Asthma is often associated with various comorbidities. The most frequently reported asthma comorbid conditions include rhinitis, sinusitis, gastroesophageal reflux disease, obstructive sleep apnea, hormonal disorders and psychopathologies. These conditions may, first: share a common pathophysiological mechanism with asthma; second: influence asthma control, its phenotype and response to treatment; and third: be more prevalent in asthmatic patients but without obvious influence on this disease. For many of these, how they interact with asthma remains to be further documented, particularly for severe asthma. If considered relevant, they should, however, be treated appropriately. Further research is needed on the relationships between these conditions and asthma.

**KEYWORDS:** asthma • chronic obstructive pulmonary disease • comorbidities • gastroesophageal reflux disease • obesity • obstructive sleep apnea • rhinitis • sinusitis • vocal cord dysfunction
Asthma is a common airway inflammatory disorder characterized by variable airway obstruction and hyperresponsiveness [301]. Asthma is of variable severity and is increasingly recognized as a condition presenting as various phenotypes [1,2]. Asthma control is the main goal of therapy and is achieved when the disease results in minimal or no symptoms, normal sleep and activities, and optimal pulmonary function [3,4]. Such control can be obtained with patient education, avoidance of environmental triggers, individualized pharmacotherapy and regular follow-up.

Numerous comorbidities can be associated with asthma and influence its clinical expression, although their specific influence remains to be characterized. They are, however, increasingly recognized as important factors to document in asthma patients as they may influence disease management and control.

Among the most frequently contributing comorbid conditions reported in asthmatic patients are rhinitis, sinusitis, gastroesophageal reflux disease (GERD), obstructive sleep apnea (OSA), hormonal disorders and psychopathologies, although other conditions, sometimes without an evident link with asthma, have been found to be highly prevalent in asthmatic patients (Figure 1) [5,6]. Indeed, analyses of large databases have shown an increased prevalence of a variety of conditions in asthmatic patients, which either influence or do not influence asthma outcomes. These large-scale analyses may, however, be biased due to contamination with, for example, patients with chronic obstructive pulmonary disease (COPD) or other conditions (Box 1).

In one of those reports, Prosser et al. used cross-sectional health services administrative data on treated adult asthma patients and on the general population from British Columbia (Canada), using a standardized comorbidity identification methodology, the Adjusted Clinical Group Case-Mix System [5]. Adults with asthma had significantly more comorbidities than the general population, such as respiratory infections, allergic rhinitis and high impact/high prevalence chronic conditions such as depression, found in one out of four adults with asthma. Children with asthma had a lower comorbidity burden than adults, but 12.6% had an associated chronic medical condition.

Gershon et al. used health administrative data of 12 million residents of Ontario, Canada, in 2005, to look at comorbidities associated with asthma, as reflected by hospitalizations, emergency department visits and ambulatory care claims [7]. Asthma was associated with increased comorbidities, resulting in increased healthcare use, decreased quality of life and poor asthma control.

Soriano et al. estimated the prevalence of comorbid diseases from an administrative data-based study including 7931 patients with asthma and matched controls [6]. The most prevalent associated condition in adult asthmatic patients was time-limited minor infections while others with a high impact and/or high prevalence were depression, hypertension, diabetes, ischemic heart disease, degenerative joint disease, cardiac arrhythmia, cancer, congestive heart failure, cerebrovascular disease and COPD. A total of 60% of adult asthma patients had at least one condition, and 12% had three or more. They also found an increased prevalence of comorbidities including various respiratory, cardiac and neurological conditions, injuries and poisonings, in individuals with asthma compared with those without asthma [6]. In both COPD and asthma, the total sum of diagnoses associated with 23 major organ systems was higher than in their matched population controls. Among incident asthma patients, the occurrence of events was generally lower than in COPD, possibly due to the younger age distribution, except for respiratory infection, but also probably due to the different
impact of the disease on various systems and to the presence of common risk factors such as smoking.

In a report by Adams et al., patients with asthma had an increased prevalence of diabetes, arthritis, heart disease, stroke, cancer and osteoporosis [8]. Van Manen et al. used a questionnaire in patients from 290 general practices over 40 years of age with asthma and/or COPD and 421 control patients [9]. Musculoskeletal conditions, insomnia, stomach and duodenal ulcers, migraine, sinusitis, depression, cancer and atherosclerosis were significantly more prevalent when patients had a diagnosis of asthma and/or COPD compared with controls. In an Australian general population health survey performed by Adams et al. on 834 adults with asthma (6609 without), arthritis, heart disease, stroke, cancer and osteoporosis were more prevalent in the presence of asthma, after age and sex adjustments [8].

Finally, more recently, Cazzola et al., looking at data from the Health Search Database of the Italian College of General Practitioners, reported that asthma was weakly associated with cardiovascular and hypertensive diseases [10]; surprisingly, the odds ratio of acute or past myocardial infarction was 0.84 (95% CI: 0.77–0.91). Furthermore, although asthma was weakly associated with depression, diabetes mellitus, dyslipidaemia, osteoporosis and rhinosinusitis, it was strongly associated with GERD and allergic rhinitis. There was no influence of age on the association of asthma with comorbidities.

In this article, we will further describe the relationships between asthma and its main associated comorbid conditions, particularly those with a potential or established influence on asthma control.

**Comorbid conditions of the upper airways**

**Rhinitis**

Prevalence of rhinitis in asthmatic patients

Asthma and allergic rhinitis frequently coexist in the same patient. Allergic rhinitic subjects have an increased risk of developing asthma [11–13]. A majority of asthmatic patients are affected by allergic rhinitis, which is often undiagnosed and untreated. It is considered that 20–50% of patients with allergic rhinitis have asthma and more than 80% of patients with asthma have rhinitis [14–17]. However, atopy does not fully explain the strong association between rhinitis and asthma. Indeed, rhinitis is also common in nonallergic asthma [13]. Nasal symptoms are associated with more severe asthma in nonatopic patients [18]. Rhinitis may even be a stronger risk factor for asthma in the nonatopic compared with the atopic population [18,19], although this was not observed in all studies [20].

