Alpine climate treatment of atopic dermatitis: a systematic review

K. B. Fieten¹,², A. C. G. Weststrate¹, E. J. van Zuuren³, C. A. Bruijnzeel-Koomen¹ & S. G. M. A. Pasmans¹,⁴

¹Department of (Pediatric) Dermatology and Allergology, University Medical Center Utrecht, Utrecht, the Netherlands; ²High Altitude Clinic Merem Dutch Asthma Center Davos, Davos, Switzerland; ³Department of Dermatology, Leiden University Medical Center, Leiden; ⁴Department of Pediatric Dermatology, Sophia Children’s Hospital, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands

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Keywords
alpine; atopic dermatitis; climate; high altitude; systematic review.

Abstract
Climate therapy has been used for decades in the treatment of atopic dermatitis (AD), but evidence of its effectiveness has not yet been assessed systematically. A systematic literature search in Medline, Embase, and the Cochrane library was performed to identify all original studies concerning alpine climate treatment. The risk of bias of individual studies was assessed following the Cochrane Handbook, and level of evidence was rated using GRADE guidelines. Fifteen observational studies were included concerning 40 148 patients. Four studies concerning 2670 patients presented follow-up data over a period of 1 year. Disease activity decreased in the majority of patients during treatment (96% of n = 39 006) and 12-month follow-up (64% of n = 2670). Topical corticosteroid use could often be reduced or stopped during treatment (82% of n = 1178) and during 12-month follow-up (72% of n = 3008). Quality assessment showed serious study limitations, therefore resulting in a very low level of evidence for the described outcomes. Randomized controlled trials designed with a follow-up period including well-defined patient populations, detailed description and measurement of applied interventions during climate therapy and using validated outcomes including cost-effectiveness parameters, are required to improve the evidence for alpine climate therapy as an effective treatment for patients with AD.

Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by subsequent exacerbations and remissions (1). Its prevalence is increasing worldwide, and AD is currently among the most common skin diseases in children (2). Itching, disturbed sleep, and time-consuming medical treatment regimens lead to a reduced experienced quality of life in patients with AD (3, 4).

AD is a complex disease with several genetic and environmental factors involved (5). A genetic predisposition leads to an atopic constitution and a disturbed immune response which results in chronic inflammation and an impaired skin barrier (6, 7). In several eczema birth cohorts, the association between AD and the subsequent development of asthma and allergic sensitization has been established (8, 9). Prevalence of allergic sensitization in children with AD varies between countries, ranging from 52% in Belgium to 83% in Australia (8). Around 30% of children diagnosed with AD will develop asthma later in life (10). Among adults with AD, there is also great variation in prevalence of allergic sensitization and asthma diagnosis (11).

Exposure to irritants and allergens, changes in physical environment (pollution, humidity), infections, and psychosocial or emotional factors are possible triggers for exacerbations (12). AD treatment is based on control of inflammation/infection, skin hydration, and trigger avoidance (13, 14). Treatment approaches include anti-inflammatory therapy with topical immunosuppressives (dermatocorticosteroids, calcineurin inhibitors) and antimicrobial treatment, according to current guidelines (13, 14). In more severe cases, phototherapy or systemic immunosuppressive treatment is needed. Patients are often reluctant and concerned about the use of corticosteroids and systemic immunosuppressive treatment. Because of the chronic nature of AD, alternative therapies are often considered, such as acupuncture, homeopathy,
dietary supplements/restrictions, and Chinese herbal medicine (15, 16). However, the efficacy of these therapies over regular therapy could not be demonstrated (17–19).

Climate therapy has been used since the 20th century for the treatment of various chronic inflammatory dermatoses and pulmonary diseases (20, 21). It combines anti-inflammatory treatment in a trigger-free environment with being hospitalized in a specialized clinic for a period of 4 weeks to 3 months. Climate therapy at seaside or mountain resorts has shown improvement in disease activity and reduced corticosteroid use in patients with AD (22–26). In asthma, treatment in high-altitude clinics has resulted in improved asthma control, asthma-related quality of life, and a reduced corticosteroid requirement (27–30). Clinics were built specifically for the rehabilitation of patients with AD or asthma in mountain areas of Switzerland (‘Dutch Asthma Center Davos’, Davos 1560 m, ‘Alexanderhausklinik Davos’, 1560 m, ‘Hochgebirgsklinik Davos’, 1560 m), Italy (‘Istituto Pio XII’ Misurina 1736 m), and south Germany (‘Santa Maria’, Oberjoch 1200 m, ‘Prinzregent Luitpolt’, Scheidegg 1000 m). However, it is unclear which mechanisms lead to the observed effect. Limited healthcare resources and further advances in evidence-based medicine have put the existence of specialized high-altitude clinics under pressure. It is important to quantify the direct and long-term effects of climate treatment, as significant improvement in AD severity is also observed after clinical treatment in unspecified climate zones (31).

