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
License: Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version
Peer reviewed version

Citation for published version (Harvard):
https://doi.org/10.1016/j.rmed.2018.08.004

Link to publication on Research at Birmingham portal

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

• Users may freely distribute the URL that is used to identify this publication.
• Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
• Users may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
• Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Download date: 26. Oct. 2019
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. Polysomnography (PSG) has
been used to demonstrate a high prevalence of OSA in asthma\textsuperscript{2}. Approximately 5-10% of asthmatics have severe or difficult to treat asthma (SDTA) that remains problematic despite optimal treatment\textsuperscript{3}. The prevalence of OSA has been reported to be as high as 95% in severe steroid dependent asthma\textsuperscript{2} and OSA can adversely impact asthma control\textsuperscript{1}. Continuous Positive Airway Pressure (CPAP) is the gold standard treatment for patients with the OSA syndrome\textsuperscript{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\textsuperscript{5}. Studies have also demonstrated that increased airway and systemic inflammation are present in patients with OSA\textsuperscript{6,7}. Additionally, CPAP treatment can reduce Fractional Exhaled Nitric Oxide (FENO)\textsuperscript{6} and improve markers of systemic inflammation such as C-reactive protein (CRP)\textsuperscript{7}. Whether CPAP improves bronchial hyperresponsiveness in OSA patients is less clear\textsuperscript{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\textsuperscript{7}. GORD can be precipitated by the large negative intrapleural pressure swings that occur in OSA\textsuperscript{7}, and CPAP treatment has been shown to improve reflux symptoms\textsuperscript{10}. CPAP has also been shown to improve insulin resistance\textsuperscript{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\textsuperscript{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)\(^\text{12}\), 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 FEV₁ 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 FEV₁ (5 studies).
or FEV₁/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 FEV₁(%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. Patients with severe asthma and co-existing OSA have been shown to have increased sputum neutrophil counts and evidence of airway remodelling. 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. 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\(^\text{14,15,16,17,18}\) 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\(^\text{19,17}\) but one of the studies\(^\text{20}\) 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\(^\text{14}\), while one of the retrospective reviews used previous home limited-channel sleep study records\(^\text{20}\). 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\(^\text{19,21}\). 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\(^\text{19,21}\). 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\(^\text{14}\). 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\(^\text{22}\). 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\(^\text{23,24,25}\).
Two of the twelve included studies evaluated asthma-related quality of life and both found a clinically significant improvement with CPAP\textsuperscript{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\textsuperscript{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\textsuperscript{15}.

Asthma control is usually measured using the validated ACT\textsuperscript{26} or ACQ\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{20}. However it is important to note that a clinically significant improvement in mean ACQ($\geq$0.5) was not reached. Shaarawy et al\textsuperscript{16} looked at fifteen poorly controlled asthmatics (ACT$\leq$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 overestimate 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