Recently, the prevalence of asthma and associated intermediary asthma end points were compared in patients with allergic rhinitis, nonallergic rhinitis and asymptomatic control children from the Copenhagen Prospective Study on Asthma in Childhood [21]. In this study, asthma was similarly associated with allergic and nonallergic rhinitis, suggesting a link between upper and lower airways beyond allergy-associated inflammation. However, allergic rhinitis was associated with increased airway responsiveness and elevated fractional exhaled nitric oxide, suggesting a different phenotype in young children with allergic compared with nonallergic rhinitis.

Cirillo et al. evaluated the presence of airway hyperresponsiveness (AHR) in a group of 342 patients with moderate-to-severe persistent allergic rhinitis alone, and investigated possible risk factors related to severe AHR [22]. 6.4% of patients had severe AHR, 21.6% of patients had mild AHR and 56.2% had borderline AHR, while 15.8% of patients had a negative methacholine test. Trees and house dust mite sensitization, rhinitis duration >5 years, and forced expiratory volume in 1 sec (FEV1) <86% of predicted were significantly associated with severe AHR.

Not only can allergic rhinitis predispose a patient to the development of asthma but it may contribute to uncontrolled asthma [23]. Using the Asthma Control Questionnaire and the mini Asthma Quality of Life Questionnaire, Vandenplas et al. showed that allergic and nonallergic rhinitis were associated with an increased risk of uncontrolled asthma and with a significant negative impact on the quality of life [24]. Furthermore, not only

![Figure 1. Some common asthma-related comorbidities.](image-url)
can allergic rhinitis impair asthma control, being associated with an increase in symptoms and disease severity, it has also been associated with increased asthma-related hospitalizations, physician's visits, and emergency department visits, and drug costs [25,26].

**Sinusitis & rhinosinusitis**

The current classification of chronic rhinosinusitis (CRS) includes conditions with and without nasal polyps, which are considered subgroups of CRS. For this condition, as for the other comorbid upper airway conditions, the association goes both ways. As much as 75% of asthmatic patients have chronic symptoms of rhino sinusitis, irrespective of asthma severity [27], although evidence of sinusitis, as assessed by sinus computed tomography (CT), may be present in up to 84% of severe asthmatic patients [28]. Conversely, the prevalence of asthma in patients with CRS can vary between 11 and 42% [29–32] depending on the diagnostic mean, compared with about 4–10% of self-reported asthma (as determined by reporting an asthma attack in the past year or currently using asthma medication) in the general population [33]. When nasal polyps are considered, the prevalence is approximately 4% of the asthmatic population, and it increases to about 15% in nonatopic asthmatic patients [38,34].

Sinus morphologic abnormalities have been significantly correlated with the rate of asthma severity in patients with and without sinusitis [39]. Significant correlations have also been noted between sinus CT scores and indicators of lower airway inflammation, including sputum eosinophils and exhaled nitric oxide (eNO) [28]. In a recent study, Guida et al. evaluated the effects of different variables on eNO in CRS subjects with and without nasal polyps [36]. Increased eNO was associated with the presence of nasal polyps, asthma and respiratory symptoms without AHR. In addition, compared with patients without nasal polyps, patients with nasal polyps who had respiratory symptoms without AHR had increased eNO and increased sputum eosinophils.

**Mechanisms**

Even in patients with rhinitis who do not have asthma, subclinical lower airways and inflammatory changes can be detected. In this regard, we and others have reported inflammatory [37] and remodeling [38,39] processes in the lower airways of nonasthmatic subjects with allergic rhinitis, somewhat similar to asthma, although usually less marked.

The ‘united airways’ hypothesis has been proposed in the past decade. It is based on the ‘one airway, one disease’ concept and therefore proposes that upper and lower airway diseases are both manifestations of the same inflammatory process [40,41]. This concept has emerged mainly from studies on allergic rhinitis in asthmatic patients [14]. For example, Braunstahl et al. observed that nasal allergen challenge can induce lower airway symptoms, inflammation and decrease in peak expiratory flows in allergic rhinitic subjects, in association with an upregulation of adhesion molecules [42]. Conversely, these authors also observed that segmental bronchial allergen challenge, in nonasthmatic allergic subjects, induced nasal symptoms, increased upper airway eosinophils and resulted in peripheral blood eosinophilia [43].

The nose and bronchi are anatomically connected, lined with a pseudostratified respiratory epithelium, and equipped with an array of innate and acquired immune defence mechanisms. Epithelial desquamation and apparent basement membrane thickening (subepithelial fibrosis) have been observed in allergic rhinitis but not to the same extent as in asthma and nonallergic CRS, probably reflecting the intensity and persistence of mucosal inflammation in the latter [38,44,45].

Several mechanisms have been proposed to explain the interaction between upper and lower airways in allergic rhinitis and asthma [40,46]. The two most accepted and probably complementary ones are increased oral breathing and systemic response. In allergic rhinitis, the impaired filtering and air-conditioning function of the nose, leading to mouth breathing, can result in increased exposure of the lower airways to allergens and other asthma triggers. This may lead to inflammatory changes and AHR. These inflammatory changes, with the release of mediators into the airways or in the peripheral circulation, may play an important role in the nasobronchial interaction. Following nasal provocation, increased eosinophil progenitors have been observed in the bone marrow [47]. In addition, Li et al. observed increased proportion of IL-5-responsive bone marrow Eo/B- colony-forming units in isolated upper, isolated lower, or combined upper and lower airway inflammation models [48]. Therefore, the systemic release of inflammatory mediators and the bone marrow release of eosinophil progenitors may act together in the process of global airway allergy. Other mechanisms have also been proposed, which
include neural reflexes and aspiration of nasal contents, although the evidence supporting a potentially significant influence is still to be obtained.

