 not 18
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice).ti.
25.	or/19-25
26.	8 not 26
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/28-43
44.	27 and 44

Embase (Ovid) search terms

1.	exp Sleep Disordered Breathing/
2.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.

3.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
4.	(OSAHS or OSA or OSAS).ti,ab.
5.	(obes* adj3 hypoventil*).ti,ab.
6.	pickwick*.ti,ab.
7.	or/1-6
8.	limit 7 to English language
9.	letter.pt. or letter/
10.	note.pt.
11.	editorial.pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/9-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice).ti.
24.	or/16-23
25.	8 not 24
26.	health economics/
27.	exp economic evaluation/
28.	exp health care cost/
29.	exp fee/
30.	budget/
31.	funding/
32.	budget*.ti,ab.
33.	cost*.ti.
34.	(economic* or pharmaco?economic*).ti.
35.	(price* or pricing*).ti,ab.
36.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
37.	(financ* or fee or fees).ti,ab.
38.	(value adj2 (money or monetary)).ti,ab.
39.	or/26-38
40.	25 and 39

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Sleep Apnea Syndromes EXPLODE ALL TREES
#2.	(sleep* adj4 (apn?ea* or hypopn?ea*))
#3.	(sleep* adj4 disorder* adj4 breath*)

#4.	(OSAHS or OSA or OSAS)
#5.	(obes* adj3 hypoventil*)
#6.	(pickwick*)
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6

B.2.2 Quality of life studies strategy

Table 25: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	1946 – 26 November 2019	Exclusions Quality of life studies
Embase	1974 – 26 November 2019	Exclusions Quality of life studies

Medline (Ovid) search terms

1.	exp Sleep Apnea Syndromes/
2.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
3.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
4.	(OSAHS or OSA or OSAS).ti,ab.
5.	(obes* adj3 hypoventil*).ti,ab.
6.	pickwick*.ti,ab.
7.	or/1-6
8.	limit 7 to English language
9.	letter/
10.	editorial/
11.	news/
12.	exp historical article/
13.	Anecdotes as Topic/
14.	comment/
15.	case report/
16.	(letter or comment*).ti.
17.	or/9-16
18.	randomized controlled trial/ or random*.ti,ab.
19.	17 not 18
20.	animals/ not humans/
21.	exp Animals, Laboratory/
22.	exp Animal Experimentation/
23.	exp Models, Animal/
24.	exp Rodentia/
25.	(rat or rats or mouse or mice).ti.
26.	or/19-25
27.	8 not 26
28.	quality-adjusted life years/

29.	sickness impact profile/
30.	(quality adj2 (wellbeing or well being)).ti,ab.
31.	sickness impact profile.ti,ab.
32.	disability adjusted life.ti,ab.
33.	(qal* or qtime* or qwb* or daly*).ti,ab.
34.	(euroqol* or eq5d* or eq 5*).ti,ab.
35.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
36.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
37.	(hui or hui1 or hui2 or hui3).ti,ab.
38.	(health* year* equivalent* or hye or hyes).ti,ab.
39.	discrete choice*.ti,ab.
40.	rosser.ti,ab.
41.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
42.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
43.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
44.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
45.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
46.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
47.	or/28-46
48.	27 and 47

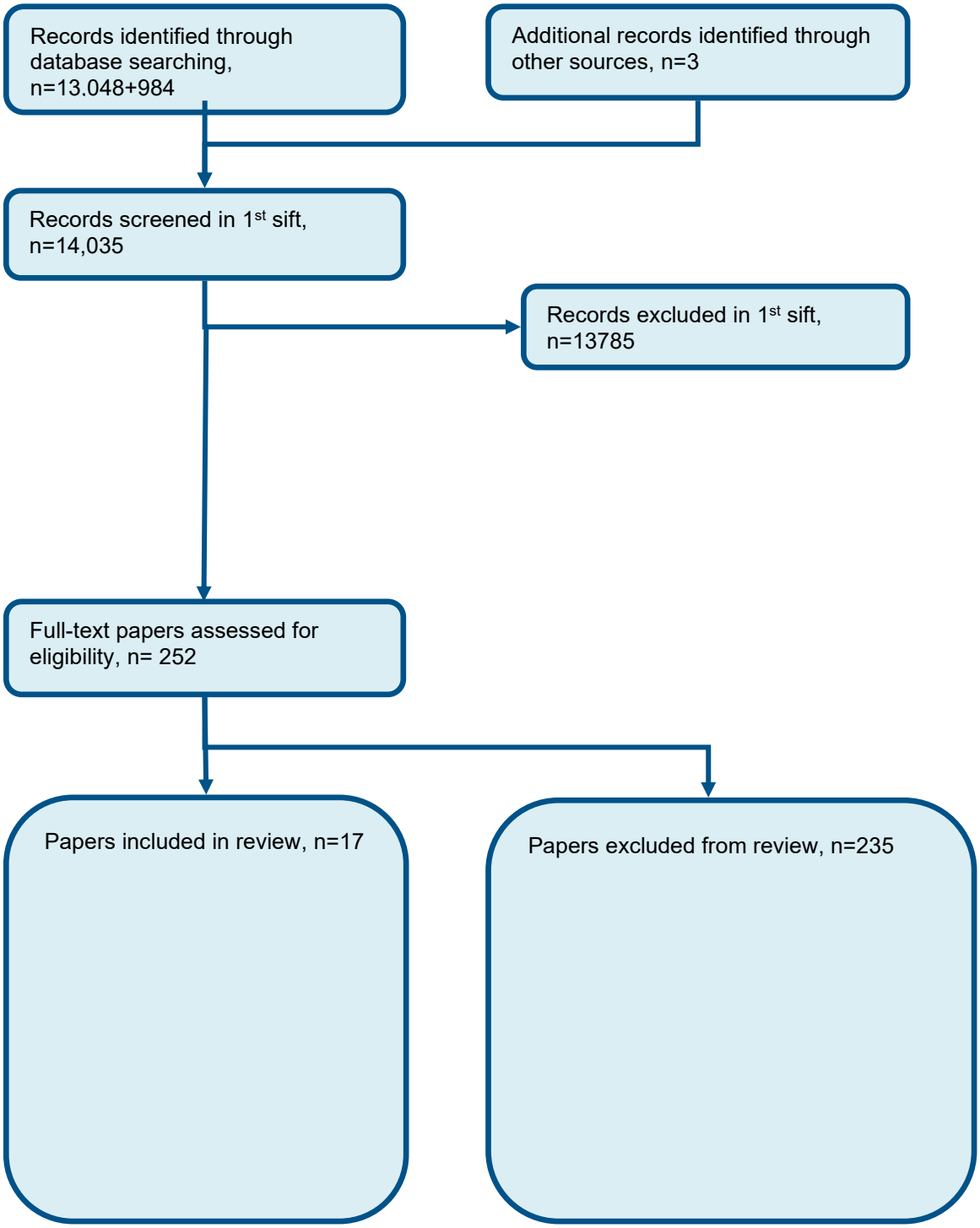
Embase (Ovid) search terms

1.	exp Sleep Disordered Breathing/
2.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
3.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
4.	(OSAHS or OSA or OSAS).ti,ab.
5.	(obes* adj3 hypoventil*).ti,ab.
6.	pickwick*.ti,ab.
7.	or/1-6
8.	limit 7 to English language
9.	letter.pt. or letter/
10.	note.pt.
11.	editorial.pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/9-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/

22.	exp Rodent/
23.	(rat or rats or mouse or mice).ti.
24.	or/16-23
25.	8 not 24
26.	quality adjusted life year/
27.	"quality of life index"/
28.	short form 12/ or short form 20/ or short form 36/ or short form 8/
29.	sickness impact profile/
30.	(quality adj2 (wellbeing or well being)).ti,ab.
31.	sickness impact profile.ti,ab.
32.	disability adjusted life.ti,ab.
33.	(qal* or qtime* or qwb* or daly*).ti,ab.
34.	(euroqol* or eq5d* or eq 5*).ti,ab.
35.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
36.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
37.	(hui or hui1 or hui2 or hui3).ti,ab.
38.	(health* year* equivalent* or hye or hyes).ti,ab.
39.	discrete choice*.ti,ab.
40.	rosser.ti,ab.
41.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
42.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
43.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
44.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
45.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
46.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
47.	or/26-46
48.	25 and 47

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of when to suspect



Appendix D: Clinical evidence tables

Study	Arda 2013[15]
Study type	Prospective cohort study
Number of studies (number of participants)	N= 40
Countries and setting	Conducted in Turkey ; Setting: hospital
Line of therapy	Not applicable
Duration of study	December 2010 to March 2012.
Method of assessment of guideline condition	Yes
Stratum	OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients diagnosed with non-arteritic anterior ischaemic optic neuropathy (NAION).
Exclusion criteria	Criteria for exclusion 1. A diagnosis of arteritic anterior ischaemic optic neuropathy by clinical presentation, erythrocyte sedimentation rate and C reactive protein. 2. Subjects who had toxic or nutritional optic neuropathy, optic neuritis or glaucoma. 3. Subjects who had any neurological diseases which can affect sleep.

Study	Arda 2013[15]
Recruitment/selection of patients	Twenty patients with a newly diagnosed NAION were included in this study. Twenty age and sex matched subjects with similar risk factors for NAION, such as DM and HT, constituted the control group. Criteria for NAION diagnosis NAION was diagnosed when the following items were present: 1. A history of sudden painless visual loss that affect VA and/or visual field. 2. Diffuse or sectoral optic disc oedema, sometimes with focal micro haemorrhages around the head of the optic nerve. 3. Lack of findings on physical or ophthalmological examination, suggesting another disorder could be causing the symptoms.
Age, gender and ethnicity	Mean ages of the patients and controls were 60.90±8.14 and 61.15±7.23 years, respectively. Sex Men (n (%)) – NAION- 14 (70.0); control- 14 (70.0) Women (n (%))- NAION- 6 (30.0); control- 6 (30.0)
Further population details	Hypertension (%):NAION- 9 (45.0); control- 9 (45.0) Diabetes mellitus (%): NAION- 11 (55.0); control- 11 (55.0) Hypercholesterolemia (%): NAION- 5 (25.0); control- 7 (35.0) Coronary artery disease (%):NAION- 2 (10.0) ; control- 2 (10.0
Extra comments	-
Indirectness of population	No indirectness
Risk factor	Non-arteritic anterior ischaemic optic neuropathy (NAION).

Study	Arda 2013[15]
Confounding variables	age and sex
Funding	This work was supported by a research grant from Erciyes University, Scientific Research Project Unit (project No: TSU-11–3717).
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NAION versus control Protocol outcome 1: Prevalence of OSA - Actual outcome: Prevalence of OSA NAION- 17/20 ; control- 13/20 Risk of bias: high not adjusted for all key confounders	
Protocol outcomes not reported by the study	None

Study	Balachandran 2019[22]
Study type	Population-based retrospective cohort study
Number of studies (number of participants)	N= 76 978 women with PCOS and N=143 077 matched control women without PCOS. Matched for age-, BMI- and location.

Study	Balachandran 2019[22]
Countries and setting	Conducted in UK ; Setting: hospital
Line of therapy	Not applicable
Duration of study	January 2000 to May 2017
Method of assessment of guideline condition	Yes
Stratum	OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion criteria: All women who were aged 18–50 years at the index date (study entry) and had a documentation of PCOS at any time during the study period were included in the exposed group. Women without documented PCOS at any time during the study period were included in the unexposed (control) arm. The index date was defined as the date of first documentation of PCOS for newly diagnosed cases and from the date patient became eligible if the first documentation of PCOS was prior to the eligibility date Each exposed patient was randomly matched to two unexposed patients (1:2 ratio) for general practice, age at index date and BMI To minimise the immortal time bias, each randomly matched eligible unexposed patient was assigned the same index date as their corresponding exposed patient. Follow-up end date (exit date) was determined from the earliest occurrence of the first documentation of OSA, transfer to another practice, death or study end. PCOS: N=76,978 No PCOS: N=143,077
Exclusion criteria	Patients with any documentation of OSA prior to the index date were excluded.

