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POSITION PAPER

Alpine altitude climate treatment for severe and uncontrolled asthma: An EAACI position paper

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Abbreviations: 6MWD, 6-minute walking distance; AACT, alpine altitude climate treatment; ACQ, asthma control questionnaire; AHR, airway hyperresponsiveness; AQLQ, asthma quality of life questionnaire; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume during the first second; FVC, forced vital capacity; HDM, house dust mite; HIF-1a, hypoxia-inducible factor 1a; ILC, innate lymphoid cells; ISWT, incremental shuttle walk test; m, meters above sea level; MCID, minimal clinically important difference; NK, natural killer cells; OCS, oral corticosteroids; PAQLQ, pediatric asthma quality of life questionnaire; PD_{20}, the provocative dose of methacholine that results in a 20% fall in FEV_1; QoL, quality of life; SMD, standardized mean difference; Th1, T helper cells type 1; Th2, T helper cells type 2; TRAP, traffic-related air pollution; Tregs, regulatory T cells; UVR, ultraviolet radiation.

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Abstract

Currently available European Alpine Altitude Climate Treatment (AACT) programs combine the physical characteristics of altitude with the avoidance of environmental triggers in the alpine climate and a personalized multidisciplinary pulmonary rehabilitation approach. The reduced barometric pressure, oxygen pressure, and air density, the relatively low temperature and humidity, and the increased UV radiation at moderate altitude induce several physiological and immunological adaptation responses. The environmental characteristics of the alpine climate include reduced aeroallergens such as house dust mites (HDM), pollen, fungi, and less air pollution. These combined factors seem to have immunomodulatory effects controlling pathogenic inflammatory responses and favoring less neuro-immune stress in patients with different asthma phenotypes. The extensive multidisciplinary treatment program may further contribute to the observed clinical improvement by AACT in asthma control and quality of life, fewer exacerbations and hospitalizations, reduced need for oral corticosteroids (OCS), improved lung function, decreased airway hyperresponsiveness (AHR), improved exercise tolerance, and improved sinonasal outcomes. Based on observational studies and expert opinion, AACT represents a valuable therapy for those patients irrespective of their asthma phenotype, who cannot achieve optimal control of their complex condition despite all the advances in medical science and treatment according to guidelines, and therefore run the risk of falling into a downward spiral of loss of physical and mental health. In the light of the observed rapid decrease in inflammation and immunomodulatory effects, AACT can be considered as a natural treatment that targets biological pathways.

KEYWORDS
altitude, asthma, climate, environment, pulmonary rehabilitation

1 | INTRODUCTION

A significant proportion of patients with asthma remains uncontrolled, despite well-designed and accepted guidelines, effective medication and the increasing availability of new therapies, such as biologicals. Suboptimal asthma control has a major impact on disease burden, quality of life, and healthcare costs. Proper identification of treatable traits, follow-up on medication adherence, maintenance of daily physical activity, avoidance of indoor and outdoor allergens, air pollution and occupational exposure, and non-pharmacological add-on therapies facilitate achieving asthma control. If still uncontrolled, referral to a severe asthma clinic to assess the asthma endotype/phenotype and suitability of additional targeted treatment with bronchial thermoplasty or biologicals is recommended.[1–4]

Alpine altitude climate treatment (AACT) has been applied for more than a century in the treatment of pulmonary diseases like asthma, and more recently for allergic diseases such as atopic dermatitis and chronic rhinitis/rhinosinusitis.[5–7] The European altitude clinics for patients with tuberculosis were built in 19th century in the clean alpine environment in close proximity to green space and forests. Currently available European AACT programs combine the avoidance of environmental triggers in the alpine climate and the physical characteristics of altitude with a personalized multidisciplinary pulmonary rehabilitation approach. The environmental mechanisms supporting the benefit provided by AACT, including the influence of altitude characteristics and the alpine climate, are not yet fully understood. In the first observations of the health benefits for patients with asthma, the mountain climate, the clear air, the radiant sun, and the absence of harmful factors were hypothesized to be protective and healing. With the aim of understanding the underlying mechanisms, the relationship of clinical symptoms with altitude was systematically studied, but rarely in a randomized controlled study. The house dust mite (HDM) was discovered as the main allergic component in environmental house dust. Allergen avoidance was thought to be the main mechanism of effect during AACT.[8] Recent studies also showed improvement in inflammatory and immunological markers in patients with different asthma phenotypes, including non-atopic, suggesting that immunomodulatory changes apart from allergen avoidance may contribute to the clinical improvement with AACT.[9–12] Furthermore, many observational studies have shown that AACT also improves clinical and functional parameters in asthma.[5–7] However, it is not yet understood which mechanisms contribute to the observed effects or which factor contributes the most. (Table 1) The EAACI Task Force on AACT aims to describe the physical and environmental characteristics of moderate altitude in the alpine climate, its immunomodulatory effects, its multidisciplinary pulmonary rehabilitation approach, and its clinical impact on uncontrolled and severe asthma and to advice, which patients might profit most from AACT.

Key messages

- A significant proportion of patients with asthma remains uncontrolled, despite increasing availability of biologicals.
- European AACT programs combine the avoidance of environmental triggers in the alpine climate and the physical characteristics of altitude with a personalized multidisciplinary pulmonary rehabilitation approach.

2 | METHODS

Two experts in the field reviewed the literature for each of the following topics: physical characteristics of altitude, environmental characteristics of the alpine climate, immunological outcomes, clinical outcomes adults, and clinical outcomes children. The search was performed using Medline, Embase, and Cochrane databases including papers published before April 24, 2021. Search terms are listed in Table S1. We focused on studies reporting treatment provided in Europe. Because of the lack of randomized trials assessing the effectiveness of AACT, we did not use GRADE to provide scientific recommendations, but we decided on an expert-based consensus approach resulting in position statements. Quality assessment of non-randomized interventional studies was done according to the National Institutes of Health (NIH) Study quality assessment tool for before–after (pre–post) studies with no control group, available at https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Items 11 and 12 of this tool were not applicable to any of the included studies and therefore replaced by the question whether all measurements from the protocol were reported to further assess reporting bias.

3 | ALTITUDE AND PHYSIOLOGICAL CHANGES

Based on the effects of altitude on human physiology and well-being in healthy individuals, altitude has been divided into low (<1200 m), moderate (1200 m–2500 m), high (2500 m–3500 m), very high (3500–5800 m), and extreme (>5800 m).[13] Other definitions consider moderate altitude up to 3000 m.[14] Physiological changes induced by hypobaric hypoxia gradually increase with incrementing altitude and are usually mild up to an altitude of 1500 m.[15,16] Acute mountain sickness (AMS) is the most common form of acute altitude illness and typically occurs in unacclimatized persons ascending to altitudes >2500 m, although it can develop at lower altitudes in highly susceptible individuals. There are large interindividual differences in susceptibility to effects of hypobaric hypoxia.[17]

At 3000 m, the inspired partial pressure of oxygen is reduced to 100 mmHg (13.3 kPa), the alveolar oxygen pressure is estimated

to be 70 mmHg (9.3 kPa), which means an arterial oxygen pressure of about 60–63 mmHg (8 kPa) and the compensatory responses to hypobaric hypoxia become increasingly evident (Table S2). 3000 m is the altitude above which many of the physiological responses that represent challenges for the human body (i.e., hypoxic ventilatory response and hypoxic pulmonary vasoconstriction)[18,19] start developing, thereby imposing an increased workload on the cardiovascular and respiratory systems. The effects of hypobaric hypoxia are very mild up to 1200 m–1500 m, may become perceptible at around 1800 m, and start to affect an increasing percentage of the population above 2500–3000 m. Most altitude clinics in the Alps are located between 1200 m and 2500 m, where hypoxia does not excessively stress the body as the reduction of pO_2 is between 15% and 20%. Thus, acute mountain sickness is an unlikely risk for most asthma patients residing at sea level, who are treated at European altitude clinics. Very seldom therapy-resistant hypertension develops, leading to a return to sea level.

Key messages

- There are large interindividual differences in susceptibility to effects of hypobaric hypoxia.
- Most European altitude clinics are located in the Alps between 1200 m and 2500 m, where hypoxia does not excessively stress the body.

4 | EFFECTS OF ALTITUDE ON LUNG PHYSIOLOGY, ADAPTATION, AND IMMUNE RESPONSE

Several physical characteristics change with increasing altitude, such as barometric pressure and inspiratory oxygen pressure, air density, relative temperature, and humidity. (Figure 1) These changes induce several physiological and immunological adaptation responses.[20–22] Rapid onset physiological adaptive responses such as hyperventilation and increased heart rate in the acclimatization process arriving at moderate/high altitude aim at increasing the efficiency of oxygen uptake, transport, and delivery to cells in various ways.[23] With longer-term altitude exposure, there is an increase in hemoglobin concentration, mitochondrial oxidative capacity, and capillary density which improve physical fitness and performance.[24–27] Altitude training is frequently used by competitive athletes to improve sea level performance. The reduced air density at altitude improves airflow and reduces airway resistance, which makes exhalation easier and reduces dynamic hyperinflation.[26,28] This may also be a useful setting for more easily engaging asthmatic patients in various physical activities at moderate altitude. This contrasts with what happens at sea level, where the higher air density may hinder effective physical training for patients. However, there are some limits to the benefits of altitude on physical activity. Above 2000 m, the reduction of maximal oxygen consumption negatively affects performance. At high altitude (i.e., >3000 m), where the ventilatory response, the cold and dry weather are more pronounced, the hyperventilation of cold air, especially during exercise, has a potential for airways dehydration, which can subsequently trigger bronchospasm.

Immunological adaptation responses may result in either immune stimulation or immune suppression. Studies at high altitude show varying degrees of immune system modulation. Healthy individuals demonstrate an increase of total white blood cells accompanied by a decrease of T helper cells ($CD4^+$ T cells), whereas cytotoxic memory T cells (CD8+T cells) remain unchanged (Figure 2).[29,30] The decrease of CD4+T cells is mainly due to a decrease of type 1 T helper (Th1) cells. $CD4^+$ T cells and $CD8^+$T cells are more activated, and they respond more rapidly after recall antigen and mitogen stimulation in vitro. B cells and natural killer (NK) cells increase in healthy individuals ascending to high altitude.[29,30] Studies in animals support the observed decreases in Th1 cells and additionally demonstrate the migration of Th2 cells from the organs and periphery to the bone marrow.[31–33]

The master regulator of hypoxic conditions, which is not only present in response to altitude but also locally in the tissue, is the hypoxia-inducible factor 1a (HIF-1α). HIF-1α is expressed in a wide array of immune and tissue-resident cells including eosinophils, dendritic cells, macrophages, neutrophils, T cells, B cells, innate lymphoid cells (ILCs), and NK cells, as well as epithelial and endothelial cells.[34] (Figure 2) Hypoxia influences chemokine responses, which can be a mechanism of a selective recruitment of the T-cell subsets and also other cells to the specific tissues, such as lungs. HIF-1α promotes transcription of FOXP3 and generation of Treg cells, which may lead to the resolution of inflammation.[35,36] Hypoxia also alters function of the antigen-presenting cells, especially macrophages and their capacity to stimulate T cells.[37] Finally, HIF-1a is a central player in maintaining gut-lung axis of microbiome homeostasis, which has been repeatedly shown to impact on asthma and allergy prevalence, phenotype, and response to treatment.[38,39]

At moderate altitudes, the beneficial physiological and immunomodulatory effects prevail[21,40] due to the subtle, yet systematic, changes in gene expression, protein translation, cell signaling followed by erythropoietic, metabolic, immunological, and other physiological adaptation responses.[20,41,42]

Key messages

- Reduced barometric pressure and inspiratory pressure, reduced air density, relative low temperature and humidity, and increased UV radiation at moderate altitude induce several physiological and immunological adaptation responses.
- The master regulator of hypoxic physiologic responses is the hypoxia-inducible factor 1a (HIF-1a) which is expressed in a wide array of immune and tissue-resident cells.
- Studies at high altitude show varying degrees of hypoxia-related immune modulation which likely already start at moderate altitude.

TABLE 1 Summary of observed effects and open questions

Observed effects	Open questions
Observational studies of AACT show improvement in • lung function (FEV1%predicted)[7,167–170] • asthma control (ACQ)[10,138,142,143] • quality of life (AQLQ)[10,138,142,143] • sinonasal symptoms (SNOT)[10,143,150] • exercise tolerance (6MWD, ISWT)[10,138,143,168] • OCS requirements and SABA overuse[10,141–143,147] • Clinical improvement after AACT is irrespective of asthma phenotype[9–11] • AACT results in sustained long-term (12 months) asthma control[142,143] • AACT compared to treatment at sea level shows a larger improvement in asthma control and OCS dependency[143] • Immunomodulatory effects are shown during AACT in patients with different phenotypes of asthma[11] • Focusing on treatable traits in patients with severe asthma leads to significant improvements in quality of life	• The contribution of the altitude-related, climate-related, environmental-related, and treatment-related factors in the observed clinical and immunological effects • The mechanisms underlying the reduction in inflammation • The immune regulatory mechanisms of the altitude climate • The added value of AACT to multidisciplinary treatment at sea level • The position of AACT in the guidelines for severe asthma treatment • The minimal and optimal duration of treatment at altitude to achieve and retain effect • The phenotype and health status profile of patients that benefit the most • Comparative efficacy between elderly and non-elderly adults • Differences in response to AACT directly after treatment and up to several months after AACT • Cost effectiveness

Abbreviations: AACT: alpine altitude climate treatment, 6MWD: 6-min walking distance, ISWT: incremental shuttle walk test, m: meters above sea level, and OCS: oral corticosteroids

5 | UV RADIATION AT MODERATE ALTITUDE

With every 1000 meters increase in altitude, the amount of ultraviolet radiation (UVR) increases by 10% to 12%.[43] Several other factors modulate the amount of UVR, such as the height of the sun in the sky, latitude, clouds, thickness of the ozone layer, and ground reflection.[43] Irradiation of the skin with UVR, both UVA and UVB, leads to cutaneous synthesis of vitaminD_3. The prevalence of vitamin D deficiency is currently relatively high in Europe.[44] In addition, vitamin D deficiency may contribute to asthma severity.[45] An increase in serum vitamin D levels was observed in 73 patients with ankylosing spondylitis who stayed at moderate altitude for 3 weeks during spring.[46] It is possible that increased UVR exposure at moderate altitude may improve serum vitamin D levels in asthmatic patients, but this should be tested in future, well-controlled, studies.[47] UVR and vitamin D share common pathways of innate immune activation primarily via antimicrobial peptide production, stimulation of Toll-like receptors, and increase of pro-inflammatory cytokine production. The same synergic action leads to adaptive immune suppression through regulation of actions of lymphocytes, mast cells, and antigen-presenting cells to dampen excessive inflammatory responses.[48]

6 | ENVIRONMENTAL CHARACTERISTICS OF THE ALPINE CLIMATE

Different altitudes harbor different climatic, flora, and fauna conditions. Environmental characteristics vary in different climate zones, because of factors like climate change and air pollution, but also regarding exposure to terpenes and aeroallergens.[49] (Figure 1) Forest trees emit a large variety of biogenic volatile organic compounds, complex mixtures containing up to 200 different compounds. In forested areas, substantial terpene emission levels are released to the atmosphere where they exert biological activities and may contribute toward reducing respiratory inflammatory processes.[50]

Moderate altitude also seems to be associated with a lower aeroallergen burden. Various studies have shown that, especially in uncontrolled asthma, environmental exposure to aeroallergens is important in disease exacerbations and symptoms.[51–53] Sensitization to HDM has been associated with asthma in several studies. Treatments targeting environmental exposure have been investigated, but conclusive evidence from randomized studies is scarce. The results of single-strategy avoidance, for example HDM allergens, demonstrated a lower efficacy than expected.[54,55] The "multiple hit" hypothesis for the origins of severe airway disease suggests that identification and removal of multiple inflammatory stimuli may delay progression of the underlying airway disease.[56] The home environment including exposure to allergens, molds, air pollution, passive smoking, or stress can be regarded as continuous multiple-hit exposure. Personalized avoidance of the most important allergens showed better results than single intervention strategies in patients with severe disease.[57–59] The integrated reduction of exposure during AACT may contribute toward reducing airways inflammation.

6.1 | House dust mites

HDM allergens have been isolated from mite feces and are highly prevalent in dust reservoirs in the domestic environment, including bedding, carpets, sofas, soft toys, and clothing.[60,61] Differences in the geographic distributions of HDM species are most likely influenced by abiotic factors such as humidity, temperature, way of living

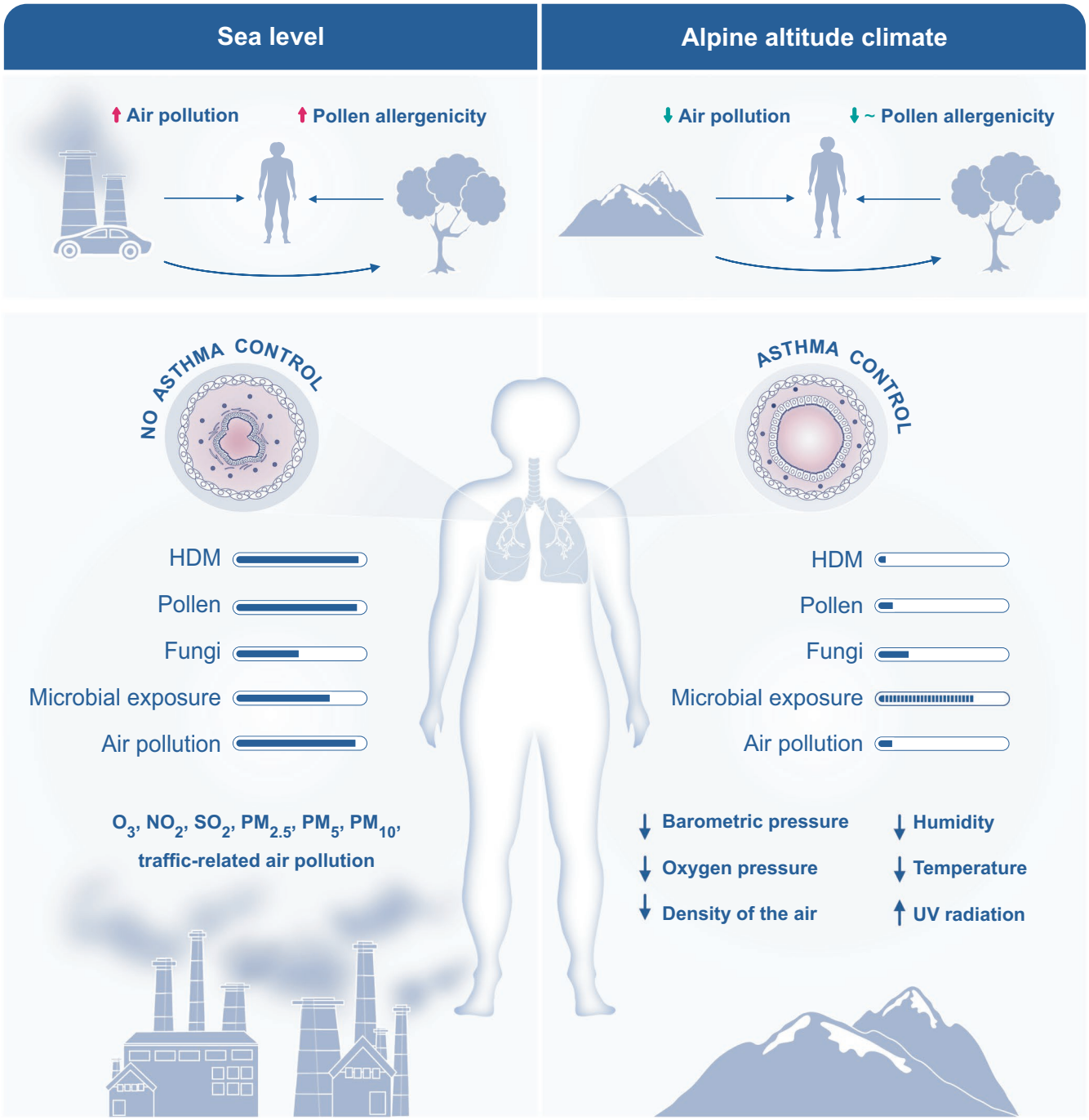

FIGURE 1 Overview of physical and environmental characteristics of the alpine altitude climate compared to sea level. Several physical characteristics change with increasing altitude, such as barometric pressure and inspiratory oxygen pressure, air density, relative temperature, and humidity. Environmental characteristics vary in different climate zones, because of factors like air pollution and climate change. The environmental characteristics of the alpine climate include reduced aeroallergen burden regarding HDM, pollen, fungi, air pollution, and different microbial exposure. HDM, house dust mite

including furniture, carpets, and available food.[62] There are several sampling techniques to assess residential exposure to HDM, collecting either airborne dust or settled dust. Vacuum cleaning a square meter of settled dust from a carpet or mattress is the most commonly used method. Earlier studies identified and counted extracted mites from the dust samples with a microscope. Currently, measurement of allergenic content of dust has replaced mite identification and counting, because it is more amenable to standardization, less time-consuming and more closely related to clinical impact.

Generally, HDM counts and HDM allergen content are lower when altitude increases.[8,63–70] Table S3 summarizes studies comparing HDM counts and HDM allergen content at different altitudes. In tropical or sub-tropical areas, this decrease was not observed.[69,71–73] Mites require a high ambient air humidity to prevent excessive water

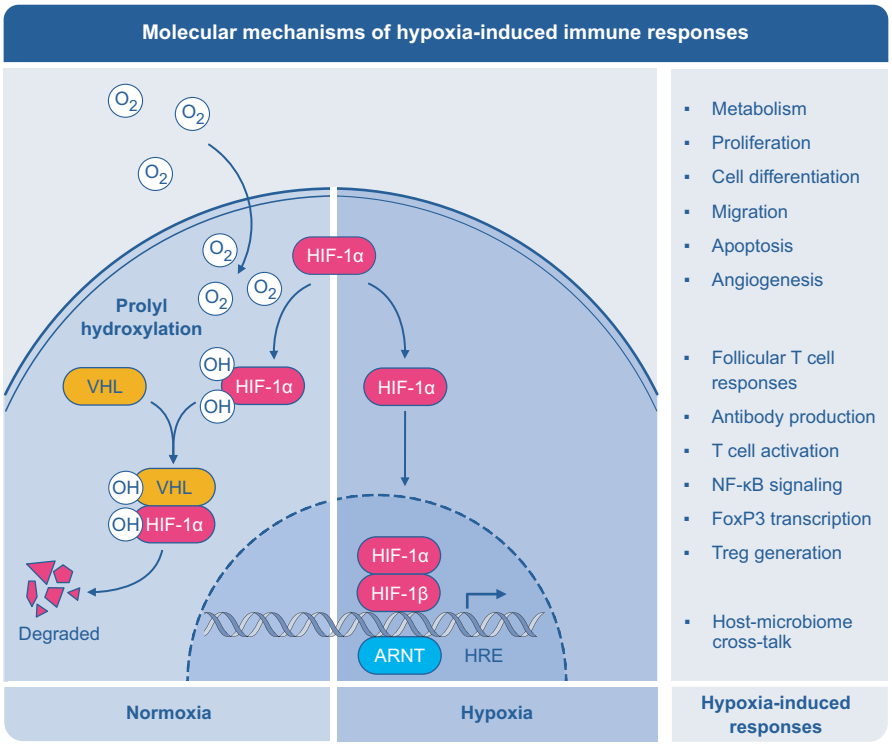

FIGURE 2 Central role of hypoxia-inducible factor 1a (HIF-1α) in hypoxia-induced immune responses. HIF-1 is expressed in a wide array of immune and tissue-resident cells including eosinophils, dendritic cells, macrophages, neutrophils, T cells, B cells, ILCs, NK cells, epithelium, and endothelium. In normoxia, HIF-1α is hydroxylated, which facilitates HIFα binding to the von Hippel-Lindau (VHL) E3 ubiquitin ligase complex, leading to fast ubiquitination and proteasomal degradation. During hypoxia, hydroxylation is inhibited by the absence of oxygen, which leads to HIFα stabilization and activation. Once stabilized, HIF-1α subunit is translocated to the nucleus, where it forms a complex with HIF-1β and other coactivators, and binds to the consensus hypoxia response elements (HRE) within target genes, involved in a large type of processes, as cellular metabolism, proliferation, differentiation, cell survival, migration, apoptosis, and angiogenesis in cell-specific manner. ARNT, arylhydrocarbon receptor nuclear translocator

loss. At lower temperatures, development and reproduction of HDM need more time compared to higher temperatures, which may contribute to the lower HDM concentrations at moderate non-tropical altitude.[74] However, a recent Austrian study showed similar HDM-allergen Der p 1 levels at different altitudes, while Der f 1 concentrations were significantly lower at high altitude.[75] In this study, mite-allergen content in areas below 1500 m was very low, corresponding to a mean Der p 1 concentration less than 0.5 μg/g dust and Der f 1 <2 μg/g dust, which might explain the lack of difference with areas in higher altitudes. The authors speculate that current building construction including better insulation, heating, and glazing, resulting in similar indoor temperature across different altitudes could partly account for their results.

6.2 | Pollen

Grass and tree pollen counts are lower at altitude than at sea level.[76–78] There is a general delay in flowering with increasing altitude, resulting in a shorter pollen season.[79] Personal thresholds for clinically relevant pollen concentrations in the air may vary among patients, but are relevant to estimate the impact of reduced exposure. There is scarce data on pollen measurement or pollen allergenicity at various altitudes directly connected to allergic rhinitis, conjunctivitis, or asthma. A recent study in pollen allergic patients showed that allergic symptoms decreased significantly within hours after arriving at an altitude of 2565 m and remained low several days after returning to 490 m.[78]

6.3 | Fungi

Fungi such as *Aspergillus* and *Alternaria* are less often recognized as a cause of respiratory allergy compared to pollen.[80] However, exposure to fungal spores (*Penicillium*, *Aspergillus*, *Cladosporium*, and *Alternaria* species) frequently induces respiratory allergy symptoms including acute respiratory failure or exacerbates current asthma symptoms in children and adults.[81–83]

Little is known about the presence or allergenicity of fungal spores at moderate altitude. There is variability in the amount of *Cladosporium* and *Alternaria alternata* spores in outdoor air, depending on geographical location, relative humidity, and temperature.[84–86] Furthermore, high and low potency spores have been recorded, with large intra-seasonal fluctuations, related to source area and species

diversity.[87] The highest *Alternaria* spore allergenicity was observed in the season with the warmest temperatures, driest conditions, and the highest levels of air pollution (ozone, PM10, and sulfur dioxide).[88] Most likely, there are less fungal spores at moderate altitude because of the low relative humidity and temperature.[81]

6.4 | Air pollution

The existing European altitude clinics are located in areas with low outdoor air pollution. Outdoor air pollution is a mixture of gaseous pollutants (ozone, nitrogen dioxide, and sulfur dioxide), particulate matter with different sizes (PM2.5, PM5, PM10), and traffic-related air pollution (TRAP). Urbanization, industrialization, and TRAP determine the level of air pollution, together with weather and landscape influences, resulting in less air pollution at alpine altitude villages.[89] However, in certain alpine settlements air pollution due to traffic and heating, remains a point of concern. Studies have linked asthma exacerbations with exposure to TRAP, identifying specific pollutants that can induce airway inflammation and airway hyperresponsiveness.[53,90] Four main mechanisms have been postulated to explain the link between air pollution and asthma exacerbations: oxidative stress and damage, inflammatory-immune responses, airway remodeling, and enhancement of respiratory sensitization to aeroallergens.[53,91] The exact mechanisms by which pollutants induce these effects are not completely clear.

Apart from the direct effect of air pollution on human health, there is an indirect effect through the interaction with the allergenicity of pollen and fungal spores. Air pollution can alter the immune-stimulatory potential of pollen: either by making the pollen more allergenic or by aggravating allergic symptoms in already sensitized individuals.[92] Fungal spores are also impacted by environmental changes.[93]

6.5 | Microbial exposure

Several studies have demonstrated differences in the airway, nasal and gut microbiome between asthmatic patients and healthy subjects.[94–96] The different microbial communities (environmental, gut, airways, nose) are able to interact with each other.[97] Furthermore, microbial communities are able to regulate immune function and may impact asthma development and severity.[98] During AACT a significant increase in microbial diversity on the skin of children with difficult to treat atopic dermatitis and asthma was observed, whereas such alpha diversity did not change in a control group treated at sea level.[99] This suggests that microbiome composition may be influenced by the alpine environment or by the moderate altitude. However, it is unclear how much time in a different environment would be needed to realize a sustained change in microbiome. Whether AACT-induced microbiome changes could play a role in the observed improvements in inflammation in asthma patients remains to be sorted out in future studies.

Key message

- The environmental characteristics of the alpine climate include a reduced aeroallergen burden regarding HDM, pollen, fungi but also air pollution and different microbial exposure.

7 | EFFECTS OF ENVIRONMENTAL CHARACTERISTICS OF THE ALPINE CLIMATE ON IMMUNE RESPONSE IN ASTHMA

Observational studies have shown that periods of lower exposure to allergens during AACT may result in significant decreases in antigen-induced basophil histamine release, total IgE, and specific IgE of asthmatic patients. (Table 2 Immunological outcomes, Figure 3) After allergen re-exposure, this effect is reversed, as specific antigen-induced basophil histamine release and serum IgE increase again.[65,100,101] Similarly, blood and sputum eosinophils significantly decreased after AACT (Tables 2, 3B, and 4B). Serum eosinophil cationic protein (ECP) and eosinophil protein X (EPX) and urinary EPX significantly decreased after AACT and increased again after return to the home environment.[102–107] Cysteinyl leukotrienes (Cys-LTs) mean level, 8-Isoprostane level, and nitrites were significantly reduced by AACT in both induced sputum and exhaled breath condensate[103,108,109] An earlier study demonstrated a decrease in monocyte activation and in the frequency of CRTH2+ (Th2) cells in peripheral blood of severe asthmatic patients who were treated with AACT at 1600 meters for at least 3 weeks.[9] Increased purinergic G protein-coupled receptor (P2Y1) activity was reported at high altitude together with down-regulation of the P2Y12 pathway through increased vasodilator-stimulated phospho-protein (VASP) phosphorylation.[110] This modification might be of special interest for the non-T2 asthma endotype, especially for the sub-endotype with a strong signal of the inflammasome pathway activation.[111] Furthermore, some studies have shown that there may be a differential impact of altitude on immunological outcomes in different phenotypes of asthma. In patients with eosinophilic allergic asthma, moderate altitude exposure decreased total and activated blood eosinophils, type 2 innate lymphoid cells (ILC2), as well as $CRTH2^+$ CD4 and CD8 T cells. These effects were either absent or less evident in patients with eosinophilic non-allergic asthma, non-eosinophilic non-allergic asthma, and healthy controls. Interestingly, the frequency of $CRTH2^+$ Treg cells, of more inflammatory phenotype than $CRTH2^-$ Tregs, decreased in all asthma phenotypes, but not in controls.[11] Reduction of serum IL-13 has been reported after

TABLE 2 Immunological results of AACT: total IgE, specific IgE, sputum eosinophils

Reference	Study population (*n*)	Treatment duration	Asthma characteristics	Study measurements	Outcome, observed change
Vervloet D et al (1982)[a]	*N* = 42	9 months	Children with positive intradermal skin tests to dermatophagoides pteronyssinus and domestic dust	T0 Sep – T3 June	Total IgE geometric mean 1047 U/ml to 603 U/ml ($p < .001$) Specific IgE to dermatophagoides, to domestic dust, and to grass pollen dropped during the stay ($p < .001$). IgG mg/100 ml mean (SEM) 1521 (105) to 1482 (61), IgA mean (SEM) 232 (21) to 251 (23) and IgM mean (SEM) 188 (19) to 174 (19)
Piacentini G et al (1993)[a]	*N* = 20	3 months	Children with allergic asthma	T0 Sep – T1 Oct – T2 Dec – T3 Jan	sIgE kU/L to *Dpt* mean ± SEM T0:58.485 ± 7.059 kU/L T1:45.067 ± 5.711 T2:48.722 ± 8.093 kU/L T3: 62.629 ± 8.055 kU/L
Boner AL et al (1993) CEA	*N* = 12	9 months	Asthmatic atopic children (sensitized to HDM)	T3 June – T0 Sep – T1 Dec	Total IgE IU/ml mean ± SEM 477.28 ± 1375 to 680.65 ± 151.4 to 472.56 ± 99.26 Dpt IgE IU/ml mean ± SEM 48.27 ± 8.97 to 57.46 ± 11.64 to 48.28 ± 10.59 Df IgE IU/ml mean ± SEM T3 21.79 ± 4.58 to 33.35 ± 7.71 to 25.2 ± 5.57
Peroni DG et al (1994)	*N* = 22	9 months	Asthmatic children allergic to HDM	Oct – Jan – June – Sep	Total IgE IU/ml mean (SD) 886 (800), 585 (434), 463 (350), 877 (701) HDM specific IgE IU/ml mean ± SD 35 ± 6.6, 332. ± 6.8, ±29.6 ± 6.7, 25.6 ± 8.5
Christie PE et al (1995)	*N* = 14	At least 1 month	Adolescents with mild atopic asthma and HDM sensitization	(1) Baseline – 3 weeks AACT (2) Baseline – 2 weeks sea level – return to AACT	Total IgE kU/L Mean (SEM) AACT 1400 (517) to 1627 (799) Sea level 1794 (631) to 2073 (796)
van Velzen E et al (1996)	*N* = 16	1 month	Children with allergic asthma	Before–after AACT	Total IgE kU/L mean (SE) 961.61(512.82) to 957.19(475.66)
Piacentini GL et al (2011)	*N* = 14	6 months	Children with mild-to-moderate asthma, sensitized to HDM or grass	T0 Sep – T1 Dec – T2 Jan – T3 Mar	Specific IgE kU/L: T0 113.89 to T1 99.52 kU/L to T3 92.83 kU/L Specific IgG4: No significant variations were found IgG4/IgE mg/kU: T0 59.6 to T1 76.75 to T3 86.84
Rijssenbeek-Nouwens LH et al (2012)	*N* = 137	12 weeks	Adults with severe refractory asthma, HDM sensitized (*n* = 68), non-HDM-sensitized (*n* = 69)	Before– after AACT	Total IgE kU/L mean (SD): 376 (7–5000) to 245 (6–4682) ($p = .003$) *N* = 43 Total IgE kU/L mean (SD): 94 (5–1781) to 58 (5–1961) ($p = .039$) *N* = 36
Basler L et al (2020)	RCT AACT *n* = 24 adults Control group at low altitude *n* = 25 adults	3 weeks FU: 3 m	Adults with asthma (ACQ >0.75)	Before–after AACT	Total IgE baseline only AACT 350 ± 445 Control group 267 ± 365 sIgE mite kUA/L AACT 23.2 (25) to 19 (18) mean change (95% CI) −4.2 (−11.3 to 2.9) Control group 37.7 (59.2) to 27.5 (53) mean change (95% CI)−10.2 (−18.9 to −1.4) sIgE pollen kUA/L AACT 14.9 (25.2) to 12.6 (22.1) mean change (95% CI) −2.31 (−5.4 to 0.79)kU/L Control group 21.5 (30.9) to 16.5 (27.8) mean change (95% CI) −4.95 (−9.69 to −0.21)

(Continues)

TABLE 2 (Continued)

Reference	Study population (*n*)	Treatment duration	Asthma characteristics	Study measurements	Outcome, observed change
Piacentini G et al[a] (1993)	*N* = 20	3 months	Children with allergic asthma	T0 Sep – T1 Oct – T2 Dec – T3 Jan	Spontaneous histamine release mean ± SEM T0:6.08% ± 0.51% T1:6.77% ± 0.54% T2:6.2% ± 0.56% T3:5.03% ± 0.57% antigen-induced histamine release mean ± SEM T0: 34.2% ± 4.7% T1:22.76% ± 4.0% T2:22.9% ± 3.2% T3:33.3% ± 5.8%
Boner AL et al (1993)[a] Allergy	*N* = 23	9 months (Sep – June)	Moderately severe HDM allergic asthmatic children	T0 Sep – T2 Mar – T3 June	Sputum eosinophils % mean ± SEM T0 14.4.3 ± 3.32 to T2 7.43 ± 2.11 to T3 5.97 ± 1.79
Piacentini GL et al (1996)[a]	*N* = 16	3 months	Asthmatic children allergic to HDM	T0 Sep – T1 Dec	Sputum eosinophils % median (Q1, Q3) of 14.02 (3.34, 28.24) to 2.08 (0, 7.4) ($p < .01$)
Piacentini GL et al (1998)[a]	*N* = 10	3 months	Children with a history of bronchial asthma and positive SPT to HDM	T0 Sep – T1 Dec – T2 Jan	Sputum eosinophils % T0 1(0;5.25) to T1 0(0,1.5) ($p < .05$) to T2 1.5 (0;3) (NS) Airway epithelial cells (%) in sputum T0: 3.50 (0.50;6.98) T1 0 (0;0.5) ($p = .012$) T2 3.9(1.50;6) ($p = .027$)
Grootendorst DC et al (2001)	AACT: *N* = 10 Sea level: *N* = 8	10 weeks FU:6w	Atopic adolescents sensitized for HDM	(1) Baseline – 4 w AACT – 8 w AACT – 6 w FU (2) Control group: 0 w 8 w 16 w	Sputum eosinophils % AACT 3.1 (0–5.6), 2.2 (0–8.6), 1.7 (0–9.4), 3.0 (0–6.0) Control group 3.0 (0–10.8), 1.6 (0–2.2), 2.6 (0–6.4)
Peroni DG et al (2001)[a]	*N* = 15	3 months	HDM sensitized children with asthma (6–14 years of age)	T0 Sep – T1 Dec – T2 Jan	Sputum eosinophils % T0: 9.0% ± 2.9% T1: 3.2% ± 0.9% T2: 5.9% ± 1.6%
Bodini A et al (2004)[a]	*N* = 12	3 months	Asthmatic children sensitized to HDM	T0 Sep – T1 Dec	Sputum eosinophils % T0 8.5 ± 1.1% to T1 3.5 ± 0.4% ($p = .011$)
Kulkarni N et al (2018)[a]	*N* = 62	3 weeks	Children with mild-to-moderate asthma (77% GINA 1 and 2)	Before–after	Sputum eosinophils % 3 (0–52) to 1 (0–30) $p = .001$

Abbreviations: FU, follow-up; HDM, house dust mite.

[a]Children were admitted to the clinics in Briançon and Misurina for an entire school year. Admission is usually in September (T0 the period of allergen avoidance starts), children go home for a 2 or 3 weeks Christmas holiday (T1 re-exposure to allergens starts) and return to the clinic from January (T2 allergen avoidance continues) until June (T3 end of school year).

3 weeks of AACT, in adults and in children.[11,12] In children with allergic asthma, a decrease in serum IL-10 has been observed, whereas in adult patients with eosinophilic asthma serum IL-5 also decreased.[11,12] This suggests that the type 2 inflammation, represented by ILC2 and Th2 cells and eosinophils, is reduced at moderate altitude in patients with allergic asthma. In addition, altitude is restoring the suppressive and regulatory phenotype of Tregs in all asthma phenotypes.[11] Reduced macrophage phagocytic activity and reduced eosinophil recruitment to the airways after AACT have also recently been proposed as a possible mechanism contributing to clinical improvement in children with mild asthma.[112]

Key messages

- There may be a differential beneficial impact of altitude on immunological outcomes in different phenotypes of asthma.
- Type 2 inflammation is reduced in patients with allergic asthma
- Altitude is restoring the suppressive and regulatory phenotype of Tregs in all asthma phenotypes
- Lower exposure to allergens results in significant decreases in antigen-induced basophil histamine release, total IgE, and specific IgE.

8 | MULTIDISCIPLINARY PULMONARY REHABILITATION FOR SEVERE ASTHMA

The international guidelines recommend a stepwise multidisciplinary approach for asthma management with the aim to achieve optimal disease control.[1,2] Several multidisciplinary treatment programs have been described, but were mostly observational without a control group. These programs reported significant improvement in asthma control, quality of life, exercise capacity, and emotional well-being.[113–120] A framework for systematic patient assessment is provided by the concept of treatable traits, divided into pulmonary, extrapulmonary, and behavioral/lifestyle factors.[3] Avoidance of environmental triggers, assessment of treatable traits, treatment of modifiable risk factors and comorbidities, non-pharmacological strategies, identifying possible obstacles to adherence, checking inhaler technique, education, and skills training have been proposed to manage uncontrolled and severe asthma.[121–124] Currently available European AACT programs follow such asthma management strategy by combining the physical characteristics of altitude with the avoidance of environmental triggers in the alpine climate and a personalized multidisciplinary pulmonary rehabilitation approach. Most AACT programs contain an extensive patient assessment, psychological and behavioral interventions, personalized exercise programs, extensive patient education, and personalized action plans for use after the end of treatment (Table S6). The content of these programs is not unique and may be used in pulmonary rehabilitation programs anywhere. For some patients, AACT is not suitable because of severe home sickness or because of personal reasons that prevent them from being away from home for a longer period of time. During AACT, regular pharmacological treatment according to treatment guidelines continues. There is no indication that its efficacy would be different at moderate altitudes, but there are no studies comparing the efficacy of bronchodilators or inhaled corticosteroids with different types of inhalers at altitude. However, the specific effectiveness of AACT may lie in the observed rapid decrease in inflammation, either because of fewer environmental triggers in the alpine climate or physical altitude climate factors and their immunomodulatory effects, or because of other yet unknown mechanisms. Medical treatment is optimized during AACT according to the most recent treatment standards. Most patients improve their asthma control, resulting in less need for SABA and optimized ICS use during AACT. Because patients improve their asthma control, there are more possibilities for exercise compared to the home environment. Routine physical exercise results in improved aerobic fitness, improved lung function parameters, reduced exercise-induced bronchoconstriction, and a further decrease in asthma symptoms. Improved asthma control supports the relevance of behavioral, environmental, and stress factors for future disease control and endorses self-management, even after AACT.

Psychological and behavioral interventions are major components of most pulmonary alpine climate treatment programs and are aimed at reducing psychological stress, obtaining appropriate adherence to treatment, as well as helping patients to cope with a chronic disease and deal with functional limitations in daily life.[125] Recent studies have supported the link between asthma (severity, control), psychological aspects (subjective perception, coping style), and mental health (anxiety, depression).[126–128] Psychological comorbidities are frequently present in patients with difficult to control disease.[129,130] Furthermore, perceived chronic or toxic stress at several levels has been associated with asthma incidence and asthma morbidity.[131–133] Reducing psychological stress may also affect neuro-immune mediators resulting in reduced airway inflammation and asthma exacerbations.[134] During AACT, patients avoid those psychosocial stress factors that are continually present in their usual everyday life by being away from home, work environment, or school, and receive psychological assessment and treatment of stress-related factors. This may lower the threshold to accept psychological help for patients, because psychological intervention is a standard component of the treatment program.

Asthma requires self-management over a long period of time, and low or inadequate health literacy has been associated with poor longitudinal asthma outcomes, increased emergency department utilization, increased symptoms, and significant adverse outcomes in adults with asthma.[135] Asthma education centered around a written action plan includes individualized self-management instructions to help maintain disease control, how to respond to exacerbations and when to seek medical help, leading to improved disease control and is described in treatment guidelines.[1,136] After AACT, personal action plans should be integrated into the patient's own environment and healthcare setting.

They also guarantee continuity in asthma care when the patient returns to the referring physician. The use of Internet-based self-management applications in the home situation contributes toward sustaining improved asthma control after AACT.[137]

Key messages

- Most AACT programs contain an extensive patient assessment, psychological and behavioral interventions, personalized exercise programs, extensive patient education, and personalized action plans for use after the end of treatment.
- The specific effectiveness of AACT may lie in the observed rapid decrease in inflammation, either because of fewer environmental triggers in the alpine climate or the physical altitude climate factors and its immunomodulatory effects or other yet unknown mechanisms.

9 | CLINICAL IMPACT OF ALPINE ALTITUDE CLIMATE TREATMENT IN ADULTS

Several European observational studies describe AACT in adults with severe or uncontrolled asthma. (Figure 4). There is great heterogeneity in inclusion criteria, resulting in different study populations regarding asthma phenotypes, but also baseline therapy, treatment duration, altitude, and outcome measures (Table S4). Quality assessment demonstrated sufficient quality for most studies while taking the non-randomized observational study design into account (Table S5). Because the effectiveness of AACT has not been assessed in a randomized controlled trial, there is no consensus on its optimal duration or cost-effectiveness. One randomized controlled trial outside Europe (Kyrgyzstan) compared rehabilitation at 700 m with 3100 m for patients with uncontrolled asthma and found no differences between the groups.[138,139] The effects of AACT on various outcomes such as asthma control and quality of life, exacerbation rate and hospitalizations, oral corticosteroid (OCS) reduction, lung function parameters, upper airways symptoms, and exercise tolerance are described in Table 3A–F. Up to 12 months after the end of AACT, observational studies demonstrate increased exercise tolerance, increased asthma control and asthma-related quality of life, decreased use of oral corticosteroids, decreased number of outpatient consultations, decreased number and duration of hospital admissions, and decreased numbers of exacerbations.[140–143]

9.1 | Impact on Asthma control and quality of life

The degree of asthma control (ACQ—Asthma Control Questionnaire) and quality of life (AQLQ – Asthma Quality of Life Questionnaire) are often used as outcome measures (Table 3A), with a validated

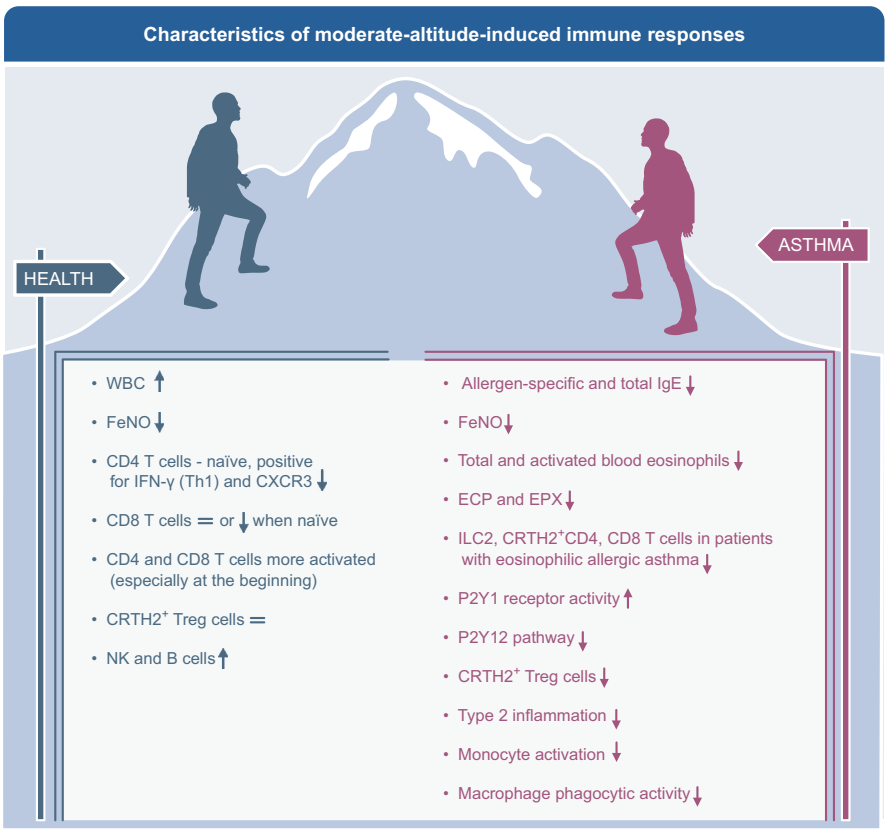

FIGURE 3 Characteristics of moderate altitude-induced immunomodulatory responses in healthy persons and asthma patients resulting in decreased inflammation. The moderate altitude environment leads to several immunomodulatory responses including a reduction of type 2 inflammation and restoring of the suppressive and regulatory phenotype of Tregs in all asthma phenotypes. Lower exposure to allergens leads to decreased antigen-induced basophil histamine release, total IgE, and specific IgE. WBC, White blood cells; CRTH2, cytotoxic regulatory T helper 2 cells; NK, natural killer; ILC, innate lymphoid cell; ECP, eosinophil cationic protein; EPX, eosinophil protein X; CXCR3, C-X-C Motif Chemokine Receptor 3; FeNO, fraction of exhaled nitric oxide

minimal clinical important difference (MCID) in score of 0.5.[144,145] In an observational study, Rijssenbeek examined (n = 137) severe asthma patients and observed statistically significant and clinically relevant improvements in ACQ and AQLQ after 12 weeks of ACT in both allergic (n = 92) and non-allergic (n = 45) patients, while background asthma medication was being tapered including OCS.[10] Fieten showed statistically significant and clinically relevant sustained improvements in ACQ and AQLQ at 12 months follow-up compared to baseline in a follow-up study from the same cohort.[142] In a prospective comparative study, de Nijs showed that after the 12-week treatment period, the group of patients treated with AACT (n = 93) had a significantly greater improvement in ACQ score and in AQLQ score relative to patients treated at sea level (n = 45).[143] After a year of follow-up, the AACT group had a significantly greater improvement in ACQ score and in AQLQ score compared to the sea level group. These studies were conducted more than 5 years apart, but show remarkably similar results in a relatively large well-defined patient group with severe asthma, supporting the direction of effect.[10,142,143] Furthermore, correlations between improvement in asthma control and changes in immunoinflammatory parameters namely eosinophils, T-cell subsets, and ILC2s have been observed.[9,11]

9.2 | Impact on FeNO

A significant reduction of FeNO during AACT has been reported in several studies, starting from the first day of arrival at altitude (Table 3B). One study differentiated between asthma phenotypes and observed significant reductions in the eosinophilic and non-eosinophilic allergic asthma phenotype, but not in the non-eosinophilic non-allergic asthma phenotype.[11] Another study reported decreased FeNO in patients with allergic and non-allergic, moderate and severe asthma, after 3-week treatment at an alpine clinic (1560 m).[9] A report involving 68 HDM-sensitized and 69 non-HDM-sensitized asthmatic patients only found a reduction in FeNO in the sensitized patients, after 12-week treatment at altitude.[10] Finally, a randomized, parallel group trial showed a greater reduction in FeNO in atopic and non-atopic asthma patients (92% atopic) who were treated for 3 weeks at high altitude (3100 m) than in those treated at low altitude (700 m), with a median between group difference (95% CI) of −18 ppb (−36 to 0).[139]

9.3 | Impact on exacerbation rate and hospitalizations

Exacerbations are a prominent feature of both poorly controlled and severe asthma. Several studies describe a decrease in number and duration of hospital admissions and less frequent exacerbations up to 1 year after AACT (Table 3C).[141–143]

9.4 | Impact on oral corticosteroid (OCS) use

A reduction in OCS use is of great clinical relevance because of the complications of its long-term use.[146] Several studies observed a reduction in OCS use after AACT treatment, either complete discontinuation of maintenance OCS use or a significant decrease in the mean daily dose (Table 3C). [10,141,147] Comparing 12 months before with 12 months after AACT, there was no change in need for or amount of maintenance oral corticosteroids.[142] However compared with patients treated at sea level, there were still 46% fewer OCS-dependent patients in the AACT-treated group, with a mean dose reduction from 18.3 mg to 7.5 mg per day (p < .001) after 12 months follow-up.[143]

9.5 | Impact on lung function outcomes

The minimal clinically important difference (MCID) in FEV_1 has not been validated for asthma, but improvements of 100–200 ml in FEV_1 are likely to be clinically relevant.[148] In a systematic review and meta-analysis, Vinnikov included 21 studies published between 1973 and 2013, and analyzed changes in FEV_1, FEV_1/FVC ratio or peak expiratory flow rate (PEF) as outcomes (Table 3D).[7] Asthma severity varied from mild to severe, altitude ranged from 1560 m to >4000 m, and duration of treatment ranged from 2 to 12 weeks. Despite the heterogeneity observed across studies, 93% of the studies reported lung function improvement with an overall pooled standardized mean difference (SMD) of 0.53 (95% CI 0.43–0.62), with a 0.50 change in SMD having been defined as a meaningful clinical difference. Efficacy was demonstrated for adults but not clearly for children, and treatment for >4 weeks was associated with a marginally greater effect size than shorter treatment.[7]

9.6 | Impact on upper airways symptoms

The close pathophysiological relationship between upper and lower airways results in associations between asthma and upper airway diseases such as allergic rhinitis, chronic rhinosinusitis with or without nasal polyps.[146] In patients with severe asthma, sinonasal involvement is almost 100%.[149] AACT has also been shown to result in improvements in sinonasal symptoms in patients with severe asthma (Table 3E).[10,143] In fact, AACT has recently been suggested as treatment for allergic rhinitis and chronic rhinosinusitis as well.[150]

9.7 | Impact on exercise capacity

Various observational studies have shown that AACT in asthmatic patients may result in improved exercise capacity (Table 3F). In an observational study, Bobokhozhadaev described a higher exercise

TABLE 3 (A) Outcomes after AACT (asthma control, asthma-related quality of life). (B) Outcomes after AACT (FeNO, blood eosinophils). (C) Outcomes after AACT (medical consumption, exacerbation rate, OCS use). (D) Outcomes after AACT (lung function). (E) Outcomes after AACT (Upper airways symptoms). (F) Outcomes after AACT (exercise capacity)

Reference	Study design	Study population (*n*)	Treatment duration	Asthma characteristics
A				
van der Schoot TA et al (1993)	Observational study	*N* = 147	3 months	Nonspecific chronic lung disease: asthma and COPD
Rijssenbeek-Nouwens, LH et al (2012)	Observational study	*N* = 137	12 weeks	Severe refractory asthma, HDM sensitized (*n* = 68)
				Severe refractory asthma, non-HDM-sensitized (*n* = 69)
Müller A et al (2018)	Observational study	*N* = 522	3 weeks FU: 6 months	Unknown
Fieten KB et al (2019)	Observational study	*N* = 101	12 weeks FU: 12 months	Severe asthma
Saxer S et al (2019)	RCT	AACT (*n* = 25) Control group at low altitude (*n* = 25)	3 weeks FU: 3 months	Adults with asthma (ACQ >0.75)
de Nijs SB et al (2020)	Prospective comparative study	AACT (*n* = 93) Control group at sea level (*n* = 45)	12 weeks FU: 12 months	Severe asthma

Reference	Study design	Study population (*n*)	Treatment duration	Asthma characteristics
B				
Karagiannidis C et al (2006)	Observational study	*N* = 72	3 weeks	Moderate allergic asthma Moderate intrinsic asthma Severe allergic asthma Severe intrinsic asthma
Rijssenbeek-Nouwens, LH et al (2012)	Observational study	*N* = 137	12 weeks	Severe refractory asthma, HDM sensitized (*n* = 68)
				Severe refractory asthma, non-HDM-sensitized (*n* = 69)
Basler L et al (2020)	RCT	AACT (*n* = 24) Control group at low altitude (*n* = 25)	3 weeks	Adults with asthma (ACQ >0.75)

Study measurements	Outcome, observed change	Outcome, observed change
Baseline – end of AACT – 6 m FU – 12 m FU		Quality of life: • Degree of limitation in daily activities 6.1(1.9) to 4.8(2.3) to 5.4(2.6) to 5.5(2.4) ($p < .05$)
Baseline – end of AACT	ACQ: 3.0 (1.0) to 1.6 (1.2) ($p < .001$)	AQLQ: 4.0 (0.9) to 5.6 (1.0) ($p < .001$)
	ACQ: 3.3 (1.0) to 1.8 (1.0) ($p < .001$)	AQLQ: 3.8 (0.9) to 5.3 (1.1) ($p < .001$)
End of AACT – monthly – 6 m FU	ACT mean: 19.86 to 19.2 to 17.16 to 15.65 to 13.99 to 13.2 ($p < .001$)	
Baseline – End of AACT – 12 m FU	ACQ median (IQR): 3.0 (1.4) to 1.0 (1.5) to 2.3 (2.0) (12 months FU) ($p < .000$)	AQLQ median (IQR): 4.0 (1.2) to 6.0 (1.1) to 5.0 (1.6) 12 months FU ($p < .000$)
Baseline – End of AACT – 3 m FU	ACQ median (quartiles): • AACT: 2.0 (1.6;3.0) to 0.9 (0.4;1.6) to 1.6 (0.9;3.0), mean difference (95% CI) −0.2 (−0.9 to 0.4) ($p > .05$) • Control group: 2.7 (1.7;3.2) to 0.8 (0.4;1.6) to 1.4 (0.9;2.1) mean difference (95% CI) −0.9 (−1.3 to −0.3) ($p < .001$)Between group difference of change from baseline to 3 months median (95% CI) 0.4 (−0.4 to 1.1)	AQLQ median (quartiles): • AACT: 3.9 (3.1;4.6) to 5.6 (4.4;6.3) to 4.9 (3.5;6.2) ($p < .001$) • Control group: 3.6 (3.1;4.8) to 5.5 (4.4;6.4) to 5.1 (3.8;5.9) ($p < .001$)Between group difference of change from baseline to 3 months median (95% CI) −0.5 (−1.6 to 0.3)
Baseline – End of AACT – 12m FU	ACQ: • AACT: 3.1 (0.9) to 1.2 (1.0) to 2.2 (1.3) ($p < .001$) • Control group: 2.4 (0.9) to 1.8 (0.9) to 2.4 (1.0) ($p = .63$)Between group difference at 12 months coefficient (SE) −0.87 (0.20) ($p < .001$)	AQLQ: • AACT: 3.9 (0.9) to 5.8 (0.9) to 4.9 (1.2) ($p < .001$) • Control group: 4.5 (0.9) to 5.3 (0.9) to 4.6 (1.0) ($p = .77$)Between group difference at 12 months coefficient (SE) 0.82 (0.23) ($p < .001$)
Study measurements	**Outcome, observed change, and mean difference from baseline**	**Outcome, observed change**
Baseline – end of AACT	FeNO ppm (mean): moderate allergic asthma: 56.95 to 27.29 ($p < .01$) moderate intrinsic asthma: 38.16 to 25.99 ($p < .05$) severe allergic asthma: 76.12 to 38.59 ($p < .01$) severe intrinsic asthma: 113.8 to 60.41 ($p < .01$)	
Baseline – end of AACT	FeNO ppb median (range): 27.6 (5–209) to 18.4 (3–70) ($p < .001$)	Blood eosinophils 10^9/L median (range): 235 (0–1050) to 210 (50–570) ($p = .033$)
Baseline – end of AACT	FeNO ppb median (range): 16 (5–224) to 16 (1–61) ($p = .058$)	Blood eosinophils 10^9/L median (range): 200 (0–880) to 200 (0–630) ($p = .207$)
Baseline – end of AACT	FeNO ppb AACT: 69 (56) to 37 (23), mean difference (95% CI) −31 (−50 to −13) ($p < .01$) Control group: 48 (33) to 39 (25), mean difference (95% CI) −8 (−24 to 8) ($p > .05$) Between group difference mean (95% CI) −31 (−50 to −13)	Blood eosinophils 10^9/L AACT: 0.46 (0.26) to 0.31 (0.18), mean difference (95% CI) −0.17 (−0.26 to −0.08) ($p < .01$) Control group: 0.43 (0.22) to 0.36 (0.24), mean difference (95% CI) −0.07 (−0.16 to 0.02) ($p > .05$) Between group difference mean (95% CI) 0.10 (−0.02 to 0.22)

(Continues)

TABLE 3 (Continued)

Reference	Study design	Study population (*n*)	Treatment duration
C			
Hlinka V et al (1992)	Observational study	*N* = 1725	3 weeks
Speelberg B et al (1992)	Observational study	*N* = 34	3 months
van der Schoot TA et al (1993)	Observational study	*N* = 147	3 months
Rijssenbeek-Nouwens, LH et al (2012)	Observational study	*N* = 137	12 weeks
Fieten KB et al (2019)	Observational study	*N* = 101	12 weeks FU: 12 months
de Nijs SB et al (2020)	Prospective comparative study	AACT (*n* = 93) Control group at sea level (*n* = 45)	12 weeks FU: 12 months

Reference	Study design	Study population (*n*)	Treatment duration
D			
Dubileĭ V et al (1973)	Observational study	*N* = 150	8 weeks
Kolesár J et al (1977)	Observational study	*N* = 15	2 weeks
Bobokhozhdaev O et al (1990)	Observational study	*N* = 44	4 weeks
Brimkulov N et al (1991)	Observational study	*N* = 132	4 weeks
Speelberg B et al (1992)	Observational study	*N* = 34	3 months
Rijssenbeek-Nouwens, LH et al (2012)	Observational study	*N* = 137	12 weeks
Müller A et al (2018)	Observational study	*N* = 522	3 weeks

Study measurements	Asthma characteristics	Outcome, observed change	Outcome, observed change
Baseline – end of AACT	Unknown	Reduction in asthma medication • Asthma medication can be stopped in 24% of asthmatic patients • Substantial reduction of inhalatory beta-adrenergic substances	
Baseline – end of AACT	Asthma ($n = 34$)	OCS use mg/day 2.9 (6.0) to 1.4 (1.4)	
Year before - year after AACT	Nonspecific chronic lung disease: asthma and COPD		Medical consumption: • Health care visits (family physician 6.9 to 4.4, and lung physician 6.6 to 5.6) • Hospital admissions number (1.2 to 0.8) and duration (24 days to 15 days)
Baseline – end of AACT	Severe refractory asthma, HDM sensitized ($n = 68$)	OCS maintenance (%) 43% to 22% ($p < .001$)	
Baseline – end of AACT	Severe refractory asthma, non-HDM-sensitized ($n = 69$)	OCS maintenance (%) 59% to 38% ($p < .001$)	
Year before - year after AACT	Severe asthma	OCS maintenance (%) 33% to 34% ($p = 1.0$) OCS use mg/day median (IQR): 2.9 (6.0) to 1.4 (1.4) ($p = .684$)	Exacerbation rate median (IQR) 3 (4) to 2 (3) ($p = .000$) % of hospitalized patients 50% to 32% ($p = .010$)
Baseline – end of AACT – 1 year FU	Severe asthma	OCS maintenance (%) AACT: 52% to 22% to 30% ($p < .001$) • Control group: 38% to 31% to 33% ($p = .50$) OCS use mg/day • AACT: 17.9 (15.7) to 5.4 (7.1) to 7.5(10.1) ($p < .001$) • Control group: 12.4 (8) to 8.5 (5.4) to 12.7 (9.4) ($p = .48$)	

Study measurements	Asthma characteristics	Outcome, observed change
Baseline – end of AACT	Mild asthma ($n = 45$)	FEV_1/FVC: 71.9 (7.4) to 88.4 (2.7)
	Moderate asthma ($n = 35$)	FEV_1/FVC: 68.7 (10.0) to 80.4 (3.3)
	Severe asthma ($n = 15$)	FEV_1/FVC: 64.0 (5.3) to 71.4 (7.1)
Baseline – end of AACT	Unknown	FEV_1%pred: 67.1 (6.6) to 69.9 (7.3)
Baseline – end of AACT	Atopic asthma ($n = 20$)	FEV_1/FVC: 54.3 (10.3) to 63.2 (17.4)
	Non-atopic asthma ($n = 24$)	FEV_1/FVC: 54.1 (10.3) to 75.1 (23.5)
Baseline – end of AACT	Mild asthma ($n = 38$)	FEV_1%pred: 74.9 (5.5) to 86.4 (7.4)
	Moderate asthma ($n = 94$)	FEV_1%pred:64.5 (17.2) to 73.3 (18.0)
Baseline – end of AACT	Asthma ($n = 34$)	FEV_1%pred: 67 (18) to 66 (21) before salbutamol FEV_1%pred: 92 (21) to 95 (19) after salbutamol
Baseline – end of AACT	Severe refractory asthma, HDM sensitized ($n = 68$)	Post-bronchodilator FEV_1%pred: 88 (20) to 94 (20) ($p = .001$)
	Severe refractory asthma, non-HDM-sensitized ($n = 69$)	Post-bronchodilator FEV_1%pred: 86 (26) to 93 (23) ($p = .004$)
Baseline – end of AACT	Unknown	FEV_1%: 72.2 (23.6) to 78.3 (22.7) ($p < .001$) FEV_1 /VC: 88.6 (17.3) to 91.8 (15.1) ($p < .001$)

(Continues)

TABLE 3 (Continued)

Reference	Study design	Study population (*n*)	Treatment duration
D			
Saxer S et al (2019)	RCT	AACT (*n* = 25) Control group at low altitude (*n* = 25)	Treatment duration: 3 weeks FU: 3 months
de Nijs SB et al (2020)	Prospective comparative study	AACT (*n* = 93) Control group at sea level (*n* = 45)	12 weeks FU: 12 months
Reference	**Study design**	**Study population (*n*)**	**Treatment duration**
E			
Rijssenbeek-Nouwens, LH et al (2012)	Observational study	*N* = 137	12 weeks
de Nijs SB et al (2020)	Prospective comparative study	AACT (*n* = 93) Control group at sea level (*n* = 45)	12 weeks FU: 12 months
Reference	**Study design**	**Study population (*n*)**	**Treatment duration**
F			
Bijl D et al (1994)	Observational study	*N* = 62	10 weeks
Rijssenbeek-Nouwens, LH et al (2012)	Observational study	*N* = 137	12 weeks
Müller A et al (2018)	Observational study	*N* = 522	3 weeks
Saxer S et al (2019)	RCT	AACT (*n* = 25) Control group at low altitude (*n* = 25)	3 weeks FU: 3 months
de Nijs SB et al (2020)	Prospective comparative study	AACT (*n* = 93) Control group at sea level (*n* = 45)	12 weeks FU: 12 months

Note: Data are presented as mean (SD), unless otherwise stated.

Abbreviations: %pred, percentage predicted; 6MWD, 6-min walking distance; ACQ, asthma control questionnaire; AQLQ, asthma-related quality of life questionnaire; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume during the first second; FU, follow-up; FVC, forced vital capacity; HDM, house dust mite; ISWT, incremental shuttle walk test; OCS, oral corticosteroids; SNOT, sinonasal outcome test; VC, vital capacity; VO2max, maximal oxygen consumption.

Study measurements	Asthma characteristics	Outcome, observed change
Baseline – end of AACT – 3 m FU	Adults with asthma (ACQ >0.75)	• FEV1%pred median (quartiles) a. AACT: 64 (59;71) to 78 (67;83) to 72 (58;85) ($p < .05$) b. Control group: 61 (42;77) to 96 (54;80) to 71 (58;83) ($p < .05$) • FVC%pred median (quartiles) a. AACT: 82 (74;92) to 91 (83;98) to 84 (78;95) ($p > .05$) b. Control group: 83 (63;93) to 87 (79;96) to 87 (77;94) ($p > .05$)
Baseline – end of AACT – 12m FU	Severe asthma	FEV_1% pred: • AACT: 86 (20) to 90 (20) to 89 (22) ($p = .003$) • Control group: 81 (26) to 81 (26) to 85 (26) after 12 months ($p = .63$)
Asthma characteristics	**Study measurements**	**Outcome, observed change**
Severe refractory asthma, HDM sensitized ($n = 68$)	Baseline – end of AACT	SNOT–20 score: 2.2 (0.8) to 1.5 (1.1) ($p < .001$)
Severe refractory asthma, non-HDM-sensitized ($n = 69$)		SNOT-20 score: 2.2 (0.8) to 1.6 (1.0) ($p < .001$)
Severe asthma	Baseline – end of AACT	SNOT-22 score: • AACT: 2.3 (0.8) to 1.2 (0.9) to 1.9 (1.0) ($p < .001$) • Control group: 2.0 (0.7) to 2.0 (1.0) to 2.0 (1.0) ($p = .87$)
Asthma characteristics	**Study measurements**	**Outcome, observed change**
Nonspecific chronic lung disease: asthma and COPD	Baseline – end of AACT – 12 m FU	VO2max L/min 1.4 (0.4) to 1.9 (0.6) to 1.8 (0.6) ($p < .001$)
Severe refractory asthma, HDM sensitized ($n = 68$)	Baseline – end of AACT	6MWD (meters): 516 (178) to 636 (219) ($p < .001$)
Severe refractory asthma, non-HDM-sensitized ($n = 69$)		6MWD (meters): 430 (182) to 575 (197) ($p < .001$)
Unknown	Baseline – end of AACT	6MWD (meters): 379.8 (106.6) to 456.98 (111) ($p < .001$)
Adults with asthma (ACQ >0.75)	Baseline – end of AACT – 3 m FU	6MWD (meters) AACT: 536 (491;571) to 571 (522;624) to 570 (517;607) ($p < .01$) Control group: 490 (452;510) to 521 (493;549) to 504 (486;536) ($p < .05$) Sit-to-stand repetitions AACT: 25 (23–28) to 36 (30–40) to 30 (27–39) ($p < .001$) Control group: 21 (19–24) to 24 (21–26) to 25 (22–28) ($p < .01$)
Severe asthma	Baseline – end of AACT – 12 m FU	ISWT (m): • AACT: 418 (224) to 575 (261) to 561 (263) ($p < .001$) • Control group: 492 (305) to 549 (324) to 539 (282) ($p = .24$)

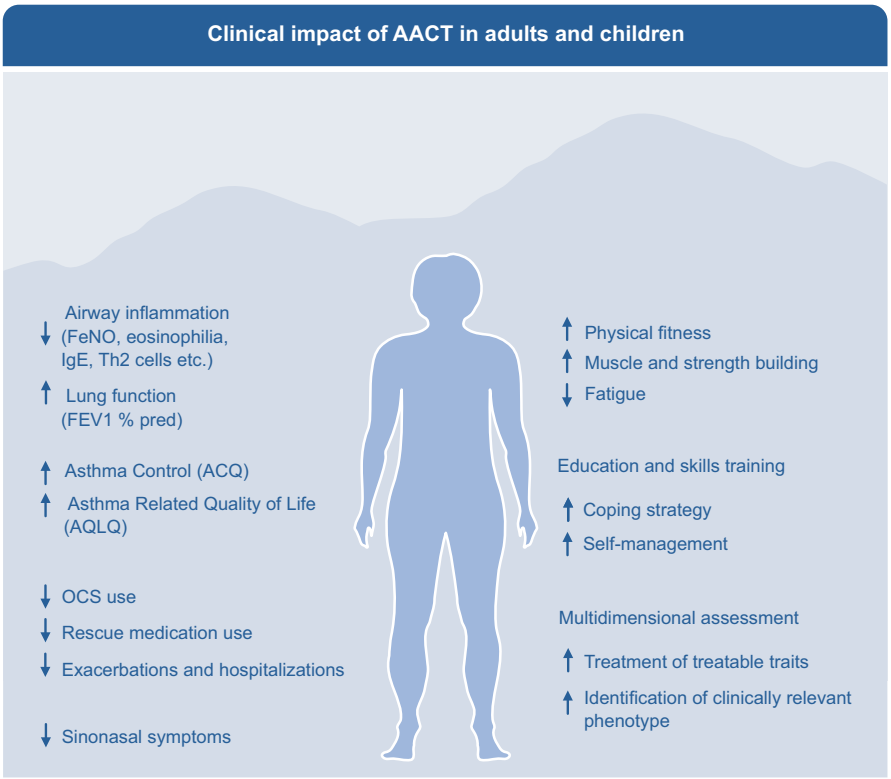

FIGURE 4 Clinical impact of alpine altitude climate treatment in adults and children. The downregulation of the airway inflammation and the immune system during AACT results in improved asthma control and quality of life, leading to reduction of OCS and rescue medication, less exacerbations and hospitalizations. With a better asthma control, patients can improve their physical fitness, fatigue, coping strategy, and self-management during the pulmonary rehabilitation including assessment of the treatable traits and asthma phenotype. AACT, alpine altitude climate treatment; OCS, oral corticosteroids

tolerance after a 4-week treatment at 1960 m in 96 adults with asthma,[151] and another study showed increased exercise tolerance (VO2max) after a 10 weeks AACT program involving regular physical exercise at 1560 m, in patients with chronic obstructive lung diseases, including asthma.[140] Rijssenbeek et al also reported a clinically relevant improvement in 6-MWD (6-min walking distance) after 12 weeks of treatment at 1560 m (Davos, Switzerland).[10] De Nijs described a clinically relevant improvement in exercise tolerance (distance during incremental shuttle walk test (ISWT)) after 12 weeks of treatment at 1560 m, and this improvement lasted up to 12 months.[143] Saxer reported an increased exercise capacity after pulmonary rehabilitation both at 700 m and 3100 m, with an increased 6MWD in both groups but significantly more sit to stand repetitions in the HA group.[138]

10 | CLINICAL IMPACT OF ALPINE ALTITUDE CLIMATE TREATMENT IN CHILDREN

The effects of AACT on different outcome measures in children with asthma are described in Table 4. Studies were observational and have mainly assessed outcomes regarding asthma control and quality of life, lung function, and AHR. Other outcomes related to exacerbation rates and hospitalizations, exercise tolerance, upper airways symptoms, and immunological outcomes were not reported. Quality assessment demonstrated sufficient quality for most studies while taking the non-randomized observational study design into account (Table S5). No randomized trials have been done.

10.1 | Impact on asthma control and asthma-related quality of life

A study involving 18 atopic adolescent asthmatics on regular inhaled treatment showed that quality of life (PAQLQ—Pediatric Asthma Quality of Life Questionnaire) improved significantly after 10 weeks of treatment at moderate altitude, an effect which was seen up to 6 weeks after the end of treatment, and less in a control group matched for asthma severity.[152] Another observational study in 32 children with problematic severe asthma, demonstrated improvement in PAQLQ after 10 weeks of AACT, associated with concomitant reduction of inhaled and oral steroids.[153]

10.2 | Impact on FeNO

Several studies involving asthmatic children have shown a significant decrease in FeNO.[12,153–157] FeNO presented a significant reduction observed after the first 2 weeks of altitude treatment with an improvement which was faster than that showed by lung function tests (i.e., FEV_1).[106]

TABLE 4 (A) Pediatric outcomes after AACT: asthma control and asthma-related quality of life. (B) Pediatric outcomes after AACT: Blood eosinophils and FeNO. (C) Pediatric outcomes after AACT: Lung function. (D) Pediatric outcomes after AACT: AHR

Reference	Study design	Study population (*n*)	Treatment duration	Asthma characteristics	Study measurements	Outcome, observed change
A						
Boner AL et al (1985)[a]	Observational study	*N* = 14	9 months	Allergic bronchial asthma	T0 Sep – T3 June	Decreased requirement for drugs Inhaled steroids discontinued
Grootendorst DC et al (2001)	Observational parallel group study	AACT: *n* = 10 Control group: *n* = 8	10 weeks FU: 6 weeks	Atopic adolescents sensitized for HDM	(1) Baseline – end of AACT – 6 w FU (2) Control group: 0 w 8 w 16 w	Asthma-related quality of life median (range) AACT: 5.0 (4.0–6.6) to 6.6 (6.1–7.0) to 6.5 (6.2–7.0) Control group: 4.8 (2.7–6.2) to 5.2 (2.9–6.4) to 5.9 (2.2–6.6)
van de Griendt EJ et al (2014)	Observational study	*N* = 43	10 weeks	Moderate-to-severe asthma, 74% PSA problematic severe asthma	Baseline – end of AACT	Asthma control test 6.5 (1.7) to 9.7 (1.7) ($p < .001$) Asthma-related quality of life 4.8 (1.2) to 6.2 (0.76) ($p < .001$)
Quignon P et al (2021)[a]	Observational study	*N* = 67	9 months	Children with severe bronchial asthma for more than 2 years, atopic or non-atopic	T0 admission (Sep) – T1 (Dec) – T2 15 days home (Jan) – T3 end of school year (June)	Assessment of asthma control % well controlled: T0 36%, T1 66%, T2 15%, T3 88% Asthma quality of life T0 113 ± 26, T1 121 ± 25, T2 121 ± 24, T3 128 ± 23 ($p < .05$)
Reference	**Study design**	**Study population (*n*)**	**Treatment duration**	**Asthma characteristics**	**Study measurements**	**Outcome, observed change**
B						
Boner AL et al (1993) CEA	Observational study	*N* = 12	9 months	Allergic asthmatic children sensitized to HDM	T3 June – T0 Sep – T1 Dec	Blood eosinophils 10^6/L (mean ± SEM) 215 ± 56, 159 ± 51, 81 ± 13
Boner AL et al (1993) Allergy	Observational study	*N* = 23	9 months	Moderately severe HDM allergic asthmatic children	T0 Sep – T2 Mar – T3 June	Blood eosinophil (%) (mean ± SEM) T0: 4.23 ± 0.56, T2: 3.4 ± 0.36, T3: 6.47 ± 0.63
Simon HU et al (1994)	Observational study	*N* = 14	5 weeks	Asthmatic children allergic to HDM	Baseline – end of AACT	Blood eosinophils 10^6/ml 0.5 to 0.3
Christie PE et al (1995)	RCT	*N* = 14	At least 1 month	Adolescents with mild atopic asthma and HDM sensitization	(1) Baseline – 3 weeks AACT (2) Baseline – 2 weeks sea level – return to AACT	Blood eosinophils 10^6/L mean (SE) AACT: 520 (127) to 411 (837) Sea level: 237 (60) to 328 (102)

(Continues)

TABLE 4 (Continued)

Reference	Study design	Study population (*n*)	Treatment duration	Asthma characteristics	Study measurements	Outcome, observed change
B						
van Velzen E et al (1996)	Observational study	*N* = 16	1 month	Children with allergic asthma	Baseline – end of AACT	Blood eosinophil counts geometric mean (SE) 372.39 (87.04)/mm^3 to 233.35 (67.83)/mm^3 ($p < 0–01$; 95% CI 0.060–0.346)
Grootendorst DC et al (2001)	Observational parallel group study	AACT: *n* = 10 Control group: *n* = 8	10 weeks FU: 6 w	Atopic adolescents sensitized for HDM	(1) Baseline – 4 w AACT – 8 w AACT – 6 w FU (2) Control group: 0 w 8 w 16 w	Blood eosinophils 10^6/L (geometric mean, range) AACT: 326.4 (31–1316) to 193.8 (88–918) to 173.6 (75–544) to 306.7 (100–840) Control group: 353.2 (200–1045), 288.3 (200–374), 246.7(143–517)
Piacentini GL et al (1999)	Observational study	*N* = 20	2 months	Asthmatic children (6–15 years) sensitized to HDM	T0 Sep – T1 2 w – T2 Dec – T3 Jan	FeNO ppb (geometric mean) T0: 16.3 T1:7.225 T2:7.77 T3:16.85
Peroni DG et al (2002)	Observational study	*N* = 18	9 months (2 weeks at home)	Moderate-to-severe asthma, sensitized to HDM	T0 Sep – T1 Dec – T2 Jan – T3 June	FeNO (ppb) (mean ± SEM) T0: 21.3 ± 3.9 T1: 11.9 ± 1.7 T2:12.5 ± 2.6 T3: 13.2 ± 2.0
Huss-Marp J et al (2007)	Observational study	*N* = 311	4–6 weeks	Children with increased FENO values at admission (>17 ppb)	Baseline – end of AACT	FeNO (ppb) geometric mean ±95% CI 38.5 ± 22.8 ppb to 20.1 ± 13.2 ppb ($p < .001$)
Piacentini GL et al (2011)	Observational study	*N* = 14	6 months	Mild-to-moderate asthma, sensitized to HDM or grass	T0 Sep – T1 Dec – T2 Jan – T3 Mar	FeNO (ppb) mean T0: 26.30 T1: 17.43 T2: 27.40 T3: 15.11 (p=.01)
van de Griendt EJ et al (2014)	Observational study	*N* = 43	10 weeks	Moderate-to-severe asthma, 74% PSA problematic severe asthma	Baseline – end of AACT	FeNO (ppb) 39.8 (26.4) to 15.2 (7.6) ($p < .001$)
Bersuch, E et al (2017)	Observational study	*N* = 344	3 weeks	Controlled, partly controlled, and uncontrolled asthma	Baseline – end of AACT	FeNO (ppb) median Controlled: 27.6–15.8 (12 ppb reduction) ($p < .001$), Partly controlled: 41.8–14.9 (27 ppb reduction) ($p < .001$) Uncontrolled: 49.9–13 (36 ppb reduction) ($p < .001$)
Kulkarni N et al (2018)	Observational study	*N* = 62	3 weeks	Children with mild-to-moderate asthma (77% GINA 1 and 2)	Baseline – 3 w AACT	FeNO (ppb) median (range) 18.85 (2.6–79.3) to 11.5 (2.1–52.2) ($p < .001$)
Quignon P et al (2021)	Observational study	*N* = 67	9 months	Children with severe bronchial asthma for more than 2 years, atopic or non-atopic	T0 Sep – T1 Dec – T2 Jan – T3 June	FeNO (ppb) 30 – 18 – 24 – 20 ($p < .05$)

TABLE 4 (Continued)

Reference	Study design	Study population (*n*)	Treatment duration	Asthma characteristics	Study measurements	Outcome, observed change
C						
Boner AL et al (1985)[a]	Observational study	*N* = 14	9 months	Allergic bronchial asthma	T0 Sep – T3 June	Improved pulmonary function
Simon HU et al (1994)	Observational study	*N* = 14	5 weeks	Asthmatic children allergic to HDM	Day 2 – Day 21 – Day 35	Lung function at rest mean (SD) FEV1 (% pred) 95.1 (9.8) to 98.3 (10.7) to 104 (14.7) PEF (% pred) 96.6 (20.8) to 99.2 (18.5) to 101 (15.4) PEF variability 17.1 (13.3) to 10.7 (6.3) to 9.5 (5.4) RV/TLC (%) 185 (28) to 171 (20) to 168 (19) FEF50 (% pred) 75.4 (5.2) to 81.5 (6.3) to 79.6 (8.7)
Christie PE et al (1995)	RCT	*N* = 14	At least 1 month	Adolescents with mild atopic asthma and HDM sensitization	(1) Baseline – 3 weeks AACT (2) Baseline – 2 weeks sea level – return to AACT	FEV_1 (l) (mean ± SEM) AACT 2.9 ± 0.3 and 2.9 ± 0.4 ($p = .35$) Sea level 3.0 ± 0.3 to 2.8 ± 0.3 ($p = .04$)
Valletta EA et al (1995)[a]	Observational study	*N* = 12	3 months	Children with mild-to-moderate asthma and house dust mite allergy	Oct – Dec – Jan	%PEF variability (median): 10.6 – 8.1 – 10.4
Benckhuijsen J et al (1996)	Observational study	*N* = 13	1 month	Asthmatic children with allergy to HDM	Before–after	FEV_1 (% pred) (mean ± SEM) 97.6 ± 6.3–101 ± 5.5
van Velzen E et al (1996)	Observational study	*N* = 16	1 month	Children with allergic asthma	Before–after	FEV1 (% pred) mean (SE) 92.1 (5.8) to 97 (5.1) PEF variability % mean (SE) 12.1 (2.5) to 7.2 (1.2) ($p < .01$)
Valletta EA et al (1997)[a]	Observational study	*N* = 14	3 months	Children with mild-moderate asthma, allergic to HDM	T0 Sep – T2 Dec	FEV_1%mean (SD): 82 (7) to 86 (6) ($p = .05$). Mean difference (95% CI): 4% (0–8) FEF_{25-75}%pred mean (SD) 61 (12) to 68 (11) ($p = .005$). Mean difference (95% CI) 7.4% (2.7–12.2) PEF % mean (SD): 95 (16) to 103 (13) ($p = .002$) Mean difference (95% CI): 8.2 (3.5–13)
Piacentini GL et al (1999)[a]	Observational study	*N* = 20	2 months	Asthmatic children (6–15 years) sensitized to HDM	T0 Sep – T1 2 w – T2 Dec – T3 Jan	FEV_1 L/min: T0 2.006 ± 0.42 to T1 2.0075 ± 0.43 to T2 2.112 ± 0.63 to T3 2.496 ± 0.63

(Continues)

TABLE 4 (Continued)

Reference	Study design	Study population (*n*)	Treatment duration	Asthma characteristics	Study measurements	Outcome, observed change
C						
Grootendorst DC et al (2001)	Observational parallel group study	AACT: $n = 10$ Control group: $n = 8$	10 weeks FU: 6 w	Atopic adolescents sensitized for HDM	(1) Baseline – 4 w AACT – 8 w AACT – 6 w FU (2) Control group: 0 w 8 w 16 w	FEV1(%) mean (SEM) AACT: 85.6 (4.5) to 94.8(4.2) to 92.6 (4.0) Control group: 86.6 (6.8) to 93.3 (4.2) to 92.5 (4.0)
Peroni DG et al (2001)[a]	Observational study	$N = 15$	3 months	HDM–sensitized children with asthma (6–14 years of age)	T0 Sep – T1 Dec – T2 Jan	FEV_1%pred median (Q1–Q3) T0 103% (99%–108%) to T1 106% (98%–110%) to T2 107% (99%–115%) RV mean (SEM) T0 117.6% (8.6%) to T1 98.0% (3.8%) to T2 133.3% (20.8%) FEF_{25-75}%pred median (Q1–Q3) T0 84% (67%–93%) to T1 92% (75%–100%) to T2 94% (78%–113%)
Peroni DG et al (2002)[a]	Observational study	$N = 18$	9 months (2 weeks at home)	Moderate-to-severe asthma, sensitized to HDM	T0 Sep – T1 Dec – T2 Jan –T3 June	FEV_1(%) (mean ± SEM) T0:100.5 ± 3.6 T1:102.0 ± 2.9 T2:105.1 ± 2.6 T3:100.5 ± 2.3 FEF_{25-75}(%) (mean ± SEM) T0:81.5 ± 5.9 T1:91.3 ± 5.1 T2:94.4 ± 5.8 T3:93.2 ± 5.9 RV (%) T0:117.7 ± 7.7 T1:96.5 ± 3.2 T2: 126.2 ± 17.2 T3:91.1 ± 6.0
Petermann F et al (2004)	Observational study	$N = 60$	4 weeks	Moderate asthma with or without HDM sensitization	Before–after	FEV_1%pred 95.27% to 99.4%
Straub DA et al (2004)	Observational study	$N = 48$	4 weeks	Asthmatic children with a normal FEV1 and positive skin prick test for HDM	Before–after	FEV_1 (% pred) mean (range) Arrival: 104.5% (80–154%) Departure: 105% (78–168%)
Piacentini GL et al (2011)[a]	Observational study	$N = 14$	6 months	Mild-to-moderate asthma, sensitized to HDM or grass	T0 Sep – T1 Dec – T2 Jan – T3 Mar	FEV_1%pred T0: 85 T3:92.75 FEV_1/FVC %pred T0: 89.5% T3:92.25% FEF25-75 T0:66.7% T3:76.87%
van de Griendt EJ et al (2014)	Observational study	$N = 43$	10 weeks	Moderate-to-severe asthma, 74% PSA problematic severe asthma	Before–after	FEV_1%pred mean (SD) 105.1(14.7) to 108.1(13.9) FEV_1/VC %pred mean (SD) 115.3(16.4) to 111.5(12.1)

TABLE 4 (Continued)

Reference	Study design	Study population (*n*)	Treatment duration	Asthma characteristics	Study measurements	Outcome, observed change
C						
Bersuch, E et al (2017)	Observational study	*N* = 344	3 weeks	Controlled, partly controlled, and uncontrolled asthma	Before–after	FEV1%pred Controlled: 96.8%–99.1%, Partly controlled: 94.2%–96.0%, Uncontrolled: 89.4%–97.1% MEF25%pred Controlled: 93.6%–95.3%, Partly controlled: 85.9%–85.7%, Uncontrolled: 75.7%–85.6% MEF75%pred Controlled: 93.1%–98.6%, Partly controlled: 88.7%–92%, Uncontrolled: 76.5%–89.2%
Kulkarni N et al (2018)[a]	Observational study	*N* = 62	3 weeks	Children with mild-to-moderate asthma (77% GINA 1 and 2)	Baseline – 3 w AACT	FEV_1%pred mean (SE) 109.5 (2.4) to 116.0 (2.04) $p = .67$ FVC %pred mean (SE) 105.8 (1.81) to 105.6 (1.89) $p = .91$ FEV_1/FVC ratio %pred mean (SE) 103.1 (1.29) to 101.8 (1.3) $p = .56$ FEF25-75%pred mean (SE) 105.3 (4.38) 102.9 (4.01) $p = .72$
Quignon P et al (2021)[a]	Observational study	*N* = 67	9 months	Children with severe bronchial asthma for more than 2 years, atopic or non-atopic	T0 Sep – T1 Dec – T2 Jan – T3 June	PEF 322 ± 97, 362 ± 101, 330 ± 94, 362 ± 98 FEV_1 2.6 ± 0.7, 2.64 ± 0.8, 2.7 ± 0.8, 2.64 ± 0.7
Reference	**Study design**	**Study population (*n*)**	**Treatment duration**	**Asthma characteristics**	**Study measurements**	**Outcome, observed change**
D						
Boner AL et al (1985)[a]	Observational study	*N* = 14	9 months	Allergic bronchial asthma	T0 Sep – T3 June	Decreased nonspecific hyperreactivity
Boner AL et al (1985)[a]	Observational study	*N* = 23	3 months	Allergic bronchial asthma	T0 Sep – T1 Dec	Only individual values reported Exercise challenge: 10 no response 7 isolated immediate bronchospasm 6 biphasic responses with immediate bronchospasm followed 4–10 h later by a late reaction sustained for at least 2 h.
Boner AL et al (1993) CEA[a]	Observational study	*N* = 12	9 months	Allergic asthmatic children sensitized to HDM	T3 June – T0 Sep – T1 Dec	Histamine PC20 FEV1 μg/ml (mean ± SEM) 2.89 ± 0.91, 5.54 ± 2.51, 6.66 ± 2.34

(Continues)

TABLE 4 (Continued)

