

ORIGINAL ARTICLE

Clinical Allergy

Effectiveness of alpine climate treatment for children with difficult to treat atopic dermatitis: Results of a pragmatic randomized controlled trial (DAVOS trial)

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Summary

Background: Alpine climate treatment has historically been used in Europe to treat atopic dermatitis (AD), but no randomized trials have been conducted to provide evidence for its effectiveness.

Objective: To investigate the long-term effectiveness of alpine climate treatment for children with difficult to treat AD.

Materials & Methods: A pragmatic, open, randomized controlled trial was conducted. Children diagnosed with AD that was considered difficult to treat, aged between 8 and 18 years and willing to be treated in Switzerland were randomized to a six-week personalized integrative multidisciplinary treatment period in a clinical setting in the alpine climate (Switzerland) or an outpatient setting in moderate maritime climate (Netherlands). Study assessments were conducted at the Wilhelmina Children's Hospital; an electronic portal was used for the collection of questionnaire data. Primary outcomes were disease activity (SAEASI), quality of life (CDLQI) and catastrophizing thoughts (JUCKKI/JU) 6 months after intervention. Other assessments were immediately and 6 weeks after intervention. Subgroup analyses concerned asthma-related outcomes. Children were randomly assigned to either the intervention or control group using a covariate adaptive randomization method, taking age and asthma diagnosis into account. Children, parents and healthcare professionals involved in treatment were not blinded to group assignment. Data were analysed according to intention-to-treat with linear mixed-effects models for continuous outcomes. The trial is registered at Current Controlled Trials ISCRTN88136485.

Results: Between 14 September 2010 and 30 September 2014, 88 children were enrolled in the trial, 84 children were randomized (41 assigned to intervention, 43 to control) of whom 77 completed the intervention (38 of 41 (93%) intervention, 39 of 43 (91%) control) and 74 completed follow-up (38 of 41 (93%) intervention, 36 of 43 (84%) control). Six months after intervention there were no significant differences between the groups on disease activity (SAEASI mean difference -3.4 (95%

CI -8.5 to 1.7)), quality of life (CDLQI mean difference -0.3 (95%CI -2.0 to 1.4)) and catastrophizing thoughts (JUCCKI/JU subscale mean difference -0.7 (95%CI -1.4 to -0.0)). Immediately and 6 weeks after intervention, disease activity and quality of life were significantly different in favour of alpine climate treatment. Mean differences on SAEASI were -10.1 (95%CI -14.5 to -5.8) and -8.4 (95%CI -12.2 to -4.6) and on CDLQI -1.9 (95%CI -3.3 to -0.5) and -1.5 (95%CI -2.8 to -0.3) immediately and 6 weeks after the intervention, respectively. There were no long-term differences on asthma-related outcomes. Five serious adverse events occurred during the study period, which were not thought to be related to the treatment.

Conclusions & Clinical relevance: For children with difficult to treat AD, there was no additional long-term benefit of alpine climate treatment, in contrast to the short-term, compared to an outpatient treatment programme in moderate maritime climate, using a personalized integrative multidisciplinary treatment approach.

KEYWORDS

asthma, atopic dermatitis, climate, environment and hygiene hypothesis, multidisciplinary, pediatrics, quality-of-life, rct, rhinitis

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by itchy lesions and subsequent exacerbations and remissions. Disease incidence has increased the last decades.¹ Currently, approximately 10%-20% of children in Western Europe are affected.¹ The majority is diagnosed with mild AD (67%), others have moderate (26%) or severe AD (7%).² Approximately, 10% of children with moderate-to-severe AD (3% of all affected children) do not respond well to regular treatment and are considered difficult to treat.³ These children are unable to gain sufficient disease control and often have an extensive treatment history, with frequent hospitalizations and use of systemic immunosuppressive treatment. Furthermore, they often have mental health problems such as anxiety and depression.⁴ AD has an adverse effect on the quality of life of affected children and their families.⁵ Increasing disease severity further reduces reported quality of life.⁶ Furthermore, AD severity is directly related to increased prevalence of asthma, allergic rhinitis or food allergies.⁷

Multidisciplinary treatment programmes, involving dermatologists, paediatric allergists, dermatology nurses and paediatric psychologists, have been developed for children who do not respond well to regular treatment and often result in clinical improvement.^{8,9} The common elements included in these programmes are education, treatment management and psychological or behavioural interventions aimed at coping with disease. In addition to improving disease activity, these programmes address itching and scratching, sleep disruption, challenges in disease management including adherence to treatment, psychosocial problems and education of children and their families. However, these programmes are mostly geared towards younger children.⁹

Climate change to seaside or mountain resorts for the treatment of allergic diseases in children has been studied before.^{10,11} Alpine climate treatment has been used for decades as a treatment option for asthma and AD in Europe.¹⁰ Children are admitted to specialized clinics for a period of 4 weeks to 3 months, while they are treated with anti-inflammatory medication within a personalized integrative multidisciplinary approach involving simultaneous treatment by dermatologists, allergists, specialized nurses, paediatric psychologists, physiotherapists and dieticians.¹⁰ The alpine climate environment is characterized by a reduced exposure to aeroallergens such as pollen and an absence of house dust mite, a decreased level of pollution and an increased exposure to UV radiation.¹¹ Observational studies have shown that alpine climate treatment improves disease activity in the long term.¹⁰ However, the effectiveness of alpine climate treatment has not been established in randomized trials.

In the DAVOS trial, we compare the effectiveness of inpatient alpine climate treatment with an outpatient treatment programme in moderate maritime climate using a personalized integrative multidisciplinary treatment approach. The objective of this pragmatic randomized controlled trial was to investigate the long-term effectiveness of alpine climate treatment for children and adolescents with difficult to treat AD.

2 | METHODS

2.1 | Study design

A pragmatic, open, randomized controlled trial was conducted in which inpatient treatment in a Dutch alpine climate clinic located at 1560 metres altitude in Switzerland (Merem Dutch Asthma Center Davos, Davos) was compared with an outpatient treatment

programme in moderate maritime climate in the Netherlands (Wilhelmina Children's Hospital, Utrecht) both using a personalized, integrative, multidisciplinary treatment approach. Study procedures were reviewed and approved by the institutional review board of the University Medical Center Utrecht, the Netherlands (09-192/K). The trial is registered at Current Controlled Trials ISRCTN88136485. The detailed study protocol has been published elsewhere.¹²

2.2 | Participants

Dutch children and adolescents with difficult to treat AD were eligible for participation in the trial. We defined difficult to treat as use of at least a class 3 topical corticosteroid and not being able to step down, or current use of systemic immunosuppressive treatment, or repeated treatment with potent topical corticosteroids or systemic immunosuppressive treatment, or a history of use of systemic treatment, or a significant impact of AD on the child's or the families quality of life, or seemingly unresponsive to conventional therapy according to current guidelines. Dermatologists and paediatricians referred potential study participants to the outpatient clinic of the Wilhelmina Children's Hospital where they were assessed for eligibility. Inclusion criteria were (i) diagnosis of moderate/severe AD; (ii) age between 8 and 18 years; (iii) fluent in the Dutch language; (iv) Internet access at home; (v) able to use the Digital Eczema Center; and (vi) willing and able to stay in Davos (Switzerland) for 6 weeks. The Digital Eczema Center is a digital patient portal with possibilities for e-consulting and online data collection with questionnaires.¹³ All study participants provided written informed consent to participate in the trial. For children younger than 12 years, both parents and guardians were asked to sign, for adolescents aged 12-16 years both the adolescent and both parents and guardians were asked to sign, adolescents aged 16 years or older were able to provide informed consent by themselves, in accordance with Dutch law.

2.3 | Randomization

Study participants were randomly assigned 1:1 to either the intervention or control group. An external, independent data manager performed a covariate adaptive randomization method with a custom-made programme in SAS (statistical analysis system) to generate the randomization sequence.¹⁴ Covariate adaptive randomization controls for imbalance between important covariates, which may result in slightly unequal groups. Consecutive groups of 8 included children were randomized, using the median age within the group as a cut-off and taking presence or absence of asthma diagnosis into account, as well as previous randomization results. Randomization results were provided to the project coordinator (FR) or the paediatric psychologist (WZ), who informed the participants by telephone. Treatment allocation was concealed. Children, parents and healthcare professionals involved in treatment were not blinded to group assignment because this was not possible.

