

ORIGINAL ARTICLE

Chronic hand eczema: A prospective analysis of the Swiss CARPE registry focusing on factors associated with clinical and quality of life improvement

Simone Cazzaniga^{1,2,3} | Barbara K. Ballmer-Weber^{4,5,6} | Nora Gräni⁴ | Philippe Spring⁷ | Andreas Bircher⁸  | Mark Anliker^{9,10} | Anne-Katharina Sonntag¹¹ | Pierre Piletta¹² | Caroline Huber^{12,13} | Thomas L. Diepgen¹⁴ | Christian Apfelbacher¹⁵  | Luigi Naldi^{2,16} | Luca Borradori¹ | Dagmar Simon¹ 

¹Department of Dermatology, Inselspital, Bern University Hospital, Bern, Switzerland

²Centro Studio, Italian Group for Epidemiological Research in Dermatology (GISED), Bergamo, Italy

³Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland

⁴Department of Dermatology, University Hospital Zurich, Zurich, Switzerland

⁵Faculty of Medicine, University of Zurich, Zurich, Switzerland

⁶Allergy Unit, Clinic of Dermatology and Allergology, Cantonal Hospital St Gallen, St. Gallen, Switzerland

⁷Department of Dermatology, University Hospital of Lausanne CHUV, Lausanne, Switzerland

⁸Department of Dermatology, University Hospital Basel, Basel, Switzerland

⁹Clinic of Dermatology and Allergology, Cantonal Hospital St Gallen, St Gallen, Switzerland

¹⁰Hautärzte am Graben, Winterthur, Switzerland

¹¹Department of Dermatology, Cantonal Hospital Aarau, Aarau, Switzerland

¹²Department of Dermatology, Geneva University Hospitals (HUG), Geneva, Switzerland

¹³Dermatology Office, Versoix, Switzerland

¹⁴Department of Clinical Social Medicine, Occupational and Environmental Dermatology, University Hospital, Ruprecht Karls University, Heidelberg, Germany

¹⁵Institute of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany

¹⁶Department of Dermatology, San Bortolo Hospital, Vicenza, Italy

Correspondence

Dr Dagmar Simon, Department of Dermatology, Inselspital, Bern University Hospital, 3010 Bern, Switzerland.
Email: dagmar.simon@insel.ch

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Background: Hand eczema (HE) is common and may follow a chronic disease course. So far, prospective studies investigating the risk factors for disease progression as a prerequisite for targeted prevention are scarce.

Objective: To evaluate the overall association of HE-associated factors with clinical and quality of life (QoL) improvement during a follow-up of 2 years.

Methods: Data of the prospective patient cohort ($N = 199$) followed by the Swiss chronic HE (CHE) registry on long-term patient management (CARPE-CH) were analysed by means of both classic regression and semantic map analyses.

Results: Both severity of HE and QoL significantly improved over the period of 2 years ($P < .001$). However, 20% of patients had moderate to severe HE after 2 years of follow-up. As factors associated with an unfavourable CHE clinical course and QoL, environmental exposures, male sex, occupational skin disease, job loss or change at baseline, allergic contact dermatitis, a chronic disease course, palmar localization and widespread eczema were identified.

Conclusions: Analysis of prospective data from CARPE-CH shows a complex pattern of associations among variables as shown by semantic map and classic statistical analyses. Factors related to occupational exposure had the highest impact on CHE.

KEYWORDS

CARPE, chronic hand eczema, clinical improvement, epidemiology, follow-up, quality of life, semantic map analysis

1 | INTRODUCTION

Hand eczema (HE) is a common disease that may affect all age groups. Because HE commonly follows a relapsing or chronic disease course, it has an immense impact on the physical and mental wellbeing of the patients, the ability of patients to work, and medical care and costs.^{1,2} Therefore, prevention of HE, in particular chronic HE (CHE), is necessary. However, the development of effective preventive strategies requires prior analysis of factors that determine the prognosis of HE. A number of epidemiological studies have investigated the incidence, prevalence and severity of HE and their risk factors in the general population, as well as in certain age and occupational groups. In order to evaluate the prognosis of HE, long-term follow-up studies are required, but, so far, prospective studies are scarce and limited to a few countries.

In a cohort of 799 HE patients, predictors of poor prognosis after 6 months included being an unskilled worker and the presence of frequent symptoms associated with severe initial disease.³ Moreover, these patients had an impaired quality of life (QoL), which, during follow-up, improved in 55.7% in parallel with clinical amelioration.⁴ In young adults, childhood eczema was the most important risk factor for HE.⁵ In a large cohort encompassing 868 HE patients, 44% still had HE, and 12% even had continuous signs after 15 years, showing the poor prognosis of HE.⁶ An even higher rate of persistence, up to 60%, was reported among patients with occupational HE after 7 to 14 years of follow-up, for which atopy and work-related chromate allergy were the main risk factors.⁷ A questionnaire-based follow-up of 4 to 5 years showed that >30% of individuals with occupational HE had changed profession, in particular those with severe HE, positive patch test reactions, young age, and low educational level.⁸ Integrated care for patients with severe CHE was reported to significantly improve clinical outcome measures after 6 months.⁹

Here, we present the epidemiology of CHE in a prospective cohort of patients in Switzerland. This study was aimed at exploring the overall association between selected factors and clinical and QoL improvement during a follow-up of 2 years, and to show the complex interaction between exposures and the consequences of CHE at follow-up by using semantic connectivity map analysis.

2 | METHODS

The CHE registry on long-term patient management (CARPE-CH) was initiated in 2011 in Switzerland as a prospective patient cohort study recruiting patients with CHE over a follow-up period of 2 years.¹⁰ It was linked to the German CARPE registry.^{11,12} Detailed demographic,

clinical and dermatological data of the patients were collected at the time of enrolment (baseline [BL]), and after 3, 6, 12, 18 and 24 months. The study was approved by the local ethics committees. All patients gave written informed consent prior to enrolment.

2.1 | Patients

Patients with HE were eligible to participate in the CARPE study, if the following criteria were met: (1) disease duration of at least 3 months or >2 flares within the last 12 months; (2) recent treatment with topical corticosteroids for HE; (3) failure to achieve long-term improvement despite adequate topical therapy; and (4) exclusion of other active severe skin diseases or acute skin infections interfering with the diagnosis of CHE.

