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

Davies, Sarah; Bishopp, Abigail; Wharton, Simon; Turner, Alice; Mansur, Adel

DOI:
10.1016/j.rmed.2018.08.004

Accepted Manuscript

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

Sarah E. Davies, Abigail Bishopp, Simon Wharton, Alice M. Turner, Adel H. Mansur

PII: S0954-6111(18)30261-0

DOI: 10.1016/j.rmed.2018.08.004

Reference: YRMED 5505

To appear in: *Respiratory Medicine*

Received Date: 29 January 2018

Revised Date: 24 July 2018

Accepted Date: 7 August 2018

Title Page

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

Author List:

1. Sarah E Davies
   Highest Degree: MBChB, MRCP
   Institutional Affiliations:
   - Birmingham Regional Severe Asthma Service, Heart of England NHS Trust, Birmingham
   - Institute of Inflammation and Ageing, University of Birmingham, UK

2. Abigail Bishopp,
   Highest Degree: MBChB, MRCP
   Institutional Affiliations:
   - Birmingham Heartlands Sleep Service, Heart of England NHS Trust, Birmingham

3. Simon Wharton
   Highest Degree: MBChB, MRCP
   Institutional Affiliations:
   - Birmingham Heartlands Sleep Service, Heart of England NHS Trust, Birmingham

4. Alice M Turner
   Highest Degree: PhD
   Institutional Affiliations:
   - Birmingham Respiratory Department, Heart of England NHS Trust, Birmingham
   - Institute of Applied Health Research, University of Birmingham, UK

5. Adel H Mansur
   Highest Degree: PhD
   Institutional Affiliations:
   - Birmingham Regional Severe Asthma Service, Heart of England NHS Trust, Birmingham
   - Institute of Inflammation and Ageing, University of Birmingham, UK

Corresponding Author:
Dr S. E Davies
Birmingham Regional Severe Asthma Service
Heart of England NHS Trust
Heartlands Hospital
Bordesley Green East
Birmingham
B9 5SS
Emails: sarah.davies@heartofengland.nhs.uk, sed349@gmail.com

Acknowledgments: We would like to acknowledge the help and support provided by Peter Nightingale, Statistician at the University of Birmingham

Systematic Review: Does Continuous Positive Airway Pressure (CPAP) treatment of Obstructive Sleep Apnoea (OSA) improve asthma-related clinical outcomes?

Introduction: A high prevalence of OSA has been observed in asthma populations, with detrimental impact on clinical outcomes.

Aim: To determine if CPAP treatment of co-existing OSA improves asthma-related symptoms and quality of life***Methods:*** Literature review of EMBASE and MEDLINE databases prior to July 2017. Study populations included asthmatics with co-existing OSA treated with CPAP, and ≥ 1 asthma-related clinical outcome measure

Results**:** 12 studies; 8 prospective quasi-experimental and 4 observational. Mean CPAP duration;19.5(2-100) weeks. Meta-analysis demonstrated significant improvement in mean Asthma Quality of Life Questionnaire scores (AQLQ and mini-AQLQ); 0.59 (95%CI; 0.25, 0.92), p=0.0006. No significant improvement was demonstrated in forced expiratory volume in one second (FEV1)%predicted; 0.32 (95%CI; -2.84, 3.47), p=0.84. Asthma Control Test/Asthma Control Questionnaire improved in 2 studies, with no improvement in 1 study. 4 studies demonstrated improvement in asthma daytime/night-time symptoms, and 3 studies showed improved asthma severity.

Conclusion: Asthmatics with co-existing OSA can experience improved quality of life with CPAP treatment. This effect appears more pronounced in severe OSA or poorly controlled asthma.

Introduction

An overlap between asthma and OSA is increasingly recognised. Epidemiological studies have shown asthmatics are more likely to report symptoms of sleep disordered breathing such as excessive daytime sleepiness, snoring and apnoeas[1]. Polysomnography (PSG) has been used to demonstrate a high prevalence of OSA in asthma[2]. Approximately 5-10% of asthmatics have severe or difficult to treat asthma (SDTA) that remains problematic despite optimal treatment[3]. The prevalence of OSA has been reported to be as high as 95% in severe steroid dependent asthma[2] and OSA can adversely impact asthma control[1]. Continuous Positive Airway Pressure (CPAP) is the gold standard treatment for patients with the OSA syndrome[4], however the efficacy of this treatment in terms of impact on co-existing asthma symptoms remains unclear.

The mechanisms through which asthma and OSA might interact are complex. Bronchial hyperresponsiveness and airway inflammation are the two key pathophysiological hallmarks of asthma[5]. Studies have also demonstrated that increased airway and systemic inflammation are present in patients with OSA[6,7]. Additionally, CPAP treatment can reduce Fractional Exhaled Nitric Oxide (FENO)[6] and improve markers of systemic inflammation such as C-reactive protein (CRP)[7]. Whether CPAP improves bronchial hyperresponsivness in OSA patients is less clear[8,9].