Study	Balachandran 2019[22]
Recruitment/selection of patients	study used data from UK general practices contributing to The Health Improvement Network (THIN) electronic database,
Age, gender and ethnicity	Age (years; mean (s.d.)): PCOS- 30.2 (7.4); without PCOS- 30.4 (7.3) All women
Further population details	BMI (kg/m2; mean (s.d.): PCOS- 28.6 (7.6) ; without PCOS- 27.4 (6.4)
Extra comments	When compared to controls, women with PCOS were more likely to have T2D (2.2 vs 1.0%), hypertension (3.0 vs 2.0%), hypothyroidism (3.9 vs 2.3%) and impaired glucose controls (HR = 2.46, 95% CI: 2.07–2.93, P < 0.001). Women with PCOS remained at increased risk of developing OSA compared to women without PCOS following adjustment for age, Townsend score, BMI, hypothyroidism at baseline, baseline and incident diabetes/IGR (adjusted HR = 2.26, 95% CI: 1.89 to 2.69, P < 0.001)
Indirectness of population	No indirectness
Risk factor	Polycystic ovary syndrome (PCOS).
Confounding variables	age at index date and BMI
Funding	One of the authors is a clinician scientist supported by the National Institute for Health Research (NIHR) in the UK : another is an NIHR Senior Investigator.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Polycystic ovary syndrome (PCOS). Vs control

Protocol outcome 1: Incidence of OSA
- Actual outcome: Incidence of OSA

Pcos: 298/76978; without PCOS- 222/10463
Risk of bias: high – not adjusted for all key confounders

The median follow-up was 3.5 years (IQR: 1.38 to 7.14)

Study	Balachandran 2019[22]
Protocol outcomes not reported by the study	None

Study	Chang 2019[45]
Study type	Prospective cohort study
Number of studies (number of participants)	N= 3650 bipolar disorder patient (BD) ; n= 18250 non-BD patients
Countries and setting	Conducted Taiwan in ; Setting: hospital
Line of therapy	Not applicable
Duration of study	Enrolled between 2000 and 2010 and followed until end of 2013
Method of assessment of guideline condition	Yes
Stratum	OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	N=3650 patients with bipolar disorder and who had no history of OSA prior to enrolment Only patients who were prescribed lithium, valproate, carbamazepine, lamotrigine, aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone for at least 28 cumulative days after the date of BD diagnosis were included in the BD cohort. N=18250 without bipolar disorder matched by sex and age
Exclusion criteria	NR

Recruitment/selection of patients	Patients who were diagnosed with BD by board certified psychiatrists during the 2000-2010 period and who had no history of OSA prior to enrolment were included in the BD cohort.
Age, gender and ethnicity	Age mean (SD): BD 39.84 (16.55); without BD- 39.80 (16.38) Male: BD 43.86%; without BD- 43.86%
Further population details	The BD cohort had a higher prevalence of baseline comorbidities, including obesity, hypertension, hyperlipidaemia, and diabetes, compared to the control cohort.
Extra comments	-
Indirectness of population	No indirectness
Risk factor	Bipolar disorder
Confounding variables	age and sex
Funding	NR
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Bipolar disorder vs control Protocol outcome 1: Incidence of OSA - Actual outcome: Incidence of OSA Adjusted HR: 1.54, 95% CI 0.99-2.37 Risk of bias: high Control not matched for all confounders	
Protocol outcomes not reported by the study	None

Study	Fletcher 1985[69]
Study type	Prospective cohort study
Number of studies (number of participants)	N=46 hypertensive men N=34 normotensive men
Countries and setting	Conducted in USA; Setting: hospital
Line of therapy	Not applicable
Duration of study	NR
Method of assessment of guideline condition	Yes
Stratum	OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	The study population consisted of 46 men with essential hypertension and 34 normotensive men as controls. Hypertension was defined as an average diastolic pressure above 90 mmHg and systolic above 140 mm Hg for men under age 45 years or above 95 mmHg for men over 45 years.
Exclusion criteria	NR
Recruitment/selection of patients	Men were selected without bias to physical habitus, except that efforts were made to recruit control and hypertensive persons of equivalent age and weight. Hypertensive men were recruited from the hypertension, medical and dermatologic clinics and from employees of the Houston veterans' administration medical centre. The normotensive controls, recruited in a similar manner, consisted of outpatients with minor dermatologic problems but no major systemic disease and of healthy employees of the veteran's administration medical centre and their relatives. Controls matched for age and weight.

Study	Fletcher 1985[69]
Age, gender and ethnicity	Age years: control- 52.4 (1.5); hypertensives- 53.9 (1.2))
Further population details	Men with hypertension and more than 10 apnoea per hour were followed prospectively during the study.
Extra comments	-
Indirectness of population	No indirectness
Risk factor	Essential hypertension
Confounding variables	age and weight
Funding	In part by a grant from the Texas Affiliate of the American Heart Association, and by the General medical research service of the veterans' administration.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: People with essential hypertension vs control Protocol outcome 1: Incidence of OSA - Actual outcome: Disordered breathing event Index [mean (SD)]: Hypertensives : 18.1 (2.7);control: 8.9 (1.8) Risk of bias: high Control not matched for all confounders	
Protocol outcomes not reported by the study	None

Study	Gaisl 2020[74]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=312) [n=208 TAA; n=104 control)
Countries and setting	Conducted in Switzerland; Setting: hospital
Line of therapy	Not applicable
Duration of study	NA
Method of assessment of guideline condition	Yes
Stratum	OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with thoracic aortic aneurysm (TAA). Presence of TAA was defined as an aortic diameter exceeding the sex-specific cut-offs at the level of sinus Valsalva (>39 mm for women, >44 mm for men) or the ascending aorta (>44 mm for women and >46 mm for men)
Exclusion criteria	Age <18 years; CPAP therapy for OSA; diagnosis of central sleep apnoea; relevant use of substances significantly modulating the respiratory drive; pregnancy; moderate to severe aortic regurgitation; moderate to severe aortic stenosis.
Recruitment/selection of patients	Patients with TAA were recruited from an ongoing cohort study. Matched controls were recruited form the outpatient clinic of the University Hospital Zurich between Jan and November 2018
Age, gender and ethnicity	82% male; age: 62 (11) years; BMI 27 (4) Kg/m2
Further population details	Patients with TAA had higher blood pressure and were significantly more often prescribed B-adrenoreceptor antagonists.

Study	Gaisl 2020[74]
Extra comments	-
Indirectness of population	No indirectness
Risk factor	thoracic aortic aneurysm (TAA).
Confounding variables	Age, sex, height, weight and left ventricular ejection fraction
Funding	NR
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: thoracic aortic aneurysm vs control Protocol outcome 1: Prevalence of OSA - Actual outcome: Prevalence of OSA Adjusted odds ratio: 1.87 [95% 1.05-3.34] Risk with TAA group- 63% (n=208); risk with control 47% (n=104) Risk of bias: low	
Protocol outcomes not reported by the study	None

Study	Hachul 2019[88]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=44) N=30 PCOS; N=14 healthy control]

Study	Hachul 2019[88]
Countries and setting	Conducted in Brazil; Setting: hospital
Line of therapy	Not applicable
Duration of study	NA
Method of assessment of guideline condition	Yes
Stratum	OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	Women with polycystic ovary syndrome (PCOS). Diagnosis of PCOS was based on the latest 2003 Rotterdam consensus, requiring the presence of at least two of the following features: (1) oligomenorrhoea or chronic anovulation, (2) clinical and/or biochemical hyperandrogenism, and (3) ultrasound appearance of polycystic ovaries. Inclusion criteria for healthy control: a regular menstrual cycle of 28-30 days, normal BMI and in the follicular phase of the menstrual cycle.
Exclusion criteria	Exclusion criteria: neurologic conditions and/or being under psychiatric treatment; use of medication for chronic diseases that might interfere with the study results; participation in another clinical study or having participated in a clinical study within a period of 3 months; being a carrier of a disease; having a history of stroke; use of hypnotic, psychotropic, psychostimulant, and/or analgesic drugs; use of hormonal contraceptives; and presence of dysmenorrhea or endometriosis that may interfere with sleep patterns. Subjects with other known causes of hyperandrogenism (such as congenital adrenal hyperplasia, androgen-secreting tumours and Cushing's syndrome), using oral contraceptives, corticosteroids, antidiabetic or lipid-lowering drugs in the previous 3 months, having a history of liver disease (such as viral hepatitis B and C, hemochromatosis and autoimmune hepatitis), diabetes mellitus, untreated hypothyroidism, renal, hepatic, cardiac or pulmonary disease, receiving treatment for sleep apnoea using medications that alter liver enzymes, with a daily ingestion of more than 20 grams of ethanol, using drugs (sympathomimetics, sympatholytics, and β-blockers), with depression or with chronic diseases were excluded.

Study	Hachul 2019[88]
Recruitment/selection of patients	A total of 55 subjects were selected to participate in the study. The volunteers, ranging in age from 16 to 45 years, were recruited from the Endocrinology Division of the Federal University of São Paulo, Brazil. 11 individuals were excluded because of missing data (8 related to the PSQI and 3 to BMI).
Age, gender and ethnicity	Gender: all females; age: healthy control: 27.9±1.7; PCOS :29.7±1.2 0.412 Body Mass Index (weight/height2): healthy control- 22.4±1.6; PCOS: 34.3±1.1
Further population details	NS
Extra comments	-
Indirectness of population	No indirectness
Risk factor	PCOS
Confounding variables	Age, BMI
Funding	NR

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PCOS vs control

Protocol outcome 1: high risk of OSA
- Actual outcome: high risk of OSA

High risk for OSA (Berlin questionnaire): PCOS: 19/30 (63.3%); control: 1/14 (7.1%);

Risk of bias: high

Control not matched for all confounders

This analysis was not a multivariate analysis and did not adjust for BMI for this outcome. There is a large baseline difference in BMI which is one of key confounders and could have been the cause of this outcome as much as the PCOS.

Study	Hachul 2019[88]
Protocol outcomes not reported by the study	None

Study	Huang 2018[104]
Study type	Registry database
Number of studies (number of participants)	N= 29,561 incident dialysis patients
Countries and setting	Conducted in Taiwan ; Setting: hospital
Line of therapy	Not applicable
Duration of study	Between 2010 and 2011
Method of assessment of guideline condition	Yes
Stratum	OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	Dialysis patients
Exclusion criteria	patients who were under 20 years of age, and those who had an OSA history), kidney transplantation, or a follow-up period of less than 90 days,
Recruitment/selection of patients	90,353 patients with newly diagnosed ESRD from 1 January 2000 to 31 December 2011. After excluding patients who were under 20 years of age, and those who had an OSA history), kidney transplantation, or a

Study	Huang 2018[104]
	follow-up period of less than 90 days, 88,801 ESRD patients were enrolled, including 78,814 HD and 9987 PD (including continuous ambulatory peritoneal dialysis and automated peritoneal dialysis) patients. Next haemodialysis (HD) with peritoneal dialysis (PD) patients were matched by age and sex in a 2:1 ratio and generated an ESRD cohort including a HD cohort consisting of 19,574 patients and a PD cohort with 9987 patients. 118,244 individuals were selected in the database who did not have a history of CKD or ESRD as the non-ESRD control cohort matched with the ESRD cohort by age, sex, and index-year in a 1:4 ratio
Age, gender and ethnicity	Men: control 55,092 (46.6 %); total ESRD 13,773 (46.6%) Mean age (SD): control- 54.0 (14.9); 54.1 (14.8)
Further population details	Coronary artery disease: control- 17,217 (14.6%); ESRD -10,153 (34.4%) Diabetes: control- 10,287 (8.70%); ESRD - 12,974 (43.9%)
Extra comments	-
Indirectness of population	No indirectness
Risk factor	end-stage renal disease (ESRD)
Confounding variables	age, sex, and index-year.
Funding	This study was supported, in part, by the Taiwan Ministry of Health and Welfare, Clinical Trial and Research Center of Excellence ; China Medical University Hospital, under the Aim for the Top University Plan of the Ministry of Education; and the Health and Welfare Surcharge of Tobacco Products, China Medical University Hospital Cancer Research Center of Excellence
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: end-stage renal disease (ESRD) vs control Protocol outcome 1: Risk of OSA Actual outcome: Risk of OSA For HD patients:	

Study	Huang 2018[104]
Adjusted ORs (95% CI): 1.31 (0.70, 2.45) For PD patients: Adjusted ORs (95% CI) : 3.05 (1.64, 5.71) - Actual outcome: Risk of bias: low	
Protocol outcomes not reported by the study	None

