

Comorbidities of pediatric asthma: A narrative review

Review Article

Javad Ghaffari (MD)^{1*}
Negar Ghaffari (MD)²

1. Molecular and Cell biology Research Center,
Mazandaran University of medical sciences,
Sari, Iran.

ORCID ID orcid.org/0000-0002-1447-8916

2. Medical Student, Mazandaran University of
medical sciences, Sari, Iran.

ORCID ID orcid.org/0000-0001-8672-1893

* Correspondence:

Javad Ghaffari (MD), Boali hospital, Sari,
Mazandaran Province, 48158-38477, I. R. Iran.

E-mail: javadneg@yahoo.com

Tel: +98 1133343018

Fax: +98 1133344506

Received: 1 April 2020

Revised: 11 July 2020

Accepted: 29 Sep 2020

Abstract

Background: Asthma is one of the most common persistent inflammatory respiratory disorders. Comorbidities are relatively common in asthma. The aim of this review study was to find comorbid disorders in children with asthma.

Methods: For the purpose of this review, we searched databases including Scopus, Google scholar, PubMed, SID, Irandoc and up-to-date. Key words for the search included children asthma, comorbidity and pediatric asthma. There were no time limitations for the search. Full text articles in English language were included in this study.

Results: Neuropsychiatric comorbidities were Attention-deficit/hyperactivity disorder (ADHD) (11.5%), oppositional defiant disorder (ODD) (10.7%), separation anxiety disorder (6.1%), social anxiety disorder (3.8%), specific phobias (2.3%), agoraphobia without panic (1.5%), (mild) manic episodes (1.1%), major depressive episodes (MDE) (0.8%), movement (tic) disorder (0.8%) and dysthymia (0.4%). The prevalence of sinusitis was 13% in children with asthma (17). Prevalence of asthma in chronic rhinosinusitis with polyposis (CRSwP) is 26–48%, but the prevalence of CRSwP in asthmatic patients is only 7%. Asthma was prevalent in 25%–35% patients with allergic rhinitis, and rhinitis symptoms were present in 75%–90% of asthmatic patients. Asthma and obstructive sleep apnea (OSA) commonly coexist. Snoring (49.5%), gastro-esophageal reflux disease (GERD) (46.3%), atopic dermatitis (27.3%), allergic sinusitis (20%) and food allergy (10.5%) were common in children with asthma.

Conclusions: Our review has revealed that allergic rhinitis, gastroesophageal reflux, obesity, food allergy, obstructive sleep apnea, allergic conjunctivitis, chronic rhinosinusitis and psychological abnormalities are common comorbidities in children with asthma.

Keywords: Allergic rhinitis, Asthma, Children, Comorbid, Eczema

Citation:

Ghaffari J, Ghaffari N. Comorbidities of pediatric asthma: A narrative review. *Caspian J Pediatr Sep 2020; 6(2): 420-5.*

Introduction

Allergic diseases are common worldwide. Asthma is one of the most common non-communicable diseases in children^[1]. Asthma is a chronic inflammatory respiratory disease that has significant morbidity and mortality in children. Asthma in children is the most common cause of emergency department visits, absence from school and hospitalization. Most common clinical manifestations of asthma are cough, wheezing and dyspnea, respectively. The prevalence of asthma is varied in different countries^[2, 3]. Globally, more than 300 million people are involved. The prevalence of asthma is higher in children^[2-4]. Unfortunately, the prevalence of allergic disorders such as asthma is increasing, likely due to the genetic susceptibilities and environmental factors, economic, and

nutritional factors [5]. The burden of asthma is high on the healthcare systems and families [6].

Etiologies of asthma are not exactly clear as well as the genetic susceptibility and environmental factors contribute in inducing and exacerbating asthma. Various Cytokines and chemokines play a role in the pathophysiology of asthma [7-9]. History and physical examination are the main diagnostic tools of asthma, although the spirometry and peak flow evaluation are useful in diagnosis and follow-up of treatment [2-5]. Managements of asthma include aversion from dangerous factors such as indoor and outdoor allergens, rescue and maintenance treatments with pharmacotherapy and in a few cases, specific allergen immunotherapy [2].

