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Prevention of hand eczema: effect of an educational program versus treatment as usual – results of the randomized clinical PREVEX trial [1]

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Detailed information about methods used in the PREVEX trial

PREVEX (PreVention of EXema) is an individually randomized, parallel-group superiority trial, investigating benefits and harms of a low-cost group counselling program versus treatment as usual, with sickness absence, HR-QoL and severity as the three co-primary outcomes in newly notified occupational HE patients.

The trial (11), includes patients with notified OHE in Region Zealand and the Capital Region of Denmark between 1 July 2012 to 30 November 2014. All occupational skin diseases notified to the Danish Labor Market Insurance (named the National Board of Industrial Injuries until 2016) were registered weekly. An invitation and a self-administered questionnaire were distributed by ordinary mail within 1-2 weeks after notification. Those living at the Island of Bornholm, and those without permanent residence in Denmark were excluded.

Inclusion criteria were self-reported HE, written informed consent, sufficiently filled out information about profession and severity of hand eczema. Exclusion criteria were age below 18 or above 65 years, permanent exclusion from workforce, inability to understand Danish , and any serious medical condition which could interfere with the results (11).

Randomization

Randomisation was performed centrally by The Copenhagen Trial Unit. Participants were randomised individually 1:1 to the intervention group versus the control group. Allocation sequence was computer-generated using concealed block sizes of 8, 6, and 4. The investigator telephoned the CTU, who then allocated the participants according to data entered in the computer system. Randomisation was stratified according to age (‘up to 39 years’ compared to ‘40 year or older’), self-reported hand eczema severity (‘none and light’ compared to ‘moderate, severe, and very severe’), and profession (‘healthcare’, ‘kitchen or cleaning staff’, ‘hairdresser or construction worker’, or ‘all other professions’) (11).

The intervention comprised the following four elements:

1) Group education about skin-protective behavior. Consisted of a 2-hours course with alternating lecturing and work-shops on basic knowledge about skin, development of eczema, and recommendations for skin protection and care, including practical demonstrations. A pamphlet with information from the course was distributed. 2) Job-specific counselling on work-related skin-protective behavior regarding allergens, irritants and practical demonstrations of relevant gloves. 3) Social guidance related to OHE, comprising information on rules and rights during an occupational injury. 4) A telephone hotline, to repeat information from the course, if required(11). We had planned to offer eligible candidates (other than HCW) a work-place visit, but since only 7.4% (14 out of 188) accepted the offer, this was abolished.

The control group had no access to the intervention programs. All participants received treatment as usual.

Data collection and outcomes

The initial questionnaire HE severity (validated photographic guide) (12), HR-QoL assessed by the validated Dermatology Life Quality Index (DLQI)(13), and self-reported occupation as well as questions on atopic disposition, knowledge of skin protection, risk behavior with respect to HE, treatment and number of visits to dermatologist. It was described in the protocol (11) that use of topical corticosteroids and visits to dermatologist would be registered from databases, however, since data was obtained from the follow-up questionnaire it was decided to use that instead.

The photographic guide used in this trial is a severity measurement tool which consists of five rows of photographs of hands with increasing intensity of eczema (clear, mild, moderate, severe and very severe) (12). The patients choose the row-number corresponding to the severity on their hands (range 1-5).

The DLQI for assessment of HR-QoL consists of 10 questions that cover the effect of skin disease on physical, social and functional aspects of life during the last week. It is possible to score between 0-30 points (0 best-30 worst) (13).

A follow-up questionnaire was sent out 12 months later, assessing the same variables.

Phone surveys of sickness absence. During the 12 months follow up each participant was interviewed every 8th week (6 times total) by an investigator; producing scores between 0 and 60 days per contact. **Blinding.** Blinding of participants was not possible. Data entry was performed blinded, where possible. The statistical analyses were performed blinded, with the two intervention groups coded, and the Steering Committee drew two conclusions and wrote two abstracts with the blind intact. After this, blinding was broken.

Primary outcomes

The three co-primary outcomes were 1) Self-reported number of days with sickness absence during the trial period; 2) HR-QoL assessed by DLQI 12 months after inclusion (13); and 3) self-evaluated HE severity assessed by use of a photographic guide 12 months after inclusion (12).

Explorative outcomes

Self-reported number of days with HE-related sickness absence during trial period was an explorative outcome reported in the present paper.

Skin protective behavior, knowledge of skin protection, self-efficacy (14) and ability to self-care at 12 months after randomization were explorative outcomes, to be reported elsewhere.

Two more explorative outcomes were planned (11) but were abolished. Data from the DREAM register concerned only 4.5% of participants. The follow-up question on sickness absence was separated in intervals that were found incompatible with collected sickness absence every two months.

Statistical analysis

Adjustment for multiple comparisons was done using Holm's procedure (15). To ensure a power of at least 80% (risk of type 2 error 20%), an inclusion of a minimum of 742 participants was decided (11), intention to treat analysis was used.