Asthma and OSA have common co-morbidities that include obesity and gastro-oesophageal reflux disease (GORD). These co-morbidities can negatively impact on asthma control[7]. GORD can be precipitated by the large negative intrapleural pressure swings that occur in OSA[7], and CPAP treatment has been shown to improve reflux symptoms[10]. CPAP has also been shown to improve insulin resistance[11], which could potentiate weight loss and improve asthma symptoms. The mechanisms through which CPAP could potentially improve asthma symptoms are illustrated in figure 1.

A high prevalence of OSA has been observed in asthma populations, with negative impact on asthma symptoms and control. CPAP is known to be an effective treatment for OSA in the general population. However, there are reports of patients developing bronchial hyperresponsiveness with CPAP treatment[9] which could clearly have a detrimental impact on asthmatic patients. The aim of this review is to ascertain the effects of CPAP on asthmatic patients with OSA, its tolerability and in particular its impact on asthma-related symptoms and quality of life.

Methods

This systematic review is registered with PROSPERO (CRD 42017074054). Standard systematic review methodology was used.

Aims

To determine if CPAP treatment of co-existing OSA improves - asthma-related quality of life, symptoms and other related clinical outcomes

Inclusion & exclusion criteria

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 (ie. abstracts, letters, and editorials)

4) Original research/data not included in published article

Search Methodology

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.

Data Extraction & Assessment of Bias

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) 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; the Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire (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)[12], which is based on the Cochrane risk of bias tool for randomised studies.

Data synthesis and analysis

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.

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 (FEV1%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.

Results

12 studies met the inclusion/exclusion criteria for this systematic review as illustrated in the PRISMA diagram (figure 2). 8 studies were prospective quasi-experimental studies and 4 were observational. No randomised, placebo-controlled studies were identified. It is important to note that the two cross-sectional studies by Teodorescu et al appear to be based on the same cohort of patients. Although the total data set in one paper was reported

as enhanced with subjects from an additional centre, in the subset of patients with asthma and OSA the numbers included are very similar in both studies (136 versus 140, with 75 patients in each study using CPAP).

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. There was improved asthma related quality of life in two studies when measured using AQLQ or mini-AQLQ (see table 1). 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.

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) (see table 2).

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 (table 3).

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 (table 4).

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 4).

Meta-Analysis

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 (figure 3).

Risk of bias

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 in figure 4 as both a bias graph and bias summary.

Discussion

This systematic review has included all current literature with regards to the impact of CPAP on co-existing asthma in patients with OSA. 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 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, particularly within the severe asthma population[2]. Patients with severe asthma and co-existing OSA have been shown to have increased sputum neutrophil counts and evidence of airway remodelling[13]. Asthma patients with a neutrophilic rather than the typical eosinophilic phenotype are less likely to respond to with high dose inhaled corticosteroids or oral corticosteroids[13]. 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[14,15,16,17,18] 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[19,17] but one of the studies[20] 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[14], while one of the retrospective reviews used previous home limited-channel sleep study records[20]. 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 reliability of OSA diagnosis[19,21]. 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[19,21]. 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[14]. 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[22]. 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[23,24,25].

Two of the twelve included studies evaluated asthma-related quality of life and both found a clinically significant improvement with CPAP [15,14], with study heterogeneity being minimal (as shown by the I_2 value of 0%; figure 3a). 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[14]. 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[15].

Asthma control is usually measured using the validated ACT[26] or ACQ[27]. 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[16]. 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[20]. 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[17,28-30]. 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[20]. However it is important to note that a clinically significant improvement in mean ACQ(≥0.5) was not reached. Shaarawy et al[16] 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[20].

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[31]. Chan et al found a significant improvement in pre-bronchodilator PEFR but this was a relatively short study of only two weeks, and formal spirometry was not recorded[32]. Interestingly Wang et al[18] 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[18]. Serrano-Pariente et al found FENO to be significantly reduced after six months of CPAP[14]. However, non-asthmatic patients with OSA can have elevated FENO levels[6] 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[6], 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[33]. 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) 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 (ACQ) when CPAP treatment is used for co-existing OSA. Potential reasons for this 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. Patients who feel reliant on medication at night might be concerned that the CPAP mask would make it harder to use their inhalers.

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 itself could act as powerful visual reminder for patients that they are receiving treatment.

Conclusion

In summary, this systematic review has demonstrated that CPAP treatment can improve asthma related quality of life and this effect appears more pronounced in severe OSA or poorly controlled asthma. Asthma symptoms and severity of asthma have also been shown to improve with CPAP but studies using standardised methods of measuring asthma control (such as ACQ) are conflicting. Multi-centre randomised placebo-controlled studies are needed to fully evaluate the impact of CPAP on asthma related symptoms and quality of life in patients with co-existing OSA. Such studies should include a range of severity for both asthma and OSA, as the literature implies that the impact is greatest in more severe OSA and more severe asthma. Studies that assess clinical outcomes measures such as the ACQ and AQLQ (which are commonly used in clinical practice) would be of most benefit in this setting.

Acknowledgements

We would like to acknowledge the help and support provided by Peter Nightingale, Statistician at the University of Birmingham

References

1. Teodorescu M, Broytman O, Curran-Everett D, et al. Obstructive sleep apnea risk, asthma burden, and lower airway inflammation in adults in the severe asthma research program (SARP) II. *J Allergy Clin Immunol Pract*. 2015;3(4):566-75.e1.