When an asthmatic patient does not respond to treatment, there are multiple questions to be asked; is the drugs' dose or way of consumption correct? Is asthma the correct diagnosis? Are there any risk factors for asthma exacerbation? Finally, are there any comorbid conditions? Sometimes asthma can be seen with other disorders, allergic (allergic rhinitis (AR), eczema, urticaria) and non-allergic (GERD, obesity, anxiety) ones [3, 4]. The comorbidity of asthma and allergic rhinitis is high in Chinese children [10]. Asthma prevalence was 25-35% in patients with AR [11].

The exact mechanism of effect of comorbid disorders on the asthma is not clear for each condition. Awareness of asthma comorbidities and their treatments can help better control asthma. The aim of

this study was to review comorbid disorders in childhood asthma.

Methods

This is a review article. We searched databases including Google scholar, PubMed, SID, Irandoc, Scopus and up-to-date. Key words for the search include: childhood asthma, comorbidity and pediatric asthma. There were no time limitations for the search. Ages up to 19 years were considered "childhood" asthma. Our inclusion criteria were childhood or pediatric asthma, English language, comorbid disorders, original articles and full text articles. All identified abstracts were assessed by two reviewers. Study quality was assessed of randomization, sample size, blinding, control group and statistical analysis.

Results

More than 500 articles were found at the first search. After evaluating article titles, 400 articles were excluded. Then, we evaluated the remaining 100 articles, of which 60 articles were either not accessible to us in full text or were not written in English, were excluded. Finally, 40 articles met the inclusion criteria and were used in this review.

The research's data are mentioned in table 1.

Table 1: Prevalence of different disorders and clinical manifestations in childhood asthma

Reference	Manifestations
12	Dysthymia (0.4%), separation anxiety disorder (6.1%), Attention-deficit/hyperactivity disorder (ADHD) (11.5%), oppositional defiant disorder (ODD) (10.7%), , social anxiety disorder (3.8%), specific phobias (2.3%), agoraphobia without panic (1.5%), (mild) manic episodes (1.1%), movement (tic) disorder (0.8%) and major depressive episodes (MDE) (0.8%).
13	Sinusitis (13%)
14	Chronic rhinosinusitis particular without nasal polyps (CRSsNP) 26–48% but prevalence of CRSwP is 7%
15	AR 15-40%
16	AR 36.0%–64.3 %
11	AR 70-90%
17	Allergic rhinitis (75%), psychological disturbance (71%), snoring (49.5%), gastro-esophageal reflux disease (GERD) (46.3%), atopic dermatitis (27.3%), allergic sinusitis (20%), and food allergy (10.5%) were common in children with asthma
18	GERD 41%
19	AD 28%
20	AR 72.6%
21	Snoring 34%
22	Mental health disorders 13.8-62 %
23	Behavior problems 35%
24	Anxiety disorder was 43.2%
25	Anxiety problems (79%), Attention and behavioral problems (48%),

Discussion:

Chronic disorders such as asthma are public health problems. They have negative effects on the mental health, physical condition and quality of life of patients. Asthma may be associated with other acute or chronic diseases that complicate the problem. Prevalence of comorbidities varies from study to study and geographical areas [17]. Comorbid disorders are important in children with asthma. The mechanisms of effect of comorbid diseases on the asthma are not clear for each situation. In some disorders, comorbid disorders induce inflammatory processes occurring in respiratory and non-respiratory system, whereas other comorbidities' mechanisms are not clear exactly. Gastroesophageal reflux disease, depression in adolescents, smoke exposure, African-American race and rhinosinusitis are risk factors and comorbidities that are especially present in severe asthma and are associated with poorly controlled disease [26]. Poor asthma control, severe persistent asthma and duration of disease more than 3 years were identified as independent asthma-related risk factors for mental health conditions in children [12]. Obesity or being overweight is a risk factor for asthma exacerbation, more frequent admission and even increased steroid resistance. Of course, the relation between obesity and asthma is not clear exactly. Obesity is associated with an increase in inflammatory phenotypes. In addition, obstructive sleep apnea (OSA) is more common in obesity, so that it complicates asthma [27-30].

Chronic rhinosinusitis (CRS), particularly CRS without nasal polyps (CRSsNP) was significantly related to childhood asthma [31]. Sinusitis is an important comorbid disorder in children with asthma [13, 14]. Coexistence of AR and CRS with asthma is correlated with poorer asthma control, more exacerbations, emergency visits and decreased quality of life [32].

Gastro-Esophageal Reflux (GER) is more common in severe asthma and induces asthma exacerbation due to Micro-aspirations, acid stimulation of the esophagus and vagus nerve stimulation. However, it is recommended to treat GER in severe asthmatic patients [33]. Sinusitis and GER are associated with children asthma exacerbation [34].

Food allergy might be comorbid with asthma, hospital admission, daytime symptoms, asthma persistent and severe asthma exacerbation are more

common in children with food allergy [35]. The prevalence of food allergy in childhood asthma was 20.7% and 32.7% in French and Chinese children, respectively [36].

Asthma and Allergic rhinitis occur concomitantly in most children. The AR is a predicting factor to induce asthma in children. The AR is a risk factor for uncontrolled or poor controlled asthma [15-16, 37-38]. Some studies reported other comorbidities of childhood asthma such as vasomotor rhinitis, allergic rhinitis, sinusitis, conjunctivitis, pneumonia, eosinophilic esophagitis, atopic dermatitis, obesity, gastro-esophageal reflux, vocal cord dysfunction, food allergy, depressive disorders and cardiovascular disease [33, 35, 17, 39-41].

Hay fever or respiratory allergies, eczema or skin allergies, sinusitis, food or digestive allergies, difficulty with emotions, concentration, behavior, or getting along and fatigue or lack of energy ≥ 3 days are more common in children asthma. Asthma attacks, emergency department visits and longer periods of medication administration were more common in patients with comorbidities [40]. The GERD, AR, AD and snoring were common in childhood asthma [18-21].

Prevalence of mental health disorders was higher in allergic asthma [22-24, 42]. Comorbidity of diseases is important when the disease itself is persistent. One study showed children with comorbid rhinitis, eczema and asthma at 4 years of age had an increased risk of having sustained comorbidities at 8 years of age [43].

Asthma and obstructive sleep apnea (OSA) commonly coexist; they have significant bidirectional interactions that cause difficulty in controlling both OSA and asthma [30]. The GERD, obesity and chronic sinusitis are an important comorbid disorders in children with asthma. Obesity leads to mechanical disadvantage of the diaphragm, low-grade inflammatory process and increased asthma manifestations [44]. Fungal sensitization (*Alternaria*, *Aspergillus*, *Penicillium*, and *Cladosporium*) has an impact on asthma severity. They are important comorbidities of asthma [44, 45]. Chronic sinusitis affects asthma by means of infection, allergic inflammation and anatomic processes [44]. Asthma and AR are considered as "one way, one disease", and the inflammatory process is the same in both [44]. Comorbidity of AR, GER, CRS, OSA, food allergy, obesity, being overweight,

neuropsychiatric issues and eczema should be considered in children with asthma and treated when diagnosed. However, some studies could not confirm these comorbidities [35, 46-47].

Psychological issues including exhaustion, stress, anxiety and depression were higher in allergic asthma and increased atopy and asthma manifestations due to the inflammatory and non-inflammatory mechanisms [42]. In our review, association between GER, CRS, and psychological abnormality has been reported in children with asthma [26-27, 33-35, 18, 22]. Various studies have stated that these disorders affect asthma exacerbations and make it more difficult to control. Most of these research reported improvement of asthma symptoms after treatment of comorbidities [33, 35, 44].

Obesity, overweight and OSA are confirmed comorbidities of childhood asthma. In many instance, treatment of these issues has good effects on asthma manifestation and quality of life [27-30, 35].

Infections of sinus especially chronic rhinosinusitis with (CRSwNP) or without nasal polyposis (CRSsNP) are a significant comorbidity of childhood asthma. We should consider sinus infection in anyone with asthma especially in children with poor or uncontrolled asthma. Improvement in asthma manifestations were seen after treatment of sinus infection [26, 13-14, 31-32, 34].

Food allergy is another common allergic disorder associated with childhood asthma. Children with asthma who have food allergies are at risk for exacerbation of asthma and anaphylaxis. Diagnosis of food allergy is mainly based on patient history. The best treatment of food allergy is to avoid triggering substances [35-36].

The AR is the most common allergic disease in the world. This review revealed that the AR is an important comorbidity in childhood asthma. Treatment of AR leads to improvement of clinical manifestations and quality of life of children with asthma [10-11, 15-16, 20, 37-38]. Early treatment and interventions to decrease AR symptoms can reduce or stop development of asthma. Allergen immunotherapy in refractory symptoms to certain inhalants (dust, grass, tree, and ragweed) may also be beneficial in the management of AR and possibly asthma [44].

The AD is another common allergic disorder especially in early years of life that is a major burden on the quality of life and asthma manifestations.

Diagnosis of AD is mainly based on clinical manifestations and AD criteria. Comorbidity of AD and childhood asthma is proven in many studies. Early diagnosis and treatment of AD improve asthma symptoms [33, 35, 39-41, 19]. A few articles have studied snoring in children with asthma and confirmed that the snoring is a comorbidity of childhood asthma. They have observed improved asthma symptoms after treatment of snoring [17, 21].

Treatment of GERD demonstrated improvement in symptoms and quality of life of children with asthma [44]. Weight loss in obese children leads to improvement of clinical symptoms and quality of life of children with asthma [44]. Treatment of OSA may improve asthma symptoms [30, 44]. Finally, more studies are needed to elucidate the mechanisms, pathways, and effective interventions of comorbid disorders. It is suggested that the meta-analysis paper should be written in the future to confirm the relationship between childhood asthma and other comorbid disorders.

In conclusion, our review revealed comorbidity of AR, GER, Obesity, Food allergy, OSA, allergic conjunctivitis, CRS and psychological abnormality in children with asthma. Early detection and intervention of comorbid disorders or condition in children with asthma are necessary. Some of these comorbid conditions subside with well controlled asthma. Good control of comorbid conditions in children with asthma can be effective in treatment of asthma.

Acknowledgement:

The authors would like to thank the Clinical Research Development Unit (CRDU) of Bu-Ali Sina Hospital, Mazandaran University of Medical Sciences, Sari, Iran for their support, cooperation and assistance throughout the period of writing the article.

Conflict of interest: The authors have no conflict of interest.

References:

1. Asthma. WHO Fact sheet no 307 [Internet]. Geneva (Switzerland): World Health Organization; 2017 Aug [cited 2017 Nov 14]. Available from:

<http://www.who.int/mediacentre/factsheets/fs307/en/#>

2. Ghaffari J, Aarabi M. The prevalence of pediatric asthma in the Islamic Republic of Iran: a systematic review and meta-analysis. *J Pediatr Rev* 2013; 1(1): 2-11.
3. Zamanfar D, Gaffari J, Behzadnia S, et al. The Prevalence of Allergic Rhinitis, Eczema and Asthma in Students of Guidance Schools in Mazandaran Province, Iran. *Open Access Maced J Med Sci* 2016; 4(4): 619-23.
4. Ghaffari J, Mohammadzadeh I, Khalilian A, et al. Prevalence of asthma, allergic rhinitis and eczema in elementary schools in Sari (Iran). *Caspian J Inter Med* 2012; 3(1): 372.
5. Ghaffari J. The prevalence of children's asthma: A few comments. *Clin respir J* 2018; 12(9): 2454.
6. Ghaffari J, Hadian A, Daneshpoor SMM, Khademloo M. Asthma Burden in the Hospitalized Patients. September 2014. *Int J Pediatr* 2014; 2(4.1): 257-66.
7. Hatami H, Ghaffari N, Ghaffari J, Rafatpanah H. Role of Cytokines and Chemokines in the Outcome of Children With Severe Asthma. *J Pediatr Rev* 2019; 7(1): 17-28.
8. Aghajani M, Rafiei A, Ghaffari J, et al. Immune Dysregulation in Children with Allergic asthma, a close Relationship between IL-17 but not IL-4 or IFN-g, and Disease Severity. *Res Mol Med (RMM)* 2018; 6(1): 16-29.
9. Kardan M, Ghaffari J, Valadan R, et al. T-bet and GATA-3 Gene Expression in Children with Allergic Asthma and Healthy Controls . *J Mazandaran Uni Med Sci* 2017; 26(146): 9-21.
10. Kou W, Li X, Yao H, Wei P. Meta-analysis of the comorbidity rate of allergic rhinitis and asthma in Chinese children. *Inter J Pediatr Otorhinolaryngol* 2018; 107: 131-4.
11. Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. *J Allergy Clin Immunol* 2000; 106(5): S201-5.
12. Zhou H, Chen Z, Zhao W, et al. Evaluation of neuropsychiatric comorbidities and their clinical characteristics in Chinese children with asthma using the MINI kid tool. *BMC pediatrics* 2019; 19(1): 454.
13. Lombardi E, Stein RT, Wright AL, et al. The relation between physician-diagnosed sinusitis, asthma, and skin test reactivity to allergens in 8-year-old children. *Pediatr Pulmonol* 1996; 22(3): 141-6.
14. Promsopa C, Kansara S, Citardi MJ, et al. Prevalence of confirmed asthma varies in chronic rhinosinusitis subtypes. *Inter Forum Allerg Rhinol (Wiley Online Library)* 2016; 6: 373-7. doi: 10.1002/alr.21674
15. Gough H, Grabenhenrich L, Reich A, et al. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. *Pediatr Allergy Immunol* 2015; 26(5): 431-7.
16. Liu W, Huang C, Wang X, et al. Multimorbidities of asthma, allergies, and airway illnesses in childhood: Chance or not chance? *J Asthma* 2017; 54(7): 687-98.
17. Kumar P, Sing G, Goyal JP, et al. Association of common comorbidities with asthma in children: a cross-sectional study. *Sudan J Paediatrics* 2019; 19(2): 88-92. <https://doi.org/10.24911/SJP.106-1544873451>
18. Ay M, Sivasli E, Bayraktaroglu Z, et al. Association of asthma with gastroesophageal reflux disease in children. *J Chin Med Assoc* 2004; 67(2): 63-6.
19. Yuksel H, Dinc G, Sakar A, et al. Prevalence and comorbidity of allergic eczema, rhinitis, and asthma in a city in western Turkey. *J Investig Allergol Clin Immunol* 2008; 18(1): 31-5.
20. Kim C-W, Lee C-W, Hur G-Y, et al. Evaluation and control of allergic rhinitis in adult patients with asthma (CARINA) in Korea. *Korean J Asthma, Allergy Clin Immunol* 2007; 27(4): 248-56.
21. Ramagopal M, Scharf SM, Roberts DW, Blaisdell CJ. Obstructive sleep apnea and history of asthma in snoring children. *Sleep Breath* 2008; 12(4): 381-92. <https://doi.org/10.1007/s11325-008-0174-x>
22. Gomez-Restrepo C, Ramirez S, Tamayo Martínez N, et al. Probable Mental Health Disorders Prevalence in Children With Chronic Conditions. Results From the National Mental Health Survey of Colombia 2015. *Rev Colomb Psiquiatr* 2016; 45(Suppl 1): 135-40.
23. Feitosa CA, Santos DN, do Carmo MBB, et al. Behavior problems and prevalence of asthma symptoms among Brazilian children. *J Psychosomatic Res* 2011; 71(3): 160-5.
24. Bussing R, Burket RC, Kelleher ET. Prevalence of anxiety disorders in a clinic-based sample of pediatric asthma patients. *Psychosomatics* 1996; 37(2): 108-15. [https://doi.org/10.1016/S0033-3182\(96\)71576-1](https://doi.org/10.1016/S0033-3182(96)71576-1).
25. Arif AA, Korgaonkar P. The association of childhood asthma with mental health and developmental comorbidities in low-income families.

- J Asthma 2015; 53(3): 277-81. doi:10.3109/02770903.2015.1089277.
26. Nyenhuis SM, Akkoyun E, Liu L, et al. Real-World Assessment of Asthma Control and Severity in Children, Adolescents, and Adults with Asthma: Relationships to Care Settings and Comorbidities. *J Allerg Clin Immunol: In Practice* 2020; 8(3): 989-96.
 27. Weinmayr G, Forastiere F, Büchele G, et al. Overweight/obesity and respiratory and allergic disease in children: international study of asthma and allergies in childhood (ISAAC) phase two. *PloS one* 2014; 9(12): e113996.
 28. Forno E, Lescher R, Strunk R, et al. Decreased response to inhaled steroids in overweight and obese asthmatic children. *J Allerg Clin Immunol* 2011; 127(3): 741-9. doi: 10.1016/j.jaci.2010.12.010
 29. Ullmann N, Mirra V, Di Marco A, et al. Asthma: Differential Diagnosis and Comorbidities. *Frontiers Pediatr* 2018; 6: 276. doi:10.3389/fped.2018.00276.
 30. Min YZ, Subbarao P, Narang I. The bidirectional relationship between asthma and obstructive sleep apnea: which came first? *J Pediatr* 2016; 176: 10-16.
 31. Won HK, Kim YC, Kang MG, et al. Age related prevalence of chronic rhinosinusitis and nasal polyps and their relationships with asthma onset. *Ann Allerg Asthma Immunol* 2018; 120(4): 389-94. doi: 10.1016/j.anai.2018.02.005.
 32. Valovirta E, Pawankar R. Survey on the impact of comorbid allergic rhinitis in patients with asthma. *BMC Pulm Med* 2006; 6: S1-3. doi: 10.1186/1471-2466-6-S1-S3
 33. Gibson PG, Henry RL, Coughlan JL. Gastro-oesophageal reflux treatment for asthma in adults and children. *Cochrane Database Syst Rev*. 2003;(2):CD001496. doi: 10.1002/14651858.CD001496. PMID: 12804410.
 34. Denlinger LC, Phillips BR, Ramratnam S, et al. National Heart, Lung, and Blood Institute's Severe Asthma Research Program-3 Investigators. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. *Am J Respir Crit Care Med* 2017; 195(3): 302-13.
 35. de Groot EP, Kreggemeijer WJ, Brand PL. Getting the basics right resolves most cases of uncontrolled and problematic asthma. *Acta Pediatr* 2015; 104 (9): 916-21. doi: 10.1111/apa.13059.
 36. Pénard-Morand C, Raheison C, Kopferschmitt C, et al. Prevalence of food allergy and its relationship to asthma and allergic rhinitis in schoolchildren. *Allergy* 2005; 60(9): 1165-71.
 37. Sasaki M, Yoshida K, Adachi Y, et al. Factors associated with asthma control in children: findings from a national Web-based survey. *Pediatr Allergy Immunol* 2014; 25(8): 804-9.
 38. Nishima S, Kozawa M, Milligan KL, Papadopoulos NG. Omalizumab and unmet needs in severe asthma and allergic comorbidities in Japanese children. *Asia Pac Allergy* 2019; 9(1): e7. doi:10.5415/apallergy.2019.9.e7
 39. Durrani SR, Mukkada VA, Guilbert TW. Eosinophilic esophagitis: an important comorbid condition of asthma? *Clin Rev Allergy Immunol* 2018; 55(1): 56-64.
 40. Mirabelli MC, Hsu J, Gower WA. Comorbidities of asthma in U.S. children. *Respir Med* 2016; 116: 34-40.
 41. Jacob L, Keil T, Kostev K. Comorbid disorders associated with asthma in children in Germany-National analysis of pediatric primary care data. *Pediatr Allergy Immunol* 2016; 27(8): 861-6.
 42. Lind N, Nordin M, Palmquist E, Nordin S. Psychological distress in asthma and allergy: the västerbotten environmental health study. *Psychol Health Med* 2014; 19 (3): 316-23. doi: 10.1080/13548506.2013.806814.
 43. Pinart M, Benet M, Annesi-Maesano I, et al. Comorbidity of eczema, rhinitis, and asthma in IgE-sensitized and non-IgE-sensitized children in MeDALL: a population-based cohort study. *Lancet Respir Med* 2014; 2(2): 131-40.
 44. Kercksmar CM, Shipp C. Management/Comorbidities of School-Aged Children with Asthma. *Immunol Allergy Clin North America* 2019; 39(2), 191-204. doi:10.1016/j.iac.2018.12.004
 45. Knutsen AP, Bush RK, Demain JG, et al. Fungi and allergic lower respiratory tract disease. *J Allergy Clin Immunol* 2012; 129(2): 280-93.
 46. Milgrom H, Berger W, Nayak A, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001; 108(2): e36.
 47. Boulet LP. Influence of comorbid conditions on asthma. *Eur Respir J* 2009; 33(4): 897-906.