For the purpose of the study, the following BL and follow-up data were considered: demographics, patient history, clinical signs and symptoms, classification of HE subtypes based on morphology (vesicular, hyperkeratotic, and fingertip dermatitis) and aetiology (atopic predisposition, allergic contact sensitization, and exposure to irritants), current treatment for CHE, occupational status and environmental exposure, sick-leave, severity, and QoL indexes. The severity of HE was assessed by use of a 5-item Physician Global Assessment (PGA) score (clear, almost clear, mild, moderate, or severe) supported by a validated photographic guide.¹³ The patient's QoL was assessed on the basis of the Dermatology Life Quality Index (DLQI).^{14,15}

For the purpose of semantic map analysis, clinical efficacy and QoL improvements at 6 months were assessed by considering the minimal clinically important difference (MCID). For the DLQI, the MCID corresponds to an absolute reduction from BL of at least 4 units,¹⁶ whereas, for PGA, we fixed the threshold to 1 unit of reduction, corresponding to the rounded value of 0.5 standard deviations (SDs).¹⁷

2.2 | Statistical analysis

Data are presented as numbers with percentages and means with SDs for categorical and continuous variables, respectively. Continuous variables were categorized by using clinically meaningful thresholds as cutoff points. The linear trend for differences across BL and follow-up assessments was tested by the use of generalized estimating equations (GEEs), with an unstructured working covariance matrix and normal, binomial or multinomial distributions for continuous, dichotomous or ordinal variables, respectively. Multivariable analysis of selected factors affecting the MCID of PGA and DLQI scores at 6 months from BL were analysed by means of logistic regression models, including terms for age, sex, at-risk occupation, occupational

skin disease (OSD) and PGA/DLQI score at BL as adjustment factors. Associations were expressed as odds ratios along with their 95% confidence intervals (CIs) and *P* values. For the purpose of the logistic regression and semantic map analyses, the last observation carried forward approach was used to impute patients lost at follow-up.

In addition, a complete longitudinal analysis was conducted in order to investigate factors associated with PGA and DLQI absolute variations at all available follow-ups. The analysis was performed by using GEEs with an unstructured working covariance matrix and a normal distribution, including the same factors as described above for adjustment purpose. Effects were expressed as score changes along with 95%CIs and *P*-values. All results were considered to be significant at a *P* value of $<.05$. Analyses were performed with SPSS version 20 (IBM, Armonk, New York).

For semantic map analysis, the overall association among selected factors was analysed by means of an algorithm that is able to compute and display the best connections between each pair of variables, taking into account other covariates in the system.¹² Data were entered into the algorithm in 2 different steps. First, we included demographics, patient history, clinical signs and symptoms, atopic diathesis, HE subtypes, occupational status, at-risk occupations, exposure to allergens and irritants, and the MCID of severity and QoL indexes at 6 months. Next, we focused on CHE treatment in the first 6 months of follow-up, as well as HE subtypes and the MCID of severity and QoL indexes at 6 months. Briefly, multiple logistic regression models were fitted by taking each time, sequentially, a variable as the predictor and the others as covariates. This process was reiterated until all variables in the model were processed. BL values of PGA and DLQI were also included in the models as adjustment factors to account for their changes at follow-up. Finally, a matrix of normalized weights in the interval $[-1, 1]$ was produced from the regression coefficients. A mathematical filter, the maximum spanning tree (MST),¹⁸ was then applied to the matrix of weights, and a semantic connectivity map was generated. The MST selects positive associations ensuring normalized correlations in the interval $[0, 1]$. The analysis was performed with MATLAB V.7.8 (The MathWorks, Natick, Massachusetts).

3 | RESULTS

The BL data on current and past CHE parameters, the latter covering 12 months prior to enrolment in the study, have been published elsewhere.¹⁰ Briefly, from October 2011 to May 2013, 199 patients were enrolled. Their mean age was 40.4 ± 14.2 years (mean $\pm$ SD), and 50.8% were females.

3.1 | Significant improvement of CHE severity and patients' QoL over 2-years of follow-up

At follow-up, data of 151 (75.9%), 133 (66.8%) and 105 patients (52.8%) were obtained at 6-month, 1-year and 2-year visits, respectively (Table 1). The severity of CHE assessed by use of the PGA score significantly decreased over the period of 2 years ($P < .001$). Accordingly, the proportions of patients with moderate and severe HE decreased (BL, 70.9%; 2 years, 20%), whereas the proportions of

patients with scores of clear and almost clear increased (BL, 5.5%; 2 years, 55.3%). Moreover, the relative number of CHE patients reporting a continuous disease course over the last 3 months decreased over the observation period of 2 years, whereas the number of patients with episodic HE (1-2 and 3-5 episodes) increased ($P = .001$). The rate of sick-leave because of CHE significantly decreased from 13.2% at 3 months to 2.9% at 2 years ($P = .007$), as did the percentage of patients who were unable to work ($P < .001$). The percentage of patients who had an OSD or had to change their job because of the CHE was stable over time.

In parallel with the decrease in HE severity, DLQI significantly improved over the follow-up period of 2 years ($P < .001$). Whereas 39.4% of patients reported an extremely/very large effect of the CHE on their QoL at BL, the proportion was reduced to 13.7% after 2 years. Correspondingly, the relative number of patients reporting no or small effects on QoL increased from 26.9% to 78.9%.

3.2 | Reduced use of topical corticosteroids and systemic therapies over 2-years of follow-up

Patients with CHE were mainly treated with topical therapies (80%-92%) over the whole period of 2 years (Table 2). In particular, potent and very potent topical corticosteroids as well as emollients with urea were applied. Notably, the use of potent/very potent topical corticosteroids decreased (BL, 64.3%; 2 years, 50.4%), whereas the application of topical calcineurin inhibitors increased (BL, 22.6%; 2 years, 40%). The relative number of patients receiving systemic therapy only slightly decreased over the follow-up period of 2 years (BL, 19.6%; 2 years, 14.3%). Whereas 12.9% of CHE patients were treated with alitretinoin at BL, the percentage of patients requiring alitretinoin after 2 years of follow-up declined to 2.9%. Reasons for discontinuing alitretinoin therapy were either improvement of HE or a lack of efficacy, but rarely adverse effects. During the follow-up period, only a few patients were treated with systemic corticosteroids, cyclosporine, acitretin, or methotrexate. Interestingly, the relative number of patients taking antihistamines drastically decreased.

3.3 | Semantic map analysis identifies exposures as the main trigger of CHE

The semantic map representing the best links among selected demographics, clinical features, HE subtypes, and occupational and environmental exposure factors, as well as prognostic and QoL indicators, at 6 months of follow-up is shown in Figure 1. As in our previous analysis,¹² exposure variables appear in the centre of the map in association with sex, for example, wet work and exposure to detergents and disinfectants related to females, and exposure to industrial oils, solvents and mechanical stress related to males. Interestingly, exposure to detergents was associated with frequent episodes (≥ 5) and vesicular HE as well as sick-leave and inability to work, which was further linked to improvements in PGA and DLQI after 6 months. We did not observe a strict demarcation between the sexes, although males were more connected to OSD and job loss or change resulting from CHE.

