

REVIEW

High-altitude treatment: a therapeutic option for patients with severe, refractory asthma?

L. H. Rijssenbeek-Nouwens¹ and E. H. Bel²

¹Dutch Asthma Centre Davos, Davos, Switzerland and ²Department of Respiratory Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

Clinical & Experimental Allergy

Abstract

High-altitude treatment has been applied for more than a century in the treatment of pulmonary diseases including asthma. Many uncontrolled and controlled studies have shown its beneficial effects in children and adolescents with house dust mite allergic asthma. A recent study also showed an improvement in markers of airway inflammation in adult patients with severe intrinsic asthma, suggesting that factors other than HDM avoidance may contribute to the beneficial influence of the high-altitude climate therapy on asthma. The dry mountain climate not only has decreased levels of mite allergens but also decreased levels of pollens, fungal spores and air pollution, as well as high exposure to UV light with immunomodulatory and anti-inflammatory effects. Treatments targeting environmental control have never been investigated systematically in severe asthma, which is surprising, as environmental factors have been recognized as important contributors to asthma severity for many years and more evidence has been accumulating ever since. Preliminary evidence shows the beneficial effects of high-altitude treatment in patients with severe refractory asthma on symptoms, lung function and oral corticosteroid requirement, irrespective of atopic status. In this narrative review, we will discuss why high-altitude treatment might be a promising therapeutic option for patients who suffer from this disabling disease.

Correspondence:

Lucia H. Rijssenbeek-Nouwens, Dutch Asthma Centre Davos, Herman Burchartstrasse 1, 7260 Davos, Switzerland.
E-mail: lrijssenbeek@nad.ch

Introduction

High-altitude treatment has been applied for > 100 years in the treatment of asthma. The high-altitude environment is characterized by dry, clean air, with reduced levels of house dust mites (HDM) [1], particulate matters [2] and moulds [3]. Many uncontrolled and controlled studies have shown the beneficial effects of high-altitude treatment in children and adolescents with HDM-allergic asthma [4]. A recent study also showed an improvement in markers of airway inflammation in adult patients with severe intrinsic asthma [5]. In the present review, we will provide a historical perspective of high-altitude treatment over the last century, evaluate the results of clinical trials up till now and explore the potential of high-altitude treatment for patients with severe, refractory asthma.

Historical perspective of high-altitude treatment for asthma

In the pre-antibiotic era, high-altitude environments, such as the Alps and the Dolomites in Europe, attracted many

patients with tuberculosis, because 'consumptive patients did very well in this climate and were benefited by staying there during the winter' [6]. At the same time, patients with other respiratory conditions, including those with asthma, also went to the mountains. The first observations of the benefits of the mountain climate for patients with asthma were reported in 1879 [7]. The author wrote: 'Asthmatic persons are so capricious that each patient has to find out for himself; a given asthmatic may lose his asthma at Davos. Only young persons should try the experiment, and persons free from emphysema'. A few years later, Turban and Spengler [8] reported the positive influence on health of the alpine climate in 143 patients with asthma. They found that 68% of all asthmatics going to Davos, situated at 1600 m above sea level, became free from asthma attacks within 2 or 3 days, that 25% improved considerably within 2 or 3 weeks and that only 7% remained uninfluenced. The beneficial effect was ascribed to the 'thin air, to the 'protective', 'roborant' and 'radiant' effect of the mountain climate, and to the change in social and psychosocial milieu. Another

explanation of the favourable effect of the mountain climate on asthma symptoms was provided by Stäubli [9], who attributed the beneficial effects of the mountain climate to the absence of harmful factors in the environment.

High altitude: a house dust mite-free environment

In search for the underlying mechanism, the relationship of asthma symptoms with altitude was studied systematically by Storm van Leeuwen et al., [10] who took patients stepwise from sea level to the Alps. His study showed that the improvement in patients' conditions started at an altitude of 1200 m and reached a maximum at 1600 m. The author speculated that the effect might be attributed to 'climate allergens'. For the final proof, he developed an allergen-free air chamber in order to obtain conditions nearly identical to high altitude in the Clinic for Allergic Diseases in Leiden, the Netherlands. Seventy-five per cent of 500 patients, who stayed overnight in these chambers, were completely cured within a few days. In his opinion, 'this shows without any doubt that the conception of the influence of climate allergens on the condition of asthmatics in various climates and at various heights is correct' [11].

More than 50 years later, Storm van Leeuwen's work was continued by Voorhorst and colleagues. They suggested a house dust allergen to be the most plausible triggering factor in allergic patients with asthma [12] and indicated the mite *Dermatophagoides pteronyssinus* as the main allergenic component of house dust [12]. Dust from houses in high-altitude mountains appeared to contain fewer HDMs and less allergen than house dust from lower parts of Switzerland and from sea level [1]. Finally, Vervloet affirmed the effect of altitude on HDMs. In dust samples from different altitudes (900–1200–1400–1600 m), he showed that not only the concentration of mites in dust but also the levels of total and specific IgE in mite-allergic children varied inversely with altitude [13]. The extremely low-humidity levels, preventing the growth of allergen-producing HDMs, therefore seemed likely to contribute to the favourable climatic conditions at high altitude.

