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# Factors associated with systemic hypertension in asthma

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## Abstract

**Purpose—**Asthmatics have unique characteristics that may influence cardiovascular morbidity. We tested the association of lower airway caliber, obstructive sleep apnea (OSA) and other asthma-related factors, with systemic hypertension (HTN).

**Methods—**Asthma individuals at specialty clinics completed the Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ). Medical records were reviewed for diagnosed HTN, OSA and comorbidities, spirometry and current medications. $FEV_1$% predicted was categorized as ≥80 (reference), 70-79, 60-69 and <60. SA-SDQ ≥36 for men and ≥32 for women defined high OSA risk.

**Results—**Among 812 asthmatics (mean age±standard deviation: 46±14 years), HTN was diagnosed in 191 (24%), OSA in 65 (8%), and OSA or high OSA risk (combined OSA variable) in 239 (29%). HTN was more prevalent in lower $FEV_1$% categories ($p<0.0001$), in subjects with OSA, and those with combined OSA variable (55% vs. 21% and 46% vs. 14%, respectively, both

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p<0.0001). With adjustment for covariates, associations with HTN remained significant for some $FEV_1$% categories (70-79% odds ratio=1.60 [95% CI: 0.90-2.87]; 60-69% 2.73 [1.28-5.79]; <60% 0.96 [0.43-2.14]), and for OSA (2.20 [1.16-4.19]). The combined OSA variable in comparison to OSA alone demonstrated a stronger association with HTN (3.17 [1.99-5.04]) in a reiteration of this model. Inhaled corticosteroids (ICS) at lowest doses, in comparison to no ICS use had an independent "protective" association with HTN (0.44 [0.22-0.90]).

**Conclusions—**In this young population, lower airways obstruction and OSA were positively associated with HTN. In contrast, lower ICS doses attenuated likelihood for HTN. Adequate control of airway inflammation at appropriate ICS doses, and screening for OSA may reduce the burden of HTN in asthma.

### Keywords

Asthma; airway obstruction; hypertension; lung; sleep apnea; obstructive

## INTRODUCTION

Asthma, obstructive sleep apnea (OSA) and systemic hypertension (HTN) are among most common chronic illnesses. Asthma and OSA affect approximately 8% and 2-4% of middle-aged adults [3, 41]. Based on NHANES, about 16% of adults 20-75 years old have stage 1 and 2 (clinical) HTN [30]. These diseases impose substantial economic burden [1, 3, 24].

In a large population-based study, asthmatics were more likely to have HTN than non-asthmatics, independent of traditional risk factors [13]. This suggests that asthma individual has a unique set of predisposing characteristics for HTN. Reduced lung function ($FEV_1$) and accompanying inflammation may be one such characteristic. The occurrence of inflammation as systemic rather than simply confined to the airways in asthma is a concept growing in acceptance [6]. Reduced lung function is linked to cardiovascular mortality [33], and systemic inflammation has been proposed as one underlying mechanism [33]. Indeed, an inverse relationship between $FEV_1$% and systemic levels of inflammatory markers was shown [31, 36], and systemic inflammation in the setting of chronic lung disease is a strong and consistent marker of future cardiovascular events [23]. Asthma comorbidities, such as rhinitis and atopy—likewise associated with low-grade systemic inflammation—may also contribute to HTN risk [6]. Asthma medications may have their own effects, since long acting bronchodilators have been associated with mortality in asthma subsets [26]. Inhaled corticosteroids at higher doses are absorbed systemically [25], and certainly, systemic corticosteroids have been shown to have undesirable effects, such as hypertension and other cardiovascular outcomes [16, 37]. These may be due, in part, to mineralocorticosteroid effects, with retention of sodium and fluid [16, 37].

OSA—a recognized cause for HTN [10]— is more prevalent in asthma [4, 21, 34]. OSA propagates an inflammatory cascade that has been implicated in the pathogenesis of cardiovascular disease [24, 32]. Asthma and OSA, however, feature a bidirectional relationship, such that OSA worsens asthma [9, 11, 17]. Given this interaction, it is possible that these disorders exacerbate each other's systemic inflammatory milieu, giving rise to an enhanced predisposition for cardiovascular disease.

To date, no studies have addressed the role of lower airway obstruction, OSA, co-morbidities and medications as risk factors for HTN in asthma patients. We therefore hypothesized that airways obstruction, OSA and higher doses of ICS will be associated with HTN in these patients. Elucidating these relationships would allow physicians to address causal factors for HTN and reduce its burden in asthma. Preliminary results were published in abstract form [35].

## METHODS

### Study Design

This was a cross-sectional study conducted at the University of Michigan (UM)- Ann Arbor (May 2004 - April 2006) and University of Wisconsin (UW)- Madison (July 2007-December 2009). Subjects were enrolled as part of a study examining the relationship between OSA and asthma which received approvals from both Institutional Review Boards. Written informed consent was obtained from each participant.

### Study Subjects

Patients with asthma, aged 18-75, at routine follow-up at Allergy and Pulmonary clinics were enrolled. Those in for urgent visits and pregnant women were excluded. Subjects had asthma diagnosed (based upon ATS criteria [2]) and managed by an academic specialist. Standard of care at visits includes history, physical exam, asthma control assessment and spirometry.