TABLE 1 Episodes of chronic hand eczema (CHE), job-related characteristics, severity and quality of life indexes at baseline (BL) and follow-up (FU) visits

		Visits						P ^a
		BL (N = 199)	3 mo (N = 171)	6 mo (N = 151)	12 mo (N = 133)	18 mo (N = 117)	24 mo (N = 105)	
Episodes of CHE in the last 12 mo (BL)/last 3 mo (FU) ^b , n (%)	1-2	7 (3.5)	69 (42.3)	65 (44.5)	52 (41.3)	57 (49.1)	52 (49.5)	.001
	3-5	15 (7.5)	19 (11.7)	16 (11.0)	12 (9.5)	10 (8.6)	18 (17.1)	
	≥6	17 (8.5)	8 (4.9)	6 (4.1)	12 (9.5)	11 (9.5)	9 (8.6)	
	Continuous	160 (80.4)	67 (41.1)	59 (40.4)	50 (39.7)	38 (32.8)	26 (24.8)	
Unable to work, n (%)	No	162 (82.2)	145 (90.1)	131 (90.3)	119 (95.2)	106 (93.0)	95 (94.1)	<.001
	Yes	35 (17.8)	16 (9.9)	14 (9.7)	6 (4.8)	8 (7.0)	6 (5.9)	
Sick-leave in the last 12 mo (BL)/last 3 mo (FU) because of CHE ^b , n (%)	No	127 (65.8)	141 (87.0)	137 (94.5)	117 (92.9)	107 (93.0)	100 (97.1)	.007
	Yes	66 (34.2)	21 (13.0)	8 (5.5)	9 (7.1)	8 (7.0)	3 (2.9)	
Job loss/change because of CHE, n (%)	No	168 (85.3)	141 (86.5)	131 (89.7)	103 (81.1)	95 (81.9)	86 (82.7)	.18
	Yes	29 (14.7)	22 (13.5)	15 (10.3)	24 (18.9)	21 (18.1)	18 (17.3)	
OSD, n (%)	No	131 (68.2)	111 (68.1)	101 (69.7)	87 (68.5)	78 (67.8)	70 (66.7)	.55
	Yes	61 (31.8)	52 (31.9)	44 (30.3)	40 (31.5)	37 (32.2)	35 (33.3)	
PGA, n (%)	Clear	1 (0.5)	11 (6.7)	20 (13.7)	20 (15.7)	21 (18.3)	22 (21.0)	<.001
	Almost clear	10 (5.0)	42 (25.8)	35 (24.0)	34 (26.8)	36 (31.3)	36 (34.3)	
	Mild	47 (23.6)	50 (30.7)	35 (24.0)	38 (29.9)	29 (25.2)	26 (24.8)	
	Moderate	112 (56.3)	47 (28.8)	45 (30.8)	28 (22.0)	25 (21.7)	15 (14.3)	
	Severe	29 (14.6)	13 (8.0)	11 (7.5)	7 (5.5)	4 (3.5)	6 (5.7)	
DLQI	Mean (SD)	9.7 (5.8)	6.1 (5.4)	6.1 (6.1)	5.4 (5.7)	5.0 (5.0)	4.2 (5.5)	<.001
	No, n (%)	7 (4.0)	31 (20.7)	35 (24.6)	35 (29.4)	32 (29.4)	33 (34.7)	
	Small, n (%)	40 (22.9)	52 (34.7)	51 (35.9)	41 (34.5)	40 (36.7)	42 (44.2)	
	Moderate, n (%)	59 (33.7)	40 (26.7)	27 (19.0)	24 (20.2)	21 (19.3)	7 (7.4)	
	Very large, n (%)	62 (35.4)	23 (15.3)	23 (16.2)	14 (11.8)	14 (12.8)	10 (10.5)	
	Extremely large, n (%)	7 (4.0)	4 (2.7)	6 (4.2)	5 (4.2)	2 (1.8)	3 (3.2)	

Abbreviations: DLQI, Dermatology Life Quality Index; mo, months; OSD, occupational skin disease; PGA, Physician Global Assessment; SD, standard deviation. Numbers may not add up to the total, owing to missing data.

^a Test for linear trend across BL and FU assessments by the use of generalized linear models for repeated measures with normal, binomial or multinomial distribution.

^b BL assessment was excluded from the test for linear trend.

Regarding follow-up variables, PGA improvement and DLQI improvement were strictly connected. Absence of improvement in PGA or DLQI showed a complex pattern of associations, including male sex, job loss/change, OSD because of CHE at BL, previous type IV allergy, diagnosis of allergic contact dermatitis, and localization of eczema on the palms and feet. The improvements in PGA and DLQI at 6 months were linked to mild or moderate pruritus at BL and being unable to work or taking sick-leave in the last 12 months.

A separate semantic map was focused on the best associations among HE treatments and subtypes, as well as differences in PGA and DLQI, at 6 months (Figure 2). Systemic and topical corticosteroids, together with alitretinoin as second-line therapy, were the main therapies applied, independently of clinical HE subtype. The associations of psoralen and ultraviolet (UV) A/UV therapy, potent corticosteroids and calcineurin inhibitors with lack of improvements in PGA and DLQI at 6 months of follow-up allowed us to assume that these therapies were applied in cases of refractory HE. On the other hand, improvements in PGA and DLQI were linked to topical therapy with urea and salicylic acid, indicating that these patients required skin care but no or fewer anti-inflammatory drugs.

3.4 | OSD, job loss/change and continuous lesions determine HE severity and QoL

The association between selected factors and improvements in PGA and DLQI at 6 months from BL are shown in Table 3. In agreement with the semantic map analysis, OSD, job loss/change at BL because of CHE and localization on the palms were significantly linked to absent or minimal improvements in PGA and DLQI.

In addition, continuous lesions of CHE in the last 12 months before study entry were associated with the absence of relevant DLQI improvement. In line with the semantic map, urea treatment correlated with relevant improvements in PGA and DLQI scores based on the MCID.

3.5 | Longitudinal analysis of factors associated with PGA and DLQI variation over a period of 2 years

Factors associated with PGA and DLQI variation at all available follow-ups are shown in Table 4. Overall, long CHE duration (≥6 years), a continuous course of HE during the follow-up period, being unable to work, concomitant eczema on the wrists or feet, the presence of

TABLE 2 Therapies for chronic hand eczema at baseline and follow-up visits

		Visits											
		Baseline		3 mo		6 mo		12 mo		18 mo		24 mo	
		n	%	n	%	n	%	n	%	n	%	n	%
Local therapies	Mild corticosteroids	1	0.5	1	0.6	1	0.7	0	0	0	0.0	0	0
	Moderate corticosteroids	10	5.0	14	8.2	16	10.6	11	8.3	8	6.8	4	3.8
	Potent corticosteroids	83	41.7	68	39.8	51	33.8	42	31.6	28	23.9	39	37.1
	Very potent corticosteroids	45	22.6	32	18.7	23	15.2	21	15.8	17	14.5	14	13.3
	Calcineurin inhibitors	45	22.6	70	40.9	63	41.7	46	34.6	43	36.8	42	40.0
	Tar/shale oils	3	1.5	2	1.2	0	0.0	6	4.5	3	2.6	4	3.8
	Urea	99	49.7	120	70.2	101	66.9	71	53.4	66	56.4	61	58.1
	Tannin	5	2.5	11	6.4	6	4.0	8	6.0	4	3.4	2	1.9
	Salicylic acid	21	10.6	18	10.5	15	9.9	8	6.0	10	8.5	4	3.8
	Iontophoresis	2	1.0	1	0.6	0	0.0	0	0.0	0	0.0	0	0
	Other local therapies	10	5.0	9	5.3	9	6.0	7	5.3	1	0.9	1	1.0
	No local therapy	36	18.1	14	8.2	14	9.3	22	16.5	21	17.9	21	20.0
UV therapies	Cream PUVA	3	1.5	4	2.3	2	1.3	1	0.8	1	0.9	0	0
	Bath PUVA	8	4.0	5	2.9	3	2.0	2	1.5	1	0.9	1	1.0
	Systemic PUVA	1	0.5	1	0.6	1	0.7	0	0.0	0	0	0	0
	Other UV therapies	6	3.0	6	3.5	2	1.3	0	0.0	1	0.9	0	0
	No UV therapy	184	92.5	155	90.6	143	94.7	130	97.7	114	97.4	104	99.0
Systemic therapies	Systemic corticosteroids	2	1.0	6	3.5	2	1.3	3	2.3	1	0.9	1	1.0
	Antihistamines	20	10.1	8	4.7	8	5.3	1	0.8	5	4.3	2	1.9
	Alitretinoin	18	9.0	22	12.9	14	9.3	15	11.3	9	7.7	3	2.9
	Acitretin	2	1.0	2	1.2	3	2.0	5	3.8	6	5.1	6	5.7
	Cyclosporine	1	0.5	0	0.0	1	0.7	0	0.0	1	0.9	1	1.0
	Methotrexate	1	0.5	0	0.0	2	1.3	2	1.5	2	1.7	3	2.9
	Other systemic therapies	2	1.0	5	2.9	5	3.3	4	3.0	2	1.7	2	1.9
	No systemic therapy	160	80.4	133	77.8	120	79.5	108	81.2	95	81.2	90	85.7