2.4 | Procedures

Both study arms used a personalized, integrative, multidisciplinary treatment approach. Different health professionals worked simultaneously and with equal contributions on defined personalized treatment goals using a treatment approach involving all the relevant aspects of the child. Before randomization, a personalized treatment plan was developed for each study participant with individual treatment goals and strategies. The multidisciplinary teams consisted of a paediatric dermatologist, a paediatric allergist (control) or paediatrician trained in atopy (intervention), a paediatric psychologist, a dermatology nurse, a physiotherapist and a research nurse. The paediatric dermatologist in the control team supervised AD treatment in both study arms. A case manager assisted in the planning of study assessments and motivated the participants to attend.

There were five study assessments: inclusion in the study (T-1), immediately before (T0) and after (T1) intervention and follow-up assessments 6 weeks (T2) and 6 months (T3) after the end of the intervention. Groups of four children or adolescents started treatment simultaneously; therefore, some children had to wait longer than others between T-1 and start of treatment. All study assessments were conducted at the Wilhelmina Children's Hospital. The treatment period was 6 weeks in both study arms, consisting of continuous inpatient treatment in the intervention group or 6 weekly visits to the outpatient clinic in the control group. Both study arms were protocolled to ensure consistency of treatment over time. During the follow-up period, there was no contact between the research team and study participants apart from the planned study assessments. However, in case of exacerbations or other problems, additional consultations were scheduled and recorded.

2.5 | Intervention and control condition

The treatment programme in Davos consisted of several fixed elements.¹² The children and adolescents attended a school within the clinic. Every day, a group physical activity was organized under supervision of a physiotherapist. Weekly individual treatment sessions were scheduled with the paediatrician, the psychologist alternating with the psychomotor therapist and the physiotherapist (if needed). The nurse monitored correct application of topical treatment in individual sessions with each child twice daily. In these sessions, health education was provided with a varying weekly theme and an AD knowledge game was played. Children or adolescents and their parents were separated during the six-week treatment period, but parents usually visited once for three to four days. In addition, the parents travelled with their children to the clinic and picked them up after the end of intervention.

During the treatment programme in Utrecht, the children and adolescents were seen almost on a weekly basis in the outpatient clinic. They had 5 consultations with the dermatologist, the dermatology nurse, 4 consultations with the paediatrician-allergist and 3

consultations with the psychologist. Children and adolescents participated in a workshop in which they demonstrated how they apply topical treatment and were educated by the dermatology nurse. They also played an AD knowledge game. In the third week, a group medical appointment was scheduled for the children and adolescents and their parents separately, about coping with AD and compliance. It is a substitute for an individual appointment with a clinician during which the participants discuss their personal experiences and advise and support each other.

2.6 | Outcome measures

Primary outcomes were disease activity assessed with the Self-Administered Eczema Area and Severity Index (SAEASI),^{15,16} health-related quality of life assessed with the Children's Dermatology Life Quality Index (CDLQI)¹⁷ and the subscale catastrophizing thoughts assessed with the JUCKKI questionnaire (children aged 8-12 years) or the JUCKJU questionnaire (adolescents aged 13-18 years).¹⁸ The SAEASI and CDLQI were chosen because disease activity and health-related quality of life are important outcome domains for AD. Using either domain has also been recommended by the recently published HOME initiative (Harmonizing Outcome Measures for Eczema).¹⁹ We found a good correlation between SAEASI and EASI in our study population ($r = .66$), which is in line with previous studies. The JUCKKI/JU measures catastrophizing thoughts about itch, which children with AD consider their most burdensome complaint. The timing of the primary end-point was chosen at 6 months post-intervention because long-term clinical effects were thought necessary to justify the costs and the impact of alpine climate treatment.

Pre-specified subgroup analyses with asthma-related outcomes included as follows: ACQ (Asthma Control Questionnaire), PAQLQ (Pediatric Asthma Quality of Life Questionnaire), FeNO (Fraction of exhaled Nitric Oxide), BHR (Bronchial Hyperresponsiveness) with a metacholine bronchial challenge and spirometric variables FEV1 (Forced Expiratory Volume in 1 second) pre- and post-bronchodilator and MEF50 (Maximal Expiratory Flow at 50%). All children were examined by a paediatrician or paediatric allergist for the symptoms of asthma, allergic rhinitis and food allergy. Food allergy was defined as a positive double-blind placebo-controlled food challenge (DBPCFC) or convincing clinical history (a reported Type I allergic reaction with acute symptoms within 2 hours after ingestion of the food) in combination with sensitization to the specific food allergen.

Secondary outcomes were EASI (Eczema Area and Severity Index), TARC (thymus and activation-regulated chemokine), pharmacological treatment, itch, nightly complaints of itch, sleep problems, BMI (body mass index), blood eosinophils, total IgE, VO2 peak/kg (maximal volume of oxygen uptake per kg), JUCKKI/JU (subscales coping), COPEKI/JU (coping with disease and itching cognitions), self-perception profile, state-trait anxiety and child autonomy. Parental secondary outcomes were disease-specific quality of life, state-trait anxiety and parenting stress.

2.7 | Statistical analysis

We previously calculated that a sample size of 72 children was needed to detect a difference of 5 points on the catastrophizing thoughts subscale of the JUCKKI/JU questionnaire (assumed SD 7.6) or 10 points in SAEASI score (assumed SD 15), with 80% power and 5% significance (two-sided).²⁰ These differences were based on a study by Staab et al²⁰ in which long-term effectiveness of a multidisciplinary six-week educational programme was assessed in children and adolescents with moderate-to-severe AD. We estimated a difference of 10 points to be clinically relevant, derived from the MCID of SCORAD and the correlation between SCORAD and SAEASI.^{16,21} To examine differences between the intervention and control group on the continuous primary and secondary outcomes, linear mixed-effects regression models were used. Missing values were not imputed. Baseline measurement was preferably T0, however when absent according to the study protocol T-1 was used. Fixed effects were included for outcomes at T0 (baseline correction), treatment group, study assessment time in weeks (6, 13 and 34 weeks corresponding to T1, T2, T3) and the interaction between treatment and assessment time. A random intercept and random slope for time per individual were included to account for correlation of measurements within children. Effect size Cohen's d was estimated to quantify the difference between groups at all study assessments. A P -value of .0167 was considered significant (after Bonferroni correction).

The JUCKKI/JU was analysed without baseline correction, because it was assessed at fewer moments (contrary to the published protocol where T2 is falsely indicated as a study assessment for this outcome). The model used measurements from T0, T1 and T3 as outcomes, including fixed effects for treatment, assessment time in weeks, and the interaction between treatment and assessment time, and a random intercept. Data relating to asthma outcomes were analysed separately for the subgroup of children with doctors diagnosed asthma. Data were analysed according to the intention-to-treat principle using IBM SPSS Statistics for Windows version 22.

3 | RESULTS

Children were assessed for eligibility at the outpatient clinic of the Wilhelmina Children's Hospital. Children not meeting inclusion criteria had mild AD ($n = 57$), did not meet the age criterion ($n = 6$), expected homesickness ($n = 13$) or had limited Dutch language proficiency ($n = 2$). Between 14 September 2010 and 30 September 2014, 88 children were enrolled in the trial (Figure 1). Seventy-seven children completed the intervention of whom 74 completed follow-up (12% drop-out rate). The last follow-up assessment was 16 June 2015. Drop-out before start of the intervention was similar in both groups but different during follow-up. There were no differences in baseline characteristics between the children who dropped out and the children who completed the study (data not shown). In addition

to the planned study assessments during follow-up, there were additional consultations for 10 children in the intervention group and 10 children in the control group (Table S1).

The exact time between study assessments varied because of rescheduling due to illness, holidays or initial no-show. The mean time between study inclusion (T-1) and baseline (T0) was 19 weeks [SD 22.0], between baseline (T0) and end of intervention (T1) 6 weeks [SD 0.8], between baseline (T0) and first follow-up (T2) 13 weeks [SD 1.5], between baseline (T0) and second follow-up (T3) 34 weeks [SD 2.5].

At trial inclusion (T-1), the intervention and control group were comparable on demographic and disease characteristics (Table 1 and Table S2). For 12 children, change of treatment (more potent topical corticosteroids or start of systemic immunosuppressives) was indicated by the paediatric dermatologist after inclusion in the study but before start of the intervention at T0, due to unacceptable disease severity. In this study population of children with difficult to treat AD, 72 (86%) were diagnosed with asthma of which 11 (13%) were diagnosed during the intervention period. Allergic rhinitis was diagnosed in 73 children (87%), with 60 (72%) children reporting

persistent (year round) symptoms. Food allergy was diagnosed in 52 children (66%).

At the primary end-point T3 (6 months after the intervention), there were no statistically significant differences between the groups on the primary outcomes (Table 2). Immediately after the intervention (T1) and 6 weeks after the intervention (T2), there were statistically significant differences between the groups regarding disease activity and quality of life (Table 2). No differences were observed on the JUCKKI/JU subscale catastrophizing (Table 2). The secondary outcomes can be found in the Tables S3-S6. There were no significant long-term differences between the groups on any of the secondary outcomes. Immediately after the intervention and in the short-term, there were differences in favour of alpine climate treatment on several clinical secondary outcomes.