Treatment
The management of asthma and rhinitis has often been considered separately, but most of the international guidelines suggest a combined approach or at least, emphasize the treatment of rhinitis as a comorbid condition in asthma [16,301]. Treatment of established rhinitis may affect asthma control and could have an impact on airway obstruction, but a direct effect of rhinitis therapy on lower airway inflammation remains to be clearly established. Studies showed that when the upper airways inflammatory process is adequately treated, asthma control can usually improve [49–51]. In addition, effective management of rhinitis may help reduce asthma-related emergency department visits and hospitalizations in patients with both conditions [52]. The treatment of allergic rhinitis has also been shown to attenuate the seasonal response to methacholine compared with placebo [53]. However, benefits have not been found in all studies [54,55]. Nevertheless, it is possible that optimal treatment of allergic rhinitis may not only improve coexisting asthma but also potentially postpone or prevent its development although remains to be examined.

Treatment of asthma and associated upper airway conditions mostly consists in environmental control and symptomatic medications. The Allergic Rhinitis and its Impact on Asthma guidelines state that a combined strategy may be used to treat upper and lower airway diseases [16]. Agents such as anti-IgE (e.g., omalizumab in severe allergic asthmatic patients insufficiently controlled by current therapy) and leukotriene-receptor antagonists (e.g., montelukast), act on both upper and lower airways, and can be associated with a concomitant improvement of both asthma and rhinitis. Montelukast has been shown to reduce both allergic rhinitis and asthma symptoms [56–58], as well as the need for β-agonist rescue medication [59]. When combined with budesonide, montelukast provided significantly greater efficiency in reducing airflow obstruction compared with doubling the dose of budesonide [56], possibly in part because of its effects on both the upper and lower airways. In adults, guidelines recommend however a long-acting β2-agonist as first choice add-on controller therapy to inhaled corticosteroids for asthma, and inhaled corticosteroids as first-choice initial maintenance treatment for rhinitis.

The anti-IgE omalizumab is mostly used in severe allergic asthma. It has been shown to reduce allergen-induced early and late responses, airway responsiveness and inflammation, as well as cutaneous response to allergens [60]. Moreover, a significant reduction in inhaled corticosteroid use, rescue medication, and asthma exacerbations has been observed in omalizumab-treated patients, compared with placebo [60,61]. In allergic rhinitis, omalizumab significantly reduced rhinitis symptoms and improved rhinitis-related quality of life [62–64]. More recently, in a post-hoc analysis on efficacy results from the Study of Omalizumab in comorbid Asthma and Rhinitis (SOLAR) [65], Humbert et al. demonstrated that allergic asthmatic patients achieving complete or marked improvement in asthma control following omalizumab had a significant improvement in rhinitis-related quality of life and that the improvement in asthma was associated with a significantly increased probability of rhinitis improvement [66].

Apart from allergen avoidance, allergen-specific immunotherapy (SIT) is the only other available treatment that can affect the natural course of allergy [67]. Previous studies showed a reduction in long-term asthma risk among allergic rhinitic patients treated with SIT [68,69]. Meta-analyses show that this treatment could be beneficial in pollen-induced rhinitis and asthma, but state that more investigations are needed to determine its efficacy in house dust mite allergy [70]. Recent studies found that adding anti-IgE therapy to SIT was significantly better at reducing symptoms of both seasonal allergic rhinitis [71] and asthma when compared with SIT alone [72], in addition to providing greater safety in adults as well as in children [73]. However, many guidelines consider SIT as a marginal treatment for asthma, although it is suggested for the types of allergic rhinitis mentioned earlier. Having said that, recent developments in new modes of immunotherapy are promising. By reducing the allergenicity of immunotherapy, synthetic peptides representing T-cell epitopes have been developed. Early studies of Fel d1 peptide have shown inconsistent results and were associated with adverse effects [74], but recent studies, using low doses of peptides, have been shown to modify clinical and laboratory parameters without inducing adverse events [75]. In a recent Phase IIa trial, Fel d1 peptide immunotherapy showed promising results in term of safety and tolerability and the dose of vaccine resulting in the greatest reduction in late-phase skin response was determined [76]. Nonetheless, further studies are required to determine the optimal dose, the dose interval and the route of administration in larger number of subjects and with peptides derived from a variety of allergens.

The treatment of CRS still remains an unmet need. In CRS with or without nasal polyps, medical treatment, including nasal and, in some of the more severe cases, oral corticosteroids, is the first therapeutic option. As for allergic rhinitis and asthma, corticosteroids are the mainstay of treatment and are the most effective drugs for treating CRS. Endoscopic sinus surgery is only recommended for cases refractory to medical therapy; in this regard, Ragab et al. observed no significant difference in quality of life between surgical and medical treatment [77]. After surgery, inhaled corticosteroid treatment is recommended to help prevent recurrence of symptoms.

Gastroesophageal reflux disease
Asthmatic patients have been found to have a much greater risk of GERD-related symptoms than the general population [78]. Patients with GERD have a significantly higher risk of concurrent asthma compared with patients without GERD [79]. The prevalence of abnormal esophageal pH is, however, highly variable, ranging from 12–85% of asthmatic patients, while GERD symptoms are reported in 50–80% of asthmatics [80,81]. Furthermore, a significant percentage of these last have silent GERD and do not experience classic symptoms such as heartburn [82,83].

Gastroesophageal reflux disease could worsen asthma either by direct effects on airway responsiveness or via aspiration-induced inflammation [84]. Conversely, the bronchoconstriction observed in
asthma as well as asthma medication may induce gastroesophageal reflux. This suggests the potential for a vicious cycle where asthma and medications used in asthma treatment may increase GERD and GERD may subsequently provoke asthma symptoms.

However, inconsistent results have been obtained in several studies on the effects of treatment of GERD on asthma outcomes [84,85]. In 2003, a Cochrane systematic review of the available literature examining the effect of GERD treatment for asthma showed that antireflux therapy did not consistently improve lung function, asthma symptoms, nocturnal asthma or the use of asthma medications [86]. The authors state that subgroups of asthma patients may gain benefit in treating GERD, but it appears difficult to predict who will be a responder. Therefore, the decision to treat this condition in regard to its possible influence on asthma should be individualized and its effects carefully assessed.