Analyses

The primary results as well as the exploratory were obtained using adjustment by protocol-specified stratification variables (11) (baseline severity of HE, age group and occupational group) as well as the baseline value of the outcome, if measured. Unadjusted analyses were done and compared to the adjusted ones.

If participants had not answered on a contact point, it was marked as missing.

Sickness absence (the number of sick days divided by the number of days observed) were analyzed according to protocol using the Poisson distribution (11).

Since DLQI scores did not fit into a linear model, the analysis outlined in the protocol was abandoned in favor of the negative binomial model, allowing for adjustment with co-variates. The binomial model was fitted with the DLQI scores as a continuous outcome. The regression was fitted to a negative binomial distribution because it offered a better fit than the Poisson distribution.

Severity scores were analyzed, according to protocol, with a proportional odds model, cumulated over the lower ordered values.

Multiple imputations were planned in the protocol but only dependent variables (i.e., the outcomes) had missing values in which case a complete case analysis should be done (16), unless auxiliary variables could be found which was not the case.

Explorative outcome

Sickness absence data was analyzed with a mixed binomial model with repeated measures according to protocol, to consider the variation in rate as a function of time. For each participant, rates of sickness absence were calculated for each of the 6 contact points and was modelled as a repeated measure of the same participant. The model included a variable T for time, varying from 1 to 6, for each two-month periods. The regression was fitted to a negative binomial distribution.

Data regarding only HE related sickness absence was analyzed using the same method as for the total amount of sickness absence in the primary outcome.

Post-hoc analyses

Per-protocol analyses were performed with respect to the three primary outcomes as 127 out of 376 never attended the course.

As earlier trials (3,5) showed more beneficial effect of an education intervention for patients with mild HE, we repeated the analysis of sickness absence data for participants with mild HE and participants with severe HE separately at entry. This was done by adding an interaction term, between the subgroup indicator and the intervention indicator.

Examination of baseline data indicated that HCW differed from other occupations by reporting less severe eczema and lower DLQI. Therefore subgroup analyses were performed of HCW and other occupations separately. This was done by adding an interaction term, between the subgroup indicator and the intervention indicator.

The program used for statistical analysis was SAS (version 9.4, SAS Institute Inc., CARY, NC, USA).

The trial has been approved by the Danish Data Protection Agency (journal number **BBH-2011-33**) and registered at ClinicalTrials.gov Identifier: NCT01899287.

Table S1. Missing data from PREVEX trial participants for planned outcomes sickness absence during the trial and severity (photographic guide) and DLQI at follow-up. [DLQI=Dermatology Life Quality Index].

	Intervention (N=376)		Control (N=380)		P-value[a] (difference)
	N	%	N	%	
Sickness absence	38	10.1	38	10.0	0.93
1st contact	40	10.6	35	9.2	0.49
2nd contact	39	10.4	33	8.7	0.41
3rd contact	53	14.1	49	12.9	0.60
4th contact	83	22.1	85	22.4	0.97
5th contact	208	55.3	217	57.1	0.74
6th contact	461	20.4	457	20.0	0.63
Total missing sickness absence					
Severity	110	29.3	126	33.2	0.25
DLQI	98	26.1	113	29.7	0.26

[a]P-values were generated using Chi-square tests.

Table S2. Per protocol crude and adjusted risk estimates for primary outcomes: Rate of sickness absence and HR-QoL (DLQI score) in the intervention group compared with the control group (reference) of the PREVEX trial. [HR-QoL=Health Related Quality of Life; DLQI=Dermatology Life Quality Index, Exp=exponential; CI=confidence interval].

	Median	Percentiles		Crude (Exp) Estimate	Adjusted[a] (Exp) Estimate	Adjusted 95% CI	P-value
		25th	75th				
Rate of sickness absence							
Intervention (n=238) Control (n=361)	0.01 0.01	0.00 0.00	0.03 0.03	0.841	0.831	0.44-1.56	0.56
HR-QoL (DLQI score)							
Intervention (n=207) Control (n=267)	3 3	1 1	7 7	1.021	0.981	0.83-1.16	0.84

[a]Covariates used in all adjusted analysis: baseline severity, occupation, age, and baseline of outcome if any.

Table S3. Per protocol crude and adjusted risk estimates for primary outcome: severity of hand eczema in the intervention group compared with the control group (reference) of the PREVEX trial. [OR=Odds ratio; CI=confidence interval].

	Intervention		Control		Crude OR[a]	Adjusted OR[a]	Adjusted 95% CI	P-value
	N	%	N	%				
Clear	68	34.0	94	37.0	1.02	0.96[b]	0.68-1.38	0.11
Mild	79	39.5	88	34.6	1	1		
Moderate	40	20.0	52	20.5				
Severe	10	5.0	14	5.5				
Very Severe	3	1.5	6	2.4				

[a] Odds of being in a higher hand eczema severity category.

[b]Covariates used in all adjusted analysis: baseline severity, occupation, age, and baseline of outcome if any.