the **BEEP** *study*

Results of the UK DCTN Barrier Enhancement for Eczema Prevention study

This newsletter gives a brief overview of the 2 year results. A more detailed publication has been prepared; you will be sent details of the manuscript when it is available. Full results, including long-term follow up will be published in 2022 in the NIHR Journal Library.

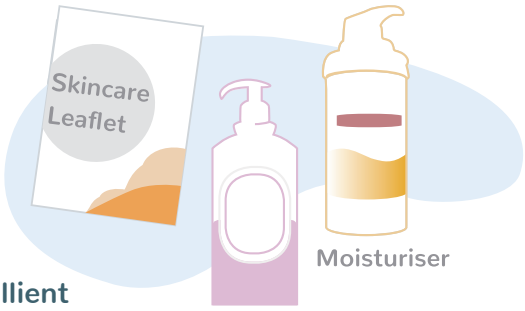
Trial Background and Design

Primary prevention is a highly desirable goal in a complex chronic disease like atopic eczema that have no cure. Emollient therapy is intended to improve the barrier function of the sin and has been suggested as a possible prevention strategy for eczema as observations suggests that skin barrier dysfunction precedes eczema development. Encouraging results from previous pilot trials supported this hypothesis.

Primary Objective: To determine whether advising parents to apply emollient daily for the first year of life in addition to providing best practice infant skin care advice can prevent the onset of eczema in high-risk children, when compared with a control group who are given the best practice infant skin care advice only.

Trial Design

The trial was a randomised, controlled, two-arm, parallel-group, multicentre, assessor-blind trial. Participants were randomised to one of two treatment groups:



1) Best practice infant skin care advice only

2) Best practice infant skin care advice PLUS advice to apply emollient daily to the child's entire body surface area for the first year of life

Questionnaires were sent to families at 3, 6, 12 and 18 months, and a face to face visit took place with a research nurse at 24 months. Optional skin prick testing was offered at the visit; depending on the outcome some families were offered an oral food challenge. Long-term follow-up questionnaires continue to be sent to all families at 36, 48 and 60 months. The long-term outcomes will be reported in 2022.

For full details of the trial background and outcomes, consult the trial protocol in your site file, or the open-access protocol publication: https://doi.org/10.1186/s13063-017-2031-3

Primary Outcome: A diagnosis of eczema between 12 and 24 months of age (defined as meeting the UK Working Party Diagnostic Criteria for Atopic Dermatitis).

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Recruitment and Retention

1394 families were randomised by 16 sites in England between November 2014 and November 2016; 693 to the intervention group and 701 to the control group. 1210/1394 children were followed up for their 24 month visit: this was a final retention rate of 87%.

2 year Results

Baseline characteristics were well balanced across treatment groups (Table 1). Median age at starting emollient in the intervention group was 11 [IQR 7, 17] days (n = 509). Adherence (emollient use at least 3-4 times per week to at least 2 body areas (face/neck, arms/legs or trunk)) was 88%, 82% and 74% at 3, 6 and 12 months. In the control group, application of a moisturiser, or use of oil for baby massage at least 3 times per week to at least 2 body areas as above, for those with no parent report of a clinical diagnosis of eczema was 18%, 17% and 15% at 3, 6, and 12 months.

Table 1

	Intervention (n = 693)	**Control (n = 701)**
Mother's age at randomisation (mean [sd])	31.7 [5.3]	31.5 [5.2]
Singleton pregnancy	690 (100%)	696 (99%)
Gestation at birth in weeks (median [25th, 75th centile])	40 [39.1, 40.9]	40 [39, 40.9]
Ethnicity of mother		
White	589 (85%)	601 (86%)
Asian	33 (5%)	40 (6%)
Black	31 (4%)	22 (3%)
Other	28 (4%)	38 (5%)
Decile of English index of multiple deprivation 2015 (mean [sd])	6 [3, 9]	6 [3, 9]
No other children living in household at screening	275 (40%)	293 (42%)
Infant gender boy	374 (54%)	359 (51%)
Vaginal delivery	482 (70%)	472 (67%)
Furry pets living in house at time of birth	295 (43%)	302 (43%)
Mother took oral antibiotics during pregnancy	210 (30%)	201 (29%)
Mother took regular pro-biotic supplements during pregnancy	33 (5%)	32 (5%)
FLG genotype for infants included in analysis[1]	n = 402	n = 414
+/+ (no mutations)	339 (84%)	352 (85%)
+/- (one *FLG* null mutation)	62 (15%)	60 (14%)
-/- (two *FLG* null mutations)	1 (<0.5%)	2 (<0.5%)

Primary Outcome: Eczema in the last 12 months (UK working party criteria at 2 years of age) was present in 23% (139/598) infants in the intervention group and in 25% (150/612) in the control group (Table 2). All sensitivity analyses were consistent with the primary analysis.