Objective

The current systematic review summarizes the existing evidence for the clinical effect of alpine climate treatment for patients with AD.

Methods

Search process

A systematic literature search was performed including original studies published until July 3rd 2013. A sensitive search strategy was designed to retrieve all relevant articles from Medline, Embase, and the Cochrane library. We searched for ['atopic dermatitis' OR ‘eczema’ OR ‘neurodermatitis’ OR ‘neurodermitis’] AND ['climate' OR ‘climatology’ OR ‘climatic therapy’ OR ‘climatic therapy’ OR ‘altitude’ OR ‘mountains’ OR ‘alpine’] as medical subject headings or as main key words in the title or abstract. Two researchers (KF and GW) selected potentially eligible reports independently. Any disagreement on inclusion of studies was resolved by discussion with the other author (SP) until consensus was reached. Reference lists of retrieved articles and previously published reviews were hand-searched to identify further relevant studies.

Inclusion and exclusion criteria

Studies were included when alpine climate treatment was mentioned in title or abstract, and part of the study population was diagnosed with AD. No limitation was set on study design, age of the patients, duration of treatment, or outcome measure. Studies written in English or German were included. Studies concerning climate treatment in other climate regions, such as maritime climate, or in artificial conditions, such as climate chambers, were excluded.

Outcomes

The main outcome was disease severity after climate therapy, measured with any scoring system. Secondary outcomes were topical or systemic corticosteroid use, disease severity during follow-up, corticosteroid use during follow-up, and other reported outcomes.

Risk of bias assessment

We assessed the risk of bias of the included studies according to the domain-based evaluation described in Chapter 8 and 13 of the Cochrane Handbook for Systematic Reviews of Interventions (32). We evaluated selection bias, performance bias, attrition bias, detection bias, reporting bias, and publication bias.

Data extraction

The following study characteristics were collected: author and year of publication, target population of the study (including age and sample size), altitude, name and location of the clinic, treatment duration, and reported outcome variables. Outcome variables direct after treatment and during follow-up were separately extracted. Not all studies reported the same outcome measures; therefore, different studies contribute to the different outcomes. Data from studies with similar outcome measures were transformed and pooled. Regarding disease severity, several scoring systems were used. All PGAs (physician graded assessments) with a 4- or 5-point scale were reduced to a 3-point scale (better, same, and worse) for comparability. One study used number of exacerbations during follow-up as an outcome, and this was transformed to a course of disease outcome where no or less exacerbations during follow-up were categorized as better, more exacerbations as worse, and the same number of exacerbations as same (33). Studies reporting SCORAD scores are reported separately. Self-assessments by patients with a 4 or 5-point scale were also transformed to a 3-point scale (better, same, and worse) and pooled.

Data on corticosteroid use were differentiated for topical and systemic treatment, reduced to a yes/no variable for current use, and pooled.

Authors were contacted to clarify results when needed. When data extraction was not possible or when no absolute patient numbers were provided and authors did not respond to the request for additional information, studies were not included in the outcome tables. The overall quality of evidence was rated using GRADE guidelines (34). The review was reported according to the PRISMA statement (35).
Data analysis

For each outcome, data from the different studies were transformed and pooled, and total and relative patient numbers were calculated. It was not possible to further analyze the extracted data or to do a meta-analysis.

Results

Studies included in the review

Results of our search strategy are shown in Fig. 1. The search yielded 143 hits in Medline and 112 hits in Embase of which 61 were duplicate hits. Of a total of 200 articles, 65 were eligible for full text screening. Three were excluded because of language (two Russian and one Bulgarian) (36–38). Two were excluded because they showed duplicate data from an already included study (33, 39). Six were excluded because they were part of two growing cohorts (33, 39–45), and the most recent publications with the largest cohorts were included (22, 46). Three were excluded because they described only individual case reports (47, 48). Fifteen studies were finally included concerning 40,148 patients. Study characteristics are shown in Table 1. No randomized trials were identified. All studies were observational, and control groups were not incorporated in the study design. The majority of studies was written in German and published in German journals, restricting their accessibility to international readers.

Risk of bias

A risk of bias assessment was carried out and summarized in Table 2.

Selection bias

Some studies used specific inclusion criteria, but most studies included patients with AD who were admitted to an alpine clinic. These patients may be different from the wider population of patients with AD. Patient characteristics of relevant atopic comorbidities, such as asthma and rhinitis, were provided, but the results of climate therapy were not differentiated accordingly. There may be further selection bias due to the language restriction on the systematic search (language bias) and because most studies were published by German research groups.