High-altitude treatment in children with allergic asthma

The first observational studies on the effects of high-altitude treatment in children with HDM-allergic asthma were performed by Kerrebijn et al. [14]. He studied 31 children with oral steroid-dependent asthma who were sent to Davos for 3 months. In all patients, corticosteroids could be discontinued without untoward effects. In approximately half of the patients, re-institution of oral corticosteroids was not necessary until at least 6 months after the child's return home. Both pituitary-adrenal function and statural growth were improved while corticosteroid therapy was interrupted [14].

To test the effect of a HDM-free environment on airway hyperresponsiveness (AHR), he subsequently studied 20 allergic asthmatic children with a sensitization to HDM during 1 year of treatment in an asthma clinic in Davos. The results showed a remarkable clinical improvement and a progressive reduction in bronchial hyperresponsiveness (BHR) [15]. This effect of an HDM-free environment on BHR was confirmed by Platts-Mills et al., [16]. He studied nine HDM-sensitized asthmatic patients who lived in hospital rooms for 2 months or more. In all patients, symptoms and early morning peak flows improved. In seven patients, anti-asthma treatment could be reduced and five patients showed a progressive improvement in AHR [16].

In a pilot study in 1985, Boner et al. [17] reported clinical improvement in 23 children with severe asthma referred to a special school in Mirusina (1756 m), Italy. After a residency at high altitude of at least 3 months, all children improved to the extent that most regular therapy could be discontinued. Subsequently, the same group reported clinical improvement in 14 children with allergic bronchial asthma after an 8-month period at high altitude [18]. These children showed decreased bronchial lability, decreased requirement for asthma medications and discontinuation of oral corticosteroids.

Over the next 20 years, Boner and colleagues published the results of a series of studies in which they used the migration of HDM-allergic, asthmatic children from sea level to a high-altitude environment and back again as a natural allergen exposure-avoidance challenge model [19–34]. By applying their model in small cohorts of 10–25 children, who acted as their own control, they obtained the following results. After a 3-month stay at high altitude, the asthmatic children showed a decline in peak expiratory flow (PEF) variability [22], and an improvement in airway responsiveness to methacholine [22], histamine [19, 21] and exercise [21]. The early and late response to HDM challenge were diminished, as well as allergen-induced AHR [21], and sputum eosinophilia [33]. There was a decrease in serum total IgE and specific IgE to HDM [21], as well as a decrease in serum eosinophil cationic protein (ECP) and urine eosinophil protein X [20, 25]. Also, the percentage of eosinophils and epithelial cells in induced sputum [24, 27, 29], as well as the level of exhaled nitric oxide [28, 30–32] and the concentrations of cys-leukotrienes and 8-isoprostane in exhaled breath condensate [27] were reduced after a few months' stay at high altitude. Forced expiratory volume in 1 s (FEV₁) did not change in most studies, but measures of small airways function (FEF 25–75 and residual volume) improved [23, 26, 29], and there was a significant improvement in deep-breath-induced bronchodilatation [35].

All these studies convincingly showed that in children with HDM-allergic asthma, a stay at high altitude led to an improvement in symptoms, AHR to specific and

nonspecific stimuli and markers of airway inflammation. Unfortunately, all these effects wore off as soon as the children returned to sea level, where the concentration of HDMs was higher than in the mountains [13]. Only if inhaled corticosteroids were administered as prophylaxis could the deterioration in airway responsiveness and inflammatory markers such as exhaled nitric oxide be prevented [31, 36].

In the meantime, other groups performed similar experiments in children with asthma during allergen avoidance at high altitude. Simon et al. [37] studied 14 HDM-allergic asthmatic children and showed an improvement of lung function and reduction of peripheral blood eosinophils after 3 weeks at high altitude in Davos. Christie et al. [38] performed a randomized-controlled study in Dutch children who were staying at the Asthma Centre in Davos for at least 1 month, and returned home for a short period of 2 weeks. As compared with the children who remained in Davos, the children who returned from the Netherlands showed a significant decline in FEV₁, an increase in airway responsiveness to histamine, accompanied by a threefold increase in urinary leukotriene E₄ (LTE₄). Van Velzen et al. [39] investigated the effect of the mountain climate on airway inflammation in 16 children who were still symptomatic despite inhaled corticosteroids. After a 1-month stay in Davos, they found an improvement in PEF variability and airway responsiveness to adenosine (but not methacholine), and a reduction in blood eosinophil counts and serum ECP. Benckhuijzen et al. [40] found similar results in HDM-allergic asthmatic children who remained uncontrolled despite the chronic use of inhaled corticosteroids and bronchodilators. After a 1-month stay at Davos, airway responsiveness to indirect stimuli (adenosine and exercise) was improved, whereas responsiveness to a direct stimulus (methacholine) was still unchanged. The authors concluded that adenosine and exercise challenge were more adequate markers of airway inflammation than AHR to methacholine.

Grootendorst et al. [41] performed a parallel controlled intervention study investigating the short- and long-term effects of high-altitude treatment in 18 children with HDM-allergic asthma, who were symptomatic despite high-dose inhalation steroids and long-acting β_2 -2-agonists. They showed a significant improvement in quality of life (QOL), FEV₁, AHR to adenosine and histamine, and urinary markers of airway inflammation (EPX, LTE₄, 9 α 11 β -PGF₂) compared with patients staying at sea level.