### Data Collection

A self-administered survey included the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ), a validated tool to identify patients at high risk for OSA [14]. SA-SDQ contains 8 symptom-items (loud snoring disruptive to the bed partner; breathing pauses during sleep; sudden gasping arousals; worsening of snoring while supine or after alcohol; nocturnal nasal congestion and sweating; and a history of hypertension), as well as demographics. Scores ≥36 for men and ≥32 for women define high risk for OSA, as validated with polysomnography (PSG) [14].

Medical records were reviewed by study physicians for established diagnoses of comorbid lung diseases (including chronic obstructive pulmonary disease), HTN and OSA and their treatment status, and related comorbidities (rhinitis, chronic sinusitis and nasal polyps). Spirometric data, asthma (inhaled corticosteroids [ICS], systemic corticosteroid, long-acting beta agonist) and antihypertensive medications at the current visit were also extracted.

### Statistical Analysis

The outcome was a clinical diagnosis of HTN, as extracted from the records. $FEV_1$% was categorized as: ≥80% (normal), 70-79% (mildly reduced), 60-69% (moderately reduced), <60% (severely reduced); for each, a dummy variable was created and referred to the normal (≥80%) category. Owing to reduced clinical recognition [40], OSA was defined as: (1) OSA (history of clinically-diagnosed and untreated OSA); and (2) combined OSA variable (high OSA risk on SA-SDQ or a history of clinically-diagnosed and untreated OSA). Doses of ICS

were classified as: low (category 1), medium (category 2) and high (category 3), per NAEPP guidelines [22]. A dummy variable was created for each ICS category and compared with "no ICS use (category 0)", as the reference. HTN subjects treated with ≥2 classes of antihypertensives were classified as having severe HTN.

Baseline variables were summarized as mean±SD for continuous and percentages for categorical variables. Two-sample t-tests, *chi*-squared or Fisher exact tests were used, as appropriate, to analyze group differences in continuous and categorical variables, respectively. Logistic regression was used to test for univariate relationships of HTN with $FEV_1$% categories, OSA or combined OSA variable, non-modifiable (age and sex) and modifiable (smoking, BMI) demographic variables, comorbidities (rhinitis, chronic sinusitis and nasal polyps), and asthma medications. Multivariate logistic regression models were then fitted with HTN as the dependent variable and categories of $FEV_1$% predicted, OSA or combined OSA variable, with stepwise adjustment for the aforementioned covariates, regardless of their univariate associations with HTN. Two-sided p-values <0.05 indicated statistical significance. Analyses were performed using SAS 9.2 software, (SAS institute; Cary, NC).

## RESULTS

Of the 1,012 subjects invited to participate, 951 (94%) consented. Of those, 64 were excluded for co-morbid lung disease. Among the remaining 887 subjects, 140 had been diagnosed with OSA of whom 75 were on treatment with continuous positive airway treatment (CPAP) and were excluded from further analyses, due to potential beneficial effects of CPAP treatment on lung function.[9] Thus, a total of 812 subjects (244 from UM and 568 from UW) were analyzed.

Sample characteristics are presented in Table 1. The majority were females, and the sample was rather young on average (46±14 yo). The mean $FEV_1$ was 92 ±16% predicted, with the majority of subjects having values ≥60% predicted. Eight percent of our subjects had a clinical diagnosis of OSA, and 27% had either high OSA risk or a history of OSA. Over three quarters (78%) were on ICS, 9% on chronic oral glucocorticoids and 59% on LABA.

The prevalence of HTN was 191 (24%) and was similar between the two centers (UM vs. UW: 27% vs. 22%, p=0.12). Among subjects with HTN, 181 (95%) were on antihypertensive medications, the rest were following diet/life-style modification measures. The prevalence of HTN increased with lower $FEV_1$% almost in a linear fashion, except for the severely reduced category (*chi*-square statistic=28, p-value<0.0001) (Figure 1). HTN was more common in individuals with vs. those without OSA (*chi*-square statistic=40, p-value<0.0001), and in those with the combined OSA variable vs. those without (*chi*-square statistic=95, p-value<0.0001) (Figure 2).

Univariate associations of HTN are shown in Table 2. With decreasing $FEV_1$% the odds for HTN increased, though no further in the lowest category. A significant association was observed for OSA, which strengthened when the combined OSA variable was analyzed. Significant positive associations with HTN were observed for high ICS doses, oral

corticosteroid and LABA. Among demographics, age and BMI demonstrated significant associations with HTN.