In the subgroup of children diagnosed with asthma, there were no relevant significant differences between the groups concerning asthma-related outcomes, apart from a significant difference in FeNO -14.1 (95%CI -24.3 to -3.9 ; $P = .007$) immediately after the intervention (T1) in favour of the intervention group. Asthma varied in severity, but was mild-to-moderate in most cases. At baseline,

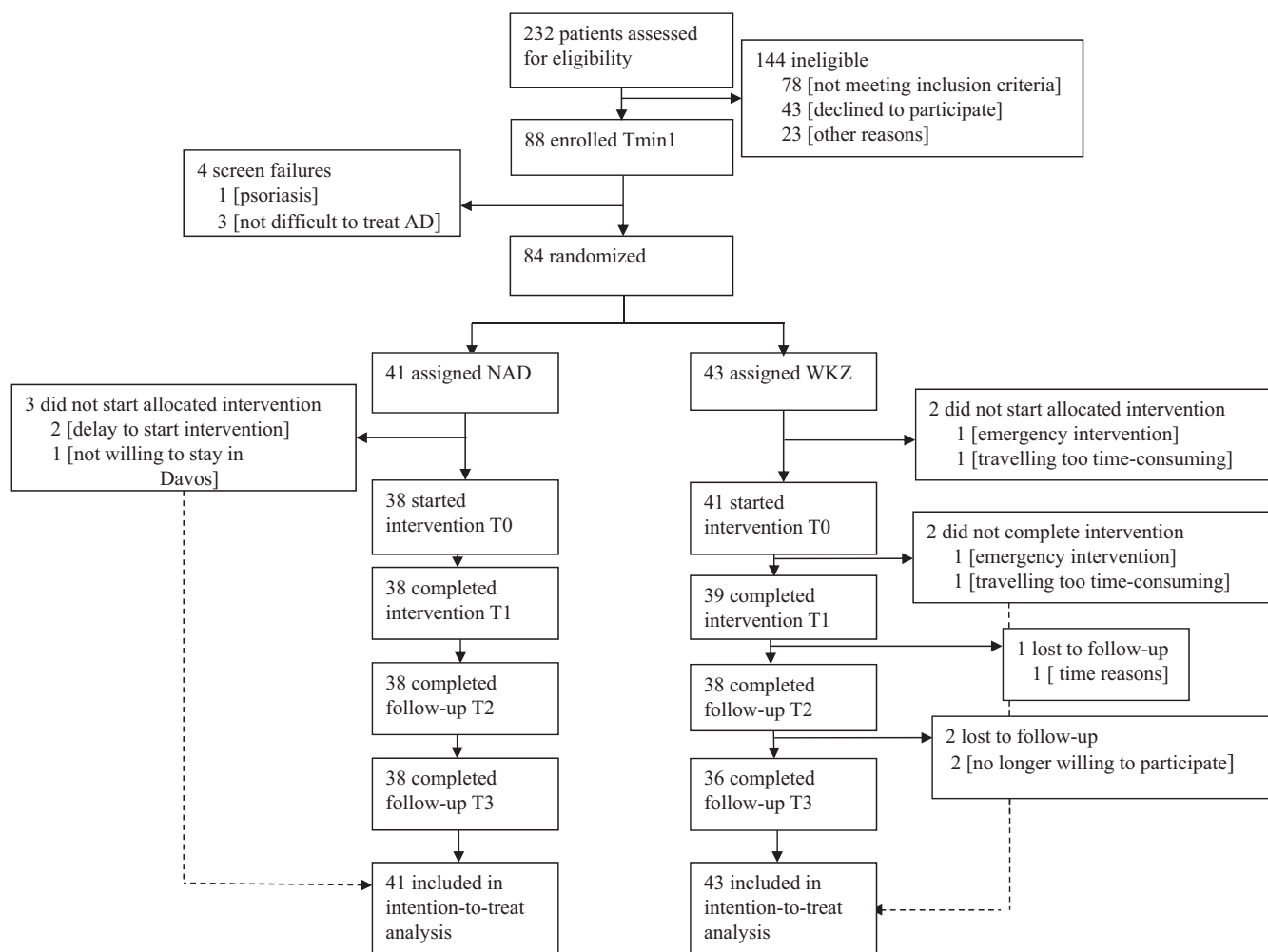


FIGURE 1 Trial profile

TABLE 1 Baseline characteristics of study participants (Tmin1)

	Intervention group n = 41	Control group n = 43
Female	18 (44%)	21 (49%)
Age (years)	12.6 (2.5)	12.4 (2.4)
Age of AD onset <6 months	35 (85%)	37 (86%)
History of systemic treatment for AD (UV therapy, cyclosporine, prednisone)	26 (63%)	26 (60%)
Current use of potent or very potent topical corticosteroids ^a	37 (90%)	40 (93%)
Current use of cyclosporine/prednisone	2 (5%)	8 (19%)
SAEASI (0-96)	31.2 (17.0)	28.3 (16.8)
BSA (%)	56 (21)	61 (21)
Diagnosis of asthma	35 (85%)	37 (86%)
Diagnosis of allergic rhinitis	37 (90%)	36 (84%)
Persistent symptoms of allergic rhinitis	33 (81%)	27 (63%)
Diagnosis of food allergy ^b	26/38 (68%)	26/41 (63%)

Data are mean (SD) or number (%) SAEASI: Self-Administered Eczema Area and Severity Index scored by caregiver. BSA: affected body surface area. AD: atopic dermatitis.

^aUK potency system used.

^bFood allergy was only diagnosed in children who started the intervention.

asthma was not well controlled in the intervention group but improved during intervention, whereas the control group remained stable throughout the study (ACQ < 1.25).²² There was no difference in bronchial hyperresponsiveness to metacholine (Table 3).

Missing data regarding metacholine challenges occurred because of instable asthma, inappropriate technique, study planning or continuation of long-acting bronchodilators.

During the study period, five serious adverse events occurred. Two children in the intervention group experienced asthma exacerbations during the first study assessment T-1 related to the metacholine challenge. During the follow-up period, one child was hospitalized for exacerbations of AD and asthma direct after study assessment T2 (control group) and one child was diagnosed with appendicitis and hospitalized between T2 and T3 (intervention group). Another child from the control group was hospitalized for AD during the intervention and subsequently dropped out of the study.

4 | DISCUSSION

This is the first randomized trial concerning the long-term effectiveness of alpine climate treatment for children or adolescents with difficult to treat AD (8-18 years). Other RCTs have assessed the effectiveness of climate change for the treatment of allergic diseases.^{23,24} Six months after alpine climate treatment, this study demonstrated no differences in the primary outcomes disease activity, health-related quality of life and catastrophizing thoughts about itch between children treated in the alpine climate (inpatient setting) or in moderate maritime climate (outpatient setting). This is in contrast to the immediate and short-term findings in favour of alpine climate treatment.

After 6 months follow-up, there were no significant differences between the groups. We hypothesize that this was caused by the personalized integrative multidisciplinary treatment the children received. It has been shown previously that multidisciplinary

TABLE 2 Primary end-points—disease activity (SAEASI), health-related quality of life (CDLQI) and catastrophizing thoughts (JUCKKI/JU)

Primary end-points	Intervention group		Control group		Primary analysis		
	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI) corrected for baseline T0	P	Effect size (Cohen's d)
SAEASI by caregiver (range 0-96)							
Baseline (T0)	38	28.2 (19.9)	37	28.3 (20.5)			
End of intervention (T1)	37	3.0 (4.2)	35	14.5 (15.3)	−10.1 (−14.5 to −5.8)	.000	0.6
First follow-up assessment (T2)	36	8.5 (8.11)	30	14.4 (12.5)	−8.4 (−12.2 to −4.6)	.000	0.5
End of follow-up (T3)	37	11.9 (9.5)	32	15.1 (12.7)	−3.4 (−8.5 to 1.7)	.185	0.2
CDLQI (range 0-30)							
Baseline (T0)	35	8.7 (5.9)	40	7.9 (5.7)			
End of intervention (T1)	34	2.9 (3.3)	31	4.8 (4.2)	−1.9 (−3.3 to −0.5)	.008	0.4
First follow-up assessment (T2)	38	4.7 (4.3)	32	5.1 (4.6)	−1.5 (−2.8 to −0.3)	.019	0.33
End of follow-up (T3)	38	4.4 (4.3)	33	4.8 (3.7)	−0.3 (−2.0 to 1.4)	.707	0.06
JUCKKI/JU Catastrophizing thoughts (range 0-4)*							
Baseline (T0)	38	2.0 (1.1)	40	1.9 (1.0)	−0.4 (−1.0 to 0.2)	.186	0.39
End of intervention (T1)	37	1.0 (0.7)	32	1.1 (0.9)	−0.5 (−1.2 to 0.1)	.111	0.49
End of follow-up (T3)	38	1.1 (0.7)	31	1.2 (1.0)	−0.7 (−1.4 to −0.0)	.047	0.66

Numbers of completed questionnaires vary due to missing data. JUCKKI/JU scores are the total scale scores divided by the number of items in each scale.

