The Effect of Obstructive Sleep Apnoea (OSA) on Health Outcomes in Patients with Asthma: Epidemiology, Impact on Asthma Control, and Effect of Treatment using Continuous Positive Airway Pressure (CPAP).

by

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Abstract

Introduction: The aim was to determine the prevalence of OSA in severe asthma (SA), the effect of OSA and the impact of CPAP treatment on asthma-related clinical outcomes.

Methods: Systematic review (SR) of the pre-existing literature, a cross-sectional study, prospective case-control study and a randomised, double-blind, placebo-controlled pilot feasibility study (RCT) were conducted.

Results: SR; 6 studies: 19-60% prevalence in asthma, 50-95% in SA, 13 questionnaire studies; 8-53% prevalence in asthma. Observational studies; 191 participants, 70% prevalence. Asthma-related quality of life, asthma control, depression scores and general quality of life worsened with increasing severity of OSA. SR; CPAP treatment can improve asthma-related quality of life particularly in more severe asthma or severe OSA. RCT; 27 participants recruited, 14 completed study. No change in AQLQ or asthma control with CPAP, but small numbers recruited with high drop-out rate (48%).

Conclusion: A high prevalence of OSA in asthma, and particularly severe asthma exists with negative impact on asthma control and quality of life. Improved asthma-related quality of life with CPAP treatment has been observed, but this was not supported with the RCT. Further research with a large multicentre RCT is needed before firm conclusions can be made on the impact of CPAP treatment.

Dedication

I am dedicating this thesis to Beth; for your long-suffering support and constant encouragement even during times of insanity! Your belief in me gave me the courage to take the plunge into the world of research and has kept me going ever since.

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Finally, I would like to thank all of my family for their constant love and support, and particularly my Mum who has always made me believe that with hard work anything is possible!

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1. Davies S, et al. P53 Co-existing obstructive sleep apnoea (OSA) adversely impacts on asthma related symptoms and quality of life *Thorax* 2018;73:A130-A131

2. Davies S, et al. P58 Systematic review: Does continuous positive airway pressure (CPAP) treatment of obstructive sleep apnoea (OSA) improve asthma-related clinical outcomes? *Thorax* 2018;73:A131-A132.

3. Davies S, et al. P195 "Syndrome Z" in the asthma population. *Thorax* 2017;72:A188-A189.

4. Davies S, et al. P202 Obstructive sleep apnoea (OSA) and non-eosinophilic asthma: an important phenotype in the severe asthma population. *Thorax* 2017;72:A192-A193.

5. Davies, S et al. M9 A high prevalence of obstructive sleep apnoea (OSA) in the severe/difficult to treat asthma (SDTA) population. *Thorax* 2016;71:A262.

6. Davies S, et al. Patients with sleep apnoea (SA) and severe/difficult to treat asthma (SDTA) have worse asthma related clinical outcomes than those with no sleep apnoea. *ERJ* 2016 48: PA2356; DOI 10. 1183/13993003.congress-2016.

Full text:

1. Davies SE, Bishopp A, Wharton S, Turner AM, Mansur AH. The association between asthma and obstructive sleep apnea (OSA): A systematic review. *J Asthma*. 2018:1-12.

2. Davies SE, Bishopp A, Wharton S, Turner AM, Mansur AH. Does continuous positive airway pressure (CPAP) treatment of obstructive sleep apnoea (OSA) improve asthma-related clinical outcomes in patients with co-existing conditions? - A systematic review. *Respir Med*. 2018;143:18-30.

Acronyms

OSA: Obstructive sleep apnoea

AHI: Apnoea hypopnoea index

ODI: Oxygen desaturation index

CPAP: Continuous positive airway pressure

LCSS: Limited-channel sleep study

PSG: Polysomnography

RDI: Respiratory disturbance index

REI: Respiratory event index

BMI: Body mass index

SDTA: Severe/difficult to treat asthma

OCS: Oral corticosteroid

ICS: Inhaled corticosteroid

BDP: Beclomethasone dipropionate

FEV_1: Forced expiratory volume in 1 second

FVC: Forced vital capacity

FENO: Fractional exhaled nitric oxide

ppb: parts per billion

PC_{20}: Provocative concentration of methacholine that results in a 20% drop in FEV_1

FEF: Forced expiratory flow

PEFR: Peak expiratory flow rates

DLCO: Diffusing capacity of the lung for carbon monoxide

TLC: Total lung capacity

IL: Interleukin

TNF-α: Tumour necrosis factor alpha

GORD: Gastro-oesophageal reflux disease

ESS: Epworth sleepiness scale

ACQ: Asthma control questionnaire

AQLQ: Asthma quality of life questionnaire

ACT: Asthma control test

EQ-5D: Euroqol-5 Dimensions

EQ-VAS: Euroqol visual analogue scale

HADS: Hospital anxiety and depression scale

IgE: Immunoglobulin E

HDL: High density lipoprotein

LDL: Low density lipoprotein

HbA1c: Haemoglobin A1c

TSH: Thyroid stimulating hormone

mmol/L: millimoles per litre

kU/L: kilo units per litre

mU/L: milliunits per litre

pg/ml: picograms per millilitre

ng/ml: nanograms per millilitre

DEXA: Dual energy x-ray absorptiometry

TBW: Total body water

FFM: Fast free mass

Streptavidin-HRP: Streptavidin horseradish peroxidase

BTS: British Thoracic Society

NAEPP: National Asthma Education and Prevention Program

GINA: Global Initiative for Asthma

SIGN: Scottish Intercollegiate Guidelines Network

AASM: American Academy of Sleep Medicine

SABA: Short acting beta agonist

LABA: Long acting beta agonist

CT: Computed tomography

BHH: Birmingham Heartland's Hospital

BRSAS: Birmingham Regional Severe Asthma Service

1 Introduction

1.1 Asthma

1.1.1 Epidemiology

Asthma is a common condition that affects 5.9% of the population in the United Kingdom, with approximately 5.4 million people requiring treatment[1,2]. The economic impact of this condition should also be noted with one billion pounds spent annually by the National Health Service (NHS) in the UK on caring for people with asthma[1]. The prevalence of this condition plateaued in the 1990s but the number of deaths reported from asthma in the UK is amongst the highest in the world, with approximately 1200 deaths attributed to this condition per year[1,2].

1.1.2 Severe/difficult to treat asthma

Asthma can be defined as a chronic inflammatory disease of the small airways that results in variable airflow obstruction and bronchial hyperresponsiveness[3,4]. Clinical symptoms of asthma include wheeze, dyspnoea and cough[4] and these tend to show diurnal variation with increased severity at night and in the early mornings[5]. The majority of asthmatics can maintain adequate control with inhaled corticosteroids and/or bronchodilator treatment as per the British Thoracic Society (BTS) guidelines[6]. However, 5-10% of asthmatics remain poorly controlled and difficult to successfully treat[7]. These patients have high medication burden, increased hospital admissions, and more frequent oral corticosteroid requiring asthma exacerbations[7]. Patients with severe asthma have traditionally required escalation to maintenance or daily oral corticosteroid use[8]. Long-term corticosteroid use is associated with adverse health outcomes including osteoporosis, cataracts, diabetes, obesity, hypertension and

depression[9]. Current management of severe asthma is geared towards elucidation of specific phenotypes and application of targeted therapy to reduce corticosteroid burden and comorbidity[10]. The current BTS/SIGN asthma treatment guidelines (2019)[11] are included in figure 1.1, and when compared to the previous treatment guidelines (2016)[12] illustrated in figure 1.2, an emphasis on early referral to specialist care for consideration of targeted therapies (i.e biological therapies) should be noted.

BTS/SIGN 2019 GUIDELINES

Step 1: Regular preventor
Low dose ICS

Step 2: Initial add-on therapy
Add inhaled LABA to low dose ICS (fixed or MART)

Step 3: Additional add-on therapies
Consider increasing ICS to medium dose OR adding LTRA
No response to LABA → consider stopping LABA

Step 4: Specialist therapies
Refer patient for specialist care

Figure 1.1 BTS/SIGN 2019 asthma treatment guidelines[11]

ICS:Inhaled corticosteroid; LABA: long acting beta agonist; MART: maintenance and reliever therapy; LTRA: leukotriene receptor antagonist

BTS/SIGN 2016 Guidelines

Step 1: Regular preventor
Low dose ICS

Step 2: Initial add-on therapy
Add inhaled LABA to low dose ICS (usually as a combination inhaler)

Step 3: Additional add-on therapies
No response to LABA → stop LABA and consider increased dose of ICS
Benefit from LABA but control still inadequate → continue LABA and increase ICS to medium dose
Benefit from LABA but control still inadequate → consider trial of other therapy eg. LTRA, S-R theophylline, LAMA

Step 4: High dose therapies
Consider trials of:
Increasing ICS to high-dose
Addition of a 4th drug eg. LTRA, S-R theophylline, beta agonist tablet, LAMA
Refer patient for specialist care

Step 5: Continuous or frequent use of oral steroids
Use daily steroid tablet in the lowest dose providing adequate control
Maintain high dose ICS
Consider other treatments to minimise use of steroid treatments
Refer patient for specialist care

Figure 1.2 BTS/SIGN 2016 asthma treatment guidelines[12]

ICS: Inhaled corticosteroid; LABA: long acting beta agonist; MART: maintenance and reliever therapy; LTRA: leukotriene receptor antagonist; S-R: slow release; LAMA: long acting muscarinic antagonist

1.1.3 Pathophysiology

Asthma can be broadly categorised into two phenotypes; 1) T_2 mediated disease that is triggered by allergy and is associated with airway eosinophilia and adaptive immunity via T cells and B cells[13]. Th2 cells secrete interleukin-4 (IL-4), IL-5, IL-9 and IL-13 cytokines[14]. These cytokines have been shown to cause eosinophilia, stimulate mast cells, switch B cells to immunoglobulin E (IgE) producing plasma calls, and are potentially involved in airway remodelling associated with chronic asthma[15]. 2) T_2 low phenotypes are associated with exposure to air pollution and infection, and characterised by airway neutrophilia[13].

1.1.4 Phenotypes

A phenotype can be defined as the composite observable characteristics or traits that result from genetic or environmental influences[16]. Asthma is a heterogeneous disease comprised of different subtypes of asthma that include; early or late onset, atopy or eosinophilia[16]. In the last decade several obesity-based studies were conducted using cluster analysis to identify asthma subtypes. This includes the Severe Asthma Research Programme (SARP) that identified five different clusters as follows[17];

Cluster 1: Early-onset atopic asthma, normal lung function, up to two controller medications, minimal healthcare utilisation.

Cluster 2: Early-onset atopic asthma and preserved lung function but with increased medication requirements and healthcare utilisation

Cluster 3: Older obese women, late-onset, non-atopic, moderate reductions in FEV_1, and frequent OCS requiring exacerbations.

Clusters 4: Equal representation of both genders, predominance of childhood onset (72%) and atopic disease (83%)

Cluster 5: Female predominance (63%), mainly later-onset disease (69%) and less atopy than cluster 4 (66%). Clusters 4 and 5 characteristically have longer duration of disease, with cluster 5 having longest. Cluster 5 also has severe airflow limitation at baseline.

The British Thoracic Society (BTS) Severe Refractory Asthma registry has also been analysed to determine cluster-specific outcomes and stability[18]. Five similar clusters were identified:

Cluster 1 (34%): Atopic with early onset disease. Highest number of intensive care unit (ITU) admissions, high exacerbation frequency, half receiving regular systemic corticosteroid therapy. Poor lung function with greatest bronchodilator reversibility.

Cluster 2 (21%): Obese with late onset disease. Frequent exacerbations. Over half receiving regular systemic corticosteroid therapy. Near normal lung function and highest depression scores.

Cluster 3 (15%): Least severe disease. Predominantly non-atopic with normal lung function. Fewest numbers receiving systemic corticosteroid therapy.

Cluster 4 (15%): Eosinophilic with late onset disease, frequent exacerbations.

Cluster 5 (15%): Significant fixed airflow obstruction with least OCS requiring exacerbations. Highest proportion of patients receiving systemic corticosteroid treatment.

1.2 Asthma and Obesity

1.2.1 The obese phenotype

The severe asthma cohorts have identified a cluster of obese asthmatics with a female predominance that tends to have non-eosinophilic, non-atopic disease. Cluster 3 of the SARP cohort in particular reports a cluster of obese females, with late onset disease[17]. Despite lower levels of atopy and eosinophilia this cluster was reported to have higher medication burden, more frequent OCS requiring exacerbations and healthcare utilisation[17]. Additionally, this cluster were reported to have symptoms disproportionate to the degree of airflow obstruction reported[17]. The BTS Severe Asthma Registry identified a cluster of obese asthmatics with late onset disease. This cluster was found to have frequent exacerbations, high depression scores and regular systemic corticosteroid use with near normal lung function[18]. Additional studies have shown increased symptoms, bronchodilator use, medication and healthcare utilisation in obese asthmatics but without the expected difference in FEV_1 or airflow obstruction[19-21].

1.2.2 The prevalence of obesity

Obesity was officially classified as a disease (ICD -10 E66) in 1990, and is defined by a body mass index (BMI) of 30 kg/m^2 or more[22-24]. In 2010, estimates suggested that 33% of men, and 28% of women were obese in England[22,25]. Morbid obesity with a BMI that exceeds 40 has tripled since 1993, and reached 2% of men and 4% of women[26]. The prevalence of obesity is continuing to increase with government data reporting up to 27% of the UK population was obese in 2015. Further estimates based on current trends have predicted that by 2050 that 60% of men and 50% of women will be classified as obese[22,27]. Obesity has several health consequences including type 2 diabetes, cardiovascular disease (coronary artery disease,

congestive heart failure, stroke, hypertension and atrial fibrillation), the metabolic syndrome, malignancy, non-alcoholic fatty liver disease and obstructive sleep apnoea[28] .

1.2.3 The correlation between asthma and obesity

Epidemiological studies have shown a correlation between asthma and obesity, with one prospective study of over 60,000 women reporting the risk of developing asthma to increase by 2.5 fold in patients with a BMI of 30 or more[13,29]. A temporal relationship is difficult to ascertain in many of the cross-sectional studies, as it is reasonable to assume that breathlessness and a reduction in physical activity secondary to asthma could itself lead to an increased risk of obesity. This could be more relevant in early-onset asthma which has been present for several years with associated steroid use. However, longitudinal studies have also demonstrated a significant relationship between obesity and incident late-onset asthma[29,30].

1.2.4 The pathophysiology of asthma and obesity

1.2.4.1 The effect on lung volumes

Obesity can result in reduced lung volumes and a restrictive pattern seen on spirometry[19]. Expiratory Reserve Volume (ERV) and Forced Vital Capacity (FVC) reduce with increasing body mass index (BMI)[31]. A study by Jones et al found that at a BMI of 40 patients have an ERV of only 28% and therefore breathe close to the residual volume[31]. In obesity, Functional Residual Capacity (FRC) has been shown to relate to airway resistance, and a linear relationship with airway conductance has previously been demonstrated and it has been suggested that these changes could related to obesity related breathing symptoms[31-36] which could potentially worsen or mimic asthma symptoms.

1.2.4.2 Bronchial hyperresponsiveness

Bronchial smooth muscle and mucosal thickening results in airway inflammation and remodelling and subsequent bronchial hyperresponsiveness[37,38]. There is data suggestive of an association between bronchial hyperresponsiveness and obesity[39], although conflicting data in this area also exists[38,40]. Bariatric surgery has also been shown to improve bronchial hyperresponsiveness[38,41].

Breathing at low lung volumes leads to increased actin-myosin cross linking in airway smooth muscle, which effectively makes the airway muscle stiffer[42,43]. The stretch of smooth muscle is a determinant of airway reactivity, and therefore it has been postulated that this airway re-modelling could impact on smooth muscle function and bronchial hyperresponsiveness[43].

1.2.4.3 Systemic inflammation

Obesity due to increased adiposity is a pro-inflammatory state with increased levels of inflammatory cytokines[43]. It has been proposed that systemic inflammation can modulate airway inflammation and potentially impact on the expression of asthma in obese individuals, although the degree of impact is unclear[44,45]. Asthma is characterised by an inflammatory response that includes mast cells, eosinophils and T lymphocytes. Several cytokines, including IL-4, IL-5, IL-6 and TNF-α are involved in this process[14]. However, a direct link between obesity and increased airway inflammation is currently lacking. Particularly, as many studies have shown obesity to be inversely related to fractional exhaled nitric oxide and sputum eosinophil counts in asthmatics[45,46].

1.2.4.3.1 Interleukin-6

IL-6 is a cytokine produced by the innate immune system (macrophages, dendritic cells, neutrophils, and mast cells), B cells, CD4 effector Th cells and some non-leukocytes[47]. IL-6 is generally considered to be a marker of inflammation and is elevated in many inflammatory conditions[48]. Levels of IL-6 are higher in obese people[49], with adipose tissue being a significant contributor[50]. Increased production of IL-6 by lung epithelial cells has also been demonstrated in asthmatic patients when compared to healthy controls[51-53]. IL-6 has been shown to upregulate Th2 cytokines IL-4 and IL-5[54]. IL-4 can increase the number of CD4+ Th2 cells, and also the number of Th2 cytokine producing eosinophils[55]. IL-5 promotes eosinophil maturation and exerts synergistic actions with potent eosinophilic chemoattractants[56,57]. IL-6 also promotes production of IL-13 and a major function of this specific cytokine is to promote mucus secretion[58,59]. It has been demonstrated that IL-13 can increase the response of airway smooth muscle cells to specific bronchoconstrictors and therefore modulate airway hyperresponsiveness[53,60]. Thus, there are several proposed mechanisms through which IL-6 can impact on the pathophysiology of asthma. Importantly, IL-6 has also been shown to be inversely correlated with FEV_1[61] and associated with loss of central airway function[53].

1.2.4.3.2 Leptin

Leptin is a pro-inflammatory cytokine that binds to specific receptors in the hypothalamus to alter expression of certain neuropeptides that regulate neuroendocrine energy function, energy intake and expenditure[62]. Additionally, leptin is thought to have a role in lung development[63]. Leptin has been shown to stimulate the production of other pro-inflammatory cytokines such as TNF-α, IL-6 and IL-12[64]. Serum leptin levels are known to increase with obesity[65].

Administration of exogenous leptin has been shown to augment induced airway inflammation[64,66]. Interestingly, a study by Holguin et al demonstrated that plasma leptin levels were higher in obese asthmatics when compared to obese controls[67]. Additionally, obese and overweight asthmatic subjects and controls had higher levels of leptin in bronchoalveolar lavage when compared to healthy weight asthmatics and controls[58,67]. Other data fails to support an association between leptin and the pathogenesis of asthma[68,69].

1.2.4.3.3 Adiponectin

Adiponectin is an anti-inflammatory cytokine produced by adipose tissue, and acts to inhibit pro-inflammatory cytokines such as TNF-α and IL-6[70]. There is a tendency for serum adiponectin to be reduced in obese individuals[71]. Adiponectin receptor cells are present in airway smooth muscle cells[72]. One hypothesis is that the reduced levels of adiponectin in obese subjects may contribute to the increased smooth muscle mass of remodelling in asthma[72,73]. Evidence for an association between adiponectin and asthma that is independent of obesity remains conflicting. Low serum adiponectin has been associated with greater odds for asthma among premenopausal women and peripubertal girls[73,74], whereas other studies have failed to demonstrate an independent association with asthma[68,69,75].

1.2.5 Corticosteroid responsiveness

Obesity is typically associated with reduced levels of fractional exhaled nitric oxide[76], lower sputum eosinophils, and increased airway neutrophilia[13,77]. Therefore, obesity has been thought to be related to a predominantly T_2 low asthma[78]. This could explain the observed reduced response to inhaled corticosteroid (ICS) when compared to normal weight

individuals[79]. However, another theory is that patients with increased BMI are more likely to have abnormal prednisolone absorption/fast prednisolone clearance[80]. Evidence also suggests that expression of certain pro-inflammatory cytokines such as TNF-α and IL-6 that are seen in obesity, are upregulated in lung macrophages in subjects with glucocorticoid resistant asthma, thus suggesting that a different cytokine environment may modify the therapeutic response to corticosteroids in obese subjects[19,81].

1.3 Obstructive Sleep Apnoea (OSA)

1.3.1 Epidemiology and clinical features

The obstructive sleep apnoea syndrome is characterised by pharyngeal collapse during sleep, frequent awakenings and disrupted sleep with resultant daytime hypersomnolence[82]. This condition is relatively common and affects approximately 2% of women and 4% of men, however OSA is also known to be present in 9% of women and 24% of men without symptoms[83]. Typical symptoms of OSA include snoring, gasping and choking[82,84]. Patients often report intermittent awakenings, with reduced total sleep time, fragmented sleep or early morning awakenings[82,84]. Other symptoms include morning headaches and nocturia[85,86]. The most significant clinical feature of OSA is considered to be chronic fatigue and daytime hypersomnolence[82]. Patients fall asleep easily during sedentary daily activities which can have significant impact on patients with neurological sequelae that includes impaired vigilance, impaired fine motor co-ordination and depression[82]. The effect of the OSA syndrome can include significant impairment on quality of life, although this is not necessarily related to the severity of the condition[87] indicating that the condition can also have detrimental effect in less severe disease.

1.3.2 Risk Factors

Obesity is a major risk factor for obstructive sleep apnoea (OSA) and particularly in patients with a body mass index of over 30, which increases the risk of OSA by 20-40%[88]. Individuals who gain 10% of their baseline weight are at six-fold increased risk of OSA progressing. Furthermore, equivalent weight loss can lead to a 20% improvement in OSA severity[89]. In a bidirectional manner, OSA is also thought to cause weight gain due to a combination of reduced activity and an increased appetite for refined carbohydrates[90,91]. Other risk factors for OSA include increasing age, male gender, sedative drugs, alcohol and smoking[92].

1.3.3 Consequences

OSA has been linked with an increased risk of road traffic accidents. Subjects with an apnoea hypopnoea index (AHI) of ≥15 have been shown to have significantly more road traffic accidents over a five year period when compared to subjects without sleep disordered breathing[93].

OSA has adverse implications with regards to cardiovascular disease, and this includes associations with hypertension, stroke, coronary artery disease, congestive cardiac failure, arrhythmias and cardiovascular mortality[94]. Epidemiological studies have shown a strong independent association between severity of OSA and arterial hypertension after adjusting for BMI and other confounders[94-96]. Large population-based studies have also shown independent associations between OSA and stroke[97,98]. The Wisconsin Sleep Cohort data reported an adjusted odds ratio for stroke of 4.33 (95% CI 1.32-14.24) for an AHI ≥ 20 when compared to no OSA[94,98]. The Sleep Heart Health Study also demonstrated an association between OSA

and self-reported ischaemic heart disease[97], a finding which is supported by other clinical studies[94,99]. The data with regards to congestive heart failure is more limited, but an association has been identified, although a temporal relationship has yet to be clarified. An increased risk of atrial arrhythmias has been reported in subjects with OSA[100] in addition to arrhythmias such as ventricular premature complexes which have also been shown to be more prevalent in subjects with moderate or severe OSA when compared to subjects without OSA[101]. Nocturnal hypoxaemia due to OSA has been shown to be an independent predictor of arrhythmia[102,103]. Importantly, severe OSA has been shown to be an independent predictor for all-cause and cardiovascular mortality[104].

1.3.4 The metabolic syndrome

Obstructive sleep apnoea has important links with the metabolic syndrome. This condition is characterised by abdominal obesity, hypertension, increased triglycerides and blood glucose with reduced high density lipoprotein (HDL) cholesterol with subsequent increased risk of type 2 diabetes mellitus and cardiovascular disease[105-107]. The metabolic syndrome has been shown to be nine times more likely in subjects with OSA, when compared to subjects without OSA, when using a regression analysis to adjust for confounders that included BMI[108]. The occurrence of OSA with the metabolic syndrome is known as "Syndrome Z"[105]. This association may partly explain the increased cardiovascular mortality associated with OSA, as the metabolic syndrome itself gives rise to a three-fold increase in ischaemic heart disease, stroke and cardiovascular disease[105,109,110].

Several biomarkers have been implemented in the pathogenesis of the metabolic syndrome, and this includes leptin, adiponectin and IL-6[111]. These adipokines are also discussed in section 1.2.4.3 in relation to asthma and OSA. Leptin is produced predominantly by adipocytes but is also produced by vascular smooth muscle cells and cardiomyocytes[111,112]. Leptin can alter the structure of vascular tissue by promoting hypertension, angiogenesis and atherosclerosis[111,112]. Increased leptin levels have been shown to be associated with the components of the metabolic syndrome but whether or not this relationship is independent of BMI remains unclear[111,112]. Adiponectin is secreted exclusively from adipocytes[111,113]. It suppresses the processes involved in atherosclerotic change and has been shown to have insulin sensitising properties[111,112,114]. Low levels of adiponectin have been shown to be associated with type 2 diabetes, hypertension and obesity[111]. Elevated IL-6 is associated with the metabolic syndrome with a correlation shown between increasing levels and the severity of the metabolic syndrome (hypertension, hypertriglyceridemia and fasting glucose levels)[111,115]. Impaired insulin signalling in the muscles and liver results in hyperglycaemia and insulin resistance[111,116]. The interaction between these inflammatory cytokines and the metabolic syndrome is illustrated in figure 1.3 adapted from a recent systematic review[111]. Other biomarkers are also involved in this process but the figure highlights the role of the adipokines discussed.

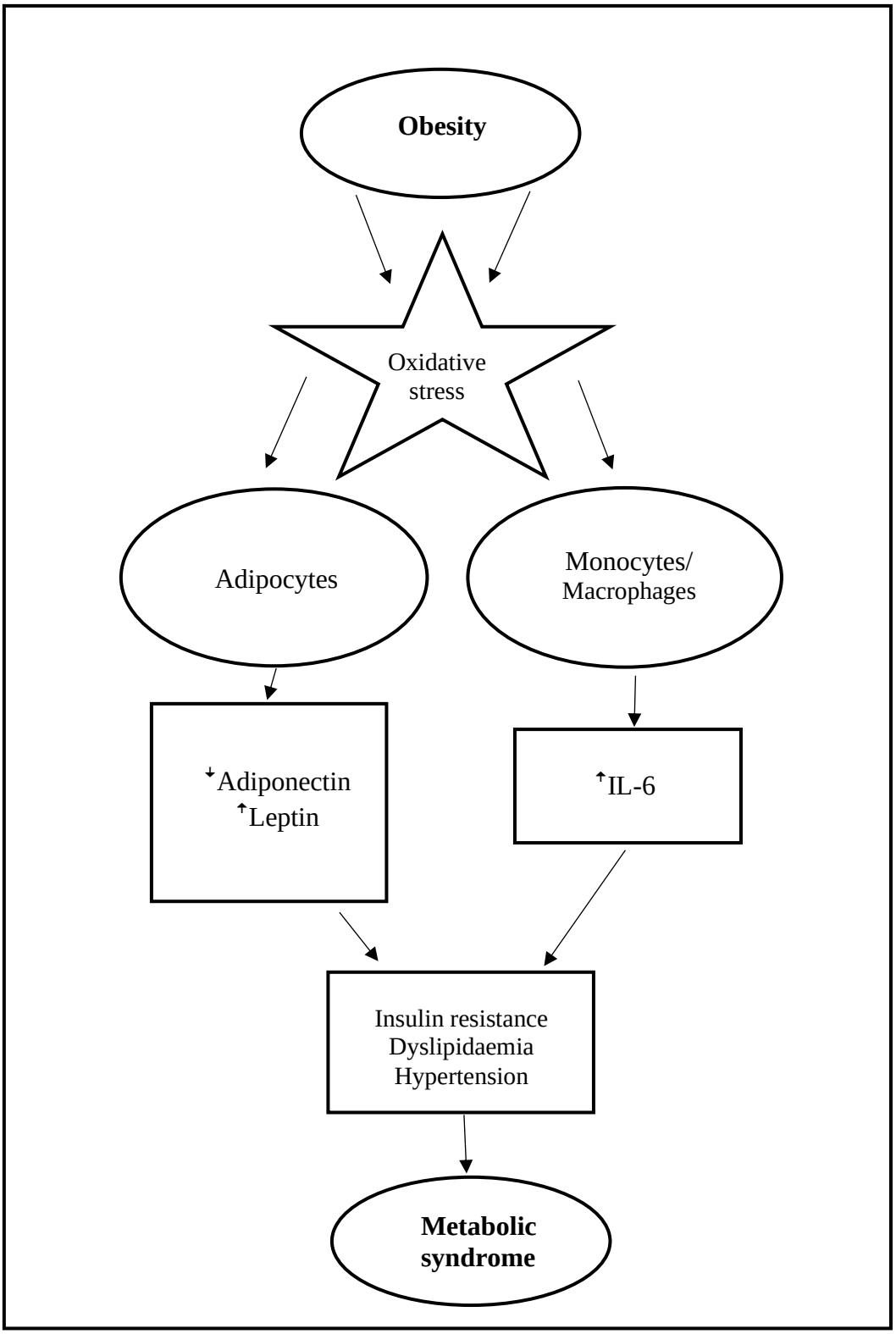


Figure 1.3 The metabolic syndrome and adipokines[111]

1.3.5 Pathophysiology

Studies have shown that one or more sites within the oral pharyngeal region are the common sites for upper airway collapse, and these regions are smaller in patients with OSA when compared to controls[117,118]. Other anatomical differences that are found in patients with OSA include changes that compromise the pharyngeal space such as a reduced mandibular body length, an inferior positioned hyoid bone and retro position of the maxilla[117,119,120]. The distance from the top of the hard palate to the base of the epiglottis is also increased in OSA subjects[117,121]. Enlargement of the soft palate or tongue also causes similar narrowing of the pharyngeal airway[117,122].

Obesity contributes to upper airway narrowing through increased volume of pharyngeal fat deposits[117,123]. Excess fat free muscular tissue in obesity increases the size of other structures in the upper airway and causes lateral wall compression[117,118,124]. Indirectly, obesity can contribute to OSA due to reduced lung volumes secondary to increased extrathoracic fat. Reduced lung volumes result in a reduced traction effect on the trachea which occurs due to negative intrathoracic pressures exerted via mediastinal structures[117]. Therefore, the lateral pharyngeal walls become thicker, with resultant narrowing of the airway[117,125].

1.3.6 Treatment

Continuous Positive Airway Pressure (CPAP) ventilation overnight is the current first line treatment for symptomatic patients with moderate or severe OSA[92]. The link with hypertension and OSA is recognised in recent clinical guidelines, and is to be taken into account when deciding on patient treatment[92,126]. CPAP has been shown to reduce blood

pressure by 3.3mmHg over 24 hours, this effect is greatest in patients with more marked nocturnal hypoxaemia (>20 4% desaturations/hour) who can achieve a 5mmHg fall in diastolic blood pressure over 24 hours with CPAP[126]. Over a five to ten year period, this is thought to reduce cardiac risk by 20% and stroke risk by 40%[92,127,128]. Other treatment options to consider in milder cases include lifestyle modification such as weight loss, smoking and alcohol cessation and avoidance of sedatives or sleeping tablets. Intra-oral devices can also be considered for mild OSA[92].

1.4 Asthma and OSA: the pathophysiological interplay

Asthma and OSA share several key pathophysiological processes that include airway inflammation, intermittent hypoxia, inflammation (upper airway and systemic) and common co-morbidities. This interplay between these two clinical conditions is illustrated in figure 1.4.

1.4.1 Shared co-morbidity

Gastro-oesophageal reflux disease (GORD) is more prevalent in people with OSA[129], due to changes in transdiaphragmatic and thoracic pressures during apnoeas[130,131]. Chronic rhinosinus disease is also more prevalent in patients with OSA when compared to those without[132]. The mechanism for this remains unclear although the repetitive hypoxia of OSA is thought to trigger inflammatory cytokines (CRP, IL-1, IL-6, IL-8, TNF-α) leading to endothelial and metabolic dysregulation[132,133]. GORD and rhinosinus disease are known to make asthma symptoms worse, through mechanisms other than increased eosinophilic airway inflammation[134]. The impact and interplay between asthma and obesity has been discussed in detail in section 1.2.

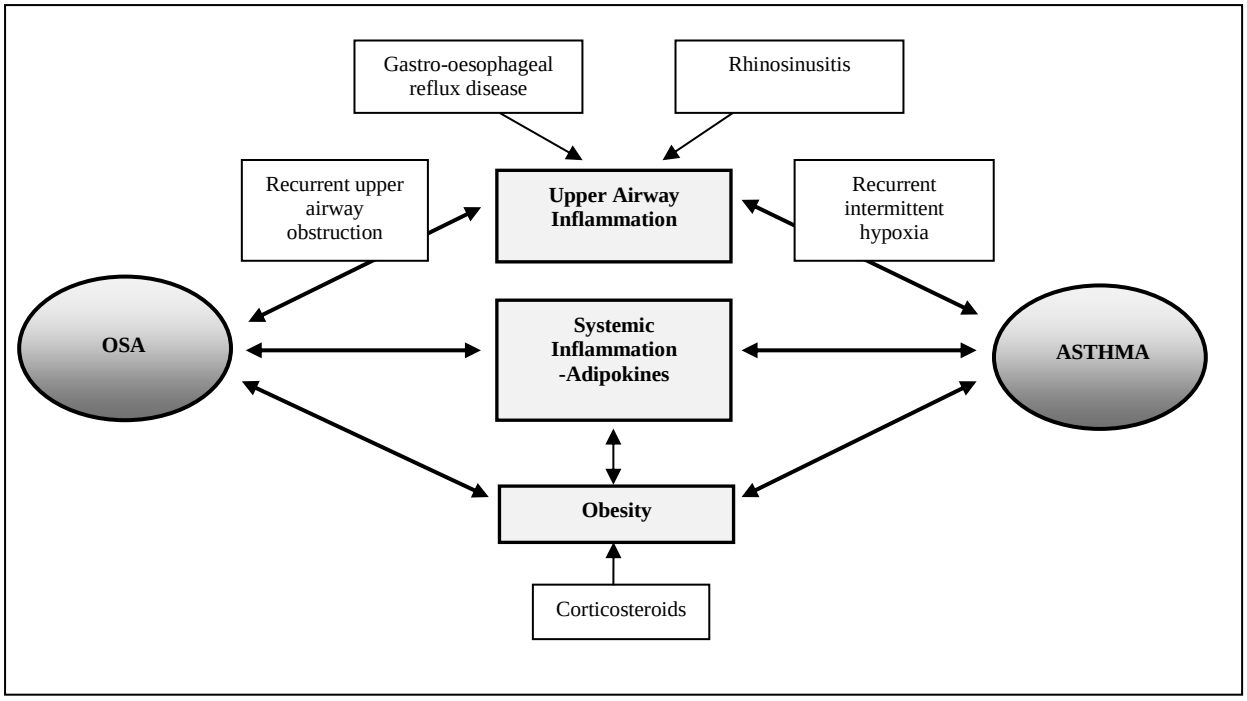


Figure 1.4 Pathophysiological interplay in the overlap of asthma and OSA[172]

1.4.2 Bronchoconstriction

Neural receptors in the laryngeal region and glottic inlet have been shown to have potent bronchoconstrictive reflex activity[135, 136]. The repeated stimulation of forced inspiration during snoring and apnoeas initiates a neural arc reflex and subsequent bronchoconstriction[135, 136]. Patients with OSA have increased vagal tone during sleep due to recurrent forced inspiratory effort against a closed glottis. Increased vagal stimulation is thought to stimulate muscarinic receptors in the airways again leading to bronchoconstriction in the lower airways and nocturnal asthma symptoms[131,137]. With normal inspiration, air moves into the airways because alveolar pressure is reduced due to the action of the inspiratory muscles[138]. During obstruction, there is increased inspiratory effort and a significant reduction in intrathoracic pressures[138]. This negative intrathoracic pressure change can potentiate bronchoconstriction in the lower airways and nocturnal asthma symptoms[139].

Chronic intermittent hypoxia has been shown to induce a T_2 low predominant cellular phenotype in the lower airways through collagen deposition and matrix degradation, leading to airflow limitation[140]. The potential mechanisms through which obstructive sleep apnoea can trigger or potentiate bronchoconstriction are summarised in figure 1.5.

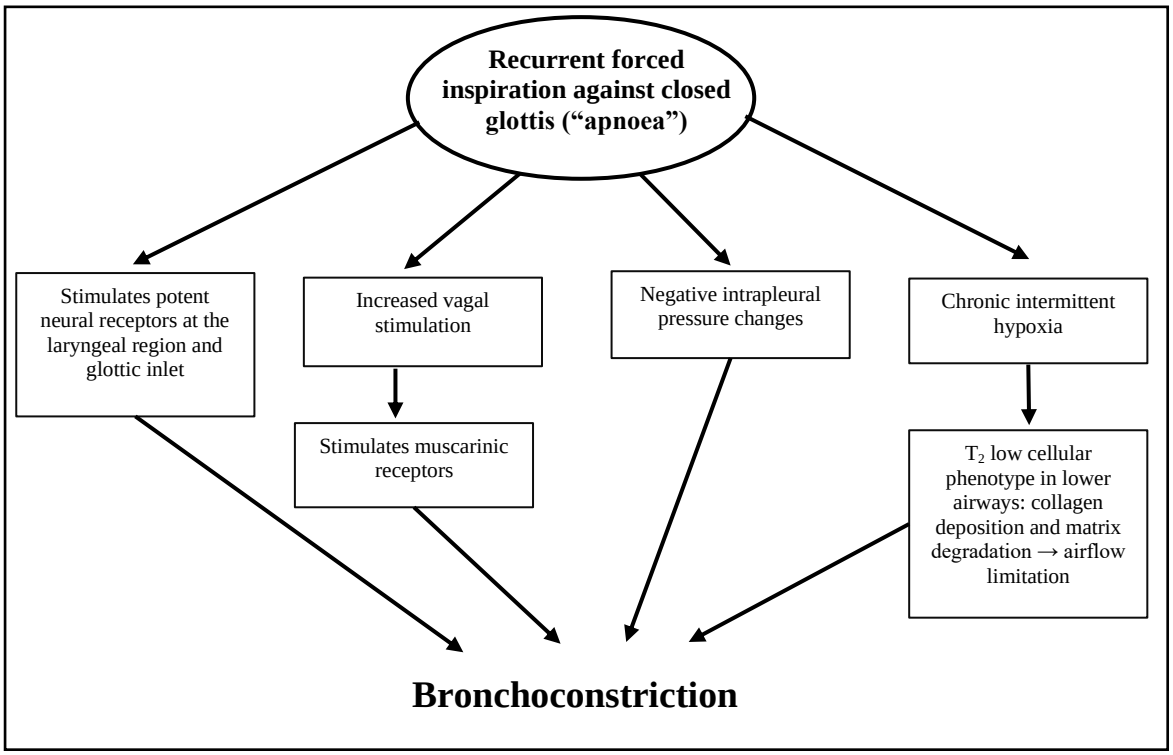


Figure 1.5 Mechanistic pathway: Recurrent apnoea and bronchoconstriction

1.4.3 Upper airway inflammation

Intermittent high pressure against a closed glottis during nocturnal apnoeas leads to local trauma and inflammation of the pharyngeal mucosa and uvula[131,141]. Subepithelial oedema and excessive inflammatory cell infiltrate has been demonstrated in upper airway biopsies from subjects with OSA[142,143]. Additionally, exhaled breath has been shown to have increased

levels of exhaled nitric oxide, 8-isoprostane and IL-6 which are suggestive of increased airway inflammation and endothelial dysfunction [143-145]. Airway inflammation can trigger bronchial hyperresponsiveness and could thus potentiate asthma symptoms in the lower airways[131,146].

1.4.4 Lower airway inflammation

Induced sputum samples and bronchial biopsies of patients with OSA have shown an increased prevalence of neutrophilic inflammation[147,148], with a lower proportion of macrophages[148]. Chronic intermittent hypoxia has been shown to stimulate production of IL-8 which contributes to neutrophil recruitment[148,149]. Patients with neutrophilic asthma are more likely to have GORD, rhinosinus disease and chest infections[150].

1.4.5 Systemic inflammation

Systemic inflammation is also thought to play a role in OSA[143,151]. The recurrent nocturnal intermittent hypoxia is thought to increase sympathetic response, and in combination with oxidative stress is thought to drive systemic inflammation in this condition[143,151,152]. Studies have shown elevated levels of pro-inflammatory cytokines, chemokines and adhesion molecules in patients with OSA when compared to matched controls[151,153-156]. Inflammatory mechanisms have been shown to play an important role in atherosclerotic plaque formation[151,157]. This inflammation within the vessels is thought to occur in response to injury, infection or lipid peroxidation[151,158]. Leucocytes mediate the adherence of monocytes to the endothelium which then releases inflammatory mediators such as TNF-α, IL-1, and chemokines such as IL-8 and adhesion molecules such as intercellular adhesion molecule 1

(ICAM-1)[151]. This inflammatory process that leads to endothelial dysfunction has implications in terms of cardiovascular disease in patients with OSA, and may contribute to the increased cardiovascular mortality previously discussed[151].

1.4.6 Corticosteroids

Patients with severe asthma often require frequent courses of oral corticosteroids or a long-term maintenance dose. Corticosteroid use can result in a local myopathic effect in the upper airways[159], and predilection for OSA. Weight gain and obesity is a side effect of corticosteroid use[9], and the shared pathophysiology between obesity, asthma and OSA has already been discussed. Additionally, it has been discussed that obesity is associated with a predominantly T_2 low mediated phenotype which may be less responsive to inhaled steroids[79]. The altered cytokine environment and abnormal prednisolone absorption may also lead to steroid resistance[19,80,81].

1.5 Body fat composition

1.5.1 Obesity

Obesity, and particularly central adiposity results in reduced lung volumes[160] which leads to a loss of caudal traction in the upper airways thus increasing collapsibility of the pharynx[161,162]. Another factor leading to increased upper airway collapsibility in OSA is fat deposition in the surrounding tissues[162,163]. Fat deposition around the thorax is also thought to reduce chest compliance and lung volumes potentially leading to increased oxygen demand[162,164].

1.5.2 OSA

There are studies that have highlighted the importance of body fat distribution in OSA. Ogretmenoglu et al measured BMI, percentage body fat and used cross-sectional CT scanning to measure abdominal visceral fat[165]. This small study found that combining body fat percentage and body fat mass using bioelectrical impedance achieved a sensitivity of 95% and specificity of 100% at diagnosing OSA (confirmed by polysomnography). CT scanning of visceral adiposity provided 100% sensitivity and specificity of detecting OSA[165]. The conclusion being that bioelectrical impedance measurements may be a reasonable alternative to screen for OSA[165].

1.5.3 Asthma

In females, total body lean tissue, android and thoracic fat tissues have been shown to inversely correlate with ERV[166]. However, the same study found the converse was true in males with a positive association demonstrated between android and thoracic lean tissue and ERV[166].

A study by Minas et al found severe asthma was associated with lower fat free mass index (FFMI) compared to patients with mild-moderate asthma, despite higher values of BMI and fat mass index (FMI)[167]. These levels were comparable to those with stage IV Chronic Obstructive Pulmonary Disease (COPD)[167]. FFMI and BMI are predictors of mortality in COPD, with low levels associated with increased risk of death[168]. However, the impact in severe asthma populations remains unclear[167].

1.6 The prevalence of OSA in asthma and the impact on asthma-related clinical outcomes

The symptoms of OSA and poorly controlled asthma can overlap. Asthmatics have poor sleep quality, reduced sleep time and reduced slow-wave sleep[101,169-172]. Epidemiological studies have also shown asthmatics are more likely to have symptoms of sleep disordered breathing such as snoring, nocturnal apnoeas and daytime hypersomnolence[101,172,173]. This overlap of clinical features potentially poses problems in identifying obstructive sleep apnoea in asthma patients, and particularly those with severe asthma and high symptom burden. Patients completing questionnaires to screen for OSA such as the Berlin questionnaire, Sleep Apnoea Scale of the Sleep Disorders Questionnaire (SA-SDQ), Epworth Sleepiness Scale and STOP BANG score points on questions that could also relate to poorly controlled asthma. For example, the SA-SDQ scores points towards an OSA diagnosis based on the following statements "I awake suddenly gasping for breath, unable to breathe", "I have a problem with my nose blocking up when I want to sleep"[174]. The SA-SDQ and the other mentioned questionnaires score points for features of daytime hypersomnolence, which could also be a consequence of nocturnal asthma symptoms resulting in night-time awakenings[174].

1.7 The impact of CPAP treatment on asthma-related clinical outcomes in OSA

CPAP is the gold standard treatment for symptomatic moderate-severe OSA, but the impact on asthma-related clinical outcomes in patients with co-existing disease is unclear. Potential mechanisms through which CPAP treatment could benefit asthma symptoms and control in patients with co-existing OSA are illustrated in figure 1.6.

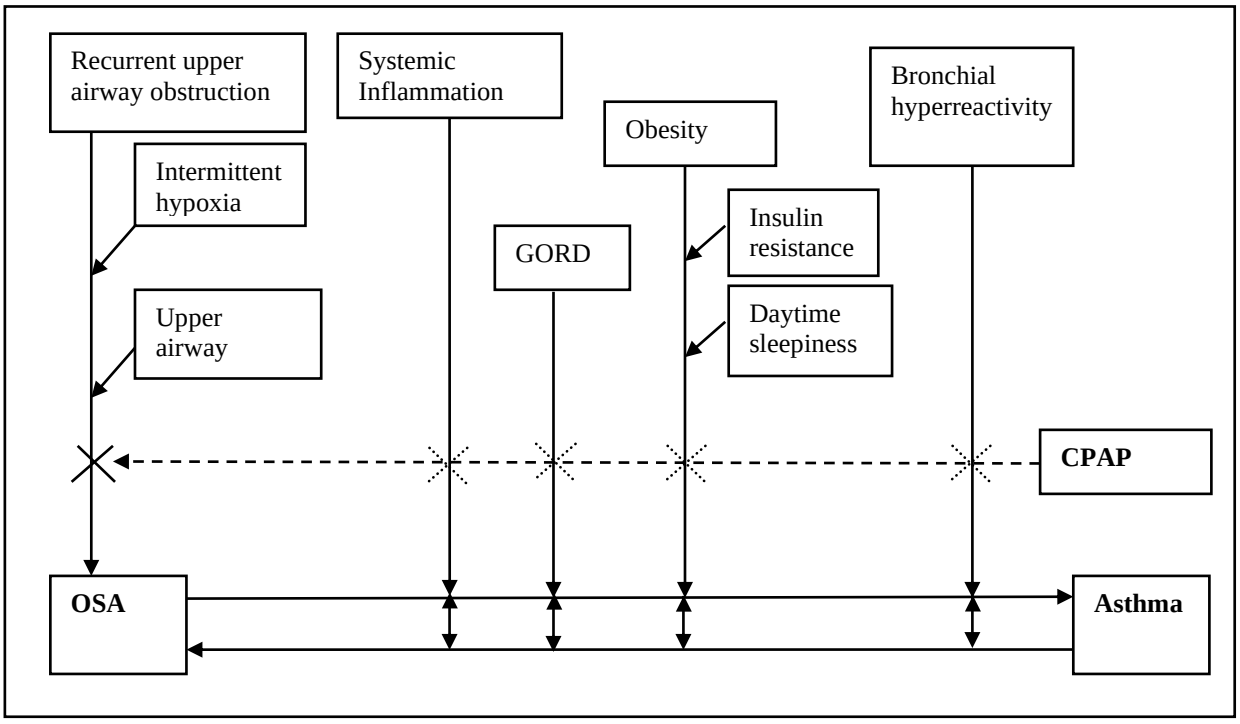


Figure 1.6 Mechanisms through which CPAP could improve asthma control[175]

CPAP treatment has been shown to reduce levels of fractional exhaled nitric oxide (FENO)[145, 175] and improve markers of systemic inflammation such as CRP[131, 175]. Gastro-oesophageal reflux is precipitated by the large negative intrapleural pressure swings[131] that occur in OSA, and CPAP treatment has been shown to improve gastro-oesophageal reflux[175,176]. CPAP has been shown to improve insulin resistance[175,177], which could potentiate weight loss and improve asthma symptoms[175]. Whether CPAP improves bronchial hyperresponsiveness in OSA patients is less clear from review of current literature[175,178,179].

1.8 Summary and aims

The association between asthma and OSA is complex and multifactorial. There is evidence to suggest a higher prevalence of OSA in asthma populations, and there are potential

mechanisms through which CPAP treatment of OSA could impact on asthma-related clinical outcomes.

The aims of this research project were to determine;

1) The prior evidence base relating asthma and OSA, and utility of CPAP in those with co-existing conditions.

2) The prevalence of OSA in a severe asthma population

3) The impact of OSA on asthma-related clinical outcomes

4) The impact of CPAP treatment on asthma-related clinical outcomes in patients with co-existing conditions.

This research project was broadly divided into four separate studies;

1) Systematic review of the literature

a) The association between asthma and OSA

b) The effect of CPAP treatment of OSA on asthma-related clinical outcomes in patients with co-existing conditions

2) Cross-sectional study: The main focus of this study was to determine the prevalence of OSA in severe asthma, and secondly evaluate the impact on asthma-related clinical outcomes. Predictors of OSA, the effect of body fat composition and the association with adipokines were also evaluated.

3) Prospective case-control study: Patients were prospectively followed up over a 12-month period. The impact of OSA on asthma-related clinical outcomes was prospectively evaluated.

4) Interventional study: To evaluate the impact of CPAP treatment of OSA on asthma-related clinical outcomes in patients with co-existing disease. This was a pilot feasibility, double-blind, randomised, placebo-controlled study.

The hypotheses of these research studies were as follows;

a) A high prevalence of OSA in severe asthma, with detrimental impact on asthma-related health outcomes.

b) Improvement in asthma-related quality of life when co-existing OSA is treated with CPAP.

2 Methodology

2.1 Systematic Review: The association between asthma and OSA[172]

2.1.1 Materials and methods[172]

A qualitative systematic review of the literature was performed with MEDLINE and EMBASE databases using the following search terms: Asthma AND (incidence OR prevalence OR odds OR risk) AND (Obstructive Sleep Apnoea OR Obstructive Sleep Apnea OR OSA OR sleep OR apnoea OR apnea OR snoring OR sleep-disordered breathing). All studies up to and including the year 2016 were included.

2.1.2 Inclusion/Exclusion process[172]

Studies were selected for full text review if they fulfilled the criteria of examining 1) a population with asthma and 2) an outcome focusing on OSA/sleep/sleep-disordered breathing or symptoms of sleep-disordered breathing or 3) comorbidities relating to either condition. Studies were excluded if not in the English language or were carried out on a paediatric population (<18 years of age).

The gold standard for diagnosis of OSA is an overnight polysomnography (PSG) test. Limited channel-sleep studies are a well-recognized clinical alternative to PSG[92,180]. The Sleep Apnoea-Scale of Sleep Disorders Questionnaire (SA-SDQ), the Berlin Questionnaire, and STOP-BANG are validated screening questionnaires used to assess risk of OSA[174,180].