<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Asthma Severity</th>
<th>OSA severity</th>
<th>Clinical Measurement</th>
<th>CPAP duration</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Lafond et al. Eur Respir J 2007;29:307-311 | N=20 completed follow up and compliant with CPAP | "Stable" asthma-Occasional respiratory symptoms and absence of exacerbation or change in maintenance therapy in the preceding month | Apnea 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 | N=99 82 completed follow up 12/82 non-compliant with CPAP (<4 hours/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>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Asthma Severity</th>
<th>OSA Severity</th>
<th>CPAP Duration</th>
<th>Clinical Measurement</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al. Am Rev Respir Dis 1988; 137:1502-1504&lt;sup&gt;24&lt;/sup&gt;</td>
<td>N=8 (asthma and OSA) 1=No OSA</td>
<td>Asthma with frequent nocturnal asthma attacks (previous respiratory arrest in 3 patients)</td>
<td>AHI &gt;5 All had symptoms of snoring/nocturnal upper airway obstruction</td>
<td>2 weeks</td>
<td>Asthma symptoms and bronchodilator requirements</td>
<td>All 9 patients in this study showed marked improvement in nocturnal and daytime asthma symptoms, with reduced bronchodilator requirements.</td>
</tr>
<tr>
<td>Ciftci et al. Respiratory Medicine 2005;99:529-534&lt;sup&gt;22&lt;/sup&gt;</td>
<td>N=16 completed study (n=19 enrolled)</td>
<td>≥1 nocturnal or early morning awakening due to asthma despite optimal treatment as per GINA guidelines</td>
<td>AHI≥15 Nasal CPAP Habitual snorers ≥4/hour night CPAP compliance</td>
<td>2 months</td>
<td>Night time asthma symptom scores 0: No symptoms 1: ≤2 times/month 2: &gt;2 times/month 3: &lt;1 times/week 4: Frequent</td>
<td>Improved significantly after CPAP treatment from 2.19±1.07 to 1.44±1.15, p=0.04</td>
</tr>
<tr>
<td>Guilleminault et al. Eur Respir J 1988;1:902-907&lt;sup&gt;29&lt;/sup&gt;</td>
<td>N=10 (group A) (Group B excluded as not clearly OSA)</td>
<td>Group A) Overweight middle aged asthmatic men with frequent nocturnal asthma attacks (N=10)</td>
<td>RDI= 51±13</td>
<td>6-9 months</td>
<td>Number of asthma attacks</td>
<td>The number of nocturnal asthma attacks improved The frequency of daytime asthma attacks did not change</td>
</tr>
<tr>
<td>Kauppi et al. Sleep Breath 2016:20;1217-1224&lt;sup&gt;20&lt;/sup&gt;</td>
<td>N=152</td>
<td>Respiratory Event Index (REI) &gt;15/h or 5-14 and symptoms of OSA</td>
<td>CPAP ≥3months (before CPAP initiation/retr ospective and last 4 weeks) Mean duration of CPAP 5.7 years (SD 4.7)</td>
<td>ACT</td>
<td>%patients using rescue medication daily Night-time symptoms</td>
<td>Significant improvement in ACT; 15.35(SD 5.3) to 19.8(SD 4.6), p&lt;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&lt;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.</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Follow-up Duration</td>
<td>COPD Severity</td>
<td>OSA Severity</td>
<td>Asthma Control</td>
<td>Asthma Exacerbation</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>---------</td>
<td>--------------------</td>
<td>---------------</td>
<td>--------------</td>
<td>----------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Serrano-Pariente. J. Allergy 2016;72(5):802-812</td>
<td>99</td>
<td>6 months</td>
<td>N=28 intermittent-mild persistent</td>
<td>Moderate-severe OSA with RDI ≥20</td>
<td>6 months</td>
<td>Asthma Control Questionnaire (ACQ)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shaarawy et al. Egyptian Journal of Chest Diseases and Tuberculosis 2013;62 (1):183-187</td>
<td>15</td>
<td>6 weeks</td>
<td>Uncontrolled despite optimal treatment</td>
<td>AHI&gt;5/h</td>
<td>6 weeks</td>
<td>Asthma Control Test (ACT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shaker et al. Egyptian Journal of Chest Disease and Tuberculosis 2017;293-298</td>
<td>12</td>
<td>3 months</td>
<td>2 (16.7%) moderate-persistent asthma</td>
<td>AHI&gt;5</td>
<td>3 months</td>
<td>Number of patients with daytime or night-time asthma symptoms</td>
</tr>
<tr>
<td>Teodorescu et al. J Asthma 2012;49(6):620-628</td>
<td>136</td>
<td>Unspecified</td>
<td>Unclear</td>
<td>Unknown-previous OSA (diagnosed by PSG) documented in notes</td>
<td>Unknown</td>
<td>Daytime and night-time asthma symptoms</td>
</tr>
<tr>
<td>Study</td>
<td>N=13 with severe OSA – pre- and post-CPAP (21 non-compliant)</td>
<td>N=77 total N=67 with asthma and OSA</td>
<td>Not known</td>
<td>Mild-Moderate OSA(≥5 AHIs30); N=33 Severe OSA (AHI&gt;30); N= 34 N= 10 (no OSA)</td>
<td>CPAP (5 year follow up) Compliance &gt;4hours for 5 days of wk</td>
<td>No. of A&amp;E visits for asthma</td>
</tr>
<tr>
<td>-------</td>
<td>-------------------------------------------------------------</td>
<td>------------------------------------</td>
<td>-----------</td>
<td>---------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------</td>
<td>-----------------------------</td>
</tr>
</tbody>
</table>
Table 3: Asthma Severity