Abbreviations: PUVA, psoralen and ultraviolet A; UV, ultraviolet.

pruritus and exposure to solvents were significantly associated with increased PGA and DLQI scores at follow-up. Interestingly, cessation or change of job because of CHE at follow-up was linked to reduced PGA or DLQI scores, which, on the other hand, were linked to occupations associated with a high risk of HE (eg, construction, mechanics, cleaning, and food and catering). When CHE therapies at follow-up were analysed, the use of mild/moderate or very potent corticosteroids was associated with disease progression, as indicated by increases in PGA and DLQI scores. Other investigated factors were not significantly associated with any PGA or DLQI variations.

4 | DISCUSSION

We present an analysis of factors associated with the clinical course of CHE in a prospective cohort of patients observed within the Swiss CARPE registry over a period of 2 years. Our study showed significant improvements in clinical signs and disease-related QoL in patients with CHE. The factors associated with HE severity and QoL impairment include exposure factors, male sex, OSD, job loss/change, allergic contact dermatitis, a continuous disease course, eczema localization on the palms and widespread eczema as identified by means of a semantic map, multivariable regression at 6 months and longitudinal

analyses. Despite a significant reduction in HE severity and QoL improvement over time, after 2 years ≈20% of CHE patients still had moderate to severe HE. These results are in agreement with previous prospective studies.^{3,6,19} In parallel with the improvement in HE, the number of patients on sick-leave because of CHE and the number unable to work significantly decreased.

In order to explore the overall complex associations among selected BL and 6-month follow-up prognostic variables, we adopted a semantic map analysis approach analogous to that used in our previous study analysing CHE-associated factors in a cohort of German and Swiss patients.¹² This method had the advantage of showing a huge amount of variables and their main interactions on 1 map, thus providing a comprehensive view of CHE. Again, we found exposure variables clustered in the centre of the map, indicating a high impact on CHE. Recent studies reported work-related HE associated with health/social work, occupational cleaning and hairdressers in women, farming, industrial occupations and painting in men, and food-related occupations overall.^{20,21} A particularly high risk of developing HE has been reported in individuals exposed to wet work.^{5,22–24}

The effect of sex on HE prognosis is still controversial. Some studies identified a higher risk, severity and chronicity of HE in males,^{12,20,23,25,26} but others did not.^{1,3,6,7,22,27,28} In our semantic map analysis, male sex and typical male occupations were closely linked to

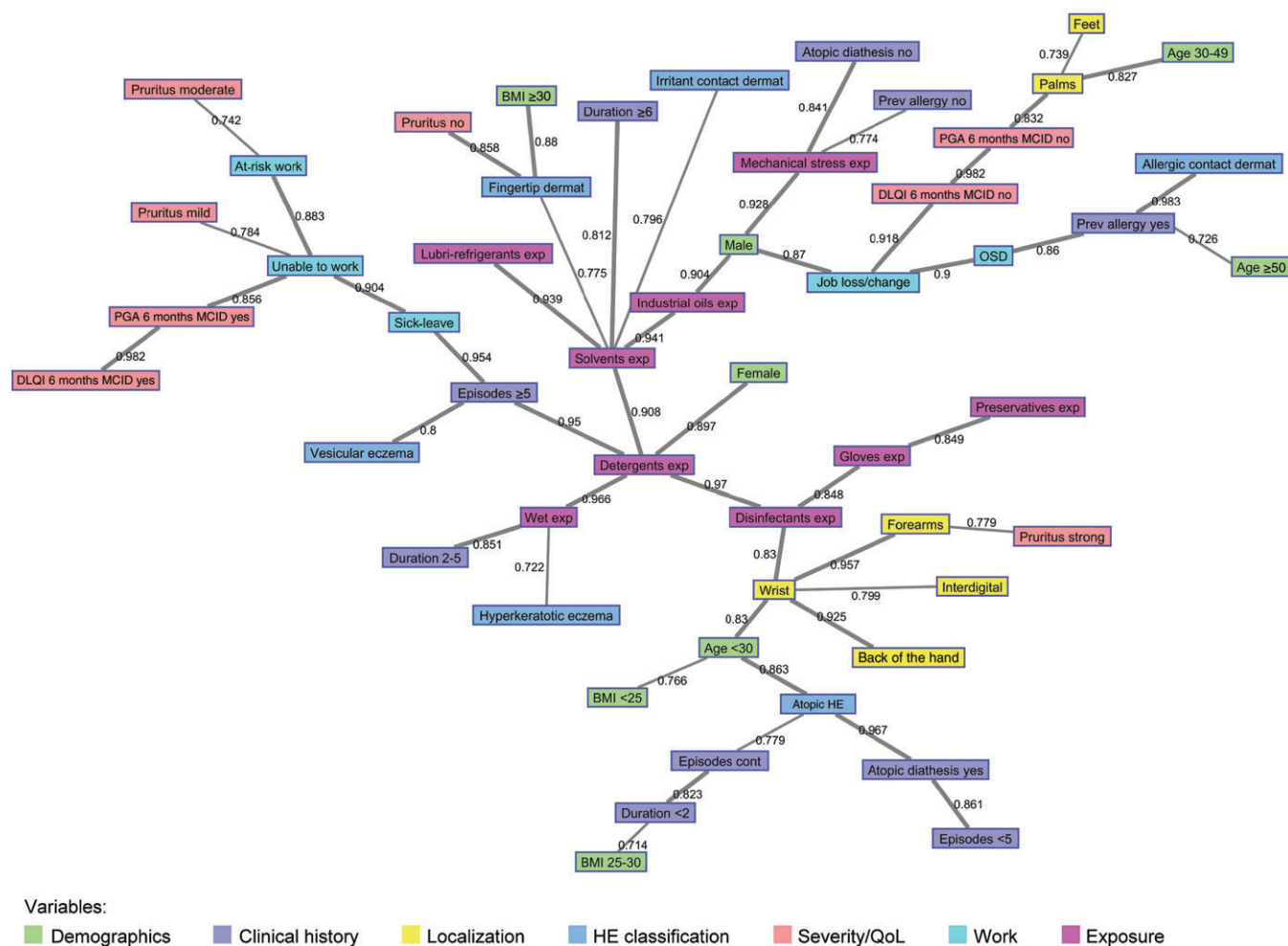


FIGURE 1 Semantic map of the associations among selected demographics, clinical features, hand eczema (HE) subtypes, occupational and environmental exposure factors, and prognostic and quality of life (QoL) indicators at 6 months of follow-up. The best links among selected variables are shown. The numbers indicate normalized correlations between 0 and 1. The line thickness corresponds to the strength of association (thin line, <0.6; medium line, 0.6–0.8; thick line, >0.8). BMI, body mass index; cont, continuous; dermat, dermatitis; DLQI, Dermatology Life Quality Index; exp, exposure; MCID, minimal clinically important difference; OSD, occupational skin disease; PGA, Physician Global Assessment; prev, previous

the persistence of HE. It should be noted that this finding could not be confirmed by classic regression or longitudinal analysis. In individuals with occupational HE, change of profession was associated with young age, positive patch test reactions, a low educational level, and severity of HE.⁸ As shown for hairdressers, CHE significantly influences the decision to change career.²⁹ Both OSD and job loss/change because of CHE at BL were associated with persistent HE after 6 months of follow-up, as found in the semantic map and confirmed by multivariable analysis. Notably, during the follow-up over a period of 2 years, job loss/change was correlated with improvements in HE severity and QoL. This finding is in line with previous studies showing a better long-term outcome of HE in patients who had changed their job.^{6,7}

Allergic contact sensitization has been associated with greater severity of HE.³ In particular, chromate allergy predicts a poor prognosis.^{3,7} In our CHE patient cohort, the diagnosis of allergic contact dermatitis was associated with a lack of HE improvement. Atopy has also been considered to be a risk factor for HE, and its severity and persistence.^{1,5,7,30} Furthermore, the presence of frequent symptoms over a period of 12 months was shown to correlate with poor prognosis of

HE.³ In our cohort, we found atopic hand eczema to be linked to chronic disease course and young age on the semantic map, and continuous skin lesions reported at BL to be associated with HE persistence during follow-up, as assessed by multivariable and longitudinal analysis. In agreement with a previous study showing that, in patients with HE, widespread eczema was a risk factor for a poor prognosis,¹⁹ an association of eczema on the wrists or feet with high PGA scores during the follow-up of 2 years was noted. HE has been shown to have a strong impact on QoL.^{4,6,19,28,31,32} Interestingly, changes in HE severity and QoL are closely linked. Thus, we found lack of improvement in HE severity and DLQI to be associated with widespread eczema, job loss/change at BL, OSD, contact allergy, and male sex.

The analysis of treatments used shows that ~80% of all patients applied topical therapies. Whereas potent/very potent corticosteroids were predominantly employed at BL, topical calcineurin inhibitors and emollients with urea were more frequently applied during follow-up. This trend most likely reflects the therapeutic algorithm followed by the study centres. The semantic map and multivariable analysis showed an overall improvement in HE linked to urea use. In our

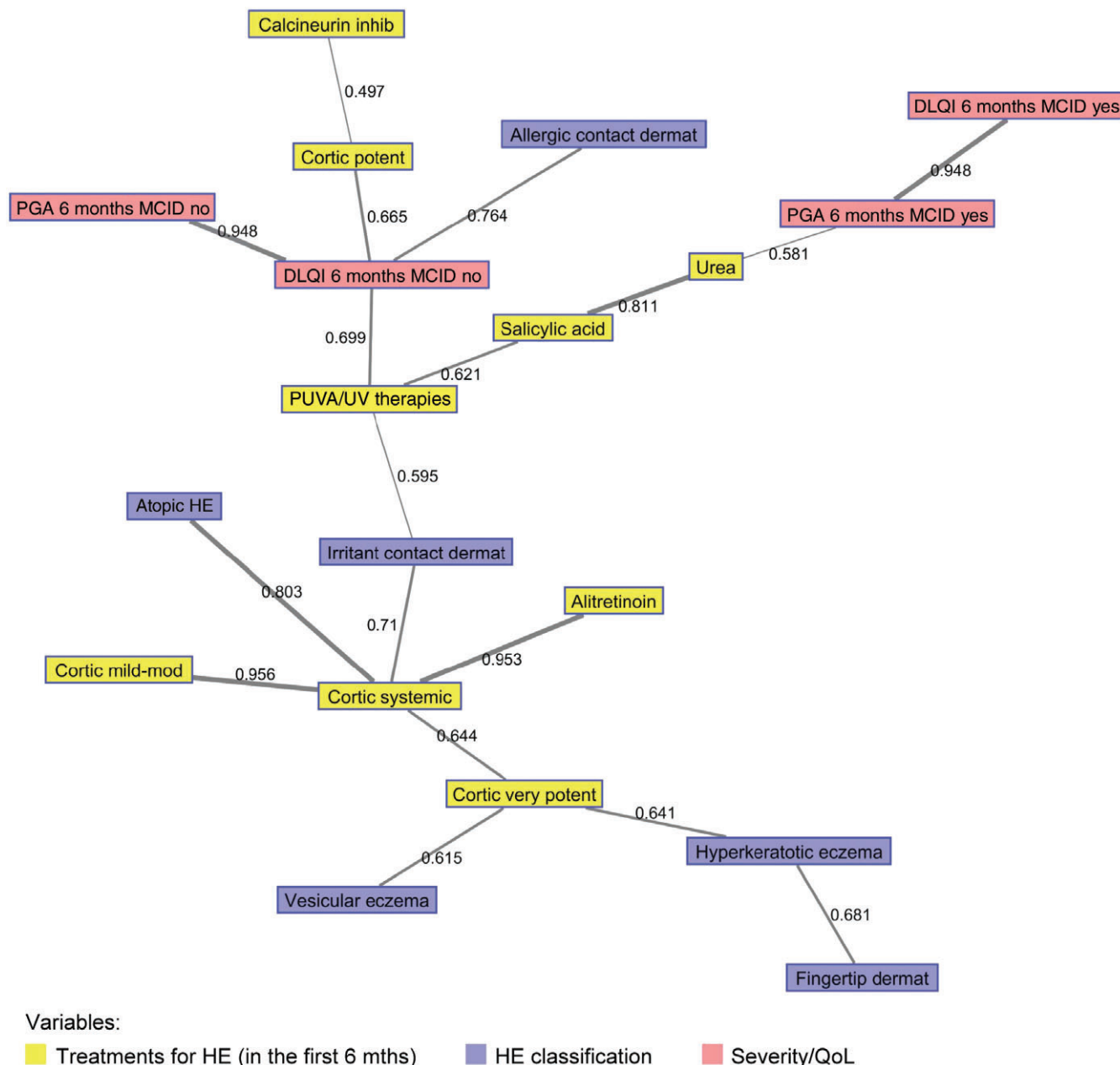


FIGURE 2 Semantic map of the associations among hand eczema (HE) treatments in the first 6 months, HE subtypes and prognostic and quality of life (QoL) indicators at 6 months of follow-up. The best links among selected variables are shown. The numbers indicate normalized correlations between 0 and 1. The line thickness corresponds to the strength of association (thin line, <0.6 ; medium line, $0.6-0.8$; thick line, >0.8). Cortic, corticosteroids; dermat, dermatitis; DLQI, Dermatology Life Quality Index; inhib, inhibitors; MCID, minimal clinically important difference; mod, moderate; PGA, Physician Global Assessment; PUVA, psoralen and ultraviolet A; UV, ultraviolet

cohort, the number of patients receiving systemic therapy is higher than that in a recent study reporting 7% of HE patients receiving oral therapy.¹⁹ Alitretinoin, which is a molecule approved for the treatment of CHE, was the most commonly applied systemic drug. However, a selection bias linked to the referral to study centres might explain the high proportion of patients treated with alitretinoin in the first year of follow-up. During the second year, the percentage of patients receiving alitretinoin decreased over time, in parallel with CHE improvement. Alitretinoin has been shown to markedly improve clinical signs and symptoms, and therefore QoL and work productivity, of patients with severe CHE.^{33,34}

The main strength of our study is the use of both semantic map analysis and classic approaches (mid-term and full longitudinal analyses). However, a possible limitation of the semantic map analysis is that the method used is entirely explorative. Thus, links emerging from this analysis do not necessarily indicate a causal connection. In addition, because of the explorative nature of our study, we did not adjust results for multiple testing.

In summary, the analysis of prospective data from CARPE-CH shows a complex pattern of associations among a huge number of variables. Although several associations could be verified with classic statistical approaches, some patterns emerging from the semantic

TABLE 3 Multivariable analysis of selected factors affecting Physician Global Assessment (PGA) score and Dermatology Life Quality Index (DLQI) minimal clinically important difference (MCID) at 6 months from baseline

	PGA MCID						DLQI MCID					
	No			Yes			No			Yes		
	n	%		n	%	OR (95%CI) ^a	n	%		n	%	P
Sex												
Male	51	49.0		47	49.5	1	66	55.5		32	40.0	1
Female	53	51.0		48	50.5	0.82 (0.44-1.52)	53	44.5		48	60.0	1.02 (0.52-2.00)
Age (years)												
<30	29	27.9		27	28.4	1	31	26.1		25	31.2	1
30-49	40	38.5		43	45.3	1.34 (0.64-2.80)	50	42.0		33	41.2	0.90 (0.41-1.95)
≥50	35	33.7		25	26.3	0.72 (0.32-1.59)	38	31.9		22	27.5	0.88 (0.38-2.01)
BMI (kg/m ²)												
<25.0	47	45.2		44	46.3	1	52	43.7		39	48.8	1
25.0-29.9	40	38.5		36	37.9	1.00 (0.51-1.95)	51	42.9		25	31.2	0.76 (0.36-1.58)
≥30.0	17	16.3		15	15.8	0.95 (0.39-2.31)	16	13.4		16	20.0	1.40 (0.55-3.55)
Duration (years)												
<2.0	34	32.7		40	42.1	1	43	36.1		31	38.8	1
2.0-5.9	30	28.8		25	26.3	0.62 (0.29-1.33)	33	27.7		22	27.5	0.76 (0.34-1.69)
≥6.0	40	38.5		30	31.6	0.56 (0.27-1.16)	43	36.1		27	33.8	0.91 (0.41-2.02)
Episodes of CHE in the last 12 months before study entry												
<5	7	6.7		10	10.5	1	8	6.7		9	11.2	1
≥5	12	11.5		10	10.5	0.63 (0.16-2.47)	12	10.1		10	12.5	0.37 (0.08-1.76)
Continuous	85	81.7		75	78.9	0.51 (0.17-1.52)	99	83.2		61	76.2	0.24 (0.07-0.87)
OSD												
No	63	60.6		74	77.9	1	74	62.2		63	78.8	1
Yes	41	39.4		21	22.1	0.46 (0.23-0.91)	45	37.8		17	21.2	0.36 (0.17-0.75)
At-risk occupation ^b												
No	41	39.4		42	44.2	1	51	42.9		32	40.0	1
Yes	63	60.6		53	55.8	0.96 (0.51-1.80)	68	57.1		48	60.0	1.33 (0.68-2.58)
Unable to work												
No	88	84.6		76	80.0	1	98	82.4		66	82.5	1
Yes	16	15.4		19	20.0	1.69 (0.71-4.01)	21	17.6		14	17.5	0.72 (0.30-1.73)
Sick leave in the last 12 months before study entry because of CHE												
No	66	63.5		66	69.5	1	80	67.2		52	65.0	1
Yes	38	36.5		29	30.5	0.88 (0.43-1.76)	39	32.8		28	35.0	1.16 (0.53-2.52)
Job loss/change because of CHE												
No	81	77.9		89	93.7	1	94	79.0		76	95.0	1
Yes	23	22.1		6	6.3	0.21 (0.07-0.61)	25	21.0		4	5.0	0.13 (0.04-0.45)
Previous type IV allergy												
No	53	51.0		44	46.3	1	57	47.9		40	50.0	1
Yes	51	49.0		51	53.7	1.87 (0.98-3.59)	62	52.1		40	50.0	0.81 (0.41-1.57)
Localization												
Palms												
No	19	18.3		27	28.4	1	26	21.8		20	25.0	1
Yes	85	81.7		68	71.6	0.45 (0.21-0.97)	93	78.2		60	75.0	0.82 (0.38-1.80)
Back of the hand												
No	52	50.0		41	43.2	1	57	47.9		36	45.0	1
Yes	52	50.0		54	56.8	1.08 (0.58-2.01)	62	52.1		44	55.0	0.91 (0.47-1.77)
Interdigital												
No	41	39.4		30	31.6	1	41	34.5		30	37.5	1
Yes	63	60.6		65	68.4	1.09 (0.57-2.07)	78	65.5		50	62.5	0.86 (0.44-1.68)

TABLE 3 (Continued)

		PGA MCID				DLQI MCID			
		No		Yes		No		Yes	
		n	%	n	%	n	%	n	%
Wrist	No	78	75.0	72	75.8	1		60	75.0
	Yes	26	25.0	23	24.2	0.74 (0.36-1.53)	.41	20	25.0
Forearms	No	92	88.5	85	89.5	1		71	88.8
	Yes	12	11.5	10	10.5	1.09 (0.42-2.84)	.86	9	11.2
Feet	No	81	77.9	70	73.7	1		61	76.2
	Yes	23	22.1	25	26.3	1.02 (0.51-2.03)	.96	19	23.8
Pruritus at baseline	No/mild	48	46.2	36	37.9	1		29	36.2
	Moderate	26	25.0	30	31.6	1.16 (0.55-2.44)	.70	23	28.8
	Strong	30	28.8	29	30.5	1.01 (0.48-2.13)	.97	28	35.0
Atopic diathesis	No/unclear	46	44.2	46	48.4	1		31	38.8
	Yes	58	55.8	49	51.6	0.78 (0.41-1.48)	.45	49	61.2
Diagnosis									
Irritant contact dermatitis	No	35	33.7	27	28.4	1		21	26.2
	Yes	69	66.3	68	71.6	1.20 (0.62-2.30)	.59	59	73.8
Atopic hand eczema	No	43	41.3	35	36.8	1		27	33.8
	Yes	61	58.7	60	63.2	1.09 (0.56-2.11)	.80	53	66.2
Allergic contact dermatitis	No	68	65.4	58	61.1	1		56	70.0
	Yes	36	34.6	37	38.9	1.50 (0.77-2.93)	.24	24	30.0
Vesicular eczema	No	60	57.7	60	63.2	1		49	61.2
	Yes	44	42.3	35	36.8	0.81 (0.43-1.52)	.51	31	38.8
Hyperkeratotic-fissured hand eczema	No	65	62.5	61	64.2	1		52	65.0
	Yes	39	37.5	34	35.8	0.83 (0.44-1.55)	.56	28	35.0
Fingertip dermatitis	No	100	96.2	88	92.6	1		74	92.5
	Yes	4	3.8	7	7.4	2.50 (0.63-9.96)	.19	6	7.5
Treatments in the first 6-months FU period									
Mild/moderate corticosteroids	No	91	87.5	86	90.5	1		72	90.0
	Yes	13	12.5	9	9.5	0.76 (0.29-2.01)	.58	8	10.0
Potent corticosteroids	No	47	45.2	39	41.1	1		36	45.0
	Yes	57	54.8	56	58.9	1.01 (0.55-1.85)	.98	44	55.0
Very potent corticosteroids	No	73	70.2	67	70.5	1		58	72.5
	Yes	31	29.8	28	29.5	0.88 (0.46-1.70)	.71	22	27.5
Calcineurin inhibitors	No	58	55.8	56	58.9	1		45	56.2
	Yes	46	44.2	39	41.1	0.75 (0.41-1.38)	.36	35	43.8

TABLE 3 (Continued)

		PGA MCID				DLQI MCID				P	OR (95%CI) ^a	P
		No		Yes		No		Yes				
		n	%	n	%	n	%	n	%			
Urea	No	32	30.8	16	16.8	1		33	27.7	15	18.8	1
	Yes	72	69.2	79	83.2	2.70 (1.29-5.64)	.008	86	72.3	65	81.2	2.33 (1.07-5.08)
Salicylic acid	No	83	79.8	83	87.4	1		98	82.4	68	85.0	1
	Yes	21	20.2	12	12.6	0.73 (0.32-1.68)	.46	21	17.6	12	15.0	0.83 (0.34-2.01)
PUVA/UV therapies	No	89	85.6	86	90.5	1		103	86.6	72	90.0	1
	Yes	15	14.4	9	9.5	0.52 (0.20-1.35)	.18	16	13.4	8	10.0	0.50 (0.18-1.35)
Systemic corticosteroids	No	101	97.1	92	96.8	1		115	96.6	78	97.5	1
	Yes	3	2.9	3	3.2	1.07 (0.18-6.33)	.94	4	3.4	2	2.5	0.73 (0.12-4.67)
Alitretinoin	No	88	84.6	80	84.2	1		100	84.0	68	85.0	1
	Yes	16	15.4	15	15.8	1.14 (0.49-2.67)	.76	19	16.0	12	15.0	0.97 (0.39-2.40)
Exposure												
Wet work	No	47	45.2	34	35.8	1		54	45.4	27	33.8	1
	Yes	57	54.8	61	64.2	1.52 (0.80-2.88)	.20	65	54.6	53	66.2	1.83 (0.92-3.63)
Detergents	No	33	31.7	28	29.5	1		40	33.6	21	26.2	1
	Yes	71	68.3	67	70.5	1.18 (0.58-2.42)	.65	79	66.4	59	73.8	1.32 (0.62-2.79)
Disinfectants	No	60	57.7	62	65.3	1		74	62.2	48	60.0	1
	Yes	44	42.3	33	34.7	0.77 (0.40-1.48)	.43	45	37.8	32	40.0	0.93 (0.46-1.88)
Cutting fluids	No	94	90.4	84	88.4	1		104	87.4	74	92.5	1
	Yes	10	9.6	11	11.6	1.78 (0.65-4.92)	.26	15	12.6	6	7.5	0.79 (0.25-2.53)
Solvents	No	80	76.9	75	78.9	1		92	77.3	63	78.8	1
	Yes	24	23.1	20	21.1	0.94 (0.46-1.93)	.86	27	22.7	17	21.2	0.85 (0.39-1.84)
Industrial oils	No	84	80.8	73	76.8	1		94	79.0	63	78.8	1
	Yes	20	19.2	22	23.2	1.38 (0.61-3.10)	.44	25	21.0	17	21.2	1.38 (0.58-3.27)
Mechanical stress	No	68	65.4	56	58.9	1		72	60.5	52	65.0	1
	Yes	36	34.6	39	41.1	1.40 (0.73-2.68)	.31	47	39.5	28	35.0	0.74 (0.37-1.50)
Preservatives	No	93	89.4	86	90.5	1		113	95.0	66	82.5	1
	Yes	11	10.6	9	9.5	0.72 (0.26-1.94)	.51	6	5.0	14	17.5	2.86 (0.94-8.64)
Gloves	No	27	26.0	22	23.2	1		34	28.6	15	18.8	1
	Yes	77	74.0	73	76.8	1.15 (0.55-2.40)	.72	85	71.4	65	81.2	1.21 (0.54-2.72)

Abbreviations: BMI, body mass index; CHE, chronic hand eczema; CI, confidence interval; FU, follow-up; OR, odds ratio; OSD, occupational skin disease; PUVA, psoralen and ultraviolet A; UV, ultraviolet.

^a OR as determined with separate multiple logistic regression models including terms for age, sex, at-risk occupation, professional disease, and PGA/DLQI at baseline.

^b Construction/mineral extraction, metal workers and electricians/mechanics, printing/processing of chemicals, textiles and plastics, hairdressers and beauticians, nursing and healthcare, cleaning, food, and catering.

TABLE 4 Longitudinal analysis of factors associated with Physician Global Assessment (PGA) score and Dermatology Life Quality Index (DLQI) variations up to 24 months from baseline

		PGA change (95%CI) ^a	P	DLQI change (95%CI) ^a	P
Sex	Male	Ref.		Ref.	
	Female	0.21 (−0.03 to 0.45)	.09	−0.21 (1.52 to −1.10)	.75
Age (years)	<30	Ref.		Ref.	
	30-49	0.07 (−0.26 to 0.39)	.69	0.52 (−1.09 to 2.13)	.52
	≥50	0.14 (−0.19 to 0.47)	.41	0.23 (−1.32 to 1.77)	.77
BMI (kg/m ²)	<25.0	Ref.		Ref.	
	25.0-29.9	0.12 (−0.15 to 0.39)	.39	1.08 (−0.20 to 2.35)	.10
	≥30.0	0.05 (−0.36 to 0.46)	.81	1.42 (−0.69 to 3.53)	.19
Duration (years)	<2.0	Ref.		Ref.	
	2.0-5.9	0.05 (−0.30 to 0.39)	.79	−1.29 (−2.83 to 0.26)	.10
	≥6.0	0.35 (0.07-0.63)	.01	0.04 (−1.46 to 1.53)	.96
Episodes of CHE in the last 3 mo at FU	<5	Ref.		Ref.	
	≥5	0.22 (−0.03 to 0.47)	.08	0.10 (−1.07 to 1.27)	.87
	Continuous	0.72 (0.54-0.90)	<.001	2.61 (1.64-3.58)	<.001
OSD (reference: no)	Yes	0.13 (−0.10 to 0.36)	.28	0.68 (−0.40 to 1.76)	.22
At-risk occupation ^b (reference: no)	Yes	0.02 (−0.25 to 0.28)	.90	−1.69 (−3.00 to −0.39)	.01
Unable to work (reference: no)	Yes	0.02 (−0.39 to 0.43)	.92	3.47 (1.60-5.34)	<.001
Sick-leave because of CHE in the last 3 mo at FU (reference: no)	Yes	−0.22 (−0.52 to 0.07)	.14	0.66 (−1.37 to 2.69)	.52
Job stop/change because of CHE at FU (reference: no)	Yes	−0.44 (−0.72 to −0.15)	.003	−0.78 (−2.23 to 0.66)	.29
Previous type IV sensitivity (reference: no)	Yes	0.01 (−0.25 to 0.28)	.93	0.58 (−0.60 to 1.76)	.34
Localization (reference: respective all other sites)					
Palms	Yes	0.18 (−0.11 to 0.46)	.23	−0.90 (−2.36 to 0.56)	.23
Back of the hand	Yes	−0.04 (−0.31 to 0.24)	.79	0.09 (−1.12 to 1.30)	.88
Interdigital	Yes	0.13 (−0.15 to 0.41)	.37	0.79 (−0.34 to 1.93)	.17
Wrist	Yes	0.49 (0.18-0.80)	.002	−0.03 (−1.23 to 1.16)	.96
Forearms	Yes	0.15 (−0.25 to 0.54)	.46	0.58 (−0.96 to 2.13)	.46
Feet	Yes	0.33 (0.03-0.63)	.03	0.92 (−0.53 to 2.37)	.21
Pruritus at baseline	No/mild	Ref.		Ref.	
	Moderate	0.34 (0.02-0.65)	.04	0.50 (−1.00 to 1.99)	.51
	Strong	0.10 (−0.23 to 0.44)	.54	0.87 (−0.79 to 2.53)	.31
Atopic diathesis	No/unclear	Ref.		Ref.	
	Yes	−0.13 (−0.80 to 0.54)	.71	−2.76 (−5.98 to 0.47)	.09
Diagnosis (reference: no)					
Irritant contact dermatitis	Yes	−0.18 (−0.43 to 0.07)	.16	−0.67 (−1.89 to 0.56)	.28
Atopic hand eczema	Yes	0.18 (−0.09 to 0.44)	.20	−0.94 (−2.50 to 0.61)	.23
Allergic contact dermatitis	No	Ref.		Ref.	
	Yes	−0.15 (−0.42 to 0.13)	.29	1.07 (−0.39 to 2.52)	.15
Vesicular eczema	Yes	0.10 (−0.15 to 0.35)	.43	−0.92 (−2.26 to 0.43)	.18
Hyperkeratotic-fissured hand eczema	Yes	−0.05 (−0.30 to 0.21)	.73	0.55 (−0.72 to 1.82)	.40
Fingertip dermatitis	Yes	−0.50 (−1.12 to 0.11)	.11	−1.50 (−4.00 to 1.01)	.24
Treatments in the last 3 mo at FU (reference: no)					
Mild/moderate corticosteroids	Yes	0.27 (0.02-0.51)	.04	1.16 (−0.30 to 2.61)	.12
Potent corticosteroids	Yes	−0.10 (−0.25 to 0.05)	.18	−0.53 (−1.11 to 0.04)	.07
Very potent corticosteroids	Yes	0.38 (0.21-0.54)	<.001	0.90 (0.01-1.78)	.047
Calcineurin inhibitors	Yes	0.15 (−0.02 to 0.33)	.09	−0.16 (−1.10 to 0.77)	.73
Urea	Yes	0.006 (−0.15 to 0.16)	.94	0.08 (−0.61 to 0.78)	.81
Salicylic acid	Yes	0.17 (−0.13 to 0.48)	.27	0.75 (−0.65 to 2.15)	.30
PUVA/UV therapies	Yes	0.11 (−0.23 to 0.45)	.54	0.92 (−1.54 to 3.39)	.46
Systemic corticosteroids	Yes	−0.14 (−1.01 to 0.74)	.76	−0.34 (−4.30 to 3.63)	.87

TABLE 4 (Continued)

		PGA change (95%CI) ^a	P	DLQI change (95%CI) ^a	P
Alitretinoin	Yes	0.25 (−0.07 to 0.58)	.13	0.16 (−1.31 to 1.62)	.83
Exposure (reference: no)					
Wet work	Yes	−0.02 (−0.29 to 0.25)	.87	−1.30 (−2.91 to −0.31)	.11
Detergents	Yes	−0.15 (−0.44, 0.14)	.31	0.08 (−1.38, 1.55)	.91
Disinfectants	Yes	0.23 (−0.03 to 0.48)	.08	0.82 (−0.44 to 2.09)	.20
Cutting fluids	Yes	0.13 (−0.29 to 0.54)	.55	0.79 (−0.77 to 2.36)	.32
Solvents	Yes	0.32 (0.03–0.61)	.03	0.24 (−0.95 to 1.42)	.70
Industrial oils	Yes	0.04 (−0.32 to 0.40)	.83	−0.21 (−1.63 to 1.20)	.77
Mechanical stress	Yes	0.08 (−0.20 to 0.37)	.57	−0.17 (−1.46 to 1.13)	.80
Preservatives	Yes	0.05 (−0.34 to 0.43)	.81	−1.49 (−2.98 to 0.001)	.05
Gloves	Yes	−0.07 (−0.37 to 0.24)	.68	0.12 (−1.49 to 1.73)	.88

Abbreviations: BMI, body mass index; CHE, chronic hand eczema; CI, confidence interval; FU, follow-up; OSD, occupational skin disease; PUVA, psoralen and ultraviolet A; Ref., reference category; UV, ultraviolet.

^a Change in scores determined by the use of separate generalized estimating equation models including terms for age, sex, at-risk occupation, OSD and PGA/DLQI at baseline.

^b Construction/mineral extraction, metal workers and electricians/mechanics, printing/processing of chemicals, textiles and plastics, hairdressers and beauticians, nursing and health care, cleaning, food, and catering.

maps should be used to set up new hypotheses that need to be investigated and tested in specific studies.

CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

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ORCID

Andreas Bircher  <http://orcid.org/0000-0002-6683-3975>

Christian Apfelbacher  <http://orcid.org/0000-0003-3805-8219>

Dagmar Simon  <http://orcid.org/0000-0001-8965-9407>

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