Results of multivariate analyses are depicted in Table 3. With progressive adjustment for covariates, although the incremental association of $FEV_1$% predicted categories was attenuated, moderately reduced $FEV_1$% maintained its statistical significance: when compared with the individuals with normal $FEV_1$% predicted, those in this category were on average 173% more likely to have a diagnosis of HTN (odds ratio=2.73, 95% Confidence Interval [1.28-5.79], p=0.009); the association of mildly reduced $FEV_1$% predicted was reduced to a trend (1.60 [0.90-2.87], p=0.11), whereas no association was seen for the severely reduced category. OSA history remained significantly associated with HTN, such that, when compared to individuals without, in those with OSA, the odds for HTN were on average 120% higher (2.20 [1.16-4.19], p=0.02), independent of all covariates. Interestingly, while not significantly associated in univariate analyses, in the multivariate model, a "protective" association of ICS doses emerged which gradually attenuated with higher doses: as compared to asthmatics not on ICS, the low dose users were 56% less likely (0.44 [0.22-0.90], p=0.02) to have HTN. The increased odds for HTN seen with high dose were lost in multivariate analysis. None of the comorbidities or other asthma medications retained independent significant associations with HTN. Reiteration of these models replacing the OSA with the combined OSA variable (Table 4) demonstrated its stronger association with HTN (3.17 [1.99-5.04], p<.0001), while the other relationships did not appreciably change.

## DISCUSSION

This study of a large sample of asthma patients is the first to report relationships that may help explain unique risk factors for HTN. We found that decreased $FEV_1$% is associated with HTN almost in a linear fashion (Table 3 and 4). Also, use of ICS appeared to have a dual perhaps counterbalancing relationship with HTN: at lower doses ICS had a "protective" association which was lost at higher doses (Table 3 and 4). Concomitant OSA was also associated with HTN, independent of traditional confounders and those more specific to this patient population (Table 3). When scores on a validated screen for OSA were included within a composite OSA variable, the strength of this association increased even further (Table 4).

Independent of other factors, decreasing $FEV_1$% was associated nearly in a linear fashion with clinically-established diagnosis of HTN (Table 3 and 4): a trend toward statistical significance was noted with mild decreases in $FEV_1$, a significant association was seen for moderately decreased $FEV_1$, and while a significant univariate association was observed for the severely reduced category (Table 2) this wasn't maintained in the final models (Table 3 and 4). These results are generally consistent with reports from population-based studies which found similar associations between $FEV_1$ and some cardiovascular outcomes and mortality, though with significant associations even for the lowest $FEV_1$ quintile category [33].

We also found a significant association of OSA with HTN (Table 3 and 4) of a greater magnitude than that observed in general populations where it has been well-recognized [27].

Evidence is mounting that patients with asthma have an increased predisposition for OSA [4, 21, 34] and that untreated OSA is an independent risk factor for poor asthma control [9, 11, 17]. Both asthma and OSA are increasingly recognized as systemic pro-inflammatory disorders, with shared similarities that may underlie the expression of HTN—in itself, an inflammatory process [28]—in this population. Inflammation is the key pathology in asthma. The complex milieu in the lower airways cross-talks with the bone marrow, causing a sustained "spillover" inflammation [6, 12], characterized by elevations in TNF-α and IL-1β [18], and IL-6 [5, 39], their levels correlate with airway reactivity [18], increase further during attacks and with allergen bronchoprovocation [39]. Additionally, asthma is associated with C-reactive protein (CRP), a sensitive marker of systemic inflammation [20]. These mediators have pleiotropic vascular properties, promoting wall stiffness, impairing nitric oxide-dependent vasodilation, and are elevated in patients with HTN [8, 28]. Furthermore, mast cells produce lipoxins and hydroxyeicosatetraenoic acids (HETEs), which interact with renal receptors producing vascular and/or glomerular vasoconstriction affecting renal hemodynamics, predisposing to HTN [7, 29]. A possible explanation of the observed $FEV_1$% associations could be that with its mild to moderate decreases, gradually enhanced levels of mediators occur and predispose to HTN. We did not find an association with HTN for the severely reduced $FEV_1$ category, which is likely due to the small number of subjects in this subset. This observation was in contrast to our expectation, and to the observation that this was the subset most frequently using highest ICS doses (*chi*-square statistic=73, $p<0.0001$) and oral corticosteroids (Fisher exact, $p<0.0001$), both of which have been linked to adverse cardiovascular outcomes [37, 38]. In OSA, the related systemic inflammation is playing a central role in its cardiovascular consequences [24, 32]. Intermittent hypoxia preferentially activates NF-kB-mediated inflammatory pathways and inflammatory cells which release inflammatory mediators such as TNF-α, IL-6, CRP, leading to vascular pathology. Treatment with CPAP attenuates levels of some of these markers [24, 32].

Our study, for the first time, suggests a "double-edged sword" relationship of ICS with HTN (Table 3 and 4): lower doses of ICS may confer a "protective" association while the opposite may be applicable for higher doses. In COPD, low dose ICS therapy reduced the likelihood of acute myocardial infarction, when controlling for other known risks [19]. This may be explained by control of inflammation, since circulating levels of CRP significantly decreased with ICS [15]. On the other hand, high dose corticosteroid users have an increased risk of hospitalization due to cardiovascular disease [38]. High corticosteroid doses were associated with increased risk for atrial fibrillation, explained in part by mineralocorticosteroid effects [37] with retention of sodium and water, thereby predisposing to HTN and atrial fibrillation [16, 37]. Doses in between (medium ICS dose, which represented over a third –37% – of our steroid users), may or may not heighten risk for HTN, as ICS differ in their potency and systemic absorption from the airways [25]. Nonetheless, corroborating the existent literature with our data renders our speculation intriguing and worthy to be prospectively tested.