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Asthma Severity</th>
<th>OSA Severity</th>
<th>CPAP Duration</th>
<th>Measurement</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kauppi et al. Sleep Breath 2016;20;1217-1224</td>
<td>N=152</td>
<td>Unknown</td>
<td>REI&gt;15/h or 5-14 and symptoms of OSA</td>
<td>CPAP &gt;3months (before CPAP initiation/retrospective and last 4 weeks)</td>
<td>Self-reported asthma severity - Visual analogue score; (0=no symptoms to 100=severe asthma symptoms)</td>
<td>CPAP &gt;3months (before treatment and last 4 weeks)</td>
<td>Significantly reduced from 48.3(29.6) to 33.1(27.4), ( p&lt;0.001 )</td>
</tr>
<tr>
<td>Shaker et al. Egyptian Journal of Chest Disease and Tuberculosis 2017;293-298</td>
<td>N=12</td>
<td>Asthma Severity</td>
<td>AHI&gt;5</td>
<td>3 months CPAP</td>
<td>Number of patients with &quot;Difficult to control asthma&quot; (asthma that could not be controlled with high dose ICS and LABA/other controller medication)</td>
<td>3 months CPAP</td>
<td>Significantly improved post CPAP; 10 (83.3%) to 3 (25%), ( p=0.004 )</td>
</tr>
</tbody>
</table>
| Teodorescu M et al. Sleep Disord.;2013;251567 | N=140      | Asthma Severity | 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Asthma severity</th>
<th>OSA severity</th>
<th>CPAP Duration</th>
<th>Clinical measurement</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonay et al.</td>
<td>N=15 (asthma) 22=Controls 13=COPD</td>
<td>Not known</td>
<td>Mean AHI pre CPAP 47±27 in asthma group 17±8 months of nasal CPAP Compliance=5.9 ±0.9h/night</td>
<td>FEV1 FEV1/FVC</td>
<td>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&lt;0.05 and FEV1/FVC, p&lt;0.05 noted.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PaO2</td>
<td>Significantly improved; 69±17 to 75±9mmHg, n=13, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PaCO2</td>
<td>Significantly reduced; 45±6 to 43±5mmHg, n=13, p&lt;0.05</td>
</tr>
<tr>
<td>Chan et al. Am Rev Respir Dis 1988; 137:1502-1504</td>
<td>N=8 (with asthma and OSA) 1=No OSA</td>
<td>Asthma with frequent nocturnal asthma attacks (previous respiratory arrest in 3 patients) AHI &gt;5 All had symptoms of snoring/nocturnal upper airway obstruction</td>
<td>2 weeks</td>
<td>Peak Expiratory Flow Rates (PEFR)</td>
<td>Mean pre-bronchodilator PEFR was significantly higher during CPAP period than control periods both in the morning (p&lt;0.05) and evening (p&lt;0.02).</td>
<td></td>
</tr>
<tr>
<td>Ciftci. T. et al. Respiratory Medicine 2005;99:529-534</td>
<td>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</td>
<td>2 months</td>
<td>FEV1% predicted</td>
<td>No significant change; 70.25±13.17 to 71.25±21.85, p=0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FEV1/FVC</td>
<td>No significant change; 66.68±15.64 to 70.75±15.37, p=0.12</td>
</tr>
<tr>
<td>Lafond et al. Eur Respir J 2007;29:307-311</td>
<td>N=20 completed follow up and compliant with CPAP &gt;4 hours/night &quot;Stable&quot; 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</td>
<td>6 weeks</td>
<td>FEV1 % predicted</td>
<td>No significant difference; 82±13.6 to 80.4±13.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20% fall in FEV1 (≤8mgmL PC20) to methacholine</td>
</tr>
<tr>
<td>Serrano-Pariente et al. Allergy 2016;72(5):802-812</td>
<td>N=99 82 completed follow up 12/82 non-compliant with CPAP (&lt;4hours/night) N=28, intermittent-mild persistent N= 71, moderate-severe persistent</td>
<td>Moderate-severe OSA with RDI ≥20 75.8% of population had RDI&gt; 30 Mean pre-CPAP RDI= 46.3 ± 20.8</td>
<td>6 months</td>
<td>FEV1% predicted</td>
<td>No significant change; 83.6±17.6 to 83.6±16.6, p=0.977</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FENO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GINA Guidelines ≥12% and 200mL increase in FEV1 to SABA</td>
</tr>
<tr>
<td>Study</td>
<td>N=15 (completed follow up)</td>
<td>Uncontrolled despite optimal treatment - ACT≤17 in last 4 weeks</td>
<td>AHÌ≥5/h Mean pre-CPAP AHÌ=23.5±10.9</td>
<td>6 weeks nocturnal CPAP</td>
<td>FEV₁% predicted</td>
<td>No significant change; 60.1±6.9 to 61.2±6.2, p&gt;0.05</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>N=77 total N=67 with asthma and OSA N=13 with severe OSA - pre and post CPAP (21 non-compliant)</th>
<th>Not known</th>
<th>Mild-Moderate OSA (≥5 AHÌ≤30); N=33 Severe OSA (AHÌ&gt;30); N=34 N= 10 (no OSA)</th>
<th>CPAP (5 year follow up) Compliance ≥4hours for 5 days of wk</th>
<th>Annual FEV₁ decline</th>
<th>Annual decline of FEV₁ in asthmatic patients with severe OSA was significantly increased compared to those with mild-moderate OSA and to those without OSA (72±17.7mL vs. 41.9±15.3mL vs. 24.3±27.5mL, p=0.046). Decline in FEV₁ was significantly lower after 2 years of CPAP (p=0.028)</th>
</tr>
</thead>
</table>
### Table 5: Summary of Results