*not corrected for baseline.

TABLE 3 Asthma-related outcomes

Secondary end-point	Intervention group		Control group		Statistical analysis	
	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI) corrected for baseline	P
ACQ 6Q						
Baseline (T0)	35	1.2 (1.1)	37	0.97 (1.03)		
End of intervention (T1)	29	0.52 (0.53)	26	0.84 (1.15)	−0.28 (−0.86 to 0.30)	.345
First follow-up (T2)	32	0.92 (0.83)	27	0.85 (1.06)	−0.20 (−0.65 to 0.25)	.370
End of follow-up (T3)	32	0.75 (0.74)	29	0.66 (0.71)	0.02 (−0.25 to 0.29)	.869
PAQLQ						
Baseline (T0)	31	5.9 (0.98)	34	6.1 (1.0)		
End of intervention (T1)	28	6.4 (0.6)	26	6.4 (0.8)	0.15 (−0.11 to 0.41)	.258
First follow-up (T2)	32	6.2 (0.9)	27	6.3 (1.1)	0.09 (−0.12 to 0.29)	.413
End of follow-up (T3)	32	6.3 (0.8)	29	6.4 (0.7)	−0.10 (−0.45 to 0.24)	.553
FeNO						
Baseline (T0)	29	45.5 (29.3)	34	41.3 (37.7)		
End of intervention (T1)	31	24.6 (18.8)	34	42.7 (34.6)	−14.1 (−24.3 to −3.9)	.007
First follow-up (T2)	31	43.9 (32.9)	32	46.6 (37.3)	−8.6 (−16.7 to −0.59)	.036
End of follow-up (T3)	30	41.8 (25.0)	26	34.7 (27.9)	7.8 (−6.9 to 22.5)	.292
Spirometry FEV1pre pp (%)						
Baseline (T0)	29	87.0 (14.1)	34	94.0 (8.9)		
End of intervention (T1)	32	92.8 (10.5)	34	94.0 (11.4)	4.32 (0.52 to 8.12)	.027
First follow-up (T2)	32	90.8 (11.5)	33	91.3 (11.6)	3.79 (0.37 to 7.2)	.031
End of follow-up (T3)	31	88.9 (12.6)	26	93.8 (11.4)	2.21 (−1.98 to 6.4)	.294
Spirometry FEV1 post pp (%)						
Baseline (T0)	29	92.7 (11.8)	34	98.1 (8.76)		
End of intervention (T1)	32	96.1 (8.7)	34	98.8 (10.5)	2.28 (−0.81 to 5.38)	.145
First follow-up (T2)	32	95.2 (9.8)	33	96.9 (11.1)	2.63 (−0.13 to 5.40)	.061
End of follow-up (T3)	31	94.6 (11.3)	26	97.6 (11.3)	3.68 (−0.48 to −6.88)	.025
Spirometry MEF50pre (L/s)						
Baseline (T0)	29	3.0 (0.98)	34	3.32 (1.12)		
End of intervention (T1)	32	3.35 (0.89)	34	3.37 (1.08)	0.26 (−0.07 to 0.59)	.119
First follow-up (T2)	32	3.32 (0.97)	33	3.20 (1.26)	0.24 (−0.07 to 0.55)	.131
End of follow-up (T3)	31	3.26 (0.97)	26	3.40 (1.04)	0.172 (−0.21 to 0.56)	.375
	n	Median (IQR)	n	Median (IQR)	Estimated difference (95%CI) corrected for baseline ^a	P
BHR PD20 (μmol)						
Baseline (T-1)	21	0.38 (0.79)	29	0.28 (0.60)		
End of follow-up (T3)	18	0.28 (0.75)	19	0.07 (0.43)	0.05 (−0.27 to 0.36)	.757

Numbers of completed questionnaires vary due to missing data.

^aBaseline is T-1. ACQ: Asthma control questionnaire, PAQLQ: paediatric asthma quality of life questionnaire, FeNO: fraction of exhaled NO, FEV1: forced expiratory volume in 1 second, MEF50pre: maximal expiratory flow, BHR: bronchial hyperresponsiveness. Pre: before the use of bronchodilator, post: after the use of bronchodilator.

treatment programmes result in sustained improved disease activity.²⁵ The use of structured education programmes, behavioural interventions to improve coping with itch, the use of written action plans and the involvement of a specialized dermatology nurse have been shown to improve disease control.^{20,26,27} The slightly better improvement of catastrophizing thoughts in the intervention group may be due to their significant clinical improvement, during which

the children have experienced that it is possible to get control of their AD. The personalized, integrative treatment programme that was used in this trial combined all of these elements. It is not likely that an increased duration of the intervention would have resulted in differences between the groups 6 months after the intervention, since optimal results were already observed after 6 weeks. The primary time-point was chosen 6 months after intervention, because

alpine climate treatment is a temporary treatment and patients have to return to their own environment after it has ended. To justify the costs and impact of alpine climate treatment, long-term effectiveness was thought more important as end-point than short-term.

Immediately and 6 weeks after intervention, there were significant differences in terms of disease activity and health-related quality of life in favour of the alpine climate treatment group as well as in secondary outcomes. A significant reduction in eosinophil counts and FeNO was observed in the intervention group suggesting reduced inflammation. Decreased eosinophilia after alpine climate treatment has been reported before, mainly in asthma studies, and is possibly related with reduced allergen exposure.²⁸⁻³⁰ TARC also decreased in both groups, which is in line with the observed reduction in disease activity. Besides the differences in climate, the clinical setting during alpine climate treatment guarantees maximal compliance with pharmacological treatment through nurse supervision of topical corticosteroid use. Compared to the outpatient programme in the moderate maritime climate, alpine climate treatment was a more intense inpatient treatment, in which parents and children are separated during the intervention period and the children have intensive contact with peers. These elements may have contributed to the greater improvement in disease activity.

The initial significant difference in clinical improvement between the intervention group and control group was gradually lost during the follow-up period. This relapse could be explained by several factors. Alpine climate treatment combines exposure to a different climate with increased medical supervision in an inpatient setting. Apart from the change in climate, children have to apply skills they learned at the clinic in their home environment with less supervision. This transition might be difficult for children. Children and parents in the control group already learned to implement the newly acquired skills directly in their daily routine during the six-week programme, and therefore, it may be easier for them to retain these skills. Furthermore, there was maximal clinical improvement in the intervention group, which only leaves room for deterioration during follow-up. Another trial concerning climate treatment was designed with a follow-up period of 3 months.²³ Children with moderate-to-severe AD were randomized to a four-week stay (with a structured day programme) in subtropical climate or stayed at home in a subarctic/temperate climate. A similar improvement was described in disease activity and quality of life compared with our study, with a statistically significant effect in favour of the subtropical group after 3 months follow-up. However, the subtropical climate group showed a similar deteriorating trend during follow-up as our intervention group, suggesting that it is difficult to retain a long-term effect after climate treatment.

Our subgroup analyses concerning asthma-related outcomes indicated no significant differences between the groups concerning asthma control or asthma-related quality of life. In our study population, asthma varied in severity, but was mild-to-moderate in most cases. Several children were diagnosed with asthma during the intervention period. Immediately and 6 weeks after intervention, we found a significant reduction in FeNO in the intervention group, which is

consistent with the previous observational studies.³¹ FEV1 in both groups was within normal range throughout the study period. Based on all these findings, we could not support an additional benefit of alpine climate treatment for children with mild-to-moderate asthma, consistent with current guidelines.³² The subgroup analyses were specified in advance in the study protocol, but this trial was not specifically powered for asthma-related outcomes. Other subgroup analyses were not specified in advance in the study protocol.