Performance bias

None of the studies mentioned an intervention protocol or any details concerning climate therapy, and it was not possible to assess whether the intervention was carried out according to protocol. Duration of climate therapy varied between patients and between different clinics. Furthermore, little or no information was provided on received pharmacological interventions other than corticosteroids during climate therapy.

Detection bias

In none of the studies, outcomes were assessed blinded. Outcome measures such as course of disease or exacerba-
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Period of data collection</th>
<th>Population (n)</th>
<th>Treatment center</th>
<th>Altitude (m)</th>
<th>Duration of treatment</th>
<th>Duration of follow-up</th>
<th>Outcome</th>
<th>Outcome during follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>à Porta 2000</td>
<td>1990–1994</td>
<td>adults (n = 97)</td>
<td>Davos: Zürcher Höhenklinik</td>
<td>1600 m</td>
<td>32 days</td>
<td>1 year</td>
<td>PGA</td>
<td>Corticosteroid use</td>
</tr>
<tr>
<td>Borelli 1967</td>
<td>1966–1967</td>
<td>Adolescents/adults (n = 230)</td>
<td>Davos: Alexanderhausklinik</td>
<td>1560 m</td>
<td>Not mentioned</td>
<td>n/a</td>
<td>Change in eosinophils</td>
<td>SPT</td>
</tr>
<tr>
<td>Borelli 1995</td>
<td>1961–1995</td>
<td>Adults/children (n = 31,438)</td>
<td>Davos: Sanatorium Valbella (Alexanderhausklinik)</td>
<td>1560 m</td>
<td>6 weeks</td>
<td>n/a</td>
<td>PGA</td>
<td>Corticosteroid use</td>
</tr>
<tr>
<td>Drosner 1988</td>
<td>1986</td>
<td>Adults (n = 56)</td>
<td>Davos: Alexanderhausklinik</td>
<td>1560 m</td>
<td>4–5 weeks</td>
<td>n/a</td>
<td>ECP</td>
<td>n/a</td>
</tr>
<tr>
<td>Duve 1991</td>
<td>Not mentioned</td>
<td>Adults/children (n = 624)</td>
<td>Davos: Alexanderhausklinik</td>
<td>1560 m</td>
<td>4–8 weeks</td>
<td>1 year</td>
<td>PGA</td>
<td>n/a</td>
</tr>
<tr>
<td>Eberlein 2009</td>
<td>2003–2004</td>
<td>Adults/children (n = 139)</td>
<td>Germany: Santa Maria, Fachklinik Allgau, Asthazentrum Buchenhöhe</td>
<td>1200 m</td>
<td>3–4 weeks</td>
<td>n/a</td>
<td>SCORAD</td>
<td>TARC</td>
</tr>
<tr>
<td>Fuchs 1959</td>
<td>1958</td>
<td>Adults (n = 393)</td>
<td>Germany: Sachsenbaude</td>
<td>1130 m</td>
<td>8 weeks</td>
<td>n/a</td>
<td>PGA</td>
<td>n/a</td>
</tr>
<tr>
<td>Heine 1995</td>
<td>1987–1988</td>
<td>Children/adolescents (n = 375)</td>
<td>Davos: Alexanderhausklinik</td>
<td>1560 m</td>
<td>Around 6 weeks</td>
<td>1 year</td>
<td>PGA</td>
<td>Corticosteroid use</td>
</tr>
<tr>
<td>Kneist 1987</td>
<td>1986</td>
<td>Adults/children (n = 1465)</td>
<td>Davos: Alexanderhausklinik</td>
<td>1560 m</td>
<td>6 weeks</td>
<td>1 year</td>
<td>PGA</td>
<td>Corticosteroid use</td>
</tr>
<tr>
<td>Petermann 2000</td>
<td>Not mentioned</td>
<td>Children/adolescents (n = 102), SCORAD &gt;25, use of systemic CS excluded</td>
<td>Germany: Santa Maria Prinzregent Luitpold</td>
<td>1200 m</td>
<td>4 weeks</td>
<td>2 years</td>
<td>SCORAD</td>
<td>n/a</td>
</tr>
<tr>
<td>Petermann 2004</td>
<td>1996–1998</td>
<td>Children/adolescents (n = 55), SCORAD &gt;25, use of systemic CS excluded</td>
<td>Germany: Santa Maria</td>
<td>1200 m</td>
<td>4 weeks</td>
<td>n/a</td>
<td>SCORAD</td>
<td>ECP</td>
</tr>
<tr>
<td>Simon 1999</td>
<td>Not mentioned</td>
<td>Adults (n = 33), use of systemic CS excluded</td>
<td>Davos: Alexanderhausklinik</td>
<td>1560 m</td>
<td>4–6 weeks</td>
<td>n/a</td>
<td>SCORAD</td>
<td>ECP</td>
</tr>
<tr>
<td>Trichskorn 1991</td>
<td>Not mentioned</td>
<td>Adults (n = 20)</td>
<td>Davos: Alexanderhausklinik</td>
<td>1560 m</td>
<td>4 weeks</td>
<td>n/a</td>
<td>SCORAD</td>
<td>ECP</td>
</tr>
<tr>
<td>Walker 1993</td>
<td>Not mentioned</td>
<td>Adults (n = 12)</td>
<td>Davos: Zürcher Höhenklinik</td>
<td>1600 m</td>
<td>3–6 weeks</td>
<td>n/a</td>
<td>Skin intensity score eosinophils</td>
<td>ECP</td>
</tr>
</tbody>
</table>