2. Yigla M, Tov N, Solomonov A, Rubin AH, Harlev D. Difficult-to-control asthma and obstructive sleep apnea. *J Asthma*. 2003;40(8):865-871.

3. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network For Understanding Mechanisms of Severe Asthma. *Eur Respir J*. 2003;22(3):470-477.

4. Scottish Intercollegiate Guidelines Network (SIGN): Management of obstructive sleep apnoea/hypopnoea syndrome in adults A national clinical guideline, June 2003; http://www.lothianrespiratorymcn.scot.nhs.uk/wp-content/uploads/2010/11/SIGN-73-management-of-obstructive-sleep-Apnoea_Hypopnoea-syndrome-in-adults.pdf. .

5. Brannan JD. Bronchial hyperresponsiveness in the assessment of asthma control: Airway hyperresponsiveness in asthma: Its measurement and clinical significance. *Chest*. 2010;138(2 Suppl):11S-17S.

6. Fortuna AM, Miralda R, Calaf N, Gonzalez M, Casan P, Mayos M. Airway and alveolar nitric oxide measurements in obstructive sleep apnea syndrome. *Respir Med*. 2011;105(4):630-636.

7. Alkhalil M, Schulman E, Getsy J. Obstructive sleep apnea syndrome and asthma: What are the links? *J Clin Sleep Med*. 2009;5(1):71-78.

8. Lin H, Wang C, Yang C, et al. Effect of nasal continuous positive airway pressure on methacholine-induced bronchoconstriction. *Respiratory Medicine*. 1995;89(2):121-128.

9. Wenzel G, Schonhofer B, Wenzel M, Kohler D. Bronchial hyperreactivity and nCPAP therapy. *Pneumologie*. 1997;51 Suppl 3:770-772.

10. Bortolotti M, Gentilini L, Morselli C, Giovannini M. Obstructive sleep apnoea is improved by a prolonged treatment of gastrooesophageal reflux with omeprazole. *Dig Liver Dis*. 2006;38(2):78-81.

11. Harsch IA, Schahin SP, Radespiel-Troger M, et al. Continuous positive airway pressure treatment rapidly improves insulin sensitivity in patients with obstructive sleep apnea syndrome. *Am J Respir Crit Care Med*. 2004;169(2):156-162.

12. Sterne J, Hernán M, Reeves B, et al. ROBINS-I: A tool for assessing risk of bias in non-randomized studies of interventions. *BMJ*. 2016;355(4919).

13. Taille C, Rouvel-Tallec A, Stoica M, et al. Obstructive sleep apnoea modulates airway inflammation and remodelling in severe asthma. *PLoS One*. 2016;11(3):e0150042.

14. Serrano-Pariente J, Plaza V, Soriano JB, et al. Asthma outcomes improve with continuous positive airway pressure for obstructive sleep apnea. *Allergy*. 2017;72(5):802-812.

15. Lafond C, Series F, Lemiere C. Impact of CPAP on asthmatic patients with obstructive sleep apnoea. *Eur Respir J*. 2007;29(2):307-311.

16. Shaarawy H, Affara N. Assessment of the prevalence of obstructive sleep apnea in patients with stable uncontrolled asthma, impact of continuous positive airway pressure treatment. *Egyptian Journal of Chest Diseases and Tuberculosis*. 2013;62(1):183-187.

17. Shaker A. Study of obstructive sleep apnea (OSA) in asthmatics. *Egyptian Journal of Chest Diseases and Tuberculosis*. 2017;66:293-298.

18. Wang TY, Lo YL, Lin SM, et al. Obstructive sleep apnoea accelerates FEV1 decline in asthmatic patients. *BMC Pulm Med*. 2017;17(1):55-017-0398-2.

19. Teodorescu M, Polomis DA, Gangnon RE, et al. Asthma control and its relationship with obstructive sleep apnea (OSA) in older adults. *Sleep Disord*. 2013;2013:251567.

20. Kauppi P, Bachour P, Maasilta P, Bachour A. Long-term CPAP treatment improves asthma control in patients with asthma and obstructive sleep apnoea. *Sleep Breath*. 2016;20(4):1217-1224.

21. Teodorescu M, Polomis D, Theodorescu M, et al. Association of obstructive sleep apnea risk or diagnosis with daytime asthma in adults . *J Asthma*. 2012;49(6):620-628.

22. Weaver TE, Maislin G, Dinges DF, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep*. 2007;30(6):711-719.

23. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. *Am Rev Respir Dis*. 1993;147(4):832-838.

24. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. *J Clin Epidemiol*. 1994;47(1):81-87.

25. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the mini asthma quality of life questionnaire. *Eur Respir J*. 1999;14(1):32-38.

26. Schatz M, Sorkness CA, Li JT, et al. Asthma control test: Reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol*. 2006;117(3):549-556.

27. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14(4):902-907.

28. Chan CS, Woolcock AJ, Sullivan CE. Nocturnal asthma: Role of snoring and obstructive sleep apnea. *Am Rev Respir Dis*. 1988;137(6):1502-1504.