The main limitation of our trial is its many outcome measures. Clearly indicating the primary and secondary outcomes, pre-specifying the analyses in advance and correcting for multiple testing reduces chance findings. The primary outcome measures disease activity and quality of life have recently been endorsed by an expert panel to be used in AD trials and validated instruments were used to assess these outcomes.¹⁹ A second limitation is that none of the health professionals assessing study outcomes were blinded and neither were the study participants; this was not possible. This might have influenced our findings, especially the questionnaire data. However, the results of the blinded assessment of the blood samples were in line with the unblinded assessments. Another limitation is that the questionnaire used to assess catastrophizing about itch was officially translated to Dutch but was not validated in the Netherlands. However, none of these limitations are likely to have led to a different conclusion of our findings. Furthermore, because this study was designed as a pragmatic trial, it is not possible to determine what contributed most to the observed outcomes.³³ Only an explanatory trial comparing inpatient treatment in alpine climate and maritime climate could determine the effect of the climate.

Previous observational studies have described alpine climate treatment as an effective treatment for AD.¹⁰ This is confirmed in this study. However, in both study arms, clinically relevant long-term improvement in disease control and health-related quality of life was observed. Immediately and 6 weeks after intervention, this study found significant differences in terms of disease activity and health-related quality of life in favour of the alpine climate treatment group as well as in the other clinical secondary outcomes, suggesting that alpine climate treatment is a treatment option when immediate dramatic results are required. However, it is likely that inpatient treatment in any hospital or the use of systemic immunosuppressives also results in significant short-term improvements.

In conclusion, we found no additional long-term benefit, in contrast to the short-term, of alpine climate treatment compared to outpatient treatment in a moderate maritime climate for children with difficult to treat AD. In this trial using a personalized, integrative, multidisciplinary treatment approach, children in both arms improved in terms of AD disease activity, health-related quality of life and catastrophizing thoughts about AD.

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CONFLICT OF INTERESTS

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AUTHOR CONTRIBUTIONS

SP EvH WZ LR KF developed the study concept, design and protocol. SP and EvH obtained funding for the study, FR and JB coordinated the study. CB SP and EvH obtained funding for the inpatient treatment of the intervention group. KF RS contributed to data collection and data preparation, analyses and interpretation of the data. WZ LF JB MV JW LR YM MUV SP contributed to the delivery of the intervention and collection and interpretation of the data. RST supervised data analysis and contributed to the interpretation of the data. CB HvO KE contributed to the interpretation of data and preparation of the report. KF drafted the report. All authors contributed to revisions of the report and approved the final version.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Supplementary tables

Table S1 Additional consultations in the intervention and control group during the total follow-up period (T1 to T3)

Reason for consultation	Number of additional consultations (n)	Number of patients intervention group	Number of patients control group	Number of additional e-consultations (n)	Number of patients intervention group	Number of patients control group	Number of additional telephone consultations (n)	Number of patients intervention group	Number of patients control group
AD	12	6	5	15	6	5	4	3	
AD treatment				9	4	2	4	2	2
AA	2	2	0						
AR	2	1	1				2	1	1
Mental health	1	1	0	1	1	0	1	0	1
Other	12	2	4	19	8	8	11	4	2
Total n	29	10	10	44	13	11	21	10	6

Multiple consultations per patient may be deduced by the number of patients stated per reason for the additional consultation. AD= Atopic Dermatitis, AA = Allergic Asthma, AR = Allergic Rhinitis

Table S2 Extension of baseline characteristics

	Intervention group (n = 41)	Control group (n = 43)
Asthma diagnosed during study, n (%)	7 (17%)	4 (9%)
Time between study inclusion T-1 and start intervention T0, mean weeks (SD)	28.2 (28.5)	10.7 (6.9)
BMI (kg/m²)	19.2 (3.2)	21.2 (5.4)
Previously treated in Davos, n(%)	2 (5%)	1 (2%)
Child's level of education, n (%)		
Special primary education	1 (2%)	4 (9%)
Primary education	15 (37%)	16 (37%)
Practical education	1 (2%)	-
Lower general secondary education	8 (20%)	15 (35%)
Intermediate vocational education	-	1 (2%)
Higher general secondary education	10 (24%)	4 (9%)
Pre-university education	6 (15%)	3 (7%)
Child's living situation, n (%)		
Father and mother	32 (80%)	28 (65%)
Mother only	6 (15%)	13 (30%)
Father only	1 (3%)	1 (2%)
Father and mother alternately	1 (3%)	1 (2%)
Number of children in the family, n (%)		
1	4 (10%)	4 (9%)
2	24 (60%)	22 (51%)
3	7 (18%)	10 (23%)
4	5 (13%)	7 (16%)
Ethnicity mother, n (%)		

Dutch	35 (85%)	32 (74%)
Surinam	2 (5%)	3 (7%)
Antillean or Aruban	1 (2%)	2 (5%)
Moroccan	-	3 (7%)
Other	2 (5%)	3 (7%)
Ethnicity father, n (%)		
Dutch	36 (88%)	34 (79%)
Surinam	2 (5%)	-
Antillean or Aruban	1 (2%)	1 (2%)
Moroccan	-	3 (7%)
Other	2 (5%)	5 (12%)
Highest level of education mother, n (%)		
Higher vocational education/university	15 (39%)	11 (26%)
Vocational education	15 (3%)	16 (38%)
Secondary education	8 (21%)	12 (29%)
Primary education	-	3 (7%)
Highest level of education father, n (%)		
Higher vocational education/university	17 (47%)	14 (38%)
Vocational education	12 (33%)	9 (26%)
Secondary education	7 (20%)	13 (38%)
Primary education	-	1 (3%)
Employment mother, n (%)		
Fulltime work	3 (8%)	3 (7%)
Part-time work	22 (59%)	17 (40%)
Self-employed	5 (14%)	4 (10%)
Disabled	3 (8%)	2 (5%)
Unemployed	-	3 (7%)
Housewife	4 (11%)	13 (31%)
Employment father, n (%)		
Fulltime work	19 (53%)	24 (62%)
Part-time work	4 (11%)	1 (3%)
Self-employed	12 (33%)	10 (26%)
Disabled	1 (3%)	2 (5%)
Unemployed	-	2 (5%)
Family problems, n (%)	12 (32%)	28 (65%)
School absence, n (%)	6 (15%)	9 (21%)
IQ, mean (SD)		
Total IQ	105.9 (16.3)	96.7 (14.9)
Verbal IQ	108.9 (15.6)	101.1 (13.9)
Performance IQ	101.4 (17.1)	92.9 (14.6)
Processing speed	101.2 (16.2)	96.4 (12.6)
CBCL, mean T-score (SD)	n = 40	n = 42
Total	55.3 (8.4)	54.9 (8.8)
Internalizing	58.8 (8.8)	58.6 (9.1)
Externalizing	49.8 (10.0)	49.5 (9.0)
Anxious/depressed	56.2 (7.9)	56.5 (7.1)
Withdrawn/depressed	57.9 (8.1)	56.6 (7.0)
Somatic complaints	64.5 (7.1)	63.7 (8.7)
Social problems	55.5 (7.0)	54.7 (6.8)
Thought problems	61.5 (8.2)	58.5 (7.3)

Attention problems	56.2 (5.0)	56.4 (5.9)
Rule-breaking behavior	52.9 (4.3)	52.8 (3.4)
Aggressive behavior	54.9 (6.0)	54.3 (5.4)
Personality (NPV-J), mean (SD); range 1-7	n = 41	n = 43
Inadequacy boys	3.3 (1.6)	3.5 (1.4)
Inadequacy girls	3.0 (1.7)	3.5 (1.5)
Persistence <12 years	4.1 (1.5)	4.1 (1.4)
Persistence >12 years	3.8 (1.3)	4.6 (1.3)
Social inadequacy	3.2 (1.5)	3.7 (1.8)
Recalcitrance	2.8 (1.1)	3.8 (1.7)
Dominance	4.1 (1.2)	4.1 (1.2)
SF-36 mother, mean (SD); range 0-100	n = 40	n = 43
Physical functioning	93.0 (16.0)	81.9 (20.3)
Social functioning	89.1 (17.9)	77.0 (28.5)
Role physical	80.6 (35.6)	70.9 (40.4)
Role emotional	90.8 (25.0)	82.2 (35.1)
Mental health	82.3 (13.7)	77.1 (17.1)
Vitality	72.9 (17.1)	64.5 (21.4)
Bodily pain	87.4 (18.3)	68.5 (24.9)
General health	74.4 (20.3)	61.5 (23.1)
Health transition	57.5 (15.2)	49.4 (19.3)
SF-36 father, mean (SD); range 0-100	n = 34	n = 32
Physical functioning	92.8 (10.2)	93.0 (8.0)
Social functioning	88.6 (14.9)	90.2 (18.2)
Role physical	91.9 (18.2)	89.1 (27.6)
Role emotional	89.2 (21.3)	99.0 (5.9)
Mental health	83.4 (12.6)	82.4 (13.8)
Vitality	75.7 (15.6)	71.6 (18.1)
Bodily pain	84.2 (16.5)	81.9 (20.4)
General health	73.8 (18.1)	67.5 (24.0)
Health transition	55.9 (19.5)	57.8 (18.4)

BMI Body Mass index, IQ intelligence quotient, CBCL child behavior checklist, NPV-J Dutch personality questionnaire-youth version, SF-36 short form health survey, SD standard deviation

Table S3 Clinical secondary outcome measures

	Intervention group		Control group		Statistical analysis	
EASI (range 0-72)	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	33	13.4 (7.9)	20	13.8 (9.7)		
End of intervention (T1)	31	2.1 (2.6)	20	6.5 (5.8)	-4.2 (-6.4 to -2.0)	0.000
First follow-up assessment (T2)	34	3.4 (4.3)	19	5.7 (7.2)	-2.8 (-4.7 to -0.8)	0.007
End of follow-up (T3)	31	5.5 (4.9)	16	5.4 (5.2)	-1.6 (-4.4 to 1.1)	0.229
TARC (pg/ml)	n	Median (IQR)		Median (IQR)	Estimated difference (95%CI)	P
Baseline (T0)	38	1110 (1703)	41	1076 (1558)		
End of intervention (T1)	38	619 (430)	38	806 (1074)	-237 (-655 to 180)	0.261
First follow-up assessment (T2)	37	722 (1038)	35	845 (645)	-250 (-601 to 100)	0.160
End of follow-up (T3)	38	921 (1013)	35	1094 (1239)	-287 (-710 to 137)	0.181
Blood eosinophils (x10⁹/L)	n	Median (IQR)		Median (IQR)	Estimated difference (95%CI)	P
Baseline (T0)	37	0.53 (0.59)	37	0.51 (0.53)		
End of intervention (T1)	37	0.25 (0.26)	37	0.63 (0.55)	-0.27 (-0.45 to -0.09)	0.003
First follow-up assessment (T2)	38	0.47 (0.59)	34	0.49 (0.58)	-0.225 (-0.515 to 0.065)	0.128
End of follow-up (T3)	38	0.31 (0.43)	35	0.56 (0.52)	-0.098 (-0.788 to 0.592)	0.781

Use of > potent topical corticosteroids or systemic immunosuppressives	n	n% use of >potent topical corticosteroids or systemic immunosuppressives	n	n% use of >potent topical corticosteroids or systemic immunosuppressives	OR (95%CI) for lower potency	P
Baseline (T0)	38	38 (100%)	41	38 (93%)		
End of intervention (T1)	38	30 (79%)	40	33 (82%)	2.98 (1.0 to 8.7)	0.046
First follow-up assessment (T2)	37	30 (81%)	39	36 (92%)	3.7 (1.5 to 9.5)	0.005
End of follow-up (T3)	38	36 (95%)	36	33 (92%)	0.46 (0.18 to 1.2)	0.114
Itch (range 0 - 4)	n	n% severe itch	n	Mean (SD)	OR (95%CI) for less itch	P
Baseline (T0)	38	25 (66%)	38	21 (55%)		
End of intervention (T1)	37	1 (3%)	35	7 (20%)	5.1 (2.2 to 11.7)	0.000
First follow-up assessment (T2)	36	3 (8%)	30	12 (40%)	3.35 (1.25 to 8.97)	0.016
End of follow-up (T3)	37	7 (19%)	32	8 (25%)	1.4 (0.6 to 3.2)	0.436
Nightly complaints of itch (range 0 - 4)	n	n% a lot	n	n% a lot	OR (95%CI) for less complaints	P
Baseline (T0)	38	15 (40%)	38	15 (40%)		
End of intervention (T1)	37	0	35	6 (17%)	2.97 (1.2 to 7.1)	0.014
First follow-up assessment (T2)	36	0	30	5 (16%)	2.5 (1.1 to 5.8)	0.03
End of follow-up (T3)	37	2 (5%)	32	5 (17%)	1.75 (0.68 to 4.49)	0.25
Sleep problems (range 0 - 3)	n	n% Sleep problems	n	n% Sleep problems	OR (95%CI) for less sleep problems	P

Baseline (T0)	36	26 (72%)	33	25 (76%)		
End of intervention (T1)	34	11 (32%)	31	23 (74%)	6.6 (2.6 to 17.1)	0.000
First follow-up (T2)	36	22 (61%)	34	25 (74%)	1.4 (0.57 to 3.62)	0.439
End of follow-up (T3)	36	21 (58%)	32	20 (62%)	1.9 (0.8 to 4.5)	0.144
BMI (kg/m²)	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	38	19.2 (3.4)	41	21.4 (5.3)		
End of intervention (T1)	38	19.1 (3.2)	39	21.7 (5.5)	-0.22 (-0.54 to 0.1)	0.181
First follow-up (T2)	38	19.5 (3.2)	38	21.2 (4.8)	-0.11 (-0.44 to 0.22)	0.493
End of follow-up (T3)	38	19.5 (3.2)	34	21.5 (4.7)	0.20 (-0.41 to 0.81)	0.520
Total IgE (kU/L)	n	Median (IQR)	n	Median (IQR)	Estimated difference (95%CI)	P
Baseline (T0)	38	2851 (3332)	38	2983 (3036)		
End of follow-up (T3)	37	1776 (3793)	35	2965 (3251)	-625.7 (-1451.4 – 199.96)	0.135
VO2 peak/kg* (mL/kg/min)	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T-1)	34	43.7 (8.3)	41	39.4 (9.3)	4.4 (0.5 – 8.3)	0.026
End of follow-up (T3)	36	46.7 (7.3)	34	41.9 (9.1)	5.3 (1.3 – 9.3)	0.010
					Group*Time (F = 0.3)	0.591

EASI (Eczema Area and Severity Index), TARC (thymus and activation regulated chemokine), BMI (body mass index), VO2 peak (maximal volume of oxygen uptake per kg). Statistical models are corrected for baseline (T0), except the VO2 peak/kg model.

Table S4 Psychosocial secondary outcomes

		Intervention group		Control group		
JUCKKI/JU	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	p
Coping with itch (range 0-4)						
Baseline (T0)	38	1.8 (0.7)	40	1.8 (0.8)	-0.2 (-0.8 to 0.3)	0.387
End of intervention (T1)	37	1.8 (1.0)	32	1.7 (0.8)	-0.3 (-0.8 to 0.3)	0.377
End of follow-up (T3)	38	1.8 (0.8)	31	1.6 (0.6)	0.3 (-0.3 to 0.9)	0.380
					Group*Time (F =1.3)	0.273
COPEKI social anxiety – depressive mood* (range 0-4)	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	18	1.2 (0.9)	19	1.2 (0.8)	-0.1 (-0.6 – 0.5)	0.804
End of intervention (T1)	17	0.9 (0.7)	15	1.2 (0.8)	-0.3 (-0.9 – 0.3)	0.284
End of follow-up (T3)	15	0.7 (0.6)	14	1.1 (1.0)	-0.3 (-0.9 – 0.3)	0.280
					Group*Time (F = 0.7)	0.503
COPEKI itching- scratching circle – stress from the disease (range 0-4)	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	18	2.0 (0.8)	19	2.1 (0.7)	-0.1 (-0.6 – 0.4)	0.728
End of intervention (T1)	17	1.6 (0.8)	15	2.1 (0.8)	-0.4 (0.9 – 0.2)	0.166
End of follow-up (T3)	15	1.8 (0.7)	14	1.8 (0.7)	0.1 (-0.5 – 0.6)	0.806
					Group*Time (F = 1.4)	0.262

COPEJU depressive mood – itching-scratching circle (range 0-4)	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	21	2.5 (0.8)	20	1.9 (0.9)	0.4 (-0.1 – 0.9)	0.117
End of intervention (T1)	19	1.8 (0.8)	17	1.5 (0.8)	0.1 (-0.5 – 0.6)	0.829
End of follow-up (T3)	23	1.7 (1.0)	17	1.3 (0.9)	0.2 (-0.4 – 0.8)	0.478
					Group*Time (F = 1.7)	0.195
COPEJU social anxiety (range 0-4)	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	21	1.9 (1.2)	20	1.5 (1.2)	0.4 (-0.4 – 1.1)	0.327
End of intervention (T1)	19	1.3 (1.1.)	17	1.1 (1.0)	-0.0 (-0.7 – 0.7)	0.986
End of follow-up (T3)	23	1.3 (1.2)	17	0.9 (1.0)	0.2 (-0.5 – 0.9)	0.551
					Group*Time (F = 1.1)	0.345
COPEJU stress from the disease (range 0-4)*	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	21	2.0 (0.8)	20	1.5 (0.8)	0.5 (-0.1 – 1.0)	0.087
End of intervention (T1)	19	1.6 (1.0)	17	1.3 (0.7)	0.1 (-0.4 – 0.7)	0.669
End of follow-up (T3)	23	1.5 (0.9)	17	1.3 (0.8)	0.1 (-0.5 – 0.6)	0.774
					Group*Time (F = 2.1)	0.137
ZBV-K trait anxiety	n	Mean decile (SD)	n	Mean decile (SD)	Estimated difference (95%CI)	P
Baseline (T0)	37	6.2 (3.4)	36	5.5 (3.3)	0.4 (-1.1 – 2.0)	0.595
End of intervention	37	5.0 (3.3)	33	4.6 (3.2)	0.1 (-1.4 - -1.7)	0.875

