INTRODUCTION

There is general consensus that psychological stress contributes to asthma. This belief has emerged from observations that psychological factors are associated with increase in asthma activity or asthma exacerbations, although reverse causation is also possible. Subsequently many efforts have been made to obtain scientific evidence in order to disentangle this association. According to the latest studies, there is a multi-level complex relationship between the effects of psychological stress and asthma mechanisms that is mediated through the endocrine, autonomic nervous and immune systems. A strong suggestion from the current literature is that psychological stress may increase the risk of respiratory infections, thus affecting asthma pathophysiology. In this review, we focus on stress-associated alterations of the immune system and the latest models that investigate this connection, in an area that certainly requires further research.

DEFINITIONS OF STRESS

There is more than one definition of psychological stress in the literature. One of the most usually quoted is that stress occurs when demands from the environment challenge an individual's adaptive capacity, or ability to cope.1 These demands include negative life events, such as job loss, exam failure, death of a loved one, family conflict, and are frequently characterised as stressors. Within this conceptualisation of stress, there has been a differentiation between stressors: those that are limited in duration, have a clear onset and offset and are termed ‘acute’, and those that are ongoing.
to infections) as they currently appear in modern environments. Such incoordination may explain the increase in prevalence of allergic diseases through reduced infectious stimulation, but also the triggering and/or exacerbation of these diseases by the same factors. Additional studies support that respiratory infections can either protect against or be detrimental for asthma, depending on their localisation. According to the results of the German Multicenter Atopic Study (MAS), a considerable protective effect was shown in children with many episodes of runny nose, presumably due to common cold viruses. However, lower respiratory tract infections, probably caused by the same viruses, increased the chances of having asthma at the age of 7. The symptomatology of asthma includes episodes of wheezing, cough and shortness of breath but in many cases the disease is underdiagnosed and undertreated. Patients frequently do not follow advice or take their medication correctly which impacts negatively on their quality of life.

Approximately 300 million people worldwide currently have asthma, and its prevalence is still increasing in many countries, according to the latest results of the International Study of Asthma and Allergies in Childhood (ISAAC). The financial burden on patients with asthma in different Western countries ranges from $300 to $1 300 per patient per year. These are aspects of a major problem of public health that explain the need for more effective management, but also suggest the heavy psychological burden that these patients carry.

ROLE OF INFECTIONS IN ASTHMA
Infections of the respiratory tract, both viral and (atypical) bacterial, are frequently associated with the pathogenesis of asthma as well as in the induction of acute asthma exacerbations. The pathogen most commonly associated with exacerbations is human rhinovirus (RV). Other viruses, including respiratory syncytial, parainfluenza, adenoviruses and more, are also implicated. RV proliferates in both upper and lower respiratory tracts by infecting the airway epithelium and inducing cellular damage and local inflammatory responses. Major determinants of the antiviral and inflammatory responses are interferons (IFNs): both IFN-β and the newly discovered IFN-λ, regulate viral clearance at the epithelial level, while IFN-γ is important in the periphery. These series of events have been modulated by bronchial epithelial cells as well as differentiated primary epithelial cells, grown at an air-liquid interface. Human experimental infections have also helped considerably in understanding the mechanisms of virus-induced asthma.

Additional mechanisms, such as potentiation of the allergic immune responses or induction of neurogenic inflammation have also been suggested. Most frequently, the first episode of asthma occurs in infancy; from a different perspective, infants who experience severe bronchiolitis have an increased chance to continue wheezing, at least throughout childhood. The debate whether the association between infection and reactive airway disease is causal is still active. Respiratory syncytial virus (RSV) has long been considered as the major aetiological agent of acute bronchiolitis and its sequelae. Lately, however, the role of RV is also gaining attention. From an epidemiological perspective, among the cohort followed by Sigurs et al. children with a history of severe RSV bronchiolitis continued to be at an increased risk of both allergic sensitisation and asthma during early adolescence. Bacterial infection, in particular Mycoplasma pneumoniae and Chlamydia pneumoniae, has also been associated with the occurrence of both chronic and acute asthma. Atypical bacteria can enhance airway hyperresponsiveness and inflammation, both of which are associated with exacerbations in patients with pre-existing asthma. Although it is less clear, there have been suggestions that atypical bacteria might also be responsible for the initiation of asthma.

STRESS AND ASTHMA (Fig. 1)
Stress can be related to asthma either through a direct effect on the immune system, or indirectly. Behaviours that are strongly associated with the presence of stressors, such as smoking, seem to raise the possibility of infection or induce pathophysiological changes that facilitate asthma exacerbations. Smoking causes bronchial irritation, increases bronchial responsiveness and causes airway sensitisation to several occupational allergens. In this way it may increase asthma severity. Smokers have been shown to be at greater risk of developing colds than non-smokers because smokers are more likely both to develop infections and to develop illness following infection. Furthermore, alcohol abuse, which is often connected with stressful life events, may render the individual more susceptible to infection. Another aspect worth mentioning is that the perception of stress differs from person to person and so it is possible for an event to be stressful for one individual but not for another. Therefore the same event may release the whole cascade for one, but will have no result on another. Perceived stress has been assessed by standardised questionnaires in order to resolve such differences.

A number of questionnaires are frequently used to validate the correlation between stress and asthma. In a recent study, adolescents completed the UCLA PTSD Reaction Index, Multidimensional Anxiety Scale for Children, and Reynolds Depression Inventory while parents completed the Impact of Events Scale-Revised, Brief Symptom Inventory, and Asthma Functional Morbidity Scale. The results showed clearly that adolescents with asthma and their parents, particularly those who have experienced a life-threatening event, have high levels of post-traumatic stress (PTS) symptoms that are linked to asthma morbidity. Interventions to improve asthma outcomes should include assessment and treatment of trauma and PTS. In another study, researchers observed that immediate post-traumatic alterations in neuroendocrine or inflammatory factors, which increase evening salivary cortisol and/or increased morning serum interleukin-6 (IL-6) concentrations, are involved in subsequent PTS disorder development in children and adolescents. The ‘Trier Social Stress Test for Children’ (TSST-C), which mainly consists of free speech and mental arithmetic tasks in front of an audience, was used to demonstrate that a blunted adrenocortical response to stress may represent a common feature of chronic allergic inflammatory processes that may be relevant in different forms of chronic manifestation of atopy. In another study, children completed questionnaires on stress processing and their well-being at school. Parents filled in a questionnaire on behavioural problems, and teachers provided data on school performance and absence rates. These data showed that children with asthma are similar to other children with regard to their stress processing at school and their psychosocial functioning.

There are a few more studies that evaluate coping with stressors in order to examine changes in physiology. A
number of asthmatic patients participated in a protocol that used a passive coping stressor (the cold pressor test), an active coping stressor (mental arithmetic), an interview about an upsetting asthma-related incident (viewed as a potential passive coping stressor given the exposure to unpleasant memories), and progressive muscle relaxation. The conclusion was that passive coping stressors and other stimuli (e.g. certain forms of relaxation) that elicit increased vagal tone may be associated with poorer asthma control, a view consistent with a significant negative correlation between the participant’s mean vagal tone response to the tasks and score on a measure of asthma self-efficacy.\(^40\)

It is suggested that written emotional disclosure improves emotional and behavioural functioning among adolescents with asthma, particularly those whose writings suggest emotional processing and cognitive restructuring.\(^41\) However, another study questions the effectiveness of written emotional expression in improving disease status of asthmatic patients.\(^42\) Nevertheless, variability within and between subjects is still difficult to assess, since it is possible that some subjects may demonstrate alterations in immunity because of the stress factor while others may not, as the described alterations do not have the same extent in each individual. In asthmatics the presence of a stressor may inflict a more severe and acute response than in healthy individuals, as psychological stress increases the sensitivity of Th-1 cells to viral signals, thus increasing vulnerability to virally induced exacerbations of asthma.

Fig. 1. A conceptual scheme connecting emotional stress with the expression of asthma.
Stress modifies inflammation and inflicts alterations on the immune function

The presence of an acute and ‘serious’ stressor may result in an altered inflammatory response. Acute situations that involve self-conscious emotions can increase the release of cortisol as stressors activate the hypothalamic-pituitary-adrenocortical (HPA) axis. In fact, white blood cells compensate for this prolonged exposure to cortisol by downregulating both the expression and function of the corresponding receptors. As a result, immune cells have diminished sensitivity to glucocorticoids and their anti-inflammatory properties and so it may be more difficult to regulate the magnitude and duration of airway inflammation.46 Stressors also have the ability to affect the autonomic nervous system (ANS).47 In addition, long-term exposure to stressors provokes increased exposure to epinephrine and norepinephrine leading to a downregulation of β-adrenergic receptors, thus decreasing their bronchodilatory effects. Finally, there are studies that indicate the possibility that a stressful event may influence cholinergic responses, eventually leading to bronchoconstriction. During stressful events the activation of the ANS induces a wide process of biochemical pathways.50,51 The secretion of IL-6 provokes stimulation of the glycocorticoid secretion and this in turn causes suppression of tumour necrosis factor alpha (TNF-α) and IL-1, while catecholamines inhibit IL-12 and stimulate IL-10 causing suppression of the innate and cellular immunity and stimulation of humoral immunity.52,53 Additional studies demonstrate that psychological stress can modulate the immune response by triggering the release of mediators through the impact of behavioural side actions that are adopted as ways of coping with stress.54 When we take the above into consideration, stress may influence cell trafficking, cell function including mitogen-stimulated blastogenesis, natural killer cell cytotoxicity, and lymphocyte production of cytokines.55 Furthermore, when subjects were exposed to short time-stressor tasks, they showed suppression of T-cell mitogenesis and increased numbers of circulating T-suppressor/cytotoxic (CD8) cells and natural killer cells. This phenomenon includes stress-elicited alteration of the production of IL-1α, IL-2, and IFN-α. Another possible mechanism of stress interaction with the immune system may be related to the increased secretion of growth hormone and prolactin along with upregulated release of endorphins and encephalins.

Stress may affect asthma through an increased risk of respiratory infections

It has been suggested that psychological stress may influence the appearance of asthma symptoms by increasing the risk of respiratory infections. Psychological stress is a risk factor for the development of cold symptoms in experimentally infected individuals, suggested in a random sample of the population that was assessed for the relationship between the occurrence of the common cold and exposure to four dimensions of stress: stressful life events, negative affect, positive affect, and perceived stress. All four aspects of stress were related to the occurrence of a common cold. Susceptibility to the common cold, mostly caused by RV, has been shown to be affected by several types of stressors. With the use of RV experimental infection protocols, several investigators have provided evidence that the development of cold symptoms in experimentally infected individuals is related to prior life events. The average number of reported major life events for the previous year was significantly higher for those who developed colds than for those who did not. Measures of affect and perceived stress before the inoculation were the same for those who did and did not develop colds. Another study indicated that, although severe acute stressful life events (less than 1 month long) were not associated with developing colds, severe chronic stressors (1 month or longer) were associated with a substantial increase in risk of disease. Moreover, the experimental infection of 394 healthy subjects led to the conclusion that psychological stress was associated, in a dose-response manner, with an increased risk of acute infectious respiratory illness, and this risk was attributable to increased rates of infection rather than to an increased frequency of symptoms after infection.

A potential consequence of stress-induced changes in immune response is suppression of host resistance to infectious agents, particularly agents that cause upper respiratory disease. For example, vascular endothelial growth factor (VEGF) levels are raised in the airways of both asymptomatic and chronic obstructive pulmonary disease (COPD) smokers. The strong correlation observed between VEGF levels in the airways and markers of airway inflammation in healthy smokers and in smokers with COPD is suggestive of VEGF as a marker reflecting the inflammatory process that occurs in smoking subjects without alveolar destruction.

**SUMMARY**

Asthma is a major burden for public health. Among the various factors that affect this complex disease, psychosocial stress seems to participate. New models for the investigation of this association are currently under scrutiny, including the use of perceived stress questionnaires in order to evaluate differences among individuals or estimate the importance of daily life events. The results of such studies may influence the management approach to asthma, to possibly include stress-control measures.

**Declaration of conflict of interest**

The authors declare no conflict of interest in relation to this article.

**REFERENCES**