CS, corticosteroids; PGA, physician graded assessment; SPT, skin prick test; SCORAD, scoring of atopic dermatitis; TARC, thymus and activation regulated chemokine; IL-16, interleukin 16; ECP, eosinophil cationic protein; EPX, eosinophil urinary protein X; TEWL, transepidermal water loss; n/a, not applicable.
tions were not clearly defined, and in most studies, unvalidated outcome measures, such as PGA, were used. When patients and dermatologists both assessed disease severity after treatment, the treating dermatologists reported greater improvement compared to the self-assessment of the patient.

**Reporting bias**

Six of fifteen included studies did not report all outcome variables that were stated in the study protocol or reported outcome variables only for a part of the cohort, without providing an explanation for the missing data. One study was designed with a follow-up period of 2 years, but did not report any data at this point (49). One study did not report absolute patient numbers but only percentages during the follow-up period, whereas another study did not present numbers but vaguely described disease activity after 6 months follow-up as ‘disease stabilized for more than 6 months in more than 50% of patients’ (50, 51).

**Attrition bias**

In none of the studies, handling of missing data or dropout during intervention was reported. During follow-up, either no absolute patient numbers were provided, making it impossible to assess the rate of loss-to-follow-up or only patients with complete data were included. When absolute patient

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### Table 2 Risk of bias assessment of studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Was AD diagnosis according to criteria?</th>
<th>Were clear inclusion/exclusion criteria used?</th>
<th>Were detailed patient characteristics on other atopic diseases provided?</th>
<th>Were concurrent interventions or unintended exposures described?</th>
<th>Validated outcome measures</th>
<th>Blinded assessment of outcome</th>
<th>Complete study protocol stated</th>
<th>All measurements from protocol reported</th>
<th>Loss-to-follow-up or dropout</th>
</tr>
</thead>
<tbody>
<tr>
<td>à Porta 2000</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>8%</td>
</tr>
<tr>
<td>Borelli 1995</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>U</td>
</tr>
<tr>
<td>Borelli 1967</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>U</td>
</tr>
<tr>
<td>Drosner 1988</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>U</td>
</tr>
<tr>
<td>Drzimalla 1999</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>49%</td>
</tr>
<tr>
<td>Duve 1991</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y†</td>
</tr>
<tr>
<td>Eberlein 2009</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>U</td>
</tr>
<tr>
<td>Fuchs 1959</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>U</td>
</tr>
<tr>
<td>Heine 1995</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>50%</td>
</tr>
<tr>
<td>Kneist 1987</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y*</td>
<td></td>
</tr>
<tr>
<td>Petermann 2000</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y*</td>
</tr>
<tr>
<td>Petermann 2004</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>U</td>
</tr>
<tr>
<td>Simon 1999</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>U</td>
</tr>
<tr>
<td>Triebskorn 1991</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>U</td>
</tr>
<tr>
<td>Walker 1993</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>U</td>
</tr>
</tbody>
</table>

Y, yes; N, no; U, unclear.

*Follow-up numbers were not mentioned.

†Only patients with complete data at all time points were included.
numbers were provided, loss-to-follow-up increased up to 50%, making attrition bias very likely.

Publication bias
For this review, only published studies were considered. None of the studies was sponsored by industry; however, most studies were carried out by alpine clinics assessing the effectiveness of their own therapy. There were no reports identified with negative results, but as there were no control groups, it was not possible to create funnel plots to find evidence of publication bias.

