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

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Abstract

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

Lucy E Bradshaw,[1] Laura A Wyatt,[1] Sara J Brown,[2,3] Rachel H Haines,[1] Alan A Montgomery,[1] Michael R Perkin,[4] Tracey H Sach,[5] Sandra Lawton,[6] Carsten Flohr,[7] Matthew J Ridd,[8] Joanne R Chalmers,[9] Joanne Brooks,[1] Richard Swinden,[1] Eleanor J Mitchell,[1] Stella Tarr,[1] Nicola Jay,[10] Kim S Thomas,[7] Hilary Allen,[11] Michael J Cork,[12] Maeve M Kelleher,[11] Eric L Simpson,[13] Stella T Lartey,[5] Susan Davies-Jones,[9] Robert J Boyle[9,11] and Hywel C Williams[9*]

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Background: Atopic eczema is a common childhood skin problem linked with asthma, food allergy and allergic rhinitis that impairs quality of life.

Objectives: To determine whether advising parents to apply daily emollients in the first year can prevent eczema and/or other atopic diseases in high-risk children.

Design: A United Kingdom, multicentre, pragmatic, two-arm, parallel-group randomised controlled prevention trial with follow-up to 5 years.

Setting: Twelve secondary and four primary care centres.

Participants: Healthy infants (at least 37 weeks' gestation) at high risk of developing eczema, screened and consented during the third trimester or post delivery.

Interventions: Infants were randomised (1 : 1) within 21 days of birth to apply emollient (Doublebase Gel®; Dermal Laboratories Ltd, Hitchin, UK or Diprobase Cream®) daily to the whole body (excluding scalp) for the first year, plus standard skin-care advice (emollient group) or standard skin-care advice only (control group). Families were not blinded to allocation.

Main outcome measures: Primary outcome was eczema diagnosis in the last year at age 2 years, as defined by the UK Working Party refinement of the Hanifin and Rajka diagnostic criteria, assessed by research nurses blinded to allocation. Secondary outcomes up to age 2 years included other eczema definitions, time to onset and severity of eczema, allergic rhinitis, wheezing, allergic sensitisation, food allergy, safety (skin infections and slippages) and cost-effectiveness.

Results: One thousand three hundred and ninety-four newborns were randomised between November 2014 and November 2016; 693 emollient and 701 control. Adherence in the emollient group was 88% (466/532), 82% (427/519) and 74% (375/506) at 3, 6 and 12 months. At 2 years, eczema was present in 139/598 (23%) in the emollient group and 150/612 (25%) in controls (adjusted relative risk 0.95, 95% confidence interval 0.78 to 1.16; $p = 0.61$ and adjusted risk difference −1.2%, 95% confidence interval −5.9% to 3.6%). Other eczema definitions supported the primary analysis. Food allergy (milk, egg, peanut) was present in 41/547 (7.5%) in the emollient group versus 29/568 (5.1%) in controls (adjusted relative risk 1.47, 95% confidence interval 0.93 to 2.33). Mean number of skin infections per child in the first year was 0.23 (standard deviation 0.68) in the emollient group versus 0.15 (standard deviation 0.46) in controls; adjusted incidence rate ratio 1.55, 95% confidence interval 1.15 to 2.09. The adjusted incremental cost per percentage decrease in risk of eczema at 2 years was £5337 (£7281 unadjusted).

No difference between the groups in eczema or other atopic diseases was observed during follow-up to age 5 years via parental questionnaires.

Limitations: Two emollient types were used which could have had different effects. The median time for starting emollients was 11 days after birth. Some contamination occurred in the control group (< 20%). Participating families were unblinded and reported on some outcomes.

Conclusions: We found no evidence that daily emollient during the first year of life prevents eczema in high-risk children. Emollient use was associated with a higher risk of skin infections and a possible increase in food allergy. Emollient use is unlikely to be considered cost-effective in this context.

Future research: To pool similar studies in an individual patient data meta-analysis.

Trial registration: This trial is registered as ISRCTN21528841.

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List of abbreviations

AE	atopic eczema
AD	atopic dermatitis
BEEP	barrier enhancement for eczema prevention
CACE	complier-average causal effect
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHU-9D	child health utility instrument-9 domains
CUA	cost–utility analysis
DNA	deoxyribonucleic acid
EASI	Eczema Area and Severity Index
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
FLG	gene encoding filaggrin
GLM	generalised linear model
GP	general practitioner
HEAP	health economics analysis plan
ICER	incremental cost-effectiveness ratio
IgE	immunoglobulin E
IPD	individual participant data
MAR	missing at random
MNAR	missing not at random
NCTU	Nottingham Clinical Trials Unit
NICE	National Institute for Health and Care Excellence
PCA	prescription cost analysis
PIC	Participant Identification Centre
POEM	Patient-Oriented Eczema Measure
PPI	patient and public involvement
PreventADALL	Preventing Atopic Dermatitis and ALLergies
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SAP	statistical analysis plan
SMS	short message service
SWAT	study within a trial
TSC	Trial Steering Committee
UKWP	United Kingdom Working Party

Plain language summary

Eczema is a troublesome itchy skin condition affecting 1 in 5 children and 1 in 10 UK adults. There is no cure and affected children are more likely to develop food allergies. We wanted to see if we could prevent eczema by protecting the skin of babies at higher risk of developing eczema (with an immediate relative with eczema, asthma or hay fever) with moisturisers used to treat dry skin. Previous research suggested that protecting the skin barrier might also prevent food allergy. One thousand three hundred and ninety-four families took part in a study; half of them were asked to apply moisturiser every day to their newborn baby for the first year and half to look after their baby's skin in the normal way. At the age of 2 years, we did not see any difference in how common eczema was between the two groups: 23% had eczema in the moisturiser group and 25% in the normal care group. It did not matter how we defined eczema – whether examined by a researcher or parent report. We did not find any differences in related conditions like asthma or hay fever either. We found that children using moisturisers had seen their doctor slightly more often for mild skin infections. There was a hint that food allergy might have been increased in the moisturiser group, but there was not enough data to be sure. We followed up the children to age 5 years, but we still did not find any benefits from using moisturisers in early life. Since this study, other similar research has been done using newer types of moisturisers, but their results are the same. This study shows that using daily moisturisers on healthy babies with a high risk of eczema does not prevent eczema. It is one less thing for busy families to worry about.

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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Chapter 1 Introduction

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Background

Terminology and disease definition: In this monograph, we use the term 'eczema' throughout as a term commonly used in the UK to denote atopic eczema (AE) [also known as atopic dermatitis (AD) in the USA and other countries]. It could be argued that using the term 'eczema' is more precise, as around 50% of cases of 'atopic' eczema are not atopic[2] [defined as immunoglobulin E (IgE) sensitivity to common environmental allergens determined by skin prick or blood tests]. The term 'eczema' is also the preferred term designated by the World Allergy Organization nomenclature committee.[3] A long list of major and minor clinical diagnostic criteria for eczema were suggested by Hanifin and Rajka in 1980 which were later refined in 1994 into a minimum list of reliable discriminators by a UK diagnostic criteria working party led by one of the authors (HW)[4] (*Table 1*).

The UK diagnostic criteria have been used for this study and are supplemented by a detailed training manual for users.[5]

Defining a new/incident case of eczema for use in prospective studies has been challenging as most definitions rightly include an element of chronicity,[6] which is important to separate true eczema from many unclassified transient irritant forms of dermatitis in early life.[7] A 1-year period prevalence is used in the UK diagnostic criteria to capture chronicity and overcome seasonal variation.

What is eczema? Eczema is a chronic inflammatory skin condition characterised by symptoms of itching, stinging and burning of the skin. Itching can lead to sleep loss, poor concentration and a reduction in quality of life. Eczema can affect any part of the body. Secondary infection of the skin with bacteria (most commonly *Staphylococcus aureus*) is common. Involvement of the cheeks and outer limbs and trunk is common in infancy, whereas in the older child, involvement of the skin creases such as behind the knees and elbow folds is common. The skin is inflamed, appearing red in lighter skin tones and a dark purple or brown colour in dark skin. Chronic scratching leads to leathery thickening of the skin (termed lichenification).

TABLE 1 United Kingdom Working Party's Diagnostic Criteria for diagnosis of AD[4]

In order to qualify as a case of AE with the UK diagnostic criteria, the child must have an itchy skin condition in the last 12 months. Plus three or more of:
Onset below age 2 years[a]
History of flexural involvement
History of a generally dry skin
Personal history of other atopic disease[b]
Visible flexural dermatitis as per photographic protocol[5]

a Not used in children under 4 years.
b In children aged under 4 years, history of atopic disease in a first-degree relative may be included.

Eczema is caused by a combination of genetic and environmental factors. Genes controlling skin barrier formation and inflammatory responses are important. Epidemiological studies indicate that environmental factors are also critical for determining disease expression: eczema has increased in prevalence over the last 30 years; people migrating from low- to high-prevalence countries develop similarly high rates in the adopted country; and eczema prevalence increases with small family size and higher socioeconomic group.[8–10] Increased sensitivity to food and environmental allergens such as house dust mite is common in eczema. The role of gut and skin microbiota in driving eczema remains controversial.[11] Most cases of childhood eczema improve in childhood but around 5% persist into adulthood.[12] Although eczema is still considered as one disease for the purpose of scientific studies and clinical trials, recent studies suggest that it is composed of several distinct sub-phenotypes or endotypes with different disease trajectories.[13] The relationship between skin barrier dysfunction and underlying upregulation of type-2-mediated immune responses is summarised elsewhere.[14]

Asthma, hay fever and food allergy (collectively called 'atopic' disorders) are also commoner in children with eczema and perhaps best considered as comorbidities rather than conditions that inevitably progress in the same individuals as part of the so-called allergic march (*Figure 1*).[16] Some children with eczema are also allergic to foods such as egg and nuts. Current thinking is that eczema in early life leads to food allergy rather than the other way around.

Eczema affects around 20% of children worldwide[17] and around 5–10% of adults.[18] Black children in the UK seem to have an increased prevalence of eczema, the reasons for which are unclear.[19] Although around two-thirds of cases of childhood eczema are mild,[20] moderate to severe eczema (*Figure 2*) can result in a significant quality-of-life impairment.[21] Having eczema or a child with eczema also confers high direct and indirect financial costs.[22]

Treatment of eczema. These are best summarised in the National Institute for Health and Care Excellence (NICE) eczema clinical knowledge summary.[23] Treatment depends to a large extent on eczema severity. In clinical practice, severity is commonly assessed using the Patient-Oriented Eczema Measure (POEM) which records eczema symptoms over the last week.[24] Mild eczema corresponds to a POEM score of 0–7, moderate 8–16 and severe/very severe ranging from 17 to 28.[25] In addition to avoiding irritants such as soap and rough clothing, mild eczema is generally treated in the community with topical application of creams and ointments such as short bursts of mild potency topical corticosteroids for

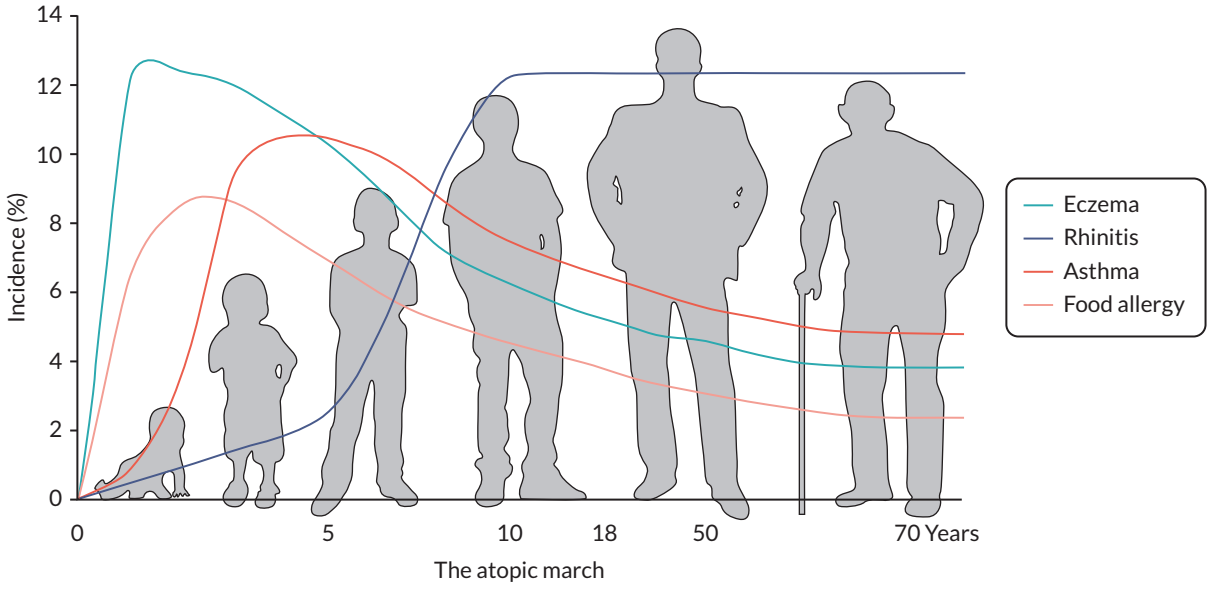

FIGURE 1 Illustration of the typical onset of symptoms of allergic diseases during childhood. Reprinted from Davidson*et al.* (2019),[15] Copyright (2023), with permission from Elsevier.

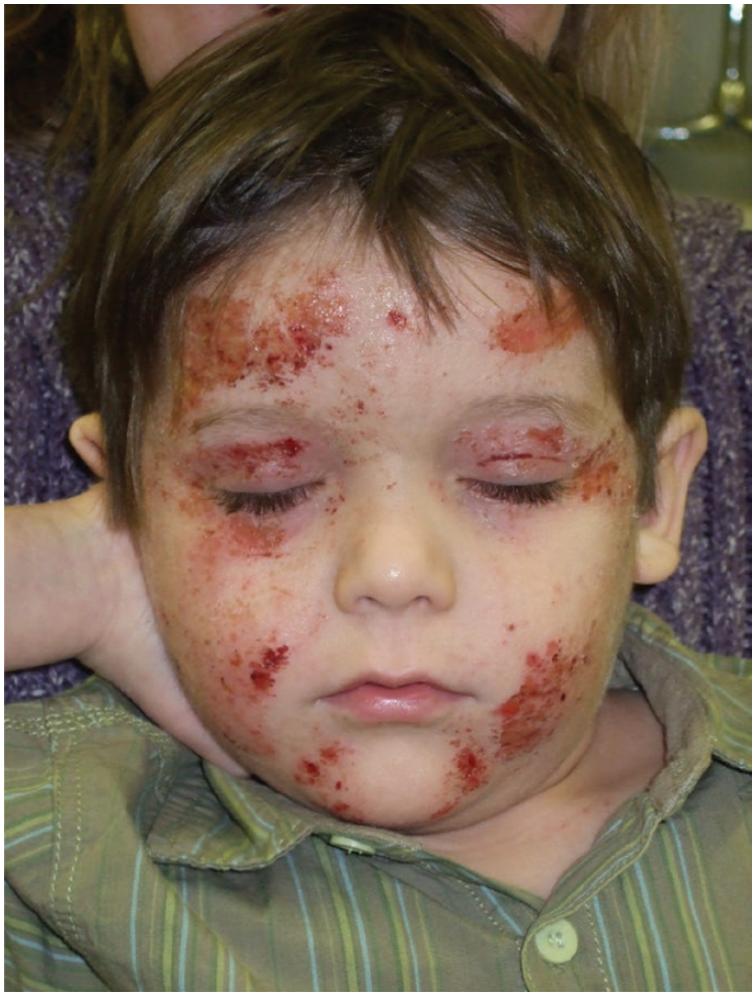

FIGURE 2 Severe eczema is associated with poor quality of life in children.

inflammatory flares and emollients for restoring the skin barrier, flare prevention and treatment of dry skin symptoms. Moderate disease requires more potent topical corticosteroids and/or the addition of topical calcineurin inhibitors such as tacrolimus and pimecrolimus, often used proactively on weekends to prevent flares. More severe eczema requires specialist input and may require third-line treatments such as ultraviolet light or systemic immunomodulatory therapy such as ciclosporin, methotrexate or biologics such as dupilumab and baricitinib.[26] Three more biologics (abrocitinib and upadacitinib – both JAK1 inhibitors, and tralokinumab – a human monoclonal antibody that inhibits interleukin-13) have recently been approved by NICE for severe eczema[27] and a large range of biologics are currently in development. There is a considerable unmet need for eczema care in the UK, with most treatment carried out at home with little contact with healthcare professionals.[14] Self-care informed by theory-based, evidence-informed online educational programmes have been shown to result in sustained benefit for managing eczema severity.[28]

While good progress has been made with new topical and systemic treatments for established eczema,[29] relatively little attention has been paid to the prevention of eczema – arguably a more desirable approach than the daily lifetime toil of applying greasy ointments or requiring expensive medicine that modify the body's immune system in individuals in whom a long chain of pathological events have already occurred (*Figure 3*).[31]

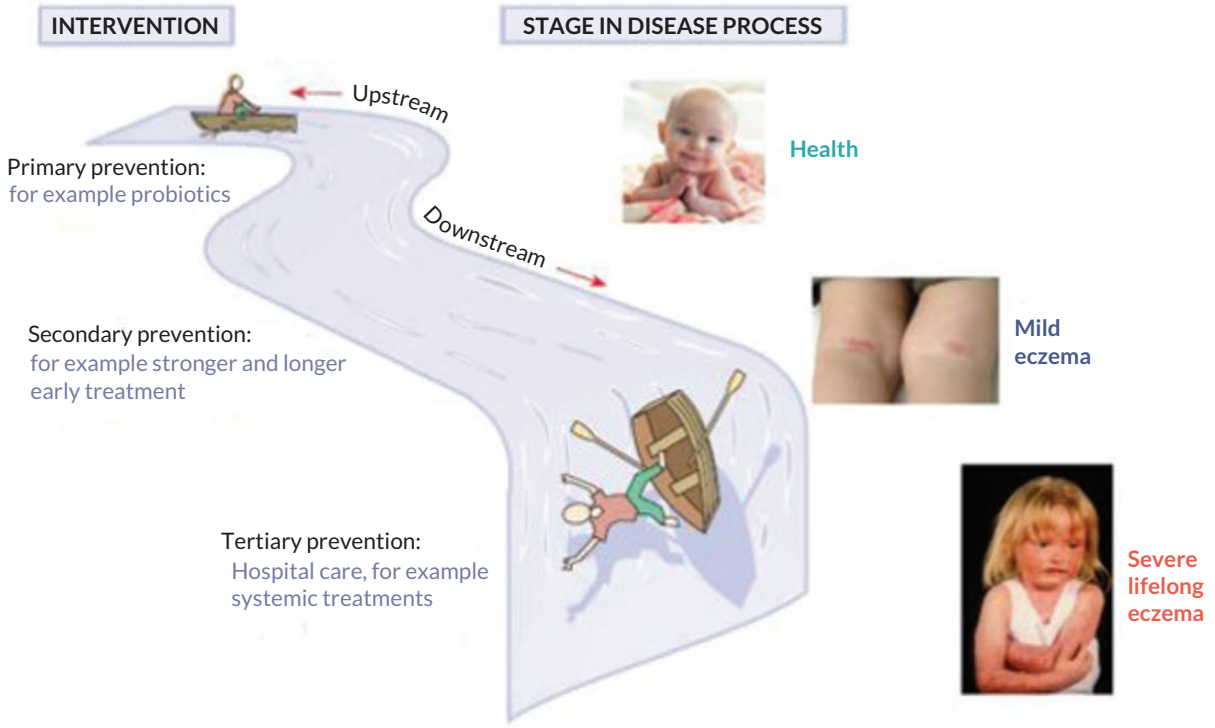

FIGURE 3 Upstream prevention of eczema is a more desirable aim than treating sick individuals with costly drugs who present after a long chain of multistage events.

Rationale for the barrier enhancement for eczema prevention trial

A summary of the approaches that have been used to try and prevent eczema and the methodological considerations for such preventive studies have been summarised elsewhere.[32] In brief, systematic reviews of prevention strategies covering exclusive and prolonged breastfeeding, or those targeting reduction in food and/or airborne allergens in pregnancy and/or shortly after birth have not shown clear benefit. Maternal/infant supplements of vitamin D has also not shown any benefit. Some evidence supports the role of probiotics to prevent eczema, but the studies are quite variable and might benefit from individual patient data meta-analysis.

Interest in the use of emollients for preventing or reducing the severity of childhood eczema has been around for many years and was suggested by one of the authors (HW) at the 2001 International Symposium of Atopic Dermatitis in Portland. Although the idea gained some traction as it was already known that dry skin preceded the development of visible eczema, it was the discovery that mutations in the gene encoding filaggrin (*FLG*), a key skin barrier protein, that accelerated interest in emollients as a potential intervention for preventing eczema.[33] *FLG* mutations have since been shown to represent the strongest and most consistent genetic risk factor for eczema. Later studies showed that *FLG*-null mutations were also associated with related atopic conditions including asthma, hay fever and peanut allergy.[34] Intense interest grew in the concept of skin barrier dysfunction as the initial step in eczema development. In addition to *FLG* mutations, skin barrier defects are thought to arise as a result of immune dysregulation, low levels of antimicrobial peptides, a general disruption in skin flora (dysbiosis).[35] The genetic predisposition to skin barrier impairment led to the idea that babies at high risk of developing eczema are born with a skin barrier that allows irritants and allergens to initiate skin inflammation and hence set up a cascade of inflammatory events that could lead to chronic eczema driven by autoimmune mechanisms as a result of chronic scratching.[36]

Emollients are used to improve the barrier function of skin by providing lipids to the outermost stratum corneum and by trapping water which in turn improves skin hydration. Emollients may prevent inflammation caused by external irritants as they are used to prevent irritant occupational hand eczema.[37] Emollients had also been shown to reduce skin inflammation in premature babies[38] as well as preventing eczema flares in those with established eczema.[39] An earlier open-label pilot study of emollient therapy from birth showed that only 15% of high-risk infants developed eczema against an expected rate of 30–50%.[40] A case-control study conducted in Kenya published in 1991 also suggested that petroleum had protective effect against the development of eczema.[41]

A workstream within a NIHR-funded programme grant conducted by several authors focused on exploring the feasibility of conducting a national trial of emollients to prevent eczema. At the time, there was considerable uncertainty of whether families with a strong history of atopic disease (eczema, asthma, hay fever) would agree to be randomised to normal care or daily application of an emollient to their newborn child. A series of pilot studies including qualitative work with families was carried out to explore emollient preferences. Full details of the pilot studies are described in the Programme Grant for Applied Research report.[42] Since some emollients such as aqueous cream had been shown to paradoxically damage the skin barrier,[43] a mechanistic study by experts in skin barrier science was done to show that the two preferred emollients did not cause any such skin barrier disruption.[44] A feasibility randomised controlled trial (RCT) of 124 families was conducted and showed that the intervention was acceptable and that it was possible to conduct a national clinical trial. Although not powered to detect a difference in eczema prevention, infants in the emollient group in the feasibility study showed a reduced risk of developing eczema at 6 months of age compared to controls [22% vs. 43%, respectively, relative risk (RR) 0.50, 95% confidence interval (CI) 0.28 to 0.90; *p*-value = 0.017].[42] Another small trial of 118 infants in Japan showed similar results, with 32% fewer neonates who received moisturiser developing eczema by week 32 when compared with control infants.[45]

On the basis of the need to prevent eczema, empirical evidence on the role of a defective skin barrier as the initial event in eczema development, growing signals from observational and randomised pilot studies, a strong case was therefore made to the NIHR *Health Technology Assessment* Programme to fund a national trial of emollients to prevent eczema in babies at high risk of developing the condition. Timing was important as interest in the potential for emollients to prevent eczema was now becoming an entrenched belief following the two small pilot studies, and parents with a strong family history of atopic disease across the world were beginning to use emollients to prevent eczema in their newborns. Commercial companies were responding to demand by developing 'designer' emollients to enhance the skin barrier. The window of public/patient and healthcare professional equipoise was limited.

We therefore sought to test the hypothesis whether daily emollient application for 12 months after birth can reduce the development of eczema.

Chapter 2 Methods

 The full barrier enhancement for eczema prevention (BEEP) trial protocol (final version 7.0, 26 February 2021) is available on the NIHR Funding and Awards website[47] and a summary protocol has been published.[46] The main changes to the protocol after the initial approval in June 2014 was the addition of secondary outcomes for confirmed diagnosis of food allergy and allergic sensitisation and the associated assessments after separate funding was obtained to complete these (added May 2016).

Trial objectives

Primary objective

To determine whether advising parents to apply emollient daily to the entire body surface area for the first year of life can prevent AE in high-risk children.

Secondary objectives

- To determine whether emollients can delay the onset and/or reduce the severity in those who develop AE.
- To determine whether emollients can prevent other allergic diseases developing.
- To determine the safety and cost-effectiveness of the prevention strategy.
- To determine whether any preventative effect is sustained into later childhood.

Trial design and setting

This was a randomised, controlled, two-arm (skin-care advice plus emollient vs. skin-care advice alone), parallel group, multicentre, assessor blind trial with 5-year follow-up and primary outcome assessed at 2 years (*Figure 4*). Recruitment took place in 12 secondary care sites and four primary care sites in England (see *Appendix 1*, *Figure 12*).

A methodological two-by-two factorial substudy was also nested within the trial to investigate the effectiveness of two interventions on the rates of follow-up data collection. The interventions were: (1) short message service (SMS) notification prior to sending questionnaires at 3, 6, 12 and 18 months

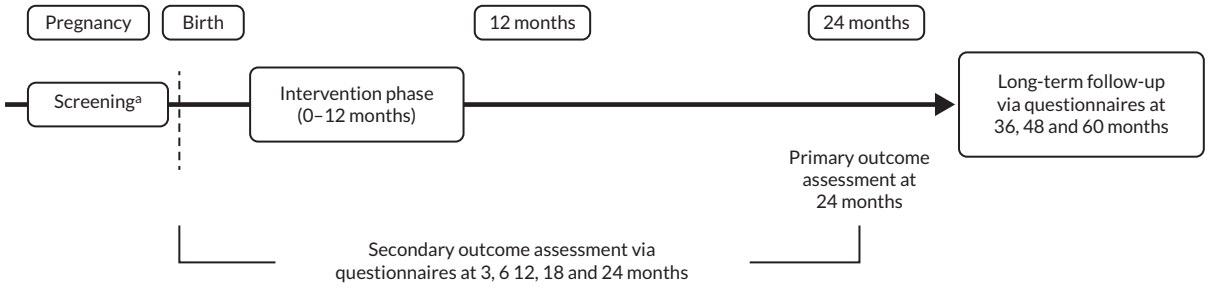

FIGURE 4 Schematic diagram showing the trial design and duration for participating families. a, Screening took place during pregnancy or within 21 days of delivery. Reproduced from Chalmers *et al.*[46] under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

versus no SMS notification and (2) sending the £10 voucher for the primary follow-up visit at 24 months with the invitation letter versus giving the voucher at the visit. Full details can be found in the studies within a trial (SWAT) registry (SWAT Repository Store ID 25).[48]

Participants and eligibility

The eligibility criteria for the participants are shown below.

Inclusion criteria

- Child had a first-degree relative with parental-reported doctor diagnosis of eczema, allergic rhinitis or asthma.
- