# Emollient application from birth to prevent eczema in high-risk children: the BEEP RCT

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# Scientific summary

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# Scientific summary

## Background

Eczema, also known as atopic eczema (AE) or atopic dermatitis, is a common inflammatory skin disease that typically starts in early life. Eczema affects around 20% of children and 10% of adults in developed countries. Although most cases are mild, moderate to severe disease can have a major impact on the quality of life of an affected child and their family. The main symptom of this systemic inflammatory disease is itching which leads to scratching, bleeding, secondary infection as well as sleep loss and the social stigma of a visible skin disease. Genetic factors such as mutations in the gene encoding filaggrin (*FLG*) – a protein that is important for maintaining skin barrier function – have been shown to be important in increasing eczema risk, severity and persistence. Epidemiological studies showing that eczema is more common in smaller families, migrant populations and in higher socioeconomic status also suggest that the environment is critically important in determining disease expression. Eczema is closely related to other 'atopic' conditions including asthma, hay fever and food allergy. Some evidence suggests that the impaired skin barrier caused by eczema in early life is an important route for the development of food allergy as a result of sensitisation through the skin.

Treatment of eczema depends on severity: mild eczema can be treated with emollients (moisturisers) and weak topical corticosteroids. Moderate eczema usually needs potent topical corticosteroids and other anti-inflammatory treatments such as topical tacrolimus, whereas severe eczema is treated by ultraviolet light or systemic treatments including ciclosporin, methotrexate, dupilumab and an emerging pipeline of new biologics.

While good progress has been made with treatment, prevention of eczema remains challenging. Strategies include avoidance of allergens (foods and house dust mite) during pregnancy and early life, exclusive breastfeeding, or different timing of introducing solids, but these have not shown convincing preventative effects. Probiotics and prebiotics have shown some benefit, but the exact strain or combination and timing of intervention remain unclear. One previously unexplored eczema prevention strategy is enhancement of the skin barrier in early life. The hypothesis is that enhancing the skin barrier could interrupt an early cascade of inflammatory events that can lead to chronic auto-immune eczema and potentially prevent skin sensitisation to common allergens that can lead to food allergy. Two small pilot studies suggested that protecting the skin of babies who had a first-degree relative with eczema, asthma or hay fever with emollients could prevent the development of eczema in the first year of life. We wanted to see whether daily emollient application for the first year of life in such high-risk babies can prevent eczema and other allergic diseases in a sustained and convincing way by means of a definitive pragmatic randomised controlled trial.

## Objectives

The primary objective was to determine whether advising parents to apply emollient daily for the first year of life could prevent eczema at 2 years of age when compared with standard skin-care advice alone in children at high risk of developing eczema.

Secondary objectives included evaluating whether prophylactic use of emollients would delay the onset of eczema or reduce eczema severity when compared to standard skin-care advice, whether any preventive effect at age 2 years was sustained up to age 5 years and to determine the safety and cost-effectiveness of such a strategy. We also sought to determine whether emollients could prevent the development of other associated allergic conditions including food allergy, asthma and hay fever up to the age of 5 years.

## Methods

We conducted a multicentre, pragmatic, two-arm parallel group randomised controlled prevention trial which recruited participants from 12 hospitals and 4 general practices in the UK.

Participants were infants of at least 37 weeks' gestation at high risk of developing eczema defined by having at least one first-degree relative with a parental report of doctor-diagnosed eczema, allergic rhinitis or asthma. Mothers had to be 16 years or older, and the consenting adult had to understand English. We excluded babies with a severe widespread skin condition that would make eczema assessment difficult; a serious health issue that would make it difficult for the family to take part in the trial; or a condition that would make the use of emollient inadvisable. Informed consent was obtained from mothers during pregnancy, or mother, father or guardian post delivery.

The intervention group was advised to use one of two study emollients (Doublebase Gel® or Diprobase Cream®) at least once daily to the whole body (excluding the scalp) until the child reached 1 year, plus standard skin-care advice (designated the 'emollient group').

The control group was advised to use standard skin-care advice only. Standard skin-care guidance, in booklet and video format at the time of randomisation, provided advice to use mild cleansers and shampoos specifically formulated for infants, and to avoid soap, bubble bath and baby wipes, and was given to both groups.