(T1)						
End of follow-up (T3)	38	5.4 (3.3)	32	5.2 (3.4)	-0.0 (-1.6 – 1.5)	0.999
					Group*Time (F = 0.3)	0.770
ZBV-K state anxiety*	n	Mean decile (SD)	n	Mean decile (SD)	Estimated difference (95%CI)	P
Baseline (T0)	37	6.6 (3.4)	40	6.4 (3.1)	0.3 (-1.1 – 1.7)	0.650
End of intervention (T1)	37	4.2 (3.0)	33	5.6 (2.7)	-1.5 (-3.0 - -0.1)	0.040
End of follow-up (T3)	38	4.8 (3.2)	32	5.4 (3.2)	-0.7 (-2.2 – 0.7)	0.323
					Group*Time (F = 3.3)	0.041
CBSK/A scholastic competence	n	Mean percentile (SD)	n	Mean percentile (SD)	Estimated difference (95%CI)	P
Baseline (T-1)	40	56.7 (33.9)	41	50.3 (35.1)	5.1 (-10.4 – 20.7)	0.513
End of intervention (T1)	37	54.5 (32.0)	35	57.9 (33.8)	-2.1 (-19.8 – 15.7)	0.818
End of follow-up (T3)	38	56.7 (30.3)	33	59.6 (32.3)	-5.8 (-25.0 – 13.5)	0.551
					Group*Time (F = 0.8)	0.440
CBSK/A social acceptance	n	Mean percentile (SD)	n	Mean percentile (SD)	Estimated difference (95%CI)	P
Baseline (T-1)	40	55.8 (34.2)	41	48.4 (29.2)	9.4 (-4.4 – 23.3)	0.178
End of intervention (T1)	37	62.1 (29.3)	35	43.8 (26.8)	10.9 (-5.4 – 27.3)	0.188
End of follow-up (T3)	38	53.9 (32.6)	33	51.0 (32.6)	-3.9 (-22.5 – 14.7)	0.676

					Group*Time (F = 1.5)	0.230
CBSK/A athletic competence	n	Mean percentile (SD)	n	Mean percentile (SD)	Estimated difference (95%CI)	P
Baseline (T-1)	40	52.5 (34.7)	41	37.2 (28.0)	16.6 (2.6 – 30.6)	0.020
End of intervention (T1)	37	49.5 (32.5)	35	43.6 (29.2)	6.7 (-9.2 – 22.6)	0.405
End of follow-up (T3)	38	48.6 (31.9)	33	47.2 (27.1)	-1.1 (-18.1 – 16.0)	0.901
					Group*Time (F = 2.7)	0.074
CBSK/A physical appearance	n	Mean percentile (SD)	n	Mean percentile (SD)	Estimated difference (95%CI)	P
Baseline (T-1)	40	40.4 (30.8)	41	33.9 (26.4)	7.0 (-5.7 – 19.7)	0.276
End of intervention (T1)	37	42.9 (29.5)	35	36.3 (25.9)	8.6 (-6.6 – 23.7)	0.267
End of follow-up (T3)	38	41.6 (30.1)	33	41.6 (33.6)	1.8 (-16.4 – 20.0)	0.845
					Group*Time (F = 0.5)	0.633
CBSK/A behavioral conduct	n	Mean percentile (SD)	n	Mean percentile (SD)	Estimated difference (95%CI)	P
Baseline (T-1)	40	70.0 (28.9)	41	64.7 (28.8)	3.3 (-8.7 – 15.4)	0.582
End of intervention (T1)	37	67.4 (29.3)	35	62.1 (27.8)	8.7 (-6.9 – 24.3)	0.271
End of follow-up (T3)	38	68.1 (28.4)	33	63.5 (29.6)	3.4 (-13.7 – 20.5)	0.692
					Group*Time (F = 0.3)	0.748
CBSK/A global self-worth	n	Mean percentile	n	Mean percentile	Estimated difference (95%CI)	P

		(SD)		(SD)		
Baseline (T-1)	40	47.5 (35.4)	41	42.4 (32.8)	4.3 (-10.9 – 19.5)	0.578
End of intervention (T1)	37	49.2 (33.6)	35	43.1 (34.1)	7.6 (-11.2 – 26.4)	0.424
End of follow-up (T3)	38	46.8 (34.7)	33	43.2 (30.8)	-0.6 (-20.7 – 19.4)	0.949
					Group*Time (F = 0.5)	0.632
CBSA close friendships	n	Mean percentile (SD)	n	Mean percentile (SD)	Estimated difference (95%CI)	P
Baseline (T-1)	24	47.8 (28.3)	22	59.3 (30.2)	-10.9 (-28.2 – 6.4)	0.210
End of intervention (T1)	20	57.5 (24.0)	19	49.8 (29.7)	5.2 (-12.1 – 22.5)	0.553
End of follow-up (T3)	23	47.2 (25.6)	20	55.9 (29.8)	-12.9 (-30.2 – 4.3)	0.138
					Group*Time (F = 2.7)	0.077
PUL autonomy (range 7-28)*	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T-1)	22	23.1 (2.9)	25	22.8 (2.6)	0.1 (-1.5 – 1.8)	0.868
End of intervention (T1)	24	24.1 (3.3)	22	24.3 (3.2)	-0.1 (-2.0 – 1.8)	0.921
End of follow-up (T3)	25	23.4 (4.1)	22	24.6 (3.0)	-0.8 (-3.1 – 1.6)	0.516
					Group*Time (F = 0.4)	0.696
PUL social optimism (range 3-12)*	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T-1)	22	10.8 (1.3)	25	10.8 (1.3)	-0.0 (-0.8 – 0.7)	0.949
End of intervention (T1)	24	11.1 (1.1)	22	11.2 (1.1)	-0.0 (-0.7 – 0.7)	0.998

End of follow-up (T3)	25	10.6 (1.6)	22	11.0 (1.2)	-0.4 (-1.2 – 0.5)	0.381
					Group*Time (F = 0.5)	0.627

COPEKI coping with disease questionnaire for children, COPEJU coping with disease questionnaire for youth, CBSK self-perception profile for children, CBSA self-perception profile for adolescents, ZBV state-trait anxiety inventory, ZBV-K state-trait anxiety inventory for children, PUL positive outcome list. *PUL was filled in by children aged 13 or older