Outcomes
The quality of the evidence for the pooled outcome measures as summarized in Table 3 was rated very low. Data extrac-
Table 4 Disease severity measured with Physician Graded Assessment or SCORAD by dermatologist or self-assessment by the patient

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study population (n)</th>
<th>Outcome (n reported for outcome)</th>
<th>Outcome (reported and n)</th>
<th>Outcome (reported and n)</th>
<th>Mean (SD) decrease from baseline</th>
<th>Follow-up</th>
<th>Outcome during follow-up (n reported for outcome)</th>
<th>Proportion (%) and (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>à Porta</td>
<td>Adults (n = 97)</td>
<td>PGA (better, same and, worse)  (n = 97)</td>
<td>99%, 1%, 0%, n = 96 n = 1, n = 0</td>
<td>Self-assessment at discharge (n = 99)</td>
<td>93%, 7%, 0%, n = 83 n = 6, n = 0</td>
<td>1 year</td>
<td>Course of disease 6-12 months after treatment (better, same and, worse) (n = 89)</td>
<td>56%, 35%, 9% n = 50, n = 31, n = 8</td>
</tr>
<tr>
<td>Borelli</td>
<td>Adults/children (n = 31 438)</td>
<td>PGA (better, same and, worse) (n = 31 438)</td>
<td>97.2%, 2.4%, 0.4%, n = 30 568, n = 754, n = 126</td>
<td>n/a</td>
<td>n/a</td>
<td>1 year</td>
<td>Course of disease 8-12 months after treatment (better, same and, worse) (n = 2392)</td>
<td>*64.8%, 24.4%, 10.8%, n = 1550, n = 584, n = 258</td>
</tr>
<tr>
<td>Drzimala</td>
<td>Adults (n = 4660)</td>
<td>PGA (better, same and, worse)  (n = 4660)</td>
<td>93.6%, 5.4%, 1%, n = 4362, n = 251, n = 47</td>
<td>n/a</td>
<td>n/a</td>
<td>1 year</td>
<td>Course of disease 8-12 months after treatment (better, same and, worse) (n = 2392)</td>
<td>56%, 35%, 9% n = 50, n = 31, n = 8</td>
</tr>
<tr>
<td>Duve</td>
<td>Adults/children (n = 624)</td>
<td>PGA (better, same and, worse) (n = 624)</td>
<td>97.6%, 2.2%, 0.2%, n = 609, n = 14, n = 1</td>
<td>n/a</td>
<td>n/a</td>
<td>1 year</td>
<td>Course of disease 8-12 months after treatment (better, same and, worse) (n = 2392)</td>
<td>56%, 35%, 9% n = 50, n = 31, n = 8</td>
</tr>
<tr>
<td>Fuchs</td>
<td>Adults (n = 393)</td>
<td>PGA (better, same and, worse)  (n = 393)</td>
<td>88.8%, 9.4%, 1.8%, n = 349, n = 37, n = 7</td>
<td>n/a</td>
<td>n/a</td>
<td>1 year</td>
<td>Course of disease 8-12 months after treatment (better, same and, worse) (n = 2392)</td>
<td>56%, 35%, 9% n = 50, n = 31, n = 8</td>
</tr>
<tr>
<td>Heine</td>
<td>Children/adolescents (n = 375)</td>
<td>PGA (better, same and, worse) (n = 329)</td>
<td>98.5%, 0.6%, 0.9%, n = 324, n = 2, n = 3</td>
<td>Self-assessment (better, same and, worse) (n = 368)</td>
<td>91%, 6%, 3%, n = 335, n = 22, n = 11</td>
<td>1 year</td>
<td>Course of disease 8-12 months after treatment (better, same and, worse) (n = 2392)</td>
<td>56%, 35%, 9% n = 50, n = 31, n = 8</td>
</tr>
<tr>
<td>Kneist</td>
<td>Adults/children (n = 1465)</td>
<td>PGA (better, same and, worse) (n = 1065)</td>
<td>96%, 3%, 1%, n = 1012, n = 30, n = 14</td>
<td>Self-assessment (better, same and, worse) (n = 1399)</td>
<td>95.5%, 0%, 1.5%, n = 1399, n = 22, n = 11</td>
<td>1 year</td>
<td>Course of disease 8-12 months after treatment (better, same and, worse) (n = 189)</td>
<td>63%, 31%, 4.9% n = 66, n = 26</td>
</tr>
<tr>
<td>Total</td>
<td>n = 39 052</td>
<td>PGA (better, same and, worse)  (n = 39 006)</td>
<td>96.5%, 3%, 0.5%, n = 37 719, n = 1088, n = 199</td>
<td>Self-assessment (better, same and, worse) (n = 1817)</td>
<td>95%, 1.5%, 1.7%, n = 1817, n = 28, n = 3</td>
<td>1 year</td>
<td>Course of disease 8-12 months after treatment (better, same and, worse) (n = 2392)</td>
<td>64%, 25%, 11% n = 1720, n = 658, n = 292</td>
</tr>
</tbody>
</table>