Study	Joo 2011[113]
Study type	Prospective cohort study
Number of studies (number of participants)	N=61 patients with acute cerebral infarction (ACI) ; n=13 patients with transient ischemic attack (TIA); N= 64 control
Countries and setting	Conducted in Korea; Setting: hospital
Line of therapy	Not applicable
Duration of study	-
Method of assessment of guideline condition	Yes
Stratum	OSAHS
Subgroup analysis within study	Not applicable

Study	Joo 2011[113]
Inclusion criteria	Patients with acute cerebral infarction (ACI) and transient ischemic attack (TIA)
Exclusion criteria	NR
Recruitment/selection of patients	Consecutive patients (aged 45 to 80 years) admitted to the Department of Neurology at the Korea University Medical Center for an ACI or transient ischemic attack (TIA), with 48 h of onset, was enrolled in the present study. Patients with any of the following were excluded: (1) a decreased level of consciousness on admission; (2) a seizure at stroke onset; (3) a baseline oxygen saturation of <95%; (4) chronic obstructive pulmonary disease; (5) a neuromuscular junction disorder (e.g., myasthenia gravis); or (6) a neurodegenerative disorder, such as, Parkinson's disease, progressive supranuclear palsy, or Alzheimer's disease. Age-matched patient's spouses or family members with no history of physician diagnosed stroke were enrolled as controls
Age, gender and ethnicity	Not reported separately for 3 groups
Further population details	ACI stroke subtypes were as follows: 23 cases of large artery atherosclerosis, 18 cases of lacunae, eight cases of cardio embolism, and 12 cases with undetermined aetiologies. Mean AHI was significantly higher in TIA (14.6±10.4) and ACI (15.6±14.7) patients than in the controls (7.8±7.0; p=0.001), but BMI was not significantly different between these three groups
Extra comments	-
Indirectness of population	No indirectness
Risk factor	(ACI) and transient ischemic attack (TIA)
Confounding variables	Sex, BMI and co-morbidities.
Funding	NR
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON:	

Study	Joo 2011[113]
acute cerebral infarction (ACI) vs control Protocol outcome 1: Prevalence of OSA - Actual outcome: Prevalence of OSA transient ischemic attack (TIA) vs control ACI- 31/61; TIA -9/13 ; control-21/64 Risk of bias: high not adjusted for all key confounders	
Protocol outcomes not reported by the study	None

Study	Julien 2009[114]
Study type	Prospective cohort study
Number of studies (number of participants)	N= 26 patients with severe asthma consecutively recruited to a difficult asthma program, n= 26 patients with moderate asthma, and 26 controls without asthma of similar age and body mass index.
Countries and setting	Conducted in Canada ; Setting: hospital
Line of therapy	Not applicable
Duration of study	Not stated
Method of assessment of guideline condition	Yes

Study	Julien 2009[114]
Stratum	OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with asthma
Exclusion criteria	Exclusion criteria for both groups included current smoking and other conditions which could lead to cardiorespiratory symptomatology. No sleep related information was obtained from subjects before recruitment into the Difficult Asthma Program or the current study. Consecutive patients enrolled in the program were approached to participate in this study. Of the patients approached during the recruitment period, 26 of 27 patients with severe asthma and 26 of 31 patients with moderate asthma consented to participate.
Recruitment/selection of patients	Subjects with asthma were recruited from the Difficult Asthma Programme.2 Recruitment to the programme was solely on the basis of asthma history. Severe asthma was defined according to American Thoracic Society criteria1 and required at least 1 major criterion: daily oral steroids for >50% of the previous 12 months, or high-dose inhaled steroid: fluticasone 1000 mg/d or equivalent, and at least 1 other add-on therapy continuously for 12 months; and minor criteria: daily short-acting b-agonist, persistent FEV1 <70% and FEV1/forced vital capacity <80% predicted, urgent visits or steroid bursts in the last 12 months, prompt deterioration with <25% steroid dose reduction, or previous near-fatal asthma within 3 years. Moderate asthma was defined as well controlled asthma symptoms (Juniper asthma control score13 <1), use of long acting b-agonist and fluticasone (or equivalent) 200 mg/d and 1000 mg/d, _2 steroid bursts in the past year and none within 3 months, total days on oral steroids <30 in the previous 12 months, FEV1 >70% predicted, and unscheduled clinical visit in the previous 12 months. Control subjects were recruited through community advertisements, which referred to a clinical study on ‘‘breathing patterns and asthma.’’ Subjects were required to be generally healthy, to be non-smoking for at least 1 year, and to have no previous history of asthma, respiratory problems, or prescription of inhalers. No sleep-related information was used in the recruitment or screening process. Potential recruits meeting eligibility criteria were included based on age, body mass index (BMI), and sex to match the asthmatic groups. Epworth sleepiness scores were obtained only after informed consent

Study	Julien 2009[114]
Age, gender and ethnicity	Age (y): severe- 48.86 (2.0); moderate- 47.9 (1.6); control- 45.5 6 (1.7) Sex (M/F) : severe- 12/14 ; moderate-14/12; control- 13/13
Further population details	Asthma quality of life scores were significantly lower (less favourable) for patients with severe asthma than for patients with moderate asthma. Eight patients with severe asthma (31%) and 2 patients with moderate asthma (8%) had previously been admitted to intensive care for asthma. Four subjects with severe asthma but no subjects with moderate asthma had previously been intubated. Epworth sleepiness scores tended to be worse among patients with severe and moderate asthma than controls, but this did not achieve statistical significance.
Extra comments	-
Indirectness of population	No indirectness
Risk factor	Asthma
Confounding variables	for age, BMI and sex
Funding	Not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Asthma vs control Protocol outcome 1: Prevalence of OSA - Actual outcome: Total AHI > 15 events/h Severe- 23/26; moderate- 15/26; control- 8/26 Risk of bias: high Control group not matched for all confounders	
Protocol outcomes not reported by the study	None

Study	Prinz 2011[179]
Study type	Prospective cohort study
Number of studies (number of participants)	N= 67
Countries and setting	Conducted in Germany Setting: hospital
Line of therapy	Not applicable
Duration of study	4 months
Method of assessment of guideline condition	Yes. Cardiorespiratory polygraphy not polysomnography
Stratum	OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with isolated severe aortic stenosis (aortic valve opening area #1.0 cm2);
Exclusion criteria	NR
Recruitment/selection of patients	42 consecutive patients (19 male; mean age 72 years), who came for further evaluation of isolated severe aortic stenosis (aortic valve opening area #1.0 cm2); all patients with diabetes mellitus and concomitant pulmonary disease, particularly those with forced expiratory volume in 1 s <50%, were excluded. Further exclusion criteria included a diagnosis of acute coronary syndrome or change of stable medication within the preceding 2 weeks. All patients had standard preoperative diagnostics, including echocardiography and left and right heart catheterisation. Right heart catheterisation was carried out to assess mean pulmonary artery pressure (mPAP) and pulmonary capillary wedge pressure (PCWP).13 In-hospital unattended cardiorespiratory polygraphy was performed after informed consent had been obtained from each patient before participation.

Study	Prinz 2011[179]
	Control group N=25 patients (14 male; 70 years), who had cardiac catheterisation based on a pathological stress test and individual risk stratification. Coronary artery disease was angiographically excluded in each of these patients. All of the control group had preserved left ventricular ejection fraction (>55%) and no valve disease. The control group was matched for age, gender and body mass index (BMI).
Age, gender and ethnicity	Age (years): severe aortic stenosis 73 (68, 78); control- 69 (67, 73) Male (n): severe aortic stenosis 19; control- 14
Further population details	BMI (kg/m2): severe aortic stenosis 24 (22, 26) ; control- 26 (25, 27)
Extra comments	-
Indirectness of population	No indirectness
Risk factor	severe aortic stenosis
Confounding variables	age, gender and body mass index (BMI
Funding	None
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: severe aortic stenosis vs control Protocol outcome 1: Prevalence of OSA - Actual outcome: Prevalence of OSA (defined as AHI ≥ 5/h) severe aortic stenosis -15/42; control- 16/25 Risk of bias: high not adjusted for all key confounders	

Study	Prinz 2011[179]
Protocol outcomes not reported by the study	None

Study	Rice 2015[182]
Study type	prospective cohort study
Number of studies (number of participants)	N= N=573 lean women (BMI of less than 25 kg/m^2) N=459 obese women (BMI of less than 25 kg/m^2)
Countries and setting	Conducted in USA; Setting: hospital
Line of therapy	Not applicable
Duration of study	2013-2014
Method of assessment of guideline condition	Yes
Stratum	OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	Overweight and obese pregnant women. Eligible women were 18 years of age or older, could speak and read Spanish, and with a gestational age between 24 to 28 weeks.
Exclusion criteria	Not stated

Study	Rice 2015[182]
Recruitment/selection of patients	This study was conducted among pregnant women attending prenatal care clinics at the Instituto Nacional Materno Perinatal (INMP) in the city of Lima, Peru between February 2013 and March 2014. The INMP, overseen by the Peruvian Ministry of Health, is the primary referral hospital for maternal and perinatal care.
Age, gender and ethnicity	Maternal Age (years) Mean (SD): 28.6 (6.2)
Further population details	Total of 1032 pregnant women between the ages of 18 and 45 years (mean age = 28.6 years, standard deviation = 6.2 years) participated in the study.
Extra comments	-
Indirectness of population	No indirectness
Risk factor	Obesity in pregnant women
Confounding variables	Maternal age, education, marital status and parity.
Funding	This research was supported by Roche Diagnostic Operations Inc. and the National Institutes of Health (NIH), National Institute for Minority Health and Health Disparities.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON:

Obesity in pregnant women vs normal weight women and overweight pregnant women

Protocol outcome 1: Prevalence of OSA
- Actual outcome:

After adjusting for confounders compared with normal weight women (<25 kg/m2), overweight women (25–29.9 kg/m2) had 3.69-fold higher odds of experiencing high risk for OSA (assessed using the Berlin questionnaire) (95 % CI: 1.82–7.50). Obese women (≥30 kg/m2) had a 13.2- fold higher odds of experiencing high risk for OSA (aOR=13.23; 95 % CI: 6.25–28.01) as compared with their lean counterparts.
Risk of bias: low

Study	Rice 2015[182]
Analysis adjusted for maternal age, education, marital status and parity	
Protocol outcomes not reported by the study	None

Study	Shen 2015[201]
Study type	retrospective cohort study
Number of studies (number of participants)	N = 155347 without asthma; N = 38840 with asthma
Countries and setting	Conducted in Taiwan ; Setting: hospital
Line of therapy	Not applicable
Duration of study	The mean follow-up period was 6.95 years (SD = 3.33) for the asthma cohort, and 6.51 years (SD = 3.44) for the comparison cohort
Method of assessment of guideline condition	Yes
Stratum	OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients above 20 years, who had been diagnosed with asthma, as the asthma cohort.
Exclusion criteria	Exclusion criteria included those diagnosed with before index date, and with incomplete gender or age information. The index date was defined as the date of asthma diagnosis.

Study	Shen 2015[201]
Recruitment/selection of patients	The comparison cohort was randomly selected from all NHI beneficiaries, no asthma, above 20 years, and was frequency-matched for gender, age (every five years), and Index year with a 1:4 ratio. The diagnosis of asthma was made based on a target history, and a comprehensive pulmonary function evaluation
Age, gender and ethnicity	Male: no asthma n=70571(45.4%); asthma n=17646 (45.4%) Mean (SD): no asthma 52.8 (18.1); asthma 53.3 (18.0)
Further population details	-
Extra comments	-
Indirectness of population	No indirectness
Risk factor	Asthma
Confounding variables	age, sex and comorbidities of hypertension, diabetes, hyperlipidaemia, COPD, CAD, stroke, rhinitis, chronic sinusitis, GERD and obesity
Funding	None
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: asthma vs control Protocol outcome 1: incidence of OSA - Actual outcome: HR for developing OSA during the follow-up years was 1.87 (95% CI = 1.61–2.17) for the asthma cohort as compared to the comparison cohort Risk of bias: low	
Protocol outcomes not reported by the study	None

Study	Subramanian 2019[216]
Study type	Retrospective cohort study
Number of studies (number of participants)	N= 360,250 exposed and 1,296,489 unexposed patient cohorts
Countries and setting	Conducted in UK; Setting: hospital
Line of therapy	Not applicable
Duration of study	2005-2017
Method of assessment of guideline condition	Yes
Stratum	OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	patients with type 2 diabetes
Exclusion criteria	Patients with a prevalent OSA diagnosis were excluded.
Recruitment/selection of patients	Adult patients aged 16 years and above registered for at least 12 months with any of the eligible general practices prior to study entry formed the source population. The exposed cohort consisted of adult patients with type 2 diabetes. Type 2 diabetes diagnosis was ascertained by the presence of any type 2 diabetes clinical code in the patient's medical record and the absence of any record of type 1 diabetes. Unexposed cohort For every exposed patient, up to 4 controls were randomly selected from an age-, sex- and BMI-matched pool of eligible patients without a record of type 2 diabetes at any time point before or during the study period. Age and BMI were matched to within 1 year and 2 kg/m2 respectively.