Taken together, our data suggest complex interactions modulating HTN risk in asthma (Figure 3). The result of reciprocally interactive pathways of asthma with OSA, in one

individual, may be an augmented systemic inflammatory response, leading to a heightened risk for HTN. Furthermore, the ICS dose alters the balance of systemic anti-inflammatory vs. mineralocorticoid effects, such that at higher doses mineralocorticoid effects take more of a role and may further augment the HTN risk (Figure 3).

The strengths of this study rely on the high participation rate (94%), yielding one of the largest samples of asthma patients. Second, these subjects were well-characterized with concomitant assessment of multiple relevant variables from medical records, objective measures (ie, spirometry) and surveys. Furthermore, the vast majority of patients with a HTN diagnosis were either using antihypertensive medications (95%) or had documentation of following diet/life-style measures (5%), enhancing the confidence in the HTN diagnosis. The prevalence of diagnosed HTN in our sample was higher than that estimated by NHANES (14%) (HTN stage 1 and 2) for adults aged 40-49 [30], the age group most heavily represented in our study; thus, such high prevalence of HTN makes this population most suitable for testing the associations of interest. There are limitations to our study. First, this is a cross-sectional study and thus it cannot prove cause and effect relationships. However, the data brought forth, in the setting of these biologically putative pathways, are provocative and merit future prospective investigation. Second, the assigned diagnosis of HTN from the chart may lead to an underestimation of the prevalence of HTN, if for example patients may not have had primary care or anti-HTN medications recorded in the system, as the specialists may be less likely to assign a diagnosis of HTN despite observations of high blood pressure readings in their office visits and more likely to defer this task to primary care. Furthermore, we did not conduct objective measures of blood pressure, to assess its control. Third, the SA-SDQ has not been validated in asthma populations. However, the observed associations for clinically-diagnosed (and untreated) OSA offer robust credence overall to the data. Additionally, the OSA in comparison to no OSA subjects, on average, scored much higher on the SA-SDQ scale (37 vs. 27, $p<0.001$). Likewise, 75% of OSA vs. only 23% of no OSA subjects (*chi*-square statistic=78, $p<0.0001$) fulfilled the criteria for high OSA risk, as validated with PSG in other patient populations [14]. Last, the SA-SDQ does contain a question assessing HTN. We know of no work that used the SA-SDQ questionnaire without any of its individual questions, and thus have no validated cut-point to use in defining our combined OSA variable, if the HTN question is excluded. Nonetheless, the associations observed when using the clinically-diagnosed OSA variable lays credence to the data observed when using the combined OSA variable. Furthermore, as is in the general population [40], OSA is likely underdiagnosed also in asthmatics, yielding further support for the analysis using the combined OSA variable. Until studies on this topic are done, this possibility cannot be refuted. Further prospective studies overcoming all these limitations are necessary.

In summary, in this large sample of asthma patients, moderately decreased $FEV_1$% and prevalent comorbidity with OSA were associated with diagnosed-HTN, independent of traditional confounders. Additionally, ICS may have a dose-related counterbalancing effect on the presence of HTN. Our data suggest that adequate control of lower airway inflammation at the most appropriate dose of ICS may attenuate cardiovascular risk, and earlier screening for OSA may allow new opportunities to reduce the burden of HTN and its

consequences in asthma. The interacting and modulating pathways that emerged in this study warrant prospective studies with objective methods and more detailed cardiovascular outcomes, to better clarify their role in cardiovascular risk in asthma.

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## Abbreviations List

| | |
|---|---|
| **AHI** | Apnea-Hypopnea Index |
| **BMI** | Body Mass Index (in kilograms per meter squared) |
| **CI** | Confidence Interval |
| **CPAP** | Continuous Positive Airway Pressure |
| **COPD** | Chronic Obstructive Pulmonary Disease |
| **CRP** | C-reactive protein |
| **$FEF_{25-75}$** | Forced Expiratory Flow between 25% and 75% of vital capacity |
| **$FEV_1$** | Forced Expiratory Volume in first second of the vital capacity |
| **FVC** | Forced Vital Capacity |
| **GERD** | Gastroesophageal Reflux Disease |
| **HTN** | Systemic hypertension |
| **IH** | Intermittent Hypoxia related to obstructive sleep apnea |
| **ICS** | Inhaled Corticosteroid |

| | |
|---|---|
| **LABA** | Long Acting $\beta_2$-Agonist |
| **LTM** | Leukotriene Modifiers |
| **NAEPP** | National Asthma Education and Prevention Program |
| **NHANES** | National Health and Nutrition Examination Survey |
| **OR** | Odds Ratio |
| **OSA** | Obstructive Sleep Apnea |
| **PEFR** | Peak Expiratory Flow Rate |
| **PSG** | Polysomnography (laboratory-based sleep study) |
| **SA-SDQ** | Sleep Apnea scale of the Sleep Disorders Questionnaire |
| **s.d** | standard deviation of the mean |

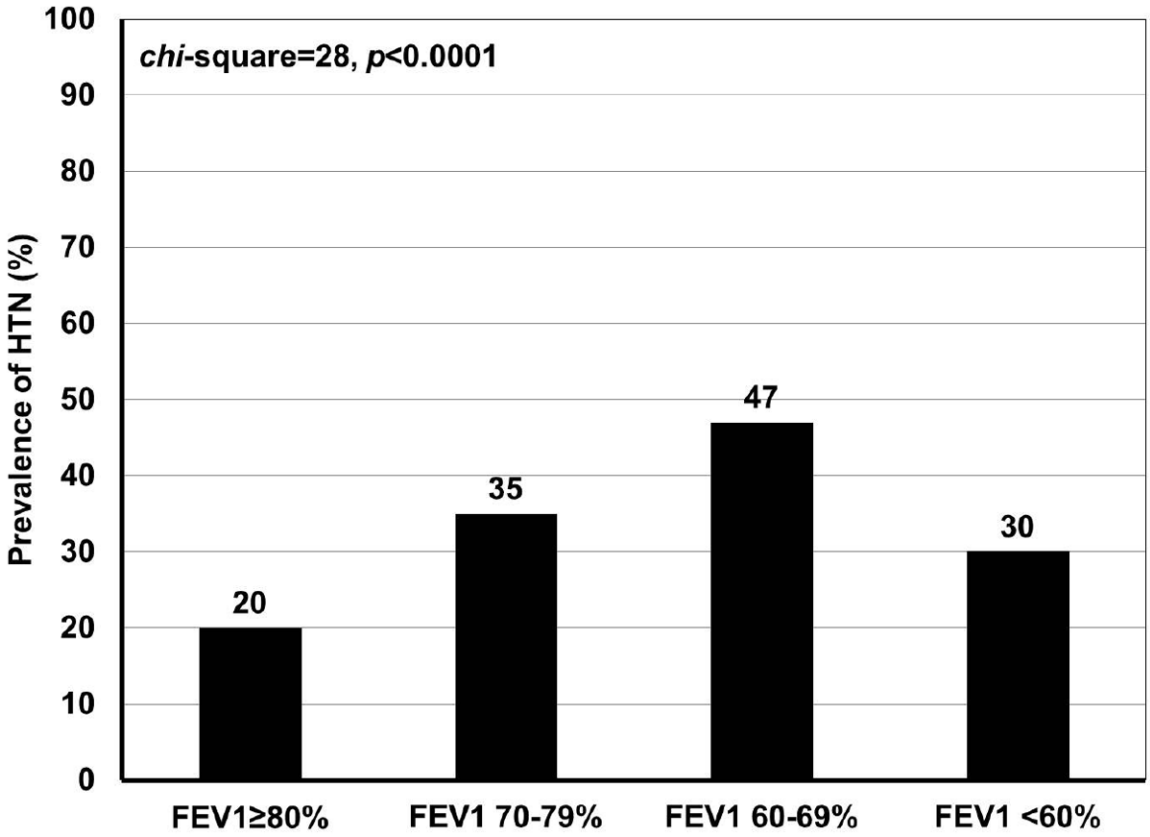


**Figure 1.**

Prevalence of systemic hypertension by categories of $FEV_1$% predicted in n=812 subjects with asthma

Abbreviations: $FEV_1$%= forced expiratory volume in first second; HTN=systemic hypertension.