Notes: *n/a: not available; †n/a: not applicable; ‡ More than 50% of patients in more than 50% of patients.
Table 4 (continued)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study population (n)</th>
<th>Outcome (n reported for outcome)</th>
<th>Mean (SD) decrease from baseline</th>
<th>Outcome during follow-up (n reported for outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eberlein 2009</td>
<td>Children (n = 43) Treatment center Oberjoch Children (n &lt; 24, exact number unknown) Treatment center Berchtesgaden Adults (n = 23) Treatment center Pfronten Adults (n &lt; 24, exact number unknown) Treatment center Berchtesgaden</td>
<td>SCORAD</td>
<td>−15.70 (12.57) n/a n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Petermann 2000</td>
<td>Children/adolescents (n = 102), SCORAD &gt;25</td>
<td>SCORAD</td>
<td>−22.70 (8.68) 2 years</td>
<td>Self-assessment of skin Not mentioned</td>
</tr>
<tr>
<td>Simon 1999</td>
<td>Adults (n = 33)</td>
<td>SCORAD</td>
<td>−12.7 n/a n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Walker 1993</td>
<td>Adults (n = 12)</td>
<td>Skin intensity score</td>
<td>51% n/a n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

n/a, not applicable.
*Percentages are deduced from graph, not mentioned in text.
†Percentages were mentioned, but no exact patient numbers.
‡Percentages do not add up to 100%.
§Excluding Kneist and Duve.
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Population (n)</th>
<th>Outcome (n reported for outcome)</th>
<th>Proportion (%) and (n)</th>
<th>Outcome (n reported for outcome)</th>
<th>Proportion (%) and (n)</th>
<th>Follow-up</th>
<th>Outcome during follow-up</th>
<th>Proportion (%) and (n)</th>
<th>Outcome during follow-up</th>
<th>Proportion (%) and (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>à Porta 2000</td>
<td>Adults (n = 97)</td>
<td>Free of topical corticosteroids (n = 71)</td>
<td>70% (50 of 71)</td>
<td>Free of systemic corticosteroids (n = 13)</td>
<td>92% (12 of 13)</td>
<td>1 year</td>
<td>Topical corticosteroid use (none, less, same, more)</td>
<td>26% (13 of 50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drzimalla 1999</td>
<td>Adults (n = 4660)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duve 1991</td>
<td>Children and adults (n = 624)</td>
<td>Free of topical corticosteroids (n = 624)</td>
<td>†**57%</td>
<td>Free of systemic corticosteroids (n = 624)</td>
<td>†**86%</td>
<td>1 year</td>
<td>Topical corticosteroid use (none, less, same, more)</td>
<td>†n = 624 none or less 77%, same 15%, more 9%</td>
<td>Systemic corticosteroid use after 12 months follow-up</td>
<td>††n = 624 90% none, 4% less, 2% same, 2% more</td>
</tr>
<tr>
<td>Heine 1995</td>
<td>Children and adolescents (n = 375)</td>
<td>Free of topical corticosteroids (n = 188)</td>
<td>75% (140 of 188)</td>
<td>Free of systemic corticosteroids (n = 7)</td>
<td>57% (4 of 7)</td>
<td>1 year</td>
<td>Topical corticosteroid use (none, less, same, more)</td>
<td>†n = 178 none 62% less 25% same 9% more 4%</td>
<td>Systemic corticosteroid use</td>
<td>†n = 133 none 94% less 3% same 1.5% more 1.5%</td>
</tr>
<tr>
<td>Kneist 1987</td>
<td>Children and adults (n = 1465)</td>
<td>Free of topical corticosteroids (n = 919)</td>
<td>84% (774 of 919)</td>
<td>Free of systemic corticosteroids (n = 82)</td>
<td>77% (63 of 82)</td>
<td>1 year</td>
<td>Topical corticosteroid use (none, less, same, more)</td>
<td></td>
<td>Total corticosteroid use (none, less, same, more) after 6 months follow-up</td>
<td>*none 40.2% less 38.5% same 17.4% more 3.8%</td>
</tr>
<tr>
<td>Total n = 7221</td>
<td>n‡ = 1178 using topical corticosteroids (n = 964 of 1178)</td>
<td>82%</td>
<td>n = 102 using systemic corticosteroids (n = 79 of 102)</td>
<td>77%</td>
<td>n‡ = 3008 (n = 2171 of 3008)</td>
<td>72%†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Follow-up numbers were not mentioned in the text.
†Data presented for entire patient cohorts and not subset of patients treated with corticosteroids.
‡Excluding Kneist.
§Excluding Duve.
¶Percentages are deduced from graph, not mentioned in text.
**Percentages do not add up to 100%. 