Secondary Outcomes: All other measures of eczema diagnosis were consistent with the primary outcome; there were no differences between groups in visible eczema at 2 years, parent report of a clinical diagnosis of eczema at 2 years, or parent completion of UK Working Party criteria at 1 and 2 years (Table 2). Eczema severity assessed either by a blinded assessment of clinician reported signs (EASI) or parent-reported symptoms (POEM) and time to onset of eczema were also similar. Similarly, no differences were noted in health utility measures (CHU-9D and EQ-5D-5L) between the two groups

Challenge proven food allergy to milk, egg or peanut was present in 7.5% (41/547) in the emollient group versus 5.1% (29/568) in the control group (adjusted relative risk 1.47, 95% CI 0.93 to 2.33 and adjusted risk difference 2.4%, 95% CI -0.5% to 5.2%).

Safety Outcomes: Parent-reported skin infections during the first year occurred in 15% (89) of infants in the intervention group and 11% (67) in the control group (adjusted incidence rate ratio of 1.55, 95% CI 1.15 to 2.09).

Results (continued)

Table 2

	Intervention	Control	Adjusted relative risk (95% CI, p-value)	Adjusted difference in risk (95% CI)
Primary outcome				
Diagnosis of eczema at 2 years according to UK Working Party diagnostic criteria (blinded outcome assessor)	139/598 (23%)	150/612 (25%)	0.95 (95% CI 0.78 to 1.16), **p = 0.61**	-1.2% (95% CI -5.9% to 3.6%)
Secondary eczema outcomes				
At 2 years				
Blinded assessment of visible eczema at 2 years	151/555 (27%)	149/568 (26%)	1.05 (95% CI 0.86 to 1.27)	1.1% (95% CI -4.0% to 6.3%)
Parent report of a clinical diagnosis of eczema between birth and 2 years	266/610 (44%)	282/616 (46%)	0.96 (95% CI 0.85 to 1.08)	-2.0% (95% CI -7.5% to 3.6%)
Eczema according to UK Working Party Diagnostic Criteria (parent completion)	187/599 (31%)	195/612 (32%)	0.98 (95% CI 0.83 to 1.16)	-0.5% (95% CI -5.7% to 4.8%)
At 1 year				
Eczema according to UK Working Party Diagnostic Criteria (parent completion)	103/516 (20%)	107/527 (20%)	0.98 (95% CI 0.77 to 1.25)	-0.3% (95% CI -5.1% to 4.6%)

The adjusted relative risk and difference in risk are estimated using Generalised Estimating Equations with the Binomial family and log/identity link respectively, with an exchangeable correlation matrix to account for randomisation being stratified by centre and number of immediate family members with atopic disease (1, 2, or more than 2) included as a covariate.

Conclusions

- No evidence was found that daily emollient use for the first year of life can delay, suppress or prevent eczema at 2 years.
- We observed an increase in parent-reported skin infections with the regular use of emollients, which may be due to increased inoculation of infant skin during application.
- We observed a small increase in food allergy in the emollient group, which could be due to enhanced transfer and uptake of food antigens leading to epicutaneous sensitisation.
- The observed effect on food allergy will be further substantiated in an ongoing prospective individual patient data meta-analysis of similar studies, led by Dr. Bob Boyle.
- Though emollients used in this trial have not been found to prevent eczema in high-risk infants, emollients should continue to be used as an effective first-line treatment in the management of eczema.

A big thank you to all the staff at the trial sites who were involved in recruiting participants and completing the follow-up visits. The trial recruited in time and had an excellent retention rate. We are confident of the quality of the data we have collected, and have you to thank you for your involvement!

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