29. Guilleminault C, Connolly S, Winkle R, Melvin K, Tilkian A. Cyclical variation of the heart rate in sleep apnoea syndrome. mechanisms, and usefulness of 24 h electrocardiography as a screening technique. *Lancet*. 1984;1(8369):126-131.

30. Ciftci TU, Ciftci B, Guven SF, Kokturk O, Turktas H. Effect of nasal continuous positive airway pressure in uncontrolled nocturnal asthmatic patients with obstructive sleep apnea syndrome. *Respir Med*. 2005;99(5):529-534.

31. Aburuz S, McElnay J, Gamble J, Millership J, Heaney L. Relationship between lung function and asthma symptoms in patients with difficult to control asthma. *J Asthma*. 2005;42(10):859-864.

32. Chan CS, Woolcock AJ, Sullivan CE. Nocturnal asthma: Role of snoring and obstructive sleep apnea. *Am Rev Respir Dis*. 1988;137(6):1502-1504.

33. Nadif R, Matran R, Maccario J, et al. Passive and active smoking and exhaled nitric oxide levels according to asthma and atopy in adults. *Ann Allergy Asthma Immunol*. 2010;104(5):385-393.

34. Lafond C, Series F, Lemiere C. Impact of CPAP on asthmatic patients with obstructive sleep apnoea. *Eur Respir J*. 2007;29(2):307-311.

35. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: Development of a questionnaire for use in clinical trials. *Thorax*. 1992;47(2):76-83.

36. Picado C, Badiola C, Perulero N, et al. Validation of the spanish version of the asthma control questionnaire. *Clin Ther*. 2008;30(10):1918-1931.

37. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: A survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59-65.

38. Bonay M, Nitenberg A, Maillard D. Should flow-volume loop be monitored in sleep apnea patients treated with continuous positive airway pressure? *Respir Med*. 2003;97(7):830-834.

Table 1: Asthma-Related Quality of Life

Study	Population	Asthma Severity	OSA severity	Clinical Measurement	CPAP duration	Outcome
Lafond et al. Eur Respir J 2007;29:307-311[34,35]	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[14,25]	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**

Table 2: Asthma Control & Symptoms

Study	Population	Asthma Severity	OSA Severity	CPAP Duration	Clinical Measurement	Outcome
Chan et al. Am Rev Respir Dis 1988; 137:1502-1504[28]	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[30]	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[29]	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[20]	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[14,27,36]	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 Asthma exacerbation frequency	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 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[16,37,]	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[17]	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[18]	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

Table 3: Asthma Severity

Study	Population	Asthma Severity	OSA Severity	CPAP Duration	Measurement	Intervention	Outcome
Kauppi et al. Sleep Breath 2016:20;1217-1224[20]	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[17]	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[19]	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**

Table 4: Lung Function and physiological measurements

Study	Population	Asthma severity	OSA severity	CPAP Duration	Clinical measurement	Outcome
Bonay et al. Respiratory Medicine 2003; 97: 830-834[38]	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	FEV1 FEV1/FVC	No significant difference in FEV1, FEV1/FVC ratio or FEF50, FEF25 or FEF25-75 following 17±8months of CPAP in asthma group. However- in control group; significant reduction in FEV1 $p<0.05$ and FEV1/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[28]	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[30]	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	FEV1% 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[34]	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[14]	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[16]	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.[18]	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 >4hours for 5 days of wk	Annual FEV1 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**)

Table 5: Summary of Results

No.	Study	Design	Population	Intervention	Asthma Diagnosis	OSA Diagnosis	Outcomes
1	Bonay et al. Respiratory Medicine 2003; 97: 830-834[38]	Quasi-experimental	N=50 (15 asthma, 13 COPD, 22 Non-Obstructive Airway Disease)	17±8 months of nasal CPAP	History or clinical evidence of asthma	PSG AHI=47±34 (whole population) AHI=47±27 (asthma), non-significant difference	In entire study population (n=50), significant decreases in FEF50 (p<0.005), FEF25 (p<0.05), FEF25-75(p<0.005) observed. No significant changes in lung function in asthma or COPD group. Significant increase in PaO2 (p<0.01) (asthma and COPD) and reduction in PCO_2(p<0.01) (asthma). Bronchial hyperresponsiveness occurred in 5/22 of the NOAD group
2	Chan et al. Am Rev Respir Dis 1988; 137:1502-1504[28]	Quasi-experimental	N=8 (with asthma and OSA) 1=No OSA	2 weeks of CPAP; 2wks of PEF pre-, during and post-CPAP	Unclear. All reported to have frequent nocturnal asthma attacks	PSG AHI>5	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). Marked improvement in nocturnal and daytime asthma symptoms. Reduced bronchodilator requirement during night and day.
3	Ciftci et al. Respiratory Medicine 2005;99:529-534[30]	Quasi-experimental	N=16	Nasal CPAP for 2 months	Unclear- GINA for optimisation only All had nocturnal asthma symptoms despite optimisation as per GINA guidelines	PSG AHI≥15	No significant different in pulmonary function tests (PFTs), but significant improvement in asthma night-time symptom scores (p=0.04)
4	Guilleminault et al. Eur Respir J 1988;1:902-907[29]	Quasi-experimental	N=10 (group A)	6-9 months of CPAP	Not stated Frequent nocturnal asthma attacks	PSG RDI=51±13	Group A only. Pre-CPAP: Mean 1 severe asthma attack during sleep every 17 days, 4 patients admitted to ICU at night >4 times/last year. Post- CPAP: no nocturnal asthma attacks, number of daytime asthma attacks unchanged.
5	Kauppi et al. Sleep Breath 2016:20;1217-1224[20]	Retrospective cross-sectional study	N=152 asthma and OSA	CPAP >3months (before CPAP initiation/retrospective and last 4 weeks) Mean duration 5.7years (SD 4.7)	Self-reported physician diagnosis Asthma severity assessed by visual analogue score (0 for no symptoms to 100 for severe symptoms) and also ACT	Home limited-channel sleep study (REI>15/h or 5-14 with symptoms of OSA)	Self-reported asthma severity decreased from 48.3(29.6) to 33.1(27.4) (p<0.001), and ACT score increased significantly from 15.35(5.3) to 19.8(4.6) p<0.001. % of patients using rescue medication daily reduced from 36 to 8% with CPAP (p<0.001)
6	Lafond et al. Eur Respir J 2007;29:307-311[34]	Quasi-experimental	N=20	6 weeks nocturnal CPAP	ATS criteria (all had 20% fall in FEV_1 ≤8mgmL^{-1}) All stable asthmatics	PSG AHI≥15	No significant changes in airway hyperresponsiveness after CPAP treatment. Asthma quality of life score improved from 5±1.2 to 5.8±0.9 (p=0.001)