Intervention adherence was measured at 3, 6 and 12 months and defined as satisfactory if emollients were applied at least three to four times per week to most of the child's body. A similar definition was used to define contamination in the control group.

The primary outcome was presence of eczema in the last year when the baby was aged 2 years, defined as meeting the United Kingdom Working Party (UKWP) Diagnostic Criteria for AE for children under 4 years. Secondary outcomes encompassed other ways of defining eczema including any parental report of a clinical diagnosis of eczema up to 2 years, parent completion of UKWP criteria at 1 and 2 years, and presence of visible eczema at 2 years recorded by a nurse masked to treatment allocation. Other eczema secondary outcomes included time to onset of eczema (based on first parent report of clinician diagnosis and first topical corticosteroid or immunosuppressant prescription); severity of eczema measured by trained nurses using the Eczema Area and Severity Index at 2 years and parent-reported Patient-Oriented Eczema Measure at 1 and 2 years.

Other secondary outcomes included parent-reported wheezing and allergic rhinitis between 1 and 2 years; allergic sensitisation (masked skin prick tests) to milk, egg, peanut, cat dander, grass pollen or dust mite at 2 years; parent-reported food allergy; parental report of clinical diagnosis of food allergy at 1 and 2 years; and allergy to milk, egg or peanut at 2 years confirmed either by oral food challenge or for cases in which no oral food challenge was done, an expert panel of experienced paediatric allergists masked to treatment allocation. The panel decisions were made using an algorithm, validated using data from a previous trial, which incorporates all available data including skin prick test results, previous reaction history, frequency of food ingestion and allergy tests done outside the trial. The main economic outcome measure was incremental cost per percentage decrease in risk of eczema at 2 years in a cost-effectiveness analysis (CEA). Cost–utility analyses using quality-adjusted life-years (QALYs) derived from the proxy Child Health Utility instrument-9 domains (CHU-9D) for the child was also conducted as a secondary analysis.

Safety outcomes were parent-reported skin infections (parents were asked what the doctor called the infection) and emollient-related infant slippages during the intervention period (year 1).

Tertiary outcomes at 3, 4 and 5 years were to evaluate if emollients in early life could also prevent later-onset allergic diseases including asthma, hay fever and food allergy, and to see whether any early possible benefits of eczema prevention were sustained. Outcomes included parental-reported presence of eczema; severity of eczema; wheezing; allergic rhinitis; food allergy symptoms and clinical diagnoses of asthma, allergic rhinitis and food allergy.

Randomisation (1 : 1) within 21 days of birth was performed using computer-generated pseudo-random code with permuted blocks of randomly varying size and concealed from the trial investigators via a web-based randomisation system. Randomisation was stratified by recruiting centre and number of first-degree relatives with eczema, asthma or hay fever (1, 2 or > 2). Research nurses conducting outcome assessments were masked to participant treatment allocation. Families were not masked to the allocated interventions and were reminded not to reveal allocation to research nurses.

The trial was powered to detect a relative reduction of 30% in the primary outcome at the 5% significance level (two-sided) with 90% power assuming that 30% of children in the control group would have eczema and 20% attrition, resulting in a sample size of 1282. The target sample size was reached faster than anticipated at which point the Trial Steering Committee permitted that all pregnant mothers who had already consented to the trial could be randomised on the birth of the baby giving a maximum possible sample size of 1400.

We analysed participants as randomised regardless of adherence with allocation using available data (i.e. without imputation for missing data) with sensitivity analyses for missing data. The adjusted relative risk (RR) and risk difference for the primary outcome were estimated using generalised estimating equations with the binomial family and log/identity link respectively, with an exchangeable correlation matrix to account for randomisation stratification by centre and number of immediate family members with atopic disease (one, two, or more than two) included as a covariate. A number of planned subgroup analyses for the primary outcome were conducted including according to *FLG* genotype, to test the hypothesis that *FLG* null genotype affects response to intensive emollient use from birth.

## Results

One thousand three hundred and ninety-four newborns were randomised between 19 November 2014 and 18 November 2016; 693 to the emollient group and 701 to the control group. Primary outcome data at 2 years were collected for 1210 infants (87%). Unblinding of research nurses prior to skin examination occurred for 12 infants in the intervention group and 6 in the control group. Adherence in the emollient group was 88% (466/532) at 3 months, 82% (427/519) at 6 months and 74% (375/506) at 12 months. In the control group, contamination due to self-directed use of emollients was reported for 18% (82/457), 17% (62/372) and 15% (49/324) at 3, 6 and 12 months, respectively, for infants who did not have a parental report of a doctor diagnosis of eczema.