Reference	Study design	Study population (*n*)	Treatment duration	Asthma characteristics	Study measurements	Outcome, observed change
D						
Boner AL et al (1993) Allergy[a]	Observational study	*N* = 23	9 months	Moderately severe HDM allergic asthmatic children	T0 Sep – T2 Mar – T3 June	Methacholine PC20-FEV1 mg/ml (mean ± SEM) T0 5.20 ± 1.72 to T2 7.43 ± 2.11 to T3 5.97 ± 1.79
Piacentini G et al (1993)[a]	Observational study	*N* = 20	3 months (Sep – Dec)	Children with allergic asthma	T0: Admission, T1 after 40 days, T2 after 80 days of allergen avoidance, T3 after 15 days of allergen exposure at sea level.	Methacholine PC20 mg/ml (mean ± SEM) T0 3.27 ± 0.95 to T1 6.76 ± 1.869 to T2 7.387 ± 2.115 to T3 7.136 ± 3.322
Peroni DG et al (1994)[a]	Observational study	*N* = 45	9 months	asthmatic children allergic to HDM 22 children (methacholine) 23 children (histamine, HDM)	Oct – Jan – June – Sep (1) Oct – Mar – June (2)	(1) methacholine PD20-FEV1 µg/ml (mean ± SD) 124 ± 213, 463 ± 612, 589 ± 664, 140 ± 125 (1) PEF decrease after exercise (%) mean ± SD 27.8 ± 20.8, 18.8 ± 15.9, 14.2 ± 12.5, 27.9 ± 12.1 (2) histamine PD20-FEV1 µg/ml mean ± SD 128.8 ± 30.5, 380 ± 47.8, 275.4 ± 34.3 (2) HDM PD20-FEV1 AUR/ml mean ± SD 47.86 ± 2.81, 95.49 ± 3.31, 117.4 ± 2.81
Christie PE et al (1995)	RCT	*N* = 14	At least 1 month	Adolescents with mild atopic asthma and HDM sensitization	(1) Baseline – 3 weeks AACT (2) Baseline – 2 weeks sea level – return to AACT	histamine PC20 mg/ml (geometric mean, range) AACT 1.5 (0.3–22) to 1.5 (0.3–32) ($p = .89$) Sea level 1.7 (0.3–16.4) to 0.9 (0.1–5.2) ($p = .04$) ($n = 5$)
Peroni DG et al (1995)	RCT	*N* = 23	12 months	Dermatophagoides pteronyssinus (Dpt)-sensitive asthmatic children aged 7–14 years	Enrollment, after 6 months, after 12 months of treatment	IT during AACT histamine PD20 mg/ml (median, interquartile range) 1.87 (1.29–4.76) to 3.80 (1.43–13.6) to 3.79 (2.16–8.44) IT group 1.62 (0.55–2.45) to 2.59 (2.15–4.28) to 2.63 (1.35–4.8) placebo
Valletta EA et al (1995)[a]	Observational study	*N* = 12	3 months	Children with mild-to-moderate asthma and house dust mite allergy	Oct – Dec – Jan	Methacholine PC20 µg/ml (median): 2.4 – 3.1 – 2

TABLE 4 (Continued)

Reference	Study design	Study population (*n*)	Treatment duration	Asthma characteristics	Study measurements	Outcome, observed change
D						
Benckhuijsen J et al (1996)	Observational study	*N* = 13	1 month	Asthmatic children with allergy to HDM	Before–after	Methacholine PC20 mg/ml (mean ± SEM) 0.4 ± 0.69–0.51 ± 0.99 AMP PC20 mg/ml (mean ± SEM) 4.87 ± 32.76–21.63 ± 31.58 %decrease FEV_1 after exercise (mean ± SEM) 26.6 ± 5.7–20.9 ± 5.5
Piacentini GL et al (1996)[a]	Observational study	*N* = 16	3 months	Asthmatic children allergic to HDM	T0 Sep – T1 Dec	Methacholine PC20 mg/ml median (lower, upper quartile: Q1, Q3) T0: 1.17 (0.74, 4.75) mg/ml T1: 3.5 (1.18, 8.87) mg/ml (p = .02)
van Velzen E et al (1996)	Observational study	*N* = 16	1 month	Children with allergic asthma	Before–after	Bronchial hyperresponsiveness Methacholine PC20 mg/ml geometric mean ± SE 0.48 ± 0.56 to 0.62 ± 0.77 AMP PC20 mg/ml geometric mean ± SE 6.21 ± 26.72 to 25.78 ± 25.6
Piacentini GL et al (1998)[a]	Observational study	*N* = 10	3 months	Children with a history of bronchial asthma and positive SPT to HDM	T0 Sep – T1 Dec – T2 Jan	Bronchial hyperresponsiveness to methacholine PC20 mg/ml median (Q1;Q3) T0: 2.75 (1.53;7.5) T1: 3.25 (1.65;15.25) (p = .038) T2: 5.25 (1.68;14.5) mg/ml (NS)

Note: Data are presented as mean (SD), unless otherwise stated.

Abbreviations: %pred, percentage predicted; AMP, adenosine monophosphate; FEF, forced expiratory flow; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume during the first second; FVC, forced vital capacity; HDM, house dust mite; MEF, maximum expiratory flow; PC20, concentration of inhaled substance that provokes a 20% decrease in the FEV_1; PEF, peak expiratory flow; RV, residual volume.

[a]Children were admitted to the clinics in Briançon and Misurina for an entire school year. Admission is usually in September (T0 the period of allergen avoidance starts), children go home for a 2 or 3 weeks Christmas holiday (T1 re-exposure to allergens starts) and return to the clinic from January (T2 allergen avoidance continues) until June (T3 end of school year).

10.3 | Impact on OCS use

Discontinuation of oral corticosteroids has been reported in 3 children after 10 weeks of AACT.[152,153]

10.4 | Impact on lung function outcomes

Several studies assessed lung function before and after AACT. A systematic review and meta-analysis including 3 randomized control trials, 2 clinical-controlled trials, and 15 single-arm studies concluded that although there was a lack of significant improvement in FEV_1 and PD_{20}, still a trend for improvement could be observed.[6] Over a 2-week period at 1560 m (Davos, Switzerland), FEV_1, MEF25, and MEF75 significantly improved in 124 asthmatic children and adolescents.[155] Similar results were observed in a group of 60 10- to 16-year-old asthmatic children, after a 4-week long treatment at altitude, together with a decrease in indices of hyperinflation and improvement in FEV_1 after exercise.[105] However, 2 weeks after returning to the Netherlands, a significant reduction in FEV_1 was observed in a group of 8 adolescents after staying at least 1 month in Davos.[158] Another study from Davos reported normal pulmonary function at admission and at discharge.[153] A follow-up study of pulmonary function carried out in 15 HDM-sensitized 6- to 14-year-old asthmatic children who stayed at Misurina, Italy (1752 m) for 12 weeks and then returned home, at sea level, for 2 weeks, demonstrated variations in residual volume, a marker of air trapping, that were related to mite-exposure variations, while there were no significant changes in spirometric parameters.[159] In another study by the same authors, in 18 HDM-sensitized allergic asthmatic children, after 3 months of AACT, residual volume showed a significant decrease with subsequent increase after 3 weeks of allergen re-exposure at home. Residual volume decreased again after the following 5 months at altitude.[154] Flow-volume indices were also investigated in children with mild-moderate asthma for 12 weeks, resulting in significant improvement of both mean forced expiratory flow FEF_{25-75}%predicted and PEF% predicted, but marginal changes in FEV_1.[160]

10.5 | Impact on specific and nonspecific airway hyperresponsiveness (AHR)

Various studies have shown that AACT decreases nonspecific AHR, delays the time to onset of allergen-induced bronchial reactions, and enhances the threshold to bronchial allergen challenge in asthmatic children. After 3 and 9 months of AACT, exercise-induced and methacholine PD20 (the provocative dose that results in a 20% fall in FEV_1) increased, but decreased after 3 months at sea level.[161] Histamine PD20 and HDM PD20 significantly increased after 6 and 9 months.[162–164] One month of AACT could not prevent a significant reduction of histamine PC20 in adolescents with atopic asthma after 2 weeks in the Netherlands.[158] Other studies did not report an improvement in nonspecific AHR to methacholine, but a progressive increase in PD20 for adenosine 5′-monophospate (AMP) and a reduction in exercise-induced airway narrowing have been reported.[102,103,165]

Key messages

- Several European observational studies describe AACT in adults and children with severe or uncontrolled asthma, but there is a lack of randomized trials or studies with a control group.
- AACT improves various outcomes such as asthma control and quality of life, exacerbation rate and hospitalizations, oral corticosteroid reduction, lung function parameters, upper airways symptoms, and exercise tolerance in adults and children.

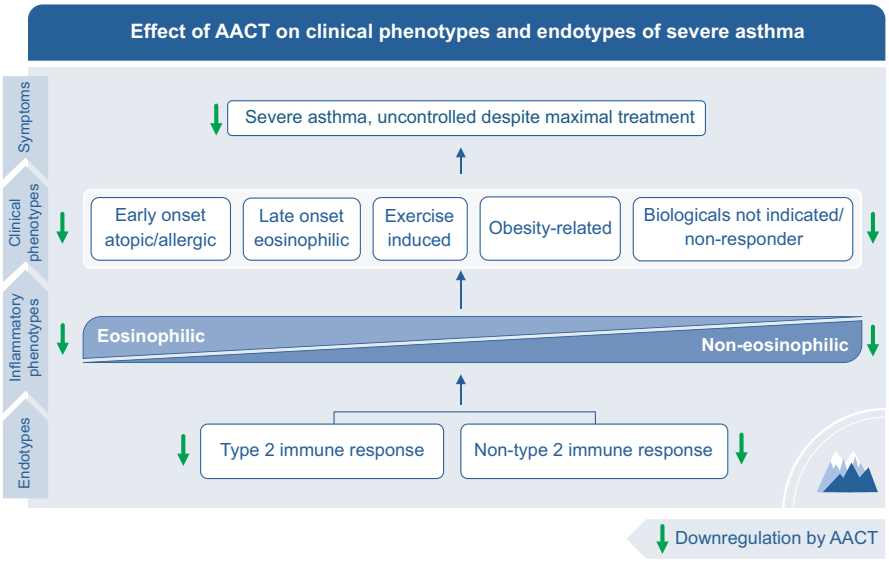

FIGURE 5 Effect of alpine altitude climate treatment on clinical and inflammatory phenotypes and endotypes of severe asthma. In patients with severe uncontrolled asthma despite maximal medical treatment, AACT offers an opportunity to regain asthma control, irrespective of the clinical or inflammatory phenotype and endotype

11 | WHICH PATIENTS MAY BENEFIT FROM AACT

From a clinical point of view, in patients with persistent uncontrolled asthma despite maximum treatment according to guidelines, AACT should be considered as a suitable treatment option. (Figure 5) These may be patients who do not respond to biologicals, who experience impaired quality of life, are oral steroid dependent, have frequent exacerbations and hospitalizations, severely impaired lung function, marked upper airway symptoms, or decreased exercise tolerance. Importantly, similar improvement in asthma control has been observed in sensitized and non-sensitized patients.[10] From an immunological point of view, the type 2 immune response, which is a significant driver of asthma pathology in eosinophilic and allergic asthma, is reduced during AACT. It is not known whether simultaneous use of biologicals targeting the IL-4 and IL-13 pathway or the IL-5 pathway during AACT further impacts the observed immune modulation. Non-eosinophilic non-allergic patients also showed decreased blood lymphocytes, improved lung function, and decreased lung inflammation after AACT.[11] Previously, no patient characteristics could predict significant improvement in AQLQ or FEV_1 after AACT.[166] These findings suggest that AACT is a treatment option irrespective of asthma phenotype. The specific effectiveness of AACT may lie in the observed rapid decrease in inflammation and immunomodulatory downregulation which enables the regain of asthma control as the basis for further improvement during multidisciplinary pulmonary rehabilitation. Further basic immunological and clinical research will be necessary to explore the opportunities of AACT as a natural treatment that targets biological pathways, and to further define which asthma phenotypes will benefit most from AACT and which patients will retain the effect most efficiently in their home environment. Randomized trials could compare AACT to other pulmonary rehabilitation programs, assess its cost-effectiveness, and identify which factor is the most contributing to the observed treatment effect. The use of European severe asthma registries that regularly collect data on patients with severe and uncontrolled asthma could also help to better understand the added value of AACT and the variation in treatment of severe asthma across Europe.

Key message

- AACT can be considered a suitable treatment option for patients with a persistent uncontrolled asthma despite maximum treatment according to guidelines.

12 | CONCLUSION AND PERSPECTIVES

Alpine altitude climate treatment takes advantage of the physical characteristics of moderate altitude and the favorable environmental characteristics of the alpine climate and combines this with personalized integrative multidisciplinary pulmonary rehabilitation approaches in an inpatient setting. These factors seem to contribute to the immunomodulatory effects reducing inflammatory responses and neuro-immune stress in patients with different asthma phenotypes.

Based on the available observational studies and expert opinion, AACT is a therapy for those asthma patients who, despite all the advances in medical science, still cannot achieve optimal control of their complex condition and therefore run the risk of falling into a downward spiral of loss of physical and mental health.

Well-designed and standardized randomized trials are needed in the future to corroborate the effects of AACT on clinical outcomes and to assess which factors mainly contribute to clinical improvements, which molecular mechanisms underlie successful AACT, and which asthma phenotypes profit more from AACT.

Core message

- The combination of altitude-related physical and alpine climate-related environmental characteristics and multidisciplinary personalized treatment during pulmonary rehabilitation support decreased inflammation and immune modulation in patients with uncontrolled asthma of all phenotypes. AACT can be seen as a natural treatment that targets biological pathways.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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