Obesity

Obesity has been increasing worldwide and has been associated with an increased prevalence of asthma [87]. A causal relationship between obesity and asthma has been suggested from animal and human studies [88–90] and an improvement in asthma symptoms, control and medication needs has been observed after weight loss in the obese [89,91–93].

Obese patients seem to present a specific asthma phenotype, associated with low lung volumes breathing, a less eosinophilic inflammatory process and a reduced response to asthma medications [90,94–96]. It has been suggested that obese asthmatic patients have an altered response to asthma medications, particularly a reduced response to inhaled corticosteroids [96,97]. Sutherland et al. reported a reduced in vitro response to dexamethasone in overweight and obese patients with asthma [98]. In this regard, a retrospective data analysis by Peters-Golden et al. suggested that obese asthmatics had an attenuated response to inhaled corticosteroids, while obese and nonobese patients had a similar response to leukotriene antagonists [97]. However, adequate comparative clinical trials remain to be performed to determine their comparative effects in this population. Such impaired response is still unexplained; it may be related to a different type of inflammation, the presence of oxidative stress or a defect of the glucocorticoid receptor, among other possible mechanisms [90].

Apart from its interference with asthma medications, how obesity can interfere with asthma control is still uncertain but may be related to various influences, such as mechanical and inflammatory changes in the respiratory system, genetic/developmental factors, or be related to the higher prevalence of comorbid conditions in obese individuals such as OSA and GERD [90].

With regards to the effects of obesity on asthma outcomes, after adjusting for demographics, smoking status, oral corticosteroid use, and evidence of GERD, Mosen et al. found that obese adults were more likely than nonobese patients to show poor asthma-specific quality of life, poor asthma control and higher asthma-related hospitalizations [99].

A Canadian study suggested that asthma is over diagnosed in about 30% of patients with self-reported physician-diagnosed asthma, and that this does not seem to be related to obesity [100,101]. However, obese individuals who make urgent visits for respiratory symptoms are more likely to receive a misdiagnosis of asthma [101]. Such misdiagnosis might be obscuring the true relationship between obesity and asthma.

Stenius-Aarniala et al. previously showed that even a modest weight loss in obese asthmatic patients can improve asthma [102]. A systematic review performed by Eneli et al. looking at the effects of weight loss and asthma outcomes showed an improvement in at least one asthma outcome after weight loss, in patients of various age, country of origin or gender [93]. However, further research remains to be conducted on the relationships between obesity and asthma and on the influence of weight loss on various clinical inflammatory and physiological parameters.

Obstructive sleep apnea

Obstructive sleep apnea is a frequent condition associated with obesity and has been considered to possibly influence asthma [103,104]. OSA has also been associated with increased AHR [105]. OSA can influence asthma and AHR in various ways. First, it is associated with an upper airway inflammatory process that has the potential to influence lower airways. In this regard, significant systemic and upper airway inflammation has been reported with OSA [106,107], and Devouassoux et al. reported bronchial neutrophilia and a high IL-8 concentration in patients with untreated OSA compared with controls [108].

Mehra et al. have suggested that OSA could cause oxidative stress and inflammation in the lower airways [109] and that it is biologically plausible that the proinflammatory effects of one disorder influence the expression of the other disorder. In keeping with this possibility, IL-6, a proinflammatory cytokine secreted by T cells and macrophages, is increased in obese patients, and may play a role in both sleep apnea and asthma, in association or not with obesity [110]. Furthermore, C-reactive protein, an acute phase reactant produced by the liver and adipocytes and influenced by IL-6 levels, has been found to be increased in sleep apnea, but is considered to be related mostly to obesity [111]. Finally, TNF-α, a cytokine involved in systemic inflammation, is also elevated in sleep apnea, independently of BMI, and may play a role in the pathogenesis of asthma [112].

Obstructive sleep apnea can possibly influence asthma in promoting GERD [113], and/or through a possible upper airway-triggered vagally mediated bronchoconstriction [114]. Lower airways can also be affected by the OSA-related increase in the resistive load [115], in particular, during sleep [114]. Continuous positive airway pressure treatment of OSA, in patients with asthma, improved asthma symptoms, rescue bronchodilator use, peak expiratory flows and asthma-specific quality of life [107,116]. Lafond et al. found, however, no significant changes in airway responsiveness after 6 weeks of nocturnal continuous positive airway pressure treatment, while patients’ asthma-related quality of life improved [116].

Otherwise, Yigla et al. found an unexpectedly high prevalence of OSA among those receiving long-term chronic or frequent bursts of oral corticosteroid therapy and suggested that this could be due to increased airway collapsibility [103]. Teodorescu et al.
also showed that a high probability of having OSA was associated with uncontrolled asthma and suggested that patients who have difficulty achieving adequate asthma control should be screened for OSA [117]. This group looked at 472 patients with asthma seen routinely at tertiary-care clinic visits, and who completed the Sleep Apnea Scale of the Sleep Disorders Questionnaire and the Asthma Control Questionnaire. High OSA risk was associated, on average, with 2.87-times higher odds for not-well-controlled asthma after adjusting for obesity and other factors known to worsen asthma control.

However, it is uncertain how much the improvement of OSA explains the improvement in asthma that follows weight loss in patients with OSA.

**Psychopathologies**

Psychological disorders and stressful conditions have often been shown to influence asthma control and management, although how psychological disturbances can influence the clinical expression of asthma is still uncertain [118,119].

Anxiety, depression and panic disorders are more frequent in asthmatic patients than in the general population [120–125]. Depression may affect control of asthma in reducing adherence to the treatment and follow-up. However, more severe forms of psychopathology, such as bipolar disorder, personality disorders and schizophrenia do not seem more frequent in asthma [2,123]. Psychological conditions may affect asthma in modulating symptoms’ report or perception, or in influencing medication compliance and follow-up, disease assessment and self-monitoring and they are associated with more frequent urgent care and hospitalizations [124–127]. Dyspnea correlates with anxiety-trait and anxiety-state, neuroticism and depression in asthmatic men [128]. Katon et al. observed that youths with asthma have an almost twofold higher prevalence of comorbid anxiety and depressive disorders compared with controls [129]. In a prospective community-based cohort study of asthmatic patients followed between age 19 and 40 years, asthma was associated with anxiety and panic disorder, while after adjusting for potentially confounding variables, active asthma also predicted subsequent panic disorder [130].

Psychosocial stress has been shown to increase the prevalence of infectious and systemic illnesses and modulate immune cell function through neural and hormonal pathways [133]. Chronic psychosocial stress can lead to a reduction in sensitivity to corticosteroid treatment, possibly in acting through glucocorticosteroid receptor expression or function. Another psychological condition, attention deficit hyperactivity disorder has been proposed as a comorbidity possibly influencing asthma. However, controversial data have been published on their relationship [132–135]. Fasmer et al. recently assessed how frequently drugs used to treat asthma and attention deficit hyperactivity disorder are prescribed to the same patients in looking at data from the Norwegian Prescription Database for 2006 [136]. There was a 65% increased overall risk (odds ratio: 1.65) of being prescribed one of the drugs if given a prescription of the other, particularly in women. The strongest associations were found for women between 20 and 49 years of age and men between 30 and 49 years of age. Therefore, these findings support comorbidity between the two disorders, although they are solely based on prescription rate. Further studies are needed to determine if common pathophysiological mechanisms are involved.

Goodwin et al. looked at the association between asthma and mental disorders and the impact of asthma and mental disorder comorbidity on functional impairment and mental health care service use among adults in the community, using data from the Canadian Community Health Survey Cycle 1.2 (n = 36,984) [137]. Mental disorders were assessed using the Composite International Diagnostic Interview. Asthma diagnoses were based on self-reporting of having been diagnosed with asthma by a healthcare professional. Asthma was associated with a significantly increased likelihood of a range of mental disorders among adults in Canada, with the strongest links between asthma and post-traumatic stress disorder, mania and panic disorder. Adults with both mental disorders and asthma had significantly higher rates of functional impairment and use of mental health services, compared with those with either asthma or mental disorders but not both.

Psychological interventions in patients with asthma, particularly children, remain uncertain, their effects being quite variable [138–141]. Yorke et al. performed a systematic review on the efficacy of psychological interventions in asthma [142]. Although quality of life was increased following cognitive behavioural therapy, firm conclusions could not be drawn due to heterogeneity and low quality of included studies. No recommendations for clinical practice could be made, confirming the need for further well-designed research and their inclusion in international asthma management guidelines. Psychological disturbances should be searched when evaluating asthma and appropriate therapy offered if considered significant.

**Respiratory infections**

**Viral**

Respiratory infections, particularly of viral origin, are a common cause of asthma exacerbations [143–145]. Viral agents are detected in about 80% of children and in 41–78% of adults, rhinoviruses being the most frequently detected both in children and adults [146]. Respiratory syncytial virus and metapneumovirus are more frequently involved in asthma exacerbations in infants, while influenza viruses are mostly associated to exacerbations in adults [146].

In asthmatic patients, both innate and adaptive antiviral immunity may be impaired. Increased viral load can contribute to airway inflammation and exacerbations [147]. Impaired interferon response following a rhinovirus infection may allow the virus to continue to replicate and damage the airway epithelium [148].

**Bacterial**

Other microorganisms, such as atypical bacteria, could play a role in asthma [149,150]. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have been involved in asthma exacerbations, persistence of asthma and long-term reduction in lung function, but their effects are still uncertain [151].
Fungal
Allergic bronchopulmonary aspergillosis is typically associated with asthma. It is associated with high blood eosinophils and IgE levels, positive skin tests and precipitins to Aspergillus, and it has been sometimes associated with severe asthma [152,153]. In fact, many patients can be sensitized to one or more fungi and this particular asthma phenotype is now characterized as ‘severe asthma with fungal sensitization’ [153]. In a recent study, Denning et al. showed that treatment with oral itraconazole, an antifungal therapy, administered for 32 weeks, significantly increased asthma quality of life compared with placebo in severe asthma with fungal sensitization patients [154]. As the link between asthma and fungal exposure as long been debated, we need to better understand the link between these conditions.

Dysfunctional breathing & vocal cord dysfunction
Vocal cord dysfunction – a paradoxical adduction of the vocal cords during inspiration – may mimic asthma [155–157]. It may or may not be related to psychological disturbances [158]. Newman et al. reported that 56% of 95 patients with paradoxical vocal cord motion disorder had concomitant asthma [156]. Hussein et al. reported vocal cord dysfunction more commonly in women and older individuals, and in association with asthma, GERD and previous abuse [158]. Psychotherapy and/or speech therapy have provided good results in many cases.

Dysfunctional breathing may affect up to 10% of the population and is more prevalent in women and in asthmatic patients [159]. This syndrome is often called the ‘hyperventilation syndrome’, because patients frequently over-breathe [160] or have an increased respiratory rate [161]. In subjects with symptoms of dysfunctional breathing, Thomas et al. showed that breathing retraining from physiotherapy intervention resulted in clinically significant improvement in health-related quality of life scores after only 1 month of treatment with a trend after 6 months [162].

Hormonal & metabolic disorders
There are many observations suggesting a role of hormonal changes in asthma. After puberty, females have a higher prevalence of adult-onset asthma and more severe asthma than males [163]. Women also experience more frequent asthma exacerbations, more hospitalizations and longer duration of admission than men [164]. A recent study investigating the relationship between the age of menarche and adult lung function and asthma among participants in the European Community Respiratory Health Survey II showed that women with early menarche had lower lung function and more asthma in adulthood [165]. Furthermore, during the premenstrual period, asthma may worsen in up to 40% of females [166]. Reducing hormonal fluctuations, for example, by the use of oral contraceptives, in women of child-bearing age, has been shown to reduce AHR [167]. During pregnancy, the one-third rule is classically mentioned, meaning that asthma improves in about one-third of women, worsens in another third, or remains stable in the others [168–171]. However, two prospective studies showed that in women with severe asthma, the condition is more likely to deteriorate than in mild asthma [172,173]. Menopause can coincide with the appearance of asthma, but whether it is the result of hormone replacement therapy is still controversial [174]. As mentioned in a previous section, obesity is often related to asthma, and this relation is stronger in females than in males [175]. This suggests a possible hormonal influence through potential interactions with obesity and insulin resistance [174]. Furthermore, in hospitalized patients, diabetes seems associated with a reduced pulmonary function [176].

Del-Rio-Navarro et al. evaluated the prevalence of metabolic syndrome in adolescents with either obesity and asthma, or obesity without asthma compared with nonobese patients with asthma, and nonobese patients without asthma [177]. Adolescent males who were obese and also had mild persistent asthma had a significantly higher prevalence of metabolic syndrome than obese males without asthma. Overall, however, asthma seemed to provide a protective effect against the prediabetes condition in males.

Asthma and thyroid disease occasionally occur together. Although a few case reports have been published, there is not much literature on the subject. Furthermore, most studies have not found hyperthyroidism to be more prevalent in asthma compared with the general population, suggesting that asthma might develop only in susceptible hyperthyroid patients [178]. Hyperthyroidism has been associated with asthma exacerbation [178,179], either treating or stopping the medication for hyperthyroidism has however shown inconsistent results [178,180,181]. Nonetheless, physicians should be aware of this condition and take suggestive symptoms into consideration as possible evidence of such comorbidity, when assessing asthmatic patients.

Chronic obstructive pulmonary disease
Chronic obstructive pulmonary disease and asthma may coexist and we previously reported a ‘hybrid’ condition between asthma and COPD in smoking asthmatics [182]. Young people with asthma who smoke may have early COPD, as indicated by more severe airway obstruction, lower carbon monoxide diffusion capacity and increased prevalence of chest tomodensitometry abnormalities. However, asthma and COPD may sometimes be difficult to distinguish [182–185].

Smoking
Smoking can change the functional phenotype of asthma, reduce treatment response and worsen outcomes. In this regard, smoking is associated with more neutrophilic airway inflammation and with a more difficult-to-control asthma, and reduced response to medications such as inhaled corticosteroids [186,187]. Finally, Lange et al. have demonstrated an accelerated decline in pulmonary function in people with asthma, particularly smokers [188].

Other conditions
There is epidemiological evidence of an overlap between asthma and atopic dermatitis in early life, in addition to being a risk factor for asthma, particularly in regard to some severe forms of asthma [189].
**Comorbidities & severe asthma**

The prevalence of comorbidities is particularly high in severe asthma, and these conditions can be quite detrimental to asthma control in such individuals [1,2,190–193]. In the National Heart, Lung, and Blood Institute cohort, Moore *et al.* found an increase in aspirin intolerance in severe compared with nonsevere asthma, as well as an increase in GERD (41 vs 12–16%), a history of sinusitis (54 vs 33–37%) and history of pneumonia (63 vs 35–36%) [190]. In another analysis of this Severe Asthma Research program cohort, Wenzel *et al.* reported that severe asthma is associated with obesity, aspirin sensitivity and sinusitis in females, and inversely associated with atopy [191]. In another study, ten Brinke *et al.* concluded that factors significantly associated with frequent asthma exacerbations in severe asthma are severe nasal sinus disease, GERD, recurrent respiratory infections, psychological dysfunction and OSA [192]. Severe asthma has also been associated with psychological disorders such as anxiety, depression and lack of trust towards healthcare providers [121,124,125].

**Comorbidities in specific populations: children & elderly patients**

The prevalence of comorbid conditions related to asthma may be different in children. A recent review by de Groot *et al.* provides an overview of this still insufficiently studied topic [194]. These authors report that, as in adults, allergic rhinitis is a very common comorbidity in pediatric asthma, although its effects on childhood asthma severity and control have not been determined. Furthermore, although obesity has been increasing in children and GERD is common in that population, their effects on asthma remain to be documented. Depressive disorders are more prevalent in childhood asthma than in nonasthmatic healthy children, but are under-recognized.

The elderly are affected by many comorbidities [195,196]. Conditions such as GERD, obesity, heart diseases and smoking-associated COPD are quite common in this population. The prevalence of rhinitis is uncertain. Neuropsychological (including depression) and degenerative problems are more frequently found in older patients and may interfere with asthma control [195]. As these conditions might cause respiratory symptoms, asthma diagnosis may be obscured or asthmatic symptoms worsened. Identification and treatment of these comorbid conditions can be both preventive and therapeutic, and can have a positive effect on asthma outcomes. Particular attention should be given to concomitant medication, as several drugs used by the elderly may interfere with asthma medication or lead to alternative therapies in order to improve both the asthma and the associated comorbid condition [196].

**How can asthma induce comorbid conditions?**

The asthmatic condition may also be responsible for the development or worsening of comorbidities. In poorly controlled asthma, the use of systemic corticosteroids, reduction of activities and exercise, and possibly poor sleep quality, can all contribute to obesity, diabetes and depression. Oral corticosteroids may predispose to glucose intolerance/diabetes, in addition to osteoporosis, increased fracture risk and pneumonia [197]. Furthermore, it is possible that the inflammatory process due to asthma influences the development or expression of other conditions, as previously mentioned.

**Investigation of comorbidities in asthma patients**

In the evaluation of asthma, recognition and treatment of comorbidities is considered essential. Algorithm-based approaches may be of assistance in detecting such conditions that may affect asthma control and its diagnosis (Table 1) [2,198].

**Conclusion & expert commentary**

Numerous comorbidities are frequently associated with asthma and may influence its clinical expression and severity. Comorbidities may influence severe asthma in various ways [199]:

- They may influence asthma phenotypes (e.g., in obesity, smoking, aspirin intolerance and allergic bronchopulmonary aspergillosis);
- They can share a similar pathophysiological process, such as in rhinitis and asthma;
- They can affect the diagnosis or assessment of control;
- They can influence asthma through a specific environmental exposure (e.g., in occupational asthma or smoking), and/or;
- They can affect the efficacy or adherence to therapy (e.g., respiratory infections, psychological disturbances).

Furthermore, medications used to treat other conditions which are not necessarily found with an increased prevalence in asthma patients but may be present in a given individual (e.g., β-blockers for coronary heart disease) can affect asthma.

The comorbid conditions that are associated with a systemic inflammatory process such as obesity, smoking, infections and OSA can possibly affect asthma through the influence of such process, as mentioned previously. Sutherland *et al.* reported that markers of systemic inflammation were increased with obesity, while, as previously known, Th2 cytokines were increased with asthma, although no significant interactions between the two were identified [200].

Various asthma inflammatory phenotypes have been described and the identification of these last can be potentially useful in the assessment of the effect of comorbid conditions on asthma and the treatment requirements [201,202]. The presence of a mainly noneosinophilic type of asthma can predict a reduced response to inhaled corticosteroids (e.g., in smokers or obese patients), while a marked eosinophilia may suggest insufficient steroid therapy (or poor compliance).

The effects of these conditions on current asthma should be looked at and appropriate measures taken accordingly in order to optimize asthma control. Rhinitis is a commonly underdiagnosed condition that is associated with poorer asthma control and it should be more commonly identified. However, the influence of GERD on asthma seems quite variable from a patient to another and, if suspected of influencing asthma, should be properly treated and its effects on asthma carefully assessed. Obesity may induce dyspnea but has also been shown to increase the prevalence of asthma confirmed by objective means; universal improvements of
asthma control after weight loss suggest that such measure should be promoted in all asthmatic patients with an increased BMI. Much remains to be known in regard to the contribution of OSA or other sleep disordered breathing conditions to asthma, particularly as it is often related to obesity; its specific influence, independently of obesity, needs further demonstration. Furthermore, the presence of psychopathologies can influence the assessment and long-term management of asthma, particularly in affecting symptom perception, treatment compliance and follow-up. Some conditions, such as vocal cord dysfunction, respiratory infections and COPD, not only can be confounders for the diagnosis of asthma, but can also modulate the clinical presentation of asthma in addition to explaining some of the clinical features and influencing treatment responses and global management of asthma. Finally, analysis of large databases reveals an increase in the prevalence of various conditions which, at first look, have no obvious relationship with asthma and do not seem to influence its course; why those diseases are more frequent with asthma may be due to diagnostic difficulties (e.g., COPD and other cardiovascular conditions, in regard to smoking), to confounding risk factors and triggers, or to unknown mechanisms.

Table 1. Assessment and management of some asthma-related comorbidities.

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Potentially useful tests</th>
<th>Management: possible treatment options</th>
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</thead>
<tbody>
<tr>
<td>Rhinitis</td>
<td></td>
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<tr>
<td>– Allergic</td>
<td>Allergy skin prick test, Serum-specific IgE</td>
<td>Avoid relevant allergen exposure, New generation oral H₁ antihistamine, Inhaled corticosteroids, LTRAs</td>
</tr>
<tr>
<td>– Nonallergic</td>
<td>ENT examination, Sinus radiography/CT scan</td>
<td>Immunotherapy, Inhaled corticosteroids, Nasal saline irrigations, Nasal anticholinergics, Oral corticosteroids, Surgical treatment</td>
</tr>
<tr>
<td>– Associated with nasal polyps</td>
<td></td>
<td></td>
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<tr>
<td>– CRS and sinusitis</td>
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<tr>
<td>GERD</td>
<td>Proton-pump inhibitor treatment trial, 24-h esophageal measurement</td>
<td>Management of lifestyle, Acid-suppressive therapy – Proton-pump inhibitor – H₂ blocker, Surgical intervention</td>
</tr>
<tr>
<td>– Oxymetry</td>
<td></td>
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<tr>
<td>Psychopathologies</td>
<td>Psychological evaluation, Nijmegen questionnaire [203]</td>
<td>Psychotherapy, Referral to psychologist/psychiatrist</td>
</tr>
<tr>
<td>Dysfunctional breathing</td>
<td>Nijmegen questionnaire [203]</td>
<td>Psychotherapy, Breathing retraining</td>
</tr>
<tr>
<td>VCD</td>
<td>Visualization of the pharynx, Laryngoscopy</td>
<td>ENT referral, Speech therapy, and so on</td>
</tr>
<tr>
<td>Hormonal and metabolic disorders</td>
<td>Hormones measurements</td>
<td>Referral to endocrinology and metabolism specialist, Treatment of the specific disorder</td>
</tr>
<tr>
<td>COPD and smoking</td>
<td>Pulmonary function tests, Chest radiography/CT scan, Exercise tests</td>
<td>Smoking cessation program, Bronchodilators, Inhaled corticosteroids, Readaptation-exercise program, Other measures and Rx</td>
</tr>
<tr>
<td>Infections</td>
<td>Specific serologies, Various identification measures, Precipitins for Aspergillus/fungal cultures, Aspergillus serology</td>
<td>Specific treatment according to the agent, if available and considered clinically significant, Systemic corticosteroids if allergic reaction to agent (e.g., ABPA)</td>
</tr>
</tbody>
</table>

† Provided only as examples. The reader is referred to current guidelines on this condition for further details.

ABPA: Allergic bronchopulmonary aspergillosis; COPD: Chronic obstructive pulmonary disease; CPAP: Continuous positive airway pressure; CRS: Chronic rhinosinusitis; ENT: Ear, nose and throat; GERD: Gastroesophageal reflux disease; LTRA: Leukotriene receptor antagonist; OSA: Obstructive sleep apnea; Rx: Treatment; VCD: Vocal cord dysfunction.
Five-year view
In the next few years, we should learn more about the potential influence of these comorbid conditions on asthma pathophysiology and how they affect asthma control or modulate treatment responses. This is particularly important for severe asthma. Comorbid conditions are increasingly recognized as important determinants of asthma phenotypes and characterization of such phenotypes will help establish more appropriate algorithms for assessment, treatment and follow-up of this disease. Comorbidities (e.g., obesity) may significantly influence the results of clinical trials and these should be considered when planning these studies. More research is needed to shed further light on the relationships and interactions between the various common comorbidities associated to asthma and their combined effects on asthma outcomes.

Key issues
- Among the most frequently reported comorbid conditions in asthmatic patients are rhinitis, sinusitis, gastroesophageal reflux disease, obstructive sleep apnea, hormonal disorders and psychopathologies.
- Comorbid conditions may influence the diagnosis and assessment of the severity and control of asthma.
- Comorbid conditions and asthma may result from, or be influenced by, similar pathophysiological processes (e.g., rhinitis, obstructive sleep apnea), or they can modulate the asthma phenotype.
- Identification and treatment of comorbidities is now recognized as an integral part of core management of asthma, particularly in the more severe forms of the disease.
- The effect of treating comorbidities on asthma severity and long-term clinical outcomes needs to be further studied.
- Asthma-related mechanisms and treatment can lead to the development of comorbid conditions that should be considered for treatment (e.g., bone loss/diabetes secondary to corticosteroids intake and sedentarity).

References
Papers of special note have been highlighted as:
- of interest
- of considerable interest

- Complete guideline on rhinitis characteristics, assessment and treatment.


26 Valovirta E, Pankar R. Survey on the impact of comorbid allergic rhinitis in patients with asthma. BMC Pulm. Med. 6(Suppl. 1), S3 (2006).


41 Rowe-Jones JM. The link between the nose and lung, perennial rhinitis and asthma – is it the same disease? Allergy 52(Suppl. 36), 20–28 (1997).


43 One of series of elegant studies showing the influence of upper airways allergen challenge on lower airways inflammation process and vice versa.


50 Fireman P. Rhinitis and asthma connection: management of coexisting upper airway allergic diseases and asthma. Allergy Asthma Proc. 21, 45–54 (2000).


Asthma-related comorbidities

Review


Interesting analysis showing that a beneficial response of anti-IgE on asthma correlates with such positive response for rhinitis, suggesting a mechanistic link between upper and lower airways in allergic asthma and rhinitis.


Cochrane meta-analysis showing that gastroesophageal reflux disease therapy did not consistently improve lung function and asthma control.


• One of the first studies showing a beneficial effect of weight loss on asthma control parameters in asthma patients with increased BMI.


111 Punjabi NM, Beamer BA. C-reactive protein is associated with sleep disordered breathing independent of adiposity. Sleep 30, 29–34 (2007).


123 ten Brinke A, Ouwerkerk ME, Bel EH, Spinhoff P. Similar psychological characteristics in mild and severe asthma. J. Psychores. 50, 7–10 (2001).


- **Good review of the effects of smoking on asthma and its response to treatment.**


- **One of the largest severe asthma series showing the prevalence of many comorbidities.**


**Website**

301 Global strategy for asthma management and prevention. Global initiative for asthma (GINA), 2006 www.ginasthma.org
To obtain credit, you should first read the journal article. After reading the article, you should be able to answer the following, related, multiple-choice questions. To complete the questions and earn continuing medical education (CME) credit, please go to www.medscape.org/journal/expertrespiratory. Credit cannot be obtained for tests completed on paper, although you may use the worksheet below to keep a record of your answers. You must be a registered user on Medscape.org. If you are not registered on Medscape.org, please click on the New Users: Free Registration link on the left hand side of the website to register. Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certificate. For questions regarding the content of this activity, contact the accredited provider, CME@medscape.net. For technical assistance, contact CME@webmd.net. American Medical Association’s Physician’s Recognition Award (AMA PRA) credits are accepted in the US as evidence of participation in CME activities. For further information on this award, please refer to www.ama-assn.org/ama/pub/category/2922.html. The AMA has determined that physicians not licensed in the US who participate in this CME activity are eligible for AMA PRA Category 1 Credits™. Through agreements that the AMA has made with agencies in some countries, AMA PRA credit is acceptable as evidence of participation in CME activities. If you are not licensed in the US and want to obtain an AMA PRA CME credit, please complete the questions online, print the certificate and present it to your national medical association.

### Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

<table>
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<tbody>
<tr>
<td>1. The activity supported the learning objectives.</td>
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<td>2. The material was organized clearly for learning to occur.</td>
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<td>3. The content learned from this activity will impact my practice.</td>
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<td>4. The activity was presented objectively and free of commercial bias.</td>
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### Questions

1. You are seeing a 48-year-old woman with a history of poorly controlled asthma despite the use of controller medications. She has multiple potential comorbid conditions that might affect the severity of her asthma, including recurrent nasal congestion. What are the most significant mechanisms that might explain the interaction between upper and lower airways in cases of concomitant allergic rhinitis and asthma?

   - A. Oral breathing and a systemic immune response
   - B. Increased mucus production and obesity
   - C. Increased mucus production and increased neutrophil aggregation
   - D. Obesity and thickened basement membranes in respiratory tissue

2. What can you tell this patient regarding the interaction between nasal symptoms and asthma?

   - A. Whereas most patients with allergic rhinitis have asthma, the converse is not true
   - B. The presence of allergic rhinitis can increase the risk for asthma-related hospitalizations
   - C. Nasal corticosteroids improve lower airway inflammation in cases of concomitant allergic rhinitis and asthma
   - D. Antihistamines improve lower airway inflammation in cases of concomitant allergic rhinitis and asthma

3. The patient is also obese and has a history of gastroesophageal reflux disorder (GERD). What should you consider regarding the interaction between asthma and these conditions?

   - A. Treatment for GERD will improve her asthma symptoms and reduce the use of asthma medications
   - B. Weight loss may improve asthma outcomes
   - C. Obese patients have a more eosinophilic inflammatory process
   - D. Obese adults are more likely to respond to inhaled corticosteroids

4. What should you consider regarding the interaction between hormonal factors and asthma in this patient?

   - A. After puberty, the prevalence of asthma declines significantly among females vs males
   - B. Women have fewer asthma exacerbations than men
   - C. Early menarche is protective against asthma
   - D. Asthma may worsen during the premenstrual period in almost half of women