Thus, high-altitude treatment has a beneficial effect on QOL, AHR and markers of airway inflammation not only for children with mild-moderate HDM-allergic asthma but also for allergic children with more severe asthma who remain symptomatic despite treatment with high doses of inhaled corticosteroids and long-acting β_2 -2-agonists.

High-altitude treatment: more than just mite-allergen avoidance?

Whether the climate at high altitude might also be beneficial for asthmatic patients with allergies other than HDM and for non-atopic patients with asthma has never been addressed systematically. However, two recent reports suggest a beneficial effect of a high-altitude climate in patients with asthma who were not allergic to HDM. The first report showed a significant reduction in the mean exhaled NO value in children after a 4–6-week inpatient rehabilitation programme in the Bavarian Alps (at 1200 m altitude), irrespective of concomitant atopic diseases or anti-asthmatic drugs [42]. The second report was even more intriguing, as it showed the beneficial effects of high-altitude treatment in adults with allergic and intrinsic moderate, severe and steroid-dependent asthma [5]. In 72 patients admitted to a high-altitude clinic in Davos, the authors observed a significant decrease in the level of exhaled nitric oxide in patients with allergic and intrinsic asthma within 3 weeks of high-altitude treatment. In their paper, the authors stated that 'especially patients with severe asthma profit from high altitude climate therapy (...) and in most cases the dose of systemic glucocorticoids can be reduced under high altitude climate therapy conditions'. As patients with intrinsic asthma showed similar reduction in airway inflammation as compared with patients with allergic asthma, the authors concluded that 'factors other than allergen avoidance (...) contribute to the beneficial influence of the high altitude climate therapy on asthma'.

The importance of environmental factors in severe asthma

Severe refractory asthma is a complex, challenging problem both in children [43] and in adults [44]. There is a major unmet need to find better treatments for patients with this disease [45]. To date, there are only a few treatment options available. Oral corticosteroids are effective in most patients, but far from optimal, due to their side-effects [46]. Targeted treatment with biologicals might be successful, but unfortunately, only in specific asthma phenotypes [47–51]. Treatments targeting environmental control have never been investigated systematically in severe asthma, which is surprising, as environmental factors have been recognized as important contributors to asthma severity for many years [52] and more evidence has been accumulating ever since [53–55].

Different environmental factors may contribute to airway inflammation in severe asthma, including perennial exposure to HDM allergen [56] and fungi [57], inadequate sunlight exposure leading to vitamin D deficiency [58] and air pollution [55].

House dust mites

Exposure to HDM undoubtedly contributes to the severity of asthma in sensitized patients [52, 56, 59]. Asthma has

convincingly been shown to be more severe in sensitized patients who are exposed to higher HDM allergen levels and effective allergen avoidance is consequently recognized as an integral part of the overall management of the sensitized asthma patient [60]. However, environmental control is difficult. Even with a major reduction in allergen levels, it may take many months before the beneficial effect on symptoms, medication use, pulmonary function, non-specific and specific BHR and immunological parameters becomes fully apparent [61]. A systematic review showed that chemical and physical methods aimed at reducing exposure to HDM allergens are not effective [62]. Therefore, allergen avoidance measures have to be multifaceted [63]. This fits in with the observation that an individualized, home-based, comprehensive, environmental intervention, decreasing indoor allergens, results in reduced asthma-associated morbidity [64].

The high-altitude climate is one of the few natural HDM-free environments and may therefore be of interest for sensitized patients with severe allergic asthma.

Fungi

There is increasing evidence of a close association between fungal sensitization and asthma severity in adults and children [57, 65, 66]. One key aspect of fungi is that they not only have potent allergenic properties but they also have the ability to actively germinate, colonize and infect the respiratory tract, providing a chronic source of allergen exposure, and thus have a much greater impact on the severity of asthma [57]. Recently, it was shown that patients sensitized to *A. fumigatus* compared with non-sensitized patients with asthma had lower lung function, more bronchiectasis and more sputum neutrophils [67]. Indeed, severe asthma patients with fungal sensitization respond favourably to oral antifungal therapy, with a clinically relevant improvement in QOL and steroid requirement [68]. More importantly, symptoms of asthma and rhino-sinusitis have been shown to improve, and medication use to decline, following the removal of indoor mould, by lowering indoor humidity [69]. Alternatively, mould control, by insulation and use of moisture-impenetrable barriers, is effective in reducing self-reported wheeze, and hospital admissions for respiratory conditions [70]. Altogether, indoor exposure to perennial allergens, including HDM and fungi, is deleterious for asthma patients, and needs to be avoided. As both HDM and fungi grow under humid conditions, it seems rational for patients with severe asthma to search for a low-humidity environment [69, 71].

Vitamin D deficiency due to limited exposure to sunlight

Vitamin D deficiency is highly prevalent in the general population, in particular among patients with chronic lung diseases. There is now accumulating evidence that

vitamin D deficiency may contribute to the severity of asthma [58]. Vitamin D deficiency is associated with increased AHR [72], lower pulmonary functions [73], worse asthma control [74] and possibly steroid resistance [75–77]. A recent study demonstrated that vitamin D levels were inversely associated with the total IgE and eosinophil count [74]. Additionally, patients with higher vitamin D levels were associated with fewer hospitalizations and decreased need for anti-inflammatory medications [74]. Low vitamin D levels may promote bronchial smooth muscle proliferation and airway remodelling in asthma [78]. Recent evidence suggests that vitamin D deficiency might lead to greater occurrences of viral respiratory tract infections [79, 80], and consequently, more asthma exacerbations [74].