7	Serrano-Pariente et al. Allergy 2016;72(5):802-812[14]	Quasi-experimental	N=99 (82 completed follow up)	CPAP for 6 months	GINA Guidelines N=28, intermittent-mild persistent asthma N= 71, moderate-severe persistent asthma	PSG (30%) Limited-channel sleep study (70%) Moderate-severe OSA with RDI ≥20	ACQ decreased from 1.39±0.61 to 1.0±0.78 (p=0.003). %uncontrolled asthma decreased from 41.4% to 17.2%(=0.006), % participants with asthma attacks/6months reduced from 35.4% to 17.2% (p=0.015), mAQLQ increased from 5.12±1.38 to 5.63±1.17 (p=0.009), significant improvements in GORD, rhinitis, bronchial reversibility, and exhaled nitric oxide (p<0.05)
8	Shaarawy et al. Egyptian journal of chest diseases and tuberculosis 2013;62 (1):183-187[16]	Quasi-experimental	N=15	6 weeks nocturnal CPAP	Proven reversible airway obstruction with spirometry pre- and post-bronchodilation. Uncontrolled despite optimal treatment (ACT of ≤17 in last 4 weeks)	PSG AHI>5/h (23.5±10.9 pre-CPAP)	No significant improvement in ACT (13.97±3.52 to 14.1±3.97, p>0.05) or FEV_1% pred (60.1±6.9 to 61.2±6.2, p>0.05) after CPAP
9	Shaker et al. Egyptian Journal of Chest Diesease and Tuberculosis 2017;293-298[17]	Quasi-experimental	N=12	Patients with asthma and OSA had 3 months of CPAP	GINA N=10/12 with "Difficult to control asthma"=could not be controlled with high dose ICS and LABA/other controller	PSG AHI>5	Significant improvement in daytime (p=0.009) and night-time (p=0.003) asthma symptoms, GORD symptoms (p=0.004), difficult to control asthma (p=0.004), FEV_1% predicted (p=0.002) and FEV_1/FVC ratio (p=0.003)
10	Teodorescu M et al. Sleep Disord.;2013:25 1567[19]	Cross-sectional questionnaire -based study	N=140 (75 using CPAP)	CPAP versus no CPAP treatment in asthma and co-existing OSA	"Specialist-diagnosed and managed" Severity step as per National Asthma Education and Prevention Programme (NAEPP) guidelines	Previous PSG diagnosis in medical notes (and use of CPAP).	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)
11	Teodorescu et al. J Asthma 2012;49 (6): 620-628	Cross-sectional questionnaire based study	N=136 with asthma and OSA (75 using CPAP)	CPAP versus no CPAP treatment	Asthma diagnosed by academic specialist (based on ATS criteria) Severity as per NAEPP guidelines	Review of medical records for previous diagnosis	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
12	Wang et al. BMC Pulmonary Medicine 2017;17[18]	Retrospective study- review of medical records	N=77 total N=67 with asthma and OSA N=13 with severe OSA	CPAP for 5 years	ATS	PSG 10=no OSA (AHI<5) 33=mild-moderate OSA (>5AHI≤ 30) 34=severe OSA(AHI>30)	Annual decline of patients with severe OSA was significantly accelerated compared to patients with mild-moderate OSA and those without OSA (p=0.046). Annual decline in FEV_1 was significantly lower after CPAP initiated (p=0.028).