Study	Subramanian 2019[216]
	Patients with a prevalent OSA diagnosis were excluded. The study cohort was derived from The Health Improvement Network (THIN), a UK primary care database, from 01/01/2005 to 31/12/2017 360,250 eligible patients with type 2 diabetes were identified; these patients were matched for age, sex and BMI to 1,296,489 patients without type 2 diabetes (unexposed/control cohort).
Age, gender and ethnicity	The matching parameters age and sex were similar between the exposed and unexposed groups (mean (SD) age 64.9 (13.3) vs 64.6 (13.6) years; male sex 55.5% vs 54.2%). Patients in the exposed cohort had a slightly higher mean BMI compared to controls (31.0 (6.5) vs 29.8 (5.8)), but the difference was within the matching range (±2 kg/m2). Compared to controls, patients with diabetes were more deprived (13.7% vs 9.9% were in the most deprived Townsend quintile), and were more likely to be of south Asian ethnicity (3.8% vs 0.9%). Patients with diabetes also had higher levels of cardiovascular diseases, including heart failure (4.8% vs 2.5%), ischaemic heart disease (19.1% vs 11.4%) and stroke/TIA (8.8% vs 5.9%) and greater usage of lipid-lowering drugs (63.7% vs 23.6%). Prevalent OSA at baseline (recorded up to 15 months after index date)
Further population details	A 15-month latency period was used for all patients. For patients with incident type 2 diabetes, index date was 15 months after the date of diagnosis; for patients with prevalent type 2 diabetes, index date was 15 months after the date the patient became eligible for inclusion. The 15-month interval was introduced to: 1) ensure that at baseline all predictors determining the risk of OSA in patients with diabetes were recorded, as the Quality and Outcomes Framework (QOF) ensures these are captured within a 15-month period; 2) limit the possibility of silent OSA preceding type 2 diabetes being misclassified as incident OSA. The unexposed patients were assigned the same index date as their corresponding exposed patient to avoid immortal time bias (27). Patients with type 2 diabetes and controls were followed from the index date until the earliest of the following end points: outcome (OSA) date, death date, date patient left practice, date the practice ceased contributing to the database and study end date (31/12/2017). Outcomes OSA was identified by a record of any relevant clinical code.
Extra comments	Data was extracted from The Health Improvement Network (THIN), an electronic primary care records database that contains anonymised medical records of over 15 million patients from 787 practices in the UK. The database is generalizable to the UK population. It consists of coded information on patient demographics,

Study	Subramanian 2019[216]
	symptoms and diagnoses, drug prescriptions, consultations, diagnostic tests and their results. THIN is particularly suitable for analysing long-term health outcomes as GPs routinely collect and coordinate the patient's data. THIN has been extensively used previously to study metabolic outcomes and to study type 2 diabetes and OSA.
Indirectness of population	No indirectness
Risk factor	Type 2 diabetes
Confounding variables	Age, sex and BMI.
Funding	Not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Type 2 diabetes vs control Protocol outcome 1: Prevalence of OSA - Actual outcome: OSA in patients with type 2 diabetes 3110 (0.88%) patients with diabetes and 5968 (0.46%) controls developed OSA during the follow-up period. Adjusted incidence rate ratio (aIRR) of OSA in patients with type 2 diabetes compared to those without was 1.48 (95% CI 1.42-1.55; p<0.001). Risk of bias: high not adjusted for all key confounders	
Protocol outcomes not reported by the study	None

Study	Terpening 2015[222]
Study type	Prospective cohort study
Number of studies (number of participants)	N=46 patients with MCI N=40 age matched controls
Countries and setting	Conducted in Australia; Setting: hospital
Line of therapy	Not applicable
Duration of study	
Method of assessment of guideline condition	Yes
Stratum	OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	People with Mild cognitive impairment (MCI)
Exclusion criteria	History of stroke, neurological disorder, head injury with loss of consciousness >30 minutes, medical conditions known to affect cognition (e.g. cancer), other psychiatric illness, mini mental examination score (MMSE) <24 and/or diagnosis of dementia, shift workers, transmeridian travel in the previous 60 days, use of medication known to affect sleep and/melatonin secretion including beta-blockers, lithium, or benzodiazepines.
Recruitment/selection of patients	46 help-seeking older adults meeting criteria for MCI were recruited from the Healthy Brain ageing clinic at the Brain & Mind research institute, Sydney, Australia. Of this 30% were amnestic MCI subtype. 40 age matched control participants were recruited from the community for comparative purposes. Participants were required to be over the age of 45 years and to be stabilised on medication prior to referral.

Study	Terpening 2015[222]
Age, gender and ethnicity	Mean age- MCI- 66.1 (8.4); control- 63.5 (8.9)
Further population details	There was higher clinician related depression and a higher level of medical burden in the MCI group as compared to the control group.
Extra comments	-
Indirectness of population	No indirectness
Risk factor	Mild cognitive impairment (MCI)
Confounding variables	Age
Funding	This study was supported by NHMRC project grant No. 632689 and an NHMRC Australia Fellowship awarded to one of the authors.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Mild cognitive impairment (MCI) vs control Protocol outcome 1: prevalence of OSA - Actual outcome: AHI (events/h of sleep) mean (SD) MCI: 14.9 (14.5); control- 12.6 (11.5) Risk of bias: high Controls not matched for all confounders	
Protocol outcomes not reported by the study	None

Study	Trois 2009[224]
Study type	Retrospective cohort study
Number of studies (number of participants)	N= 16 with Down syndrome (DS); n= 48 without Down syndrome (DS)
Countries and setting	Conducted in USA; Setting: hospital
Line of therapy	Not applicable
Duration of study	NR
Method of assessment of guideline condition	Yes
Stratum	OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with DS, aged ≥ 18 years, were eligible if they had no acute inter current infection at the time of the study and had not undergone prior treatment for OSAS during adulthood (such as continuous positive airway pressure therapy or uvulopalatopharyngoplasty). Subjects who were treated during childhood (e.g., with tonsillectomy and adenoidectomy) were eligible for participation because certain risk factors for OSAS, such as obesity and hypothyroidism, can become manifest during adulthood in the DS population. Controls were obtained retrospectively from a clinical database of 3,934 patients who underwent standard diagnostic nocturnal polysomnography12 at the Johns Hopkins University Adult Sleep Center for evaluation of suspected OSAS. Three controls were selected for each subject with DS, based on the first 3 sequential controls in the database that most closely matched the DS subjects for age, sex, and body mass index (BMI). Forty-eight matched controls were obtained from the database. These subjects were well-matched to the DS cohort, with 50% being male, a median (range) age of 33 (17–56) years (non-significant), and mean BMI of 29 (20–52) kg/m^2 (non-significant).
Exclusion criteria	Not stated

Study	Trois 2009[224]
Recruitment/selection of patients	Subjects were recruited from the local Association of Retarded Citizens (ARC), Parents of Down Syndrome (PODS) group meetings and the Kennedy Krieger Down Syndrome Clinic. The Kennedy Krieger Institute serves the needs of individuals with developmental disabilities
Age, gender and ethnicity	Age (years): DS 33 (19-56); control 33 (17-56) Male, (N, %): DS 8 (50) :control 24 (50)
Further population details	16 adults with DS underwent evaluation for sleep disordered breathing. Interventions: Polysomnographic results were compared to a retrospective sample of adult patients referred for clinically suspected OSAS.
Extra comments	-
Indirectness of population	No indirectness
Risk factor	Down syndrome (DS)
Confounding variables	age, sex and BMI
Funding	Grants NHLBI and NIH/National Center for research resources grant to the Johns Hopkins University School of Medicine.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Down syndrome (DS) vs control Protocol outcome 1: Risk of OSA - Actual outcome: Sleep efficiency in (%) Down syndrome: 67% (16-95) Control: 88% (15-99)	

Study	Trois 2009[224]
Risk of bias: high Actual outcome: Total sleep time (min) Down syndrome: 307 (71-455) Control: 380 (84-698) Risk of bias: high Actual outcome: Obstructive apnoea hypopnea index (N/hr) Down syndrome: 37 (0-118) Control: 16 (0-148) Risk of bias: high	
Protocol outcomes not reported by the study	None

Study	Van dijk 2011[229]
Study type	Retrospective cohort study
Number of studies (number of participants)	N= 99 adult patients with type 1 diabetes (55 men, 44 women, duration of diabetes 26.9±1.2 years) N= 99 age-, sex- and BMI-matched non-diabetic controls.
Countries and setting	Conducted in The Netherlands ; Setting: hospital

Study	Van dijk 2011[229]
Line of therapy	Not applicable
Duration of study	Not stated
Method of assessment of guideline condition	Yes
Stratum	OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	patients with type 1 diabetes mellitus
Exclusion criteria	Exclusion criteria for both groups were: (1) previously diagnosed sleep disorders; (2) psychiatric disorders and/or use of psychotropic medication; (3) pregnancy or lactation; (4) working in nights shifts in the last 3 months; (5) travelling across time zones in the previous month; (6) age <18 years; (7) other endocrine disorders; (8) neuropathy caused by other conditions than type 1 diabetes; (9) chronic co-morbidity, other than peripheral neuropathy, associated with pain; and (10) chronic use of glucocorticoids.
Recruitment/selection of patients	99 consecutive patients with type 1 diabetes mellitus (55 men, 44 women) attending the outpatient clinic of the Leiden University Medical Center, and 99 age-, sex- and BMI-matched non-diabetic controls recruited by advertisement. Every patient with type 1 diabetes was individually matched with one non-diabetic healthy control for age, sex and BMI.
Age, gender and ethnicity	Age: type 1 diabetes 43.9±1.3; control 44.1±1.3 years
Further population details	Patients with type 1 diabetes used more frequently ACE inhibitors, calcium antagonists, statins, angiotensin II receptor antagonists and anti-platelet agents. According to the HADS, both anxiety (5.0±0.4 vs 3.7±0.3, p=0.004) and depression scores (3.3±0.4 vs 1.6±0.2, p=0.001) were significantly higher in the patients with type 1 diabetes. Thirteen patients (13.1%) had elevated scores for anxiety and depression (total HADS score 13 or more) vs six (6.1%) of the controls (p=0.267). The mean duration of the diabetes was 26.9±1.2 years. HbA1c values were 7.8± 0.1% (62±1.3 mmol/mol).

Study	Van dijk 2011[229]
Extra comments	-
Indirectness of population	No indirectness
Risk factor	type 1 diabetes
Confounding variables	age, sex and BMI
Funding	Support for this study from the Clinical Research Grant from the European Foundation for the Study of Diabetes (EFSD)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: type 1 diabetes mellitus vs control

Protocol outcome 1: risk of OSA

Actual outcome:

sleep quality PSQI (Pittsburgh Sleep Quality Index)>5 = poor sleepers

type 1 diabetes: 36/99

control: 20/99

Risk of bias: high

Actual outcome:

ESS total score

type 1 diabetes:5.9 (0.4)

control : 5.1 (0.4)

Actual outcome:

Study	Van dijk 2011[229]
type 1 diabetes: 17/99 control: 5/99 Risk of bias: high	
Protocol outcomes not reported by the study	None

Study	Yin 2019[250]
Study type	Retrospective cohort study
Number of studies (number of participants)	Primary headache disorders (PHD) cohort N=1346; Comparison cohort N=5384
Countries and setting	Conducted in Taiwan; Setting: hospital
Line of therapy	Not applicable
Duration of study	Not stated
Method of assessment of guideline condition	Yes
Stratum	OSAHS
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients in longitudinal health insurance database (LHID) who were diagnosed for PHDs for the first time from 2000 to 2005 were identified according to the International Classification of

Study	Yin 2019[250]
	Headache Disorders, Second Edition criteria (N=1346).
Exclusion criteria	Patients diagnosed of PHDs before 2000 were excluded to increase the likelihood of identifying new cases.
Recruitment/selection of patients	From the beginning of 2000 to the end of 2005 during which a patient was first diagnosed with PHDs was set as the index date. randomly selected 5384 subjects (a sample size fourfold that of the PHDs group) from LHID, frequency matched with the study cohort in terms of age, sex, index date and comorbidities (chronic obstructive pulmonary disease [COPD], hypertension, diabetes, hyperlipidaemia, stroke, obesity and depression). Each patient was then followed up from the index date until the occurrence of SA
Age, gender and ethnicity	Male :PHD 387 (28.75); comparison cohort 1548 (28.75)
Further population details	There were no significant differences in distribution of age, sex and comorbidities between the PHDs group and the matched controls.
Extra comments	-
Indirectness of population	No indirectness
Risk factor	Primary headache disorders (PHD)
Confounding variables	Age, sex, index date and comorbidities (chronic obstructive pulmonary disease [COPD], hypertension, diabetes, hyperlipidaemia, stroke, obesity and depression).
Funding	This study was supported in part by grants from the Tri-Service General Hospital, Ministry of Science and Technology, Teh- Tzer Study Group for Human Medical Research Foundation (A1031031).
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Primary headache disorders (PHD) vs control Protocol outcome 1: risk of OSA - Actual outcome: incidence of sleep apnoea HR (95% CI): 2.17 (1.26 to 3.7) Risk of bias: low	

Study	Yin 2019[250]
Protocol outcomes not reported by the study	None

Appendix E: Forest plots

E.1 People with hypertension vs control

Figure 2: Apnoea index

Study or Subgroup	hypertensives Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fletcher 1985	10	2.3	46	3.3	0.7	34	100.0%	6.70 [5.99, 7.41]
Total (95% CI)			**46**			**34**	**100.0%**	**6.70 [5.99, 7.41]**

Heterogeneity: Not applicable
Test for overall effect: Z = 18.62 (P < 0.00001)

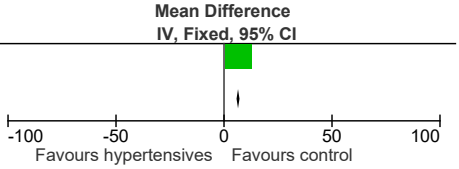
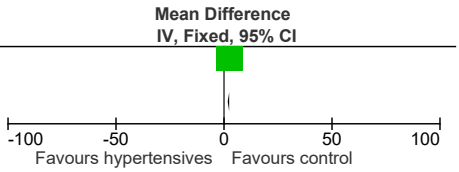


Figure 3: Hypopnoea index

Study or Subgroup	hypertensives Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fletcher 1985	8.1	1	46	5.6	1.4	34	100.0%	2.50 [1.95, 3.05]
Total (95% CI)			**46**			**34**	**100.0%**	**2.50 [1.95, 3.05]**

Heterogeneity: Not applicable
Test for overall effect: Z = 8.87 (P < 0.00001)

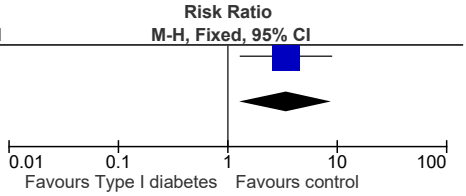


E.2 People with type I diabetes vs control

Figure 4: High risk OSA

Study or Subgroup	Type I diabetes Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Van dijk 2011	17	99	5	99	100.0%	3.40 [1.31, 8.86]
Total (95% CI)		**99**		**99**	**100.0%**	**3.40 [1.31, 8.86]**
Total events	17		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.51 (P = 0.01)

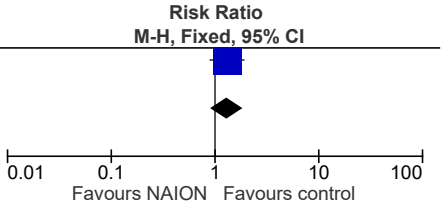


E.3 People with non-arteritic anterior ischaemic optic neuropathy

Figure 5: Prevalence of OSA

Study or Subgroup	NAION Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Arda 2013	17	20	13	20	100.0%	1.31 [0.90, 1.89]
Total (95% CI)		**20**		**20**	**100.0%**	**1.31 [0.90, 1.89]**
Total events	17		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.16)



E.4 People with PCOS vs People without PCOS

Figure 6: Incident OSA

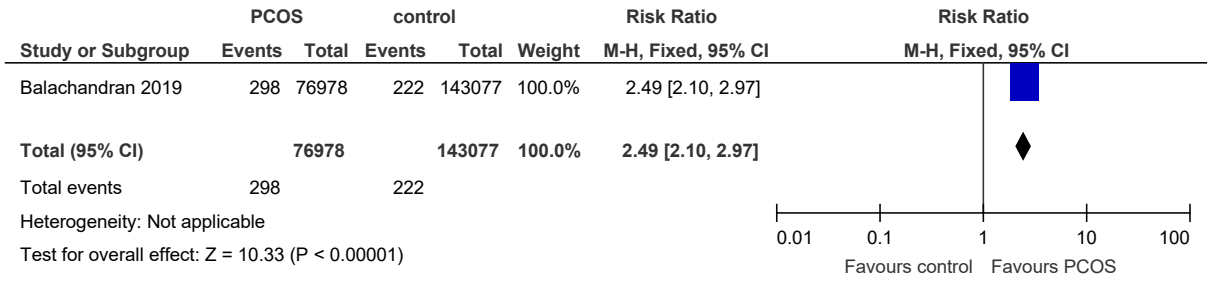
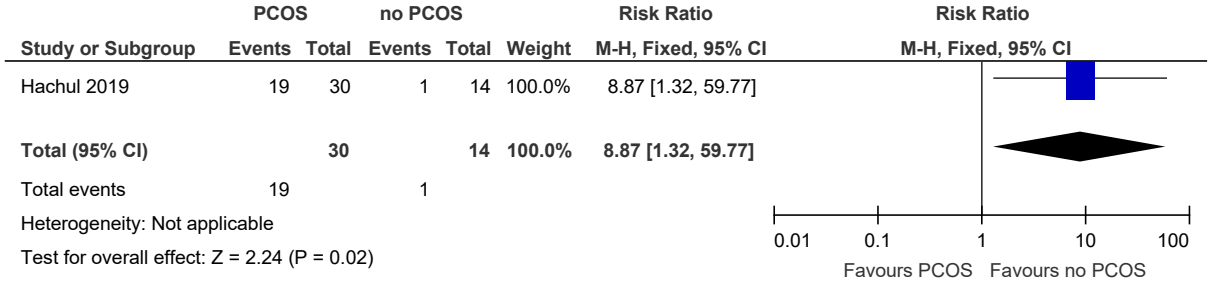
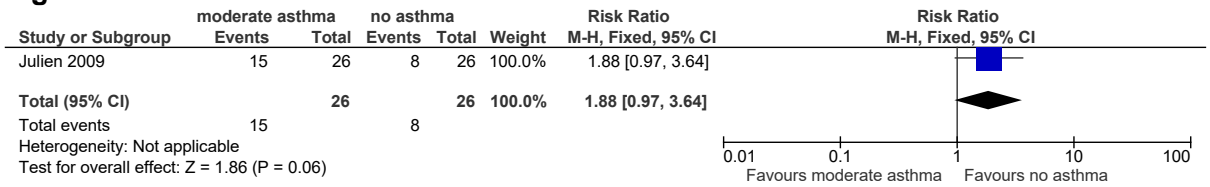


Figure 7: Risk of OSA



E.5 People with moderate asthma vs People with no asthma

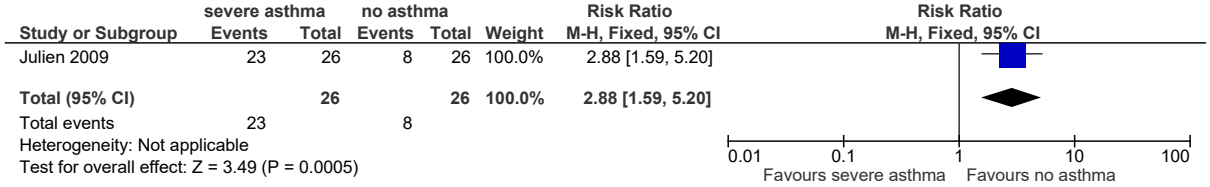
Figure 8:Prevalence of OSA -total AHI >15 events/hour



<Insert Note here>

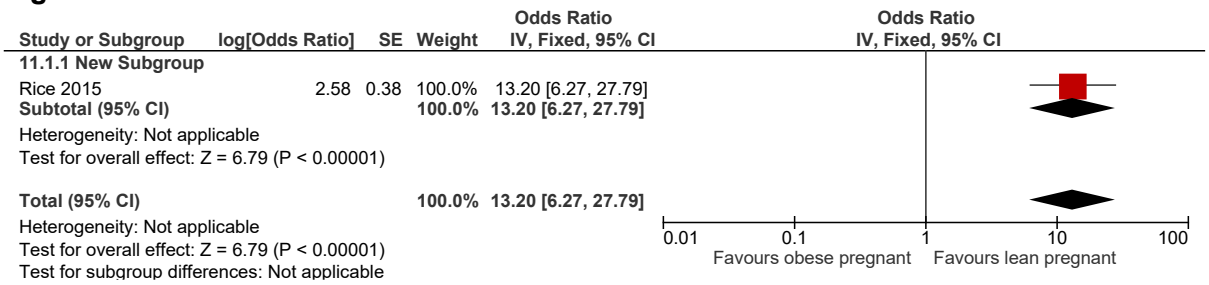
E.6 People with severe asthma vs People with no asthma

Figure 9: Prevalence of OSA -total AHI >15 events/hour



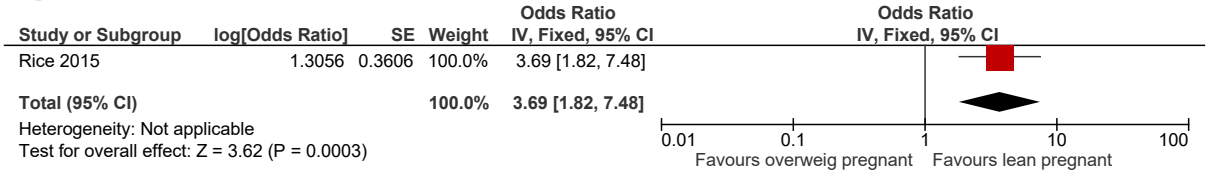
E.7 Obese pregnant women vs lean pregnant women

Figure 10: OSA



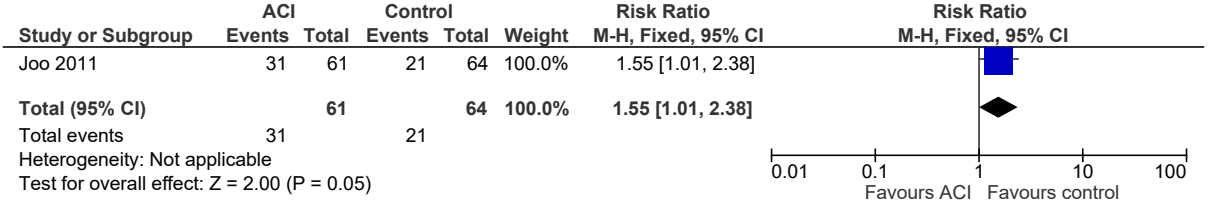
E.8 Overweight pregnant women vs lean pregnant women

Figure 11: OSA



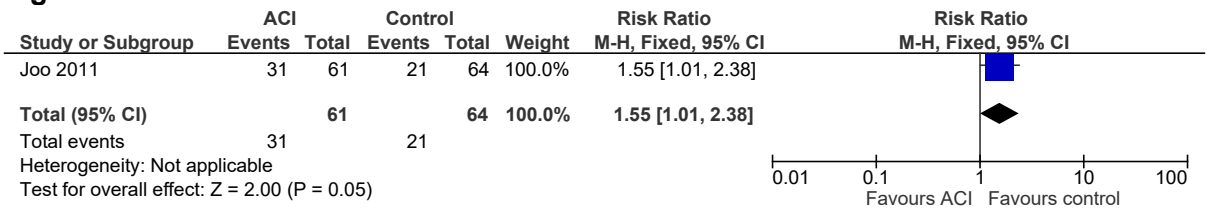
E.9 People with acute cerebral infarction vs control

Figure 12: Prevalence of OSA



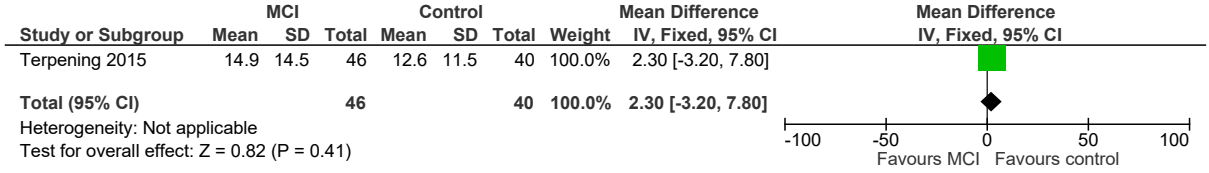
E.10 People with transient ischaemic attack vs control

Figure 13: Prevalence of OSA



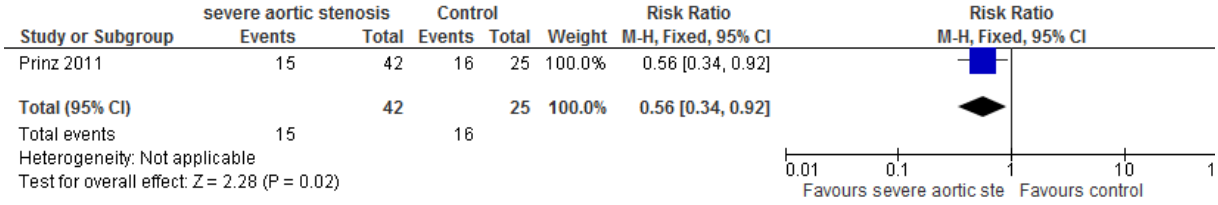
E.11 People with mild cognitive impairment vs control

Figure 14: AHI



E.12 People with severe aortic stenosis vs control

Figure 15: Prevalence OSA



Appendix F: GRADE tables

Table 26: Clinical evidence profile: People with primary headache disorder vs control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Primary headache disorder	Control	HR (95% CI)	Absolute		
incidence of sleep apnoea												
1	observational studies	serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	20/1346 (1.5%)	37/5384 (0.69%)	HR 2.17 (1.259 to 3.739)[2]	8 more per 1000 (from 2 more to 19 more)	⊕⊕OO LOW	CRITICAL

[1] Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] multivariate cox proportional hazards regression analysis measured HR

Table 27: Clinical evidence profile: People with asthma vs control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Asthma	Control	HR (95% CI)	Absolute		
incidence of OSA												
1	observational studies	serious risk of bias2	no serious inconsistency	no serious indirectness	no serious imprecision	None	328/38840 (0.84%)	521/155347 (0.34%)	HR 1.87 (1.61 to 2.17)[1]	3 more per 1000 (from 2 more to 4 more)	⊕⊕OO LOW	CRITICAL

[1] Model adjusted for age, sex and comorbidities of hypertension, diabetes, hyperlipidaemia, COPD, CAD, stroke, rhinitis, chronic sinusitis, GERD and obesity

2 Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 28: Clinical evidence profile: People with moderate asthma vs People without asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moderate asthma	No asthma	Relative (95% CI)	Absolute		
prevalence of OSA -total AHI >15 events/hour												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	None	15/26 (57.7%)	30.8%	RR 1.88 (0.97 to 3.64)	271 more per 1000 (from 9 fewer to 813 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Default MID (0.5XSD) used to assess imprecision Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs .

Table 29: Clinical evidence profile: People with severe asthma vs People without asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe asthma	No asthma	Relative (95% CI)	Absolute		
prevalence of OSA -total AHI >15 events/hour												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	23/26 (88.5%)	30.8%	RR 2.88 (1.59 to 5.2)	579 more per 1000 (from 182 more to 1000 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 30: Clinical evidence profile: People with Bipolar disorder vs control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bipolar disorder	Control	HR (95% CI)	Absolute		
Incidence of OSA												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	28/3650 (0.77%)	90/18250 (0.49%)	HR 1.54 (0.99 to 2.37)[3]	3 more per 1000 (from 0 fewer to 7 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Default MID (0.5XSD) used to assess imprecision. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs ., GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.
3 Adjusted for demographics and baseline co-morbidities.

Table 31: Clinical evidence profile: People with hypertension vs control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hypertensives	Control	Relative (95% CI)	Absolute		
apnoea index (Better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	46	34	-	MD 6.7 higher (5.99 to 7.41 higher)	⊕OOO VERY LOW	CRITICAL
hypopnoea index (Better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	46	34	-	MD 2.5 higher (1.95 to 3.05 higher)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 32: Clinical evidence profile: People with type I diabetes vs control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Type I diabetes	Control	Relative (95% CI)	Absolute		
high risk OSA												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	17/99 (17.2%)	5.1%	RR 3.4 (1.31 to 8.86)	122 more per 1000 (from 16 more to 401 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 33: Clinical evidence profile: People with non-arteritic anterior ischaemic optic neuropathy vs control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Patients with non-arteritic anterior ischaemic optic neuropathy	Control	Relative (95% CI)	Absolute		
Prevalence of OSA												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[1]	None	17/20 (85%)	65%	RR 1.31 (0.9 to 1.89)	201 more per 1000 (from 65 fewer to 578 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[2] Default MID (0.5XSD) used to assess imprecision. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.

Table 34: Clinical evidence profile: People with PCOS vs People without PCOS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCOS	Without PCOS	Relative (95% CI)	Absolute		
incident OSA												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	298/76978 (0.39%)	2.1%	RR 0.18 (0.15 to 0.22)	17 fewer per 1000 (from 16 fewer to 18 fewer)	⊕OOO VERY LOW	CRITICAL
high risk for OSA (Berlin questionnaire)												
1	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	19/30 (63.3%)	7.1%	RR 8.87 (1.32 to 59.77)	559 more per 1000 (from 23 more to 1000 more)	⊕⊕OO LOW	CRITICAL

[1] Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 35: Clinical evidence profile: Obese pregnant women vs lean pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Obese pregnant women	Lean pregnant women	Relative (95% CI)	Absolute		
OSA												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	28/109 (25.7%)	12/573 (2.1%)	OR 13.2 (6.27 to 27.79)[1]	199 more per 1000 (from 97 more to 352 more)	⊕⊕OO LOW	CRITICAL

[1] adjusted odds ratio

Table 36: Clinical evidence profile: overweight pregnant women vs lean pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overweight pregnant women	Lean pregnant women	Relative (95% CI)	Absolute		
OSA												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	28/109 (25.7%)	12/573 (2.1%)	OR 3.69 (1.82 to 7.48)[1]	52 more per 1000 (from 17 more to 117 more)	⊕⊕OO LOW	CRITICAL

[1] adjusted odds ratio

Table 37: Clinical evidence profile: People with acute cerebral infarction vs control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acute cerebral infarction	Control	Relative (95% CI)	Absolute		
prevalence of OSA												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	31/61 (50.8%)	32.8%	RR 1.55 (1.01 to 2.38)	180 more per 1000 (from 3 more to 453 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Default MID (0.5XSD) used to assess imprecision. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs . GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.

Table 38: Clinical evidence profile: People with transient ischaemic attack vs control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transient ischaemic attack	Control	Relative (95% CI)	Absolute		
prevalence of OSA												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	9/13 (69.2%)	32.8%	RR 2.11 (1.27 to 3.49)	364 more per 1000 (from 89 more to 817 more)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 39: Clinical evidence profile: People with mild cognitive impairment vs control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mild cognitive impairment	Control	Relative (95% CI)	Absolute		
AHI (Better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	None	46	40	-	MD 2.3 higher (3.2 lower to 7.8 higher)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Default MID (0.5XSD) used to assess imprecision. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs .

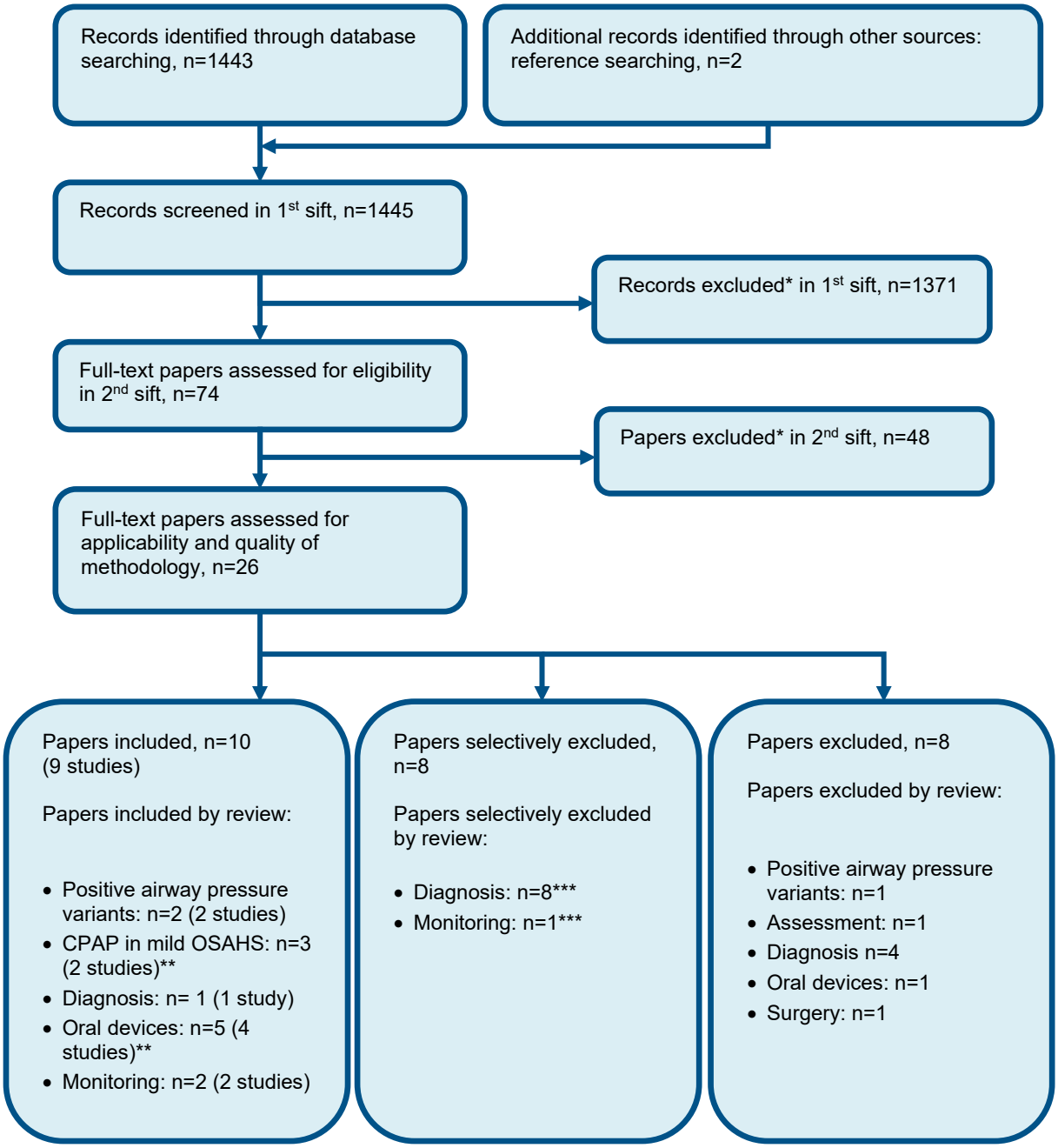
Table 40: Clinical evidence profile: People with severe aortic stenosis vs control

Table 26: Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe aortic stenosis	Control	Relative (95% CI)	Absolute		
prevalence OSA												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	15/42 (35.7%)	64%	RR 0.56 (0.34 to 0.92)	282 fewer per 1000 (from 51 fewer to 422 fewer)	⊕OOO VERY LOW	CRITICAL

[1] Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Default MID (0.5XSD) used to assess imprecision. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs . GC considered the clinical importance of the effect estimate for each analysis on a case by case basis, taking into consideration the increment of the risk factor and the outcome under study.

Appendix G: Health economic evidence selection

Figure 16: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language
** Two studies (in three papers) were included for two different questions
*** One study was considered for two different questions

Appendix H: Excluded studies

H.1 Excluded clinical studies

Table 41: Studies excluded from the clinical review

Reference	Reason for exclusion
Abd el Kader 20101	Case control study
Abumuamar 20182	This study aimed to determine the prevalence and clinical predictors of OSA in patients with atrial fibrillation. No relevant comparison group.
Adderley, 20203	Inappropriate comparison – both groups with type 2 diabetes
Agha, 20194	Inappropriate comparison- Type 2 diabetes and OSA versus Type 2 diabetes but without OSA.
Ajayi 20195	Full text paper not available
Akintunde 20126	The study aims to describe the prevalence of snoring and OSA among hypertensive subjects in South Western, Nigeria. No relevant comparison group.
Al-Abri 20157	The aim of the study was to estimate the frequency of OSAS among patients with epilepsy and to study the seizure characteristics among those patients with co-morbid OSAS. . No relevant comparison group.
Albuquerque 20129	Study aimed to assess the relationship between EDS and SDB in patients with atrial fibrillation. No relevant comparison group. .
Al-Jahdali 20118	Inappropriate study design- cross-sectional study
Altaf 201710	The study aimed to determine the interrelationships of OSA and sight-threatening diabetic retinopathy in subjects with T2D and to assess whether OSA is associated with diabetic retinopathy progression. No relevant comparison group.
Anderson 201211	Study evaluated the prevalence of sleep disordered breathing in a community cohort with chronic mental illness on long-term psychotropic medication. No relevant comparison.
Andreas 199612	Sleep apnoea in patients with coronary artery disease. No comparison.
Annakkaya 201213	Full text paper not available
Antony 201414	No relevant risk factor. Study aimed to ascertain the validity of two screening scales for obstructive sleep apnoea (OSA) in pregnancy and to establish the prevalence of OSA in pregnancy.
Areias 201216	Paper not in English
Arnulf 200217	SDB in Parkinson disease. No appropriate comparison.
Aronson 201418	Prevalence of SDB in patients with acute myocardial infarction. No relevant comparison.
Arzt 200620	Not matched control group. No multivariate analysis.
Arzt 201619	study investigated the prevalence of sleep-disordered breathing (SDB) and its predictors in patients with stable chronic heart failure (HF). No relevant comparison.
Asker 201521	Sleep apnoea in heart failure- no comparison.
Barreto 202023	No control group

Reference	Reason for exclusion
Bassetti 199624	No multivariate analysis or matched controls.
Bassetti 199725	SDB in patients with acute supra and infra tentorial strokes. No appropriate comparison.
Beland 201526	Sleep apnoea in Parkinson's disease. No relevant comparison.
Bianchi 201427	Goals of the study were to evaluate the prevalence of sleep apnoea in a large cohort of patients with myotonic dystrophy. No relevant comparison.
Bitter 200928	Study investigated the prevalence and type of SDB in patients with heart failure with normal left ventricular ejection fraction (HFNEF). No relevant comparison.
Bitter 201229	Aim of the study was to investigate whether assessment of specific symptoms can elucidate presence of SDB in CHF patients. No relevant comparison group.
Blackwell 201530	No relevant risk factor. To assess if SDB is associated with cognitive decline.
Blagojevic-Bucknall 201931	Gout – risk factor not in the protocol.
Bodez 201632	Study assessed prevalence, severity, and prognostic value of sleep-disordered breathing (SDB) in cardiac amyloidosis (CA). No relevant comparison group.
Boentert 201833	Study aimed to investigate the prevalence of different subtypes of SDB among patients with amyotrophic lateral sclerosis undergoing sleep studies for the first time. No relevant comparison group.
Borel 201734	Study aimed to determine the prevalence of OHS in ambulatory obese patients not previously referred to a pulmonologist for suspicion of sleep breathing disorders. No relevant comparison group.
Borsini 201835	Sleep apnoea in patients with hypertension. No appropriate comparison.
Bosanquet 201136	Study estimated the prevalence of OSA among patients with VTE. No relevant comparison.
Bublitz 201837	To assess the prevalence of OSA in pregnant women with gestational diabetes mellitus. No relevant comparison.
Buchwald 199438	No appropriate comparison
Buse 201939	Inappropriate study design-study based on cross-sectional surveys
Cai 201340	Survey
Camilo 201641	SDB in acute ischemic stroke patients. No appropriate comparison.
Carmelli 200042	Study examined the association between changes in obesity from midlife to late adulthood and overnight recording of respiration during sleep. No relevant comparison.
Ceide 201543	Study assessed associations of depression and anxiety with risk of OSA among Non-Hispanic Blacks. No relevant comparison.
Chan 201044	The objectives of the study were to determine the prevalence and severity of OSA and its clinical presentation in patients with TIA and minor stroke. No relevant comparison.
Cheng 201846	Study evaluated the prevalence of OSA in patients with PE. No relevant comparison.

Reference	Reason for exclusion
Cherkassky 200347	Prevalence of sleep apnoea in stroke patients. No appropriate comparison.
Cochen de Cock 201048	No useful outcomes. Study did not directly compare prevalence of OSA in people with Parkinson's disease to sex age matched controls. Study compared prevalence with healthy controls in Japan (not matched)
Colao 201849	Conference abstract
Costantino 202051	No relevant intervention. systematic review and meta-analysis for studies evaluating hypoglossal nerve stimulation
Corra 200650	The aim of the present study to determine the relationship between exertional oscillatory ventilation and central sleep apnoea in stable CHF patients. No relevant comparison.
Desalu 201752	Survey
Dominguez 201853	Prevalence obstructive sleep apnoea in pregnant women with extreme Obesity. No relevant comparison.
Dong 202054	Systematic review- screened for relevant references.
Donnellan 202055	No useable outcomes.
Donovan 201956	No relevant comparison.
Drager 200957	OSA in patients with metabolic syndrome. No relevant comparison.
Dyken 199658	OSA IN stroke. Control group not matched. No multivariate analysis.
El-Aatty 201559	Case control study
Elkholy 201260	Inappropriate study design- case-control study
Ezzat 201561	Control group not matched for key confounders. No multivariate analysis.
Facco 201062	Prevalence of sleep disturbances in pregnancy. No relevant comparison.
Fan 201963	Study conducted analysis to delineate the association of OSA with subsequent cardiovascular events after ACS onset. No relevant comparison.
Fehr 201864	OSA in post-traumatic disorder. No appropriate comparison.
Ferguson 199665	People with amyotropic lateral sclerosis- not relevant risk factor in protocol
Ferreira 201066	Study aimed to determine the prevalence of SA in HF and to identify potential risk factors for SA in HF population. No relevant comparison.
Fisse 201767	The aim of the study was to investigate whether the diagnosis of SRBD in patients with acute ischemic stroke is associated with specific lesion locations. No relevant comparison. No relevant risk factor assessed.
Fisser 201768	SDB in patients with STEMI. No relevant comparison group.
Foley 199970	No appropriate comparison. Associations of symptoms of sleep apnoea with cardiovascular disease.
Franzen 201571	Prevalence of SDB in Fabry disease. Not relevant risk factor
Friedman 201172	Inappropriate comparison. Sleep parameters between patients with mild and moderate/severe sleep apnoea.
Gabryelska 201873	Prevalence of OSA IN Rapid eye movement behaviour disorder (RBD). No relevant comparison group.
Gami 200775	This study sought to identify whether obesity and obstructive

Reference	Reason for exclusion
	sleep apnoea (OSA) independently predict incident atrial fibrillation/flutter (AF).
Geib 201576	SDB in patients with CHF. No appropriate comparison.
Geovanini 201677	Study investigated the association between obstructive sleep apnoea (OSA) severity with markers of overnight myocardial injury in patients with refractory angina. No relevant comparison.
Gille 201778	Study aimed to determine the prevalence and determinants of obstructive sleep apnoea (OSA) in patients with newly diagnosed idiopathic pulmonary fibrosis (IPF). No relevant comparison.
Glantz 201379	Study aimed to address the occurrence and predictors of OSA among revascularised patients with CAD. No relevant comparison. Cross-sectional report.
Godoroja 201680	Study investigated the extent to which anthropometric measurements can be used to identify the presence of significant OSA (Apnoea/Hypopnoea Index (AHI) > 20) in adult patients. No relevant risk factor assessed.
Grigg-Damberger 201481	Literature review
Guilleminault 200282	SDB in post-menopausal women. No appropriate comparison.
Gunduz 201883	No relevant comparison. Study evaluated the prevalence of OS in mild hypoxemic COPD patients without OSA symptoms and compared characteristics of OS and COPD patients.
Guo 201884	Sleep apnoea in patients with untreated acromegaly. No relevant comparison.
Gupta 201685	Survey
Guven 201486	Aim of the study was to evaluate the presence of OSA in patients with difficult-to-treat asthma (DTA). No relevant comparison.
Haarmann 201987	Inappropriate population. People with diagnosed OSA
Harada 201890	Sleep apnoea in patients with coronary heart disease. No appropriate comparison.
Harada 201989	No control group
Harbison 200291	To determine the prevalence and course of sleep-disordered breathing in acute stroke inpatients. No comparison.
Hayano 201292	Not adjusted for key confounders. No multivariate analysis
Hein 201797	The aim of the study was to examine the prevalence and risk factors of moderate to severe obstructive sleep apnoea syndrome in a large sample of insomnia sufferers. No comparison.
Heck 201793	Cross-sectional study
Heffner 201294	No comparison group
Hein 201796	Same as Hein 2017 (above)
Hein 201995	Excessive day time sleepiness in major depression. No appropriate comparison.
Hernandez Voth 201798	OSAHS in patients with severe chronic respiratory insufficiency. No appropriate comparison.
Herrscher 201199	Sleep apnoea in heart failure outpatients. No appropriate comparison.

Reference	Reason for exclusion
Hobzova 2018100	Occurrence of sleep apnoea in patients with nocturnal hypertension. No relevant comparison.
Holcomb 2016101	Study aimed to prospectively examine the incidence and risk factors for sleep apnoea in consecutive brain injury rehabilitation admissions. No relevant comparison.
Holmqvist 2015102	No appropriate comparison. OSA vs No OSA
Hoyer 2010103	Case control study
Huang 2017105	Systematic review screened for relevant references
Hui 2017106	Study aimed to identifies the risk factors for OSA in CRS to determine who should be screened for OSA among patients with chronic rhinosinusitis. No relevant comparison.
Ifergane 2016107	Study evaluated clinical characteristics and laboratory markers of inflammation and coagulability associated with OSA severity during the acute post stroke period. No relevant comparison.
Jaimchariyatam 2019108	OSA as a risk factor for preeclampsia-eclampsia. No appropriate comparison.
Jasti 2018109	Sleep disorders in patients with Parkinsonism. No relevant comparison.
Javaheri 1995112	Study aimed to determine the prevalence and effect of sleep-disordered breathing in ambulatory patients with stable, optimally treated congestive heart failure. No relevant comparison.
Javaheri 1998111	Sleep apnoea in patients with stable heart failure. No appropriate comparison.
Javaheri 2006110	Prevalence of sleep apnoea in heart failure. No relevant comparison.
Kaneko 2003115	The study hypothesised that in patients with stroke undergoing rehabilitation, the presence of SA will be associated with a greater degree of functional impairment and a consequent longer hospitalisation than in patients with stroke but without SA. Not relevant comparison (Patients with SA vs Patients with no SA)
Kashine 2012116	Study investigated the prevalence of SDB patients with acromegaly. Not relevant comparison
Katzan 2019117	Full text paper not available.
Kezban 2012118	Inappropriate study design- cross-sectional study
Khan 2015119	Case control study
Kiyokuni 2018120	Study investigated the hypothesis that SDB is related to renal dysfunction in patients with ACS who undergo PCI. Not relevant comparison
Kunisaki 2015122	HIV patients. Not relevant risk factor.
Kosovali 2013121	Inappropriate comparison- patients with pulmonary embolism vs people with OSA.
Kwon 2015123	Study aimed to examine the cross-sectional association of SDB metrics and sleep quality with AF. No relevant comparison.
Lam 2010124	OSA in type 2 diabetes. No appropriate comparison.
Leao 2016125	Study aimed to determine the prevalence of OSA in patients with ACS and evaluate prognostic impact of OSA and continuous positive airway pressure (CPAP) therapy in these patients. No relevant comparison group.

Reference	Reason for exclusion
Lecomte 2013126	Data from a survey
Lee 2011127	Study aimed to determine the effect of severe obstructive sleep apnoea (OSA) on long-term outcomes after myocardial infarction. No relevant comparison
Lee 2019128	No appropriate risk factor. Risk of hypertension in snorers.
Lee 2019129	Full text paper not available
Leonavicius 2014130	The aim of the study was to evaluate the prevalence of sleep disturbances in a Lithuanian community sample of individuals with the relapsing remitting multiple sclerosis (RRMS). No relevant comparison group.
Leong 2014131	Cross-sectional study
Leroyer 1995132	Sleep apnoea in coronary heart disease. No appropriate comparison group.
Lin 2015133	Longitudinal cohort study. No comparison.
Lindenauer 2014134	Study compared the characteristics, treatments, and outcomes of patients with pneumonia who did or did not have OSA. No relevant comparison (patients with OSA vs patients without OSA)
Linhart 2015135	The aim of the study was to investigate the frequency of SDB in patients with severe aortic stenosis. No relevant comparison group.
Lisi 2015136	Study assessed impact of OSA on LV abnormalities in untreated uncomplicated essential hypertensive patients. No relevant comparison group.
Liu 2013137	The study's aim was to utilise questionnaires that assess OSA risk and symptoms to test the hypothesis that the most insulin-resistant subset of obese individuals is at highest risk for OSA. No relevant comparison (insulin resistant vs insulin sensitive obese patients)
Liu 2017138	People already diagnosed with sleep apnoea
Lofaso 2000139	Nasal resistance in unselected consecutive snorers referred for suspected sleep disorders was measured. No relevant comparison.
Lombardi 2018140	OSA in heart failure. No relevant comparison.
Loo 2020141	No control group
Lopes Neto 2013142	Inappropriate study design- cross-sectional study. To evaluate the frequency of obstructive sleep apnoea (OSA) in obese patients scheduled for bariatric surgery. No relevant comparison.
Lopez 2008143	Study reported prevalence of OSA in morbidly obese patients presenting for weight loss surgery. No relevant comparison.
Ludka 2014144	Study investigated the prevalence of SA and examined the day-night variation of onset of MI in acute MI patients. No relevant comparison. Retrospective study.
Macdonald 2008145	Study aimed to determine the current prevalence of sleep disordered breathing in a congestive heart failure clinic. No relevant comparison.
Mahdavinia 2017146	Systematic review. Screened for relevant references.
Marti-Almor 2020149	No control group
Manni 2003147	The aim of the study was to evaluate the rate and features of obstructive sleep apnoea (OSA) in adult epilepsy patients. No relevant comparison.

Reference	Reason for exclusion
Manu 1994148	Sleep apnoea in chronic fatigue. No appropriate comparison.
Mason 2012151	No information on matched controls- not clear if adjusted for key confounders. Prevalence for SDB only reported for patients with macular oedema not for control group.
Mason 2011150	To determine the prevalence of obstructive sleep apnoea (OSA) in patients with Abdominal aortic aneurysms. No relevant comparison.
McCarter 2018152	OSA in refractory epilepsy. No relevant comparison.
Meireles, 2020155	Inappropriate comparison- acute heart failure vs chronic heart failure.
Medeiros 2013153	Cross-sectional study
Mehra 2006154	SDB in acute coronary syndrome patients. No relevant comparison.
Mestron 2004156	Spanish acromegaly registry. No multivariate analysis
Min 2015157	Study aimed to determine the clinical, laboratory, and polysomnographic features of resistant HTN that are significantly associated with OSA. No relevant comparison (controlled hypertension vs and resistant hypertension groups.
Miyazaki 2015158	Control not matched for key confounders. No multivariate analysis
Mokhlesi 2019160	Inappropriate study design- cross sectional study
Mohsenin 1995159	No relevant outcomes
Morantes-Caballero 2019161	No useable outcomes. Study aimed to determine the effects of air pollution on acute exacerbation of chronic obstructive pulmonary disease
Moreno-Lopez 2011162	Inappropriate comparison. Survey of EDS in consecutive patients with MSA and comparison with patients with Parkinson disease (PD)
Mubarik 2016163	OSA in bariatric surgery patients. No relevant comparison group.
Myles 2018164	Not relevant risk factor-schizophrenia
Nair 2019165	Sleep apnoea in acute ischaemic stroke. No appropriate comparison.
Nicholl 2012167	Sleep apnoea in CKD. No appropriate comparison.
Oldenburg 2007168	Evaluation of the prevalence and nature of sleep-disordered breathing (SDB) in patients with symptomatic chronic heart failure (CHF) receiving therapy. No relevant comparison group.
Ong 2009169	The aim of the study was to examine the frequency of OSA in people with major depressive disorder. No relevant comparison group.
Padeletti 2009170	SDB in acute heart failure decompensation. No relevant comparison group.
Pampati 2016171	Retrospective cohort study. Study aimed to assess the prevalence of symptomatic OSAS in chronic spinal pain patients receiving chronic opioid therapy and determine the association of OSAS with multiple risk factors and comorbidities. No relevant comparison group.
Papanas 2010172	Not relevant risk factor. The aim of the study was to examine the prevalence of metabolic syndrome (MS) and its

Reference	Reason for exclusion
	components among obstructive sleep apnoea (OSA) patients vs controls.
Parra 2000173	To investigate the prevalence and behaviour of sleep-related breathing disorders (SRBDs) associated with a first-ever stroke or transient ischemic attack (TIA). No relevant comparison
Paulino 2009174	Study assessed the prevalence of sleep-disordered breathing and its associated risk factors in French patients with heart failure. No relevant comparison
Pedrosa 2010175	OSA in mild atrial fibrillation. No relevant comparison
Peruvemba 2012176	Cross-sectional study
Petrossians 2017177	Survey of acromegaly patients. No relevant comparison
Pien 2014178	SDB in pregnancy. No relevant comparison
Rao 2008180	Study assessed the prevalence of and risk factors for sleep disturbances in the acute post-traumatic brain injury (TBI) period. No appropriate comparison.
Reading 2009181	Cross-sectional study
Rogers 2015183	Study investigated risk of OSA among blacks with metabolic syndrome. No relevant comparison
Rogers 2020184	Risk factor not in protocol-black people with metabolic syndrome
Romdhane 2018185	Not in English
Romero 2010186	Retrospective chart review.
Rose 2014187	No relevant risk factor. Sleep disordered breathing (SDB) in patients on opioids for chronic pain
Rosenow 1996188	Sleep apnoea in treated acromegaly. No appropriate comparison.
Sankari 2015189	The objectives of this study were to examine predictors of SDB diagnosis and to estimate rates of SDB treatment in Spinal cord injury or disorder patients. No relevant comparison
Sapina-Beltran190	No control group
Sawanyawisuth 2013191	Paper aimed study factors associated with OSA-induced hypertension in those patients with age more than 60 years. No relevant comparison.
Schipper 2016192	OSA in patients with transient ischaemic attack. No appropriate comparison.
Schreiber 2018193	Prevalence of sleep apnoea among COPD patients. No relevant comparison.
Schulz 2007194	Prevalence and type of SDB among CHF patients. No relevant comparison.
Schutt 2015195	Controls not matched/no multivariate analysis
Seetho 2015196	Study investigated whether OSA was associated with serum urate in severe obesity and whether continuous positive airway pressure (CPAP) treatment was associated with a fall in urate. No relevant comparison.
Seguro 2018197	Study aimed to confirm that severe OSAHS is less symptomatic in HT patients than normotensive patients using ESS. All patients with severe OSAHS at baseline. Not appropriate population.

Reference	Reason for exclusion
Sharma 2015198	The aim of this study was to conduct a clinical pathway evaluation (CPE) among obese patients admitted to a tertiary care hospital. No relevant comparison.
Sharma 2016199	Study aimed to prospectively examine the impact of sleep disorders on GH, preeclampsia, LBW, low Apgar score, and GDM in Indian pregnant women. No relevant comparison group.
Shen 2016200	Rheumatoid arthritis. Not relevant risk factor.
Sheu 2015202	Not appropriate risk factor and comparison. The goal of the study was to investigate the risk for Parkinson disease during a 5-y follow-up period after a diagnosis of OSA using a population based dataset.
Shibazaki 2013203	SDB in patients with atrial fibrillation. No appropriate comparison.
Shim 2011204	Cross-sectional study-inappropriate study design
Shimohata 2012205	Study aimed to ascertain the prevalence of EDS in Japanese multiple system atrophy patients by using the Epworth Sleepiness Scale (ESS). No relevant comparison group.
Shinoda 2019206	Cross-sectional study
Siarnik 2016207	Inappropriate comparison- aim of the study was to compare polysomnographic, clinical, and laboratory characteristics of wake-up (WUS) and non-wake-up acute ischemic strokes (NWUS).
Sjostrom 2002208	Case control study
Soler 2015209	SDB in patients with COPD. No appropriate comparison.
Soreca 2015210	No relevant comparison. Study assessed the feasibility of in-home screening for sleep apnoea in patients with bipolar disorder.
Stewart 2020213	Full text paper not available.
Steveling 2014211	Cross-sectional study. Study aimed to evaluate the prevalence and possible predictors of the COPD-OSAHS overlap syndrome and its association with comorbidities in a cohort of COPD patients. No comparison.
Stevenson 2008212	Matched case control study
Stoohs 1996214	SDB in hypertension. No appropriate comparison.
Stubbs 2016215	Systematic review. Screened for relevant references.
Szymanski 2015217	The aim of the study was to establish whether atrial fibrillation patients with coexisting OSA have higher stroke risk. No comparison.
Tahrani 2013218	Aim of this study was to assess the impact of OSA on the estimated glomerular filtration (eGFR) decline in patients with type 2 diabetes. No relevant comparison.
Tam, 2019219	No useable outcomes
Tami 1998220	OSA in patients who snore. No appropriate comparison.
Tateishi 1994221	SDB in patients with coronary artery disease. No appropriate comparison.
Tremel 1999223	The aim was to define the prevalence of sleep respiratory disturbance in patients after an episode of acute left ventricular failure and the subsequent change after heart failure therapy. No relevant comparison.
Tseng 2019225	No control group
Turcani 2015226	

Reference	Reason for exclusion
	Study aimed to determine the ratio of concurrence of OSA in patients hospitalized for COPD exacerbation. No relevant comparison.
Utriainen 2013227	Cross-sectional study
Van den Broecke 2014228	No appropriate risk factor and comparison. Study assessed the feasibility of SDB screening at the early phase of ACS.
Vazir 2007230	The aim of this study was to determine the prevalence and characteristics of SDB in male patients with NYHA class II symptoms of CHF. No relevant comparison.
Venkateswaran 2014231	Study aimed to determine the prevalence of COPD-OSAHS overlap syndrome and the predictors of OSA in patients with COPD. No relevant comparison.
Venturi 2011232	Cross-sectional study
Vgontzas 1994234	case series
Vgontzas 2000233	Control group not matched for key confounders. No multivariate analysis
Vorderwulbecke 2020235	Full text paper not available.
Wang 2019236	No useable outcomes
Webster 2001237	Sleep apnoea win patients with traumatic brain injury. No appropriate comparison group.
West 2006239	No relevant risk factors
Wei 2020238	Cross-sectional study
Wilson 2020241	Sleep disordered breathing not specifically OSA
Witassek 2019244	No control group
Wilson 2020240	Sleep disordered breathing not specifically OSA
Wilson 2018242	Cross-sectional study
Wilton 2018243	Rheumatoid arthritis. Not relevant risk factor.
Wongvilairat 2019246	Allergic rhinitis. Not relevant risk factor. No control group
Wolters 2020245	No control group. No useable outcomes.
Worsnop 1998247	Control group not matched. No multivariate analysis.
Wu 2020248	Cross-sectional study
Yeh 2010249	Study aimed at identifying practical clinical predictors of OSA for bariatric patients. No relevant comparison group.
Yoon 2020251	No control group
Yumino 2009252	To determine whether the influence of sleep apnoea (SA) on the risk of death differs in patients with ischaemic and in those with non-ischaemic heart failure (HF). No relevant comparison group.
Zeng 2013253	Systematic review- screened for relevant check references

H.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below.

None.