Thus, vitamin D deficiency seems to be an important, as yet unrecognized, factor contributing to asthma control, severity and prognosis. Several controlled trials are now underway to investigate whether the administration of high doses of vitamin D₃ leads to improvement of severe asthma (<http://www.ClinicalTrials.gov>).

Air pollution

The health effects of air pollution have been subject to intense study in recent years. Air pollution is now considered to be a major environmental health issue [55]. Exposure to particulate matter and volatile organic compounds is associated with worse respiratory health [81], and an increased risk of hospitalizations and ICU admissions for asthma, especially in children [82, 83]. Long-term exposure to relatively low levels of air pollution is associated with a higher prevalence of respiratory symptoms and a decline in lung function in adults [84, 85]. Diesel exhaust triggers asthma symptoms and enhances airway inflammation in patients with asthma [86]. In a randomized crossover study, short-term exposure to diesel traffic in an urban roadside environment resulted in a significant decrease in lung function and an increase in inflammatory markers in sputum and exhaled breath condensate [87]. Nitrogen dioxide and ozone may exacerbate severe asthma and even cause death among patients with asthma [88]. Alternatively, reduction of air pollution exposure contributes to improved respiratory health in children [89] and attenuation of the rate of decline in lung function in healthy adults [90]. In children with asthma, 1 week at a summer camp in a less-polluted rural environment at a 1500 m altitude led to a rapid reduction in airway inflammation and an improvement of airway function [91].

Taken together, long- and short-term exposures to air pollution have adverse effects on lung function, respiratory symptoms and airway inflammation in children and adults, whereas reduction in air pollution exposure improves lung function and respiratory health.

High altitude: the ideal environment for patients with severe asthma

The climate at high altitude offers unique conditions for patients with asthma, in particular those with severe disease. First, because of the low relative and absolute indoor and outdoor humidity, the mountain climate is not only free of HDMs but also relatively free of other airborne allergens that are associated with severe asthma including fungal spores and moulds [1, 13, 53, 71]. Indeed, as a result of the dryness at high altitude, the number of *Cladosporium* spp. spores is 25–50% that of lower areas and *Alternaria* spores only 1–3% [3]. Patients with pollen allergies might also benefit from a mountain climate. Because the slopes are covered by snow for 6 months of the year, the pollen season is short, and clinically relevant pollen concentrations are only found for a few days per year (*Source: Meteoschweiz*). These low airborne allergen concentrations also offer additional possibilities for allergen testing in patients with severe allergic asthma, and for the initiation of immunotherapy under allergen-free or low allergen conditions.

Second, the high-altitude climate may have a direct physiological benefit because of the lower viscosity of the air and lower oxygen concentration. The decreased density of the air reduces respiratory resistances and increases inspiratory and expiratory flows, promoting full expansion of the lungs and decreasing lung resistance, which makes it easier to breathe [92]. This may also help to improve exercise capacity and physical fitness in patients with severe asthma.

Third, by moving to the mountains, the patients are literally moved away from psychological stress at home or at work. Psychological stress has been shown to enhance airway inflammation by modulating immune cell function through neural and hormonal pathways [93]. Chronic stress is associated with reduced responsiveness to corticosteroids [94] and causes asthma exacerbations in children [95]. Stress-reducing interventions have been shown to have beneficial effects on asthma severity [96] and contact with the natural mountain environment offers an effective way of achieving stress reduction. Of course, this is not unique for the mountains, but holds true for any relaxing environment far away from home.

Fourth, the Alps and Dolomites are well known for their abundance of sunshine. Exposure to UV light stimulates vitamin D photosynthesis in the skin and may modulate the immune system, thereby potentially reducing the severity of chronic diseases, such as asthma [58, 97].

Fifth, the mountain outdoor climate in the Alps is far less polluted than the climate in other parts of Europe at sea level such as the Netherlands. For example, in 2005, the particulate matter (PM₁₀) in the Alps was < 10 µg/m³, whereas it was 20–40 µg/m³ in the Netherlands and > 45 µg/m³ in some parts of Northern Italy [2].

Finally, asthma clinics such as the ones in Davos, the Italian or the Bavarian supply structured, quality-controlled comprehensive tailor-made treatment plans for children and adults with severe asthma, which includes achievement of full asthma control, reduction of (oral) corticosteroids to the lowest effective level, exercise training, asthma education and self-management, and psychological support. For the above-mentioned reasons, such programmes are likely to lead to better outcomes than similar interventions at sea level, although this has to be confirmed by randomized-controlled trials.

Taken together, the high-altitude climate offers more than decreased levels of HDM allergens. It also offers decreased exposure to pollens, fungal spores and air pollution, as well as lower work of breathing, relief from stress and high UV-light exposure with a potential immunomodulatory effect. Because of these characteristics, it provides the ideal environment for patients with asthma, both atopic and non-atopic, and might be a valuable treatment option in patients with severe, refractory disease.

High-altitude treatment for severe asthma: old concept, new evidence

Preliminary data investigating the effects of high-altitude treatment in adults with severe, refractory asthma show promising results. In allergic patients with or without sensitization to HDMs, and also in patients with intrinsic asthma, high-altitude treatment for 12 weeks in the asthma clinic in Davos leads to an improvement in asthma control, asthma-related QOL, pre- and post-bronchodilator FEV₁, fraction of exhaled NO, and total and specific IgE, with a concomitant reduction in the use of oral corticosteroids [98, 99]. The improved asthma control creates the opportunity for the patients to optimize their exercise tolerance and improve physical fitness.

The next step will be to study the long-term benefits of this high-altitude treatment programme in terms of asthma control, QOL and exacerbation rate. If patients with severe refractory asthma are able to maintain their physical fitness and asthma control at acceptable levels for prolonged periods of time without exacerbations or hospital admissions, periodic rehabilitation programmes at high altitude would constitute an elegant treatment option for these compromised patients.

Future research perspectives

To date, there is a surprising lack of data on the beneficial effects of high-altitude treatment in adults with severe refractory asthma. Because patients with this serious disorder depend on drugs that either have serious side-effects or are only effective in small subsets of patients, more research is urgently needed. Firstly, it has to be demonstrated in randomized-controlled trials that the

effect of high-altitude treatment is superior to a similar treatment programme at sea level. This has never been done before. In all the published studies, patients were their own controls or were not randomized into treatment arms, which might have introduced a selection bias. Secondly, it has to be investigated whether the beneficial effects of high-altitude treatment differ between different phenotypes of severe asthma, and what characterizes the patients with the most favourable re-

sponse. Thirdly, the environmental factors and inflammatory mechanisms that are associated with clinical and functional improvement as a result of high-altitude treatment should be explored in more detail, especially in patients without allergic sensitization. Finally, the relative potential of a high-altitude intervention in terms of costs, duration and sustainability as compared with current established and experimental treatments should be investigated.

References

- Spieksma FT, Zuidema P, Leupen MJ. High altitude and house-dust mites. *Br Med J* 1971; 1:82-4.
- European Environment Agency. *Air quality maps of Europe*. 2010. Available at <http://www.eea.europa.eu/themes/air/airbase/interpolated>
- Leuschner RM, Boehm W. Pollen and inorganic particles in the air of climatically very different places in Switzerland. *Grana* 1981; 20:161-7.
- Platts-Mills TA, Chapman MD. Dust mites: immunology, allergic disease, and environmental control. *J Allergy Clin Immunol* 1987; 80:755-75.
- Karagiannidis C, Hense G, Rueckert B *et al*. High-altitude climate therapy reduces local airway inflammation and modulates lymphocyte activation. *Scand J Immunol* 2006; 63:304-10.
- Anonymous. Davos and the Enghadine. *Lancet* 1876; 101:482-3.
- Allbutt C. The past winter in Davos. *Lancet* 1879; 114:76-8 and 118-9.
- Turban K, Spengler L. Resultate der Asthmapbehandlung im Hochgebirge. *Jahresb schweiz balneol Gesellsch* 1906; 2:72.
- Stäubli K. Ueber die Indikat und Kontra-Indikat des Hohenklimas. *Deutsche med Wschr* 1912; 4.
- Storm van Leeuwen W, Varekamp H, Bien Z. Asthma bronchiale und Klima. *Klin Wschr* 1924; 3:520.
- Storm van Leeuwen W. Asthma and Tuberculosis in relation to "Climate Allergens". *Br Med J* 1927; 2:344-7.
- Voorhorst R, Spieksma F.Th.M, Varekamp H. *House-dust atopy and the house-dust mite Dermatophagoides pteronyssinus (Trouessart 1897)*. Leiden: Stafleu's Scientific Publishing Company, 1969.
- Vervloet D, Penaud A, Razzouk H *et al*. Altitude and house dust mites. *J Allergy Clin Immunol* 1982; 69:290-6.
- Kerrebijn KF, de Kroon JP, Roosenburg JG, Zuidema P. Corticosteroid therapy of children with chronic aspecific respiratory disease. Discontinuation of the treatment in the mountains. *Ned Tijdschr Geneesk* 1967; 111: 2353-9.
- Kerrebijn KF. Endogenous factors in childhood chronic nonspecific lung disease; methodological aspects in population studies. In: Orie N.G.M, van der Lende R, eds. *Bronchitis III*. Assen, the Netherlands: Royal Van Gorkum, 1970; 38-48.
- Platts-Mills TA, Mitchell EB, Nock P, Tovey ER, Moszoro H, Wilkins SR. Reduction of bronchial hyperreactivity during prolonged allergen avoidance. *Lancet* 1982; 3:675-8.
- Boner A, Niero E, Antolini I, Warner JO. Biphasic (early and late) asthmatic responses to exercise in children with severe asthma, resident at high altitude. *Eur J Pediatr* 1985; 144:164-6.
- Boner AL, Niero E, Antolini I, Valletta EA, Gaburro D. Pulmonary function and bronchial hyperreactivity in asthmatic children with house dust mite allergy during prolonged stay in the Italian Alps (Misurina, 1756 m). *Ann Allergy* 1985; 54:42-5.
- Piacentini GL, Martinati L, Fornari A *et al*. Antigen avoidance in a mountain environment: influence on basophil releasability in children with allergic asthma. *J Allergy Clin Immunol* 1993; 92: 644-50.
- Boner AL, Peroni DG, Piacentini GL, Venge P. Influence of allergen avoidance at high altitude on serum markers of eosinophil activation in children with allergic asthma. *Clin Exp Allergy* 1993; 23:1021-6.
- Peroni DG, Boner AL, Vallone G, Antolini I, Warner JO. Effective allergen avoidance at high altitude reduces allergen-induced bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 1994; 149: 1442-6.
- Valletta EA, Comis A, Del CG, Spezia E, Boner AL. Peak expiratory flow variation and bronchial hyperresponsiveness in asthmatic children during periods of antigen avoidance and reexposure. *Allergy* 1995; 50:366-9.
- Valletta EA, Piacentini GL, Del CG, Boner AL. FEF25-75 as a marker of airway obstruction in asthmatic children during reduced mite exposure at high altitude. *J Asthma* 1997; 34:127-31.
- Piacentini GL, Vicentini L, Mazzi P, Chilosì M, Martinati L, Boner AL. Mite-antigen avoidance can reduce bronchial epithelial shedding in allergic asthmatic children. *Clin Exp Allergy* 1998; 28: 561-7.
- Piacentini GL, Peterson C, Peroni DG, Bodini A, Boner AL. Allergen avoidance at high altitude and urinary eosinophil protein X. *J Allergy Clin Immunol* 1999; 104:243-4.
- Peroni DG, Piacentini GL, Costella S *et al*. Mite avoidance can reduce air trapping and airway inflammation in allergic asthmatic children. *Clin Exp Allergy* 2002; 32:850-5.
- Bodini A, Peroni D, Vicentini L *et al*. Exhaled breath condensate eicosanoids and sputum eosinophils in asthmatic children: a pilot study. *Pediatr Allergy Immunol* 2004; 15:26-31.
- Piacentini GL, Peroni DG, Bodini A, Boner AL. Exhaled nitric oxide in children with asthma at high altitude. *J Allergy Clin Immunol* 2007; 120:1226-7.
- Peroni DG, Piacentini GL, Vicentini L, Costella S, Pietrobelli A, Boner AL. Effective allergen avoidance reduces residual volume and sputum eosinophils in children with asthma. *J Allergy Clin Immunol* 2001; 108:308.
- Piacentini GL, Del Giudice MJ, Bodini A *et al*. Exhaled NO reduced on allergen avoidance. *Allergy* 2001; 56:251-2.

- 31 Piacentini GL, Bodini A, Costella S *et al.* Exhaled nitric oxide in asthmatic children exposed to relevant allergens: effect of flunisolide. *Eur Respir J* 2000; 15:730–4.
- 32 Piacentini GL, Bodini A, Costella S *et al.* Allergen avoidance is associated with a fall in exhaled nitric oxide in asthmatic children. *J Allergy Clin Immunol* 1999; 104:1323–4.
- 33 Piacentini GL, Martinati L, Mingoni S, Boner AL. Influence of allergen avoidance on the eosinophil phase of airway inflammation in children with allergic asthma. *J Allergy Clin Immunol* 1996; 97:1079–84.
- 34 Sensi LG, Piacentini GL, Nobile E *et al.* Changes in nasal specific IgE to mites after periods of allergen exposure-avoidance: a comparison with serum levels. *Clin Exp Allergy* 1994; 24: 377–82.
- 35 Milanese M, Peroni D, Costella S *et al.* Improved bronchodilator effect of deep inhalation after allergen avoidance in asthmatic children. *J Allergy Clin Immunol* 2004; 114:505–11.
- 36 Boner AL, Comis A, Schiassi M, Venge P, Piacentini GL. Bronchial reactivity in asthmatic children at high and low altitude. Effect of budesonide. *Am J Respir Crit Care Med* 1995; 151:1194–200.
- 37 Simon HU, Grotzer M, Nikolaizik WH, Blaser K, Schoni MH. High altitude climate therapy reduces peripheral blood T lymphocyte activation, eosinophilia, and bronchial obstruction in children with house-dust mite allergic asthma. *Pediatr Pulmonol* 1994; 17:304–11.
- 38 Christie PE, Yntema JL, Tagari P, Ysselstijn H, Ford-Hutchinson AW, Lee TH. Effect of altitude on urinary leukotriene (LT) E₄ excretion and airway responsiveness to histamine in children with atopic asthma. *Eur Respir J* 1995; 8:357–63.
- 39 van Velzen E, Van Den Bos JW, Benckhuijsen JA, van ET, de BR, Aalbers R. Effect of allergen avoidance at high altitude on direct and indirect bronchial hyperresponsiveness and markers of inflammation in children with allergic asthma. *Thorax* 1996; 51:582–4.
- 40 Benckhuijsen J, van den BJW, van Velzen E, de Bruijn R, Aalbers R. Differences in the effect of allergen avoidance on bronchial hyperresponsiveness as measured by methacholine, adenosine-5'-monophosphate, and exercise in asthmatic children. *Pediatr Pulmonol* 1996; 22:147–53.
- 41 Grootendorst DC, Dahlen SE, Van Den Bos JW *et al.* Benefits of high altitude allergen avoidance in atopic adolescents with moderate to severe asthma, over and above treatment with high dose inhaled steroids. *Clin Exp Allergy* 2001; 31:400–8.
- 42 Huss-Marp J, Kramer U, Eberlein B *et al.* Reduced exhaled nitric oxide values in children with asthma after inpatient rehabilitation at high altitude. *J Allergy Clin Immunol* 2007; 120:471–2.
- 43 Hedlin G, Bush A, Lodrup CK *et al.* Problematic severe asthma in children, not one problem but many: a GA2LEN initiative. *Eur Respir J* 2010; 36: 196–201.
- 44 Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. *Lancet* 2006; 368: 780–93.
- 45 Barnes PJ. New therapies for asthma: is there any progress? *Trends Pharmacol Sci* 2010; 31:335–43.
- 46 Walsh LJ, Wong CA, Osborne J *et al.* Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. *Thorax* 2001; 56:279–84.
- 47 Brightling C, Berry M, Amrani Y. Targeting TNF- α : a novel therapeutic approach for asthma. *J Allergy Clin Immunol* 2008; 121:5–10.
- 48 Busse WW, Corren J, Lanier BQ *et al.* Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001; 108: 184–90.
- 49 Haldar P, Brightling CE, Hargadon B *et al.* Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; 360:973–84.
- 50 Nair P, Pizzichini MM, Kjarsgaard M *et al.* Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009; 360:985–93.
- 51 Berry MA, Hargadon B, Shelley M *et al.* Evidence of a role of tumor necrosis factor α in refractory asthma. *N Engl J Med* 2006; 354:697–708.
- 52 Call RS, Ward G, Jackson S, Platts-Mills TA. Investigating severe and fatal asthma. *J Allergy Clin Immunol* 1994; 94: 1065–72.
- 53 Peden D, Reed CE. Environmental and occupational allergies. *J Allergy Clin Immunol* 2010; 125:S150–60.
- 54 Ho SM. Environmental epigenetics of asthma: an update. *J Allergy Clin Immunol* 2010; 126:453–65.
- 55 Bernstein JA, Alexis N, Bacchus H *et al.* The health effects of non-industrial indoor air pollution. *J Allergy Clin Immunol* 2008; 121:585–91.
- 56 Wang J, Visness CM, Calatroni A, Gergen PJ, Mitchell HE, Sampson HA. Effect of environmental allergen sensitization on asthma morbidity in inner-city asthmatic children. *Clin Exp Allergy* 2009; 39:1381–9.
- 57 Denning DW, O'Driscoll BR, Hogaboam CM, Bowyer P, Niven RM. The link between fungi and severe asthma: a summary of the evidence. *Eur Respir J* 2006; 27:615–26.
- 58 Sandhu MS, Casale TB. The role of vitamin D in asthma. *Ann Allergy Asthma Immunol* 2010; 105:191–9.
- 59 Custovic A, Taggart SC, Francis HC, Chapman MD, Woodcock A. Exposure to house dust mite allergens and the clinical activity of asthma. *J Allergy Clin Immunol* 1996; 98:64–72.
- 60 National Institutes of Health, National Heart, Lung, and Blood Institute., Global initiative for asthma. Global strategy for asthma management and prevention. NHLBI/WHO workshop report, 2008. Available at <http://www.ginasthma.org> (accessed April 2010).
- 61 Custovic A, Simpson A, Chapman MD, Woodcock A. Allergen avoidance in the treatment of asthma and atopic disorders. *Thorax* 1998; 53:63–72.
- 62 Gotzsche PC, Johansen HK, Schmidt LM, Burr ML. House dust mite control measures for asthma. *Cochrane Database Syst Rev*, 18 October 2004, 18;(4): CD001187 2004;CD001187.
- 63 Platts-Mills TA. Allergen avoidance in the treatment of asthma: problems with the meta-analyses. *J Allergy Clin Immunol* 2008; 122:694–6.
- 64 Morgan WJ, Crain EF, Gruchalla RS *et al.* Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med* 2004; 351: 1068–80.
- 65 Delfino RJ, Coate BD, Zeiger RS, Seltzer JM, Street DH, Koutrakis P. Daily asthma severity in relation to personal ozone exposure and outdoor fungal spores. *Am J Respir Crit Care Med* 1996; 154: 633–41.
- 66 Zureik M, Neukirch C, Leynaert B, Liard R, Bousquet J, Neukirch F. Sensitisation

- to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey. *BMJ* 2002; 325:411–4.
- 67 Fairs A, Agbetile J, Hargadon B, Bourne M *et al.* IgE sensitisation to *Aspergillus fumigatus* is associated with reduced lung function in asthma. *Am J Respir Crit Care Med* 2010; 182:1362–8.
 - 68 Denning DW, O'Driscoll BR, Powell G *et al.* Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitization: the Fungal Asthma Sensitization Trial (FAST) study. *Am J Respir Crit Care Med* 2009; 179: 11–8.
 - 69 Burr ML, Matthews IP, Arthur RA *et al.* Effects on patients with asthma of eradicating visible indoor mould: a randomised controlled trial. *Thorax* 2007; 62:767–72.
 - 70 Howden-Chapman P, Matheson A, Crane J *et al.* Effect of insulating existing houses on health inequality: cluster randomised study in the community. *BMJ* 2007; 334:460–9.
 - 71 Burge HA. An update on pollen and fungal spore aerobiology. *J Allergy Clin Immunol* 2002; 110:544–52.
 - 72 Brehm JM, Schuemann B, Fuhlbrigge AL *et al.* Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. *J Allergy Clin Immunol* 2010; 126:52–8.
 - 73 Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin d and pulmonary function in the third national health and nutrition examination survey. *Chest* 2005; 128:3792–8.
 - 74 Brehm JM, Celedon JC, Soto-Quiros ME *et al.* Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med* 2009; 179:765–71.
 - 75 Sutherland ER, Goleva E, Jackson LP, Stevens AD, Leung DY. Vitamin D levels, lung function, and steroid response in adult asthma. *Am J Respir Crit Care Med* 2010; 181:699–704.
 - 76 Searing DA, Zhang Y, Murphy JR, Hauk PJ, Goleva E, Leung DY. Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. *J Allergy Clin Immunol* 2010; 125:995–1000.
 - 77 Banerjee A, Damera G, Bhandare R *et al.* Vitamin D and glucocorticoids differentially modulate chemokine expression in human airway smooth muscle cells. *Br J Pharmacol* 2008; 155:84–92.
 - 78 Clifford RL, Knox AJ. Vitamin D – a new treatment for airway remodelling in asthma? *Br J Pharmacol* 2009; 158: 1426–8.
 - 79 Sabetta JR, DePetrillo P, Cipriani RJ, Smardin J, Burns LA, Landry ML. Serum 25-hydroxyvitamin d and the incidence of acute viral respiratory tract infections in healthy adults. *PLoS One* 2010; 5:e11088.
 - 80 Ginde AA, Mansbach JM, Camargo CA Jr. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 2009; 169:384–90.
 - 81 O'Connor GT, Neas L, Vaughn B *et al.* Acute respiratory health effects of air pollution on children with asthma in US inner cities. *J Allergy Clin Immunol* 2008; 121:1133–9.
 - 82 Silverman RA, Ito K. Age-related association of fine particles and ozone with severe acute asthma in New York City. *J Allergy Clin Immunol* 2010; 125:367–73.
 - 83 Gilliland FD. Outdoor air pollution, genetic susceptibility, and asthma management: opportunities for intervention to reduce the burden of asthma. *Pediatrics* 2009; 123 (Suppl. 3):S168–73.
 - 84 Zemp E, Elsasser S, Schindler C *et al.* Long-term ambient air pollution and respiratory symptoms in adults (SAPALDIA study). The SAPALDIA Team. *Am J Respir Crit Care Med* 1999; 159:1257–66.
 - 85 Ackermann-Lieblich U, Leuenberger P, Schwartz J *et al.* Lung function and long term exposure to air pollutants in Switzerland. Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. *Am J Respir Crit Care Med* 1997; 155:122–9.
 - 86 Nordenhall C, Pourazar J, Ledin MC, Levin JO, Sandstrom T, Adelroth E. Diesel exhaust enhances airway responsiveness in asthmatic subjects. *Eur Respir J* 2001; 17:909–15.
 - 87 McCreanor J, Cullinan P, Nieuwenhuijsen MJ *et al.* Respiratory effects of exposure to diesel traffic in persons with asthma. *N Engl J Med* 2007; 357: 2348–58.
 - 88 Sunyer J, Basagana X, Belmonte J, Anto JM. Effect of nitrogen dioxide and ozone on the risk of dying in patients with severe asthma. *Thorax* 2002; 57: 687–93.
 - 89 Avol EL, Gauderman WJ, Tan SM, London SJ, Peters JM. Respiratory effects of relocating to areas of differing air pollution levels. *Am J Respir Crit Care Med* 2001; 164:2067–72.
 - 90 Downs SH, Schindler C, Liu LJ *et al.* Reduced exposure to PM10 and attenuated age-related decline in lung function. *N Engl J Med* 2007; 357: 2338–47.
 - 91 Renzetti G, Silvestre G, D'Amario C *et al.* Less air pollution leads to rapid reduction of airway inflammation and improved airway function in asthmatic children. *Pediatrics* 2009; 123: 1051–8.
 - 92 Skloot G, Permutt S, Togias A. Airway hyperresponsiveness in asthma: a problem of limited smooth muscle relaxation with inspiration. *J Clin Invest* 1995; 96:2393–403.
 - 93 Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. *Brain Behav Immun* 2007; 21:993–9.
 - 94 Haczku A, Panettieri RA Jr. Social stress and asthma: the role of corticosteroid insensitivity. *J Allergy Clin Immunol* 2010; 125:550–8.
 - 95 Sandberg S, Paton JY, Ahola S *et al.* The role of acute and chronic stress in asthma attacks in children. *Lancet* 2000; 356:982–7.
 - 96 Bosley CM, Corden ZM, Cochrane GM. Psychosocial factors and asthma. *Respir Med* 1996; 90:453–7.
 - 97 Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357:266–81.
 - 98 Rijssenbeek-Nouwens LH, Bron AO, Naves C, Weller F, Weersink EJ, Bel EH. How persistent is “persistent airflow limitation” in severe asthma. *Eur Respir J* 2006; 28 (Suppl. 50).
 - 99 Rijssenbeek-Nouwens LH, Fieten KB, Bron AO, Weersink EJ, Sterk PJ, Bel EH. Clinical improvement in patients with severe asthma at high altitude occurs irrespective of allergy to house dust mite. *Am J Respir Crit Care Med* 2010; 181, A5416.