<table>
<thead>
<tr>
<th>No</th>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Intervention</th>
<th>Asthma Diagnosis</th>
<th>OSA Diagnosis</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bonay et al. Respiratory Medicine 2003; 97:830-834</td>
<td>Quasi-experimental</td>
<td>N=50 (15 asthma, 13 COPD, 22 Non-Obstructive Airway Disease)</td>
<td>17±8 months of nasal CPAP</td>
<td>History or clinical evidence of asthma</td>
<td>PSG</td>
<td>In entire study population (n=50), significant decreases in FEF50 (p&lt;0.005), FEF25 (p&lt;0.05), FEF25-75 (p&lt;0.005) observed. No significant changes in lung function in asthma or COPD group. Significant increase in PaO2 (p&lt;0.01) (asthma and COPD) and reduction in PCO2 (p&lt;0.01) (asthma). Bronchial hyperresponsiveness occurred in 5/22 of the NOAD group.</td>
</tr>
<tr>
<td>2</td>
<td>Chan et al. Am Rev Respir Dis 1988; 137:1502-1504</td>
<td>Quasi-experimental</td>
<td>N=8 (with asthma and OSA) 1=No OSA</td>
<td>2 weeks of CPAP; 2wks of PEF pre-, during and post-CPAP</td>
<td>Unclear. All reported to have frequent nocturnal asthma attacks</td>
<td>PSG</td>
<td>Mean pre-bronchodilator PEFR was significantly higher during CPAP period than control periods both in the morning (p&lt;0.05) and evening (p&lt;0.02). Marked improvement in nocturnal and daytime asthma symptoms. Reduced bronchodilator requirement during night and day.</td>
</tr>
<tr>
<td>3</td>
<td>Ciftci et al. Respiratory Medicine 2005;99:529-534</td>
<td>Quasi-experimental</td>
<td>N=16</td>
<td>Nasal CPAP for 2 months</td>
<td>Unclear- GINA for optimisation only All had nocturnal asthma symptoms despite optimisation as per GINA guidelines</td>
<td>PSG</td>
<td>No significant different in pulmonary function tests (PFTs), but significant improvement in asthma night-time symptom scores (p=0.04)</td>
</tr>
<tr>
<td>4</td>
<td>Guilleminault et al. Eur Respir J 1988;1:902-907</td>
<td>Quasi-experimental</td>
<td>N=10 (group A)</td>
<td>6-9 months of CPAP</td>
<td>Not stated</td>
<td>PSG</td>
<td>Group A only. Pre-CPAP: Mean 1 severe asthma attack during sleep every 17 days, 4 patients admitted to ICU at night &gt;4 times/last year. Post-CPAP: no nocturnal asthma attacks, number of daytime asthma attacks unchanged.</td>
</tr>
<tr>
<td>5</td>
<td>Kauppi et al. Sleep Breath 2016:20;1217-1224</td>
<td>Retrospective cross-sectional study</td>
<td>N=152 asthma and OSA</td>
<td>CPAP &gt;3months (before CPAP initiation/retrospective and last 4 weeks) Mean duration 5.7years (SD 4.7)</td>