At age 2 years, eczema was present in 139 (23%) of 598 infants in the emollient group and in 150 (25%) of 612 infants in the control group [adjusted RR 0.95, 95% confidence interval (CI) 0.78 to 1.16; $p = 0.61$; adjusted risk difference −1.2%, 95% CI −5.9% to 3.6%]. All sensitivity analyses conducted, including using multiple imputation for missing primary outcome data, were consistent with the primary analysis. There was no evidence of an interaction effect with allocated group for the primary eczema outcome in any of the subgroup analyses (including *FLG* genotype). Other eczema definitions supported the results of the primary analysis. Eczema severity and time to onset of eczema were also similar in the two groups.

Mean number of skin infections per child in year 1 was 0.23 [standard deviation (SD) 0.68] in the emollient group versus 0.15 (SD 0.46) in the control group; adjusted incidence rate ratio 1.55 (95% CI

1.15 to 2.09). Infant slippage incidents were reported for 15/584 (2.6%) in the emollient group and 11/584 (1.9%) in the control group.

Food allergies to milk, egg or peanut at 2 years were confirmed in 41/547 (7.5%) infants in the emollient group and 29/568 (5.1%) in the control group (adjusted RR 1.47, 95% CI 0.93 to 2.33). The largest difference was in the proportion of infants with confirmed food allergy to egg, with an adjusted RR of 1.56 (95% CI 0.92 to 2.65). Results of other measures of food allergy and food sensitisation were similar. The proportion of infants with allergic rhinitis, wheezing and allergic sensitisation to cat dander, grass pollen and dust mite was similar between groups at 2 years. The differences in quality of life (using CHU-9D for the child and EuroQol-5 Dimensions, five-level version for the main carer) between the two groups were very small.

Although the emollient intervention period was the first year of life, parents in the emollient group continued to report more frequent moisturiser application through to 5 years than in the control group. By 5 years, 188/608 (31%) parents in the emollient group had reported a clinical diagnosis of eczema in their child since 12 months, compared with 178/631 (28%) in the control group (adjusted RR 1.10, 95% CI 0.93 to 1.30). A diagnosis of food allergy by 5 years was reported for 92/609 (15%) allocated to emollients and 87/632 (14%) allocated to control (adjusted RR 1.11, 95% CI 0.84 to 1.45). Similarly, the percentage of parents reporting that their child had a clinical diagnosis of asthma or allergic rhinitis by 5 years were similar in the two groups.

In the complete-case CEA mean cost was £398.23 (SD 1408.39) per child in the emollient group ($n$ = 598) and £312.16 (SD 1105.04) in the control group ($n$ = 610). When intervention use was combined with other health resource use, the adjusted incremental cost was £87.45 (95% CI −54.31 to 229.27). The adjusted difference in the proportion of children without eczema at 2 years was 0.0164 (95% CI −0.0329 to 0.0656) higher in the emollient group compared to the control group. The adjusted incremental cost per percentage decrease in risk of eczema was £5337 at 2 years. Adjusted QALYs for children were very slightly improved (i.e. higher) in the emollient group at 2 years.

## Conclusions

We found no evidence of a useful preventive effect of emollients for eczema at our primary outcome time of 2 years. The failure to show a reduction in eczema was consistent regardless of how eczema was assessed. Some evidence of an increase in skin infections during the intervention period and a possible increase in food allergy at age 2 years was observed. No benefit was observed for time to onset of eczema or eczema severity, and no benefits were observed for eczema, asthma, hay fever or food allergy in longer-term follow-up to 5 years. Emollient use is unlikely to be considered cost effective in this context.

Inclusion of individual patient data from all similar eczema prevention studies in further meta-analysis may provide a clearer assessment of whether emollients can prevent eczema and related diseases and provide more certainty about potential harms.

### *Implications for health care*

The study does not support the use of emollients to prevent eczema and has found a small signal of possible harms, so this intervention cannot be recommended for health care or public health use. As the study relates to *prevention* of eczema, emollients should continue to be used as part of standard treatment for eczema.

## Trial registration

This trial is registered as ISRCTN21528841.

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## This article

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