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Table 5 Corticosteroid use
Table 6 Eosinophil markers

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Population (n)</th>
<th>Outcome</th>
<th>ECP mean (SD)</th>
<th>Number of eosinophils mean (SD)</th>
<th>EPX</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borelli 1967</td>
<td>Adolescents/adults (n = 140)</td>
<td>Change in number of eosinophils</td>
<td></td>
<td>n = 80 less, n = 15 unchanged, n = 25 more</td>
<td></td>
<td>No correlation calculated with clinical outcome. Magnitude of change not calculated. Data not reported for all patients. Statistical significance not reported.</td>
</tr>
<tr>
<td>Eberlein 2009</td>
<td>Adults/children (n = 139/n = 165)</td>
<td>Change in number of eosinophils ECP</td>
<td>Berchtesgaden 24.0 (15.1) to 21.7 (11.7) P &lt; 0.05, Oberjoch 20.0 (20.2) to 16.9 (12.0) p not reported Pfronten 16.9 (21.3) to 15.2 (15.4) p not reported</td>
<td>Berchtesgaden 5.8 (3.4) to 4.8 (2.4) P &lt; 0.05, Oberjoch 280.0 (231.2) to 247.3 (172.4), Pfronten 4.6 (3) to 4.3 (3.5)</td>
<td></td>
<td>Results are divided by treatment center and not by diagnosis (AD, asthma and COPD reported together)</td>
</tr>
<tr>
<td>Petermann 2004</td>
<td>Children/adolescents (n = 59), SCORAD &gt;25</td>
<td>ECP</td>
<td>No change in ECP after treatment P = 0.7</td>
<td></td>
<td>Decrease in EPX after treatment P = 0.000</td>
<td>Significant correlation between SCORAD and EPX, not ECP</td>
</tr>
<tr>
<td>Simon 1999</td>
<td>Adults (n = 33)</td>
<td>ECP</td>
<td>Median ECP 33 mcg to 17.5 mcg P = 0.001</td>
<td></td>
<td></td>
<td>Parallel improvement in SCORAD, significant correlation with ECP calculated, p not mentioned</td>
</tr>
<tr>
<td>Walker 1993</td>
<td>Adults (n = 12)</td>
<td>Number of eosinophils ECP</td>
<td>21% decrease P &lt; 0.05</td>
<td>43% decrease P &lt; 0.003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
tion was complicated because of incomplete reporting; therefore, not all studies with relevant outcomes could be included.

**Disease activity**

Direct after climate treatment, disease activity was decreased in the majority of 39,503 patients (included in 11 studies) as scored by a dermatologist. Validated scoring systems, such as SCORAD, were used in four studies including 451 patients (49, 52–54). PGA was used in seven studies including 39,052 patients (22, 46, 50, 51, 55–57). In three studies including 1922 patients, patients were asked to judge their clinical improvement and reached similar conclusions as the dermatologist, but differed on the degree of improvement (51, 55, 57). Six studies were designed with a follow-up period, but one did not report outcomes of the 2-year follow-up period, the other mentioned percentages, and no exact patient numbers during follow-up (49, 51). Dropout during follow-up was not addressed in any of the studies, and one study simply excluded patients with incomplete data. In the remaining four studies, 2,670 patients were asked to return questionnaires after 3, 6, and 12 months to judge AD activity with a scoring system, a global assessment or period until first relapse (50, 55–57) (Table 4). The majority (64%) of these patients reported a decreased disease activity up to 12 months after treatment and an overall improved course of disease compared to the year before treatment.

**Corticosteroid use**

Corticosteroid use was mentioned in six studies, but one study did not differentiate between patients with AD, psoriasis, contact dermatitis, and other diagnoses, and its data could therefore not be included in Table 5 (46). In one study, percentages were mentioned, but these did not add up to 100% [50]. In the three studies in which exact patient numbers on topical corticosteroid use are mentioned, 1178 of 1937 patients (61%) used topical corticosteroids at start of climate therapy (51, 55, 57). Corticosteroid use during follow-up is reported in most studies for the whole patient cohort, including patients who were not using corticosteroids during climate treatment. Only one study provided data on topical corticosteroid use during follow-up in the subgroup of patients who were able to stop corticosteroids during climate therapy (55).

**Other outcomes**

Several studies were identified reporting biomarkers or other translational parameters (Table 6). Five studies including 634 patients measured number of eosinophils, eosinophil cationic protein (ECP), and eosinophil protein X (EPX) in urine direct after climate treatment (52–54, 58, 59). ECP decreased in three of four studies, EPX decreased in one study, and number of eosinophils decreased in three studies parallelising the observed improvement in SCORAD. A significant corre-

Skin prick tests with intracutaneously applied histamine, serotonin, acetycholine, and bradykinin showed a decrease in skin reactivity after alpine climate therapy; statistical significance was not calculated (58). Skin prick tests with recall antigens showed a significant increase in skin reactivity after climate therapy (60). Transdermal water loss decreased significantly after treatment, but remained high compared to healthy controls (61). TARC levels were stable before and after treatment at different clinics (52).

