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