Questionnaires used to assess the severity of symptoms, such as daytime sleepiness (e.g., Epworth sleepiness scale), were not included unless known to have specific validation for prediction of obstructive sleep apnoea risk. The sensitivity and specificity of the accepted diagnostic tests and validated questionnaires are reported in table 2.1. All studies that involved formal overnight sleep tests were found to use PSG rather than limited-channel sleep studies or overnight oximetry, but were not excluded on this basis. This review included studies that have demonstrated OSA diagnosis (using PSG) or OSA risk through the use of validated questionnaires. Table 2.2 illustrates how the included studies have made the diagnosis of OSA and also if robust asthma diagnostic criteria were used. Studies using non-validated questionnaires were excluded. Studies were also excluded if they showed clear bias in the selection of asthma patients based on symptoms of sleep-disordered breathing.

Table 2.1 Sensitivity and specificity of detecting OSA (AHI≥5)[172]

Test/Questionnaire	**Sensitivity**	**Specificity**
Limited-Channel Sleep Study (LCSS)[92,180]	32-100%	33-100%
Overnight Oximetry[92,180]	87% (SE 4%, CI 36-100%)	65% (SE 7%, CI 23-99%)
Questionnaires (pooled data that includes STOP-BANG, SA-SDQ and Berlin)[174,180]	77.0% (95% CI: 73.0-80.0%; I^2 = 78.1%)	53.0% (95% CI: 50-57%; I^2 = 88.8%).

Table 2.2 Method of asthma/OSA diagnosis[172]

	ATS/GINA asthma diagnosis	
OSA Diagnosis	**Yes**	**No**
PSG	2	4
Validated questionnaire (SA-SDQ, STOP-BANG, Berlin)	8	5

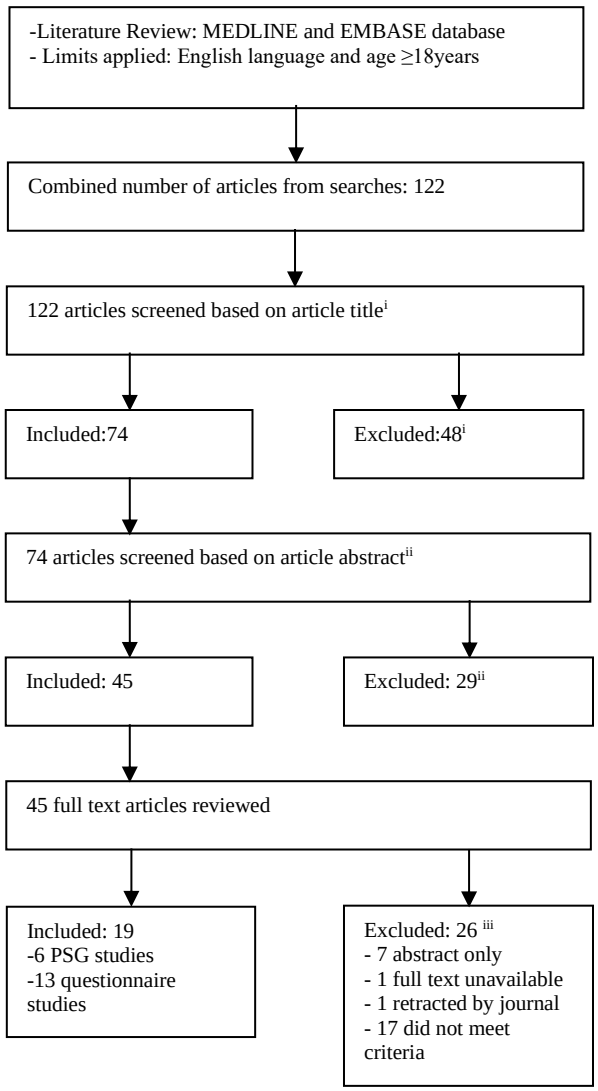
Secondly, to evaluate asthma-related clinical outcomes in patients with co-existing OSA, included studies were reviewed to determine if measures including the Asthma Control Test (ACT), Asthma Quality of Life Questionnaire (AQLQ), and Asthma Control Questionnaire (ACQ) were reported. Alternative clinical measures such as the number of emergency department visits/hospital admissions/intensive care admissions, frequency of OCS requiring exacerbations and persistent daytime and night-time asthma symptoms were also included.

2.1.3 Data synthesis/extraction[172]

Data were extracted from studies by one reviewer and checked by a second to determine if the inclusion/exclusion criteria were met (see Figure 2.1). Studies were then re-reviewed to evaluate clinical outcomes in OSA versus no-OSA.

2.1.4 Assessment of bias[172]

Bias was assessed using the Briggs scale[181] by two reviewers independently. This involved completing the appropriate critical appraisal tool dependant on the study type being evaluated. Any disagreements between the two reviewers were resolved through discussion.



[i]***Excluded after review of title: Studies that had clearly no relevance to the topic area (asthma and OSA)***
[ii]***Excluded after review of abstract: Studies that used non-validated questionnaires or included the wrong study populations not relevant to aims of the review***
[iii]***Excluded after review of full text: Studies that did not meet inclusion/exclusion criteria or showed bias that impacted on the primary aim of this review***

Figure 2.1 PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) [172]

The PICO diagram for this systematic review is illustrated in figure 2.2.

P= Participants with asthma or severe asthma

I= Co-existing obstructive sleep apnoea

C= Healthy asthmatics/severe asthmatics (no co-existing OSA)

O= Prevalence of OSA, Asthma-related health outcomes

Figure 2.2 PICO diagram

The PICO tool is helpful at focussing clinical questions. P: Population/problem; I: Intervention/exposure; C: Comparison; O: Outcome

2.2 Observational studies: Cross-sectional and prospective case-control

2.2.1 Recruitment

Unselected recruitment of participants from the Birmingham Regional Severe Asthma Service (BRSAS) and associated respiratory clinics within the same trust occurred between January 2016 and April 2017. The patients approached to participate were under current/recent review, met the inclusion/exclusion criteria and lived within an appropriate distance. Invitation letters with a Participant Information Sheet (PIS) that included information on the observational studies were given to patients whilst attending clinic or posted to potential participants (see appendix 2).

Participants attended for a baseline visit (visit 1) as part of the cross-sectional study, and were asked if they would participate in the prospective case-control study which required an additional visit (visit 2) at 12 months.

2.2.2 Inclusion/Exclusion Criteria

2.2.2.1 Inclusion Criteria

1) Patients seen within BRSAS or other respiratory clinics within Heart of England NHS Foundation Trust with a diagnosis of asthma

2.2.2.2 Exclusion Criteria

1) Inability to comply with a limited-channel sleep study

2) Predominant non-asthma diagnosis e.g. vocal cord dysfunction (VCD), breathing pattern disorder (BPD)

3) Pregnancy, participant preference or inability to comply with a whole body composition Dual-Energy X-ray Absorptiometry (DEXA) scan resulted in the participant being excluded from body composition DEXA imaging, but did not affect other aspects of study participation.

2.2.3 Visit Schedules

2.2.3.1 Visit 1 (Baseline visit)

1) Informed consent obtained (see appendix 3)

2) Clinical data collected- Using standardised proforma and Dendrite database/asthma clinic letters (see clinical measurements, section 2.2.4)

4) Epworth Sleepiness scale (ESS)

5) Bioelectrical Impedance Measurements, Body Mass Index (BMI)

6) Home limited-channel sleep study

2.2.3.2 Visit 2 (12 months +/- 6 months)- Participants included in prospective study only

1) Clinical data again collected (see clinical measurements, section 2.2.4)

2) Spirometry and Fractional Exhaled Nitric Oxide (FENO) measurements

2.2.3.3 Additional Visits (if required)

1) Blood tests- If consented and not taken during visit 1 or 2

2) Completion of healthcare questionnaires (if not completed correctly during scheduled visit)

3) Whole body composition DEXA scan visit (if selected, met criteria and gave valid informed consent)

2.2.4 Clinical Measurements

2.2.4.1 Clinical Data (visit 1 and 2)

1) Basic demographics; age, gender, ethnicity, smoking history, medication use and co-morbidities

a) Smoking status; participants were categorised into one of the three following groups: Non-smoker (never smoked or previous negligible social smoking or smoking pack years <1), ex-smoker (no current cigarette use) or current smokers. Total pack years were calculated using an online calculator[182].

b) Ethnicity; participants were categorised as Caucasian, Asian, Afro-Caribbean or Other.

c) Medication history; medications were checked with patients with particular reference to asthma medications. The current dose of inhaled corticosteroid was checked with the patient and the equivalent beclomethasone dipropionate (BDP) dose was calculated using the same criteria as that of the LASER clinical research trial[183].

d) Co-morbidities; self-reported Gastro-oesophageal reflux disease (GORD), rhinosinus disease, hypercholesterolaemia, ischaemic heart disease (IHD), diabetes and hypertension were recorded.

e) Health care utilisation; The preceding number of self-reported annual oral corticosteroid (OCS) requiring exacerbations, Accident and Emergency (A&E) visits, emergency GP visits and hospital admissions were recorded, as was total High Dependency Unit (HDU) or Intensive Care Unit (ITU) requirements for asthma.

2) Health related questionnaires:

a) Visit 1: ACQ-7[184] was recorded from the participants most recent NHS clinical visit. Participants were asked to complete ACQ-6 on the day of visit 1 as spirometry was not performed on this visit (which is a requirement for ACQ-7). Hospital Anxiety and Depression Scale (HADS) [185,186], AQLQ[184,187,188], Euroqol-5 Dimensions (EQ-5D) [189] and Euroqol-Visual Analogue Scale (EQ-VAS) [189] were completed if participant agreed.

b) Visit 2: ACQ-7[184] was recorded using spirometry taken that day. HADS[185,186], AQLQ[184,187,188], EQ-5D[189] and EQ-VAS[189] were completed if participant agreed.

3) Spirometry and Fractional Exhaled Nitric Oxide (FENO)

a) Visit 1: Spirometry and FENO were recorded from the participants most recent asthma clinical review. Spirometry readings included; Forced Expiratory Volume in 1 second (FEV_1), Forced Vital Capacity (FVC) and FEV_1/FVC ratio.

b) Visit 2: Spirometry and FENO performed by research registrar. Spirometry measurements were performed using Carefusion microlab equipment. The machine was calibrated on each day of use. FEV_1 and FVC measurements were performed as guided by the American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria[190]. The aim was to

achieve three acceptable manoeuvres and for the two best readings to be reproducible with less than 150ml or 5% variability[190]. FENO measurements were recorded using NIOX vero equipment.

Gas transfer readings or lung volumes measured previously as part of clinical care were also recorded if available from clinical records (eg. the Dendrite severe asthma database). As the location for the study was a tertiary asthma centre, these measurements were often completed at other NHS trusts within the UK.

4) Asthma and metabolic makers: Blood samples for eosinophil count, immunoglobulin E (IgE), thyroid stimulating hormone (TSH) and metabolic screen (HbA1c and lipid profile) were taken up to 18 months following the baseline visit by the research registrar. These samples were taken for processing by the Heart of England NHS trust laboratories on the same day that they were taken. Samples were reported through the clinical database (concerto) as they would be in standard NHS care. Abnormal results were appropriately actioned by the research registrar. Participants who did not have a blood test as part of the study had the most recent bloods recorded from their clinical care if completed between 18 months prior and 18 months following the research visit.

2.2.4.2 Healthcare-related questionnaires

2.2.4.2.1 Asthma Quality of Life Questionnaire (AQLQ)

The AQLQ is used to measure asthma-related quality of life using four domains within asthma; symptoms, activity limitation, emotional function and environmental stimuli. There are 32 questions in total, on a seven-point scale (7=not impaired at all, 0=severely impaired).

The overall score is the mean of all the responses, and a change of 0.5 indicates a clinically significant change[184,187,188]. An example is shown in appendix 4

2.2.4.2.2 Asthma Control Questionnaire (ACQ-7)

The ACQ-7 is used to measure asthma control. The questionnaire consists of seven questions (5 top-scoring symptoms, FEV_1% predicted and daily rescue bronchodilator use). Participants are asked to recall their asthma symptoms over the last week and respond to questions on a seven-point scale (0=no impairment, 6=maximum impairment), while clinical staff record FEV_1 % predicted. The mean is then calculated to determine the score. A score of >1 is said to represent less well-controlled asthma, and a change of 0.5 is the minimal clinically significant change[184]. An example is shown in appendix 5

2.2.4.2.3 Euroqol-5 Dimensions (EQ-5D)

The EQ-5D has two components which are used to rate health-related quality of life; the EQ-5D descriptive system and the Euroqol-Visual Analogue Score (EQ-VAS)[189]. The descriptive system comprises of five dimensions; mobility, self-care, usual activities, pain/discomfort and anxiety depression. Each dimension has five levels; no problems, slight problems, moderate problems, severe problems and extreme problems[189]. The visual analogue score records the patients perceived health on a vertical visual analogue scale with endpoints labelled “the best health you can imagine” and “the worst health you can imagine”[189]. An example of EQ-5D is shown in the appendix 6, and EQ-VAS in appendix 7.

2.2.4.2.4 Hospital Anxiety and Depression Scale

This questionnaire consists of seven questions for anxiety, and seven questions for depression[186]. The questions are interspersed throughout the questionnaire but are scored separately for anxiety and for depression[186]. A score of 8 for anxiety has a specificity of 0.78, and a sensitivity of 0.9. A score of 8 for depression has a specificity of 0.79 and a sensitivity of 0.83[185,186]. An example is shown in the appendix 8.

2.2.4.2.5 Epworth Sleepiness Scale (ESS) [191]

The ESS is used to asses daytime sleepiness in the context of sleep medicine. It is a self-administered questionnaire of 8 questions that assess the probability of the respondent falling asleep. A score of <10 is generally considered normal. Respondents can score up to 24, with higher scores representing increased daytime sleepiness, which is a feature of obstructive sleep apnoea and other forms of sleep disordered breathing[191]. An example is shown in appendix 9.

2.2.4.3 Obesity and body fat composition

1) Participants height and weight were measured, to calculate BMI (visit 1)

2) Body fat composition measurements were taken using bioelectrical impedance measurements from the TANITA BC 420 MA body composition analyser (visit 1). Measurements included: body fat %, muscle mass, total body water % (TBW%), visceral fat rating, fat free mass (FFM).

3) A cohort of patients underwent detailed body composition measurements using whole body Dual Energy X-ray Absorptiometry (DEXA) scanning (additional visit). Measurements

included: body fat %, fat mass, lean mass, total mass, android fat %, gynoid fat %, android/gynoid ratio, FFM, % fat trunk/%fat legs ratio, trunk/limb fat mass ratio.

4) A cohort of patients also had a plasma and serum sample taken for measurement of adipokines; leptin, adiponectin and interleukin-6 (IL-6) (visit 1/2/additional visit) (section 2.2.6)

2.2.4.4 Screening for OSA

1) Epworth sleepiness scale (ESS) questionnaire[191]. All participants were asked to complete this, to assess for symptoms of sleepiness (visit 1 and visit 2).

2) Overnight diagnostic sleep test: Participants completed a home limited-channel sleep study using RespMed Embletta Gold equipment. Those unable to complete a home limited-channel sleep study were asked to undergo full inpatient polysomnography (PSG) using Embla S7000 equipment. Sleep studies were downloaded and reported using Remlogic software, version 3.

Participants with a pre-existing diagnosis of OSA already established on CPAP were not required to perform a sleep test, but were offered a repeat test as part of the study (visit 1).

2.2.4.4.1 Overnight sleep studies/polysomnography

1) Limited-channel sleep study

Participant airflow and snoring was recorded via a nasal pressure transducer (cannula). Respiratory effort was recorded via thoracic and abdominal belts. Oxygen saturation and heart rate were monitored via pulse oximetry. The majority of studies were scored by the research registrar after receiving appropriate training from a respiratory physiologist. These studies were then reviewed by the respiratory physiologist. Borderlines or positive studies were then

reviewed again by a respiratory physician with a specialist interest in sleep medicine. The limited-channel sleep study recordings were scored as per the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events (version 2.2)[192]. This was updated to version 2.3 during the course of the study but the changes did not affect the scoring criteria for limited-channel sleep studies.

Definitions and scoring criteria used were as follows;

a) Obstructive apnoea events were scored when there was a drop of ≥ 90% in the airflow signal with a duration of ≥ 10 seconds and continued or increased inspiratory effort throughout the event period.

b) Central apnoea events were scored when there was a drop of ≥ 90% in the airflow signal with a duration of ≥10 seconds and absent inspiratory effort throughout the event period.

c) Mixed apnoea events were scored when there was a drop of ≥ 90% in the airflow with a duration of ≥10 seconds and absent inspiratory effort in the initial portion of the event followed by resumption of inspiratory effort in the second portion.

d) Hypopnoea; events were scored when a drop of ≥30% in the airflow signal was detected during ≥10 seconds with a ≥3% oxygen desaturation.

e) Apnoea-Hypopnoea Index (AHI); this was calculated as the sum of the scored respiratory events divided by the total number of sleep hours.

f) Oxygen Desaturation Index (ODI); this was calculated as the sum of all the oxygen desaturations divided by the total number of sleep hours.

g) Severity of OSA was graded using the apnoea hypopnoea index (AHI): no-OSA; (AHI)<5, mild OSA; ≥5AHI<15, moderate OSA; ≥15AHI<30, severe OSA; AHI≥30[92].

The aim was to achieve a recording that was a minimum of 4 hours duration, with a nasal flow rate recording of ≥80% and oxygen saturation recording of ≥80%. Patients that did not achieve this were asked to complete a second home limited-channel sleep study or a full inpatient polysomnography. If the recording still did not meet these criteria (or the participant refused inpatient PSG), then the study was re-reviewed to determine if it was of sufficient quality to include (regardless of this criteria) and if not, then the participant was excluded from the study. An example of a limited-channel sleep study diagnostic of OSA is shown in figure 2.3, and an example of a normal study is shown in figure 2.4.

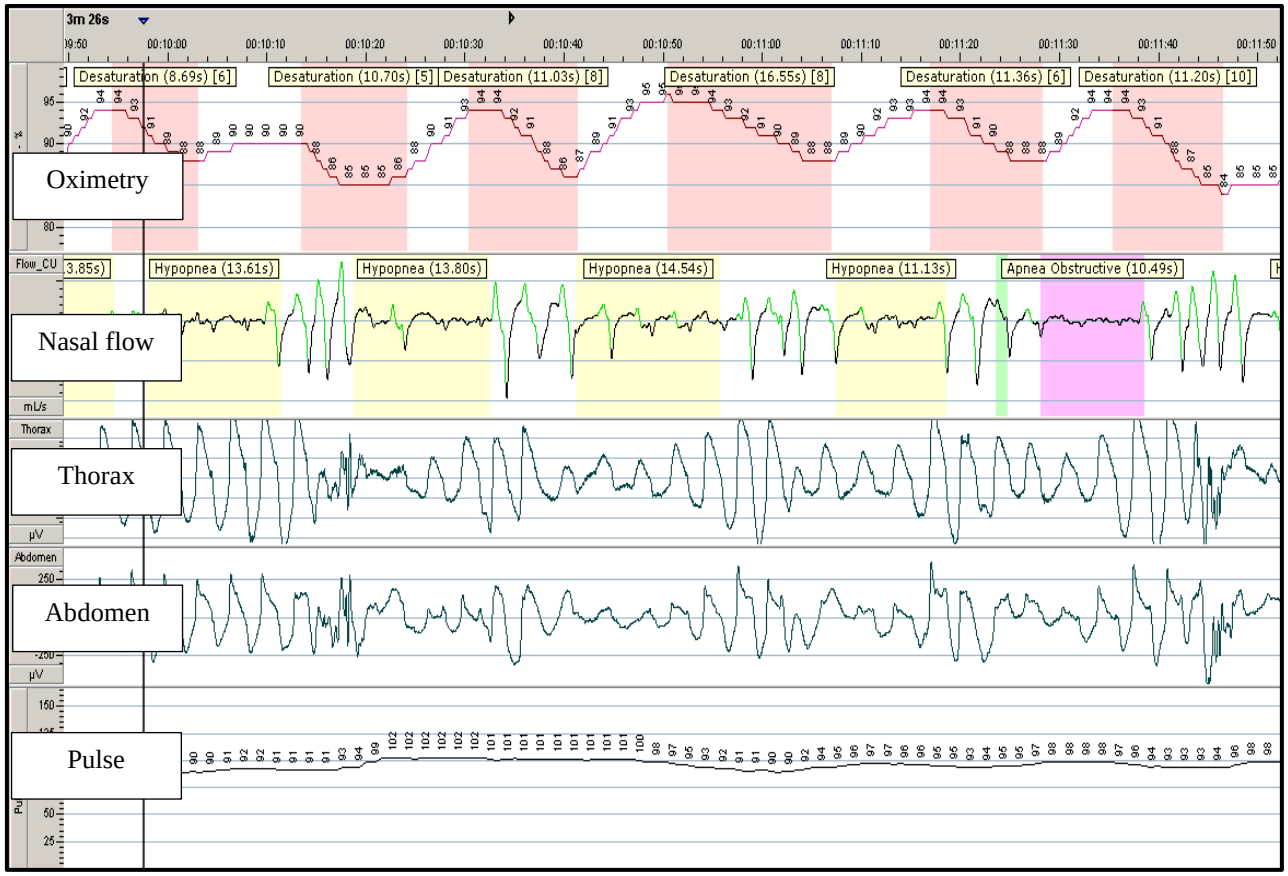


Figure 2.3 Limited-Channel sleep study- Positive for OSA

This is a screen-shot of a limited-channel sleep recording that was positive for obstructive sleep apnoea. The oximetry trace shows oxygen desaturations of ≥3%. Corresponding hypopnoeas (drops of ≥30% from baseline) and an apnoea (drop of ≥90%from baseline) can be seen in the nasal flow trace.

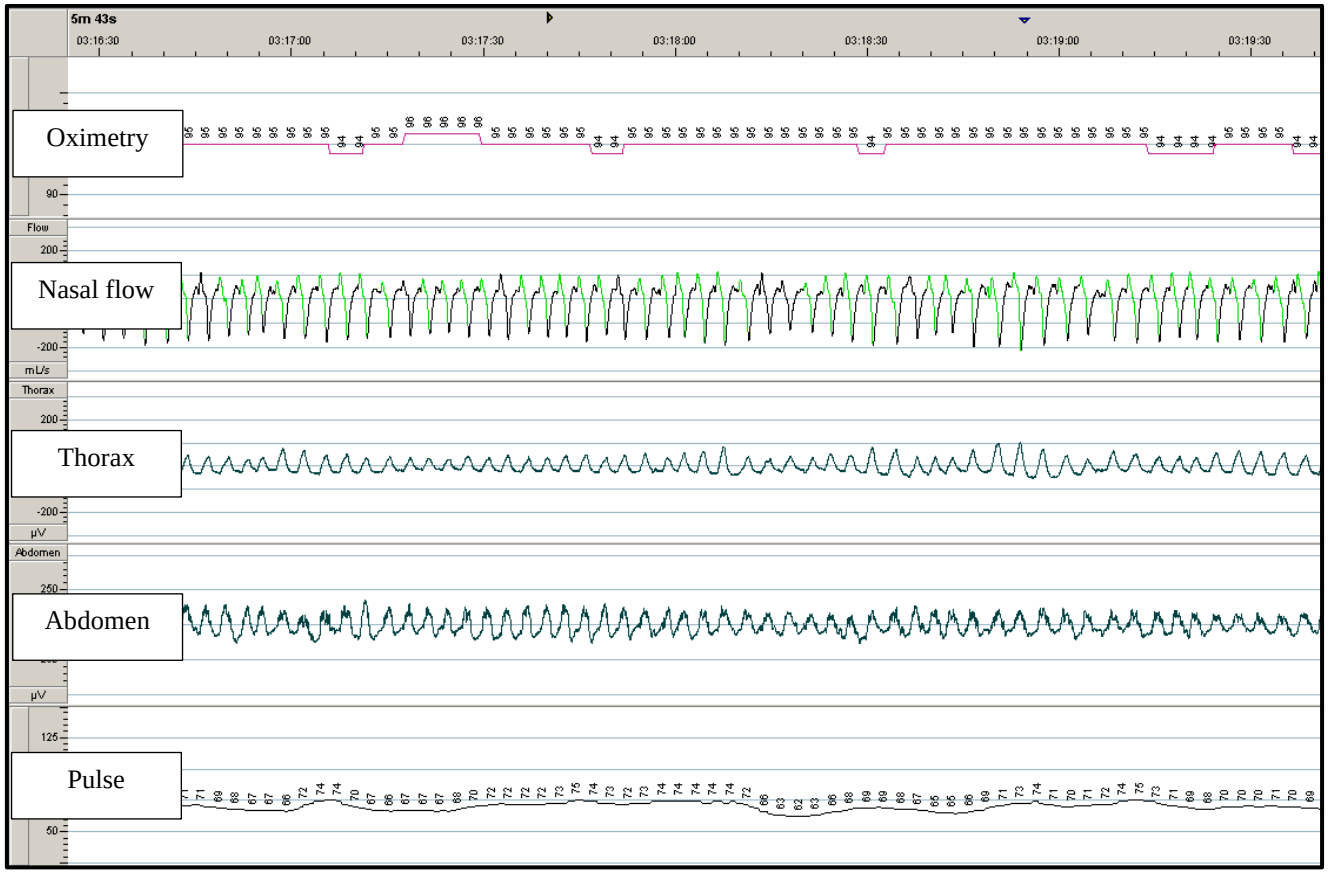


Figure 2.4 Limited-channel sleep study- Negative for OSA

This is a screen-shot of a limited-channel sleep study that was negative for obstructive sleep apnoea. The oximetry, nasal flow, thorax and abdominal traces remain within normal limits.

2) Full inpatient polysomnography (PSG):

Participants unable to complete an adequate limited-channel sleep study recording were asked to undergo a full inpatient polysomnography (PSG). The full inpatient PSG included additional electroencephalogram (EEG), electrooculogram (EOG), submental electromyogram (EMG), limb movements and nasal-oral thermistor measurements. These were scored using the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events (version 2.3) guidelines[192] by trained sleep physiologists then reviewed and reported by a trained sleep physician.

2.2.5 Asthma diagnosis

Participants under the care of the tertiary asthma service (BHH) underwent systematic evaluation as per centre protocol to confirm asthma diagnosis and assess severity. Participants were categorised as severe asthma if on a minimum of step 4 of the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines network (SIGN) 2016 guidelines for asthma management[12]. This includes requirement for high dose inhaled corticosteroid (equivalent of ≥ 1000 micrograms BDP) and a total of three controller medications, or requirement of four controller medications, or requirement for maintenance oral corticosteroids, or requirement for biological therapy. Controller medications included long acting beta agonists (LABA), leukotriene receptor antagonists (LTRA), long acting muscarinic antagonists (LAMA) or theophyllines.

2.2.6 Adipokines: Enzyme Linked Immunosorbent Assays (ELISAs)

Following the ethical amendment described in section 2.2.8, participants that consented underwent a blood test and a sample of both serum and plasma were stored as frozen samples and later allowed to defrost for analysis. The plasma samples were used to analyse the leptin and IL-6 concentration, and the serum samples were used to analyse the adiponectin concentration. All samples were processed using the DuoSet ELISAs purchased from R&D systems[193]. The process of the ELISA technique is illustrated in figure 2.5 adapted from the R&D website[194].

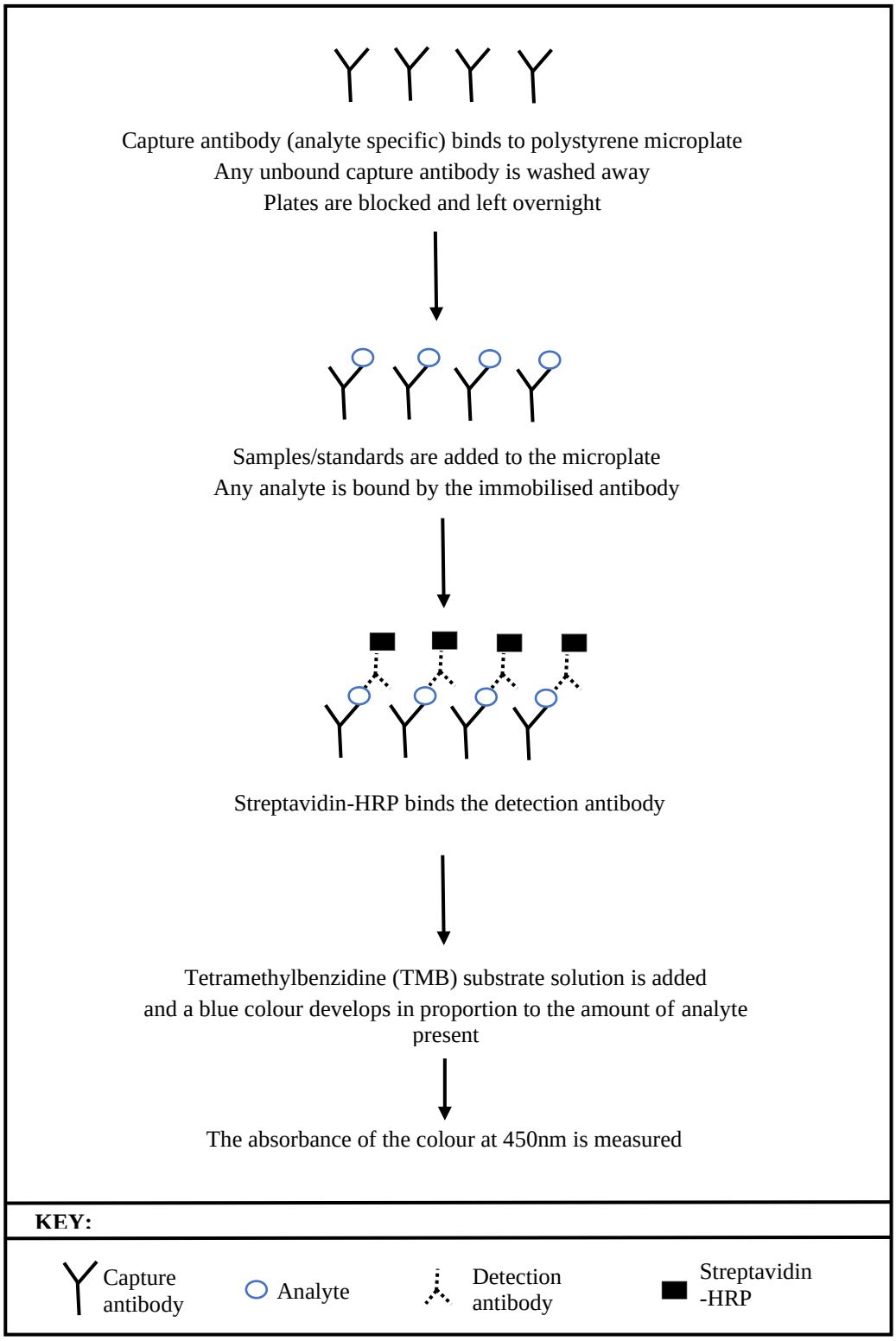


Figure 2.5 Principles of the ELISA technique[194]

2.2.6.1 List of materials & solutions used[193]

a) 96 well microplates

b) Plate sealers

c) Phosphate-buffered saline (PBS): 137nM NaCL, 2.7 mM KCL, 8.1mM Na_2HPO_4, 1.5mM KH_2PO_4, pH 7.2-7.4, 0.2μm filtered

d) Wash Buffer: 0.05% Tween 20 in PBS, pH 7.2-7.4

e) Reagent Diluent: 1% BSA in PBS, pH 7.2-7.4, 0.2 μm filtered

f) Substrate Solution: 1:1 mixture of Color Reagent A (H_2O_2) and Color Reagent B (Tetramethylbenzidine)

g) Stop Solution: 2 N H_2SO_4

2.2.6.2 Leptin

The plasma samples obtained for leptin concentrations were processed using the DuoSet ELISA development system, produced by R & D systems[193]. A 1 in 100 dilution of the samples was used. 10μL of each plasma sample was diluted in 990μL of Reagent Diluent.

2.2.6.2.1 Reagent preparation[193]

The reagents used included; streptavidin-HRP, human leptin capture antibody, human leptin detection antibody and human leptin standard which had been stored at 2-8 degrees Celsius. All reagents were brought to room temperature before use.

2.2.6.2.1.1 *Streptavidin-HRP*

Each vial contained 2mL of streptavidin conjugated to horseradish-peroxidase. This was diluted to the working concentration specified on the vial label using Reagent Diluent (1:40).

To achieve 11ml 520µL:

1:40=288 µL streptavidin-HRP in 11ml 232 µL diluent

2.2.6.2.1.2 *Human leptin capture antibody:*

Each vial contained 480µg/ml of mouse anti-human leptin antibody when reconstituted with 0.5ml of PBS. Dilute to working concentration of 4µg/mL in PBS, without carrier protein.

Calculation:

480µg/ml → 4µ/mL (divide by 120)

Need:

9600µL x 1.2= 11,520µL = 11ml 520µL PBS (11ml 424µL)

11520µL /120 = 96µL capture antibody.

2.2.6.2.1.3 *Human Leptin Detection Antibody:*

Each vial contained 1.5µg/mL of biotinylated mouse anti-human Leptin antibody when reconstituted with 1.0mL of Reagent Diluent. This was diluted to a working concentration of 25ng/mL in Reagent Diluent.

Calculation:

Stock concentration: 1.5µg/mL

Working concentration: 25ng/mL

Total final volume: 11,520µl (192µl of 1.5µg/mL stock + 11ml 328µl of reagent diluent)

2.2.6.2.1.4 *Human Leptin Standard*

Each vial contained 200ng/mL of recombinant human leptin when reconstituted with 0.5mL of deionised or distilled water.

200ng/ml → 2000 pg/ml (2ng/ml), final volume 1000µL

1:100 → 10µL of 200ng/ml standard + 990µL of Reagent Diluent → 2000pg/ml (1000µL)

A seven-point standard curve using 2-fold serial dilutions in Reagent Diluent, and a high standard of 2000pg/mL was used. 1000µL of high standard was prepared for each plate assayed. This process is illustrated in figure 2.6[193].

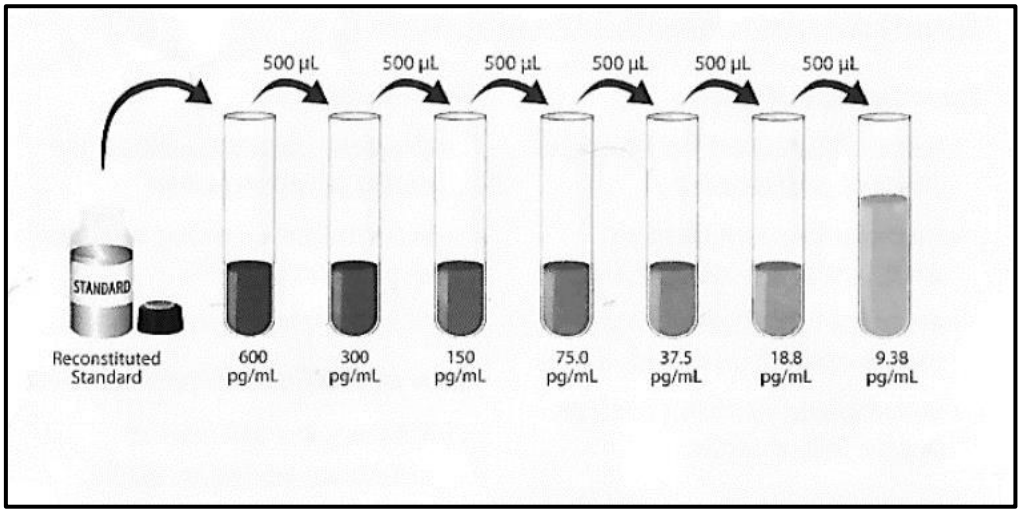


Figure 2.6 Preparation of seven-point standard curve[193]

2.2.6.3 Elisa Protocol[193]

1) Plate Preparation[193]

a) The capture antibody was diluted to the working concentration in PBS without carrier protein. A 96-well microplate was coated with 100µL per well of the diluted Capture Antibody. The plate was sealed and incubated overnight at room temperature.

b) Each well was aspirated and washed with Wash Buffer three times. Each well was washed with wash buffer (300µL) with complete removal of liquid at each step. The plate was inverted and blotted against clean paper towels between each wash.

c) The plate was blocked by adding 300µL of Reagent Diluent to each well. The plate was then incubated at room temperature for 1 hour.

d) The wash was repeated (as in step b).

2) Assay Procedure[193]

a) 100µL of sample was added to each well (or standard in Reagent Diluent). The plate was covered with an adhesive strip and incubated for 2 hours at room temperature.

b) The wash was repeated (same as step b of plate preparation)

c) 100µL of the Detection Antibody (diluted in Reagent Diluent) was added to each well. The plate was covered with an adhesive strip and incubated for 2 hours at room temperature.

d) The wash was repeated (same as step b of plate preparation).

e) 100µL of the working dilution of Streptavidin-HRP was added to each well. The plate was covered and incubated for 20minutes at room temperature, whilst avoiding placing the plate in direct light.

f) The wash was repeated (same as step b of plate preparation).

g) 100µL of Substrate Solution was added to each well. This was incubated for 20minutes at room temperature, whilst avoiding placing the plate in direct light.

h) 50µL of Stop Solution was added to each well. The plate was gently tapped to ensure thorough mixing.

i) The optical density of each well was determined immediately using a microplate reader set at 450nm. Wavelength correction was then used to correct for optical imperfections in the plate.

2.2.6.4 IL-6

The plasma samples obtained for IL-6 concentrations were processed using the DuoSet ELISA development system, produced by R & D systems[193]. The same general ELISA protocol was followed[193]. There were differences in the reagents and their preparation which will be described in further detail. The plasma samples were undiluted for the processing of IL-6.

The reagents included Streptavidin-HRP, Mouse Anti-Human IL-6 Capture Antibody, Biotinylated Goat Anti-Human IL-6 Detection Antibody and Recombinant Human IL-6 Standard. The unopened kits were stored at 2-8^{o}C. Reagents were brought to room temperature before use. All components sat for a minimum of 15 minutes with gentle

agitation after initial reconstitution. Working dilutions were then prepared and used immediately.

2.2.6.4.1 Reagents

2.2.6.4.1.1 *Streptavidin-HRP*

Each vial contained 2ml of streptavidin conjugated to horseradish peroxide. A 40 fold dilution was performed with Reagent diluent.

12 ml (12,000µl) / 40 = 300µL Streptavidin-HRP added to 11ml 700µL of Reagent Diluent.

2.2.6.4.1.2 *Mouse Anti-Human IL-6 Capture Antibody*

Provided: 1 vial of 120µg Capture Antibody

A working concentration of 2µg/ml was needed. To achieve this:

0.5ml PBS added to vial → 120µg in 0.5ml PBS (240µg/ml) (stock)

Need: 96 wells x 100µL = 9600µL x 1.2 (for loss) = 11 520µL

Therefore: 96µL of stock was added to 11ml 424µL PBS to get working concentration of 2µg/ml

2.2.6.4.1.3 *Biotinylated Goat Anti-Human IL-6 Detection Antibody*

Provided: 3µg of Detection Antibody

A working concentration of 50ng/ml was needed. To achieve this:

1ml of Reagent Diluent was added to vial → 3µg in 1ml diluent (stock)

Need: 96 wells x 100µL = 9600µL x 1.2 (for loss) = 11 520 µL

Therefore: 192µL of stock was added to 11ml 424µL Reagent Diluent to get working concentration of 50ng/ml

2.2.6.4.1.4 *Recombinant Human IL-6 Standard*

Provided: 1 vial of 90ng of Standard

A working concentration of 9.38-600 pg/ml was needed. To achieve this:

0.5ml of distilled water was added to vial → 90ng in 0.5 H_2O of stock (180ng/ml)

Concentration of high standard = 600pg/ml

Need: 1000µL of top standard

Therefore: Add 3.33µL of stock to 996.67µL of Reagent Diluent to get top standard. Then serial dilutions performed to get standard curve (see figure 2.6[193]).

2.2.6.5 Adiponectin

The serum samples obtained for adiponectin concentration were again processed using the DuoSet ELISA development system, produced by R & D systems[193]. The same general ELISA protocol was followed[193]. There were differences in the reagents and their preparation which will be described in further detail. The reagents used included; streptavidin-HRP, mouse anti-human adiponectin capture antibody, biotinylated mouse anti-human adiponectin detection antibody and recombinant human adiponectin standard. The reagents were stored at 2-8ºC and brought to room temperature before use. The samples were diluted by 1:10,000.

2.2.6.5.1 Reagents

2.2.6.5.1.1 *Streptavidin-HRP*

Each vial contained 1mL of streptavidin conjugated to horseradish peroxide. A 1 in 200 dilution was performed with Reagent diluent.

To produced 12ml of solution, 60µL of streptavidin was added to 11940µL of reagent diluent.

2.2.6.5.1.2 *Mouse anti-human adiponectin capture antibody*

1ml of PBS was added to vial of 360µg of capture antibody.

64µg of the vial was then added to 11,456µL PBS to get a working concentration of 2µg/ml.

100µL was then added to each well in the plate and left overnight.

2.2.6.5.1.3 *Biotinylated mouse anti-human adiponectin detection antibody*

1ml of reagent diluent was added to the vial of 180µg of detection antibody. 64µL of this was then added to 11,456µL reagent diluent to get a working concentration of 1µg/ml.

2.2.6.5.1.4 *Recombinant human adiponectin standard*

0.5ml of reagent diluent was added to the vial of 170ng of standard to produce concentration of 340ng/ml. Then, 11.76µL of this stock standard was added to 988.24µL of reagent diluent to produce 1000µL of the high standard. Serial dilutions were then performed as per figure 2.6[193].

2.2.6.6 Calculation of ELISA results

Calculations and graphs were analysed and produced using Microsoft EXCEL software. There were duplicate readings for each standard and each sample optical density (O.D) measured. The average zero standard O.D was subtracted. The coefficient of variation (CV) was calculated for each standard and sample. A CV of <20 was accepted. All values less than the lower limit of quantification (LLQ) of the assay were excluded. The LLQ for each assay were as follows: leptin; 31.3 picograms per millilitre (pg/ml), IL-6; 9.38 pg/ml and adiponectin 62.5 pg/ml.

A standard curve was produced by plotting the mean absorbance for each standard on the y-axis against concentration of adipokine on the x-axis with a best fit curve drawn through the points on the graph. An example of a standard curve produced is illustrated in figure 2.7. Depending on the results obtained, alternatively a linear trendline was applied to the data rather than forcing the line to go through zero. For the samples that were diluted (leptin and IL-6), the concentration read from the standard curve was multiplied by the dilution factor.

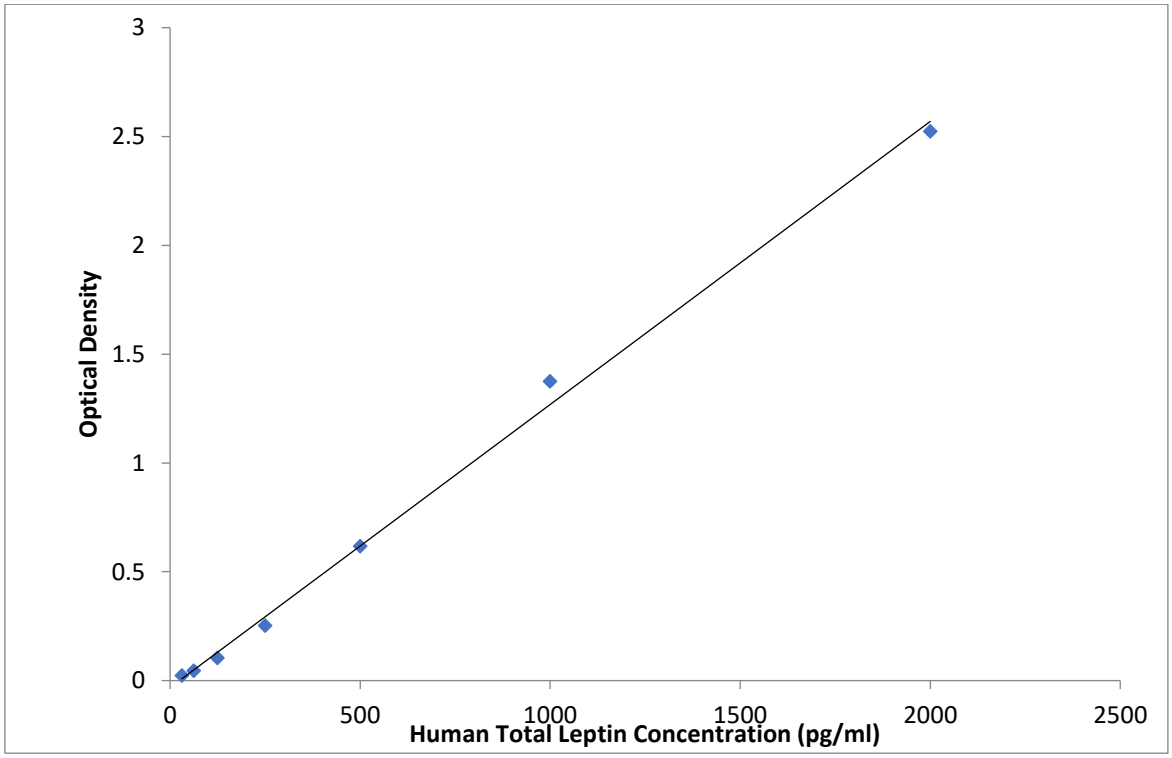


Figure 2.7 Example of a standard curve produced

2.2.7 Statistical analysis

2.2.7.1 Cross sectional study

The results were analysed using International Business Machines (IBM) Statistical Package for Social Sciences (SPSS), version 23. Variables were tested for normality using histograms,

Q-Q plots and the Shapiro-Wilk test. Parametric values were presented as mean ± SD. Non-parametric variables were presented as median (Q1, Q3).

2.2.7.1.1 Univariate analysis

To compare the two groups (OSA versus no-OSA); parametric data were analysed using an unpaired T-Test and non-parametric data were analysed using a Mann-Whitney test. Categorical data were analysed using Fisher's Exact test or Kendall's tau-b.

To assess clinical outcomes in relation to OSA the participants were categorised into ordered groups according to severity of OSA; no-OSA (AHI<5), mild OSA (≥5AHI<15), moderate OSA (≥15AHI<30) and severe OSA (AHI≥30). The CPAP group was removed from this section of the analysis as this is not an ordered group. The Jonkheere-Terpstra test for trend was used to analyse the trend of each clinical outcome with regards to severity of OSA, $p<0.05$ taken as a statistically significant trend. Kendall's tau-b or Fisher's Exact Test were used to analyse categorical data.

Asthma-related healthcare utilisation was analysed in cross-tabulation format with Kendall's tau b. This is due to the small numbers that were reported (median values), to enable the reader to appreciate any trends seen even if they did not reach statistical significance.

To determine the trend between severity of OSA and bioelectrical impedance measurements, variables were compared against AHI using Spearman's rho correlation coefficient with r_s and

p values reported, $p<0.05$ determined statistical significance. To determine if the effect seen was independent of BMI, the same analysis was performed with BMI and the bioelectrical impedance variables. Participants in the DEXA subgroup (n=59) were categorised into either the OSA (AHI≥5) group or the no-OSA (AHI<5) group. Body composition variables were compared in the two groups using a Mann-Whitney test. The correlation with AHI was also assessed using Spearman's rho correlation coefficient, which was also corrected for gender.

To determine the trend between severity of OSA and adipokine levels, the Jonkheere-Terpstra test was again used. The participants were then categorised according to BMI and the same test again used to determine if the effect seen could be related to BMI. The CPAP group was removed from this section of the analysis as it did not form an ordered group. Spearman's rho correlation coefficient was also used to analyse the trend between adipokine concentration and AHI.

2.2.7.1.2 Multivariate analysis

Multivariate analysis using binary logistic regression were used to determine predictors of OSA (AHI≥5) in asthma. Independent variables based on known risk factors for OSA were selected for the model and the Hosmer and Lemeshow goodness of fit test was used to determine how well the data fit the model. Higher p values ($p>0.05$) were accepted as an acceptable fit for the model. A Receiver Operating Characteristics (ROC) curve was created to plot the true positive rate (y-axis) against the false positive rate (x-axis). The area under the curve was calculated to determine how well each variable could distinguish between OSA and no-OSA. Independent variables with an area under the curve equal to 0.5 were unable to

distinguish between the two groups. Variables with an area equal to 1 had no overlap between the two groups. Statistical significance was assumed in variables with p values <0.05.

2.2.7.2 Prospective case-control study

The same statistical methodology was used for the prospective study. Multivariate analysis was not performed due to smaller number of participants, and predominantly non-statistically significant results identified in the univariate analysis.

2.2.8 Ethical approval (observational studies)

Ethical approval was obtained from the Health Research Authority (HRA) following review at the West Midlands-Black Country Research Ethics Committee. REC reference number: 12/WM/0049. The approval letter is shown in appendix 1.

Initial ethical approval was obtained in 2012. This was followed by two further substantial amendments with reference to the observational studies:

1) November 2015. This was a substantial amendment that included changes to staff and supervisors and major review of the protocol. The cross-sectional and prospective case-control study were combined together, and the number of participants was reduced from 1000 to 200. A subgroup of participants in the observational study were to undergo DEXA scan (60 participants) and the remainder to undergo bioelectrical impedance measurements.

2) December 2016. This was a further substantial amendment in reference to the observational studies to enable 100 participants to undergo blood tests for asthma biomarkers

and adipokines. Additionally, a full inpatient polysomnography was to be acceptable if the participant could not undergo an adequate limited-channel sleep study.

2.3 Systematic review and meta-analysis: The effect of CPAP treatment of OSA on asthma-related clinical outcomes in patients with co-existing conditions[175]

2.3.1 Inclusion & Exclusion criteria[175]

To be included in this review, studies had to meet the following criteria:

1) A population of asthmatics with co-existing obstructive sleep apnoea. Studies with mixed populations were included if data for asthmatics with co-existing OSA were presented separately.

2) Treatment with CPAP

3) Measurement of ≥ 1 asthma-related clinical outcome

Studies were excluded based on the following criteria:

1) Not written in English

2) Non-adult populations (<18 years)

3) Full text article not available (i.e. abstracts, letters, and editorials)

4) Original research/data not included in published article

2.3.2 Search methodology[175]

Literature search was performed using EMBASE and MEDLINE databases. The search terms included “asthma OR asthmatic” AND “obstructive sleep apnoea/apnea OR OSA” AND “continuous positive airway pressure OR CPAP”. All studies up to and including July 2017 were included.

2.3.3 Data extraction & assessment of bias[175]

Two independent reviewers assessed the results of the searches generated in EMBASE and MEDLINE databases. Studies generated from the above searches were assessed as per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) diagram (figure 2.8) and reviewed in accordance with the inclusion/exclusion criteria, with any disagreements between the reviewers resolved through discussion.

The reviewers assessed each study to identify if ≥ 1 asthma-related clinical outcome was measured. Clinical outcomes included; ACT, ACQ, AQLQ and daytime/night-time asthma symptoms. Additional outcome measures included; lung function, exacerbation frequency, accident and emergency (A&E) visits or hospital admissions, and, any other outcomes thought clinically relevant by both reviewers.

Studies were assessed for bias by the two reviewers, with any disagreement resolved through discussion. Bias was assessed using the ROBINS-I (Risk of Bias in Non-Randomised Studies of Interventions), which is based on the Cochrane risk of bias tool for randomised studies[195].

The following forms of bias were assessed for each study; confounding, selection bias, misclassification bias, performance bias, attrition bias, detection bias and reporting bias.

1) Confounding: The association between intervention and outcome differs from its causal effect[196].

2) Selection bias: This occurs when some eligible participants, follow-up time, or outcome events are excluded in a way that creates an association between the intervention and the outcome[196].

3) Misclassification bias: Misclassification of intervention status[196].

4) Performance bias: Systematic differences between the groups in the care provided, or differences in exposure to factors other than the intervention currently under review[197].

4) Attrition bias: Systematic differences between the groups in the participant withdrawals from the study[197].

5) Detection bias: Systematic differences between groups in how outcomes are determined[197].

6) Reporting bias: Systematic differences between unreported and reported findings[197].

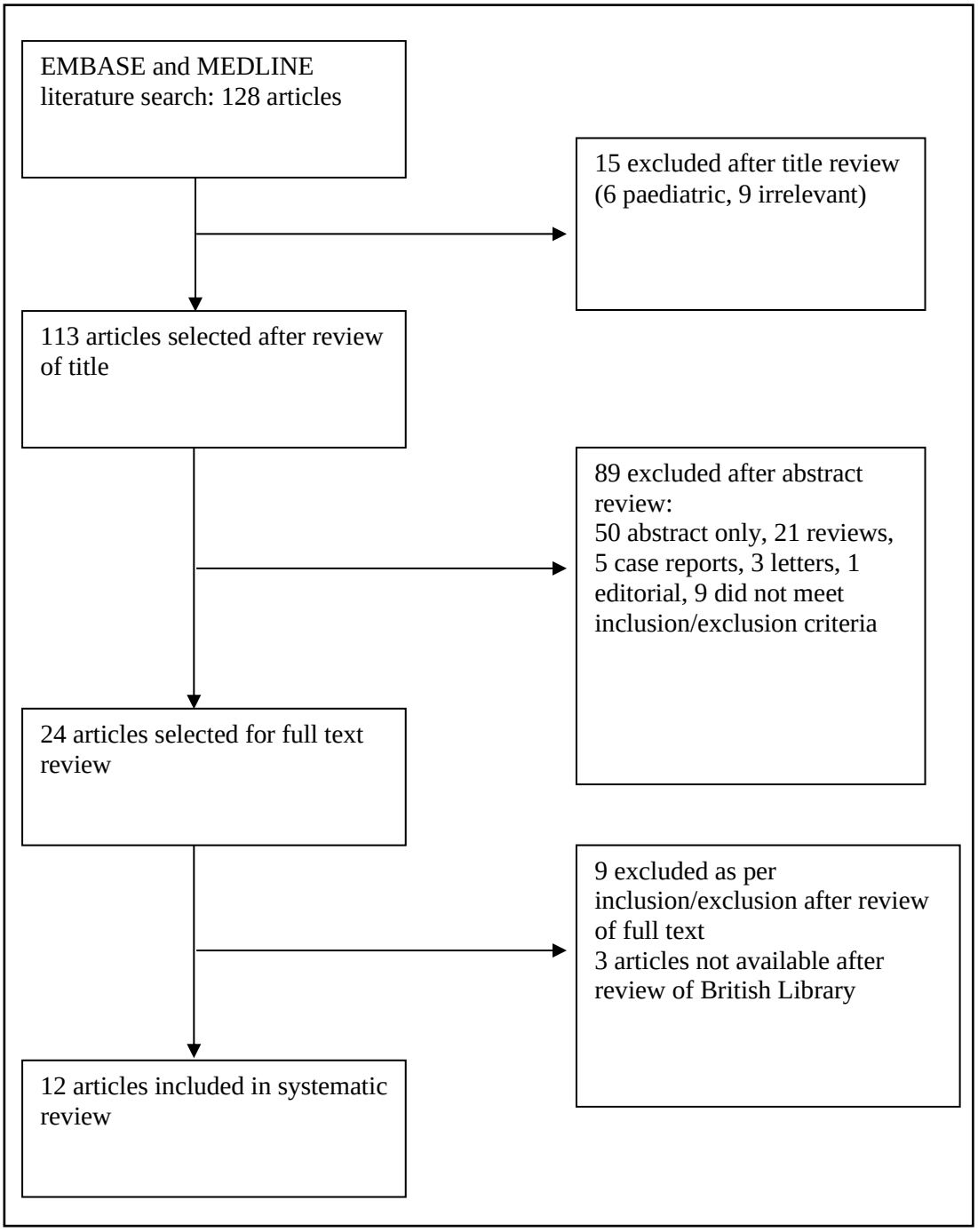


Figure 2.8 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[175]

The PICO diagram for this systematic review is illustrated in figure 2.9.

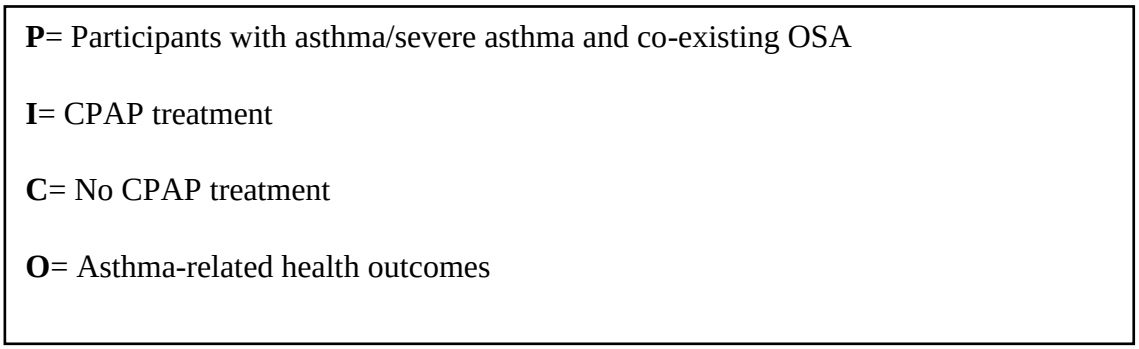


Figure 2.9 PICO diagram

The PICO tool is helpful at focussing clinical questions. P: Population/problem; I: Intervention/exposure; C: Comparison; O: Outcome; CPAP: Continuous Positive Airway Pressure

2.3.4 Data synthesis and analysis[175]

Studies were categorised into groups according to the clinical outcome measured; 1) asthma quality of life, 2) asthma control/symptoms, 3) asthma severity and 4) lung function and physiological measures.

2.3.5 Statistical analysis[175]

The reviewers judged that there was sufficient data to meta-analyse 1) AQLQ and mini-AQLQ and 2) lung function; Forced Expiratory Volume in 1 second- % predicted (FEV_1%pred). RevMan (Review Manager) version 5.3 was used for the meta-analysis. A fixed effects model was used to calculate mean difference in pre and post CPAP values for these outcome measures. A narrative synthesis was used to describe the remaining data, as

clinically significant heterogeneity in the measuring of other clinical outcomes precluded meta-analysis.

2.4 Interventional study

2.4.1 Design

The interventional study was a prospective double-blind, randomised controlled, parallel pilot feasibility study.

2.4.2 Aims

The primary outcome of the study was to determine the effect of CPAP treatment on asthma-related quality of life in participants with co-existing severe asthma and OSA. This was measured using the AQLQ.

Secondary outcomes of the study included;

1) ACQ-7, EQ-5D, EQ-VAS, HADS

2) Health care utilisation; Accident and Emergency (A&E) visits, hospital admissions and GP visits, frequency of OCS requiring exacerbations

3) Changes in FEV_1, FEV_1/FVC ratio

4) Asthma markers: peripheral eosinophil count, FENO

5) Markers of the metabolic syndrome: Cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides.

2.4.3 Recruitment

Participants identified during the cross-sectional study with severe asthma and OSA were invited to participate in the interventional study. Additional participants were referred from associated respiratory clinics, or from within the BRSAS regional multidisciplinary team (MDT). A participant information leaflet was provided to potential participants that expressed an interest (an example is shown in appendix 11).

2.4.4 Inclusion/Exclusion criteria

2.4.4.1 Inclusion Criteria

1) A diagnosis of OSA: apnoea/hypopnoea index (AHI) ≥10 per hour)

2) Bronchial asthma confirmed by one of the following:

- Airflow variability with a mean diurnal peak expiratory flow (PEF) variability ≥15% during baseline 2 week period
- Airway reversibility with variability in FEV_1 by ≥12% or 200ml after short acting beta agonist (SABA) or methacholine challenge or spontaneously between clinic visits

c) Current inhaled steroid use of ≥BDP 1000 equivalent, plus a second controller (long-acting β2 agonist, anti-muscarinic, theophylline, or leukotriene receptor antagonist), and/or systemic corticosteroids

3) ACQ-7 ≥ 1.5 (in previous 6 months)

4) Age ≥18 – 75 years old.

5) Given their informed consent

2.4.4.2 Exclusion Criteria

1) Clinically significant underlying co-morbidities that were perceived by the investigator to undermine the outcomes of the study or affect subject's safety (e.g. significant coronary artery disease, diabetes, hypertension, heart failure – at the discretion of the investigator)

2) Any evidence of contra-indications for CPAP (e.g. previous intolerance, mask claustrophobia, nasopharyngeal abnormalities)

3) Current smokers, and ex-smokers with >15 pack year history

4) Recent severe asthma exacerbation (within 4 weeks) requiring additional oral corticosteroids or hospital admission

5) Vocal cord dysfunction as the leading diagnosis

6) Patients who have undergone anti-reflux surgery within the preceding six months

7) Patients who have been started on omalizumab, or other immune modifying treatment (e.g. methotrexate, or other cytotoxic agents) in the preceding six months.

8) Clinically significant underlying other pulmonary disease such as bronchiectasis, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), or previous lung resection.

9) Clinically significant underlying psychiatric/psychological condition

10) Poor compliance with asthma medication or inability to follow study protocol

11) Excessive daytime sleepiness defined by Epworth Sleepiness Score (ESS) >15 (unless patient declines CPAP therapy as part of NHS care), or falling asleep if driving (offered CPAP on the NHS as part of their usual clinical care)

12) Commercial vehicle driver

2.4.5 Study design and randomisation

Participants that met the inclusion/exclusion criteria were randomised to one of the following groups:

1) Usual supportive asthma care with CPAP therapy (group X) for 3 months, or,

2) Usual supportive asthma care with sham CPAP (group Z) for 3 months.

An independent person created an Excel spreadsheet that randomly allocated the participant number to either group X or group Z.

2.4.6 Blinding

This was a double-blind study with both participants and researcher blinded to the type of CPAP device used. Both machines were provided by one manufacturer and looked similar apart from the leak in the circuit which was not easily identifiable by the participant.

The only two people who were unblinded were the independent person involved with the computer-generated randomisation process, and the sleep physiologist/respiratory research nurse who set up the CPAP/sham devices. The physiologist/research nurse were tasked to trouble shoot device related problems and record data usage from the CPAP/sham CPAP data download.

At each visit, the researcher encouraged participant use of CPAP/sham CPAP, without inspecting the mask or machine. If any issues with the machine or mask were raised by the participant, these were deferred to the physiologist who was unblinded. The data remained blinded until the full data analysis was complete.

2.4.7 CPAP/sham CPAP Therapy

CPAP is a device that delivers a stream of compressed air at a prescribed pressure via a nose or full-face mask and hose, splinting the airway so that unobstructed breathing is possible[198]. Sham CPAP is a version of CPAP in which the apparatus has been modified so that pressure levels at the mask interface are <1cmH_2O. This is achieved by creating a leak in the circuit which releases the pressure. The sham CPAP machine looks similar to the CPAP machine and therefore gives the impression of therapy but with no therapeutic effect. A photograph of the standard CPAP machine is illustrated in figure 2.10, and the sham CPAP machine in figure 2.11. Sham CPAP is recognised as an effective placebo device against CPAP[199], with the patients not aware which form of therapy they are receiving i.e. placebo CPAP or therapeutic CPAP. Both machines have a data card which is used to record information on, including usage time.

Philips-Respironics REMSTAR Auto™ CPAP or Philips-Respironics REMSTAR Auto™ Sham CPAP were provided to each patient with an appropriately fitted nasal mask. Participants were provided with a demonstration of how a CPAP machine works, general education, and the participant was expected to demonstrate to the physiologist or research nurse that he or she can apply the CPAP mask and switch on the machine by themselves.

Figure 2.10 Standard CPAP machine

Figure 2.11 Sham CPAP machine

The Sham CPAP machine was similar to the standard CPAP machine except a leak was present in the mask (indicated by arrow).

CPAP: Continuous positive airway pressure

2.4.8 Clinical measurements

The following measurements were to be taken at baseline (visit 0) and 3 months+/-3 weeks (visit 2):

2.4.8.1 Asthma related indices, questionnaires and healthcare utilisation

1) AQLQ, ACQ-7, HADS, EQ-5D, EQ-VAS

2) Number of OCS requiring asthma exacerbations, emergency GP and A&E visits and hospital admissions

3) Medication use including oral corticosteroids

2.4.8.2 Sleep / breathing physiology

1) Apnoea – hypopnoea Index (AHI)

2) Time spent under 90% oxygen saturations

3) Mean oxygen saturations during the night

4) Minimum oxygen saturations

5) CPAP adherence

2.4.8.3 Subjective sleepiness: at baseline and each follow-up visit:

1) Epworth sleepiness scale (appendix 9) and Stanford sleepiness scale (appendix 10).

The Stanford sleepiness scale is an additional subjective measure of sleepiness at a specific moment in time, with respondents selecting the most appropriate of seven responses[200].

2.4.8.4 Demographics and clinical measurements

1) Age, gender, co-morbidities, smoking status

2) BMI

3) Clinical measurements (heart rate, blood pressure),

4) Biochemical markers of the metabolic syndrome: HbA1c, cholesterol, HDL, LDL and triglycerides (same methods as section 2.2.4)

5) Asthma biomarkers: Peripheral eosinophil count, FENO, IgE

5) Spirometry: FEV_1, FVC, FEV_1/FVC flow-volume loops (same methods as section 2.2.4)

2.4.8.5 Additional visits

Telephone consultation: The sleep physiologist or research registrar aimed to speak with the participant at 48 hours (+/- 48 hours) from baseline to determine if there were any problems with ongoing participation in the study.

Visit 1: The aim was for this visit to occur 2 weeks from the baseline visit (+/- 2 weeks): Participants were asked to attend for a visit with the research registrar to determine if there were any problems and review progress (or alternatively a telephone consultation was offered depending on participant preference).

2.4.9 Statistical analysis

This was a pilot study and the intention was to recruit 30 participants into each arm (CPAP or sham CPAP) with an expectant drop-out rate of 10 in each group. Assuming a common standard deviation of 0.5 for AQLQ, a sample size of 20 cases per arm would have had an

87% power at 5% significance level to detect a mean difference of 0.5. This was a pilot study and therefore the sample size was not based on a calculation. A sample size of 30 for each arm of the study was chosen as this was thought to be a reasonable sample size for a pilot study as suggested by Lancaster et al[201]. The minimal clincally significant change for AQLQ is 0.5. With a sample size of 20 per arm (after allowing for 10 drop outs per arm), a difference in the means of 0.5 can be detected with 87% power if the standard deviation is 0.5.

The results were analysed in IBM SPSS, version 23. Variables were tested for normality using histograms, Q-Q plots and the Shapiro-Wilk test. Parametric values are presented as mean ± SD. Non-parametric variables are presented as median (Q1, Q3).

Within each group, the pre and post-intervention values were compared using a Wilcoxon test. The post-intervention values in the treatment group were then compared to the post-intervention values in the placebo group using a Mann-Whitney test. Following any statistically significant result ($p<0.05$) in this provisional analysis there were two further comparisons; 1) The pre-intervention values were compared between the two groups using a Mann-Whitney and 2) the difference in pre and post-intervention values was calculated for each participant and compared between the two groups using a Mann-Whitney test.

2.4.10 Ethical approval (interventional study)

Ethical approval was obtained from the Health Research Authority following review at the West Midlands-Black Country Research Ethics Committee. REC reference number: 12/WM/0049.

Initial ethical approval for the study was obtained in 2012, a copy is provided in appendix 1. A copy of the participant information sheet is included in appendix 11, and a copy of the consent form in appendix 12. All participants were advised not to drive if sleepy. Any participant who complained of sleepiness as a result of their OSA, and deemed to be at risk of a road traffic accident was removed from the trial and offered standard CPAP therapy as part of NHS care. Participants who had OSA and were sleepy were advised to inform the Driver and Vehicle Licensing Agency (DVLA) as per DVLA guidelines.

Substantial ethical amendments:

1) November 2015: A substantial amendment was completed to account for change of staff and supervisors. The protocol was revised and BMI as an exclusion criterion was removed. The upper age limit was increased from 65 years to 75 years.

2) April 2016: The following inclusion criteria were modified to aid recruitment: variability of peak flow was included, and the required variability in FEV_1 was reduced to 12 % (with evidence of airflow obstruction). ACQ ≥1.5 was used to demonstrate poorly controlled asthma, rather than exacerbation and hospital admission rate. The exclusion criterion for the Epworth sleepiness score was changed from ≥15 to >15.

3) August 2016: The two-week follow up visit after the CPAP / sham CPAP set up was modified to enable this to occur via telephone. ACQ ≥ 1.5 was modified to “within the previous 6 months”.

4) December 2016: To enable the CPAP / sham CPAP to be set up at an alternative visit to the baseline visit, if the set up was not possible on the day of the baseline visit.

3 Results: The association between asthma and OSA- Systematic Review

3.1 Introduction[172]

The primary aim of this systematic review was to determine the association between asthma and OSA. Secondly, to determine the impact of OSA on asthma-related clinical outcomes in patients with co-exiting conditions.

3.2 Results

A total of 19 studies were identified for inclusion in this systematic review (6 PSG and 13 questionnaire based). A PICO diagram with the identified asthma-related clinical outcomes is illustrated in figure 3.1.

P= Participants with asthma or severe asthma

I= Co-existing obstructive sleep apnoea

C= Healthy asthmatics/severe asthmatics (no co-existing OSA)

O= 1) Prevalence of OSA, 2) Asthma-related health outcomes identified: ACT, AQLQ, FEV_1 % predicted, severe asthma exacerbations, ED visits, hospital admissions, ITU admissions, persistent daytime or night-time symptoms, poorly controlled asthma

Figure 3.1 PICO diagram

The PICO tool is helpful at focussing clinical questions. P: Population/problem; I: Intervention/exposure; C: Comparison; O: Outcome

ACT: Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire; FEV_1: Forced Expiratory Volume in 1 second; ED: Emergency Department; ITU: Intensive Care Unit

3.2.1 Association between asthma (non-severe) and OSA[172]

3.2.1.1 Studies using PSG for OSA diagnosis (table 3.1)

The prevalence of OSA was reported at 19.2-60% [202,203,204,205]. Julien et al reported a prevalence of 6/26 (23%) in moderate asthma was compared to 3/26 (12%) in the control group, but this did not reach statistical significance (p=0.303) [206]. Zidan et al demonstrated an OSA prevalence of 18/30 (60%) in asthma compared to 2/12 (17%) of controls (p<0.001)[203]. A prospective cohort study by Shaarawy et al demonstrated a prevalence of OSA of 15/60 (25%) in patients with asthma[204]. Wang et al demonstrated a significantly higher prevalence of OSA in asthma subjects of 28/146 (19.2%) versus matched controls of 15/157 (9.6%), (p=0.016)[205]. Teodorescu demonstrated incident OSA of 22/81 (27%) in asthma compared to 75/466 (16%) in controls over multiple 4 year intervals (p=0.02)[202].

3.2.1.2 Studies using questionnaires to assess OSA risk (table 3.2)[172]

Thirteen questionnaire based studies met the inclusion/exclusion criteria, of which twelve demonstrated increased prevalence of OSA in asthma at a range of 8% to 52.6%, whilst one study showed no association. In the latter study by Karachalioua et al, there was no association between asthma and snoring (OR=1.01; CI: 0.76-1.35), apnoeas (OR=1.22; CI: 0.79-1.88) or excessive daytime sleepiness (OR=1.39; CI: 0.83-2.35)[207].

3.2.2 Association between severe/difficult to treat asthma (SDTA) and OSA

3.2.2.1 Studies using PSG for OSA diagnosis (table 3.1)[172]

Two studies looked at the association between severe difficult to treat asthma (SDTA) and prevalence of OSA [206, 208]. Julien et al reported a prevalence of OSA of 50% (13/26) in severe asthma and 6/26 (23%) in moderate asthma compared to 3/26 (12%) in controls[206]. There was

significantly more OSA in severe versus moderate asthma (p=0.044) and severe versus controls (p=0.003), but not when comparing moderate to controls (p=0.303). A study of 22 difficult to treat asthma patients by Yigla et al showed a particularly high prevalence of OSA at 21/22 (95.5%)[208].

3.2.2.2 Studies using questionnaires to assess OSA risk (table 3.2)[172]

Only four of the thirteen studies reported asthma severity in relation to OSA risk. Teodorsecu et al showed a significant difference in OSA risk in severe asthma versus normal controls (24/94, 26% vs 4/146, 3%, p=0.04) and non-severe asthma versus normal controls (26/161, 16% vs 4/146, 3%, p=0.02)[209]. However, there was no significant correlation for OSA risk in severe asthma compared to non-severe asthma[209]. A study of asthmatic patients from a tertiary care centre demonstrated a prevalence of 97/244 (39.7%) of high OSA risk and additionally that asthma severity step was predictive of OSA risk (OR 1.6[95%CI 1.26-2.03], p<0.0001)[210]. However, a study of 177 asthmatic patients by Aukley et al showed a similar prevalence of OSA risk in asthma of 70 (39.5%) but did not show a correlation between OSA risk and asthma severity (p=0.183)[173]. A study of 115 asthmatics found 39/79 (49%) of women and 12/36 (33%) of men had high OSA risk. This study included 38 (33%) asthmatics on treatment severity step 4, however correlation between asthma severity and OSA risk was not clearly presented[169]. Teodorescu et al looked at OSA risk in the elderly (20/154, 13%) compared to the young (45/659, 7%). OSA was associated with an almost 7 times greater likelihood of severe asthma in older individuals, which was of greater magnitude than the younger population (OR=2.16) [211]

3.2.3 OSA and asthma-related clinical outcomes[172]

3.2.3.1 Studies using PSG for OSA diagnosis (table 3.1)[172]

Only three of the six included PSG based studies reported on asthma-related clinical outcomes. Of these, two showed worse clinical outcomes with co-existing OSA. A recent prospective cross-sectional cohort by Wang et al demonstrated that subjects with OSA had an increased prevalence of severe asthma exacerbations when compared to asthmatics without OSA ($p<0.001$)[205]. The AHI significantly correlated with the number of severe exacerbations (odds ratio 1.322, 95% CI 1.148-1.523, $p<0.001$)[205]. Zidan et al used FEV_1% as a marker of asthma severity to demonstrate this as a significant predictor for the development of OSA, $p<0.001$[203]. Julien et al showed that AHI did not correlate with asthma severity or other control scores, including %FEV_1 and AQLQ scores[206].

3.2.3.2 Studies using questionnaires to assess OSA risk (table 3.2)[172]

Only 6/13 questionnaire studies evaluated OSA risk in relation to asthma-related clinical outcomes. Of these, 4 studies reported worse clinical outcomes in patients with high OSA risk, with a further 2 studies reporting no significant difference in clinical outcomes. Teodorescu et al[209] demonstrated that high OSA risk was related to worse AQLQ scores ($p<0.0001$), increased number of emergency department (ED) visits ($p=0.001$), increased number of hospital admissions ($p=0.005$) and increased number of admissions to the Intensive care Unit (ITU) ($p=0.01$). A cross-sectional study by Teodorescu et al[212] showed an association between high OSA risk and both persistent daytime ([OR]1.96[95% CI=1.31-2.94]) and night-time(1.97[1.32-2.94]) asthma symptoms. A further study of 427 asthma patients showed high OSA risk was associated with 2.87 times higher odds for having poorly controlled asthma (95%C, 1.54-5.32) [213]. A cross-sectional study of 244 asthmatics demonstrated that high OSA risk was associated with both daytime ($p<0.0001$) and night-time

(p=0.0006) asthma symptoms[210]. Tay et al demonstrated in a univariate analysis that asthmatics with OSA have worse ACT (p=0.034) and worse AQLQ (p=0.029), but this was not shown in a multivariate analysis of the same study. This study also showed no significant difference in the number of exacerbations in the OSA group versus no-OSA group[214]. A cross-sectional study by Kim et al showed the high risk OSA group to have lower ACT scores than the low risk OSA group, however this did not reach statistical significance (p= 0.091)[215].

Table 3.1: Table of characteristics: studies that include diagnostic sleep test (PSG) for OSA[172]

Study	Study Design	Population	Asthma diagnosis	OSA diagnosis	Outcomes
1. Julien et al. J Allergy Clin Immunol 2009;124(2):371-6[206]	Cross-sectional	n=26 severe asthma n=26 moderate asthma n=26 controls	ATS guidelines	PSG	19/52 (36.5%) of total asthma population had OSA versus 3/26 (12%) of control group. 13/26 (50%) with severe asthma had OSA, 6/26 (23%) with moderate asthma had OSA and 3/26 (12%) of control group had OSA (p=0.007). AHI did not correlate with asthma severity or control scores (FEV_1%pred or AQLQ scores).
2. Shaarawy et al. Egyptian Journal of Chest Diseases and Tuberculosis 2013;62(1)[204]	Cross-sectional (with additional prospective interventional component)	n=60 with asthma Centre for allergy and respiratory disease	"Proven reversible airway obstruction" and "long history of bronchial asthma"	PSG	15/60 (25%) of asthma subjects had OSA. Mean AHI 23.5±10.9. No significant change in FEV_1 or ACT after 6/52 treatment with CPAP.
3. Teodorescu t al. JAMA 2015;313(2):156-164[202]	Prospective cohort study	Asthma: n=81 No asthma: n=466 (total n=547) Taken from Wisconsin Sleep Cohort Study	Self- reported (on 2 occasions)	PSG every 4 years (all had negative PSG at baseline)	22/81 (27%) (95%CI, 17-37%) of asthma subjects experienced incident OSA compared to 75/466 (16%) (95%CI, 13-19%) of non-asthma subjects observed over 4 year intervals (p=0.02). Asthma duration was related to incident OSA (RR 1.07 per 5 year increment in asthma duration, 95%CI, 1.26-5.89), (p=0.045).
4. Yigla et al. J Asthma. 2003;40(8):865-71[208]	Cross-sectional	n=22 (all with asthma) Continuous OCS:14 OCS burst: 8	Reversibility>15% + for severe (daily symptoms>6m, ICS + LABA, OCS >2/year or continuous)	PSG	21/22 (95.5%) prevalence of OSA Significantly higher prevalence of OSA in patients receiving continuous OCS compared to short bursts of OCS (p< 0.05)

5. Wang et al. Sleep Medicine.2016;(26)1–5[205]	Prospective cross-sectional cohort study	n=146 asthma n=157 controls Asthma follow up outpatient clinics	Physician diagnosed	PSG	28/146 (19.2%) of asthma subjects had OSA compared to 15/157 (9.6%) of controls, p=0.016. RR 2.25 (95%CI, 1.15-4.40), (p=0.016). Annual number of severe asthma exacerbations was significantly higher in the OSA group compared to the no-OSA group (p<0.001). AHI significantly correlated with the number of exacerbations (p<0.001).
6. Zidan et al. Egyptian Journal of Chest Diseases and Tuberculosis 2015;64(2):425–430[203]	Cross-sectional	n=30 with asthma n=12 healthy controls Asthma outpatient clinic	Physician diagnosis. GINA to assess control	PSG	18/30 (60%) of asthmatics had OSA vs 2/12 (17%) of controls, p<0.001. Presence of OSA associated with worse asthma control (p<0.001) (using FEV_1%pred).

OSA: Obstructive sleep apnoea; AHI: Apnoea hypopnoea index; PSG: Polysomnography; CPAP: Continuous positive airway pressure; OCS: Oral corticosteroid; AQLQ: Asthma quality of life questionnaire; ACT: Asthma control test; FEV_1: Forced expiratory volume in 1 second; ATS: American Thoracic Society; GINA: Global initiative for asthma

Table 3.2 Table of characteristics: studies that include validated questionnaires to assess OSA risk[172]

Study	Study Design	Population	Asthma Diagnosis	OSA diagnosis	Outcomes
1. Auckley, D. et al. Sleep Medicine 2008;9(5):494-499[173]	Cross-sectional	Asthma n=177 Control n=328 (non-asthma patients recruited from general medical outpatient clinics)	Physician diagnosed. Recruited from asthma and internal medicine clinics	Berlin Questionnaire	Risk of OSA was higher in the asthma group compared to controls: 70/177 (39.5%) vs 89/328 (27%), (p=0.004). In the asthma group, risk for OSA did not correlate with asthma severity (p=0.183).
2. Braido, F. et al. Respir Care 2014;59(12):1851-1856[216]	Cross-sectional	Total n=1,941 Asthma alone=740 Asthma + allergic rhinitis= 1,201 (Recruited by general practitioners during a control visit)	Physician diagnosis as per GINA guidelines	STOP-BANG	1020/1941 (52.6%) of all asthma subjects were high risk for OSA.
3. Ferguson, S. et al. Lung 2014;192(5): 675–683[217]	Cross-sectional	n=812 asthma (routine follow up at allergy and asthma clinics)	American Thoracic Society (ATS)	SA-SDQ	140/887 pre-existing OSA diagnosis, with 75/140 on CPAP and excluded 239/812 (29%) had high OSA risk.
4. Karachaliou, F et al. Prim Care Respir J. 2007;16(4):222-8[207]	Cross - sectional	n=1501 Asthma =218	2 respiratory physicians: (a) longstanding history of asthma from childhood or adolescence (b) a history of atopy was considered indicative of asthma; (c) significant reversibility of airway obstruction on spirometry (i.e. increase of at least 12% and 200 mL in baseline FEV_1 after administration of 400μg salbutamol)	Berlin Questionnaire and Epworth Sleepiness Scale	Subjects with a diagnosis of asthma were more likely to be obese (OR=1.50; CI: 1.12-2.04), but there was no association with snoring (OR=1.01; CI: 0.76-1.35), breathing pauses (OR=1.22; CI: 0.79-1.88), and excessive daytime sleepiness (OR=1.39; CI: 0.83-2.35).

5. Kim, M.Y. Annals of allergy, asthma and immunology 2013;110(4):253-257[215]	Cross-sectional	Total n= 217 (with asthma) Controls=0 Randomly recruited from tertiary care clinic	1. Airway reversibility with FEV_1>12% and 200mL post SABA or methacholine provocation causing 20% fall of 16mgml or less 2. Persistent symptoms 3. Physician diagnosis of asthma (need all 3)	Berlin Questionnaire	89/217 (41.0%) were high risk for OSA. The high OSA risk group had a lower ACT score than the low OSA risk group, but it was not statistically significant; 20.9±3.6 vs 21.5±3.3 (p=0.091).
6. Kumar, R et al. J Assoc Physicians India. 2013 Sep;61(9):615-8[218]	Cross-sectional	n= 328 with asthma Outpatients of Vallabhbhai Patel Chest Institute	GINA guidelines (reversibility of more than 12% or increase of 200 ml in FVC or FEV_1 after 200 micrograms of inhaled salbutamol)	Berlin Questionnaire (and ESS). Sub-group had home PSG	BQ was positive 60/328 (18.29%) of asthmatic patients. ESS was positive in 35/328 (10.67%) of asthma patients. (Only 17/60 patients had home PSG- 6 mild, 7 moderate, 4 severe OSA).
7. Tay, T.R et al. Respirology 2016;21(8):1384-1390[214]	Cross-sectional	n=90 asthma	Specialist physician diagnosis after review of investigations (76 had variable airflow obstruction)	Clinical symptoms and Berlin questionnaire[17] score ≥2 OR Previous positive PSG	OSA or high OSA risk in 35/90 (38.9%). No significant difference in number of exacerbations in OSA vs no OSA: 19 (48.7%) vs 16 (31.4%), p=0.094. Univariate analysis showed asthmatics with OSA to have worse ACT (p=0.034) and worse AQLQ (p=0.029) but not in multivariate analysis.
8. Teodorescu, M et al. J Allergy Clin Immunol Pract 2015;3(4):566-75[209]	Cross-sectional	Severe asthma(SA)=94 Non-severe asthma(NSA)= 161 Normal Controls(NC)= 146 (Substudy to the observational Severe Asthma Research Program –SARP II)	Episodic respiratory symptoms, reversible airflow obstruction (documentation of variability of FEV_1 and/or FVC by 12% and 200 cm^3 either spontaneously or after two puffs of inhaled albuterol), and/or a positive methacholine test	SA-SDQ	24/94 (26%) of severe asthma, 26/161 (16%) of non-severe asthma and 4/146 (3%) of controls had high OSA risk (p<0.0001). There was a significant difference for SA vs NC (p=0.04) and NSA vs NC (p=0.02) but not for SA vs NSA. (Patients with history of OSA or CPAP use excluded) High OSA risk related to worse AQLQ scores (p<0.0001), ED visits (p=0.001), hospital stays (p=0.005) and ITU admissions (p=0.01)

9. Teodorescu, M et al. Sleep Disord.2013;251567[211]	Cross-sectional	n=813 -154(19% elderly) -659 (81% young) n=140 (previous OSA diagnosis) Recruited from outpatient respiratory clinics	Diagnosed by specialist Asthma severity as per NAEPP guidelines	SA-SDQ	High OSA risk in 20/154 (13%) older patients compared to 45/659 (7%) younger patients (p=0.01). Therefore, overall prevalence 65/813 (8%) OSA was associated with nearly 7 times greater likelihood of severe asthma in an older individual (OR = 6.67). This relationship was of greater magnitude than in younger subjects (OR = 2.16).
10. Teodorescu, M et al. J Asthma. 2012;49(6):620–628[212]	Cross-sectional	n=828 subjects with asthma Allergy and Pulmonary subspecialty clinics	ATS guidelines. Asthma diagnosed and managed by academic specialist	SA-SDQ and review of medical notes for historical diagnosis.	136/828 (16%) had established OSA-75/136 (55%) of these were on CPAP and excluded from analysis. Of the remaining 752, 212 (28%) had high OSA risk High OSA risk associated with persistent daytime (odds ratio[OR]1.96[95% CI=1.31-2.94]) and night-time(1.97[1.32-2.94]) asthma symptoms
11. Teodorescu, M et al. Chest 2010;138(3):543–550[213]	Cross-sectional	n= 472 with asthma From tertiary care clinic visits	Asthma or allergy specialist at tertiary centre- using ATS guidelines. ACQ for control	SA-SDQ	Total of 511 asthmatics recruited, 63 had pre-existing OSA and the 39 receiving treatment were excluded 109/472 (23%) categorised as high risk for OSA. High OSA risk associated with 2.87x higher odds for having poorly controlled asthma (95%CI, 1.54-5.32, (p=0.0009) using ACQ full version.
12. Teodorescu, M et al. Chest. 2009;135(5):1125-32[210]	Cross-sectional	n=244 asthma Asthma patients from routine clinical visits to the asthma-airways centre	Physician diagnosis, after medical records review Asthma severity measured using: National Asthma Education and Prevention Program guidelines (NAEPP)	SA-SDQ	75/284 (26%) had known OSA diagnosis and 40/75 (53%) of these patients were receiving CPAP and excluded from further analysis. 97/244 (39.7%) had high OSA risk. Asthma severity step was predictive of OSA risk OR 1.60(95%CI 1.26-2.03), p<0.0001 High OSA risk associated with daytime (p<0.0001) and night-time (p=0.0006) asthma symptoms. There was a significant inverse relationship with FEV_1%pred (p=0.002).

13. Teodorescu, M et al. Sleep Medicine 2006;7(8):607–613[169]	Cross-sectional	n= 115 asthmatic patients (routine asthma follow-up visits)	Physician diagnosis Severity as per NAEPP guidelines	SA-SDQ	135 included, 40 (29.6%) had pre-existing OSA and 20/40(50%) were being treated for OSA and excluded. High OSA risk in 39/79 (49%) of women and 12/36 (33%) of men. ESS correlated with SA-SDQ ($p<0.0001$) and asthma severity step ($p=0.04$) (but did not correlate with asthma severity step in multiple regression model).

OSA: Obstructive sleep apnoea; AHI: Apnoea hypopnoea index; PSG: Polysomnography; CPAP: Continuous positive airway pressure; OCS: Oral corticosteroid; AQLQ: Asthma quality of life questionnaire; ACT: Asthma control test; ESS: Epworth sleepiness score; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; ATS: American Thoracic Society; GINA: Global initiative for asthma; NAEPP: National Asthma Education and Prevention Program guidelines

4 Results: Observational Studies

4.1 Cross-sectional study

The primary aim of this study was to determine the prevalence of OSA in severe asthma. Secondary aims included determining the impact of OSA on asthma-related clinical outcomes, identifying predictors of OSA in severe asthma and evaluating the impact and association of body fat composition and adipokines.

4.1.1 Recruitment of participants

208 unselected participants were recruited in total between January 2016 and April 2017. Following initial recruitment, 17 participants were subsequently excluded after failure to obtain a satisfactory sleep study, leaving a final study population of 191 participants. 27 of the 191 participants had a pre-existing diagnosis of OSA and were established on CPAP prior to recruitment. The remaining 164 participants underwent an overnight sleep study to diagnose or exclude OSA. The recruitment process is illustrated in figure 4.1.

4.1.2 Sleep studies

191 participants in total were included; 27 participants had pre-existing OSA and were already established on CPAP, 164 had an overnight sleep study to confirm or exclude OSA. 151 of the 164 participants had successful home overnight limited-channel sleep studies (LCSS); 1 had an overnight NOX at the same centre (BHH), 1 had a home LCSS at a different centre. 13 of the 164 participants in the untreated group required inpatient polysomnography, of which 8 were scored using cardio-respiratory monitoring and 5 were scored using full polysomnography.

For the remaining 27 participants in the CPAP treated group; for 25 participants established on CPAP the pre-CPAP sleep study was retrieved if possible, 2 participants from the CPAP group had a LCSS off CPAP. A summary of the participants with pre-existing OSA on CPAP is illustrated in table 4.2.

Participants were categorised by severity of OSA according to the apnoea hypopnoea index (AHI): No-OSA; AHI<5, Mild OSA; ≥5AHI<15, moderate OSA; ≥15AHI<30, severe OSA; AHI≥30. For 5 participants in the pre-exiting OSA group (treated with CPAP), the oxygen desaturation index (ODI) was available but an AHI was not. The oxygen desaturation index (ODI) was then used to categorise severity in these 5 participants, using the same groups.

4.1.3 Home limited-channel sleep studies (n=153)

Participants were included in the research study if an acceptable sleep study recoding was achieved. Duration of the recording and the percentage time of nasal flow and oxygen saturations is recorded in table 4.1.

The target for an acceptable LCSS was a recording of a minimum 4 hours duration, with a nasal flow recording and oxygen saturation recording of ≥80% the duration of the recording. Studies that did not meet these criteria were re-reviewed to determine if the sleep study was of sufficient quality to be included.

Table 4.1 Criteria for limited-channel sleep study (LCSS)

Parameter	**Mean (SD)** **Median (Q1, Q3)**
Test Duration (hours) n= 153	7.96 (1.61) 8.08 (6.98, 8.98)
% time nasal flow recorded (n=152)	95.03 (10.69) 100.00 (95.78, 100.00)
% time oxygen saturation recorded (n=152)	97.48 (6.41) 99.60 (98.90, 99.80)

The duration of time that the sleep study recorded is included, and the percentage of time nasal flow and oxygen saturations recorded.

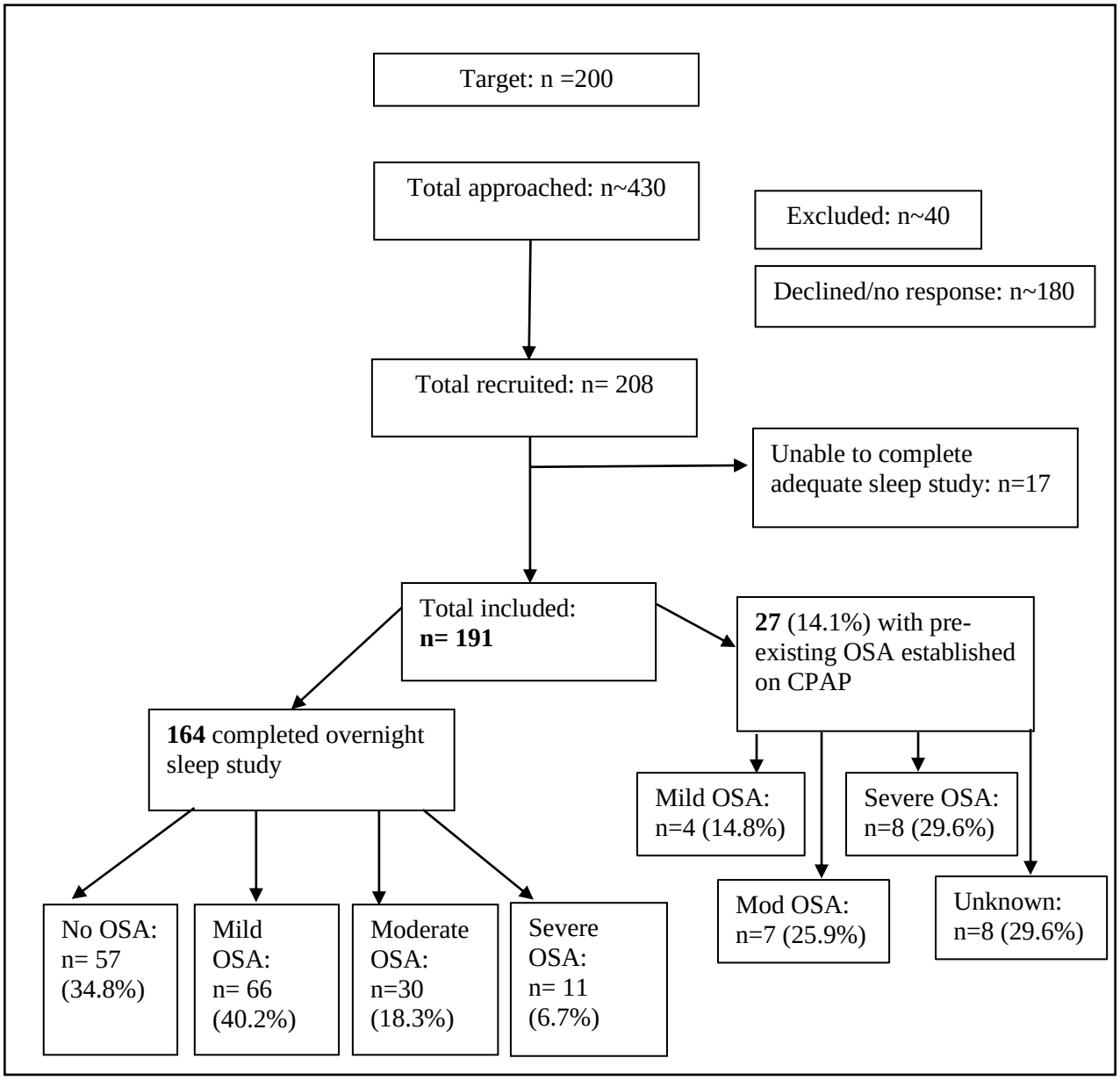


Figure 4.1 Recruitment process for the cross-sectional study

The aim was to recruit 200 participants. The patients approached to participate in clinic or by post were under current/recent review and lived within an appropriate distance to the centre. Those who did not meet the inclusion/exclusion criteria were excluded. 208 were initially recruited and underwent a limited-channel sleep study, but 17 were of an unacceptable quality and the participants declined further repeat study or full inpatient polysomnography so were subsequently excluded. 164 participants had a successful overnight sleep study and were categorised by severity of OSA using the apnoea hypopnoea index (AHI). 27 participants with pre-existing OSA on CPAP were recruited and severity of OSA was classified using either AHI or the oxygen desaturation index (ODI).

4.1.4 Pre-existing OSA, established on CPAP ("CPAP group")

A total of 27 participants had a pre-existing diagnosis of OSA and were established on CPAP. 2 participants chose to have a home limited-channel sleep study which was recorded off CPAP and reported in the results. The original pre-CPAP sleep study or dictated report was sought for the remaining 25 participants, and obtained in 19. A summary of the diagnostic methods and severity of OSA for these 27 participants is included in table 4.2. It was not always clear from the report which diagnostic sleep test the participant underwent, and this is recorded using the investigators best judgement and interpretation of the report. The severity of OSA for the CPAP group is as follows (n=27): 8 (29.6%) severe OSA, 7 (25.9%) (moderate OSA), 4 (14.8%) mild OSA, 8 (29.6%) unknown severity. Severity in the CPAP treated group is based on either the AHI or ODI.

Table 4.2 Summary of participants with pre-existing OSA on CPAP: Diagnosis and severity (n=27)

Participant No.	Type of recording	Year of Recording	ODI	AHI
1	LCSS	2015	-	17
2	LCSS	2014	-	15
3	-	-	-	84.6
4	-	2015	-	82
5	-	-	-	-
6	LCSS	2011	26.9	25.8
7	LCSS	2008	8.2	
8	LCSS	2009		40
9	LCSS	2013	15	13.4
10	LCSS	2013	-	18.4
11	LCSS	2006	21	
12	-	2015	-	-
13	LCSS	2015	-	38
14	LCSS	2015	-	12
15	-	-	-	-
16	Overnight oximetry (OO)	2009	44	-
17	-	-	-	-
18	OO	2014	-	22.27
19	-	-	-	-
20	-	-	-	-
21	-	-	-	-
22	-	-	-	-
23	OO	2011	-	48.6
24	unclear	2010	47.5	
25	OO	-	21	
26	LCSS (during study)	2016	23.1	13.1
27	LCSS (during study)	2016	45.8	45.4

The table illustrates the diagnostic method for the 27 participants with pre-existing OSA already established on CPAP. If the original report was unavailable, the investigators best judgement was used to determine the method of diagnosis based on the available information.

LCSS: limited-channel sleep study; OO: overnight oximetry; ODI: oxygen desaturation index; AHI: apnoea hypopnea index

4.1.5 The prevalence of OSA

The total population included 191 participants; 134 (70.2%) had OSA, 57 (29.8%) had OSA excluded. In the undiagnosed group (n=164); 66 (40.2%) had mild OSA, 30 (18.3%) had moderate OSA, 11 (6.7%) had severe OSA. In the CPAP treated group (n=27); 4 (14.8%) had mild OSA, 7 (25.9%) had moderate OSA, 8 (29.6%) had severe OSA and for 8 (29.6%) the severity was unknown.

The overall prevalence of OSA in the study population (n=191), including the participants with pre-existing OSA on CPAP is as follows: No-OSA; 57 (29.8%), mild OSA; 70 (36.7%), moderate OSA; 37 (19.4%), severe OSA 19 (9.9%) and unknown severity 8 (4.2%). This summary of the total population is illustrated in figure 4.2. A summary of the basic demographics of the population is included in table 4.3.

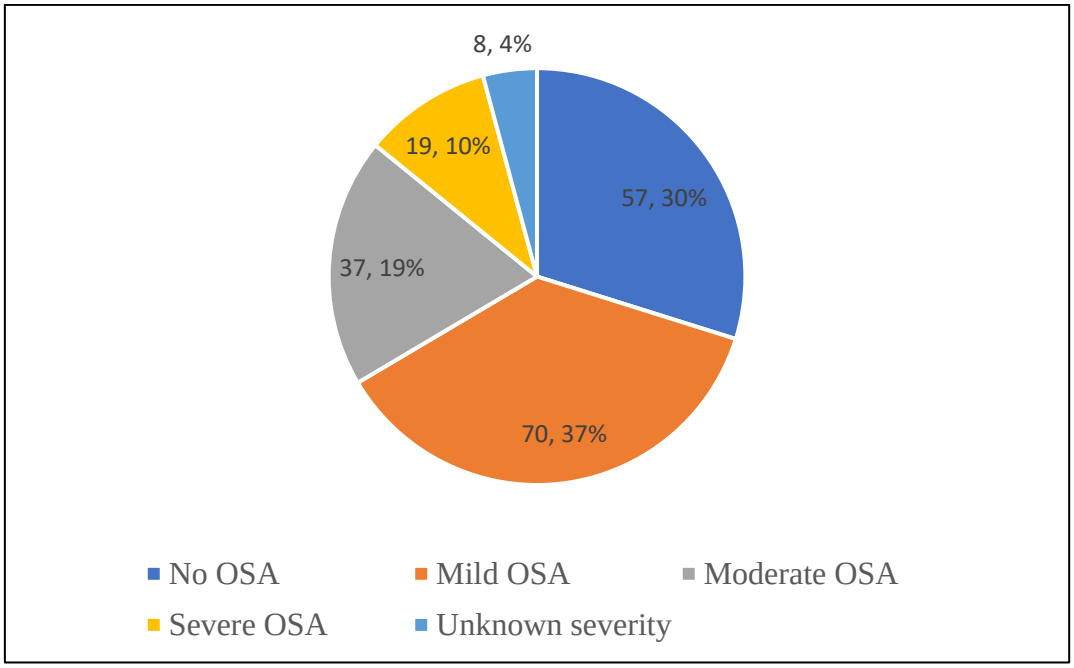


Figure 4.2 Prevalence and severity of OSA in the total population (n=191)

This figure illustrates the proportion of participants who had OSA excluded with a negative sleep study and the proportion with mild, moderate and severe OSA. The 27 participants with pre-existing OSA on CPAP are included in the total figures.

OSA: obstructive sleep apnoea; CPAP: Continuous Positive Airway Pressure

Table 4.3 Basic demographics of the total study population

Demographic	**Mean ± SD** **Median (Q1, Q3)**
Gender (n=191)	137 females (71%)
Age (years) (n=191)	48.7 ± 12.48
Body Mass Index (kg/m^2) (n=185)	32.1 (27.1, 36.8)
Ethnicity (n=187)	150 Caucasian (79%), 22 Asian (12%), 11 Afro-Caribbean (6%), 4 Other (2%)
Proportion meeting severe asthma criteria (n=187)	169 (88%)
ICS dose (micrograms/day, BDP) (n=186)	2000.0 (1600.0, 3000.0)
Maintenance OCS (n=186) (mg)	70 (37%) • 10 (5, 15) mg • 11 ± 7.8 mg
Smoking status (n=187)	125 Non-smokers (65%) 48 Ex-smokers (25%); Pack years, n=47; 10.0 (4.0, 18.0) 14 Current smokers (7%); Pack years, n=14; 16.5 (6.5, 30.0)
Smoking pack years (n=186) (years)	0.0 (0.0, 5.0) 4.8 ± 10.5
Current biological treatment (n=187)	35 (18%): 33 (94%) omalizumab, 1 (3%) benralizumab, 1 (3%) lebrikizumab
Triamcinolone depot injection (n=186)	2 (1%)
Antifungal treatment (n=185)	7 (4%)
Prophylactic antibiotics (n=185)	36 (19%)

The demographics of the total study population, proportion meeting severe asthma criteria and medication use are recorded in the table.

ICS: Inhaled corticosteroid; OCS: Oral corticosteroid, BDP: Beclomethasone dipropionate

4.1.6 General predictors of OSA in the untreated population

These results are displayed in table 4.5 and show that BMI ($p<0.001$), body fat % ($p=0.002$) and age ($p<0.001$) were significantly higher in the OSA (AHI≥5) group when compared to the no-OSA group (AHI<5). Gender was not significant in this analysis, but was significant in the multivariate analysis and this is likely due to the effect of gender differences in BMI (see table 4.4).

For further analysis, a comparison was also made between the moderate-severe OSA group (AHI≥15) and the no-OSA (AHI<5) group, using the same statistical approach. The results of this analysis are illustrated in table 4.6 and show that ESS ($p=0.003$), BMI ($p<0.001$) and body fat% ($p=0.008$) are significantly higher in the OSA (AHI≥15) group compared to the no-OSA group, whereas age now fails to reach statistical significance ($p=0.076$).

Table 4.4 Gender differences in BMI, total population

	BMI (kg/m^2)	**p value**
Female	n=132 32.3 (27.3, 37.3)	**0.028**
Male	n=53 30.2 (25.5, 34.8)	

The table illustrates the difference in BMI between male and female participants.

BMI: Body Mass Index

Table 4.5 Comparison of OSA (AHI≥5) versus no-OSA (AHI<5), untreated population

Variable	**No-OSA (AHI<5) (n=57)** **Mean ± SD** **Median (Q1, Q3)**	**OSA (AHI≥5) (n=107)** **Mean ± SD** **Median (Q1, Q3)**	**p value**
ESS	n=55 9.0 (5.0, 12.0)	n=105 10.0 (7.0, 14.5)	0.066
BMI (kg/m^2)	n=56 26.9 (24.0, 32.2)	n=103 32.3 (29.1, 36.8)	**<0.001**
Body fat %	n=54 36.7 (23.6, 39.9)	n=102 41.2 (30.9, 46.4)	**0.002**
Gender	n=57 46 female, 11 male	n=107 76 female, 31 male	0.194
Smoking pack years (years)	n=56 0.0 (0.0, 0.0)	n=104 0.0 (0.0, 3.8)	0.131
ICS dose (micrograms/day, BDP)	n=56 2000.0 (1000.0, 3000.0)	n=103 2000.0 (2000.0, 3000.0)	0.464
Maintenance OCS dose (mg)	n=23 (40.4%) 7.5 (5.0, 10.0)	n=34 (33%) 10.0 (5.0, 13.3)	0.281
Age (years)	n=57 41.8 ± 15.4	n=107 52.1 ± 10.9	**<0.001**

Basic demographics of the untreated population (those with pre-existing OSA on CPAP are excluded) are compared between the two groups; OSA(AHI≥5) and no-OSA(AHI<5).

ESS: Epworth sleepiness score; BMI: body mass index; ICS: inhaled corticosteroid; OCS: oral corticosteroid; BDP: beclomethasone dipropionate (equivalent dose); OSA: obstructive sleep apnoea; AHI; apnoea hypopnoea index

Table 4.6 Comparison of OSA (AHI≥15) versus no-OSA, untreated population

Variable	**No-OSA (AHI<5)** **Mean ± SD** **Median (Q1, Q3)**	**OSA (AHI≥15)** **Mean ± SD** **Median (Q1, Q3)**	**p value**
ESS	n=120 9.0 (5.0, 12.8)	n=40 11.0 (9.0, 15.8)	**0.003**
BMI	n=121 29.5 (25.7, 34.8)	n=38 34.8 (30.7, 37.0)	**<0.001**
Body fat %	n=117 37.5 (27.0, 44.0)	n=39 43.0 (34.2, 48.3)	**0.008**
Gender	n=123 94 female, 29 males	n=41 28 females, 13 males	0.219
Smoking pack years	n=119 0.0 (0.0, 1.0)	n=41 0.0 (0.0, 7.5)	0.050
ICS does (micrograms, BDP)	n=118 2000 (1900, 3000)	n=41 2000 (1550, 2650)	0.411
Maintenance OCS (yes/no)	n=118 43 (36.4%)	n=41 14 (34.1%)	0.790
Maintenance OCS dose (mg)	n=43 7.5 (5.0, 10.0)	n=14 10.0 (6.9, 20.0)	0.124
Age (years)	n=123 47.6 ± 13.8	n=41 51.5 ± 10.6	0.076

Basic demographics of the untreated population (those with pre-existing OSA on CPAP are excluded) are compared between the two groups; OSA(AHI≥15) and no-OSA(AHI<5) to determine any differences between moderate-severe OSA and no-OSA.

ESS: Epworth sleepiness score; BMI: body mass index; ICS: inhaled corticosteroid; OCS: oral corticosteroid; BDP: beclomethasone dipropionate (equivalent dose); OSA: obstructive sleep apnoea; AHI; apnoea hypopnoea index

4.1.7 Multivariate analysis for predictors of OSA(AHI≥5), untreated population

Binary logistic regression was performed using the Likelihood Ratio (L.R) approach. This was due to the number of variables selected and the relatively low number in the no-OSA group (n=52) when compared to the OSA group (n=97). 149 cases in total had sufficient data with regards to the variables selected, and were included in the analysis. Hosmer and Lemeshow test; chi-square 10.5, p=0.229. BMI (p<0.001), age (p<0.001) and male gender (p=0.034) were the only significant predictors of OSA (AHI≥5) in the untreated population (see table 4.7). The non-significant variables are displayed in table 4.8.

A ROC curve was produced (figure 4.3) with the significant variables and predicted probability from the binary logistic regression analysis. The areas under the ROC curve are displayed in table 4.9; BMI (p<0.001) and age (p<0.001) are again significant, whereas gender is not (p=0.324).

Table 4.7 Binary logistic regression: significant predictors of OSA (AHI≥5), untreated population

Variable	**S.E**	**p value**	**O.R**	**C.I**	
BMI	0.043	**<0.001**	1.219	1.121	1.325
Age	0.019	**<0.001**	1.082	1.043	1.123
Gender	0.519	**0.034**	0.332	0.120	0.918
Constant	1.731	0.000	0.000		

Table illustrating variables found to be significant at predicting OSA (AHI≥5).

BMI: body mass index; OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; S.E: standard error; O.R: odds ratio

Table 4.8 Binary logistic regression: non-significant variables for prediction of OSA (AHI≥5), untreated population

Variable	p value
ESS	0.151
Body fat %	0.632
Smoking pack years	0.791
ICS dose (BDP)	0.259
OCS dose (mg)	0.518
Overall statistic	0.607

Variables found to be non-significant in the binary logistic regression analysis are displayed in this table.

ESS: Epworth sleepiness score; ICS: inhaled corticosteroid; OCS: oral corticosteroid

Table 4.9 Areas under ROC curve: Predictors of OSA (AHI≥5), untreated population

Variable	Area	S.E	p value	C.I	
BMI	0.728	0.042	**<0.001**	0.645	0.811
Age	0.706	0.046	**<0.001**	0.616	0.795
Gender	0.547	0.047	0.324	0.455	0.645
Predicted probability	0.821	0.036	0.000	0.749	0.892

The variables found to be significant predictors of OSA (AHI≥5) in the binary logistic regression were used to generate a ROC curve and the areas under the curve are displayed in this table along with the predicted probability.

ROC: Receiver operating characteristic; BMI: body mass index; OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index

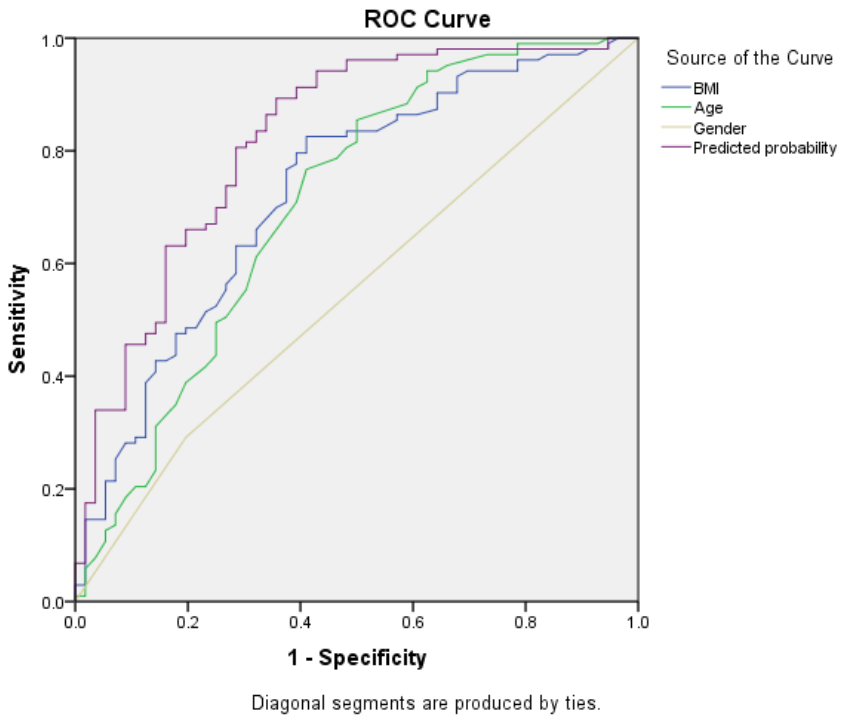


Figure 4.3 ROC curve: Significant variables from binary logistic regression for predictors of OSA (AHI≥5), untreated population

Variables found to be predictive of OSA and the predicted probability were used to generate this ROC curve

ROC: Receiver operating characteristic; BMI: body mass index; OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; ESS: Epworth sleepiness score

4.1.8 Multivariate analysis for predictors of moderate-severe OSA (AHI≥15), untreated population

The same method for binary logistic regression was used to determine predictors of moderate-severe OSA (AHI≥15). The same variables were entered into the model using the L.R approach. 149 cases in total had sufficient data regarding variables and were included in the model; 111 without moderate-severe OSA, and 38 with moderate-severe OSA. Hosmer and Lemeshow test; chi-square 4.566, p=0.803. Again, BMI (p<0.001) and gender (p=0.013) were

found to be predictive of OSA. However, for moderate-severe OSA, age was not found to be predictive (p=0.152), whereas the Epworth sleepiness score (ESS) was (p=0.044). The significant variables are displayed in table 4.10, and the non-significant variables in table 4.11.

Table 4.10 Binary logistic regression: significant predictors of moderate-severe OSA (AHI≥15) in the untreated population

Variable	**S.E**	**p value**	**O.R**	**C.I**	
BMI	0.033	**<0.001**	1.131	1.061	1.207
Gender	0.485	**0.013**	0.299	0.116	0.773
ESS	0.041	**0.044**	1.085	1.002	1.175
Constant	1.115	<0.001	0.006		

Significant predictors of moderate-severe OSA (AHI≥15) identified from the binary logistic regression are displayed in this table.

BMI: body mass index; OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; S.E: standard error; O.R: odds ratio; ESS: Epworth sleepiness score

Table 4.11 Binary logistic regression: non-significant variables for prediction of OSA (AHI≥15) in the untreated population

Variable	**p value**
Age	0.152
OCS dose (mg)	0.522
ICS dose (micrograms, BDP)	0.732
Smoking pack years	0.382
Body fat %	0.083
Overall statistics	0.347

The variables found not to be predictive of moderate-severe OSA are displayed in this table.

OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; OCS: oral corticosteroid; ICS: inhaled corticosteroid

A ROC curve for the significant predictors of moderate-severe OSA is illustrated in figure 4.4 for the variables found to be predictive in the binary logistic regression model. The areas under the curve were calculated and displayed in table 4.12. BMI ($p<0.001$) and Epworth sleepiness score ($p=0.006$) were significant, whereas gender was not ($p=0.332$).

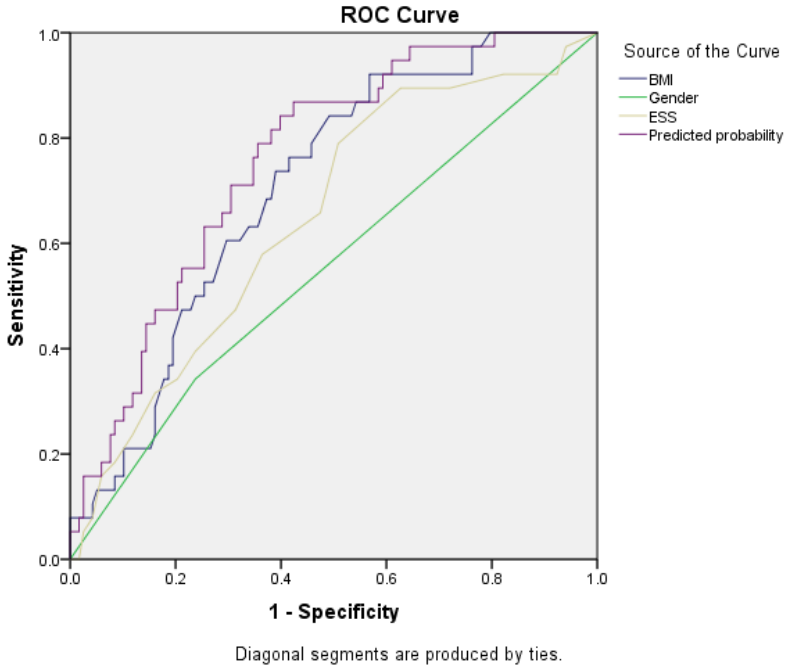


Figure 4.4 ROC curve: Significant predictors of OSA (AHI≥15), untreated population

The variables found to be significant for prediction of moderate-severe OSA from the binary logistic regression analysis were used to produce this ROC curve.

ROC: Receiver operating characteristic; BMI: body mass index; ESS: Epworth sleepiness score: OSA; obstructive sleep apnoea; AHI: apnoea hypopnoea index

Table 4.12 Areas under ROC curve; Predictors of moderate-severe OSA (AHI≥15), untreated population

Variable	Area	S.E	p value	C.I	
BMI	0.706	0.044	<**0.001**	0.620	0.793
Gender	0.552	0.055	0.332	0.445	0.660
ESS	0.649	0.050	**0.006**	0.552	0.747
Predicted probability	0.757	0.041	0.001	0.676	0.838

The areas under the ROC curve for variables found to be significant in the prediction of moderate-severe OSA are displayed in this table.

ROC: Receiver operating characteristic; BMI: body mass index; ESS: Epworth sleepiness score; OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index

4.1.9 Multivariate analysis for predictors of OSA (AHI≥5), total population

Binary logistic regression was again performed using a forward Likelihood Ratio approach with the same variables, however the total population including the participants with pre-existing OSA established on CPAP were included. All participants in the CPAP group were assumed to have an AHI≥5. There were 171 cases in total (due to available data with regards to variables). Hosmer and Lemeshow test; chi-square 8.538, p=0.383. Again, the only significant variables were BMI (p<0.001), male gender (p=0.026) and age (p<0.001). The results are displayed in tables 4.13 and 4.14.

Table 4.13 Significant variables, binary logistic regression, AHI≥5, total population

Variable	**S.E**	**p value**	**O.R**	**C.I**	
BMI	0.042	**<0.001**	1.235	1.138	1.342
Gender	0.506	**0.026**	0.324	0.120	0.872
Age	0.019	**<0.001**	1.083	1.044	1.124
Constant	1.729	<0.001	0.000		

The table illustrates significant predictors of OSA identified from the binary logistic regression. The whole population including those with pre-existing OSA on CPAP were included in this analysis.

BMI: body mass index; OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; CPAP: Continuous Positive Airway Pressure; S.E: standard error; O.R: odds ratio

Table 4.14 Non-significant variables, binary logistic regression, AHI≥5, total population

Variable	**p value**
ESS	0.134
Body fat %	0.946
Smoking pack years	0.716
ICS dose (micrograms, BDP)	0.384
OCS dose (mg)	0.485
Overall statistic	0.645

The variables found not to be predictive of OSA from the binary logistic regression analysis are included in this table. The whole population including those with pre-existing OSA on CPAP are included in this analysis.

OSA: Obstructive sleep apnoea; AHI: Apnoea hypopnoea index; OCS: Oral corticosteroid; ICS: Inhaled corticosteroid; CPAP: Continuous positive airway pressure

A ROC curve has been produced for the significant variables, and the predicted probability from the forward L.R logistic regression (figure 4.5). The area under the curve for each variable was calculated with BMI ($p<0.001$) and age ($p<0.001$) found to be significant, whereas gender ($p=0.163$) was not significant (table 4.15).

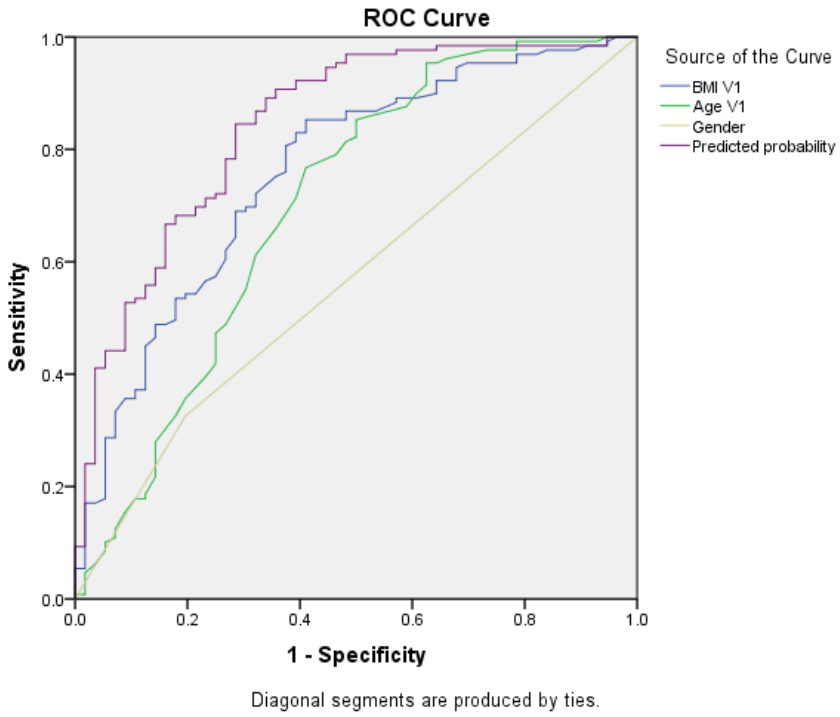


Figure 4.5 ROC curve: Significant predictors of OSA (AHI≥5), total population

Variables found to be significant for the prediction of OSA from the binary logistic regression model were used to produce a ROC curve. The total population including participants with pre-existing OSA already established on CPAP were included in this analysis.

ROC: Receiver operating characteristic; BMI: body mass index; ESS: Epworth sleepiness score; OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; CPAP: Continuous positive airway pressure

Table 4.15 Areas under ROC curve, significant predictors of OSA (AHI≥5), total population

Variable	**Area**	**S.E**	**p value**	**C.I**	
BMI	0.760	0.039	**<0.001**	0.684	0.836
Gender	0.565	0.045	0.163	0.477	0.652
Age (years)	0.701	0.046	**<0.001**	0.611	0.790
Predicted probability	0.843	0.032	<0.001	0.779	0.906

The variables found to be significant predictors of OSA (AHI≥5) in the binary logistic regression were used to generate a ROC curve and the areas under the curve are displayed in this table along with the predicted probability. The total population including the participants with pre-existing OSA on CPAP were included.

ROC: Receiver operating characteristic; BMI: body mass index; OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; CPAP: Continuous positive airway pressure

4.1.10 Multivariate analysis for predictors of moderate-severe OSA (AHI/ODI≥15), total population

This section of the analysis included the total population (including the CPAP treated group). Severity of OSA was based on AHI, apart from in 5 of the participants who had severity of OSA determined as per ODI. As previously discussed, the severity of OSA was not known for 8 of the participants with pre-existing OSA established on CPAP. All participants with an AHI (or ODI if AHI not available) ≥15 were included. The same variables as before were entered into the L.R binary logistic regression model. 49 participants with moderate-severe OSA, and 114 without moderate-severe OSA were included as had sufficient data with regards to the variables entered. Hosmer and Lemeshow test; chi-squared 6.897, p=0.548. In this analysis; BMI (p<0.001), male gender (p=0.001) and ESS (p=0.031) were all found to be significant predictors of moderate-severe OSA.

Table 4.16 Significant variables, binary logistic regression, AHI/ODI ≥15, total population

Variable	S.E	p value	O.R	C.I	
BMI	0.030	**<0.001**	1.141	1.076	1.209
Gender	0.442	**0.001**	0.222	0.093	0.528
ESS	0.038	**0.031**	1.085	1.007	1.168
Constant	1.038	0.000	0.006		

The table illustrates significant predictors of moderate-severe OSA identified from the binary logistic regression. The whole population including those with pre-existing OSA on CPAP were included in this analysis.

BMI: body mass index; ESS: Epworth sleepiness score; OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; CPAP: Continuous Positive Airway Pressure; S.E: standard error; O.R: odds ratio

Table 4.17 Non-significant variables, binary logistic regression, AHI/ODI ≥15, total population

Variable	p value
Age	0.163
OCS dose (mg)	0.600
ICS dose (micrograms, BDP)	0.662
Smoking pack years	0.420
Body fat %	0.491
Overall statistics	0.686

The variables found not to be predictive of moderate-severe OSA from the binary logistic regression analysis are included in this table. The whole population including those with pre-existing OSA on CPAP are included in this analysis.

OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; OCS: oral corticosteroid; ICS: inhaled corticosteroid; CPAP: continuous positive airway pressure

A ROC curve has been produced for the significant variables AHI/ODI≥15, and the predicted probabilities from the forward L.R logistic regression (figure 4.6). The area under the curve

for each variable was calculated with BMI (p<0.001) and Epworth sleepiness score (p=0.034) found to be significant, whereas gender was non-significant (p=0.217). These results are shown in table 4.18

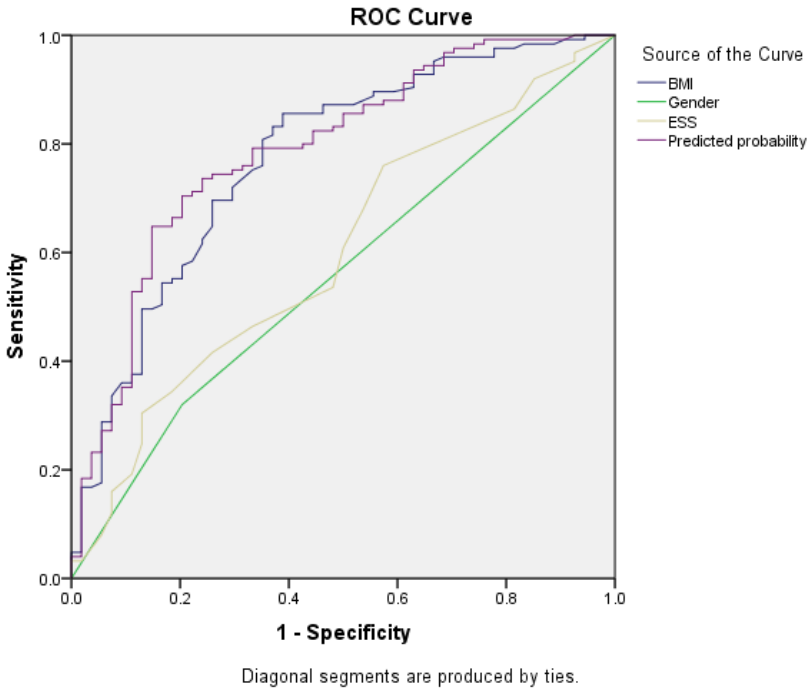


Figure 4.6 ROC curve: Significant predictors of moderate-severe OSA (AHI≥15), total population.

Variables found to be significant for the prediction of moderate-severe OSA from the binary logistic regression model were used to produce a ROC curve. The total population including participants with pre-existing OSA already established on CPAP were included in this analysis.

ROC: Receiver operating characteristic; BMI: body mass index; ESS: Epworth sleepiness score; OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; CPAP: Continuous positive airway pressure

Table 4.18 Areas under ROC curve, significant predictors of OSA (AHI≥15), total population

Variable	Area	S.E	p value	C.I	
BMI	0.774	0.039	**<0.001**	0.698	0.850
Gender	0.558	0.046	0.217	0.468	0.648
ESS	0.600	0.046	**0.034**	0.510	0.689
Predicted probability	0.789	0.037	<0.001	0.716	0.863

The variables found to be significant predictors of moderate-severe OSA in the binary logistic regression were used to generate a ROC curve and the areas under the curve are displayed in this table along with the predicted probability. The total population including the participants with pre-existing OSA on CPAP were included.

ROC: Receiver operating characteristic; BMI: body mass index; OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; CPAP: Continuous positive airway pressure

4.1.11 Asthma biomarkers in OSA

Peripheral eosinophilia and FENO in the OSA group (AHI≥5) were compared to the no OSA group (AHI<5) using a Mann-Whitney test with no significant difference identified between the two groups (table 4.19). There was also no significant difference when comparing participants without OSA to those with moderate-severe OSA (AHI≥15) (table 4.20)

Table 4.19 Asthma biomarkers in OSA (AHI≥5) vs no-OSA, untreated population

	OSA (AHI≥5) **Median (Q1, Q3)**	**No-OSA** **Median (Q1, Q3)**	**p value**
FENO (ppb)	n=98 29.0 (14.0, 50.0)	n=55 35.0 (12.0, 72.0)	0.158
Peripheral eosinophil count ($x10^9$/L)	n=56 0.22 (0.12, 0.43)	n=100 0.22 (0.11, 0.40)	0.809

Comparison of asthma biomarkers in participants with OSA and those without OSA.

FENO: Fractional exhaled nitric oxide; ppb: parts per billion; OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index

Table 4.20 Asthma biomarkers in moderate-severe OSA (AHI≥15) vs no-OSA, untreated population

	OSA (AHI≥15) Median (Q1, Q3)	**No-OSA Median (Q1, Q3)**	**p value**
FENO (ppb)	n=37 32.0 (13.0, 55.0)	n=116 30.0 (14.0, 58.0)	0.964
Peripheral eosinophil count ($x10^9$/L)	n=38 0.22 (0.11, 0.38)	n=118 0.22 (0.12, 0.43)	0.660

Comparison of asthma biomarkers in participants with moderate-severe OSA and those without OSA.

FENO: Fractional exhaled nitric oxide; ppb: parts per billion; OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index

4.1.12 Clinical outcomes in the untreated OSA group

4.1.13 Basic demographics

The basic demographics of this population are illustrated in table 4.21. Participant age ($p<0.001$), smoking ($p=0.033$) and BMI ($p<0.001$) increased with increasing severity of OSA. The number of participants requiring biological treatment reduced as severity of OSA increased ($p=0.002$). There was no correlation between increasing severity of OSA and inhaled corticosteroid dose (ICS) ($p=0.992$), maintenance prednisolone dose ($p=0.130$), fractional exhaled nitric oxide (FENO) ($p=0.303$), FEV_1% predicted (0.344), transfer factor (DLCO) ($p=0.813$) or total lung capacity (TLC) ($p=0.577$). There was a trend towards reducing FEV_1/FVC ratio with increasing severity of OSA, although this did not reach statistical significance ($p=0.055$)

Table 4.21 Basic demographics of the untreated population

Demographic	**No-OSA**	**Mild OSA**	**Moderate OSA**	**Severe OSA**	**p-value**
Age (n=164) (years)	n=57 41.8 ±14.4	n=66 52.5 ±11.2	n=30 51.8 ±11.3	n=11 50.6 ±8.9	**p<0.001**
Smoking (pack years) (n=160)	n=56 0 (0.0, 0.0)	n=63 0 (0.0, 3.0)	n=30 0 (0, 3.3)	n=11 2.0 (0.0, 12.0)	**p=0.033**
BMI (kg/m^2) (n=159)	n=56 26.9 (24.0, 32.2)	n=65 31.5 (28.0, 36.0)	n=28 34.8 (31.1, 36.8)	n=10 33.7 (29.6, 37.9)	**p<0.001**
ICS (micrograms, BDP), (n=159)	n=56 2000 (1000, 3000)	n=62 2000 (2000, 3188)	n=30 2000 (1500, 4000)	n=11 2000 (1600, 2500)	p=0.992
% requiring maintenance OCS (n=159)	n=56 23 (41%)	n=62 20 (32%)	n=30 11 (37%)	n=11 3 (27%)	p=0.394
Maintenance OCS dose (mg), (n=57)	n=23 7.5 (5.0, 10.)	n=20 8.5 (5.0, 11.5)	n=11 10.0 (5.0, 20.0)	n=3 10.0 (10.0, n/a)	p=0.130
FEV$_1$ % predicted (n=164)	n=57 72.0 (57.0, 96.0)	n=66 68.5	n=30 68.5 (52.5, 87.0)	n=11 72.5 (51.5, 89.3)	p= 0.344
FEV$_1$/FVC ratio (n=160)	n=54 71.0 (61.8, 81.3)	n=66 70.0 (58.8, 77.0)	n=30 66.0 (55.0, 76.5)	n=10 64.5 (51.8, 78.5)	p=0.055
FENO (ppb) (n=153)	n=55 35.0 (12.0, 72.0)	n=61 25.0 (15.0, 44.5)	n=29 33.0 (12.5, 57.5)	n=8 23.5 (13.0, 41.0)	p=0.303

DLCO (%predicted) (n=55)	n=19 81.0 (71.8, 94.0)	n=19 88.0 (85.4, 98.0)	n=12 86.5 (75.3, 99.0)	n=5 73.0 (59.0, 91.0)	p=0.813
TLC (% predicted) (n=48)	n=19 92.0 (86.0, 106.0)	n=16 97.0 (88.8, 110.8)	n=10 99.8 (86.0, 120.0)	n=3 90 (n/a	p=0.577
% requiring biological treatment (n=160)	n=56 17 (30.4%)	n=63 11 (17.5%)	n=30 3 (10%)	n=11 0	**p=0.002**

Participants were categorised into severity of OSA, and analysed for any trend with increasing severity of OSA.

OSA: obstructive sleep apnoea; BMI: body mass index; FENO: Fractional exhaled nitric oxide; ppb: parts per billion; DLCO: transfer factor; TLC: total lung capacity

4.1.14 Quality of life and health questionnaires, untreated population

There was a trend for worsening ACQ scores, (ACQ-7; p=0.032, ACQ-6; p=0.001, ACQ-5; p=0.001), AQLQ (p=0.043), HADS-depression (p=0.005), EQ-5D (p=0.017), EQ-VAS (p=0.014) with worsening severity of OSA. There was no significant trend detected for HADS-Anxiety (p=0.839) (see table 4.22).

Table 4.22 Health questionnaires, untreated population

Questionnaire	No-OSA	Mild OSA	Moderate OSA	Severe OSA	Jonckheere Terpstra
ACQ-7 (n=121)	n=44 2.68 ±1.42	n=47 2.96 ±1.23	n=25 3.21 ±1.34	n=5 4.06 ±0.91	**p=0.032**
ACQ- 6 (n= 137)	n=42 2.65 ±1.45	n=56 2.73 ±1.10	n=29 3.29 ±1.02	n=10 3.97 ±0.74	**p=0.001**
ACQ- 5 (n=137)	n=42 2.61 ±1.39	n=56 2.70 ±1.06	n=29 3.22 ±0.99	n=10 4.00 ±0.76	**p=0.001**
AQLQ (n=102)	n=34 4.20 (2.90, 5.43)	n=41 4.30 (3.30, 5.35)	n=21 4.00 (2.65, 4.70)	n=6 2.55 (2.20, 3.20)	**p=0.043**
HADS-A (n=105)	n=34 8.00 (4.00, 12.25)	n=43 7.00 (4.00, 10.00)	n=20 8.00 (6.25, 12.00)	n=8 9.00 (5.00, 14.00)	p=0.839
HADS-D (n=105)	n=34 4.50 (2.00, 10.00)	n=43 7.00 (4.00, 10.00)	n=20 8.50 (6.25, 12.75)	n=8 9.50 (5.75, 11.75)	**p=0.005**
EQ-5D (n=126)	n=35 8.0 (6.0, 10.0)	n=54 8.0 (6.0, 9.0)	n=27 9.0 (8.0, 11.0)	n=10 9.5 (8.0, 10.3)	**p=0.017**
EQ-VAS (n=126)	n=36 64.5 (41.3, 79.5)	n=54 60.0 (43.8, 78.5)	n=26 50.0 (40.0, 70.0)	n=10 42.5 (27.5, 53.8)	**p=0.014**
ESS (n=160)	n=55 9.0 (5.0, 12.0)	n=65 9.0 (5.5, 14.0)	n=30 11.0 (9.0, 16.0)	n=10 11.5 (7.3, 15.8)	**p=0.008**

Participants were categorised into severity of OSA and analysed for trend with regards to different health questionnaires

ACQ: Asthma control questionnaire; AQLQ: Asthma quality of life questionnaire; HADS: Hospital anxiety and depression scale; EQ-5D: Euroqol-5 dimensions; EQ-VAS: Euroqol-visual analogue scale; ESS: Epworth sleepiness scale

4.1.15 Asthma biomarkers

There was no significant trend for IgE (immunoglobulin E) or peripheral eosinophil count with increasing severity of OSA (table 4.23).

Table 4.23 Blood results; asthma biomarkers, untreated population

	No-OSA	**Mild OSA**	**Moderate OSA**	**Severe OSA**	**Jonckheere-Terpstra**
Peripheral eosinophil count ($x10^9$/L) (n=156)	n=56 0.22 (0.12, 0.42)	n=62 0.22 (0.12, 0.45)	n=29 0.24 (0.12, 0.45)	n=9 0.20 (0.09, 0.38)	p=0.698
IgE (kU/L) (n=133)	n=49 165.0 (66.0, 414.0)	n=53 117.0 (36.5, 463.0)	n=22 217.0 (40.3, 389.0)	n=9 126.0 (46.0, 362.0)	p=0.317

IgE: immunoglobulin E

4.1.16 Biochemical markers of the metabolic syndrome

There was no significant trend for serum cholesterol across the four groups, but there was an increase in triglycerides ($p<0.001$) with a reduction in HDL (high density lipoprotein) as severity of OSA ($p=0.023$) increased. HbA1c % (haemoglobin A1c) also increased as severity of OSA increased ($p=0.004$). There was no trend for LDL or TSH (thyroid stimulating hormone), see table 4.24.

Table 4.24 Biochemical markers of the metabolic syndrome, untreated population

	No-OSA	**Mild OSA**	**Moderate OSA**	**Severe OSA**	**Jonckheere-Terpstra**
Cholesterol (mmol/L) (n=134)	n=47 5.2 (4.6, 5.9)	n=51 5.7 (4.9, 6.3)	n=26 5.1 (4.7, 5.9)	n=10 5.5 (4.7, 6.2)	p=0.839
Triglycerides (mmol/L) (n=134)	n=47 1.1 (0.8, 1.8)	n=51 1.4 (1.0, 2.0)	n=26 1.9 (1.3, 2.4)	n=10 2.3 (1.5, 2.5)	**p<0.001**
HDL (mmol/L) (n=133)	n=4 1.6 (1.3, 1.9)	n=51 1.5 (1.2, 1.8)	n=25 1.4 (1.1, 1.7)	n=10 1.2 (1.00,1.85)	**p=0.023**
LDL (mmol/L) (n=130)	n=46 2.9 (2.7, 3.5)	n=51 3.3 (2.7, 3.9)	n=24 2.8 (2.3, 3.7)	n=9 3.4 (2.6, 3.9)	p=0.995
HbA1c (%) (n=133)	n=44 5.6 (5.2, 5.9)	n=53 5.8 (5.5, 6.0)	n=27 5.8 (5.4, 6.3)	n=9 6.1 (5.7, 7.2)	**p=0.004**
TSH (mU/L) (n=132)	n=44 1.3 (1.0, 1.6)	n=52 1.2 (0.7, 1.8)	n=26 1.2 (0.8, 1.6)	n=10 1.4 (0.7, 2.2)	p=0.562

The participants in the untreated group were categorised as per severity of OSA. Blood results were analysed to determine any trend in relation to markers of the metabolic syndrome.

HDL: High density lipoprotein; LDL: Low density lipoprotein; HbA1c: Haemoglobin A1c; TSH: Thyroid stimulating hormone

4.1.17 Asthma-related healthcare utilisation, untreated population

There was no significant trend for asthma-related healthcare utilisation across the four groups. This included annual OCS requiring exacerbations (p=0.979), annual GP (General Practitioner) visits (p=0.101), annual A&E (Accident and Emergency) visits (p=0.051) annual hospital admissions (p=0.480) and total High Dependency Unit (HDU)/Intensive Care Unit requirement (p=0.746). These results are illustrated in tables 4.25-4.29.

Table 4.25 Annual OCS requiring exacerbations

Annual OCS requiring exacerbations (n=160)	**No-OSA n=56**	**Mild OSA n=63**	**Moderate OSA n=30**	**Severe OSA n=11**	**Kendall's tau-b**
0-2	20 (35.7%)	26 (41.3%)	8 (26.7%)	3 (27.3%)	0.979
3-5	13 (23.2%)	23 (36.5%)	10 (33.3%)	4 (36.4%)	
6-10	11 (19.6%)	7 (11.1%)	9 (30%)	1 (9.1%)	
>10	12 (21.4%)	7 (11.1%)	3 (10%)	3 (27.3%)	

OSA: Obstructive sleep apnoea; OCS: oral corticosteroid

Table 4.26 Annual GP visits

Annual GP visits	**No-OSA n=56**	**Mild OSA n=63**	**Moderate OSA n=30**	**Severe OSA n=11**	**Kendall's tau-b**
0-4	39 (69.6%)	43 (68.3%)	15 (50%)	6 (54.5%)	0.101
5-9	8 (14.3%)	6 (20%)	6 (20%)	3 (27.3%)	
≥10	9 (16.1%)	9 (30%)	9 (30%)	2 (18.2%)	

OSA: obstructive sleep apnoea; GP: General Practitioner

Table 4.27 Annual A&E visits

Annual A&E visits	**No-OSA n=56**	**Mild OSA n=63**	**Moderate OSA n=30**	**Severe OSA n=11**	**Kendall's tau-b**
0-4	49 (87.5%)	58 (92.1%)	29 (96.7%)	11 (100%)	0.051
5-9	4 (7.1%)	2 (3.2%)	1 (3.3%)	0	
≥10	3 (5.4%)	3 (4.8%)	0	0	

OSA: Obstructive sleep apnoea; A&E: Accident and Emergency

Table 4.28 Annual hospital admissions

Annual hospital admissions	**No-OSA n=56**	**Mild OSA n=63**	**Moderate OSA n=30**	**Severe OSA n=11**	**Kendall's tau-b**
0-4	53 (94.6%)	59 (93.7%)	29 (96.7%)	11 (100%)	0.480
5-9	2 (3.6%)	3 (4.8%)	1 (3.3%)	0	
≥10	1 (1.8%)	1 (1.6%)	0	0	

OSA: Obstructive sleep apnoea

Table 4.29 Total HDU/ITU requirement

Total No. HDU/ITU admissions	**No-OSA n=55**	**Mild OSA n=63**	**Moderate OSA n=29**	**Severe OSA n=11**	**Kendall's tau-b**
None	39 (70.9%)	45 (71.4%)	16 (55.2%)	10 (90.9%)	0.746
Yes (≥1)	16 (29.1%)	18 (28.6%)	13 (44.8%)	1 (9.1%)	

HDU: High Dependency Unit; ITU: Intensive Care Unit

4.1.18 Metabolic syndrome co-morbidities, untreated population

The percentage of patients with hypercholesterolaemia (p=0.002), diabetes (p=0.010) and hypertension (p=<0.001) increased significantly with increasing severity of OSA. This was not the case for ischaemic heart disease (p=0.417), see table 4.30.

Table 4.30 Metabolic syndrome co-morbidities in the untreated population

	No-OSA	**Mild OSA**	**Moderate OSA**	**Severe OSA**	**Kendall's tau-b**
Hypercholesterolaemia (n=159)	n=56 9 (16.1%)	n=62 20 (32.3%)	n=30 13 (43.3%)	n=11 5 (45.5%)	**p=0.002**
Diabetes (n=159)	n=56 4 (7.1%)	n=62 9 (14.5%)	n=30 8 (26.7%)	n=11 3 (27.3%)	**p=0.010**
Ischaemic Heart Disease (n=158)	n=56 1 (1.8%)	n=61 1 (1.6%)	n=30 1 (3.3%)	n=11 1 (9.1%)	p=0.417
Hypertension (n=159)	n=56 7 (12.5%)	n=62 17 (27.4%)	n=30 11 (36.7%)	n=11 7 (63.6%)	**p<0.001**
Gastro-oesophageal reflux disease (n=156)	n=55 34 (61.8%)	n=61 37 (60.7%)	n=29 23 (79.3%)	n=11 9 (81.8%)	p=0.079

Participants were categorised according to severity of OSA. The proportion of self-reported metabolic syndrome co-morbidities (and gastro-oesophageal reflux disease) and the trend with increasing severity of OSA is displayed in the table.

OSA: Obstructive sleep apnoea

4.1.19 Clinical outcomes in participants with untreated moderate-severe OSA compared to those with pre-existing OSA established on CPAP treatment

Participants with untreated moderate-severe OSA (AHI≥15) were compared to the participants with pre-existing OSA established on CPAP treatment to determine if CPAP could potentially impact on clinical outcomes in in asthmatics with co-exiting OSA. The hypothesis being that those in the CPAP-treated group should have improved asthma-related clinical outcomes when compared to the untreated OSA group (moderate-severe). However, there was no significant difference in markers of asthma control, quality of life, healthcare utilisation, FEV_1% predicated and FEV_1/FVC between the two groups. (table 4.31 and table 4.32)

Table 4.31 Lung function and healthcare utilisation; the untreated moderate-severe OSA group versus the CPAP treated group

	Untreated mod-severe OSA n=41	**CPAP-treated group n=27**	**p-value**
FENO (ppb)	n=37 32.0 (13.0, 55.0)	n=24 18.5 (12.3, 33.5)	p=0.100
FEV_1%	n=41 69.0 (53.0, 87.5)	n=25 70.0 (56.5, 87.5)	p=0.968
FEV_1/FVC	n=40 66.0 (55.0, 76.5)	n=25 73.0 (66.5, 79.0)	p=0.072
OCS requiring exacerbations/12m	n=41 5.0 (1.5, 7.0)	n=24 3.5 (1.3, 7.5)	p=0.424
GP visits/12m	n=41 4.0 (0.0, 10.0)	n=24 2.5 (0.0, 4.0)	p=0.075

The participants with newly diagnosed untreated moderate-severe OSA (AHI≥15) were compared to those with pre-existing OSA already established on CPAP.

OSA: Obstructive sleep apnoea; CPAP; Continuous positive airway pressure; FENO; Fractional exhaled nitric oxide; ppb: parts per billion; FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity;

Table 4.32 Health associated questionnaires; the untreated moderate-severe OSA group versus the CPAP treated group

	Untreated mod-severe OSA n=41	**CPAP-treated group n=27**	**p-value**
ACQ-7	n=30 3.35 ±1.30	n=23 3.58 ±1.04	p=0.499
ACQ-6	n=39 3.47 ±0.99	n=18 3.18 ±1.24	p=0.348
ACQ-5	n=39 3.42 ±0.99	n=18 3.16±1.28	p=0.397
AQLQ	n=27 3.80 (2.30, 4.40)	n=15 3.90 (2.80, 4.30)	p=0.664
HADs-A	n=28 8.00 (5.25, 12.00)	n=15 10.00 (3.00, 13.00)	p=0.929
HADs-D	n=28 8.50 (6.25, 12.00)	n=15 7.00 (5.00, 10.00)	p=0.128
EQ-5D	n=37 9.00(8.00, 11.00)	n=16 8.50 (8.00, 11.75)	p=0.717
EQ-VAS	n=36 46.0 (32.5, 65.0)	n=16 49.0 (20.0, 67.5)	p=0.727

The participants with newly diagnosed untreated moderate-severe OSA (AHI≥15) were compared to those with pre-existing OSA already established on CPAP.

OSA: Obstructive sleep apnoea; CPAP; Continuous positive airway pressure; ACQ: Asthma control questionnaire; AQLQ: Asthma quality of life questionnaire; HADS: Hospital anxiety and depression scale; EQ-5D: Euroqol-5 dimensions; EQ-VAS: Euroqol-visual analogue scale; ESS: Epworth sleepiness scale

4.1.20 Body fat composition; bioelectrical impedance measurements

Bioelectrical impedance measurements are reported for 181 participants. The correlation between AHI (or ODI) and the bioelectrical impedance measurements is illustrated in table 4.33. All values showed a significant correlation with AHI/ODI.

Table 4.33 Correlation between AHI/ODI and bioelectrical impedance, total population

Bioelectrical impedance measurement	**r_s**	**p value (Spearmans's rho correlation coefficient)**
BMI (kg/m^2) (n=177)	0.481	**<0.001**
Body fat % (n=173)	0.252	**0.001**
Muscle mass (n=172)	0.345	**<0.001**
Total Body Water % (TBW%) (n=170)	-0.203	**0.008**
Visceral fat rating (n=171)	0.554	**<0.001**
Fat Free Mass (kg) (n=172)	0.345	**<0.001**

Body fat composition using bioelectrical impedance measurements were collected from all participants that consented. The correlation between severity of OSA and the body fat composition measurements was analysed (severity of OSA was determined using either the apnoea hypopnoea index or oxygen desaturation index).

To determine if any variables could have a relationship with AHI independent of BMI, the same analysis was performed between BMI and the bioelectrical impedance measurements table 4.34). A significant relationship between all variables and BMI was noted ($p<0.001$).

Table 4.34 Correlation between BMI and bioelectrical impedance, total population

Bioelectrical impedance measurement	**r_s**	**p value (Spearmans's rho correlation coefficient)**
Body fat % (n=181)	0.734	**<0.001**
Muscle mass (n=180)	0.409	**<0.001**
Total Body Water % (TBW%) (n=178)	-0.667	**<0.001**
Visceral fat rating (n=179)	0.731	**<0.001**
FFM (kg) (n=180)	0.409	**<0.001**

The table illustrates the correlation between body fat composition measurements (obtained by biolectircal impedance measures) and BMI

FFM: Fat free mass; BMI; Body mass index

4.1.21 Body fat composition; whole body DEXA scan measurements

A subgroup of 59 participants underwent detailed body composition measurements using whole body composition DEXA (Dual-energy X-ray absorptiometry) scans. In total; 19 (32%) had no-OSA (AHI≤5) and 40 (68%) had OSA (AHI≥5). The basic demographics of these 59 participants, including severity of OSA is illustrated in table 4.35.

A comparison of the DEXA body composition measurements in the OSA group (AHI≥5) versus the no-OSA group are recorded in table 4.36. The OSA group were significantly older (p=0.018) but there were no other significant differences in the basic demographics between the two groups.

Table 4.35 Demographics of DEXA population (n=59)

Demographic	**Mean ± SD or Median (Q1, Q3)**
Age (years) (n=59)	50.5 ±12.6
Gender (n=59)	42 female, 17 males
Smoking (y/n) (n=58)	Non-smokers: 38 (64.4%), Ex-smokers:16 (27.1%) Current smokers: 4 (6.8%)
Smoking (pack years) (n=58)	0.0 (0.0, 6.5)
ICS dose (micrograms/day, BDP) (n=58)	2000.0 (1900.0, 2575.0)
Maintenance OCS (mg/day) (n=57)	17 (30%) 10.0 (5.0, 18.5) mg
FEV_1 % predicted (n=59)	74.0 (57.0, 96.0)
FENO (ppb) (n=56)	28.5 (14.0, 52.8)
OSA (severity) (n=59)	None 19 (32.2%), Mild 23 (39%), Mod 6 (10.2%), Severe 3 (5.1%), CPAP 8 (13.6%)

The demographics of the total population that underwent body composition DEXA scan measurements are included in the table.

OSA: Obstructive sleep apnoea; DEXA: Dual-energy X-ray absorptiometry; FEV_1: Forced expiratory volume in 1 second; FENO: Fractional exhaled nitric oxide; ppb: parts per billion

Table 4.36 Body composition DEXA demographics, OSA (AHI≥5) vs no-OSA

Demographic	**No-OSA n=19**	**OSA (AHI≥5) n=40**	**p-value**
Age (years) (n=59)	n=19 43.5 ± 16.6	n=40 53.8 ± 8.6	**0.018**
Gender (n=59)	n=19 15 females, 4 males	n=40 27 females, 13 males	0.339
Smoking (pack years) (n=58)	n=19 0.0 (0.0, 6.0)	n=39 0.0 (0.0, 10.0)	0.417
ICS dose (BDP) (n=58)	n=19 2000 (1000, 2000)	n=39 2000 (2000, 3000)	0.101
% requiring maintenance OCS	n=19 6 (32%)	n=38 11 (29%)	0.839
Maintenance OCS dose (mg) (n=17)	n=6 8.5 (5.0, 12.5)	n=11 10.0 (5.0, 20.0)	0.591
FEV_1 % pred (n=59)	n=16 92.0 (70.7, 99.3)	n=40 89.0 (71.3, 99.0)	0.745
FENO (ppb) (n=56)	n=19 35.0 (12.0, 72.0)	n=37 23.0 (14.0, 43.0)	0.148

Participants who underwent DEXA scan measurements were categorised as having OSA (AHI≥5) or had OSA excluded (AHI<5). The basic demographics of the two groups were compared in the above table.

OSA: Obstructive sleep apnoea; DEXA: Dual-energy X-ray absorptiometry; FEV_1: Forced expiratory volume in 1 second; FENO: Fractional exhaled nitric oxide; ppb: parts per billion

A summary of the DEXA body composition measurements are recorded in table 4.37. The DEXA body composition measurements and BMI are also compared in the OSA (AHI≥5) group to the no-OSA group. BMI (p<0.001), android/gynoid ratio (p=0.006), FMI (p=0.003), %fat trunk/%fat legs (p=0.012) and trunk/limb fat mass ratio (p=0.016) were all significantly higher in the OSA group (AHI≥5) when compared to the no-OSA group. There was no significant difference in body fat % between the two groups (p=0.085), figure 4.8. The results of the other body composition measurements are illustrated in figures 4.9-4.12.

Table 4.37 DEXA measurements (n=59)

Measurement	**Total Population (n=59)** **Median (Q1, Q3)**
BMI (kg/m^2) (n=58)	30.2 (26.3, 35.3)
Fat mass (g) (n=59)	30558.1 (24779.9, 37768.9)
Lean mass (n=59)	50500.2 (42777.3, 58507.6)
Total mass (n=59)	82803.0 (70594.3, 96800.8)
Body Fat % (n=59)	37.5 (31.3, 41.8)
Android Fat% **(n=58)**	37.7 (31.6, 42.6)
Android/Gynoid ratio (n=58)	0.99 (0.86, 1.11)
Fat Mass Index (Fat mass/height^2) **(n=53)**	11.4 (8.4, 14.5)
% fat trunk/%fat legs ratio (n=52)	0.92 (0.82, 1.06)
Trunk/limb fat mass ratio (n=52)	1.09 (0.91, 1.34)

DEXA: Dual-energy X-ray absorptiometry

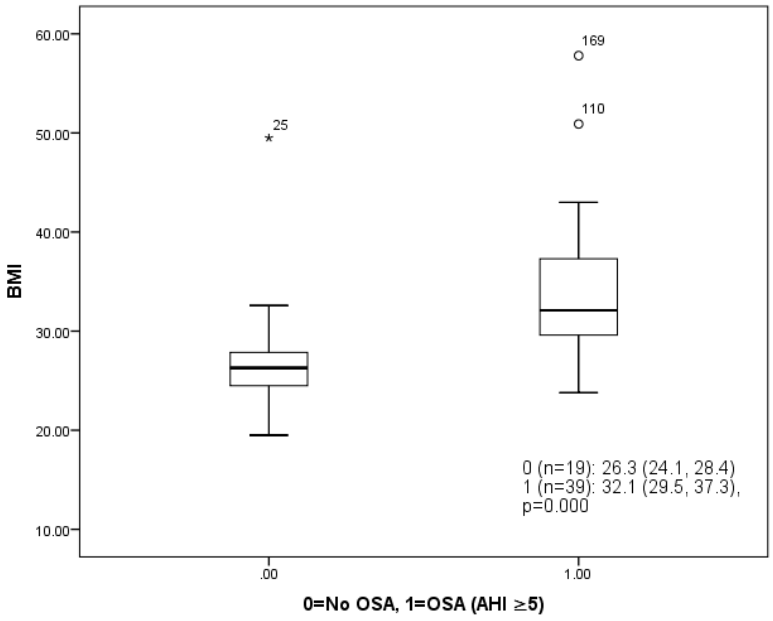


Figure 4.7 Body mass index (BMI) in the OSA group (AHI≥5) vs no-OSA group (DEXA population)

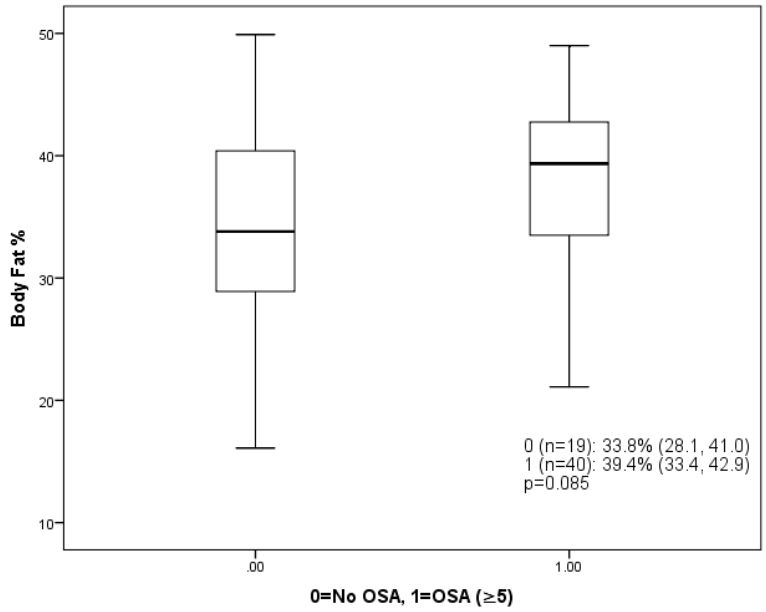


Figure 4.8 Body fat% in the OSA group (AHI≥5) vs the no-OSA group (DEXA population)

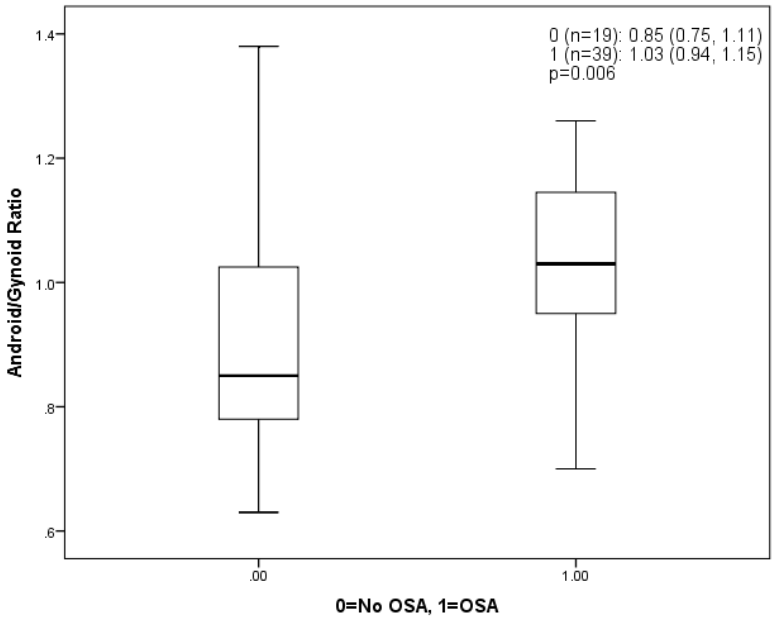


Figure 4.9 Android/Gynoid ratio in the OSA group (AHI≥5) vs the no-OSA group (DEXA population),

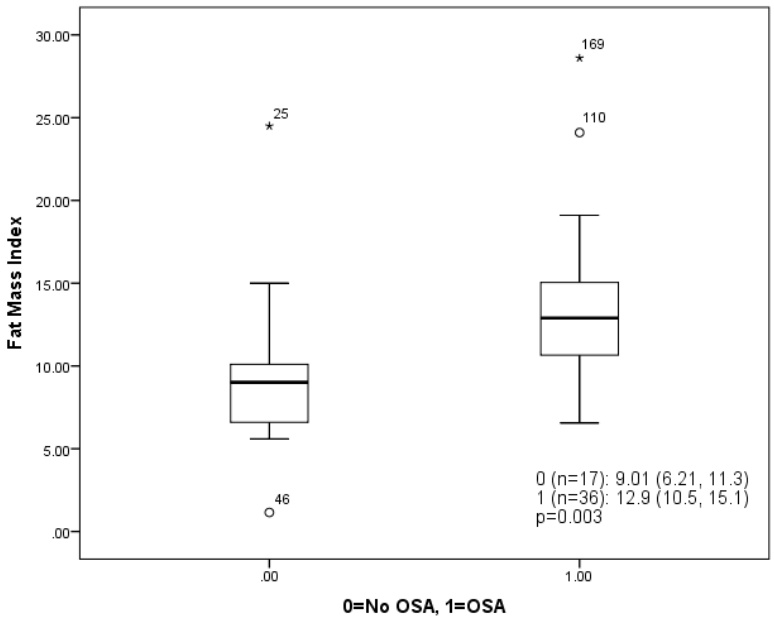


Figure 4.10 Fat mass index (fat mass/height^2) in the OSA (AHI≥5) group versus the no-OSA group (DEXA population)

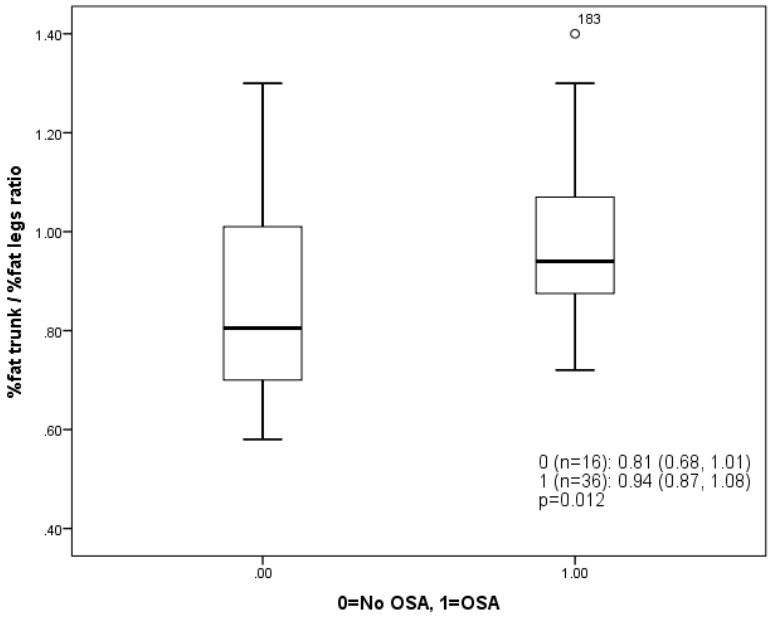


Figure 4.11 %fat trunk/%fat legs ratio in the OSA (AHI≥5) group versus the no-OSA group (DEXA population)

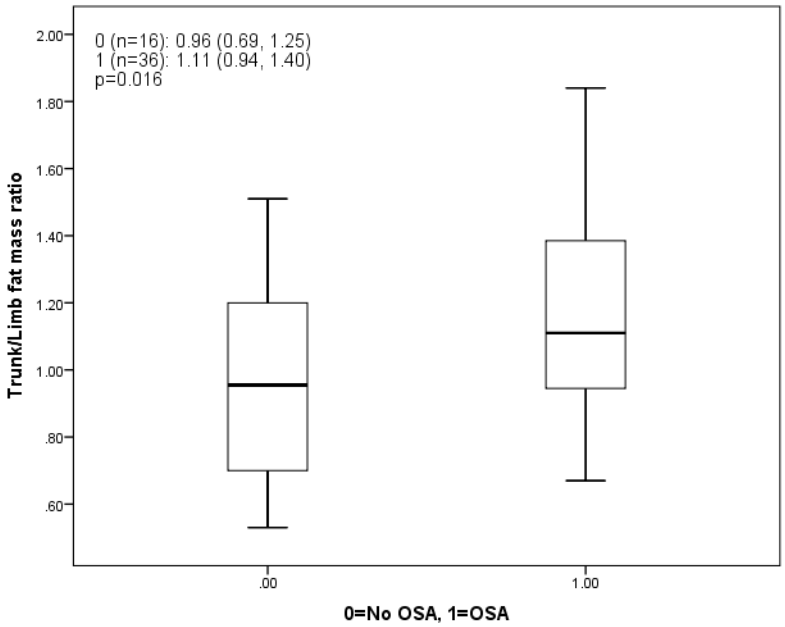


Figure 4.12 Trunk/limb fat mass ratio in the OSA (AHI≥5) versus the no-OSA group (DEXA population)

The correlation between body composition measurements from the DEXA scans and severity of OSA is reported in table 4.38 using Spearman's rho correlation co-efficient.

Table 4.38 Correlation between AHI/ODI and DEXA body composition measurements

Measurement	**r_s value**	**Spearman's rho correlation coefficient**
Body fat % (n=56)	0.244	**0.070**
Android fat % (n=55)	0.414	**0.002**
Gynoid fat % (n=55)	0.037	0.790
Android/gynoid ratio (n=55)	0.402	**0.002**
Fat Mass Index (n=51)	0.541	**<0.001**
%fat trunk/%fat legs (n=49)	0.387	**0.006**

The correlation between body composition measurements (taken using DEXA scans) and severity of OSA (measured using AHI or ODI) is displayed in this table.

OSA: Obstructive sleep apnoea; DEXA: Dual-energy X-ray absorptiometry; AHI: Apnoea hypopnoea index; ODI: Oxygen desaturation index

The DEXA group was then divided by gender, and the correlation between body fat composition measurement and severity of OSA was analysed using Spearman's rho correlation coefficient and summarised in table 4.39. After adjusting for gender; body fat percentage (r_s=0.431, p=0.006), android fat % (r_s=0.501, p=0.001) and android/gynoid ratio (r_s=0.558, p<0.001), fat mass index (r_s=0.601, p<0.001), %fat trunk/%fat limb ratio (r_s=0.555, p<0.001) and trunk/limb fat mass ratio (r_s=0.498, p=0.002) all increased with increasing severity of OSA in females. Whereas, gynoid fat % showed no correlation (p=0.602). In

males there was no significant correlation noted with any of the body composition variables apart from fat mass index (p=0.028).

To determine if the positive correlation seen between increasing severity of OSA and body fat composition variables could be related to BMI, the same correlation using Spearman's rho correlation was conducted between BMI and body composition variables corrected for gender (table 4.40). In males, android/gynoid ratio (p=0.905), %fat trunk/%fat limb ratio (p=0.317) and trunk/limb fat mass ratio (p=0.195) showed a non-significant correlation. All other body composition variables showed a positive correlation with increasing BMI.

Table 4.39 DEXA body composition values- Correlation with AHI/ODI, as per gender

Measurement	**Females n=42**			**Males n=17**		
	n	r_s	p	n	r_s	p
Body fat %	40	0.431	**0.006**	16	0.253	0.345
Android fat %	40	0.501	**0.001**	15	0.363	0.184
Gynoid fat %	40	0.085	0.602	15	0.257	0.355
Android/gynoid ratio	40	0.558	**<0.001**	15	0.034	0.904
Fat Mass Index	39	0.601	**<0.001**	12	0.629	**0.028**
%fat trunk/% fat limbs	36	0.555	**<0.001**	13	0.157	0.608
Trunk/Limb fat mass ratio	36	0.498	**0.002**	13	0.249	0.413

Participants who underwent whole body composition DEXA scan were divided into male and female. The correlation between severity of OSA (using AHI/ODI) and body composition measurements were analysed to determine if the effect was different between gender.

OSA: Obstructive sleep apnoea; DEXA: Dual-energy X-ray absorptiometry; AHI: Apnoea hypopnoea index; ODI: Oxygen desaturation index

Table 4.40 DEXA body composition values; Correlation with BMI, as per gender

Measurement	**Females n=42**			**Males n=17**		
	n	r_s	p	n	r_s	p
Body fat %	41	0.652	**<0.001**	17	0.784	**<0.001**
Android fat %	41	0.607	**<0.001**	16	0.637	**0.008**
Gynoid fat %	41	0.325	**0.038**	16	0.632	**0.009**
Android/gynoid ratio	41	0.485	**0.001**	16	0.032	0.905
Fat Mass Index	39	0.869	**<0.001**	13	0.940	**<0.001**
%fat trunk/% fat limbs	37	0.499	**0.002**	14	0.289	0.317
Trunk/Limb fat mass ratio	37	0.415	**0.011**	14	0.369	0.195

Participants who underwent whole body composition DEXA scan were divided into male and female. The correlation between body composition measurements and BMI were analysed to determine if the positive correlation previously seen between severity of OSA and DEXA body composition measurements could be related to BMI.

OSA: Obstructive sleep apnoea; DEXA: Dual-energy X-ray absorptiometry; BMI: Body mass index

4.1.22 Adipokine results, total population

In total; 104 adiponectin, 38 IL-6 and 35 leptin results have been reported. A summary of these results is reported in table 4.41 and the distribution of the results for each adipokine is illustrated in figures 4.13-4.15.

Table 4.41 Summary of adiponectin concentrations, total population

Adipokine	**Total**	**Median (Q1, Q3)** **Mean ± SD**
Adiponectin (µg/ml)	n=104	2.7 (0.9, 4.9) 3.1 ± 2.6
IL-6 (picograms/ml)	n=38	120.8 (24.3, 614.6) 327.3 ± 370.8
Leptin (nanograms/ml)	n=35	18.9 (9.7, 33.3) 26.1 ± 25.8

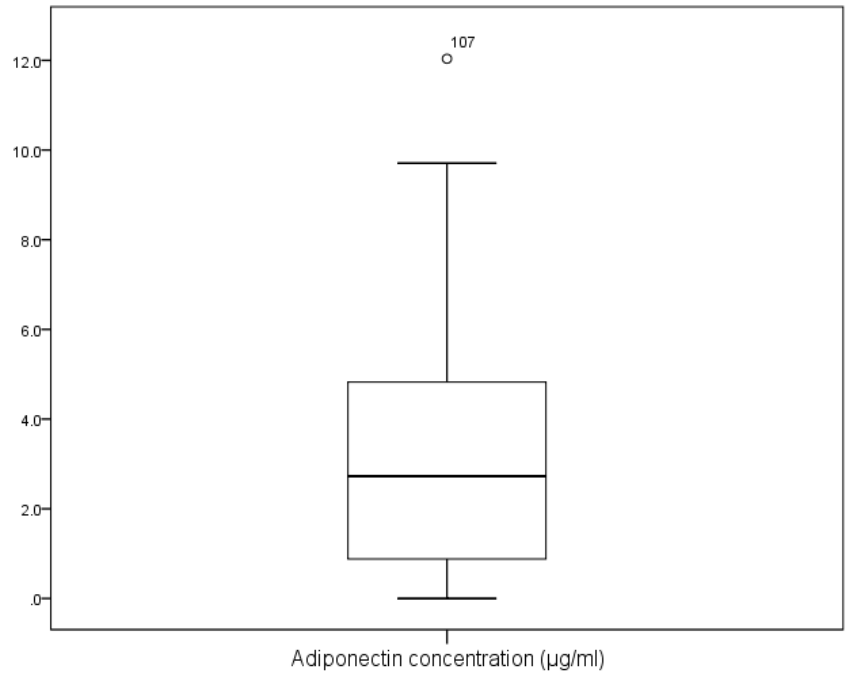


Figure 4.13 Distribution of adiponectin concentration, n=104

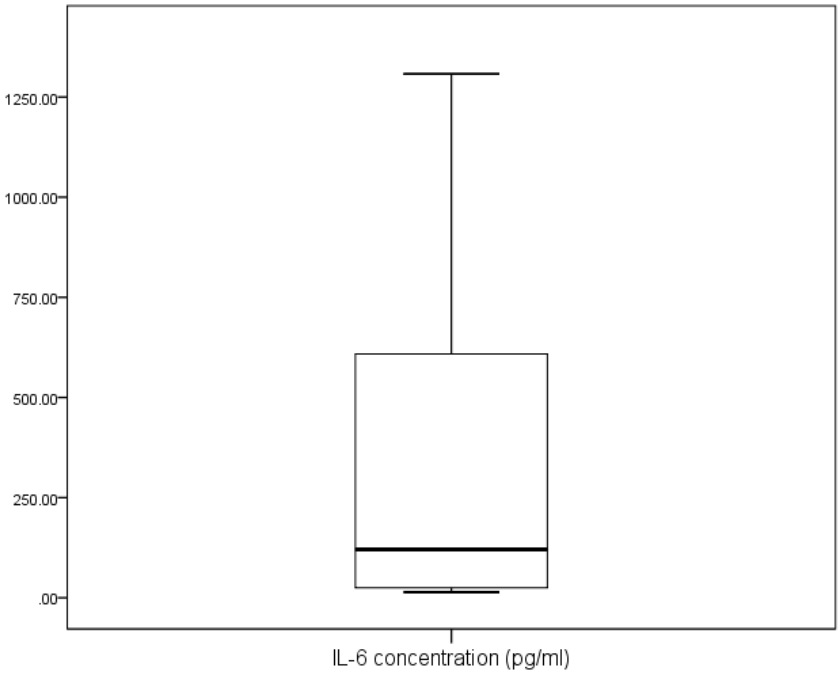


Figure 4.14 Distribution of IL-6 concentration, n=38

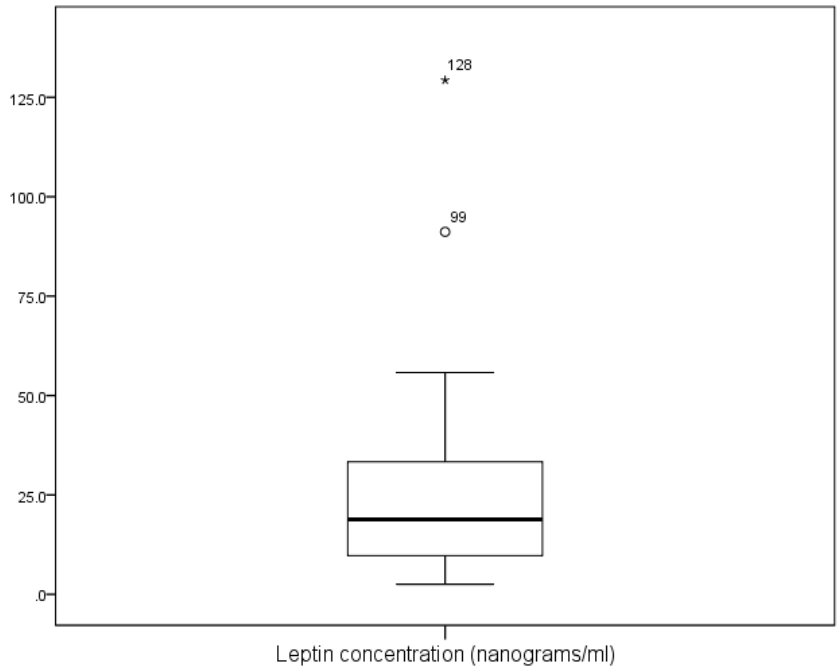


Figure 4.15 Distribution of leptin concentration, n=35

The concentration of leptin was found to be higher in the OSA group (AHI≥5) when compared to the no-OSA group, and this trend reached statistical significance (p=0.024). No significant trend was noted for adiponectin or IL-6. These results are shown in table 4.42 and figure 4.16.

The correlation between leptin concentration and increasing severity of OSA was further examined using Spearman's rho correlation to analyse AHI and the different adipokine concentrations. The trend for all three, including leptin failed to reach statistical significance although the correlation between leptin and AHI was stronger than the other adipokines (see table 4.43).

Table 4.42 Comparison of adipokine concentrations in the OSA group (AHI≥5) versus no-OSA group (AHI<5)

Adipokine	**No-OSA** **Median (Q1, Q3)** **Mean ± SD**	**OSA (AHI≥5)** **Median (Q1, Q3)** **Mean ± SD**	**p value**
Adiponectin (µg/ml) **(n=104)**	n=35 3.5 (0.9, 4.7) 3.4 ± 2.4	n=69 2.5 (0.5, 5.0) 3.0 ± 2.8	0.224
IL-6 (pg/ml) **(n= 38)**	n=16 123.7 (26.4, 523.9) 301.1 ± 343.9	n=22 120.8 (22.3, 648.8) 346.4 ± 396.1	0.872
Leptin (ng/ml) **(n=35)**	n=13 10.8 (8.6, 18.2) 15.2 ± 13.6	n=22 24.1 (15.1, 40.5) 32.6 ± 29.2	**0.024**

Participants with a successful adipokine measurement were split into either the OSA group (AHI/ODI≥5) or the no-OSA group. The two groups were then compared to look for any significant differences in adipokine concentration.

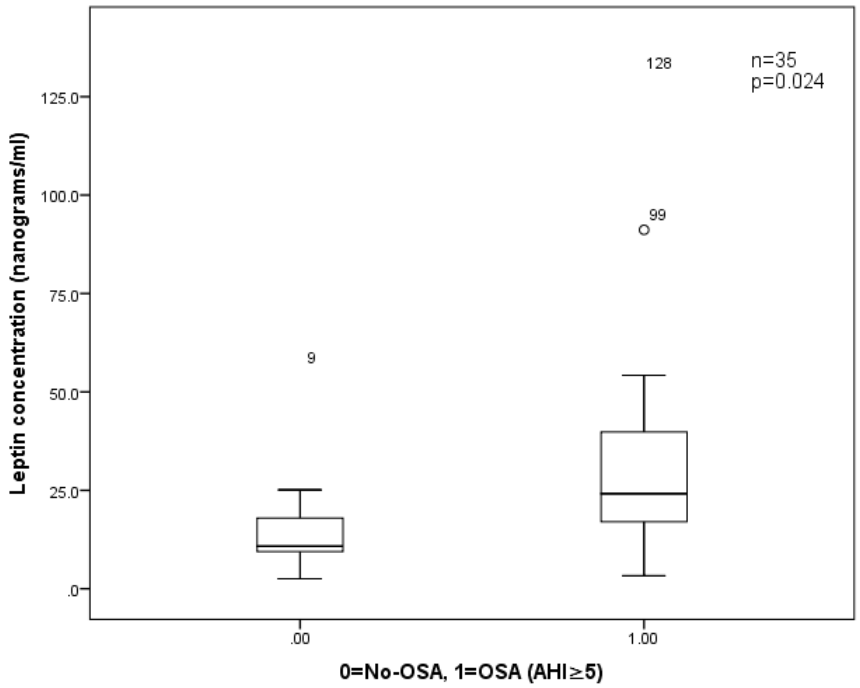


Figure 4.16 Leptin concentration, OSA group (AHI≥5) versus no-OSA group (AHI<5)

Table 4.43 The correlation between adiponectin concentration and severity of OSA

Adipokine	**n**	**r_s**	**p**
Adiponectin (µg/ml)	102	-0.185	0.062
IL-6 (pg/ml)	38	-0.005	0.977
Leptin (ng/ml)	35	0.298	0.083

The correlation between severity of OSA (measured using AHI or ODI) and adipokine concentration was analysed using Spearman's rho correlation coefficient.

To determine if the effect seen with leptin and OSA was related to BMI, the adipokines were compared with increasing severity of BMI (see table 4.44). The concentration of leptin was found to significantly increase with BMI (p=0.001).

Table 4.44 Adipokine concentration and BMI

Adipokine	**BMI<25** **Mean ± SD** **Median (Q1, Q3)**	**≥25 BMI <30** **Mean ± SD** **Median (Q1, Q3)**	**BMI ≥ 30** **Mean ± SD** **Median (Q1, Q3)**	**p value Jonckheere-Terpstra**
Adiponectin (µg/ml)	n=17 3.4 ± 3.1 2.7 (0.8, 4.7)	n= 28 3.7 ± 2.9 3.7 (1.0, 5.6)	n=55 2.7 ± 2.3 2.4 (0.5, 4.3)	0.172
IL-6 (pg/ml)	n=8 364.5 ± 527.5	n=13 382.7 ± 331.0	n=16 283.0 ± 331.6	0.735
Leptin (ng/ml)	n=10 12.3 ± 7.1 10.1 (7.0, 18.0)	n=8 26.4 ± 41.8 11.5 (9.6, 19.5)	n=16 32.8 ± 20.6 31.6 (19.5, 41.8)	**0.001**

Participants were categorised into ordered groups according to severity of BMI. Analysis was performed to determine any trend in adipokine concentration with increasing BMI.

IL-6: interleukin-6; BMI: Body mass index

4.2 Prospective case-control study

4.2.1 Basic demographics of population

86 of the 191 participants in total from the cross-sectional study were recruited to the prospective case-control study. All participants in the cross-sectional study were asked to participate, and 86 gave consent and attended for the prospective visit 12 months later (V2).

Mean duration between the baseline visit (V1, for the cross-sectional study) and visit 2 was 12.4 ± 1.8 months, median 12.4 months (11.7, 13.4). The shortest time duration between visits was 5.1 months, the longest duration was 16.3 months. The flow of recruitment is illustrated in figure 4.17.

The basic demographics of the population included in the prospective case-control study are displayed in table 4.45.

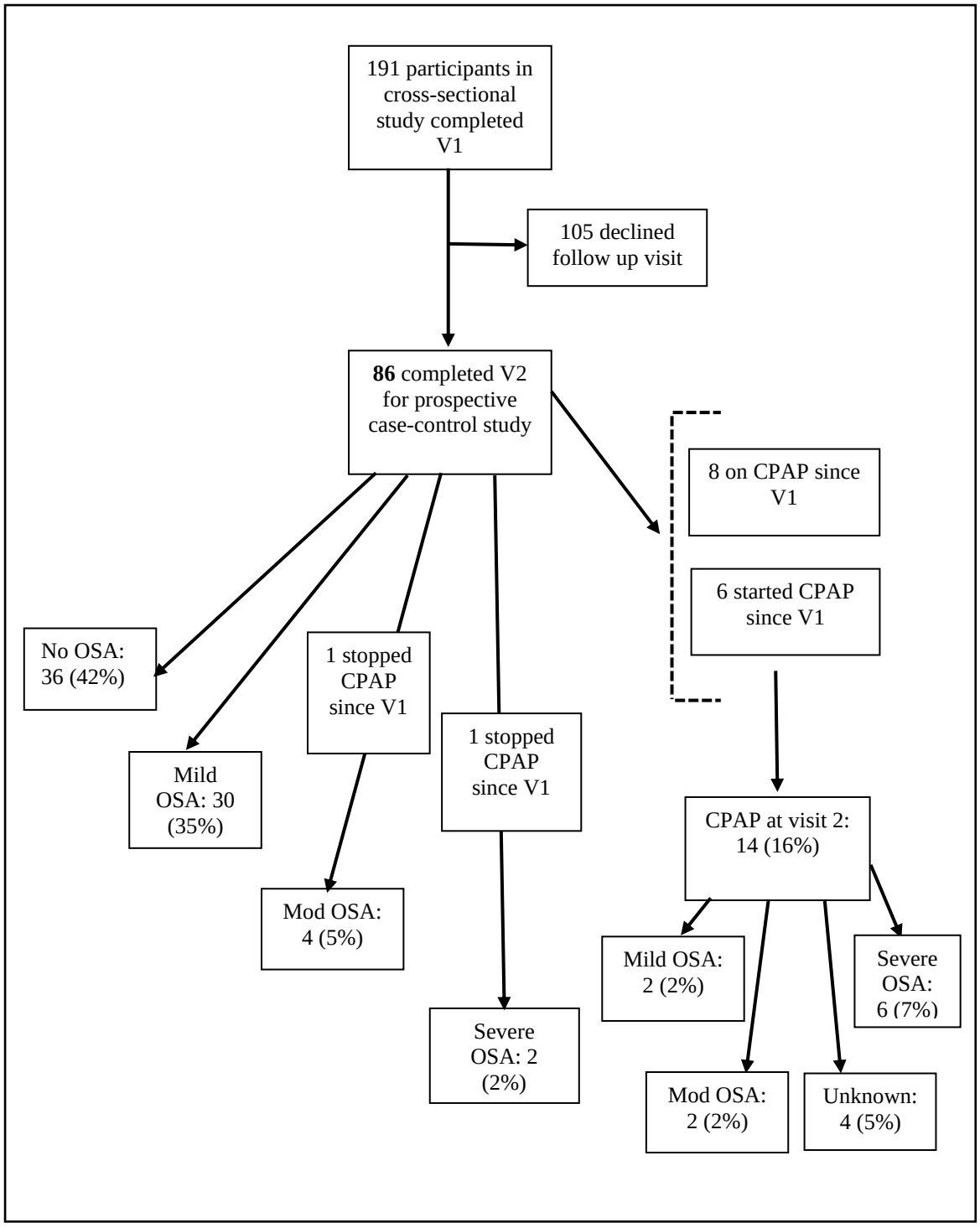


Figure 4.17 Flow of recruitment from cross-sectional study to prospective case-control study

The figure illustrates how participants from the cross-sectional study completed the baseline visit (V1) and subsequently those that completed the 12 month follow-up visit were included in the prospective case-control study. The prevalence and severity of OSA at V2 is included in the figure.

OSA: Obstructive sleep apnoea; CPAP; Continuous positive airway pressure; V1: visit 1 (baseline visit); V2: 12 month follow up visit

Table 4.45 Basic demographics

Demographic	**Mean (SD)** **Median (Q1, Q3)**
Gender (n=86)	56 females (65.1%)
Age (years) (n=86) **(V1)**	49.5 (40.8, 56.0)
BMI (kg/m^2) (n=83) **(V1)**	29.8 (26.0, 34.2)
Ethnicity (n=83) **(V1)**	Caucasian= 71 (83%) Asian=10 (5%) Black=1 (1%) Other=1 (1%)
Smoking pack years (n=83) (V1)	0.0 (0.0, 6.0) Non-smokers: 57 (66%), Ex-smokers: 18 (21%), Current smokers: 8 (9%)
ICS dose (micrograms/day, BDP) **n=86**	2000 (1375, 2125)
Maintenance OCS (%) (n=86)	28 (32.6%)
Maintenance OCS dose (mg) (n=28)	9.0 (5.0, 10.0)
FEV_1 (% pred) (n=83)	73.0 (56.0, 85.0)
FEV_1/FVC (n=83)	73.0 (64.0, 80.0)
FENO (ppb) (n=79)	23.0 (14.0, 51.0)
Biological treatment (n=85)	4 (4.7%)
Antifungals (n=86)	5 (5.8%)
Triamcinolone depot injection (n=86)	2 (2.3%)
Prophylactic antibiotics (n=85)	17 (19.8%)

The basic demographics of the participants included in the prospective case-control study are displayed in the table. Gender, age, BMI and ethnicity were recorded at the baseline visit, the remaining data was collected at the 12 month follow up visit (V2)

ICS: inhaled corticosteroid; OCS: oral corticosteroid; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; FENO: Fractional exhaled nitric oxide

A summary of participants employment is included in table 4.46. 10.5% of the population were at least partly limited in their employment due to asthma, a further 29.1% were not working due to ill-health related to asthma.

Table 4.46 Summary of employment history

	Number of participants (n=86)
Employment (n=86)	None= 41 (47.7%) Current= 35 (40.7%) Retired= 10 (11.6%)
Asthma preventing work (n=84)	No= 50 (58%) Partly= 9 (10.5%) Yes= 25 (29.1%)

Participants were asked to report if they were currently working, and if asthma limited their ability to work (either fully or partly).

4.2.2 The prevalence of OSA at visit 2

In the total population (n=86); 36 (42%) had no-OSA, 32 (37%) had mild OSA, 6 (7%) had moderate OSA, 8 (9%) had severe OSA and the severity was unknown for 4 of the participants (5%) from the CPAP treated group. This is illustrated in figure 4.18.

At the time of visit 2, a total of 14 participants were using CPAP. 8 participants had remained on CPAP since visit 1, 6 participants had started CPAP since visit 1, and 1 participant had been started on CPAP only a few days earlier and for the purposes of the analysis was in the "no-CPAP" group. 2 participants had stopped using CPAP or were very poorly compliant since visit 1. A further 5 participants were still awaiting review for consideration of CPAP.

Participants were again categorised into severity of OSA according to the apnoea hypopnoea index (AHI): No-OSA; AHI<5, Mild OSA; ≥5AHI<15, moderate OSA; ≥15AHI<30, severe OSA; AHI≥30. 2 of the 8 participants who had pre-existing OSA and were established on OSA had an oxygen desaturation index (ODI) available that was used to grade severity of OSA (but no AHI). The sleep data for participants included in this study is included in table 4.47.

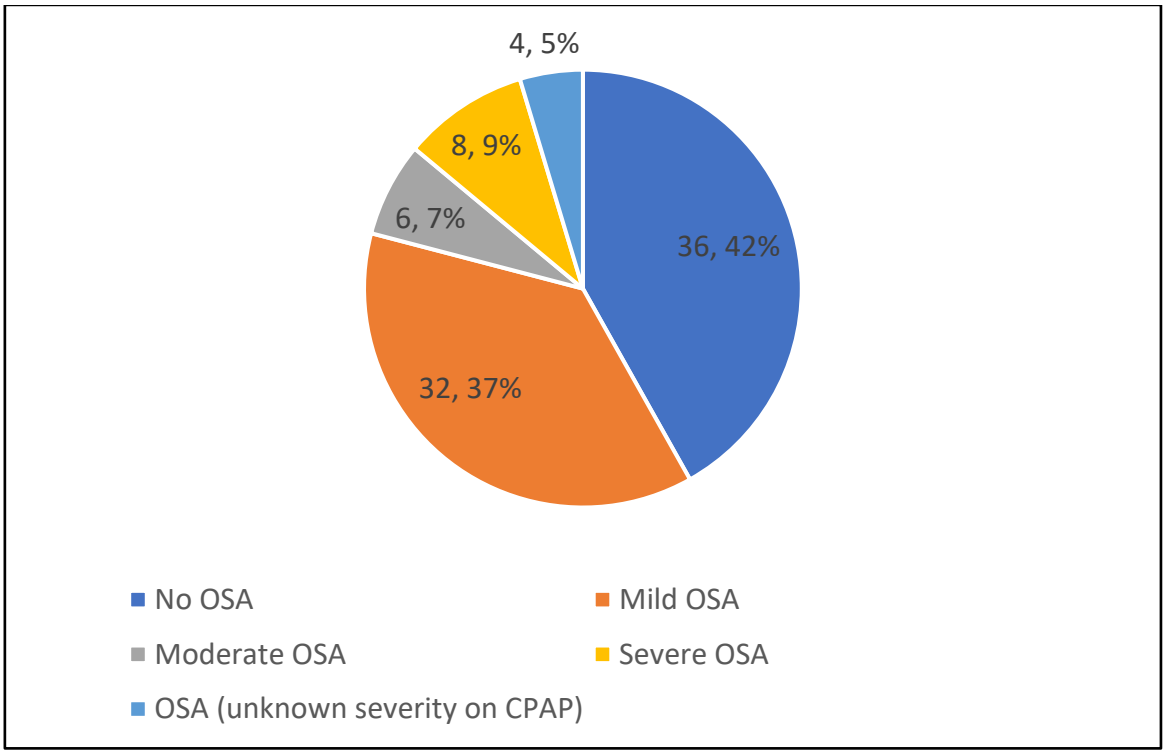


Figure 4.18 The prevalence of OSA at visit 2

All participants were categorised according to presence and severity of as per AHI (or ODI in two participants). The overall prevalence of OSA in the population at the 12 month follow up visit is illustrated in the figure.

OSA: Obstructive sleep apnoea; CPAP: Continuous positive airway pressure; AHI: Apnoea hypopnoea index; ODI: oxygen desaturation index

Table 4.47 Sleep data

Sleep Data	**Median (Q1, Q3)**
Average nocturnal oxygen saturations (%) (n=77)	99.7 (92.6, 100.0)
% flow recording (n=77)	99.7 (92.6, 100.0)
% oxygen saturation recording (n=77)	99.6 (99.1, 99.9)
Duration of recording (hours) (n=77)	8.0 (6.8, 9.0)
CPAP (V1) (n=86)	10 (11.6%)
CPAP (V2) (n=86)	14 (16.3%) -8 remained on CPAP from V1 (2 stopped/not using CPAP at time of V2) -6 started CPAP after V1

The table shows the sleep data for the available diagnostic sleep tests for those included in the case-control prospective study. The breakdown of those on CPAP at visit 1 (baseline visit) and visit 2 (12 month follow up visit) is also included. The aim was for a sleep recording of ≥4 hours duration, with nasal flow recording and oxygen saturation recording of ≥80%. Sleep studies that did not meet these criteria were re-reviewed to determine if they were of acceptable quality for the participant to be included.

4.2.3 Basic demographics in the untreated population

The participants established on CPAP were removed from this section of the analysis to allow comparison of demographics and medication use with increasing severity of OSA. Age ($p<0.001$) and BMI ($p<0.001$) were found to significantly increase with increasing severity of OSA. These results are displayed in table 4.48.

Table 4.48 Demographics as per severity of OSA, untreated population

Demographic	**No-OSA n=36**	**Mild OSA n=30**	**Moderate OSA n=4**	**Severe OSA n=2**	**p-value**
Age (n=72) (years) (V1)	n=36 41.0 (29.3, 49.3)	n=30 52.5 (49.0, 58.0)	n=4 51.0 (45.5, 67.0)	n=2 57.0 (n/a)	**<0.001**
Smoking (pack years) (n=69) (V1)	n=35 0.0 (0.0, 0.0)	n=28 0.0 (0.0, 2.8)	n=4 2.5 (0.5, 12.8)	n=2 5.0 (n/a)	0.107
BMI (kg/m^2) (V1) (n=69)	n=35 26.3 (24.0, 29.5)	n=30 30.5 (28.2, 35.3)	n=2 40.7 (n/a)	n=2 33.9 (n/a)	**<0.001**
ICS (micrograms, BDP), (n=72) (V2)	n=36 2000 (1000, 2950)	n=30 2000 (2000, 2000)	n=4 2500 (1250, 3750)	n=2 1900 (n/a)	0.286
% requiring maintenance OCS (n=72)	n=36 13 (36.1%)	n=30 8 (26.7%)	n=4 1 (25%)	n=2 0	0.243
% on biological treatment (n=72)	n=36 3 (8.3%)	n=30 1 (3.3%)	n=4 0	n=2 0	0.243

Participants were categorised into ordered groups according to severity of OSA to enable comparisons to be made across the groups.

BMI: Body mass index; ICS: Inhaled corticosteroid; OCS: Oral corticosteroid; BDP: Beclomethasone dipropionate

4.2.4 Asthma outcomes, the untreated population

There was no significant trend observed in spirometry measures, FENO (fractional exhaled nitric oxide), peripheral eosinophil count or IgE (immunoglobulin E) with increasing severity of OSA (table 4.49).

Table 4.49 Asthma markers, untreated population

Demographic	**No-OSA**	**Mild OSA**	**Moderate OSA**	**Severe OSA**	**p-value**
FEV_1 % predicted (V2) (n=70)	n=35 77.0 (52.0, 91.0)	n=29 72.0 (57.5, 84.5)	n=4 84.0 (73.0, 92.0)	n=2 67.0 (n/a)	0.982
FEV_1/FVC ratio (V2) (n=70)	n=35 74.0 (58.0, 85.0)	n=29 71.0 (64.5, 79.0)	n=4 76.5 (66.8, 83.3)	n=2 67.0 (n/a)	0.638
FENO (ppb) (n=67) (V2)	n=34 24.0 (12.8, 84.8)	n=28 20.5 (15.0, 34.0)	n=3 11.0 (n/a)	n=2 41.5 (n/a)	0.458
Peripheral eosinophil count ($x10^9$/L) (n=71)	n=36 0.24 (0.13, 0.43)	n=39 0.21 (0.11, 0.49)	n=4 0.22 (0.12, 0.34)	n=2 0.26 (n/a)	0.563
IgE (kU/L) (n=75)	n=35 172 (62, 416)	n=31 48 (23, 384)	n=5 198 (16, 349)	n=4 102 (32, 491)	0.053

Participants were categorised into ordered groups according to severity of OSA to enable comparisons to be made across the groups.

FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; FENO: Fractional exhaled nitric oxide; IgE: immunoglobulin E

4.2.5 Asthma-related healthcare utilisation, total population

Comparisons were made in asthma-related healthcare utilisation between the OSA group (AHI≥5) and the no-OSA (AHI<5). There was no significant difference between the two groups for any of the healthcare utilisation parameters measured (tables 4.50-4.53).

Table 4.50 Annual number of OCS requiring exacerbations in the no-OSA group compared to the OSA group (AHI≥5)

Annual number of OCS requiring exacerbations	**No-OSA (AHI<5) n=36**	**OSA (AHI≥5) n=50**	**p value Kendall's tau-b**
0	9 (25.0%)	4 (8.0%)	0.345
1-4	15 (41.7%)	29 (58.0%)	
5-9	8 (22.2%)	12 (24.0%)	
≥10	4 (11.1%)	5 (10.0%)	

Table 4.51 Annual number of emergency GP visits in the no-OSA group compared to the OSA group (AHI≥5)

Annual number of emergency GP visits	**No-OSA (AHI<5) n=36**	**OSA (AHI≥5) n=50**	**p value Kendall's tau-b**
0	15 (41.7%)	15 (30.0%)	0.886
1-4	11 (30.6%)	26 (52.0%)	
5-9	7 (19.4%)	8 (16.0%)	
≥10	3 (8.3%)	1 (2%)	

Table 4.52 Annual number of A&E visits in the no-OSA group compared to the OSA group (AHI≥5)

Annual number of A&E visits	**No-OSA (AHI<5) n=36**	**OSA (AHI≥5) n=50**	**p value Kendall's tau-b**
0	23 (63.9%)	33 (66%)	0.759
1-4	9 (25.0%)	14 (28.0%)	
5-9	4 (11.1%)	1 (2%)	
≥10	0	2 (4%)	

A&E: Accident and Emergency

Table 4.53 Annual number of hospital admissions in the no-OSA group compared to the OSA group (AHI≥5)

Annual number of hospital admissions	**No-OSA (AHI<5) n=36**	**OSA (AHI≥5) n=49**	**p value Kendall's tau-b**
0	26 (72.2%)	37 (75.5%)	0.870
1-4	9 (25%)	8 (16.3%)	
5-9	1 (2.8%)	2 (4.1%)	
≥10	0	2 (4.1%)	

4.2.6 Health-related questionnaires, untreated population

There was no significant difference between the OSA (AHI≥5) and the no-OSA group in terms of health-related questionnaires (table 4.54).

Table 4.54 Health-related questionnaires, comparison between OSA (AHI≥5) group and no-OSA group, untreated population

Questionnaire	**No-OSA n=36**	**OSA (AHI≥5) n=36**	**p-value**
ACQ-7	n=34 2.7 (1.5, 3.6)	n=31 2.6 (1.9, 3.4)	0.782
AQLQ	n=31 4.1 (3.3, 6.0)	n=32 4.1 (3.1, 5.0)	0.368
EQ-5D	n=34 9.0 (5.0, 10.0)	n=31 8.0 (6.0, 10.0)	0.894
EQ-VAS	n=34 60.0 (35.0, 81.3)	n=32 63.0 (41.8, 80.0)	0.753
HADS-A	n=29 6.0 (2.0, 12.5)	n=29 9.0 (2.5, 14.0)	0.548
HADS-D	n=29 6.0 (1.5, 9.5)	n=29 6.0 (2.0, 10.0)	0.994

Participants were categorised into either the OSA group (AHI≥5) or no-OSA group dependant on their AHI. Health-related questionnaire scores were then compared between the two groups.

OSA: Obstructive sleep apnoea; AHI: Apnoea hypopnoea index; ACQ: Asthma control questionnaire; AQLQ: Asthma quality of life questionnaire; HADS: Hospital anxiety and depression scale; EQ-5D: Euroqol-5 dimensions; EQ-VAS: Euroqol-visual analogue scale;

4.2.7 Metabolic syndrome co-morbidities, total population

The total population was divided into either the no-OSA group (AHI<5) or the OSA group (AHI≥5) to compare co-morbidities relating to the metabolic syndrome between the two groups. There was significantly more hypertension (p<0.001) and dyslipidaemia (p=0.006) in the OSA group (table 4.55).

Table 4.55 Metabolic syndrome co-morbidities, total population

	No-OSA (AHI<5)	**OSA (AHI≥5)**	**Fisher's Exact Test p-value**
Diabetes (n=86)	n=36 4 (11.1%)	n=50 9 (18%)	0.544
Dyslipidaemia (n=86)	n=36 6 (16.7%)	n=50 23 (46%)	**0.006**
Hypertension (n=86)	n=36 3 (8.3%)	n=50 23 (46%)	**<0.001**
GORD (n=86)	n=36 23 (63.9%)	n=50 27 (54%)	0.385
Thyroid dysfunction (n=82)	n=33 4 (12.1%)	n=49 4 (8.2%)	0.708
Ischaemic Heart Disease (n=85)	n=36 0 (0%)	n=49 3 (6.1%)	0.259

Participants were categorised as either no-OSA or OSA. The percentage of self-reported co-morbidities were then compared between the two groups.

OSA: Obstructive sleep apnoea syndrome; AHI; Apnoea hypopnoea index; GORD: Gastro-oesophageal reflux disease

4.2.8 Biochemical markers of the metabolic syndrome, total population

Blood results relating to the metabolic syndrome were compared between the two groups. HbA1c % (p=0.001) and triglyceride levels (p=0.010) were significantly lower in the no-OSA group when compared to the OSA group (table 4.56).

Table 4.56 Biochemical markers of the metabolic syndrome, OSA (AHI≥5) versus no-OSA, total population

	No-OSA (AHI<5)	**OSA (AHI≥5)**	**p value**
Cholesterol (mmol/L) (n=81)	n=33 5.2 (4.5, 5.9)	n=48 5.5 (4.7, 6.3)	0.405
Triglycerides (mmol/L) (n=81)	n=33 1.2 (0.9, 1.9)	n=48 1.7 (1.2, 2.5)	**0.010**
HDL (mmol/L) (n=81)	n=33 1.7 (1.3, 1.9)	n=48 1.5 (1.2, 1.8)	0.222
LDL (mmol/L) (n=80)	n=32 2.9 (2.7, 3.5)	n=48 3.1 (2.4, 3.7)	0.852
HbA1c (%) (n=82)	n=34 5.5 (5.1, 5.8)	n=48 5.8 (5.6, 6.1)	**0.001**
Thyroid Stimulating Hormone (TSH) (mU/L) (n=78)	n=30 1.3 (0.9, 1.5)	n=48 1.1 (0.7, 1.6)	0.206

Participants were categorised as either no-OSA or OSA (AHI≥5). Blood results that were collected during the study were analysed to enable comparisons between the two groups.

OSA: Obstructive sleep apnoea; AHI; Apnoea hypopnoea index; HDL: High density lipoprotein; LDL: Low density lipoprotein; HbA1c: Haemoglobin A1c

5 Results: Does continuous positive airway pressure (CPAP) treatment of obstructive sleep apnoea (OSA) improve asthma-related clinical outcomes in patients with co-existing conditions? - Systematic Review

5.1 Introduction

The aim of this systematic review was to determine the impact of CPAP treatment of co-existing OSA on asthma-related clinical outcomes in patients with co-existing conditions.

5.2 Summary of results[175]

12 studies met the inclusion/exclusion criteria for this systematic review. 8 studies were prospective quasi-experimental studies and 4 were observational. No randomised, placebo-controlled studies were identified.

The mean duration of CPAP for the prospective quasi-experimental studies was 19.5 weeks (range 2-100 weeks). The duration of CPAP in the cross-sectional or retrospective studies ranged from "current treatment" to 5.7 years. The PICO diagram is illustrated in figure 5.1 with a summary of the asthma-related outcomes identified during this review of the literature.

P= Participants with asthma/severe asthma and co-existing OSA

I= CPAP treatment

C= No CPAP treatment

O= Asthma-related health outcomes identified: 1) Asthma control; AQLQ, mini-AQLQ, ACQ, ACT, daytime or night-time asthma symptoms, A&E visits, asthma exacerbation frequency. 2) Asthma severity; GINA, NAEPP, VAS. 3) Lung function and physiological measurements; methacholine challenge, airway reversibility, FEV_1, FEV_1/FVC, PEFR, FENO, arterial oxygen and carbon dioxide levels

Figure 5.1 PICO diagram

The PICO tool is helpful at focussing clinical questions. P: Population/problem; I: Intervention/exposure; C: Comparison; O: Outcome;

CPAP: Continuous Positive Airway Pressure; AQLQ: Asthma Quality of Life Questionnaire; ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; A&E: Accident and Emergency; GINA: Global Initiative for Asthma) guidelines; NAEPP: National Asthma Education and Prevention Program; VAS: Visual Analogue Scale; FEV_1: Forced Expiratory Volume in 1 second; FENO: Fractional Exhaled Nitric Oxide

5.2.1 Asthma-related quality of life (table 5.1)[175]

There was improved asthma related quality of life in two studies when measured using AQLQ or mini-AQLQ. Meta-analysis of available Asthma Quality of Life data was possible after combining the results of AQLQ and mini-AQLQ, which have similar scores and clinical interpretation.

5.2.2 Asthma control (table 5.2)[175]

Asthma control was reported in 3 studies; 1 study used the ACQ and demonstrated significant improvement post-CPAP, 2 studies used the ACT and 1 demonstrated significant improvement, the other did not. 4 further studies evaluated daytime and/or night-time asthma

symptoms with all 4 reporting improvements with CPAP. 1 study demonstrated a non-significant reduction in A&E visits (p=0.058). 1 study found a significant reduction in asthma exacerbation frequency with CPAP (p=0.015).

5.2.3 Asthma severity (table 5.3)[175]

Asthma severity was measured in 3 studies. Methods of measuring severity of asthma included GINA (Global Initiative for Asthma) guidelines, NAEPP (National Asthma Education and Prevention Program) guidelines and a visual analogue score, with each study using a different method. An improvement of asthma severity was seen in all 3 following CPAP.

5.2.4 Lung function and physiological measurements (table 5.4)[175]

Bronchial airway responsiveness was assessed in 2 studies. One study used the methacholine challenge test and showed no significant improvement with CPAP, the other study assessed airway reversibility and demonstrated a significant improvement with CPAP.

6 studies reported changes in FEV_1 with CPAP. 2 studies were excluded from meta-analysis due to lack of sufficient data or a significant difference in the study design. Four studies were combined in a meta-analysis. There was no significant improvement in FEV_1 (5 studies) or FEV_1/FVC ratio (3 studies). Peak expiratory flow rates improved in the 1 study that reported it. Arterial oxygenation and arterial carbon dioxide levels improved in the 1 study that reported this outcome and FENO also improved in 1 study.

Table 5.1 Asthma-related quality of life[175]

Study	Population	Asthma Severity	OSA severity	Clinical Measurement	CPAP duration	Outcome
Lafond et al. Eur Respir J 2007;29:307-311[219,220]	n=20 Completed follow up and compliant with CPAP (≥4 hours/night)	"Stable" asthma- Occasional respiratory symptoms and absence of exacerbation or change in maintenance therapy in the preceding month	Apnoea Hypopnoea Index (AHI)≥15 Mean pre-CPAP AHI=48.1±23.6	AQLQ	6 weeks	Significant improvement in AQLQ; 5.0±1.2 to 5.8±0.9, **p=0.001** At baseline, AQLQ was inversely correlated with patients BMI (rho= -0.5, p=0.02). Following CPAP, the AQLQ positively correlated with BMI (rho=0.5, p=0.03) and AHI at baseline (rho=0.5, p=0.03) Following CPAP, the BMI was correlated with the improvement in the emotional (rho=0.5,p=0.02) and environmental domains (rho=0.5, p=0.01) of AQLQ The AHI at baseline was correlated with improvement in the symptomatic (rho=0.6, p=0.01), emotional (rho=0.6, p=0.01) and environmental domains (rho=0.5, p=0.05)
Serrano-Pariente et al. Allergy 2016;72(5):802-812[221,222]	n=99 82 completed follow up 12/82 non-compliant with CPAP (<4hours/night)	n=28, intermittent-mild persistent asthma n= 71, moderate-severe persistent asthma	Moderate-severe OSA with Respiratory Disturbance Index (RDI) ≥20 Mean pre-CPAP RDI= 46.3±20.8	Mini AQLQ	6 months	Significant improvement in mini AQLQ; 5.12±1.38 to 5.63±1.17, **p=0.009** ***Asthma Severity*** Intermittent mild asthma; 5.77±0.93 to 6.04±0.85, p=0.303 Mod-severe asthma; 4.87±1.45 to 5.48±1.24, **p=0.012** ***OSA Severity*** RDI≤30; 5.23±1.44 to 5.68±1.41, p=0.324 RDI>30; 5.08±1.37 to 5.62±1.11, **p=0.013**

OSA: Obstructive sleep apnoea; AHI: Apnoea hypopnoea index; RDI: Respiratory disturbance index; CPAP: Continuous positive airway pressure; OCS: Oral corticosteroid; AQLQ: Asthma quality of life questionnaire; BMI: Body mass index

Table 5.2 Asthma control and symptoms[175]

Study	Population	Asthma Severity	OSA Severity	CPAP Duration	Clinical Measurement	Outcome
Chan et al. Am Rev Respir Dis 1988; 137:1502-1504[223]	n=8 (asthma and OSA) 1=No OSA	Asthma with frequent nocturnal asthma attacks (previous respiratory arrest in 3 patients)	AHI >5 All had symptoms of snoring/nocturnal upper airway obstruction	2 weeks	Asthma symptoms and bronchodilator requirements	All 9 patients in this study showed marked improvement in nocturnal and daytime asthma symptoms, with reduced bronchodilator requirements.
Ciftci et al. Respiratory Medicine 2005;99:529-534[135]	n=16 completed study (n=19 enrolled)	≥1 nocturnal or early morning awakening due to asthma despite optimal treatment as per GINA guidelines	AHI≥15 Nasal CPAP Habitual snorers ≥4/hours night CPAP compliance	2 months	Night time asthma symptom scores 0: No symptoms 1: ≤2 times/month 2: >2 times/month 3: <1 times/week 4: Frequent	Improved significantly after CPAP treatment from 2.19±1.07 to 1.44±1.15, **p=0.04**
Guilleminault et al. Eur Respir J 1988;1:902-907[224]	n=10 (group A) (Group B excluded as not clearly OSA)	Group A: Overweight middle-aged asthmatic men with frequent nocturnal asthma attacks (n=10)	RDI= 51±13	6-9 months	Number of asthma attacks	The number of nocturnal asthma attacks improved. The frequency of daytime asthma attacks did not change.

Kauppi et al. Sleep Breath 2016:20;1217-1224[225]	n=152 Mean compliance 6 hours/day (SD 2.5) but range 0-10.2 hrs/day	Unknown	Respiratory Event Index (REI) >15/h or 5-14 and symptoms of OSA	CPAP >3months (before CPAP initiation/retrospective and last 4 weeks) Mean duration of CPAP 5.7 years (SD 4.7)	ACT %patients using rescue medication daily Night-time symptoms	Significant improvement in ACT; 15.35(SD 5.3) to 19.8(SD 4.6), **p<0.001** - Significant correlation between values of ACT at baseline and those of asthma severity (visual analogue score) at baseline (r(102)=-0.721,p=0.000) -Patients that were female, lower baseline ACT and higher VAS severity score at baseline more likely to have clinically significant change in ACT (≥3). A slight decrease in weight (mean -1.6kg) during follow up was associated with a significant increase in ACT, p=0.007 - Regression analysis showed female gender, baseline BMI, baseline ACT were significant predictors of ACT modifications. %patients using rescue medication daily; Reduced from 36 to 8% **(p<0.001)** Night-time symptoms; % of patients reporting no night-time symptoms increased from 28% to 55% (**p<0.001)**
Serrano-Pariente. J. Allergy 2016;72(5):802-812[221,226,227]	n=99 82 completed follow up 12/82 non-compliant with CPAP (<4hours/night)	n=28, intermittent-mild persistent n= 71, moderate-severe persistent	Moderate-severe OSA with RDI ≥20 Mean pre-CPAP RDI= 46.3±20.8	6 months	Asthma Control Questionnaire (ACQ) Well-controlled asthma	Significantly improved mean ACQ; 1.39±0.91 to 1.0±0.78, **p=0.003** ***Asthma Severity*** Intermittent-Mild; 0.88±0.54 to 0.71±0.45, p=0.226 Mod-severe;1.58±0.95 to 1.11±0.85, **p=0.003** ***OSA Severity*** RDI≤30; 1.47±0.88 to 1.02±0.88, p=0.113 RDI>30; 1.36±0.92 to 0.99±0.76, **p=0.012** ***% asthmatics well-controlled;*** Percentage of patients with well-controlled asthma (ACQ≤0.75) increased from 28% to

					Asthma exacerbation frequency	38%. Percentage of patients with not well-controlled asthma(ACQ≥1.5) decreased from 41% to 17% **(p=0.006)** ***Asthma Exacerbation Frequency:*** The percentage of patients with at least one exacerbation decreased from 35.4%(n=35) to 17.2%(n=17), **p=0.015**
Shaarawy et al. Egyptian Journal of Chest Diseases and tuberculosis 2013;62 (1):183-187[204,228,]	n=15 (completed follow up)	Uncontrolled despite optimal treatment -ACT≤17 in last 4 weeks	AHI>5/h Mean pre-CPAP AHI=23.5±10.9	6 weeks	Asthma Control Test (ACT)	No significant improvement; 13.97±3.52 to 14.1±3.97, p>0.05
Shaker et al. Egyptian Journal of Chest Disease and Tuberculosis 2017;293-298[229]	n=12	2 (16.7%) moderate-persistent asthma 10(83.3%) severe-persistent asthma (GINA)	AHI>5 Mean AHI and compliance with CPAP not reported	3 months CPAP	Number of patients with daytime or night-time asthma symptoms	Daytime symptoms; 11 (91.7%) pre-CPAP to 5(41.7%) post-CPAP, **p=0.009** Night-time symptoms; 11 (91.7%) pre-CPAP to 4 (33.3%) post-CPAP, **p=0.003**
Teodorescu et al. J Asthma 2012;49(6):620-628	n=136 with asthma and OSA (75 using CPAP)	Unclear	Unknown-previous OSA (diagnosed by PSG) documented in notes	Unknown	Daytime and night-time asthma symptoms Asthma symptoms >2days/week: "persistent daytime symptoms" Asthma symptoms>2 nights/month: "persistent night time symptoms"	CPAP was associated with lower odds for persistent daytime asthma symptoms 0.5(0.25-1.00), p=0.049 but not night-time symptoms 0.62(0.31-1.22), p=0.16. Relationships strengthened when adjusted for obesity

Wang et al. BMC Pulmonary Medicine 2017;17[230]	n=13 with severe OSA – pre- and post-CPAP (21 non-compliant) n=77 total n=67 with asthma and OSA	Not known	Mild-Moderate OSA(≥5 AHI≤30); n=33 Severe OSA (AHI>30); n= 34 n= 10 (no OSA)	CPAP (5 year follow up) Compliance >4hours for 5 days of wk	No. of A&E visits for asthma	Non-significant reduction in number of A&E visits per/year in severe OSA patients treated with CPAP; 0.52±0.62 to 0.35±0.52, p=0.058

OSA: Obstructive sleep apnoea; AHI: Apnoea hypopnoea index; RDI: Respiratory disturbance index; REI: Respiratory event index; CPAP: Continuous positive airway pressure; GINA: Global initiative for asthma; OCS: Oral corticosteroid; ACT: Asthma control test; ACQ: Asthma control questionnaire

Table 5.3 Asthma severity[175]

Study	Population	Asthma Severity	OSA Severity	CPAP Duration	Measurement	Intervention	Outcome
Kauppi et al. Sleep Breath 2016:20;1217-1224[225]	n=152 Compliance with CPAP 6hrs/night (SD 2.4)	Unknown Self-reported using visual analogue scale	REI>15/h or 5-14 and symptoms of OSA	CPAP >3months (before CPAP initiation/ retrospective and last 4 weeks) Mean duration 5.7 years (SD 4.7)	Self-reported asthma severity -Visual analogue score; (0=no symptoms to 100=severe asthma symptoms)	CPAP >3months (before treatment and last 4 weeks)	Significantly reduced from 48.3(29.6) to 33.1(27.4), **p<0.001**
Shaker et al. Egyptian Journal of Chest Disease and Tuberculosis 2017;293-298[229]	n=12	2 (16.7%) moderate-persistent asthma 10(83.3%) severe-persistent asthma (GINA)	AHI>5 Mean AHI and compliance with CPAP not reported	3 months CPAP	Number of patients with "Difficult to control asthma" (asthma that could not be controlled with high dose ICS and LABA/other controller medication)	3 months CPAP	Significantly improved post CPAP; 10 (83.3%) to 3 (25%), **p=0.004**

Teodorescu M et al. Sleep Disord.;2013:251567[211]	n=140 (75 using CPAP)	Asthma Severity Step (NAEPP) Severe asthma; 76 (49%) older subjects 257 (39%) younger subjects	Unknown	CPAP compared to no CPAP treatment of OSA	Asthma severity step – Measured as per NAEPP guidelines	CPAP compared to no CPAP treatment of OSA	In older subjects, CPAP was associated with reduced likelihood of worse asthma step by 86% (0.14(0.04-0.56), **p=0.005**, and of severe asthma by 91% (0.09(0.02-0.49), **p=0.005**. In younger subjects, CPAP attenuated the likelihood of worse asthma step by 58% (0.42(0.20-0.88), **p=0.02** and that of severe asthma by 57% (0.43(0.18-1.03), **p=0.06**

OSA: Obstructive sleep apnoea; AHI: Apnoea hypopnoea index; REI: Respiratory event index; CPAP: Continuous positive airway pressure; ICS: Inhaled corticosteroid; GINA: Global initiative for asthma; NAEPP: National asthma education and prevention programme; LABA: Long acting beta agonist

Table 5.4 Lung function and physiological measurements[175]

Study	Population	Asthma severity	OSA severity	CPAP Duration	Clinical measurement	Outcome
Bonay et al. Respiratory Medicine 2003; 97: 830-834[231]	n=15 (asthma) 22=Controls 13=COPD	Not known	Mean AHI pre CPAP 47±27 in asthma group	17±8 months of nasal CPAP Compliance=5.9±0.9h/night	FEV_1 FEV_1/FVC	No significant difference in FEV_1, FEV_1/FVC ratio or FEF50, FEF25 or FEF25-75 following 17±8months of CPAP in asthma group. However- in control group; significant reduction in FEV_1 $p<0.05$ and FEV_1/FVC, $p<0.05$ noted.
					PaO_2	Significantly improved; 69±17 to 75±9mmHg,n=13,**$p<0.05$**
					$PaCO_2$	Significantly reduced; 45±6 to 43±5mmHg,n=13,**$p<0.05$**
Chan et al. Am Rev Respir Dis 1988; 137:1502-1504[223]	n=8 (with asthma and OSA) 1=No OSA	Asthma with frequent nocturnal asthma attacks (previous respiratory arrest in 3 patients)	AHI >5 All had symptoms of snoring/nocturnal upper airway obstruction	2 weeks	Peak Expiratory Flow Rates (PEFR)	Mean pre-bronchodilator PEFR was significantly higher during CPAP period than control periods both in the morning **($p<0.05$)** and evening **($p<0.02$).**
Ciftci. T. et al. Respiratory Medicine 2005;99:529-534[135]	n=16 completed study (n=19 enrolled, 1=intolerance, 2=insufficient CPAP use),	≥1 nocturnal or early morning awakening due to asthma despite optimal treatment as per GINA guidelines	AHI≥15 Nasal CPAP Habitual snorers ≥4/hours night CPAP compliance	2 months	FEV_1% predicted	No significant change; 70.25±21.17 to 71.25±21.85, p=0.64
					FEV_1/FVC	No significant change; 66.68±15.64 to 70.75±15.37, p=0.12

Lafond et al. Eur Respir J 2007;29:307-311[219]	n=20 Completed follow up and compliant with CPAP >4 hours/night	"Stable" asthma- Occasional respiratory symptoms and absence of exacerbation or change in maintenance therapy in the preceding month	AHI≥15 Mean pre-CPAP AHI=48.1±23.6	6 weeks	FEV_1 % predicted	No significant difference; 82±13.6 to 80.4±13.6
					20% fall in FEV_1 (≤8mgmL PC_{20}) to methacholine	No significant difference post CPAP; PC_{20} 2.2 (95% CI 1.3-3.5) to 2.5 (95%CI 1.4-4.5), p=0.3 -A reduction in PC_{20} was noted in 3 patients -Baseline PC_{20} was significantly higher in those that showed improvement to those that did not; 7.3mgmL^{-1} vs. 1.7, p=0.02
Serrano-Pariente et al. Allergy 2016;72(5):802-812[221]	n=99 82 completed follow up 12/82 non-compliant with CPAP (<4hours/night)	n=28, intermittent-mild persistent n=71, moderate-severe persistent	Moderate-severe OSA with RDI ≥20 75.8% of population had RDI> 30 Mean pre-CPAP RDI= 46.3 ± 20.8	6 months	FEV_1% predicted	No significant change; 83.6±17.6 to 83.6±16.6, p=0.977
					FENO	Significant reduction; 29.9±18.7 to 22±12.5, **p=0.041**
					GINA Guidelines ≥12% and 200mL increase in FEV_1 to SABA	Significantly reduced post CPAP, **(p<0.001)**
Shaarawy et al. Egyptian journal of Chest Diseases and Tuberculosis 2013;62 (1):183-187[204]	n=15 (completed follow up)	Uncontrolled despite optimal treatment -ACT≤17 in last 4 weeks	AHI>5/h Mean pre-CPAP AHI=23.5±10.9	6 weeks nocturnal CPAP	FEV_1% predicted	No significant change; 60.1±6.9 to 61.2±6.2, p>0.05
					FEV_1/FVC	No significant change: 70.3 ± 8.2 to 72.5 ± 8.5, p>0.05

Wang et al. BMC Pulm Med. 2017;17(1):55-017-0398-2.[230]	n=77 total n=67 with asthma and OSA n=13 with severe OSA - pre and post CPAP (21 non-compliant)	Not known	Mild-Moderate OSA(≥5 AHI≤30); n=33 Severe OSA (AHI>30); n=34 n= 10 (no OSA)	CPAP (5 year follow up) Compliance >4 hours for 5 days of wk	Annual FEV_1 decline	Annual decline of FEV_1 in asthmatic patients with severe OSA was significantly increased compared to those with mild-mod OSA and to those without OSA(72±61.7mL vs. 41.9±45.3mL vs. 24.3±27.5mL, **p=0.046**.). Decline in FEV_1 was significantly lower after 2 years of CPAP (**p=0.028**)

OSA: Obstructive sleep apnoea; AHI: Apnoea hypopnoea index; RDI: Respiratory disturbance index; CPAP: Continuous positive airway pressure; COPD: Chronic obstructive pulmonary disease; GINA: Global initiative for asthma; ACT: Asthma control test; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; FEF: Forced expiratory flow; PEFR: Peak expiratory flow rate; FENO: Fractional exhaled nitric oxide; PC_{20}: the provocative concentration of methacholine that results in a 20% drop in FEV_1; SABA: Short acting beta agonist

5.3 Meta-Analysis[175]

Mean asthma quality of life scores (AQLQ and mini-AQLQ) improved significantly by 0.59 (95% CI 0.25, 0.92), p=0.0006 with CPAP. No significant improvement was demonstrated in FEV_1(%pred); 0.32 (95% CI -2.84, 3.47), p=0.84. These results are illustrated using forest plots (figures 5.2 and 5.3).

5.4 Risk of bias[175]

The potential for bias in each study was assessed using the ROBINS-I scale. A high risk of bias due to confounding was present in at least 4/12 studies with unclear evidence in 3/12. There was also high risk of selection and misclassification bias in 4/12 studies. The overall risk of bias for all 12 studies is illustrated both a bias graph (figure 5.4) and bias summary (figure 5.5).

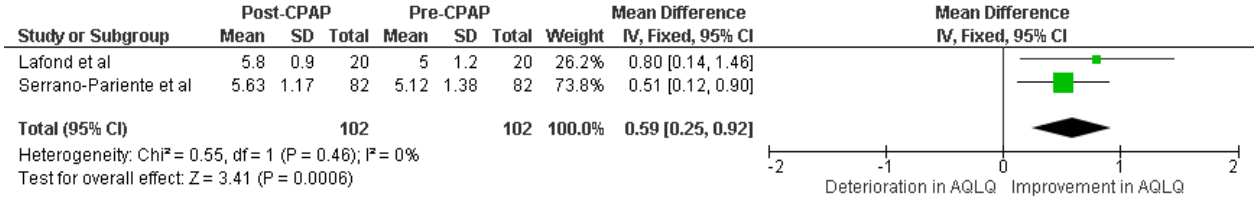


Figure 5.2 Asthma related quality of life (AQLQ/mini-AQLQ)[175]

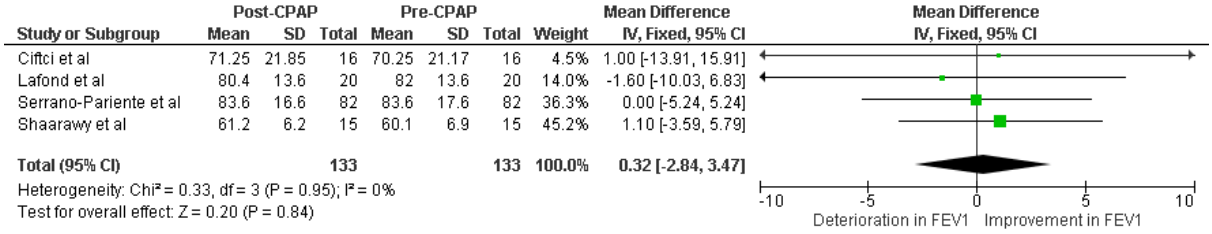


Figure 5.3 Lung function (FEV_1 % predicted)[175]

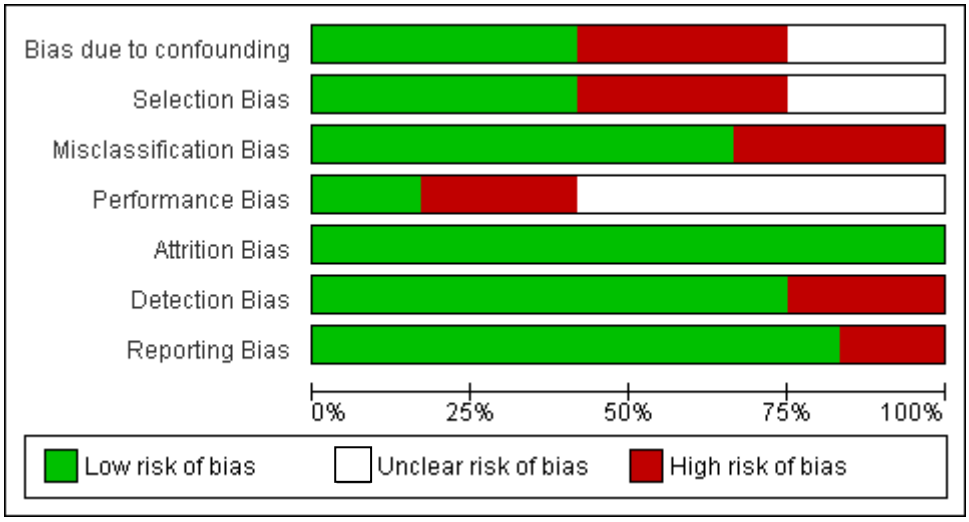


Figure 5.4 Risk of bias graph for quasi-experimental studies[175]

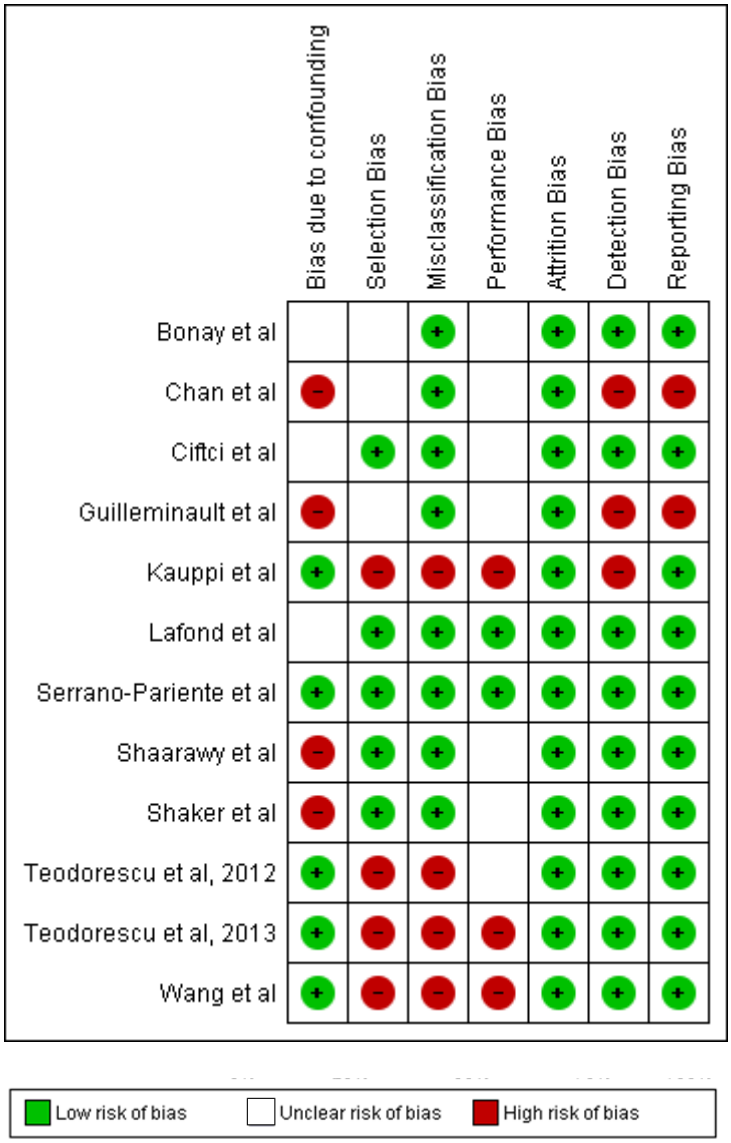


Figure 5.5 Risk of bias summary for quasi-experimental studies[175]

6 Results: Interventional Study

6.1 Introduction

The interventional study was a double-blind, randomised, placebo-controlled pilot feasibility study to determine the impact of CPAP (continuous positive airway pressure) treatment of co-existing OSA (obstructive sleep apnoea) on asthma-related quality of life.

6.2 Recruitment and randomisation

The target for recruitment was 60 participants. In total 27 were recruited and included in the intention to treat analysis. 17 were randomised to the treatment group with 9 completing the study; drop-out rate 47%. 10 were randomised to the placebo group, with 5 completing the study; drop-out rate 50%. The overall drop-out rate for the study was 48%. 2 participants were randomised but not initiated on the intervention as they both withdrew consent for the study; 1 of these participants was randomised to receive treatment and the other was randomised to the placebo arm. The recruitment and randomisation process are illustrated in figure 6.1. A summary of the baseline demographics is recorded in table 6.1 and baseline data in table 6.2.

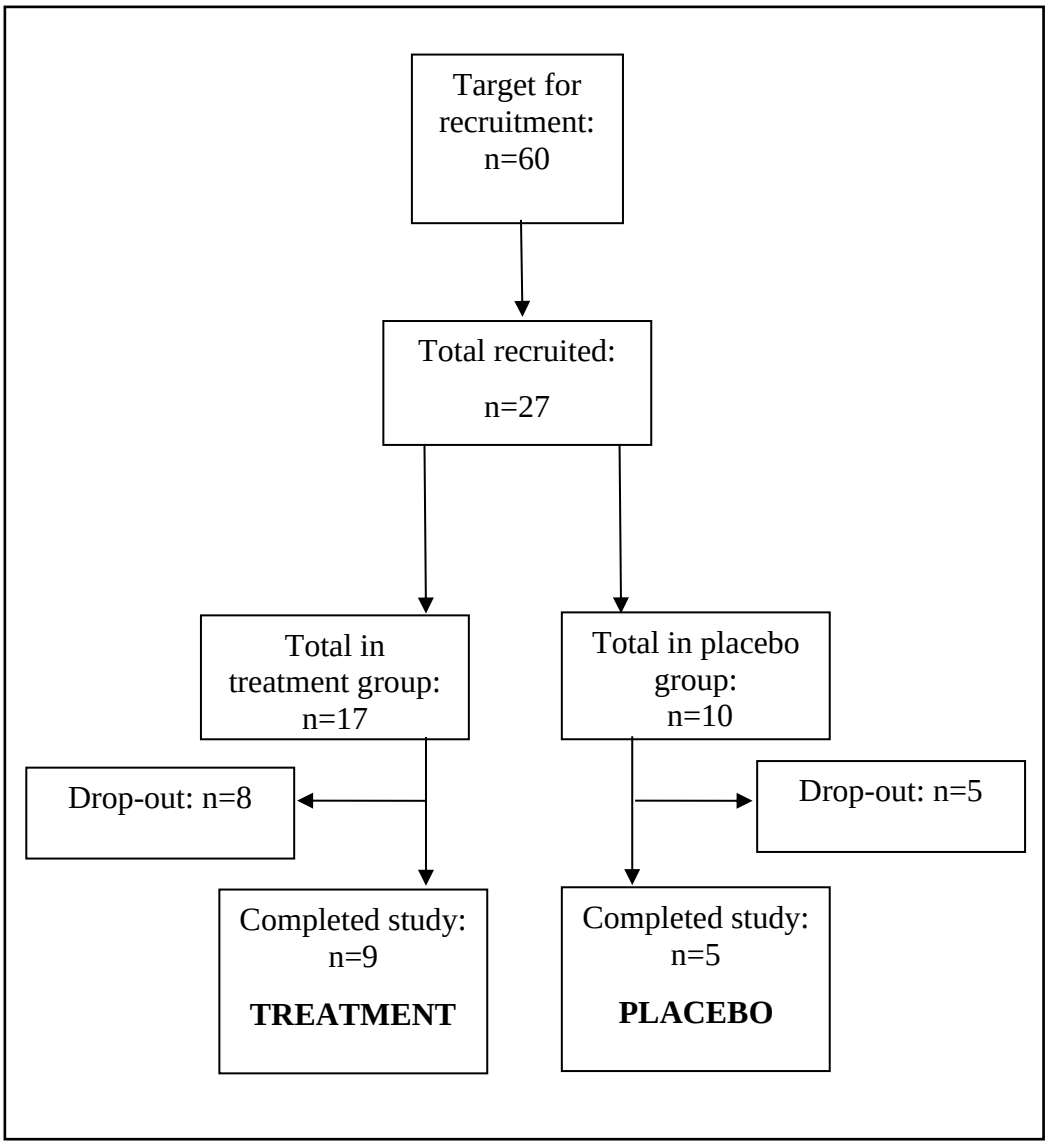


Figure 6.1 Interventional study: Recruitment and randomisation

The figure illustrates the target number for recruitment, the total numbers randomised to the treatment and placebo groups and finally the total number of participants completing the study in each arm.

Table 6.1 Basic demographics of study population

Demographic	**Median (Q1, Q3)**
Gender (n=27)	23 females (85%)
Age (years) (n=27)	52.0 (42.0, 58.0)
BMI (kg/m^2) (n=27)	33.7 (30.8, 36.3)
Smoking pack years (n=27)	0.0 (0.0, 3.0)
ICS dose (micrograms/day, BDP) (n=27)	2000.0 (1600.0, 3000.0)
Maintenance OCS requirement (%) (n=26)	7 (25.9%)
Maintenance OCS dose (mg) (n=7)	5.0 (2.0, 10.0)
Biological therapy, omalizumab (%) (n=27)	2 (7.4%)
FEV$_1$ (% predicted) (n=27)	71.0 (57.0, 90.0)
FEV$_1$/FVC ratio (n=27)	72.0 (55.0, 75.0)
FENO (ppb) (n=26)	37.0 (23.0, 59.0)

BMI: Body mass index; ICS: Inhaled corticosteroid; OCS: Oral corticosteroid; BDP: Beclomethasone dipropionate; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; FENO: Fractional exhaled nitric oxide; ppb: parts per billion

Table 6.2 Baseline data for study population

	Mean (SD) **Median (Q1, Q3)**
ACQ-7 (n=27)	2.70 (2.10, 3.90)
AQLQ (n=24)	4.35 (3.20, 5.23)
HADS-A (n=25)	6.00 (3.50, 13.50)
HADS-D (n=25)	7.00 (3.00, 10.00)
EQ-5D (n=26)	8.50 (6.75, 9.25)
EQ-VAS (n=25)	63.00 (45.00, 80.00)
ESS (n=25)	7.00 (4.50, 13.50)
Peripheral eosinophil count ($x10^9$/L) (n=26)	0.22 (0.10, 0.44)
IgE (kU/L) (n=26)	252.5 (63.0, 814.3)
Cholesterol (mmol/L) (n=26)	5.2 (4.8, 6.0)
HbA1c % (n=26)	5.8 (5.4, 6.2)
TSH (mU/L) (n=27)	1.4 (0.9, 2.0)

These readings were completed at baseline (V1) for the participants in the study population.

ACQ: Asthma control questionnaire; AQLQ: Asthma quality of life questionnaire; HADS: Hospital anxiety and depression scale; EQ-5D: Euroqol-5 dimensions; EQ-VAS: Euroqol-visual analogue scale; ESS: Epworth sleepiness score; IgE: Immunoglobulin E; HbA1c: Haemoglobin A1c; TSH: Thyroid stimulating hormone

6.3 Sleep data and compliance

Sleep data and compliance are presented in table 6.3. However, unfortunately these were not available for all CPAP machines. The date of the CPAP initiation also did not correlate with the set-up dates of each machine; therefore, it was difficult to ascertain the accuracy of the CPAP recordings and compliance data. The cause of this technical problem was uncertain.

6.4 Qualitative Data

There was an overall drop-out rate of 48%. The reasons reported by participants as barriers to continuing with treatment were;

- not wanting to use the mask on holiday
- irritation and flare of facial eczema
- noisy machine
- cold air
- uncomfortable to use
- the feeling of a gasping sensation and the need to use nebulisers after use of CPAP
- worsening nasal congestion

Table 6.3 Sleep data: Diagnostic sleep studies and CPAP downloads

	Median (Q1, Q3)
AHI **(n=27)**	16.5 (12.6, 23.8) Treatment group (n=17): 14.6 (12.4, 25.6) Placebo group (n=10): 17.6 (14.2, 22.9)
ODI **(n=26)**	18.6 (14.3, 27.0)
Severity of OSA **(n=27)**	12 (44.4%) mild, 11 (40.7%) moderate, 4 (14.8%) severe
Nocturnal oxygen saturations **(n=25)**	92.6 (91.3, 93.6)
% time flow rate recording **(n=25)**	100.0 (98.4, 100.0)
% time oxygen saturation recording **(n=25)**	99.7 (99.1, 99.8)
Total duration of sleep study (mins) **(n=25)**	510.0 (464.5, 560.0)
Time duration between V1 and final visit (months) **(n=14)**	3.8 (0.6) 3.7 (3.4, 4.3) Range: 2.8-5 months
Time duration between V1 and CPAP set up (n=24) (weeks)	4.3±4.4 4.0 (1.8, 4.8)
Duration CPAP recorded (days) **(n=11)**	66.6 (22.8) 66.0 (62.0, 83.0) Range: 7-93
Total blower time (days) (n=15)	6.8 (10.0) 2.1 (0.7, 9.3) Range: 0-32.3

The baseline data from the diagnostic sleep studies is included in the table. Data downloaded from the CPAP machines with regard to compliance and machine usage is also included.

OSA: Obstructive sleep apnoea; AHI: Apnoea hypopnoea index; ODI: Oxygen desaturation index; CPAP: Continuous positive airway pressure

6.5 Asthma related-quality of life

The AQLQ (Asthma Quality of Life Questionnaire) scores both pre and post-intervention (CPAP/placebo) were compared in both the treatment and the placebo group. There was no significant difference in either group (table 6.4). The post-intervention scores were also compared between the two groups and there was no significant difference observed, p=0.524 (table 6.5). The change in AQLQ post intervention for each participant is illustrated in figures 6.2 and 6.3.

Table 6.4 AQLQ pre and post-intervention

	Pre-intervention Median (Q1, Q3)	**Post-intervention Median (Q1, Q3)**	**Statistical test**	**p value**
Treatment (n=9)	n=9 4.40 (3.30, 4.85)	n=8 4.40 (3.73, 5.58)	Wilcoxon	0.207
Placebo (n=5)	n=4 4.55 (3.18, 5.18)	n=5 3.80 (3.00, 5.10)	Wilcoxon	0.715

The pre and post-intervention AQLQ scores were compared in both the treatment and placebo groups.

AQLQ; Asthma Quality of Life Questionnaire

Table 6.5 AQLQ: Comparison of post-intervention values between groups

	Treatment (n=8)	**Placebo (n=5)**	**Statistical test**	**p value**
Post-intervention	4.40 (3.73, 5.58)	3.80 (3.00, 5.10)	Mann-Whitney	0.524

The AQLQ scores following intervention were compared between the two groups.

AQLQ; Asthma Quality of Life Questionnaire

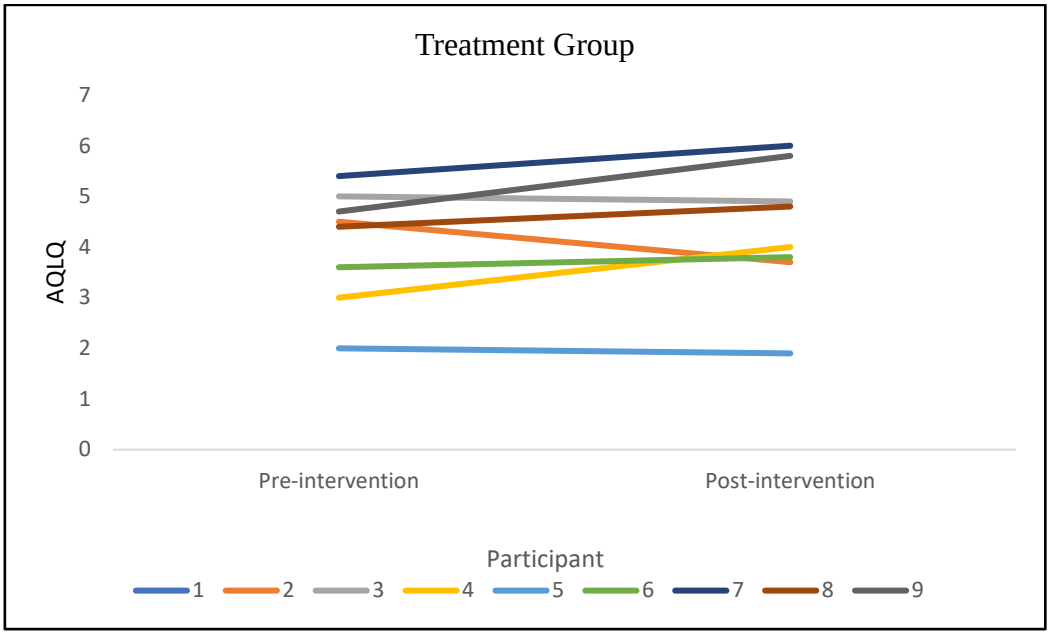


Figure 6.2 AQLQ: Comparison of pre and post-intervention values, Treatment Group

The AQLQ scores pre and post intervention for each participant in the Treatment Group are illustrated in this diagram

AQLQ; Asthma Quality of Life Questionnaire

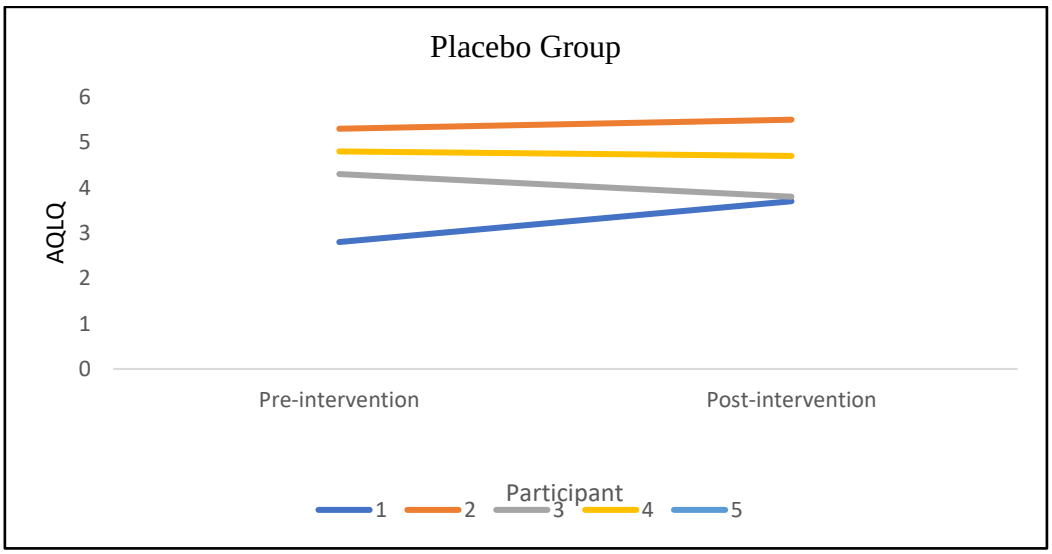


Figure 6.3 AQLQ: Comparison of pre and post-intervention values, Placebo Group

The AQLQ scores pre and post intervention for each participant in the Placebo Group are illustrated in this diagram

AQLQ; Asthma Quality of Life Questionnaire

6.6 Asthma control

The ACQ-7 (Asthma Control Questionnaire) was used to evaluated asthma control pre and post intervention (CPAP/placebo). There was no significant difference in either group (table 6.6). The post-intervention scores were also compared between the two groups and there was no significant difference observed, p=0.438 (table 6.7). The change in ACQ-7 for each participant post intervention is illustrated in figures 6.4 and 6.5.

Table 6.6 ACQ-7 pre and post-intervention

	Pre-intervention Median (Q1, Q3)	**Post-intervention Median (Q1, Q3)**	**Statistical test**	**p value**
Treatment (n=9)	n=9 2.60 (1.95, 3.75)	n=9 2.10 (1.70, 3.70)	Wilcoxon	0.120
Placebo (n=5)	n=5 2.9 (2.3, 3.3)	n=5 2.40 (2.20, 3.40)	Wilcoxon	0.715

The pre and post-intervention ACQ-7 scores were compared in both the treatment and placebo groups.

ACQ: Asthma Control Questionnaire

Table 6.7 ACQ-7: Comparison of post-intervention values between groups

	Treatment (n=9)	**Placebo (n=5)**	**Statistical test**	**p value**
Post-intervention	2.10 (1.70, 3.70)	2.40 (2.20, 3.40)	Mann-Whitney	0.438

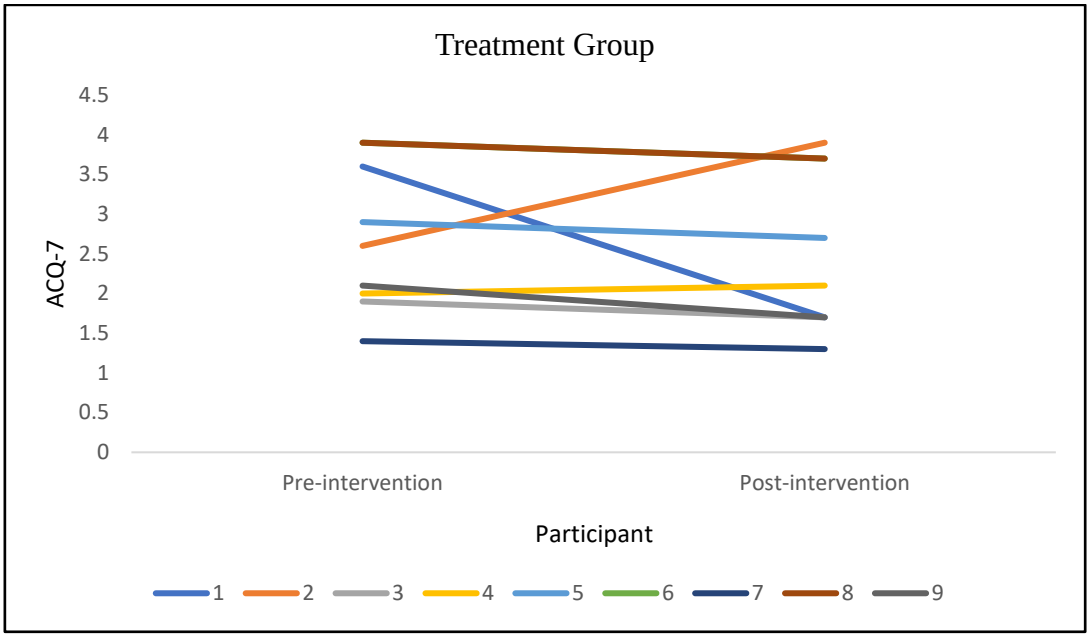


Figure 6.4 ACQ-7: Comparison of pre and post-intervention values, Treatment Group

The ACQ-7 scores pre and post intervention for each participant in the Treatment Group are illustrated in this diagram

ACQ-7: Asthma Control Questionnaire-7

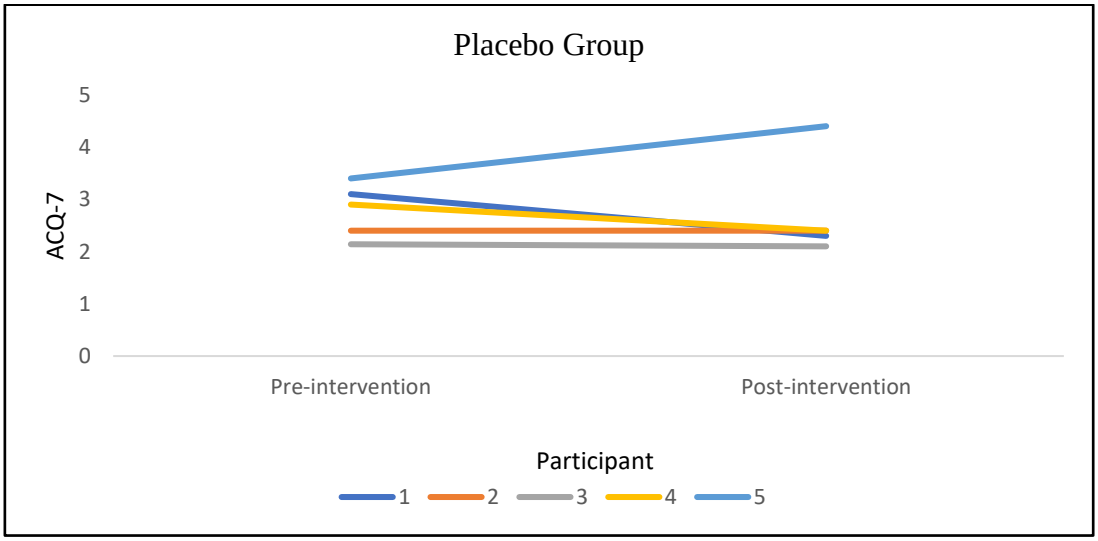


Figure 6.5 ACQ-7: Comparison of pre and post-intervention values, Placebo Group

The ACQ-7 scores pre and post intervention for each participant in the Placebo Group are illustrated in this diagram

6.7 General health-related questionnaires

Health related questionnaire scores pre and post-intervention were compared in both the treatment and placebo groups. There was no significant difference in either group for any of the following health-related questionnaire post-intervention; EQ-5D (Euroqol-5 Dimension), EQ-VAS (Euroqol-Visual Analogue Scale) or HADS (Hospital Anxiety and Depression Score) (see table 6.8).

The post-intervention values of the treatment group were then compared to the post-intervention values of the placebo group to determine if there were any significant differences in health-related quality of life following the intervention (table 6.9). There was no significant difference between the treatment and placebo group for EQ-5D ($p=0.083$), HADS-A ($p=0.933$) or HADS-D ($p=0.073$). However, a significant difference was identified for EQ-VAS ($p=0.019$) between the treatment and placebo group.

Table 6.8 Health-related questionnaires pre and post-intervention

	Pre-intervention Median (Q1, Q3)	**Post-intervention Median (Q1, Q3)**	**Statistical test**	**p value**
EQ-5D (n=9) ***Treatment***	n=9 7.0 (6.0, 8.5)	n=9 8.00 (5.00, 8.00)	Wilcoxon	0.305
EQ-5D (n=5) ***Placebo***	n=5 9.0 (8.5, 10.5)	n=5 10.00 (7.50, 10.00)	Wilcoxon	0.458
EQ-VAS (n=9) ***Treatment***	n=8 75.0 (50.0, 80.0)	n=8 75.00 (62.50, 91.50)	Wilcoxon	0.115
EQ-VAS (n=5) ***Placebo***	n=5 59.0 (50.0, 60.0)	n=5 50.00 (40.00, 60.00)	Wilcoxon	0.102
HADS-A (n=9) ***Treatment***	n=9 6.0 (2.5, 13.5)	n=8 7.50 (5.25, 13.0)	Wilcoxon	0.833
HADS- A (n=5) ***Placebo***	n=5 5.0 (2.5, 14.5)	n=4 7.50 (5.25, 12.75)	Wilcoxon	0.285
HADS-D (n=9) ***Treatment***	n=9 5.0 (3.0, 7.5)	n=8 4.00 (1.25, 6.50)	Wilcoxon	0.088
HADS-D (n=5) ***Placebo***	n=5 10.0 (6.0, 11.0)	n=4 10.00 (6.00, 13.25)	Wilcoxon	0.102

The health-related questionnaires were recorded pre and post-intervention (with CPAP or placebo). The pre and post values were then compared within the treatment group, and also within the placebo group.

EQ-5D: Euroqol-5 dimension; EQ-VAS: Euroqol-visual analogue scale; HADS: Hospital anxiety and depression scale

Table 6.9 Health-related questionnaires: comparison of post-intervention values between groups

Post intervention score	**Treatment (n=9)**	**Placebo (n=5)**	**Statistical test**	**p value**
EQ-5D	8.00 (5.00, 8.00)	10.00 (7.50, 10.00)	Mann-Whitney	0.083
EQ-VAS	75.00 (62.50, 91.50)	50.00 (40.00, 60.00)	Mann-Whitney	**0.019**
HADS-A	7.50 (5.25, 13.0)	7.50 (5.25, 12.75	Mann-Whitney	0.933
HADS-D	4.00 (1.25, 6.50)	10.00 (6.00, 13.25)	Mann-Whitney	0.073

The post-intervention values in the treatment group were compared to the post-intervention values in the placebo group.

EQ-5D: Euroqol-5 dimension; EQ-VAS: Euroqol-visual analogue scale; HADS: Hospital anxiety and depression scale

6.7.1 EQ-VAS

There was no significant difference in the pre and post-intervention scores for EQ-VAS in either the treatment or the placebo group (table 6.8). However, when comparing the post intervention scores between the treatment group and the placebo group, the score was a significantly higher in treatment group when compared to the placebo group, p=0.019 (table 6.9, figure 6.6).

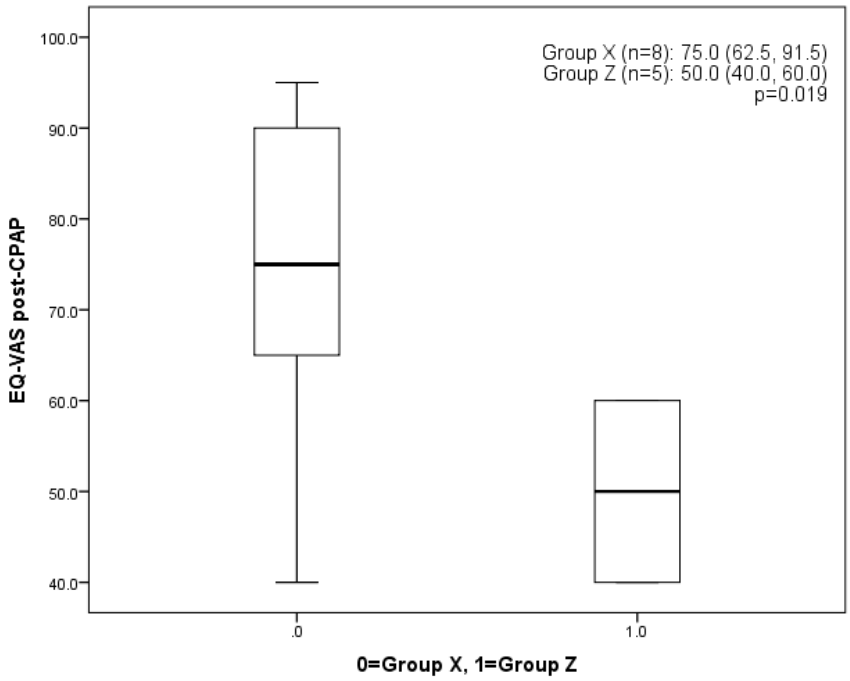


Figure 6.6 EQ-VAS: Comparison of post-intervention values between groups (group X=treatment, group Z=placebo)

The post-intervention EQ-VAS score for the treatment group was compared to the post-intervention EQ-VAS score for the placebo group.

EQ-VAS; Euroqol-Visual Analogue Score

To further evaluate this significant finding the pre-intervention EQ-VAS scores were compared between the treatment group and the placebo group, with no significant difference found, p=0.171 (table 6.10).

Table 6.10 EQ-VAS: Comparison of pre-intervention scores between groups

	Treatment (n=9)	**Placebo (n=5)**	**Statistical test**	**p value**
Pre-intervention	n=8 75.0 (50.0, 80.0)	n=5 59.0 (50.0, 60.0)	Mann-Whitney	0.171

The pre-intervention EQ-VAS score in the treatment group was compared to the pre-intervention score in the placebo group.

EQ-VAS; Euroqol-Visual Analogue Scale

Further analysis of the EQ-VAS score involved calculating the difference between pre and post-intervention scores for each participant. The difference between the treatment group and the placebo group was then compared, and a significant difference was again found (table 6.11). The score was found to improve in the treatment group; 6.5 (-0.75, 15.00) but worsen in the placebo group; -9.0 (-10.0, 0.0), p=0.045.

Table 6.11 EQ-VAS: Difference in pre and post intervention- comparison between groups

	Treatment (n=8)	**Placebo (n=5)**	**Statistical test**	**p value**
Difference in pre and post-intervention scores	6.50 (-0.75, 15.00)	-9.0 (-10.0, 0.0)	Mann-Whitney	**0.045**

The difference in the pre-treatment EQ-VAS and post-treatment EQ-VAS was calculated for each participant. The difference in scores pre and post intervention was then compared between the two groups.

EQ-VAS; Euroqol-Visual Analogue Scale

6.7.2 Sleepiness Scales; ESS and SSS

Analysis of the Epworth sleepiness scale (ESS), found no significant improvement from pre-intervention to post-intervention in either group (table 6.12). However, the treatment group showed a significantly improved post-intervention score when compared to the placebo group, p=0.045 (table 6.13, figure 6.7). There was no significant difference in the pre-intervention scores between the two groups, p=0.106 (table 6.14).

To further evaluate this significant value seen for ESS scores, the difference between pre and post intervention scores was calculated for each participant. A Mann-Whitney test was then used to compare the difference between treatment group and the placebo group, a non-significant difference (p=0.214) was noted (table 6.15).

On analysis of the Stanford sleepiness scale (SSS), there was no significant difference in pre and post-intervention scores for either group (table 6.12). There was also no significant difference in the post-intervention scores when the two groups were compared (p=0.648), (table 6.13).

Table 6.12 Sleepiness scores; ESS and SSS pre and post-intervention

	Pre-intervention Median (Q1, Q3)	**Post-intervention Median (Q1, Q3)**	**Statistical test**	**p value**
ESS (n=9) ***Treatment***	n=9 6.0 (2.5, 11.5)	n=8 4.00 (0.25, 8.75)	Wilcoxon	**0.040**
ESS (n=5) ***Placebo***	n=4 14.5 (8.8, 15.0)	n=4 12.00 (7.50, 16.50)	Wilcoxon	0.705
SSS (n=9) ***Treatment***	n=9 3.0 (2.0, 4.0)	n=7 2.0 (1.0, 3.0)	Wilcoxon	0.157
SSS (n=5) ***Placebo***	n=5 4.0 (2.0, 5.5)	n=4 2.5 (1.3, 4.5)	Wilcoxon	0.257

The pre-intervention ESS score was compared to the post-intervention score in both groups.

ESS: Epworth Sleepiness Scale; SSS: Stanford sleepiness scale

Table 6.13 Sleepiness scales: Comparison of post-intervention values between groups

	Treatment (n=8)	**Placebo (n=5)**	**Statistical test**	**p value**
ESS Post-intervention	4.0 (0.25, 8.75)	12.00 (7.50, 16.50)	Mann-Whitney	**0.045**
SSS Post-intervention	n=7 2.0 (1.0, 3.0)	n=4 2.5 (1.3, 4.5)	Mann-Whitney	0.648

The post-intervention ESS score in the treatment group was compared to the post-intervention ESS score in the placebo group.

ESS: Epworth Sleepiness Scale; SSS: Stanford sleepiness scale

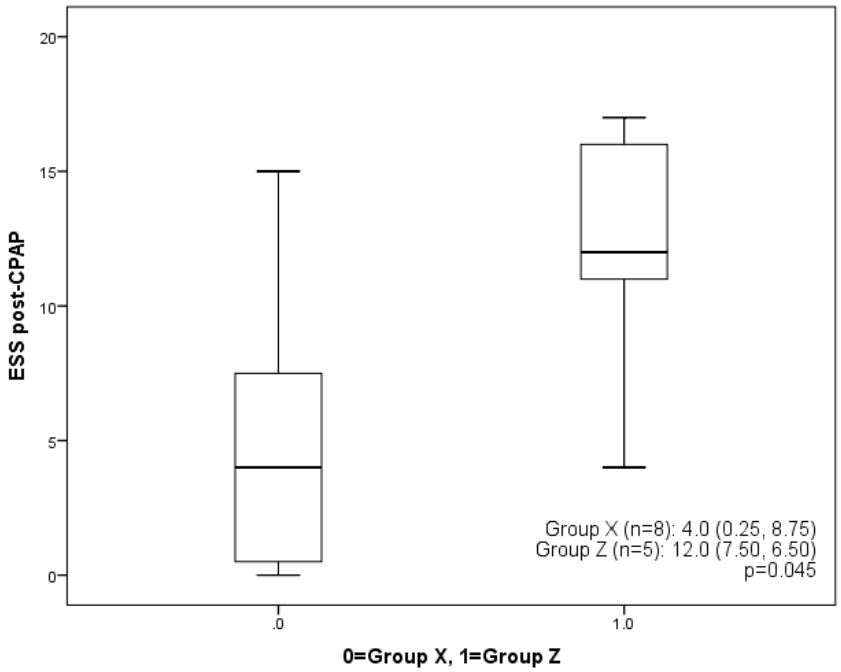


Figure 6.7 ESS: Comparison of post-intervention values between groups (group X=treatment, group Z=placebo)

The post-treatment ESS in the treatment group (group X) was compared to the post-treatment ESS in the placebo group (group Z).

ESS: Epworth Sleepiness Scale

Table 6.14 ESS: Comparison of pre-intervention values between groups

	Treatment (n=9)	**Placebo (n=5)**	**Statistical test**	**p value**
Pre-intervention	n=9 6.0 (2.5, 11.5)	n=4 14.5 (8.8, 15.0)	Mann-Whitney	0.106

The pre-intervention ESS score in the treatment group was compared to the pre-intervention score in the placebo group.

ESS: Epworth Sleepiness Scale

Table 6.15 ESS: Difference in pre and post intervention scores- comparison between groups

	Treatment (n=8)	**Placebo (n=4)**	**Statistical test**	**p value**
Difference in pre and post-intervention scores	-2.5 (-4.8, -0.3)	-1.0 (-3.0, 2.5)	Mann-Whitney	0.214

The difference between the pre-intervention ESS score and post-intervention ESS score was calculated for each participant. The difference between the two groups was then compared.

ESS: Epworth Sleepiness Scale

6.7.3 Lung function and Fractional exhaled nitric oxide (FENO) pre and post- intervention

There was no significant difference noted between pre and post-intervention scores for either the treatment group or the placebo group for FEV_1% predicted, FEV_1/FVC ratio or FENO (table 6.16). Comparison of the post-intervention values for each variable also did not reveal any significant change (table 6.17).

Table 6.16 Spirometry and FENO measurements pre and post-intervention

	Pre-intervention Median (Q1, Q3)	**Post-intervention Median (Q1, Q3)**	**Statistical test**	**p value**
FEV_1 % predicted ***Treatment***	n=9 73.0 (59.5, 96.0)	n=9 81.00 (58.50, 94.00)	Wilcoxon	0.866
FEV_1 % predicted ***Placebo***	n=5 88.0 (60.0, 99.5)	n=5 89.00 (73.00, 96.00)	Wilcoxon	0.461
FEV_1/FVC ***Treatment***	n=9 70.0 (54.0, 79.0)	n=9 70.00 (59.00, 78.50)	Wilcoxon	0.732
FEV_1/FVC ***Placebo***	n=5 74.0 (56.0, 82.0)	n=5 73.00 (62.00, 80.50)	Wilcoxon	0.715
FENO (ppb) ***Treatment***	n=8 38.0 (21.0, 42.5)	n=8 45.00 (27.50, 49.00)	Wilcoxon	0.080
FENO (ppb) ***Placebo***	n=5 37.0 (26.5, 114.0)	n=5 48.00 (22.50, 207.00)	Wilcoxon	0.225

The pre-intervention spirometry and FENO measurements were compared to the post-intervention measurements in both groups.

FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; FENO: Fractional exhaled nitric oxide; ppb: parts per billion

Table 6.17 Spirometry and FENO: Comparison of post-intervention values between groups

	Treatment Median (Q1, Q3)	**Placebo Median (Q1, Q3)**	**Statistical test**	**p value**
FEV_1 % pred	n=9 81.00 (58.50, 94.00)	n=5 89.00 (73.00, 96.00)	Mann-Whitney	0.518
FEV_1/FVC	n=9 70.00 (59.00, 78.50)	n=5 73.00 (62.00, 80.50)	Mann-Whitney	0.699
FENO (ppb)	n=8 45.00 (27.50, 49.00)	n=5 48.00 (22.50, 207.00)	Mann-Whitney	0.518

The post-intervention spirometry and FENO measurements were compared between the treatment group and the intervention group.

FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; FENO: Fractional exhaled nitric oxide; ppb: parts per billion

6.7.4 Peripheral eosinophil count

There was no significant difference in pre and post intervention values for peripheral eosinophilia for either group (table 6.18). There was also no significant difference in the post treatment values when the two groups were compared (table 6.19).

Table 6.18 Peripheral eosinophil count pre and post-intervention

	Pre-intervention Median (Q1, Q3)	**Post-intervention Median (Q1, Q3)**	**Statistical test**	**p value**
Treatment ($x10^9$/L)	n=9 0.29 (0.11, 0.52)	n=8 0.35 (0.11, 0.64)	Wilcoxon	0.674
Placebo ($x10^9$/L)	n=4 0.40 (0.10, 0.55)	n=4 0.36 (0.04, 0.75)	Wilcoxon	1.000

Peripheral eosinophil count pre-intervention was compared to the peripheral eosinophil count post intervention in the two groups.

Table 6.19 Peripheral eosinophil count; comparison post intervention

	Treatment Median (Q1, Q3)	**Placebo Median (Q1, Q3)**	**Statistical test**	**p value**
Eosinophil count ($x10^9$/L)	n=8 0.35 (0.11, 0.64)	n=4 0.36 (0.04, 0.75)	Mann-Whitney	0.724

Peripheral eosinophil count post-intervention in the treatment group was compared to the peripheral eosinophil count post-intervention in the placebo group.

6.7.5 Biochemical markers of the metabolic syndrome

Blood results associated with the metabolic syndrome were analysed pre and post-intervention. There was no significant difference between the pre and post-intervention cholesterol, triglyceride, high density lipoprotein (HDL) or low density lipoprotein levels (LDL) (table 6.20). The post-intervention levels were compared between the treatment and the placebo group, and again there was no significant difference found with any of the metabolic syndrome markers (table 6.21).

Table 6.20 Biochemical markers of the metabolic syndrome pre and post-intervention

	Pre-intervention Median (Q1, Q3)	**Post-intervention Median (Q1, Q3)**	**Statistical test**	**p value**
Cholesterol (mmol/L) ***Treatment***	n=8 5.90 (5.05, 6.00)	n=8 5.70 (4.55, 6.18)	Wilcoxon	0.865
Cholesterol (mmol/L) ***Placebo***	n=5 5.20 (4.20, 6.25)	n=5 5.32 (1.65) 5.90 (3.85, 6.50)	Wilcoxon	0.588
Triglycerides (mmol/L) ***Treatment***	n=8 1.75 (1.20, 2.35)	n=8 1.55 (1.05, 3.08)	Wilcoxon	0.400
Triglycerides (mmol/L) ***Placebo***	n=5 1.30 (0.95, 2.10)	n=5 1.40 (1.00, 1.65)	Wilcoxon	0.498
LDL (mmol/L) ***Treatment***	n=8 3.34 (2.16, 3.97)	n=7 2.70 (2.15, 3.34)	Wilcoxon	0.600
LDL (mmol/L) ***Placebo***	n=5 3.16 (1.67, 4.20)	n=5 3.44 (2.02, 3.97)	Wilcoxon	0.686
HDL (mmol/L) ***Treatment***	n=8 1.65 (1.58, 1.95)	n=8 1.53 (1.20, 1.88)	Wilcoxon	0.310
HDL (mmol/L) ***Placebo***	n=5 1.38 (1.14, 2.10)	n=5 1.67 (1.15, 2.08)	Wilcoxon	0.893

Blood results (markers of the metabolic syndrome) pre-intervention were compared to levels post intervention in the two groups.

HDL: High density lipoprotein; LDL: Low density lipoprotein

Table 6.21 Biochemical markers of the metabolic syndrome: Comparison of post-intervention values

	Treatment Median (Q1, Q3)	**Placebo Median (Q1, Q3)**	**Statistical test**	**p value**
Cholesterol (mmol/L)	n=8 5.70 (4.55, 6.18)	n=5 5.32 (1.65)	Mann-Whitney	0.943
Triglycerides (mmol/L)	n=8 1.55 (1.05, 3.08)	n=5 1.40 (1.00, 1.65)	Mann-Whitney	0.524
LDL (mmol/L)	n=7 2.70 (2.15, 3.34)	n=5 3.44 (2.02, 3.97)	Mann-Whitney	0.343
HDL (mmol/L)	n=8 1.53 (1.20, 1.88)	n=5 1.67 (1.15, 2.08)	Mann-Whitney	0.833

Blood results (markers of the metabolic syndrome) taken post-intervention were compared between the treatment group and the placebo group.

HDL: High density lipoprotein; LDL: Low density lipoprotein; HbA1c: Haemoglobin A1c

6.7.6 Healthcare utilisation

The annual oral corticosteroid (OCS) exacerbation rate, GP visits, A&E visits and hospital admission rates were divided by 4 to give a 3 monthly value that was comparable to the three-month period observed during the study. There was no significant difference in any of these rates when comparing pre-intervention to the post-intervention values in both groups (table 6.22).

However, when the post-intervention values were compared between the two groups, there were significantly more OCS requiring exacerbations in the placebo group when compared to the treatment group ($p<0.001$) (table 6.23). To further explore this, the difference between exacerbation rate was calculated for each participant and then the two groups compared using a Mann-Whitney test (table 6.24). However, there was a non-significant result when comparing the treatment group to the placebo group, indicating there was no difference in the OCS requiring exacerbation rate between the two groups ($p=0.083$).

Table 6.22 Healthcare utilisation pre and post-intervention

	Pre-intervention Median (Q1, Q3) Mean±SD	**Post-intervention Median (Q1, Q3) Mean±SD**	**Statistical test**	**p value**
OCS exacerbations ***Treatment***	n=9 0.75 (0.38. 1.88) 1.11±0.99	n=9 0.00 (0.00, 1.00) 0.44±0.73	Wilcoxon	0.235
OCS exacerbations ***Placebo***	n=5 1.0 (0.38, 2.25) 1.25±0.97	n=5 2.00 (1.00, 2.50) 1.80±0.84	Wilcoxon	0.066
GP visits ***Treatment***	n=9 0.25 (0.13, 1.75) 1.08±1.74	n=9 0.00 (0.00, 2.00) 1.11±2.09	Wilcoxon	0.438
GP visits ***Placebo***	n=5 0.75 (0.63, 1.75) 1.10±0.80	n=5 2.00 (0.00, 2.00) 1.20±1.10	Wilcoxon	0.684
A&E visits ***Treatment***	n=9 0.00 (0.00, 0.13) 0.06±0.11	n=9 0 0	Wilcoxon	0.157
A&E visits ***Placebo***	n=5 0.00 (0.00, 0.63) 0.25±0.35	n=5 0.00 (0.00, 0.50) 0.20±0.45	Wilcoxon	0.655
Hospital admissions ***Treatment***	n=9 0.00 (0.00, 0.13) 0.06±0.11	n=9 0 0	Wilcoxon	0.157
Hospital admissions ***Placebo***	n=5 0.10±0.22 0.00 (0.00, 0.25)	n=5 0.00 (0.00, 0.50) 0.20±0.45	Wilcoxon	0.317

The pre-intervention values were calculated by dividing the annual number of events by 4. These were compared to the post-intervention values (number of events during the three month study period) in both the treatment group and the placebo group

OCS; oral corticosteroid; GP; General Practitioner; A&E: Accident and Emergency

Table 6.23 Healthcare utilisation: Comparison of post-intervention rates

	Treatment Median (Q1, Q3)	**Placebo Median (Q1, Q3)**	**Statistical test**	**p value**
OCS exacerbations	n=9 0.00 (0.00, 1.00) 0.44±0.73	n=5 2.00 (1.00, 2.50) 1.80±0.84	Kendall's	**<0.001**
GP visits	n=9 0.00 (0.00, 2.00) 1.11±2.09	n=5 2.00 (0.00, 2.00) 1.20±1.10	Kendall's	0.496
A&E visits	n=9 0 0	n=5 0.00 (0.00, 0.50) 0.20±0.45	Kendall's	0.271
Hospital admissions	n=9 0 0	n=5 0.00 (0.00, 0.50) 0.20±0.45	Kendall's	0.271

The post-intervention healthcare utilisation rates were the number of exacerbations or GP/A&E visits or hospital admissions during the three month study period. These results were compared between the treatment group and the intervention group.

OCS; oral corticosteroid; GP; General Practitioner; A&E: Accident and Emergency

Table 6.24 OCS requiring exacerbations: Difference in pre and post-intervention scores-comparison between groups

	Treatment	**Placebo**	**Statistical test**	**p value**
Difference in pre and post-intervention scores	n=9 -0.5 (-1.9, 0.5)	n=5 0.5 (0.3, 0.9)	Mann-Whitney	0.083

The pre-intervention values were calculated by dividing the annual number of events by 4. The difference between the number of OCS requiring exacerbations pre-intervention and the number of OCS requiring exacerbations during the 3 month study period were calculated for each participant. This difference was then compared between the two groups.

OCS: oral corticosteroid

7 Discussion

7.1 The association between asthma and obstructive sleep apnoea (OSA)[172]

In this systematic review we observed a high prevalence of OSA in asthma of 19-60%, and this was higher in severe/difficult to treat (SDTA) populations at 50-95%. OSA risk assessed using validated questionnaires reports a prevalence of 8-52.6%. Clinical outcomes were worse in asthma patients with co-existing OSA. This prevalence is similar to that reported in a meta-analysis by Kong et al[232], who demonstrated a prevalence of OSA of 49.5%, and OSA risk of 27.5%. However, the latter study did not analyse asthma severity or report on associated clinical outcomes.

All studies reported an increased prevalence of OSA when using polysomnography (PSG) diagnosis. Only one study reported data refuting the relationship between asthma and OSA risk[207], and this was a questionnaire based study. The latter study did have robust asthma diagnostic criteria, so the conflicting results are notable. However, asthma severity measures were not reported and it is possible that this population represents a milder asthma subgroup followed up in primary care.

The concomitant diagnosis of OSA and asthma was associated with worsened asthma-related clinical outcomes. However, this finding was not universal between studies. Two PSG studies demonstrated worse clinical outcomes in OSA[203,205], whereas one PSG study showed no significant difference[206]. All six questionnaire studies that looked at clinical outcomes showed worse outcomes in OSA. However, although Tay et al demonstrated worse Asthma Control Test scores (ACT) and Asthma Quality of Life Questionnaire scores (AQLQ) in the OSA

group using a univariate analysis, this was not reproduced in a multivariate analysis[214]. Kim et al demonstrated a worsening of ACT scores with OSA that failed to reach significance[215].

Only two PSG studies reported a prevalence of OSA in severe asthma. The study by Yigla et al demonstrated a particularly high OSA prevalence of 95%, but this population had above normal body mass index and neck circumference[208]. Additionally, corticosteroid use could be an independent predictor of OSA due to local myopathic effects in the upper airways[159]. Julien et al found an increased prevalence of OSA in severe asthma (50%) and also in moderate asthma (23%), with a prevalence of 12% in controls, although this was not significant in moderate asthma compared to controls[206]. A questionnaire based study reported a prevalence of OSA in severe asthma as 26% compared to 16% in non-severe asthma and 3% in controls[209]. Both studies used robust asthma and severe asthma criteria. Questionnaires to diagnose OSA rely on OSA symptoms, and it may be that the OSA prevalence in this study is more reflective of the symptomatic general population at 2% in women and 4% in men[83], which is matched more closely in the study control group (3%). Julien et al used PSG to diagnose OSA, which does not rely on symptoms and this may explain the higher prevalence in the control group (12%)[206] which is closer to that of the asymptomatic general population of 9% of women and 24% of men[83].

All studies were systematically reviewed by two independent reviewers and only those that used either a PSG or validated questionnaire were included in this review. A pooled systematic analysis that included the Sleep Apnoea Scale of the Sleep Disorders Questionnaire (SA-SDQ), Berlin and STOP-BANG questionnaires reported sensitivity and specificity to be 77% and 53% respectively[174].

There are limitations to this review, particularly concerning the diagnostic criteria of both clinical conditions. Although the questionnaires are validated for the detection of OSA risk, there is still potential for error as an overnight sleep study is required for diagnosis with full polysomnography being recognised as the gold standard. Alternative methods such as limited-channel sleep studies are often recognised alternatives but interestingly none of the studies used this method. It should also be noted that the questionnaires have not been specifically validated in asthma populations and clinical symptoms of OSA and asthma can overlap. Participants were also included in studies without consistent confirmation of asthma diagnosis. It is notable that of the six PSG studies, two of these studies relied on a previous physician diagnosis of asthma, one study used self-reported asthma and one study used unquantified reversible airway obstruction. Only two studies had criteria similar to the American Thoracic Society (ATS) or Global Initiative for Asthma (GINA) guidelines. Of the questionnaire based studies, only eight of the thirteen studies demonstrated evidence of robust asthma diagnostic criteria.

It is reasonable to assume that many of the participants in the questionnaire based studies by Teodorescu et al could overlap. The cross-sectional study in 2012[212] has reported that it is an expansion of other studies included in this review[169,210,213]. The impact of this should be considered, particularly given the limited number of studies available.

The effect of confounders such as body mass index (BMI) are not adequately accounted for in all studies. Yigla et al found an unexpectedly high prevalence of OSA in severe asthma at 95%[208], which could be attributed to steroid use. However, the average BMI and neck circumference were both higher than normal in this population, both of which are independent

risk factors for OSA. Without a control group it is difficult to ascertain the cause of this unexpectedly high prevalence of OSA. The population studied by Shaarawy et al[204] also had a mean BMI that would fall within obese range, but the prevalence of OSA in this group is lower than other PSG based studies with lower BMI populations. Zidan[203] and Julien[206] et al also had overweight populations, but mean BMI was not significantly different from the control groups. Obesity is an important co-morbidity to consider, not only because it increases the likelihood of OSA but also due to the association with asthma. The interplay between obesity, asthma and OSA is complex and it would be ideal to ascertain the direction of this relationship but given the cross-sectional nature of the majority of studies this is beyond the scope of this review.

Despite the discussed limitations, this systematic review of the current evidence found an association between OSA and asthma that is stronger than that of the general population[83]. The impact of OSA on asthma-related clinical outcomes in co-existing conditions was inconclusive. The aim of the observational study was to further explore these questions in a cross-sectional and prospective manner using formal overnight limited-channel sleep studies to diagnose or exclude OSA.

7.2 Observational Studies

7.2.1 Cross-sectional

7.2.1.1 Strengths and findings

This cross-sectional study adds to the current limited literature already discussed with regards to the association between asthma and OSA, and the impact of OSA on asthma-related

clinical outcomes. Participants underwent either a limited-channel sleep study or full polysomnography to exclude or diagnose OSA. Participants in the CPAP group had a pre-existing diagnosis of OSA and were already established on treatment. This is in contrast to current literature, where the majority of studies relied on questionnaires to diagnose OSA risk rather than confirm a diagnosis of OSA using formal sleep studies[172]. This cross-sectional study focused predominantly on severe/difficult to treat asthma, with the majority (88%) having a diagnosis of severe asthma. A high prevalence of OSA (70%) was noted in this population. Recent systematic review identified only two comparable studies involving severe asthma populations; Julien et al found a 50% prevalence of OSA in severe asthma[206], and Yigla et al found a prevalence of 95%[208].

The cross-sectional study population was predominantly female (71%), middle-aged (mean age 48.7 years), Caucasian (79%), non-smoking (65%), with a high median BMI (32.1) and required high doses of inhaled corticosteroids (median 2000 micrograms/day BDP equivalent). This is comparable to data collected from the severe asthma British Thoracic Society (BTS) registry on other severe asthma populations within the United Kingdom (UK)[233]. However, interestingly the cross-sectional population had a maintenance oral corticosteroid use of 37% which is relatively low when compared to the BTS registry data of 57.4%[233]. The median dose of oral corticosteroids was also slightly lower at 10mg (5, 15mg) when compared to the median dose of 15mg reported in the BTS registry data[233].

Body Mass Index (BMI) ($p<0.001$), increasing age ($p<0.001$) and male gender ($p=0.026$) were found to be predictors of OSA ($AHI\geq5$) in this severe asthma population. These are well

known risk factors for the development of OSA in general populations. Interestingly, the Epworth Sleepiness Scale (ESS) did not predict OSA in this particular model. The ESS is used to asses daytime sleepiness in the context of sleep medicine[191]. Further analysis of the Epworth sleepiness score showed that the ESS was a predictor for moderate-severe OSA (AHI≥15), p=0.031, along with BMI (p<0.001) and male gender (p=0.001). The test for trend also showed a significant increase in ESS with increasing severity of OSA (p=0.008). Sleep quality is known to be poor in severe asthma, with frequent awakenings and reduced slow-wave sleep due to poorly controlled asthma symptoms[101,169-172]. This likely results in increased daytime hypersomnolence. This could explain why the ESS fails to reliably predict milder cases of OSA in this population.

Oral corticosteroid use is thought to be a predictor of OSA, particularly given the local myopathic effect in the upper airway which is thought to predispose to the development of OSA[159]. However, oral corticosteroid use was not found to be a predictor of OSA in our severe asthma population. Furthermore, there was no significant difference when comparing the no-OSA group to either the OSA (AHI≥5) group (p=0.281) or the moderate-severe OSA group (p=0.124). However, it should be noted that only 37% of the total population required maintenance corticosteroid use, which is relatively low when compared to other severe asthma populations[233].

Standardised questionnaires including the ACQ-7, AQLQ, EQ-5D, EQ-Visual Analogue, EQ-VAS and HADS were used to evaluate clinical outcomes in relation to severity of OSA. There was a significant trend for worsening scores with increasing severity of OSA in all of these

questionnaires with the exception of HADS-Anxiety. This suggests that OSA negatively impacts on asthma control and quality of life in addition to general health-related quality of life scores. However, there was no significant trend noted for FEV_1% predicted, FEV_1/FVC ratio or healthcare utilisation which included annual number of OCS requiring exacerbations/GP visits/A&E visits/hospital admissions and total HDU/ITU requirement. Systematic review found only three comparable studies that used PSG based methods of diagnosis to report asthma-related clinical outcomes in relation to OSA. Of these three studies, Wang et al found an increased number of severe asthma exacerbations with more severe OSA[205], Zidan et al found that FEV_1 worsened with increasing severity of OSA[203]. In contrast, Julien et al found no correlation between AHI and asthma severity, FEV_1 or AQLQ scores[206].

One hypothesis was that asthma control, quality of life scores and healthcare utilisation would be better in the CPAP treated group when compared to the untreated moderate-severe OSA group. However, direct comparison of the two groups found no statistically significant difference. The number in the CPAP group was relatively low (n=27), which could account for this failing to reach statistical significance.

Interestingly, the number of participants requiring biological treatment significantly decreased with increasing severity of OSA (p=0.002), despite significantly worsening asthma symptoms and quality of life. The trend for IgE which can be a marker of allergy was not significantly lower with increasing severity of OSA and neither was peripheral eosinophil count or FENO. The predominant biological treatment was omalizumab during the recruitment stage, and anti-

IL-5 therapy was only just being introduced, a small number of participants were in clinical trials with other biological treatments (eg.lebrikizumab).

The proportion of participants with self-reported hypercholesterolemia ($p=0.002$), diabetes ($p=0.010$) and hypertension ($p<0.001$) increased with increasing severity of OSA. This was supported by increasing levels of serum triglycerides ($p<0.001$) and HbA1c ($p=0.004$) with increasing severity of OSA. HDL decreased with increasing severity of OSA ($p=0.023$).

A subgroup of 59 participants underwent detailed whole body composition measurements using DEXA scanning. Percentage body fat ($p=0.006$), percentage android fat ($p=0.001$), android/gynoid ratio ($p<0.001$), fat mass index ($p<0.001$), percentage fat trunk/percentage fat limb ratio ($p<0.001$) and trunk/limb fat mass ratio ($p=0.002$) were all found to correlate with AHI in females. In males, it was only fat mass index (FMI) that was found to significantly correlate with AHI/ODI ($p=0.028$). This may be because the number of males who underwent a DEXA scan was comparably lower (17 versus 42 females). In females, all body composition measurements were found to significantly correlate with BMI. In males, FFM ($p<0.001$), body fat % ($p<0.001$), android fat % ($p=0.008$) and gynoid fat % ($p=0.009$) were also found to correlate with increasing BMI.

Increasing BMI has been shown to be a risk factor for OSA. This study has shown increasing FMI to be associated with increasing severity of OSA in both genders, however this effect is not independent of BMI. In clinical practice, BMI is likely to be a simpler tool for the prediction of OSA and more readily available than DEXA scanning.

The concentration of leptin was higher in the OSA group (AHI≥5) when compared to the no-OSA group (p=0.024). However, a significant correlation with leptin and increasing severity of OSA using AHI/ODA was not found (p=0.083). As expected, the correlation of leptin significantly increased with increasing BMI: BMI<25; leptin 10.1 (7.0, 18.0) ng/ml, ≥25 BMI <30; leptin 11.5 (9.6, 19.5) ng/ml and BMI ≥30; leptin 31.6 (19.5, 41.8) ng/ml, p=0.001. This is comparable to other literature which has demonstrated mean serum leptin concentrations of 34.78 ± 13.96 ng/ml in obese subjects, and mean leptin levels of 10.6 ± 4.2 ng/ml in non-obese subjects[234]. Studies show exogenous leptin can augment induced airway inflammation[64,66], but evidence of a direct association with asthma is lacking[68,69].

Wong et al found plasma IL-6 levels to be higher in allergic asthma when compared to healthy controls; 3.42 (0.00-10.51) pg/ml compared to 0.61 (0.00-4.42) pg/ml, but this did not reach statistical significance[235]. The median concentration of IL-6 (OSA and no-OSA) found during the cross-sectional study was comparatively higher at 120.8 (24.3, 614.6) pg/ml and mean 327.3 ± 370.8 pg/ml when compared to the study by Wong et al. However, as previously discussed IL-6 levels are increased in diabetes and hypertriglyceridemia[111,115] and this was not accounted for in the analysis, which may partly explain this difference, and the large standard deviation noted. A small study of 18 participants with OSA, and 20 controls found higher levels of plasma IL-6 in those with OSA 6.4 ± 3.7 pg/ml compared to controls 4.9 ± 2.9 pg/ml, p<0.05[236]. However, this finding was not replicated in the cross-sectional study; no-OSA 123.7 (26.4, 523.9) pg/ml versus OSA (AHI≥5); 120.8 (22.3, 648.8) pg/ml, p=0.872.

There was no significant difference in adiponectin levels between the no-OSA and the OSA group (AHI≥5); 3.5 (0.9, 4.7) µg/ml versus 2.5 (0.5, 5.0) µg/ml, p=0.224. Although, previously a study by Zeng et al did find that adiponectin levels in obesity were significantly lower in the moderate (15.1 µg/ml) p=0.017, and severe OSA (11.7 µg/ml) p=0.002 groups when compared to the no-OSA group (18.3 µg/ml). However, the finding was not replicated in non-obese individuals[237].

7.2.2 Prospective case-control study

7.2.2.1 Strengths and findings

This prospective case-control study enabled longitudinal data to be collected over a twelve-month period. The population was again comparable to other severe asthma populations and was predominantly female (65%), middle-aged (median 49.5 years), Caucasian (83%) with high BMI (median 29.8). Although BMI was slightly lower than the cross-sectional study (median 32.1).

Age (p<0.001) and BMI (p<0.001) were again found to increase with increasing severity of OSA. In contrast to the cross-sectional study there was no significant correlation with asthma symptoms (ACQ), asthma quality of life (AQLQ), anxiety and depression scores (HADS) or general quality of life scores (EQ-5D and EQ-VAS) with increasing severity of OSA. This could be due to the relatively low number of participants (n=86) when compared to the cross-sectional study (n=191). Again, there was no significant correlation with healthcare utilisation and severity of OSA. As expected, there was significantly more hypertension (p<0.001) and dyslipidaemia (p=0.006) in the OSA group (AHI≥5) when compared to the no-OSA group.

Additionally, levels of triglycerides were significantly higher in the OSA (AHI≥5) group; 1.7 (1.2, 2.5) mmol/L when compared to the no-OSA group; 1.2 (0.9, 1.9) mmol/L (p=0.010). A similar finding was found with HbA1c (%) which was significantly higher in the OSA group, p=0.001.

7.2.3 Limitations

There is possibility of a bias towards recruiting participants with OSA in the observational studies. There were over 900 patients in the dendrite severe asthma database, but it was unclear how many of these were under active/recent follow up at the time of recruitment. Some patients were no longer attending the service for various reasons such as moving to a different region or centre and had not been followed up recently in the severe asthma service. Efforts were made to recruit patients regardless of symptoms of sleepiness but a degree of bias may not have been entirely avoidable. Participants with awareness of the symptoms of obstructive sleep apnoea are more likely to participate in a study they feel is relevant to them and any symptomatology they may be experiencing. Additionally, clinicians or nurses aware of the study criteria may have instinctively encouraged patients with sleep symptoms into a study that appeared clinically relevant to them. This could potentially have led to an increase in the observed prevalence of OSA in this population. However, this process of screening patients for OSA is more reflective of a real-life severe asthma population and the recruitment and therefore prevalence in likely to be reflective of this. This single-centre observational study has added to the current literature, as systematic review identified only a small number of pre-existing studies with similar criteria. However, large multicentre studies recruiting consecutive patients with severe asthma are required to more accurately measure the actual prevalence of OSA in severe asthma. Additionally, the use of a large national dataset such as

the Clinical Practice Research Datalink (CPRD)[238] would provide further insight into the true prevalence of OSA in asthmatics within the UK. The CPRD links data from primary care to other health related data to provide a longitudinal, representative UK population health dataset that includes over 45 million patients.

The median BMI (32.1) is in the obese range which will have impacted on the high prevalence of OSA in this population, as BMI is known to be a risk factor for OSA. However, as previously described this BMI is comparable to other severe asthma populations across the UK and is therefore reflective of a real-life severe asthma population. Ideally, comparison with a control group of asthmatics with a healthy BMI would have occurred, but this would have been difficult to achieve as weight gain and obesity is prevalent within severe asthma.

One of the key strengths of this study is that all participants have undergone a diagnostic sleep study to diagnose obstructive sleep apnoea. It should be appreciated that in a small proportion of the study population a full polysomnography (PSG) was conducted (in the event of failing to complete a home limited-channel sleep study (LCSS) of acceptable quality). A full PSG is generally more sensitive than a LCSS and therefore these participants may have an AHI that is higher than what would be observed on a LCSS. This was only a small proportion of participants (n=13, 7.9%) in the undiagnosed sleep apnoea group (n=164). 8 of these PSGs were scored using the cardio-respiratory monitoring, whereas 5 were scored using full polysomnography. Ideally all participants would have had the same diagnostic test, however this again is likely to be reflective of a real-life asthma population as not all patients would achieve an acceptable reading from a home sleep study. The participants in the CPAP group

all had a diagnosis of pre-existing OSA and were established on CPAP prior to the start of the study. Although best efforts were made to obtain the original sleep report this was not always possible due to the time that had elapsed between diagnosis and the start of the study. A proportion of participants had been diagnosed based on an overnight oximetry report which is not thought to be as sensitive or specific as a LCSS. However, all participants had been assessed at a centre with the skills and facilities to diagnose OSA and establish CPAP treatment.

The proportion of participants on maintenance oral corticosteroids was relatively low at 37%. Median inhaled steroid doses were high, as expected, at 2000 micrograms/day (BDP equivalent). There was a small proportion of participants taking nebulised steroids (7%) or receiving triamcinolone injections (1%), and this was not taken into account during the analysis. The nebulised steroid use was often intermittent and inconsistent. Therefore, the effect on the analysis is likely to be negligible.

7.2.4 Does Continuous Positive Airway Pressure (CPAP) treatment of obstructive sleep apnoea (OSA) improve asthma-related clinical outcomes in patients with co-existing conditions?[175]

This systematic review has included all current literature with regards to the impact of CPAP on co-existing asthma in OSA patients. We found evidence to support the hypothesis that CPAP significantly improves asthma-related quality of life. The majority of studies found that daytime or night-time asthma symptoms improve with CPAP. However, current evidence

does not support an improvement in clinically significant asthma control using standardised measures such as the ACT or Asthma Control Questionnaire (ACQ). CPAP does not improve lung function in this meta-analysis, but this finding is of unclear clinical significance in the asthmatic population.

The findings of this review are important because a high prevalence of OSA has been consistently reported in asthma, and particularly within severe asthma populations[208]. Patients with severe asthma and co-existing OSA have been shown to have increased sputum neutrophil counts and evidence of airway remodelling[239]. Asthma patients with a neutrophilic rather than the typical eosinophilic phenotype are less likely to respond to high dose inhaled corticosteroids or oral corticosteroids[239]. This review demonstrates that CPAP treatment can improve asthma-related quality of life and symptoms in patients with co-existing asthma and OSA. This has important implications for the screening of asthma patients for the presence and the subsequent treatment of OSA, particularly within severe or refractory asthma populations.

In five of the twelve studies[221,240,204,229,230] there was clear evidence of the application of robust asthma diagnostic criteria following international guidelines. Asthma severity was measured in two of the studies in accordance with current guidelines[211,229] but one of the studies[225] used patient-reported symptoms via a visual analogue scale. Polysomnography (PSG) is the gold-standard tool for the diagnosis of OSA and this was the case in eight of the studies. One study used limited-channel sleep studies in 70% and PSG in 30% of patients[221], while one of the retrospective reviews used previous home limited-channel sleep study records[225]. Two cross-sectional questionnaire-based studies relied on records of a previous

OSA diagnosis, however no information was provided concerning the diagnostic method used or the OSA severity. This raises questions about the reliability of the OSA diagnosis[211,212]. As previously mentioned, these two studies appear to include data from the same study population. However, the two studies report different outcomes and have therefore both been reported in this review[211,212]. It was reassuring to note that the majority of studies used PSG for the diagnosis of OSA, although limited-channel sleep studies are a well-recognised alternative. The duration of CPAP treatment varied between studies and ranged from two weeks to twenty-five months for the prospective studies. OSA patients often take longer than a month to become fully complaint with CPAP and this could account for differences in results seen, particularly as Serrano-Pariente et al demonstrated bigger improvements in both ACQ and mini AQLQ at six months when compared to three months of CPAP treatment[221]. Five of the twelve studies reported CPAP compliance of at least four hours per night. This is generally regarded as the minimum hours of CPAP required to improve sleepiness scores in OSA[241]. However, the duration of CPAP use per night needed to improve asthma-related clinical outcomes is not known.

Asthma-related quality of life is measured using either the validated AQLQ or the abbreviated mini-AQLQ. The AQLQ assesses four domains within asthma (symptoms, activity limitation, emotional function and environmental stimuli). The AQLQ scale ranges from 0 (worst) to 7 (best) and a change of 0.5 would signify a clinically meaningful change[188,187,222]. Two of the twelve included studies evaluated asthma-related quality of life and both found a clinically significant improvement with CPAP [240,221], with study heterogeneity being minimal (as shown by the I_2 value of 0%; figure 5.2). Of note, the duration of CPAP was six weeks in the study by Lafond et al compared to six months in the study by Serrano-Pariente et al. However,

AQLQ takes into account asthma-related quality of life over the preceding four weeks and would therefore be appropriate in both studies. Serrano-Pariente et al demonstrated a mean significant improvement of 0.51. However an improvement of 0.5 or more was only demonstrated in patients with either moderate-severe asthma (0.61) or severe OSA (0.54), and the results failed to reach statistical significance or clinical relevance in either mild asthma or mild-moderate OSA[221]. Lafond et al demonstrated a mean improvement of 0.8, and this was correlated with both body mass index (BMI) and severity of OSA. Severity of asthma was not reported in this study and the AQLQ results were not compared between severe OSA and mild-moderate disease[240].

Asthma control is usually measured using the validated ACT[242] or ACQ[227]. There was significant heterogeneity in the study designs, populations and outcome measures which precluded meta-analysis of asthma control scores. Shaarawy et al used a prospective quasi-experimental study design with robust asthma diagnostic criteria and included a group of poorly controlled asthmatics[204]. Conversely, although the study population was much larger in the study by Kauppi et al, it was based on retrospective recall of symptoms and ACT pre-CPAP which was then compared to current ACT. The mean duration of CPAP was more than 5 years and therefore a significant risk of recall bias is present with this particular study[225]. Four studies reported improvements in daytime and/or night-time asthma symptoms using different scoring systems or visual analogue scores, but without reporting formal ACT/ACQ scores, making it impossible to make comparisons[135,223,224,229]. Two studies (one using ACT and one using ACQ) found an improvement with CPAP, whereas one study (using ACT alone) found no significant improvement. Serrano-Pariente et al demonstrated significant improvement in patients with either moderate-severe asthma or severe OSA at baseline[221].

However, it is important to note that a clinically significant improvement in mean ACQ (≥0.5) was not reached. Shaarawy et al[204] looked at fifteen poorly controlled asthmatics (ACT≤17 at baseline) and found no improvement in ACT scores after CPAP. Shaarawy et al studied a population with less severe OSA (mean AHI 23.5) compared to Serrano-Pariente et al (46.3) and this could potentially account for these findings. Kauppi et al was the only study to demonstrate both a clinically and statistically significant improvement in ACT with CPAP. In this study, poor ACT scores at baseline were significant predictors of clinical improvement in ACT but severity of OSA was not a predictor[225].

Meta-analysis of FEV_1(% predicted) measurements pre- and post-CPAP demonstrated no significant improvement with CPAP. The clinical importance of this is unclear as asthmatics have variable lung function and a proportion of severe asthmatics have fixed airflow obstruction. Lung function does not correlate with measures of asthma control in asthmatics with fixed airflow obstruction. Only two studies reported the FEV_1/FVC ratio, which is a measure of airflow obstruction and none of the studies adjusted for patients with fixed airflow obstruction. This makes clinical interpretation of these results difficult because improvement in FEV_1 would only be expected to reduce symptoms and measures of control in those without chronic fixed airflow obstruction[243]. Chan et al found a significant improvement in pre-bronchodilator peak expiratory flow rates (PEFR) but this was a relatively short study of only two weeks, and formal spirometry was not recorded[244]. Interestingly Wang et al[230] when looking retrospectively at serial lung function pre- and post-initiation of CPAP, found that CPAP significantly reduced annual FEV_1 in asthmatics with severe OSA compared to mild-moderate OSA and no-OSA[230]. Serrano-Pariente et al found fractional exhaled nitric oxide (FENO) to be significantly reduced after six months of CPAP[221]. However, non-asthmatic

patients with OSA can have elevated FENO levels[145] potentially attributable to upper airway inflammation secondary to repetitive upper airway obstruction. FENO has been shown to reduce after CPAP therapy in non-asthmatics with OSA[145], although this effect has not been shown in all studies. Another important factor is that cigarette smokers were included in this study. Cigarette smoke is known to affect FENO[245]. This makes interpretation of this result in one study difficult.

CPAP therapy can improve quality of life in patients with moderate-severe OSA, and it is logical that this can also impact on asthma-related quality of life (AQLQ scores) and the improvement that has been seen in this review. It is difficult to fully separate quality of life improvements seen as a result of treating OSA, from improvements as a result of reduced asthma symptoms. This review has found conflicting evidence with regards to asthma control and symptoms (ACQ) when CPAP treatment is used for co-existing OSA. Reasons for this may include that CPAP may be poorly tolerated, particularly in severe asthma. The CPAP masks are recognised as being claustrophobic for some people, and this effect may be exacerbated in asthmatics who struggle with nocturnal symptoms of breathlessness and awakenings due to their asthma. Ease of reliever medication during the night whilst the CPAP mask is in situ may also pose concern for asthmatics who feel reliance on this medication during the night.

This systematic review's key strength is that it includes all study populations of asthmatics with co-existing OSA that have received CPAP treatment. We were able to evaluate a number of different asthma-related clinical outcomes including quality of life scores, asthma control/symptoms, asthma severity and lung function/physiological measures. Meta-analysis

enabled pooled results of asthma quality of life scores and lung function. Nevertheless, limitations include the small number of studies currently available, and heterogeneity of outcome measurements meant that meta-analysis was only possible in two of the clinical outcomes. Furthermore, the individual studies did not report variability of change from pre- to post-CPAP values, so to enable meta-analysis the pre- and post-CPAP groups had to be analysed as independent groups which may have resulted in an over-estimate of variability in each study. However, because we assumed greater variability than was present this is unlikely to have affected the overall trend of results as the improvement seen in AQLQ will still be at least as statistically significant as the result calculated. The lack of placebo-controlled studies should also be carefully considered when interpreting the results of this review. The placebo effect is well recognised within medical trials, and the CPAP device in itself could act as a powerful visual prompt for patients receiving treatment.

7.3 Interventional study

This was a randomised, double-blind, placebo-controlled pilot feasibility study to determine the impact of co-existing OSA on asthma-related quality of life. To our knowledge, this is the first RCT with sham CPAP to be conducted with regards to this particular topic. Systematic review identified only 12 previous studies that evaluated the effect of CPAP treatment of co-existing OSA on asthma-related clinical outcomes, and these studies were prospective quasi-experimental or observational in design[175]. Meta-analysis of these previous studies suggests that CPAP could potentially have a positive impact on asthma-related quality of life, but the evidence is not yet available to reach any firm conclusions on this topic[175].

7.3.1 Study findings

The overall drop-out rate during the study was 48% which is higher than the expected drop-out rate of 10 participants per group (33%). There were several key problems noted during the study that accounted for the high drop-out rate. Participants reported general problems such as "not wanting to take the machine on holiday", and the fact that the machine is "noisy", "cold" and "uncomfortable to use". Participants also reported problems more specific to a severe asthma population that included; "facial eczema", "a gasping sensation and need for nebuliser use" and worsening "nasal congestion". It was thought that there would be more of an issue with sham-CPAP as the patient would not have the improvement in sleep symptoms to encourage ongoing use, however the drop-out rate was similar in both the CPAP group (47%) and the placebo group (50%).

As expected, due to the low number of participants that completed the study, the results were predominantly non-significant, including AQLQ which was the primary outcome of the study. The median pre-intervention AQLQ was 4.4 (3.30, 4.85) and remained at 4.4 (3.73, 5.58) post intervention with CPAP. However, in the placebo group there was a trend for worsening AQLQ with a reduction from 4.55 (3.18, 5.18) to 3.80 (3.00, 5.10) post sham CPAP which is above the minimal clinically significant change, although this failed to reach statistical significance ($p=0.715$). Asthma control assessed using the ACQ was found to improve by 0.5 post intervention, in both the treatment and the placebo groups which is the minimal clinically significant difference, but this failed to reach statistical significance in either group.

The EQ-Visual Analogue Score (EQ-VAS) did not significantly change post intervention in either group. The EQ-VAS values remained static in the treatment group; 75.0 (50.0, 80.0) pre-intervention to 75 (62.5, 91.5) post-CPAP, whilst decreasing in the placebo group from 59.0 (50.0, 60.0) to 50.0 (40.0, 60.0) post sham CPAP. However, when comparing the post-intervention values between the two groups there was noted to be a significant difference ($p=0.019$). The baseline pre-intervention value in the CPAP treated group was higher than that of the placebo group which could have contributed to this effect although it did not reach statistical significance. To further explore the difference noted in the post-intervention values, the difference between pre and post-CPAP scores was calculated for each participant and compared between the two groups. A significant result was again noted ($p=0.045$). Although it is plausible that those in the placebo group experienced a deterioration in quality of life as a result of the sham CPAP, this should be cautiously interpreted particularly given the difference in the pre-intervention values between the two groups.

There was no significant difference in the number of OCS requiring exacerbations from pre-intervention to post-intervention in either group. A significant difference was noted in the post-treatment values ($p<0.001$). The difference between the number of OCS requiring exacerbations pre-intervention and the number during the 3 month study period was then calculated for each participant. This difference was compared between the two groups and was non-significant ($p=0.083$) making it unlikely that CPAP treatment had any impact on the number of OCS requiring exacerbations.

The Epworth sleepiness score (ESS) was higher at baseline in the placebo group; 14.5 (8.8, 15.0) when compared to the treatment group; 6.0 (2.5, 11.5) although this difference was not statistically significant (p=0.106). Post-intervention with CPAP, the ESS significantly improved in the treatment group (p=0.040), with no significant change in the placebo group (p=0.705). The post-intervention ESS was also significantly lower in the treatment group post-intervention when compared to the placebo group (p=0.045). However, when the difference pre and post intervention was calculated for each participant and compared this failed to reach statistical significance (p=0.214). It is possible that the improvement initially seen was at least partly due to the difference in the baseline readings between the two groups.

7.3.2 Technical problems

There were technical issues with the set up and initiation of the study that impacted on the recruitment and retainment of participants. Initially, the CPAP/sham set up was to be conducted at the baseline visit once consent had been obtained by the research registrar. However, due to pressures on standard service provision by the sleep department this proved difficult to coordinate, and there was a significant wait before participants could be set up on CPAP/sham. In the meantime, participants were reviewed at routine asthma clinic appointments and had changes to medication which then excluded them from the study, or perhaps lost interest in the study due to the wait time for initiation. To rectify this, visits were adapted to allow the baseline visit with the research registrar and the CPAP/sham setup with the respiratory physiologist to be conducted at two separate visits. However, there were then significant delays between the baseline visit and the CPAP/sham set up and concern that this could impact on the validity of the results. Participants may also have attended for the baseline visit but then failed to attend the CPAP/sham CPAP set up which would then need to

be rescheduled and added to further delays. On a few occasions the delay was so significant that this led to the baseline visit having to be repeated. In an attempt to rectify this situation, two of the respiratory research nurses received training on the CPAP/sham CPAP set up. This enabled participants to have the baseline visit and CPAP set up in one visit.

7.3.3 Recruitment and retainment of participants

Recruitment to the study proved difficult and the target number of 30 participants in each arm was not reached. The standard deviation of the changes from the pre-intervention AQLQ to the post-intervention AQLQ (0.6) is much smaller than the standard deviation of the pre-intervention AQLQ (1.0) and of the post-intervention AQLQ (1.2). This is not surprising, as within-subject variability is often less than between-subject variability. Even so, the observed standard deviation of the changes is greater than 0.5 and the observed differences in the means between the two arms (whether using the post values or the changes) are less than 0.5. Both of these facts suggest that even if the target sample size had been reached, a significant difference between the two arms may not have been shown.

All participants from the cross-sectional study who tested positive for OSA with an AHI≥5 were screened for the interventional study. Initially, participants were noted to be failing the screening based on the strict severe inclusion criteria and this triggered amendments to the protocol (which were discussed in the methods section). There were however other barriers to recruitment that were more difficult to overcome. Some participants struggled with the idea of receiving a placebo treatment for three months when the standard treatment was readily available through standard NHS care particularly in the context of struggling with ill-health

due to pre-existing severe asthma. There were ethical concerns with regard to driving with some participants and those who admitted to feeling excessively sleepy while driving were immediately referred for standard CPAP regardless of their ESS due to safety concerns.

Another barrier to recruitment was that anti-IL-5 therapy for severe asthma became available at our severe asthma centre at a similar time as recruitment to the interventional study. This was a clear exclusion to the study that could not be modified due to the potential impact on the outcome of the study. Some participants chose to start anti-IL-5 therapy rather than participate in the interventional study.

A high overall drop-out rate was noted during the study of 48%, however this was similar in the treatment group (47%) when compared to the placebo group (50%). The existing literature does imply that research studies involving CPAP treatment of OSA in asthma populations are possible, with Serrano-Pariente et al recruiting 99 participants to a study that measured asthma quality of life and asthma control pre and post six months of CPAP[221]. 82 participants completed this study, and 71 of the total population was reported to have moderate-severe asthma[221]. A significant improvement in AQLQ and ACQ was reported[221]. Lafond et al also demonstrated an improvement in AQLQ in a smaller study of 20 participants, although these were reported to have "stable" asthma[240]. However, there was no placebo-arm in either study and with the visibility and semi-invasive nature of CPAP there is clear potential for a placebo effect to be observed in non-randomised controlled studies. The interventional study (pilot RCT) has shown that sham CPAP is as tolerable as standard CPAP in severe asthma populations. Selecting participants with more severe OSA may improve compliance, as those

with milder OSA are known to have limited benefit with regards to sleep symptomatology. The study by Serrano-Pariente et al included a cohort with more severe OSA[221], when compared to the interventional study which required only an AHI of 10.

AQLQ is a reasonable outcome measure to determine the effect on asthma-related quality of life, with questions relating specifically to asthma symptoms and exposures. ACQ is also a useful outcome measure to determine the effect of CPAP on asthma control, with questions targeted specifically at asthma symptoms. Neither the AQLQ or ACQ which has questions specifically targeted at asthma showed a significant trend post intervention. Other secondary outcomes included the general health questionnaires, EQ-5D, EQ-VAS and HADS, which could potentially be impacted on by improvements in OSA through CPAP treatment, rather than be related specifically to severe asthma. Rescue oral corticosteroid, spirometry and biomarkers specific to asthma and the metabolic syndrome were also included as secondary outcome measures but these are difficult to fully evaluate over the relatively short study period with CPAP/sham in this pilot study. AQLQ takes into account the preceding four weeks of asthma related symptoms, and ACQ is based on the previous week of asthma symptoms which makes these questionnaires more suitable for this relatively short placebo-controlled study.

There were specific problems related to asthma populations that could be addressed in any future studies attempted. This would include more regular review with regards to worsening co-morbidities such as facial eczema, nasal congestion and nocturnal asthma symptoms and pre-emptively trouble shooting with regards to solutions that could improve compliance e.g.

ensuring adequate nasal steroids are prescribed, facial creams and closer support with nocturnal asthma/sleep symptoms.

The resources to set up the CPAP/sham promptly and ability for follow-up and trouble-shooting of the CPAP/sham by a non-blinded team member with experience of CPAP would also help with the recruitment and retainment of participants. Careful attention to specific asthma-related co-morbidities is important. To recruit the required number of severe asthma participants it is likely that a multi-centre approach is needed, particularly given the current increasing availability of alternative treatments including biological therapy which would impact on any study results.

8 Conclusions and future work

A high prevalence of OSA in asthma (19-60%) and particularly severe asthma (50-95%) was indicated through systematic review of the literature in the small number of studies that used formal sleep studies to diagnose asthma. A high prevalence of OSA (70%) in severe asthma was again found in the cross-sectional study. The impact of OSA on asthma-related clinical outcomes was unclear through systematic review of pre-existing literature, however the cross-sectional study found that asthma quality of life, asthma control and general health-related quality of life deteriorates with increasing severity of OSA. Additionally, co-morbidities such as dyslipidaemia, hypertension and diabetes are more prevalent with increasing severity of OSA. These finding highlight the importance of identifying OSA in severe asthma populations and the need to screen for associated co-morbidities.

The Epworth Sleepiness Score did not predict mild cases of OSA in this severe asthma population, but did identify moderate-severe OSA. This is likely due to certain overlapping clinical features shared by the two conditions, such as poor sleep and frequent awakenings leading to increased daytime hypersomnolence. There is an argument for a different tool specific to severe asthma populations to be developed. This would enable milder cases of OSA to be identified and patients to be advised with regards to initial conservative management of the condition. This could potentially prevent more severe cases of OSA from developing, particularly given the high prevalence of OSA in severe asthma.

Systematic review of the literature indicates that studies involving CPAP treatment of OSA are tolerated in asthma populations, although it is unclear if this extrapolates to severe asthma. Observational and quasi-experimental studies have shown an improvement in asthma-related quality of life particularly in more severe asthma or more severe OSA, but this is by no means conclusive. The pilot feasibility RCT found no difference in asthma-related quality of life with CPAP treatment but the numbers recruited were small and there was a high overall drop-out rate. A non-significant trend towards worsening asthma-related quality of life (AQLQ) and general quality of life (EQ-VAS) with sham CPAP was noted when compared to no treatment. Despite this, the sham CPAP was tolerated as well as standard CPAP in this severe asthma population with a similar drop-out rate in the placebo (50%) and treatment groups (47%).

Further research implemented in this area should ideally recognise the higher than expected drop-out rate in severe asthma, and account for this in the preceding power calculations to determine the number of participants needed to recruit to each arm of the study. Review of the literature suggests that a study that recruited participants with moderate-severe OSA may be more likely to show a positive effect with CPAP therapy. However, there was a trend towards worsening AQLQ in the sham CPAP group which needs to be considered in any future research studies. This trend, along with the high drop-out rate in both arms of the study does create potential debate about the acceptability of completing a placebo-controlled study in this area, particularly as CPAP is an established treatment with proven benefits for patients with moderate-severe OSA. However, the safety and tolerability of CPAP treatment of OSA in participants with severe asthma has yet to be fully determined and also needs considering in the design of future research studies.

There is a high prevalence of OSA within severe asthma populations, with detrimental impact on asthma-related health outcomes. There is suggestion in the literature that CPAP treatment of OSA could have a positive impact on asthma-related quality of life and the pilot feasibility RCT has demonstrated that sham CPAP is as well tolerated as standard CPAP in this population. A further multi-centre RCT with specific attention to the asthma-related problems highlighted is needed to conclusively determine if CPAP treatment of OSA could improve asthma-related outcomes in those with co-existing conditions.

9 Appendices

9.1 Appendix 1: Ethical approval letter, Observational and Interventional studies (page 1 of 4)

NHS
Health Research Authority

NRES Committee West Midlands - The Black Country

North West REC Centre
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4 Minshull Street
Manchester
M1 3DZ

Telephone:
Facsimile:

10 April 2012

Dr Adel Mansur
Consultant physician and honorary senior lecturer
Heart of England NHS Foundation Trust
Respiratory Department
Birmingham Heartlands Hospital
Birmingham
B9 5SS

Dear Dr Mansur

Study title:	**The Effects of Obstructive Sleep Apnoea (OSA) on Health Outcomes in Obese Patients with Asthma: Epidemiology, Impact on Asthma Control, and Effect of Treatment Using Continuous Positive Airway Pressure (CPAP)**
REC reference:	**12/WM/0049**
Protocol number:	**N/A**

Thank you for your letter of 26 March 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and Dr Sonksen.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

NHS
Health Research Authority

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter from Dr Amanda James		01 February 2012
REC application: 70026/288650/1/235		01 February 2012
Protocol		25 November 2011
Summary/Synopsis: Flow Chart	1	25 November 2011
Investigator CV: Adel H Mansur		10 June 2011
Investigator CV: Dr Shahrad Taheri		08 June 2011
Investigator CV: Dr Dev Banerjee		
Investigator CV: Dr Amanda C James		26 October 2011
Letter from Statistician from Neil Thomas		21 November 2011

Appendix 1: Ethical approval letter, Observational and Interventional studies (page 3 of 4)

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Instructions for use of CPAP System		
Questionnaire: EQ-5D		
Questionnaire: The Epworth Sleepiness Scale		
Questionnaire: Stanford Sleepiness Scale		
Questionnaire: Reflux Cough Questionnaire		
Questionnaire: Asthma Quality of Life Questionnaire		
Questionnaire: Asthma Control Questionnaire		
Questionnaire: Hospital Anxiety and Depression Scale		
Referees or other scientific critique report from Dr Rob Niven		10 November 2011
Response to Request for Further Information from Dr Amanda James		26 March 2012
GP/Consultant Information Sheets: Epidemiological and Observational Studies - highlighted changes	2	15 March 2012
GP/Consultant Information Sheets: Interventional Study - highlighted changes	2	15 March 2012
Participant Information Sheet: Epidemiological and Observational Studies - highlighted changes	2	15 March 2012
Participant Information Sheet: Interventional Study - highlighted changes	2	15 March 2012
Participant Consent Form: Epidemiological and Observational Studies - highlighted changes	2	15 March 2012
Participant Consent Form: Interventional Study - highlighted changes	2	15 March 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National

Appendix 1: Ethical approval letter, Observational and Interventional studies (page 4 of 4)

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Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/WM/0049	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

[redacted]

On behalf of
Dr Jeff Neilson
Chair

Email: [redacted]

Enclosures: "After ethical review – guidance for researchers"

A Research Ethics Committee established by the Health Research Authority

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9.2 Appendix 2: Participant Information Sheet, (Observational studies), Version 7: 20/1/2017, (page 1 of 7)

Birmingham Heartlands Hospital
Bordesley Green East
Birmingham
B9 5SS
Tel: [redacted]

Patient information sheet

The Effect of Obstructive Sleep Apnoea (OSA) on Health Outcomes in Patients with Asthma: Epidemiology, Impact on Asthma Control, and Effect of Treatment using Continuous Positive Airway Pressure (CPAP).

Epidemiological and Observational Study

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

This study has two aspects to it: an epidemiological and observational study, and an interventional study. This information sheet gives details of the epidemiological and observational study. There is a separate patient information sheet that details the interventional study. You do not need to take part in the interventional study to be part of the epidemiological and observational study.

Part one of this information sheet provides information about the purpose of this study as well as what will happen to you if you decide to take part. Part two gives you detailed information about the conduct of the study. Please ask us if there is anything that is not clear to you, or if you would like any further information. Take your time to decide whether or not you wish to take part.

You will be given a copy of this sheet and a signed consent form to keep if you decide to take part in this study. If you consent, we will also send copies to your GP.

Part 1:

Epidemiology Study:

What is the purpose of the study?
The purpose of this study is to find out how many patients who are seen in the Birmingham Regional Severe Asthma Service (BRSAS) are affected by Obstructive Sleep Apoea (OSA). OSA is a condition in which the upper airways are partially or completely closed off during sleep. This condition may have an impact on asthma symptoms, especially those that happen at night. Knowing this information will help us and others to know better when to look for this condition in other patients with uncontrolled asthma symptoms.

Why have I been invited to take part?
You are being seen in the Birmingham Regional Severe Asthma Service (BRSAS) and the epidemiology study aims to screen for Obstructive Sleep Apnoea (OSA) in 200 patients that are seen in our clinic with asthma.

Do I have to take part?
It is up to you to decide. We will describe the study and go through this information sheet with you, which we will then give to you to keep. If you wish to take part, we will then ask you to sign a consent form to show you have agreed to this. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?
If you agree to participate in the study, you will be asked to have two additional investigations around the time that you come to the BRSAS. These two investigations are a limited sleep study and an electrical impedance measurement. You may also be selected to have a body composition DEXA scan
Both of these investigations are available directly at Heartlands Hospital.

The limited sleep study is an investigation that looks for Obstructive Sleep Apnoea (OSA) and is carried out for one night in your own home whilst you sleep. The pattern of breathing you have whilst asleep is monitored using two elasticated belts: one worn around your chest and the other around your stomach. The flow of air that you breathe in and out is measured using nasal prongs similar to those used in hospital to deliver oxygen. Your body's oxygen levels are measured using a saturation probe that is placed on your finger, similar to that used in the clinic. These are then connected with leads to a recording box that is approximately the size and weight of the old style walkman. You will be shown how to wear the limited sleep study and given a machine to take home with you to wear that night whilst you sleep. You will also be given a short questionnaire called the Epworth Sleepiness Score (ESS) to complete, which asks about symptoms of OSA. You then need to return the equipment and the questionnaire at your next convenience and we will analyse your data and contact you with the results as soon as possible.

The bioelectrical impedance measurement involves standing on a set of measuring scales similar to those that are used to measure weight. This will provide an estimate of the body fat composition but is not as detailed as the DEXA scan.

The body composition DEXA scan is available at the MIDRU building at Heartlands Hospital. It is similar to the chest x-ray that you will have before your routine BRSAS clinic appointment. It measures your body fat and lean tissue content and gives a picture of where in your body fat is carried. This information can be compared with other people of the same age and sex as you. This is important in OSA as excess fat around the neck area is thought to increase the risk of OSA. The test takes around 10 minutes to complete, and is similar to the DEXA scan you may have had in the past that looked at your bone strength (osteoporosis). The results of this test will be given to you at your next appointment.

A sub-group of patients will also be asked to have blood tests that will include asthma related biomarkers and metabolic profile (this is not compulsory). These bloods tests include full blood count, CRP, IgE, TSH, cholesterol and diabetes screen. These blood tests will be available for use in your clinical care at the asthma clinic and also for research purposes. We will also check leptin, adiponectin and IL-6. These are markers related to asthma and lipids/fats in the body, which will be useful for research purposes only. These samples will be processed at the Queen Elizabeth Hospital by the research team. Samples will not be stored after the study is completed and will be destroyed.

You may also be asked to fill out questionnaires related to asthma and quality of life.

What are my responsibilities?
The only thing we would ask is that you return the limited sleep study equipment so that this can be used for other patients in the study.

What other investigations / treatments are available?
The limited sleep study in combination with the Epworth Sleepiness Score (ESS), are considered the *Gold Standard* for investigating for Obstructive Sleep Apnoea. If your clinical symptoms suggest this diagnosis, you would be offered these tests on the NHS anyway.

What are the possible risks of taking part?
The limited sleep study is completely safe. Occasionally people find it uncomfortable to wear the equipment whilst they sleep. If this is the case for you, it can easily be taken off by undoing a buckle. This will be shown to you when you are given the equipment.

The body composition DEXA scan is obtained using x-rays so you will receive a very small radiation dose equivalent to about a single day of average background radiation in the UK. You would not have received this scan as part of routine clinical care and so this scan and radiation dose is additional.

All females of child bearing age will require a negative urine pregnancy test prior to having the scan.

What are the possible benefits in taking part?
It may be that we find Obstructive Sleep Apnoea when we wouldn't have been expecting it from the symptoms that you discuss with your doctor. If we discover that you do have Obstructive Sleep Apnoea, this will be treated through the NHS as usual.

The body composition DEXA scan provides a colour picture of your whole body highlighting areas where excess fat is carried. You may find this interesting to see, and it may help you and your doctor with weight loss motivation and management, as well as providing additional information about your risk of other health problems, for example heart disease, by looking at the way in which fat is distributed on your body.

What happens when the research study is finished?
The information from your limited sleep study and body composition DEXA scan will be kept in your NHS notes along with all your other routine care information. This information will be available to the BRSAS team, and to yourself and your GP. If the investigations show Obstructive Sleep Apnoea or problems with excess fat distribution, you will be referred to the appropriate NHS services that deal with these conditions, and ongoing care will continue even after the research study finishes.

Observational Study

What is the purpose of this study?
The purpose of this study is to use the data collected as part of the epidemiological study, as well as information collected as part of your routine NHS care, to help us understand which patients with asthma are more likely to have Obstructive Sleep Apnoea. This will help us with identifying and managing patients in the future. Many patients will take part in both the epidemiological part and the observational part but some patients will be part of the observational study only.

Why have I been invited to take part?
We are inviting patients who are seen in the Birmingham Regional Severe Asthma Service (BRSAS) or other respiratory clinics within the trust. The majority of the information we will be looking at will be information that will be being collected as part of your NHS care and as part of the UK British Thoracic Society asthma registry, for example, lung function, steroid use, weight etc.

Do I have to take part?
It is up to you to decide. We will describe the study and go through this information sheet with you, which we will then give to you to keep. If you agree to take part, we will then ask you to sign a consent form to show you have agreed to this. You are free to withdraw at any time, without giving a

reason. This would not affect the standard of care you receive. You have the option of taking part in just the observational study and not the epidemiological or interventional aspects of the study if you wish.

What will happen to me if I take part?
If you agree to participate in this aspect of the study, information collected as part of your routine visits to the BRSAS, plus/minus information collected as part of the epidemiological study, will be kept with your NHS notes and on a confidential database. This information will then be analysed, looking at the differences in patients with asthma who have / do not have Obstructive Sleep Apnoea. If you agree to participate in the study, you will be asked to have two additional investigations around the time that you come to the BRSAS. These two investigations are a limited sleep study and bioelectrical impedance measurement. You may also be selected to have a body composition DEXA scan. If you have already had a diagnosis of OSA confirmed (you may already be receiving CPAP) then you will not require a repeat sleep study.

What are my responsibilities?
You have no specific responsibilities to this aspect of the study.

What are the possible advantages / disadvantages of taking part?
There are no specific advantages or disadvantages of taking part in the observational study as the data being collected is part of your routine clinical care in the Birmingham Regional Severe Asthma Service (BRSAS). The advantages and disadvantages of collecting additional data from the epidemiological study (that is also being used for the observational study) are covered above in the epidemiological study section of this patient information sheet.

What are the possible risks of taking part?
The limited sleep study is completely safe. Occasionally people find it uncomfortable to wear the equipment whilst they sleep. If this is the case for you, it can easily be taken off by undoing a buckle. This will be shown to you when you are given the equipment.

The body composition DEXA scan is obtained using x-rays so you will receive a very small radiation dose equivalent to about a single day of average background radiation in the UK. You would not have received this scan as part of routine clinical care and so this scan and radiation dose is additional. All females of child bearing age will require a negative urine pregnancy test prior to having the scan.

What happens when the research study is finished?
The information collected from your NHS Birmingham Regional Severe Asthma Service visits and from your epidemiological study investigations (limited sleep study, bioelectrical impedance and body composition DEXA

scan), will be kept in your NHS notes along with all your other routine care information. This information will be available to the BRSAS team, and to yourself and your GP. If the investigations show Obstructive Sleep Apnoea or problems with fat distribution, you will be referred to the appropriate NHS services that deal with these conditions, and ongoing care will continue even after the research study finishes.

Interventional Study

Patients who have been identified as having asthma AND Obstructive Sleep Apnoea, will be offered to take part in our interventional study. This aspect of the study involves treatment with a device called Continuous Positive Airway Pressure (CPAP). Further details of this aspect of the study, is given in the interventional study patient information sheet, available from the research and BRSAS teams.

Part 2:

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the condition and treatment being studied. If this were to happen your research doctor or nurse will discuss it with you and you can decide whether you wish to continue in the study.

What will happen if I don't want to carry on with this study?

You can withdraw from the study at any time and your care will not be affected. Information collected previously during the study may still be used.

What if there is a problem?

Any complaint about the way you have been dealt with or any possible harm you might suffer will be addressed immediately. If you agree to take part in the study you will be provided with a telephone number to contact in the event of a problem or emergency.

Complaints

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, you can complain directly to Dr Sarah Davies (the researcher) or to Dr Adel Mansur, Consultant Respiratory Physician, The Birmingham Regional Severe Asthma Service (BRSAS)+ Heartlands Hospital, Birmingham on telephone number [redacted] extension [redacted]. Independent complaints can be made through the NHS Patient Advise and Liaison Service (PALS) available on [redacted]

Harm

If you are harmed as a direct result of taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's

negligence, then you may have grounds for a legal action against the sponsor (Heart of England NHS Trust) but you may have to pay your legal costs.

Will my taking part in the study be kept confidential?
Any information which is collected about you during the course of the research will be kept strictly confidential. Only the research team will have access to the research data about you. Data collected for research purposes as well as routine NHS care will be available to your NHS team in the strictest of confidence as per the General Medical Council good practice guidelines. Research data collected will have your name and address removed and a unique research subject number will be allocated instead. Your data will be stored securely in a locked cupboard within the research centre at Heartlands Hospital for a period of 3 years. NHS data will be kept in your medical records for at least ten years, as per NHS guidelines.

With your permission, we will inform your GP of your participation in this study. At the time of reading this, your Consultant has agreed to our asking you to participate in the study. Results from the study may eventually be submitted for publication in appropriate medical journals, as well as on the BRSAS website, but strict confidentiality will be maintained at all stages.

Who is organising and funding the research?
All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect your safety, wellbeing and dignity. This study has been reviewed and given a favourable opinion by the West Midlands Research Ethics Committee. The design has also been reviewed by an independent UK asthma expert.

If you would like to participate in the study or have any questions, please contact Dr Sarah Davies on:

Tel:
Email:

Please do not hesitate to contact the study team if you have any concerns or questions during the course of the study.

Dr Sarah Davies
Clinical Research Fellow

9.3 Appendix 3: Consent from (Observational studies), Version 6: 20/1/2017, page 1 of 2

Use patient label
Patient name:

DOB:

Site Number:

Study Number:

+

Birmingham Heartlands Hospital
Bordesley Green East
Birmingham
B9 5SS
Tel: [redacted]

CONSENT FORM – Epidemiological and Observational Study, Version 6, 20/1/2017

The Effect of Obstructive Sleep Apnoea (OSA) on Health Outcomes in Patients with Asthma: Epidemiology, Impact on Asthma Control, and Effect of Treatment Using Continuous Positive Airway Pressure (CPAP).

Chief Investigator: Dr Adel Mansur

Please initial boxes

1. I confirm that I have read and understand the participant information sheet Version 7, 20/1/2017, for the above study and been given a copy. I have had the opportunity to ask questions and have had these answered satisfactorily. ☐
2. I understand that participation is voluntary, and that I am free to withdraw consent at any time, without giving any reason and without my medical care or legal rights being affected. ☐
3. I understand that the details regarding my clinical condition will be kept on a database. This information will be treated with the strictest of confidentiality. Information from 12 months prior to my first BRSAS clinic appointment can also be used. ☐
4. I agree to the use of my samples in this research project, as described on the participant information sheet. ☐
5. I agree to undergo body composition DEXA scanning if selected ☐
6. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
7. I agree to my GP being informed of my involvement in this study. ☐
8. I agree to take part in the epidemiology and observational part of this research project, as described in the patient information sheet Version 7, 20/1/2017 ☐

Name of Participant	Signature	Date
Name of Person taking consent	Signature	Date

1 copy for participant; 1 copy for Principal Investigator; 1 copy to be kept with hospital notes.

9.4 Appendix 4: Asthma Quality of Life Questionnaire (AQLQ), (page 1 of 4)

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S)
(UNITED KINGDOM VERSION)
SELF-ADMINISTERED

PATIENT ID_____

DATE_____

Please complete **all** the questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

HOW **LIMITED** HAVE YOU BEEN **DURING THE LAST 2 WEEKS** IN THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA?**

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK-RELATED ACTIVITIES* (tasks you have to do at work)	1	2	3	4	5	6	7
**If your are not employed or self-employed, these should be tasks you have to do most days.*							
5. SLEEPING	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS?**

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

Appendix 4: Asthma Quality of Life Questionnaire (AQLQ), (page 2 of 4)

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S)
(UNITED KINGDOM VERSION)
SELF-ADMINISTERED

PATIENT ID_____

DATE_____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
7. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
8. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?	1	2	3	4	5	6	7
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS?**

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
13. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of CHEST HEAVINESS?	1	2	3	4	5	6	7

Appendix 4: Asthma Quality of Life Questionnaire (AQLQ), (page 3 of 4)

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID_____
(UNITED KINGDOM VERSION)
SELF-ADMINISTERED DATE_____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	1	2	3	4	5	6	7
16. Feel the need to CLEAR YOUR THROAT?	1	2	3	4	5	6	7
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	1	2	3	4	5	6	7
18. Experience DIFFICULTY BREATHING OUT as a result of your asthma?	1	2	3	4	5	6	7
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	1	2	3	4	5	6	7
20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?	1	2	3	4	5	6	7
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
22. Feel bothered by HEAVY BREATHING?	1	2	3	4	5	6	7
23. Experience asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION OUTSIDE?	1	2	3	4	5	6	7
24. Were you WOKEN AT NIGHT by your asthma?	1	2	3	4	5	6	7
25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

Appendix 4: Asthma Quality of Life Questionnaire (AQLQ), (page 4 of 4)

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID_____
(UNITED KINGDOM VERSION)
SELF-ADMINISTERED DATE_____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
27. Feel AFRAID OF GETTING OUT OF BREATH?	1	2	3	4	5	6	7
28. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
29. Has you asthma INTERFERED WITH GETTING A GOOD NIGHT'S SLEEP?	1	2	3	4	5	6	7
30. Have the feeling of FIGHTING FOR AIR?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS?**

	Most Not Done		Several Not Done		Very Few Not Done		No Limitation
31. Think of all the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks? How much has your range of activities been limited by your asthma?	1	2	3	4	5	6	7

9.5 Appendix 5: Asthma Control Questionnaire-7 (ACQ-7) (page 1 of 1)

Date:

Affix Patients Hospital Label

ASTHMA CONTROL QUESTIONNAIRE ©
Please answer questions 1-6

1.	On average, during the past week, how often were you **woken by your asthma** during the night?	0 1 2 3 4 5 6	Never Hardly ever A few minutes Several times Many times A great many times Unable to sleep because of asthma
2.	On average, during the past week, how **bad were your asthma symptoms when you woke** up in the morning	0 1 2 3 4 5 6	No Symptoms Very mild symptoms Mild symptoms Moderate symptoms Quite severe symptoms Severe symptoms Very severe symptoms
3.	In general, during the past week, how **limited were you in your activities** because of your asthma	0 1 2 3 4 5 6	Not limited at all Very slightly limited Slightly limited Moderately limited Very limited Extremely limited Totally limited
4.	In general, during the past week, how much **shortness of breath** did you Experience because of your asthma?	0 1 2 3 4 5 6	None A very little A little A moderate amount Quite a lot A great deal A very great deal
5.	In general, during the past week, how much of the time did you **Wheeze**?	0 1 2 3 4 5 6	No at all Hardly any of the time A little of the time A moderate amount of the time A lot of the time Most of the time All the time
6.	On average, during the past week, how many **puffs of short-acting Bronchodilator** (e.g. Ventolin) have you used each day?	0 1 2 3 4 5 6	None 1-2 puffs most days 3-4 puffs most days 5-8 puffs most days 9-12 puffs most days 13-16 puffs most days More than 16 puffs most days

To be completed by a member of the clinical staff

7.	FEV_1 Pre-bronchodilator: ..... FEV_1 Predicted ..... FEV_1 % predicted ..... (Record actual values on the dotted lines and score the FEV1% predicted in the next column)	0 1 2 3 4 5 6	>95% predicted 95-90% 89-80% 79-70% 69-60% 59-50% <50% predicted

TOTAL SCORE=_____
42

9.6 Appendix 6: Euroquol-5D (EQ-5D) (page 1 of 1)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

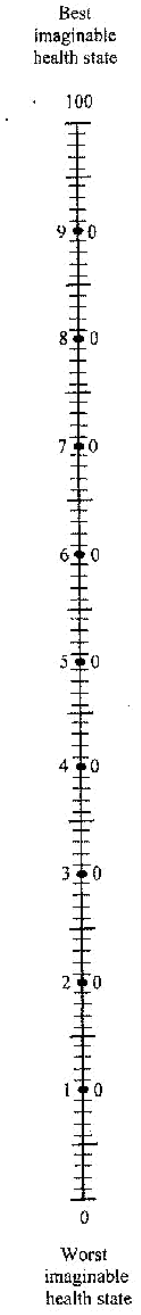
2

9.7 Appendix 7: Euroqol-Visual Analogue Scale (EQ-VAS), (page 1 of 1)

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



3

9.8 Appendix 8: Hospital Anxiety and Depression Scale (HADS), (page 1 of 3)

Must be completed pre-bronchodilator

Patient study number ☐☐☐ Date ☐☐/☐☐/☐☐

This questionnaire is designed to help us understand how you feel. Please read each item and put a tick in the box next to the reply which comes closest to how you have been feeling **in the past week.**
Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or "wound up":

☐ Most of the time
☐ A lot of the time
☐ From time to time, occasionally
☐ Not at all

I still enjoy the things I used to enjoy:

☐ Definitely as much
☐ Not quite so much
☐ Only a little
☐ Hardly at all

I get a sort of frightened feeling as if something awful is about to happen:

☐ Very definitely and quite badly
☐ Yes but not too badly
☐ A little, but it doesn't worry me
☐ Not at all

I can laugh and see the funny side of things:

☐ As much as I always could
☐ Not quite so much now
☐ Definitely not so much now
☐ Not at all

Worrying thoughts go through my mind:

☐ A great deal of the time
☐ A lot of the time
☐ From time to time but not too often
☐ Only occasionally

Appendix 8: Hospital Anxiety and Depression Scale (HADS), (page 2 of 3)

Patient study number ☐☐☐ Date ☐☐/☐☐/☐☐

I feel cheerful:

☐ Not at all
☐ Not often
☐ Sometimes
☐ Most of the time

I can sit at ease and feel relaxed:

☐ Definitely
☐ Usually
☐ Not often
☐ Not at all

I feel as if I am slowed down:

☐ Nearly all the time
☐ Very often
☐ Sometimes
☐ Not at all

I get a sort of frightened feeling like "butterflies" in the stomach:

☐ Not at all
☐ Occasionally
☐ Quite often
☐ Very often

I have lost interest in my appearance:

☐ Definitely
☐ I don't take so much care as I should
☐ I may not take quite as much care
☐ I take just as much care as ever

I feel restless as if I have to move:

☐ Very much indeed
☐ Quite a lot
☐ Not very much
☐ Not at all

Appendix 8: Hospital Anxiety and Depression Scale (HADS), (page 3 of 3)

Patient study number ☐☐☐ Date ☐☐/☐☐/☐☐

I look forward with enjoyment to things:

☐ As much as I ever did
☐ Rather less that I used to
☐ Definitely less than I used to
☐ Hardly at all

I get sudden feelings of panic:

☐ Very often indeed
☐ Quite often
☐ Not very often
☐ Not at all

I can enjoy a good book or radio or TV programme:

☐ Often
☐ Sometimes
☐ Not often
☐ Very seldom

☐
☐

9.9 Appendix 9: Epworth Sleepiness Scale (ESS), (page 1 of 1)

Affix patient sticker here

NHS
University Hospitals Birmingham
NHS Foundation Trust

Sleep questionnaire

Todays Date...../...../.....

Welcome to the Birmingham Heartlands Sleep Clinic
In order to make your visit to the clinic as efficient as possible, I would be grateful if you can spend a few moments answering the questions below. It will only take a few minutes and will help us to assess your sleep problem. All answers are treated as confidential.

Epworth Sleep Questionnaire
How likely are you to doze off or fall asleep in the following situations, in comparison to just feeling tired? This refers to your usual way of life in recent times. Even if you haven't done some of these things recently, try to work out how they would have affected you. Use the scale to choose the most appropriate number for each situation.

It is important that you answer each question as best you can.

If high chance of dozing you score 3
If moderately chance of dozing you score 2
If slight chance of dozing you score 1
If would never doze you score 0

Situation	**score**
Sitting and reading	
Watching TV	
Sitting, inactive in a public place e.g. theatre or meeting	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch (no alcohol)	
In a car, while stopped for a few minutes in the traffic	

Total score =

Many thanks for your cooperation

9.10 Appendix 10: The Stanford sleepiness scale (SSS), (page 1 of 1)

Stanford Sleepiness Scale

This is a quick way to assess how alert you are feeling. If it is during the day when you go about your business, ideally you would want a rating of a one. Take into account that most people have two peak times of alertness daily, at about 9 a.m. and 9 p.m. Alertness wanes to its lowest point at around 3 p.m.; after that it begins to build again. Rate your alertness at different times during the day. If you go below a three when you should be feeling alert, this is an indication that you have a serious sleep debt and you need more sleep.

An Introspective Measure of Sleepiness
The Stanford Sleepiness Scale (SSS)

Degree of Sleepiness	**Scale Rating**
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

9.11 Appendix 11: Participant Information Sheet (PIS), Interventional study, page 1 of 7

Birmingham Heartlands Hospital
Bordesley Green East
Birmingham
B9 5SS
Tel: [redacted]

Patient information sheet, Version 6 (15/11/2016)

The Effect of Obstructive Sleep Apnoea (OSA) on Health Outcomes in Patients with Asthma: Epidemiology, Impact on Asthma Control, and Effect of Treatment using Continuous Positive Airway Pressure (CPAP).

Interventional Study

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

This study has two aspects to it: an epidemiological and observational study, and an interventional study. This information sheet gives details of the interventional study only. Information on the epidemiological and observational aspects of this study is given in a separate information sheet available from the research and the (Birmingham Regional Severe Asthma Service (BRSAS).

Part one of this information sheet provides information about the purpose of the interventional study, as well as what will happen to you if you decide to take part. Part two gives you detailed information about the conduct of the study in general. Ask us if there is anything that is not clear to you, or if you would like any further information. Take time to decide whether or not you wish to take part.

You will be given a copy of this sheet and a signed consent form to keep if you decide to take part in this study. We will also send copies to your GP.

1

Part 1:

Interventional Study

What is the purpose of the study?
The purpose of this study is to collect preliminary information on the effects of a device called Continuous Positive Airway Pressure (CPAP) on asthma and sleep apnoea outcomes, for example asthma related quality of life, symptom control, steroid use, exacerbation frequency and tolerability of the CPAP machine itself.

Why have I been invited to take part?
Approximately 60 patients attending the Birmingham Regional Severe Asthma Service will take part in this study. Those chosen to be involved in the interventional aspect of the study will be those with proven asthma AND Obstructive Sleep Apnoea (OSA), and who are not already receiving CPAP therapy or excessively sleepy in the daytime due to their OSA. In this situation, your doctor will refer you to the Sleep and Ventilation Unit, Heartlands Hospital, as per usual NHS care and British Thoracic Society guidelines.

Do I have to take part?
It is up to you to decide. We will describe the study and go through this information sheet with you, which we will then give to you to keep. If you agree to take part, we will then ask you to sign a consent form to show you have agreed this. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?
If you do not already have a diagnosis of Obstructive Sleep Apnoea (but it is suspected) then we will arrange for you to have a limited–channel overnight sleep study to test for this. The limited sleep study is an investigation that looks for Obstructive Sleep Apnoea (OSA) and is carried out for one night in your own home whilst you sleep. The pattern of breathing you have whilst asleep is monitored using two elasticated belts: one worn around your chest and the other around your stomach. The flow of air that you breathe in and out is measured using nasal prongs similar to those used in hospital to deliver oxygen. Your body's oxygen levels are measured using a saturation probe that is placed on your finger, similar to that used in the clinic. These are then connected with leads to a recording box that is approximately the size and weight of the old style walkman. You will be shown how to wear the limited sleep study and given a machine to take home with you to wear that night whilst you sleep.
Following this, if you have OSA (and asthma) then you will be asked if you would like to participate in this interventional study. If you agree to take part in this study (and you meet the other inclusion criteria then you will be asked to sign a consent form to confirm you would like to take part. Following this, you will be asked to attend Heartlands Hospital on three additional occasions over

three months. This study is a pilot double blinded parallel study comparing using the CPAP device to a dummy CPAP device ((placebo) called sham-CPAP. Further information about these devices is given below.

You will be allocated to receive either CPAP or sham CPAP. This allocation is done at random and by an independent person. There is no way of you or the researcher knowing beforehand or during the study which device you are receiving. At the end of the three month study period, the type of device you have been using will be revealed to you, and if you have experienced benefit from CPAP treatment, this will be offered to you for long term use on the NHS.

At the first visit you will see our research respiratory physiologist. He/she will introduce you to your CPAP or sham CPAP device, fit your individual facemask, and show you how to use it. This will take up to an hour. You will have an overnight oximetry performed on the first night on the machine to see if any settings alteration is required or not (on a rare scenario you may have to have a second overnight oximetry for the same reason).Two days later, the research doctor or nurse will telephone you in order to answer any initial issues you have about the device. At this first visit you will also meet with the research doctor for approximately an hour. During this time, baseline investigations will be done. These include questionnaires about your asthma and obstructive sleep apnoea symptoms, blood tests, lung function measurements, general observations for example weight, induced sputum (see further information below), current medication doses, any asthma exacerbations or visits to your GP or hospital, and a physical examination.

You will have a second hospital visit two weeks after being started on your CPAP / sham CPAP device. This will be to see the research doctor and troubleshoot any problems with the device or your health. If needed, the respiratory physiologist will be available to also see you to make any adjustments to your individual CPAP / sham CPAP device.

A third and final visit will occur after three months of receiving CPAP or sham CPAP. At this visit you will be seen by the research doctor for approximately an hour again, where you will have a physical examination, complete the same questionnaires as at baseline, have blood tests, lung function measurements, general observations, induced sputum, medication checks and discuss any asthma exacerbations or GP / hospital visits that you have had. At this visit you will be offered to switch to treatment CPAP under usual NHS care at the sleep and ventilation clinic, Heartlands hospital.

What is CPAP and sham CPAP?
CPAP is the treatment of choice for obstructive sleep apnoea (OSA) as per NICE guidance 2008. CPAP is a device that delivers a stream of compressed air at a prescribed pressure via a nose or full-face mask and hose, splinting the airway (keeping it open under air pressure) so that unobstructed breathing is possible.

Sham CPAP is a version of CPAP in which the apparatus has been modified

so that there is a leak in the circuit which releases the pressure. The sham CPAP machine looks similar to the CPAP machine and therefore gives the impression of therapy but with no therapeutic effect. Sham CPAP is recognised as an effective placebo device against CPAP. Both CPAP and sham CPAP machines have a data card which is used to record information including usage time.

A face or nasal mask is used with both devices. The CPAP set up takes up to an hour, and is done at Heartlands Hospital by the sleep physiologist. This time will cover a demonstration of how a CPAP machine works and general education.

What does the induced sputum investigation involve?

Induced sputum analysis is a test that we can use to look at exact levels of markers of inflammation and infection in your airways. Although we can routinely test sputum that you may naturally expectorate (cough up) for infection, by 'inducing' sputum the lower airways are also sampled. This may give us a more accurate idea of what inflammatory processes are occurring in your airways. Not everyone is able to induce sputum, so in those cases we would have to rely on any sputum samples that had been spontaneously produced.

The induced sputum procedure is carried out at Heartlands hospital by a member of the asthma research team. Patients complete an initial lung function test before testing starts to enable monitoring of any changes in lung function when the test is underway. Before starting the test, medication to open the airways is given (e.g. salbutamol / Ventolin nebuliser / inhaler). You are then instructed to breathe in and out through a mouthpiece attached to a nebuliser (whilst wearing a noseclip) containing saline (salt water) solution. After seven minutes you are asked to rinse out your mouth with water then clear your mouth of any excess saliva. You will be instructed to next attempt to cough using a 'huffing' technique to bring up any sputum you have produced into the container provided. At this point lung function testing is repeated to ensure that your breathing has not got any worse from when you started the test. This procedure is repeated with different concentrations of saline for up to a maximum of six times, lung function is monitored throughout for safety reasons. The sputum sample is then transported on ice for processing and analysis in the laboratory.

Sputum induction is a relatively safe test and very well tolerated by most patients. The medication given before the test prevents the airways from becoming 'twitchy' during the procedure. Side-effects of the test include nausea, cough and sore throat. These symptoms would usually pass very quickly following the end of the test.

What are my responsibilities?

During the study you will need to use your CPAP / sham CPAP device every night whilst you sleep. If you go away on holiday, the device can be taken with

you. If you are planning on flying, most airlines are happy for you to take the device with you so long as they have prior warning. Further information on this can be discussed with the research doctor.

What other treatments are available?
CPAP is the *Gold standard* treatment for moderate to severe obstructive sleep apnoea. Mild obstructive sleep apnoea is usually treated with lifestyle changes, for example weight reduction. Sometimes an individualised mouth guard, called a mandibular advancement device can be used instead. This is used during sleep and acts by pulling forward the lower jaw and reduce the chances of blocking the upper airway with the tongue during sleep.

What are the possible disadvantages and risks of taking part?
The CPAP and sham CPAP devices are used with a face or nasal mask. This mask is similar to the one used with a nebulizer, but is tighter fitting to your face in order not to release any pressure. Some people find this tight fitting uncomfortable or claustrophobic. There is a quick release buckle which you will be shown which allows the mask to be removed if this occurs. Some patients have experienced soreness and/or redness on the bridge of their nose, particularly if the mask is too tight. The masks come in varying sizes so can be adjusted if this happens. The CPAP and sham CPAP machines make a low volume buzzing noise when in use. This buzzing noise can affect the sleep quality of both the participant and their sleeping partner. Some people get runny nose with the air going in the nose.

Very rarely, the delivery of a pressure into the airways can cause a puncture to the lung (pneumothorax). This is highly unlikely with CPAP as the pressures being used are low and the machines we are using are technologically advanced and are therefore able to detect and work with your own individual breathing pattern and pressure (auto-titration) on a breath-to-breath basis. If a punctured lung does occur, this usually causes a sudden and immediately increased breathlessness often associated with a sharp chest pain. Immediate removal of the CPAP is advised followed by immediate medical review in hospital.

Some patients with Obstructive Sleep Apnoea are excessively sleepy in the day time. The standard advice given to patients in the NHS with suspected Obstructive Sleep Apnoea is that patients are not to drive or operate heavy machinery if they are feeling excessively sleepy. Within English law, that individual person has the responsibility of informing the DVLA that they are being investigated for Obstructive Sleep Apnoea. The DVLA will then make a decision about that individual's ability to continue driving safely on the roads whilst they are awaiting investigation. This applies to patients who are included in this study, however, those who are excessively sleepy will be offered treatment with CPAP on the NHS and be excluded from this study.

What are the possible benefits of taking part?
We hope that the active treatment of obstructive sleep Apnoea with CPAP will improve your asthma control and particularly impact on your night time

symptoms, exacerbation rate and overall medication requirement, but this cannot be guaranteed. There is extensive evidence that CPAP improves the symptoms of obstructive sleep Apnoea, for example excessive day time sleepiness. The information we get from this study may help us treat future patients with asthma.

You will be reimbursed up to a maximum of £20 for travel expenses related to the additional hospital appointments.

What happens when the research study is finished?
If you have experienced benefit from receiving treatment with CPAP, at the end of the study you will be offered ongoing treatment with CPAP from the Heartlands Hospital Sleep and Ventilation clinic.

Part 2:

What if new information becomes available?
Sometimes during the course of a research project, new information becomes available about the condition and treatment being studied. If this were to happen your research doctor or nurse will discuss it with you and you can decide whether you wish to continue in the study.

What will happen if I don't want to carry on with this study?
You can withdraw from the study at any time and your care will not be affected. Information collected previously during the study may still be used.

What if there is a problem?
Any complaint about the way you have been dealt with or any possible harm you might suffer will be addressed immediately. If you agree to take part in the study you will be provided with a telephone number to contact in the event of a problem or emergency.

Complaints
If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, you can complain directly to Dr Sarah Davies (the researcher) or to Dr Adel Mansur, Consultant Respiratory Physician, The Birmingham Regional Severe Asthma Service, Heartlands Hospital, Birmingham on telephone number [redacted] extension [redacted] Independent complaints can be made through the NHS Patient Advise and Liaison Service (PALS) available on [redacted].

Harm
If you are harmed as a direct result of taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action against the sponsor (Heart of England NHS Trust) but you may have to pay your legal costs.

Appendix 11: Participant Information Sheet (PIS), Interventional study, (page 7 of 7)

Will my taking part in the study be kept confidential?
Any information which is collected about you during the course of the research will be kept strictly confidential. Only the research team will have access to the research data about you. Data collected for research purposes as well as routine NHS care will be available to your NHS team in the strictest of confidence as per the General Medical Council good practice guidelines. Research data collected will have your name and address removed and a unique research subject number will be allocated instead. Your data will be stored securely in a locked cupboard within the research centre at Heartlands Hospital for a period of 3 years. NHS data will be kept in your medical records for at least ten years, as per NHS guidelines.

With your permission, we will inform your GP of your participation in this study. At the time of reading this, your Consultant has agreed to our asking you to participate in the study. Results from the study may eventually be submitted for publication in appropriate medical journals, as well as on the Birmingham Regional Severe Asthma Service website, but strict confidentiality will be maintained at all stages.

Who is organising and funding the research?
All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect your safety, wellbeing and dignity. This study has been reviewed and given a favourable opinion by the west midlands Research Ethics Committee. The design has also been reviewed by an independent UK asthma expert.

If you are interested in taking part in the study or have any questions, please contact the researcher Dr Sarah Davies:

Tel:
Email:

Please do not hesitate to contact the study team if you have any concerns or questions during the course of the study.

Dr Sarah Davies
Research Fellow to Dr AH Mansur,
Birmingham Regional Severe Asthma Service

7

9.12 Appendix 12: Consent form, Interventional study, (page 1 of 2)

Use patient label
Patient name:

DOB:

Site Number:

Study Number:

Birmingham Heartlands Hospital
Bordesley Green East
Birmingham
B9 5SS
Tel:

CONSENT FORM – Interventional Study Version 6 (15/11/2016)

The Effect of Obstructive Sleep Apnoea (OSA) on Health Outcomes in Patients with Asthma: Epidemiology, Impact on Asthma Control, and Effect of Treatment Using Continuous Positive Airway Pressure (CPAP).

Chief Investigator: Dr Adel Mansur

Please initial boxes

1. I confirm that I have read and understand the participant information sheet Version 6, 15th November 2016, for the above study and been given a copy. I have had the opportunity to ask questions and have had these answered satisfactorily. ☐
2. I understand that participation is voluntary, and that I am free to withdraw consent at any time, without giving any reason and without my medical care or legal rights being affected. ☐
3. I understand that the details regarding my clinical condition will be kept on a database. This information will be treated with the strictest of confidentiality. ☐
4. I agree to have induced sputum samples taken and used for the research purpose as described in patient information sheet Version 6, 15th November 2016 ☐
5. I agree to the use of my samples in this research project, as described on the participant information sheet. ☐
6. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
7. I agree to my GP being informed of my involvement in this study. ☐
8. I agree to take part in the INTERVENTIONAL part of this research project, as described in the patient information sheet Version 6, 15th November 2016 ☐

Appendix 12: Consent form, Interventional study, (page 2 of 2)

Name of Participant	Signature	Date
Name of Person taking consent	Signature	Date

1 copy for participant; 1 copy for Principal Investigator; 1 copy to be kept with hospital notes.

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