Figure 1: Mechanistic effect of CPAP improving asthma in co-existing OSA

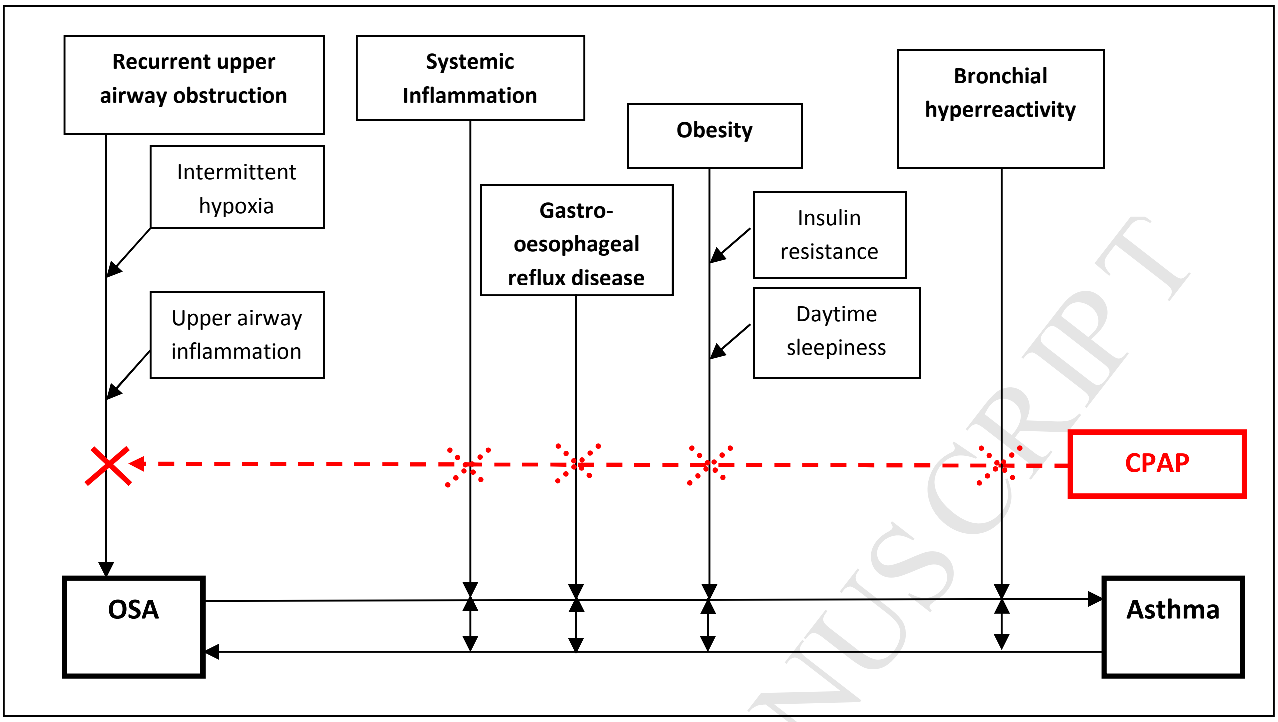


Figure 2: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)

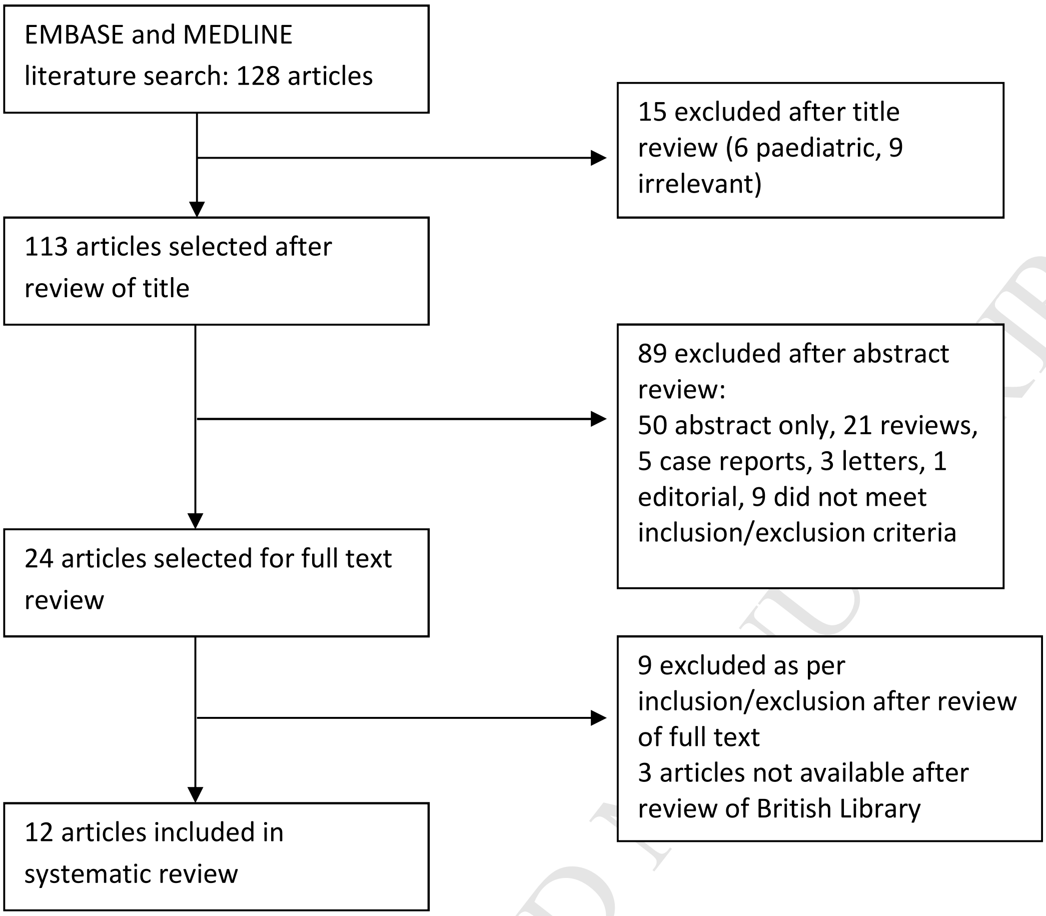
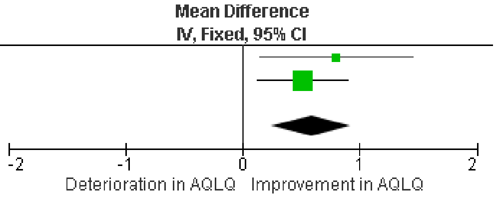


Figure 3: Meta-Analysis of Clinical Outcomes pre and post CPAP

a) Asthma related quality of life (AQLQ/mini-AQLQ)

	Post-CPAP			Pre-CPAP				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Lafond et al	5.8	0.9	20	5	1.2	20	26.2%	0.80 [0.14, 1.46]
Serrano-Pariente et al	5.63	1.17	82	5.12	1.38	82	73.8%	0.51 [0.12, 0.90]
Total (95% CI)			**102**			**102**	**100.0%**	**0.59 [0.25, 0.92]**
Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%								
Test for overall effect: Z = 3.41 (P = 0.0006)								



b) Lung Function (FEV1% predicted)

	Post-CPAP			Pre-CPAP				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Ciftci et al	71.25	21.85	16	70.25	21.17	16	4.5%	1.00 [-13.91, 15.91]
Lafond et al	80.4	13.6	20	82	13.6	20	14.0%	-1.60 [-10.03, 6.83]
Serrano-Pariente et al	83.6	16.6	82	83.6	17.6	82	36.3%	0.00 [-5.24, 5.24]
Shaarawy et al	61.2	6.2	15	60.1	6.9	15	45.2%	1.10 [-3.59, 5.79]
Total (95% CI)			**133**			**133**	**100.0%**	**0.32 [-2.84, 3.47]**
Heterogeneity: Chi² = 0.33, df = 3 (P = 0.95); I² = 0%								
Test for overall effect: Z = 0.20 (P = 0.84)								

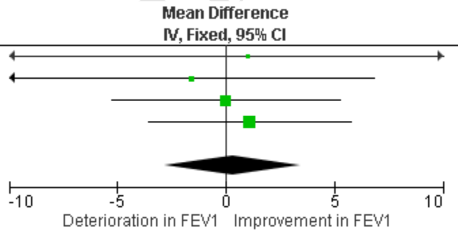
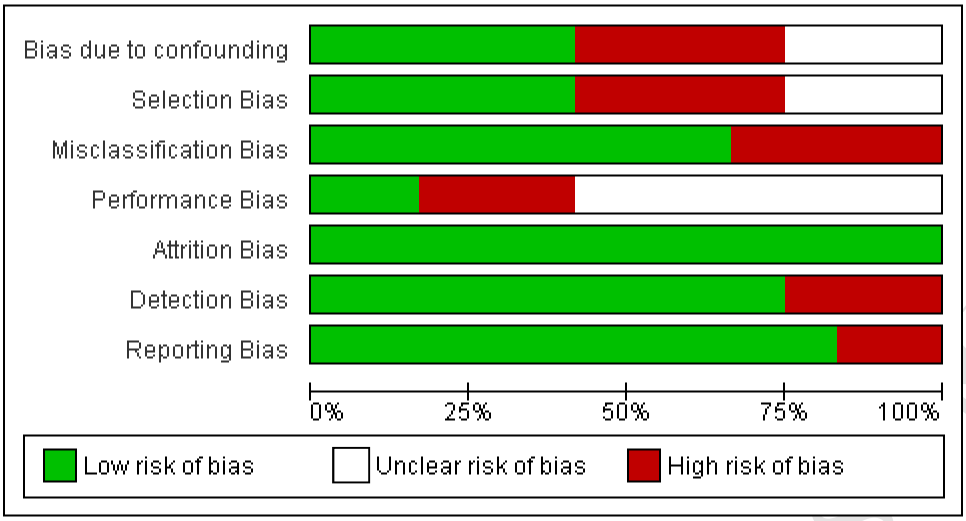


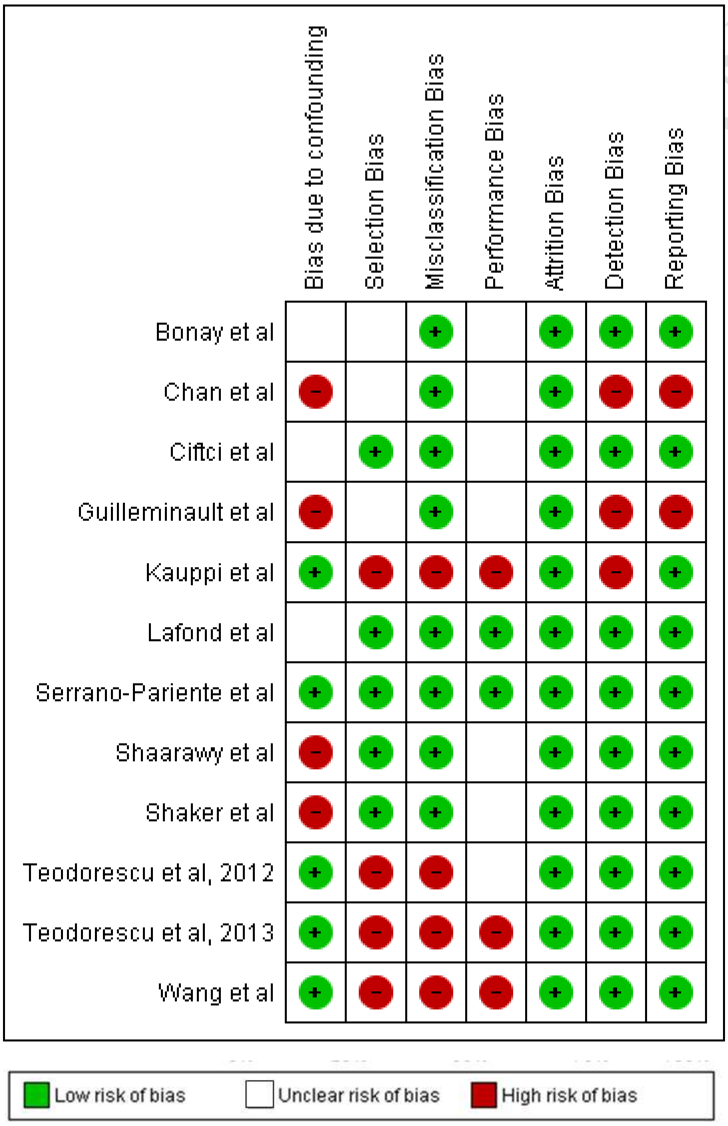
Figure 4: Risk of bias for quasi-experimental studies

A) Risk of bias graph, B) Risk of bias summary

A)



B)



Highlights

- **CPAP treatment of co-existing OSA can improve asthma-related quality of life**
- **Asthma symptoms and severity of asthma have also been shown to improve with CPAP, but studies using standardised methods of measuring asthma control (such as ACQ) are conflicting**
- **Multi-centre placebo-controlled studies are needed to fully evaluate the impact of CPAP treatment of co-existing OSA on asthma-related clinical outcomes**

Title: 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

Author List:

1. Sarah E Davies
   Highest Degree: MBChB, MRCP
   Institutional Affiliations:
   - Birmingham Regional Severe Asthma Service, Heart of England NHS Trust, Birmingham
   - Institute of Inflammation and Ageing, University of Birmingham, UK

2. Abigail Bishopp,
   Highest Degree: MBChB, MRCP
   Institutional Affiliations:
   - Birmingham Heartlands Sleep Service, Heart of England NHS Trust, Birmingham

3. Simon Wharton
   Highest Degree: MBChB, MRCP
   Institutional Affiliations:
   - Birmingham Heartlands Sleep Service, Heart of England NHS Trust, Birmingham

4. Alice M Turner
   Highest Degree: PhD
   Institutional Affiliations:
   - Birmingham Respiratory Department, Heart of England NHS Trust, Birmingham
   - Institute of Applied Health Research, University of Birmingham, UK

5. Adel H Mansur
   Highest Degree: PhD
   Institutional Affiliations:
   - Birmingham Regional Severe Asthma Service, Heart of England NHS Trust, Birmingham
   - Institute of Inflammation and Ageing, University of Birmingham, UK

Corresponding Author:
Dr S. E Davies
Birmingham Regional Severe Asthma Service
Heart of England NHS Trust
Heartlands Hospital
Bordesley Green East
Birmingham
B9 5SS
Emails: sarah.davies@heartofengland.nhs.uk, sarah.davies11@nhs.net

Conflict of Interest Statement (for each author):

1. Sarah Davies: SD has received funding for educational talks or support to attend conferences from GSK, AstraZeneca, TEVA, and non-financial support from Philips Respironics for research
2. Abigail Bishopp: None
3. Simon Wharton: None
4. Alice Turner: AMT has received funding for educational talks or support to attend conferences from: Boehringer, AZ, GSK, Chiesi, Novartis, and her institution has received non-financial support from ResMed for research related to COPD
5. Adel Mansur: Personal fees and non-financial support from GSK, AZ, NAPP, NOVARTIS, PI and others (outside the submitted work)

Acknowledgments: We would like to acknowledge the help and support provided by Peter Nightingale, Statistician at the University of Birmingham