<td>Self-reported physician diagnosis Asthma severity assessed by visual analogue score (0 for no symptoms to 100 for severe symptoms) and also ACT</td>
<td>Home limited-channel sleep study (REI&gt;15/h or 5-14 with symptoms of OSA)</td>
<td>Self-reported asthma severity decreased from 48.3(29.6) to 33.1(27.4) (p&lt;0.001), and ACT score increased significantly from 15.35(5.3) to 19.8(4.6) p&lt;0.001. % of patients using rescue medication daily reduced from 36 to 8% with CPAP (p&lt;0.001)</td>
</tr>
<tr>
<td>6</td>
<td>Lafond et al. Eur Respir J 2007;29:307-311</td>
<td>Quasi-experimental</td>
<td>N=20</td>
<td>6 weeks nocturnal CPAP</td>
<td>ATS criteria (all had 20% fall in FEV1 ≤8mgmL⁻¹) All stable asthmatics</td>
<td>PSG</td>
<td>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&lt;0.001)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Intervention</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Serrano-Pariente et al. (2016)</td>
<td>Quasi-experimental</td>
<td>99</td>
<td>CPAP for 6 months</td>
<td>ACQ decreased from 1.39±0.61 to 1.0±0.78 (p=0.003), %uncontrolled asthma decreased from 41.4% to 17.2% (p=0.006), % participants with asthma attacks/months 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&lt;0.05)</td>
</tr>
<tr>
<td>8. Shaarawy et al. (2013)</td>
<td>Quasi-experimental</td>
<td>15</td>
<td>6 weeks nocturnal CPAP</td>
<td>No significant improvement in ACT (13.97±3.52 to 14.1±3.97, p&gt;0.05) or FEV1% pred (60.1±6.9 to 61.2±6.2, p&gt;0.05) after CPAP</td>
</tr>
<tr>
<td>9. Shaker et al. (2017)</td>
<td>Quasi-experimental</td>
<td>12</td>
<td>CPAP for 3 months</td>
<td>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), FEV1% predicted (p=0.002) and FEV1/FVC ratio (p=0.003)</td>
</tr>
<tr>
<td>10. Teodorescu et al. (2013)</td>
<td>Cross-sectional questionnaire-based study</td>
<td>140</td>
<td>CPAP versus no CPAP treatment in asthma and co-existing OSA</td>
<td>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</td>
</tr>
<tr>
<td>11. Teodorescu et al. (2012)</td>
<td>Cross-sectional questionnaire-based study</td>
<td>136</td>
<td>CPAP versus no CPAP treatment</td>
<td>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</td>
</tr>
<tr>
<td>12. Wang et al. (2017)</td>
<td>Retrospective study-review of medical records</td>
<td>77</td>
<td>CPAP for 5 years</td>
<td>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 FEV1 was significantly lower after CPAP initiated (p=0.028).</td>
</tr>
</tbody>
</table>
Figure 1: Mechanistic effect of CPAP improving asthma in co-existing OSA