Table S5 Parental secondary outcome measures

QoL psychosomatic wellbeing mother (range 9-45)*	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	34	33.2 (4.8)	38	31.6 (4.8)	1.8 (-0.6 – 4.2)	0.141
End of intervention (T1)	37	34.5 (5.2)	36	33.2 (5.4)	1.3 (-1.1 – 3.7)	0.274
End of follow-up (T3)	34	36.3 (6.1)	31	33.9 (5.5)	2.5 (-0.0 – 4.9)	0.047
					Group*Time (F = 0.7)	0.514
QoL effects on social life mother (range 6-30)	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	34	24.8 (3.9)	38	24.6 (4.1)	0.7 (-1.2 – 2.5)	0.459
End of intervention (T1)	37	26.0 (4.0)	36	24.9 (4.4)	1.0 (-0.9 – 2.8)	0.302
End of follow-up (T3)	34	26.4 (4.4)	31	25.5 (3.9)	0.6 (-1.4 – 2.5)	0.563
					Group*Time (F = 0.2)	0.816
QoL confidence in medical treatment mother (range 5-25)*	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	34	19.1 (2.9)	38	18.7 (3.0)	0.5 (-0.8 – 1.8)	0.469
End of intervention (T1)	37	20.9 (3.0)	36	19.6 (2.8)	1.5 (0.2 – 2.8)	0.026
End of follow-up (T3)	34	21.6 (2.4)	31	20.6 (3.1)	1.2 (-0.1 – 2.6)	0.079
					Group*Time (F = 1.2)	0.290
QoL emotional coping mother (range 4-20)*	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	34	14.8 (2.6)	38	14.5 (2.4)	0.4 (-0.8 – 1.6)	0.518
End of intervention (T1)	37	16.0 (2.7)	36	14.8 (2.8)	1.1 (-0.1 – 2.2)	0.079
End of follow-up (T3)	34	16.6 (2.6)	31	16.0 (2.7)	0.6 (-0.6 – 1.9)	0.297
					Group*Time (F = 0.9)	0.407
QoL acceptance of the disease mother (range 2-10)*	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	34	8.1 (1.4)	38	7.4 (2.0)	0.6 (-0.1 – 1.4)	0.111
End of intervention (T1)	37	8.6 (1.6)	36	7.9 (1.8)	0.6 (-0.1 – 1.3)	0.119
End of follow-up (T3)	34	8.7 (1.6)	31	7.8 (1.9)	0.7 (-0.1 – 1.5)	0.068
					Group*Time (F = 0.1)	0.878
QoL psychosomatic wellbeing father (range 9-45)*	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	32	33.6 (3.9)	24	34.7 (6.2)	-0.0 (-2.7 – 2.6)	0.971
End of intervention (T1)	30	35.2 (4.3)	21	35.5 (5.8)	0.7 (-2.0 – 3.3)	0.622
End of follow-up (T3)	21	37.9 (4.3)	17	35.9 (5.5)	1.1 (-1.7 – 4.0)	0.423
					Group*Time (F = 0.6)	0.538
QoL effects on social life father (range 6-30)	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	32	25.1 (3.8)	24	26.3 (3.2)	-0.4 (-2.2 – 1.3)	0.606
End of intervention (T1)	30	25.8 (2.5)	21	27.4 (2.3)	-0.4 (-2.2 – 1.3)	0.612
End of follow-up (T3)	21	27.1 (2.2)	17	26.6 (3.9)	-0.0 (-1.8 – 1.8)	0.998
					Group*Time (F = 0.2)	0.824

QoL confidence in medical treatment father (range 5-25)*	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	32	18.4 (2.8)	24	18.3 (2.4)	0.4 (-1.0 – 1.8)	0.572
End of intervention (T1)	30	20.2 (2.4)	21	19.1 (2.6)	1.3 (-0.1 – 2.7)	0.078
End of follow-up (T3)	21	21.2 (2.1)	17	20.5 (2.7)	0.8 (-0.8 – 2.3)	0.317
					Group*Time (F = 0.7)	0.502
QoL emotional coping father (range 4-20)*	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	32	14.8 (2.4)	24	15.4 (3.0)	-0.0 (-1.3 – 1.2)	0.954
End of intervention (T1)	30	15.6 (2.1)	21	15.4 (2.7)	0.6 (-0.7 – 1.9)	0.368
End of follow-up (T3)	21	16.9 (1.8)	17	16.2 (2.4)	0.9 (-0.5 – 2.2)	0.214
					Group*Time (F = 1.4)	0.265
QoL acceptance of the disease father (range 2-10)*	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	32	7.5 (1.7)	24	7.6 (2.0)	0.1 (-0.9 – 1.0)	0.860
End of intervention (T1)	30	7.9 (1.4)	21	7.9 (1.7)	0.1 (-0.9 – 1.1)	0.840
End of follow-up (T3)	21	8.2 (1.4)	17	8.1 (2.0)	0.3 (-0.8 – 1.4)	0.565
					Group*Time (F = 0.1)	0.909
NOSI-K parenting stress mother (range 1-7)*	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T-1)	40	3.8 (1.8)	44	3.7 (1.5)	0.1 (-0.6 – 0.9)	0.695
End of intervention (T1)	37	3.5 (1.8)	36	3.9 (2.0)	-0.3 (-1.1 – 0.4)	0.371
End of follow-up (T3)	34	3.2 (1.7)	32	3.6 (1.6)	-0.4 (-1.2 – 0.4)	0.284
					Group*Time (F = 2.9)	0.060
NOSI-K parenting stress father (range 1-7)	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T-1)	34	4.3 (1.6)	33	3.9 (1.7)	0.3 (-0.5 – 1.1)	0.494
End of intervention (T1)	28	4.2 (1.6)	22	3.6 (1.7)	0.2 (-0.6 – 1.1)	0.590
End of follow-up (T3)	21	3.2 (1.5)	18	4.4 (1.7)	-0.9 (-1.9 – -0.0)	0.047
					Group*Time (F = 5.9)	0.004
ZBV trait anxiety mother	n	Mean decile (SD)	n	Mean decile (SD)	Estimated difference (95%CI)	P
Baseline (T-1)	40	4.5 (2.7)	44	4.9 (2.7)	-0.3 (-1.5 – 0.8)	0.560
End of intervention (T1)	37	3.7 (2.7)	37	4.3 (2.6)	-0.5 (-1.7 – 0.7)	0.407
End of follow-up (T3)	34	3.2 (2.6)	32	4.0 (2.3)	-0.9 (-2.1 – 0.3)	0.125
					Group*Time (F = 0.8)	0.436
ZBV trait anxiety father	n	Mean decile (SD)	n	Mean decile (SD)	Estimated difference (95%CI)	P
Baseline (T-1)	34	4.2 (2.4)	34	5.0 (3.0)	-0.7 (-2.0 – 0.6)	0.276
End of intervention (T1)	29	3.8 (2.3)	22	4.6 (2.8)	-1.4 (-2.7 – 0.0)	0.050
End of follow-up (T3)	21	2.6 (1.8)	18	4.1 (2.8)	-1.6 (-3.1 – -0.2)	0.029
					Group*Time (F = 1.4)	0.242
ZBV state anxiety corticosteroid use mother	n	Mean decile (SD)	n	Mean decile (SD)	Estimated difference (95%CI)	P
Baseline (T-1)	40	5.6 (2.5)	43	6.3 (2.2)	-0.7 (-1.7 – 0.3)	0.170
End of intervention (T1)	37	4.5 (2.3)	36	5.2 (2.3)	-0.7 (-1.7 – 0.3)	0.150

End of follow-up (T3)	34	3.9 (1.9)	31	5.2 (2.2)	-1.3 (-2.3 - -0.3)	0.015
					Group*Time (F = 0.7)	0.513
ZBV state anxiety corticosteroid use father*	n	Mean decile (SD)	n	Mean decile (SD)	Estimated difference (95%CI)	P
Baseline (T-1)	34	6.4 (2.4)	33	5.7 (3.0)	0.6 (-0.7 – 1.9)	0.350
End of intervention (T1)	29	5.5 (2.4)	21	4.9 (3.2)	-0.0 (-1.5 – 1.4)	0.964
End of follow-up (T3)	21	3.9 (2.2)	17	4.7 (2.7)	-1.5 (-3.0 – 0.0)	0.057
					Group*Time (F = 5.2)	0.007

QOL quality of life, NOSI-K parental stress index-short form, ZBV state-trait anxiety inventory *Analyzed without random slope

Table S6A Pharmacological treatment for AD during the study period (intervention group).

Intervention group						
Used topical corticosteroids / systemic immunosuppressives	none	Tac /emovate /protopic	Cutivate/ elocon	Betnelan/ betamethason	Dermovate	Prednisone / cyclosporin
Inclusion (Tmin1) n(%)	2 (5%)	2 (5%)	14 (34%)	19 (46%)	2 (5%)	2 (5%)
Baseline (T0) n(%)			17 (41%)	12 (29%)		9 (22%)
End of intervention (T1) n(%)	3 (8%)	5 (13%)	16 (42%)	13 (34%)		1 (3%)
First follow-up assessment (T2) n(%)		7 (19%)	16 (43%)	13 (35%)		1 (3%)
End of follow-up (T3) n(%)	1 (3%)	1 (3%)	16 (42%)	8 (21%)	3 (8%)	9 (24%)

See Table S3 for differences between the groups

Table S6B Pharmacological treatment for AD during the study period (control group).

Control group						
Used topical corticosteroids / systemic immunosuppressives	none	Tac /emovate /protopic	Cultivate/ elocon	Betnelan/ betamethason	Dermovate	Prednisone / cyclosporin
Inclusion (Tmin1) n(%)	1 (2%)	1 (2%)	14 (33%)	19 (44%)	0	8 (19%)
Baseline (T0) n(%)	1 (2%)	2 (5%)	10 (24%)	17 (42%)	2 (5%)	9 (22%)
End of intervention (T1) n(%)		7 (17%)	9 (23%)	15 (37%)	1 (3%)	8 (20%)
First follow-up assessment (T2) n(%)		3 (8%)	12 (31%)	15 (38%)	2 (5%)	7 (18%)
End of follow-up (T3)	1	2 (6%)	13 (36%)	14 (39%)	3 (8%)	3 (8%)

n(%)	(3%)					
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See Table S3 for differences between the groups