**Discussion**

**Main findings**

Our systematic search for the effect of alpine climate therapy of patients with AD has identified only observational studies. The largest study is a cohort of 31,480 patients treated in a clinic in Davos, Switzerland, from 1961 to 1995 (46). Disease activity was decreased in 96% of patients at the end of climate therapy. Topical as well as systemic corticosteroid use could be reduced or stopped during treatment in 80% of patients. Up to 12 months after treatment, 64% of patients reported a decreased disease activity; an overall improved course of disease compared to the year before treatment and 72% reported no or reduced topical corticosteroid use. Similar results were reported for children and adults.

**Risk of bias**

The quality of the body of evidence for the separate outcomes was very low. All identified studies had methodological and other limitations. In most identified studies, clinical improvement was scored by the physician as improved, not improved, or worsened. Physician global assessments are also used nowadays, because they are fast and easy to perform and give a good indication of the course of disease when repeated over time (62). In more recent studies, SCORAD was used to measure clinical activity during climate therapy, allowing for a more objective estimation of the treatment effect (49, 52, 53, 59). However, the measurements were not performed by an independent and blinded physician.

The majority of available data is provided by three alpine clinics, reporting on patients with AD who were treated in these clinics during a certain time period. Selection bias is a problem, because there have been no generally accepted criteria for whom alpine climate therapy should be provided (46). Also, the position of climate therapy in the healthcare system changed over time, decreasing its availability to patients with AD. The relatively low rate of topical corticosteroid use could imply that patients with mild AD or concomitant diagnoses of severe asthma and mild AD were overrepresented in the study sample. However, patient characteristics were not well described, and data on other pharmacological therapy were not provided. In most studies, style of reporting was very global and details were often lacking, making it difficult to interpret the data. Six studies
were designed with a follow-up period, but risk of bias was substantial due to the high dropout rates. Clinical efficacy during follow-up is important for reasons of cost-effectiveness as long-term beneficial effects may show the added value of alpine climate therapy compared to other treatment options.

It has been hypothesized that the lack or low level of respiratory allergens may contribute to the clinical effect of alpine treatment. The results in this systematic review of alpine climate therapy for patients with AD are very similar to what was reported of alpine climate therapy for patients with AA (20). However, the latter was no systematic review and no level of evidence was assigned to the reported findings. Also, beneficial effects of alpine climate therapy irrespective of atopic status have been reported in children and adults with AA (30, 59, 63). But because no trials have been conducted and no control groups were included in the observational studies, there is no reliable data on which elements of alpine climate treatment are responsible for the observed effect. Multidisciplinary evaluation and treatment in a regular outpatient setting for several days also shows reduction of disease activity, corticosteroid use, and improved quality of life up to 2 years after the described treatment program (31, 64). This suggests that apart from the climate, other elements may be important during alpine climate therapy, for example the multidisciplinary approach or the increased adherence to treatment.

**Conclusion**

To our knowledge, this is the first systematic review on the outcomes of alpine climate treatment of patients with AD

**Conflicts of interest**

The authors declare that they have no conflicts of interest.

**Author contributions**

KF participated in literature search, data collection and analysis, manuscript writing, and final approval of the manuscript. GW participated in literature search, data collection, and final approval of the manuscript. EZ participated in data analysis, critical revision, and final approval of the manuscript. CBK participated in critical revision and final approval of the manuscript. SP participated in literature search, data collection and analysis, critical revision, and final approval of the manuscript. All authors read and approved the final manuscript.

**References**

18. Roll S, Reinhold T, Pucht D, Brinkhaus B, Icke K, Staab D et al. Comparative effectiveness of homeopathic vs. conventional therapy in usual care of atopic eczema in using the Cochrane Handbook for assessing risk of bias, GRADE guidelines for assessing level of evidence, and PRISMA guidelines for reporting. The results of this systematic review provide very low quality evidence that alpine climate therapy results in decreased disease activity and reduced corticosteroid requirement direct and up to 1 year after treatment in patients with AD. Randomized controlled trials designed with a follow-up period including well-defined patient populations, detailed description, and measurement of applied interventions during climate therapy and using validated outcomes including cost-effectiveness parameters are required to improve the evidence for alpine climate therapy as an effective treatment for patients with AD.
Alpine climate treatment of atopic dermatitis