OSA → Recurrent upper airway obstruction → Intermittent hypoxia → Upper airway inflammation

OSA → Systemic Inflammation

OSA → Obesity

OSA → Gastro-oesophageal reflux disease

OSA → Insulin resistance → Daytime sleepiness

OSA → Bronchial hyperreactivity

CPAP

OSA → Asthma

Bronchial hyperreactivity

Gastro-oesophageal reflux disease

Insulin resistance

Daytime sleepiness

OSA

Asthma

Recurrent upper airway obstruction

Intermittent hypoxia

Upper airway inflammation

Systemic Inflammation

Obesity

Systemic Inflammation

Gastro-oesophageal reflux disease

Insulin resistance

Daytime sleepiness

OSA

Asthma

Bronichal hyperreactivity

Figure 1: Mechanistic effect of CPAP improving asthma in co-existing OSA
Figure 2: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)

EMBASE and MEDLINE literature search: 128 articles

113 articles selected after review of title

89 excluded after abstract review: 50 abstract only, 21 reviews, 5 case reports, 3 letters, 1 editorial, 9 did not meet inclusion/exclusion criteria

24 articles selected for full text review

9 excluded as per inclusion/exclusion after review of full text
3 articles not available after review of British Library

15 excluded after title review (6 paediatric, 9 irrelevant)

12 articles included in systematic review
Figure 3: Meta-Analysis of Clinical Outcomes pre and post CPAP

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

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Post CPAP</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Pre CPAP</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latran et al</td>
<td>5.8</td>
<td>0.9</td>
<td>20</td>
<td></td>
<td>5.2</td>
<td>1.2</td>
<td>20</td>
<td></td>
<td>0.68 (0.14, 1.48)</td>
<td>1.33</td>
</tr>
<tr>
<td>Sierra-Pariente et al</td>
<td>5.83</td>
<td>1.17</td>
<td>32</td>
<td></td>
<td>5.13</td>
<td>1.39</td>
<td>32</td>
<td></td>
<td>0.61 (0.12, 0.93)</td>
<td>1.33</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>102</td>
<td></td>
<td></td>
<td></td>
<td>102</td>
<td></td>
<td></td>
<td></td>
<td>0.59 (0.25, 0.92)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Post CPAP</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Pre CPAP</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critel et al</td>
<td>71.25</td>
<td>21.85</td>
<td>16</td>
<td>76.25</td>
<td>21.17</td>
<td>16</td>
<td></td>
<td></td>
<td>4.5% (13.91, 15.81)</td>
<td>1.00</td>
</tr>
<tr>
<td>Latran et al</td>
<td>68.4</td>
<td>13.6</td>
<td>26</td>
<td>82</td>
<td>13.8</td>
<td>28</td>
<td></td>
<td></td>
<td>14.0% (10.03, 18.83)</td>
<td>1.00</td>
</tr>
<tr>
<td>Sierra-Pariente et al</td>
<td>63.6</td>
<td>16.6</td>
<td>82</td>
<td>83.6</td>
<td>17.6</td>
<td>82</td>
<td></td>
<td></td>
<td>18.3% (6.24, 30.48)</td>
<td>1.00</td>
</tr>
<tr>
<td>Shahnaz et al</td>
<td>51.2</td>
<td>6.2</td>
<td>16</td>
<td>60.1</td>
<td>8.9</td>
<td>15</td>
<td></td>
<td></td>
<td>45.3% (3.08, 91.70)</td>
<td>1.00</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>133</td>
<td></td>
<td></td>
<td></td>
<td>133</td>
<td></td>
<td></td>
<td></td>
<td>0.32 (2.84, 3.47)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.33, df = 3 (P = 0.92), I² = 0%
Test for overall effect Z = 2.80 (P = 0.04)
Figure 4: Risk of bias for quasi-experimental studies

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

A) Bias due to confounding:
- Selection Bias:
- Misclassification Bias:
- Performance Bias:
- Attrition Bias:
- Detection Bias:
- Reporting Bias:

0% 25% 50% 75% 100%

Low risk of bias Unclear risk of bias High risk of bias

B) Bias due to confounding:
- Bonay et al:
- Chan et al:
- Cifoni et al:
- Guilleminault et al:
- Kauppi et al:
- Lafond et al:
- Serrano-Pantoni et al:
- Shaarawy et al:
- Shaker et al:
- Teoedoscu et al, 2012:
- Teoedoscu et al, 2013:
- Wang et al:

Low risk of bias Unclear risk of bias High risk of bias
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