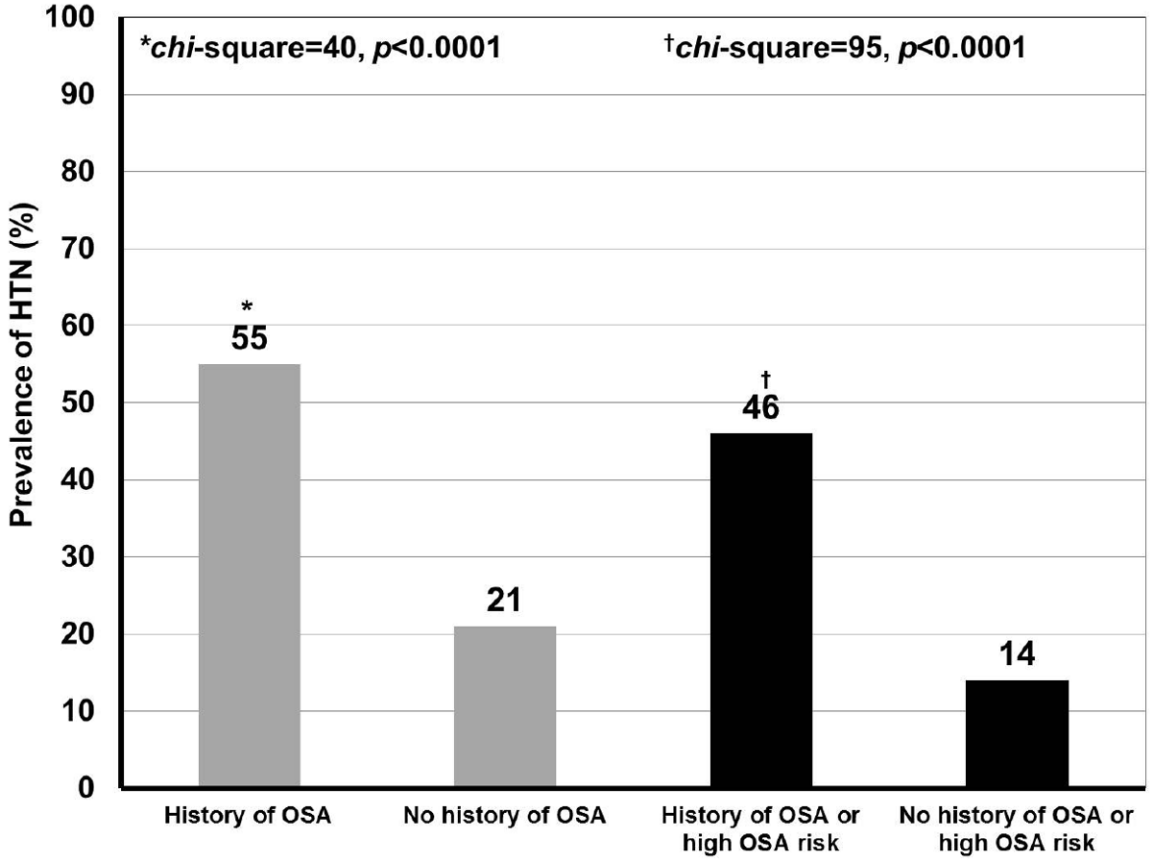


**Figure 2.**

Prevalence of systemic hypertension in asthma subjects with and without OSA, and with or without OSA or high OSA risk on SA-SDQ*

Abbreviations: HTN=systemic hypertension; OSA= obstructive sleep apnea (diagnosed and untreated).

*defined as scores on Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) ≥36 for men and ≥32 for females.[27]

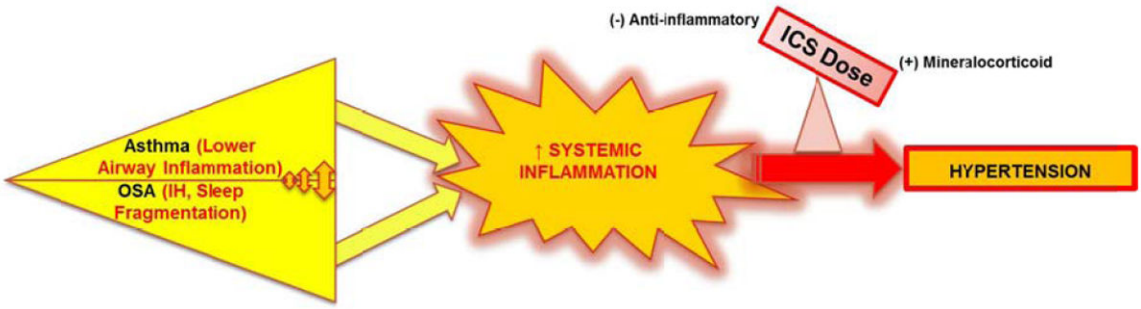


**Figure 3.**

Proposed interaction between asthma, OSA and inhaled corticosteroid in modulating risk for systemic hypertension in patients with asthma

Both asthma and OSA (via intermittent hypoxia—IH, sleep fragmentation) are associated with sustained inflammatory states, which share similarities and could predispose to cardiovascular morbidity, such as HTN. Since asthma and OSA feature a bidirectional interaction, it is possible that in one individual, these disorders exacerbate each other's systemic inflammatory state, giving rise to an augmented systemic inflammatory response, leading to a heightened risk for HTN. The ICS dose, by altering the balance of anti-inflammatory vs. mineralocorticoid effects may further modulate the HTN risk. See Discussion for details.

Abbreviations: OSA= obstructive sleep apnea; IH=intermittent hypoxia caused by obstructive sleep apnea; ICS= inhaled corticosteroid.

## Table 1

Demographic, physiologic and clinical characteristics of n=812 subjects with asthma

| Characteristic | Mean±SD or Number (%) |
|---|---|
| Age (years) | 46±14 |
| Gender (female) | 541 (67%) |
| BMI (kg/m$^{2)}$ | 29.0±6.8 |
| Current smoking | 37 (5%) |
| $FEV_1$ (% predicted) | 92±19 |
| ≥80% | 621 (77%) |
| 70-79% | 89 (11%) |
| 60-69% | 49 (6%) |
| 50-59% | 32 (4%) |
| 40-49% | 9 (1%) |
| <40% | 5 (1%) |
| FVC (% predicted) | 92±16 |
| $FEV_1$/FVC | 76±9 |
| $FEF_{25-75}$ (% predicted) | 69±31 |
| History of rhinitis | 734 (90%) |
| History of chronic sinusitis | 246 (30%) |
| History of nasal polyps | 120 (15%) |
| ICS use | 631 (78%) |
| Low dose | 189 (23%) |
| Medium dose | 235 (29%) |
| High dose | 207 (25%) |
| Oral corticosteroids | 70 (9%) |
| LABA | 475 (59%) |
| SA-SDQ | 28±7 |
| High OSA risk on SA-SDQ | 221 (27%) |
| History of OSA | 65 (8%) |
| History of OSA or high OSA risk on SA-SDQ* | 239 (29%) |

* defined as scores on Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) ≥36 for men and ≥32 for females.[27]

Abbreviations: s.d.= standard deviation; BMI= body mass index; $FEV_1$%= forced expiratory volume in first second; FVC%=forced vital capacity; FEF $_{25-75}$%= forced expiratory flow between 25% and 75% of vital capacity (all these physiologic variables are expressed as percentages of predicted values); ICS= inhaled corticosteroid; LABA=Long acting β-agonist; OSA=obstructive sleep apnea (diagnosed and untreated); SA-SDQ= Sleep Apnea scale of the Sleep Disorders Questionnaire.

## Table 2

Univariate associations of systemic hypertension in n=812 subjects with asthma.

| Variable | Odds Ratio | 95% Confidence Interval | p-value |
|---|---|---|---|
| $FEV_1$ (% predicted) categories: | | | |
| ≥80% | Reference | - | - |
| 70-79% | 2.19 | 1.35-3.53 | 0.001 |
| 60-69% | 3.62 | 2.00-6.56 | <.0001 |
| <60% | 1.79 | 0.93-3.46 | 0.08 |
| History of OSA | 4.74 | 2.82-7.98 | <.0001 |
| History of OSA or high OSA risk on SA-SDQ* | 5.18 | 3.66-7.32 | <.0001 |
| Age | 1.10 | 1.08-1.11 | <.0001 |
| Gender | 0.92 | 0.65-1.30 | 0.63 |
| BMI | 1.09 | 1.06-1.11 | <0.0001 |
| Smoking | 0.62 | 0.25-1.50 | 0.29 |
| Rhinitis | 0.66 | 0.40-1.10 | 0.11 |
| Chronic sinusitis | 1.65 | 1.18-2.32 | 0.004 |
| Nasal polyps | 1.96 | 1.29-2.98 | 0.002 |
| ICS dose: | | | |
| Low dose | 0.86 | 0.50-1.45 | 0.56 |
| Medium dose | 1.21 | 0.75-1.95 | 0.44 |
| High dose | 2.18 | 1.37-3.48 | 0.001 |
| Oral corticosteroids | 2.07 | 1.24-3.46 | 0.006 |
| LABA | 1.60 | 1.14-2.26 | 0.007 |

*defined as scores on Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) ≥36 for men and ≥32 for females.[27]

Abbreviations: $FEV_1$%= forced expiratory volume in first second; OSA= obstructive sleep apnea (diagnosed and untreated); BMI= body mass index; ICS= inhaled corticosteroid; LABA=long acting β-agonist.

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**Table 3**

Associations of systemic hypertension with $FEV_1$% predicted, with adjustment for history of OSA (diagnosed and untreated), demographic and other asthma-related variables.

| | ODDS RATIO ADJUSTED FOR HISTORY OF OSA | | ODDS RATIO ADJUSTED FOR HISTORY OF OSA, NON-MODIFIABLE RISK FACTORS (AGE, SEX) | | ODDS RATIO ADJUSTED FOR HISTORY OF OSA, NON-MODIFIABLE AND MODIFIABLE RISK FACTORS (BMI, SMOKING) | | ODDS RATIO ADJUSTED FOR HISTORY OF OSA, NON-MODIFIABLE AND MODIFIABLE RISK FACTORS, AND ASTHMA-RELATED VARIABLES | |
|---|---|---|---|---|---|---|---|---|
| | ***ORs (95%CI)*** | ***p-value*** | ***ORs (95% CI)*** | ***p-value*** | ***ORs (95% CI)*** | ***p-value*** | ***ORs (95% CI)*** | ***p-value*** |
| $FEV_1$% categories | | | | | | | | |
| 70-79% | 2.00 (1.22-3.28) | 0.006 | 1.78 (1.02-3.10) | 0.04 | 1.65 (0.94-2.92) | 0.08 | 1.60 (0.90-2.87) | 0.11 |
| 60-69% | 3.03 (1.63-5.64) | 0.0004 | 3.37 (1.66-6.84) | 0.0008 | 3.15 (1.50-6.59) | 0.002 | 2.73 (1.28-5.79) | 0.009 |
| <60% | 1.48 (0.75-2.95) | 0.26 | 1.42 (0.68-3.04) | 0.36 | 1.19 (0.55-2.57) | 0.66 | 0.96 (0.43-2.14) | 0.93 |
| History of OSA | 4.37 (2.54-7.54) | <.0001 | 3.49 (1.93-6.32) | <.0001 | 2.29 (1.23-4.27) | 0.009 | 2.20 (1.16-4.19) | 0.02 |
| Age | - | - | 1.10 (1.08-1.12) | <.0001 | 1.10 (1.08-1.12) | <.0001 | 1.10 (1.08-1.14) | <.0001 |
| Gender | - | - | 0.68 (0.45-1.02) | 0.06 | 0.76 (0.50-1.15) | 0.19 | 0.70 (0.46-1.08) | 0.11 |
| BMI | - | - | - | - | 1.08 (1.05-1.11) | <.0001 | 1.08 (1.04-1.11) | <.0001 |
| Smoking | - | - | - | - | 0.68 (0.23-2.02) | 0.49 | 0.64 (0.21-1.99) | 0.45 |
| Rhinitis | | | | | | | 1.04 (0.53-2.04) | 0.91 |
| Chronic sinusitis | - | - | - | - | - | - | 1.34 (0.85-2.09) | 0.21 |
| Polyps | - | - | - | - | - | - | 1.34 (0.76-2.39) | 0.32 |
| ICS Doses | | | | | | | | |
| Low | - | - | - | - | - | - | 0.44 (0.22-0.90) | 0.02 |
| Medium | - | - | - | - | - | - | 0.62 (0.31-1.24) | 0.18 |
| High | - | - | - | - | - | - | 0.79 (0.38-1.67) | 0.54 |
| Oral corticosteroids | - | - | - | - | - | - | 1.50 (0.78-2.91) | 0.22 |
| LABA | - | - | - | - | - | - | 1.29 (0.76-2.20) | 0.34 |

Abbreviations: ORs=odds ratio; CI= confidence interval; $FEV_1$%= forced expiratory volume in first second; OSA= obstructive sleep apnea (diagnosed and untreated); BMI= body mass index; ICS= inhaled corticosteroid; LABA=long acting β-agonist.

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**Table 4**

Associations of systemic hypertension with $FEV_1$% predicted, with adjustment for combined OSA variable (history or high OSA risk on SA-SDQ*), demographic and other asthma-related variables.

| | ODDS RATIO ADJUSTED FOR OSA (HISTORY OR HIGH RISK ON SA-SDQ*) | | ODDS RATIO ADJUSTED FOR OSA, NON-MODIFIABLE RISK FACTORS (AGE, SEX) | | ODDS RATIO ADJUSTED FOR OSA, NON-MODIFIABLE AND MODIFIABLE RISK FACTORS (BMI, SMOKING) | | ODDS RATIO ADJUSTED FOR OSA, NON-MODIFIABLE AND MODIFIABLE RISK FACTORS AND ASTHMA-RELATED VARIABLES | |
|---|---|---|---|---|---|---|---|---|
| | ***ORs (95%CI)*** | ***p-value*** | ***ORs (95% CI)*** | ***p-value*** | ***ORs (95% CI)*** | ***p-value*** | ***ORs (95% CI)*** | ***p-value*** |
| $FEV_1$% categories | | | | | | | | |
| 70-79% | 1.77 (1.06-2.95) | 0.03 | 1.47 (0.83-2.61) | 0.18 | 1.49 (0.84-2.64) | 0.18 | 1.47 (0.82-2.64) | 0.20 |
| 60-69% | 2.60 (1.37-4.92) | 0.004 | 2.76 (1.34-5.69) | 0.006 | 2.88 (1.35-6.13 | 0.006 | 2.53 (1.18-5.46) | 0.02 |
| <60% | 1.41 (0.70-2.86) | 0.33 | 1.32 (0.61-2.87) | 0.49 | 1.24 (0.57-2.71) | 0.59 | 1.01 (0.45-2.29) | 0.97 |
| OSA (combined variable) | 4.75 (3.34-6.77) | <.0001 | 4.43 (2.97-6.62) | <.0001 | 3.30 (2.10-5.18) | <.0001 | 3.17 (1.99-5.04) | <.0001 |
| Age | - | - | 1.10 (1.08-1.12) | <.0001 | 1.10 (1.08-1.12) | <.0001 | 1.10 (1.08-1.12) | <.0001 |
| Gender | - | - | 0.85 (0.56-1.29) | 0.43 | 0.87 (0.57-1.34) | 0.53 | 0.82 (0.53-1.27) | 0.37 |
| BMI | - | - | - | - | 1.05 (1.02 -1.08) | 0.004 | 1.05 (1.01-1.08) | 0.006 |
| Smoking | - | - | - | - | 0.54 (0.18-1.59) | 0.26 | 0.51 (0.17-1.56) | 0.24 |
| Rhinitis | - | - | - | - | - | - | 0.96 (0.49-1.88) | 0.91 |
| Chronic sinusitis | - | - | - | - | - | - | 1.32 (0.84-2.09) | 0.24 |
| Polyps | - | - | - | - | - | - | 1.21 (0.67-2.19) | 0.53 |
| ICS Doses | | | | | | | | |
| Low | - | - | - | - | - | - | 0.44 (0.21-0.89) | 0.02 |
| Medium | - | - | - | - | - | - | 0.59 (0.29-1.18) | 0.13 |
| High | - | - | - | - | - | - | 0.77 (0.36-1.65) | 0.50 |
| Oral corticosteroids | - | - | - | - | - | - | 1.43 (0.73-2.78) | 0.30 |
| LABA | - | - | - | - | - | - | 1.17 (0.68-2.00) | 0.57 |

*defined as scores on Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) ≥36 for men and ≥32 for females.[27]

Abbreviations: ORs=odds ratio; CI= confidence interval; $FEV_1$%= forced expiratory volume in first second; OSA= obstructive sleep apnea (diagnosed and untreated); BMI= body mass index; ICS= inhaled corticosteroid; LABA=long acting β-agonist.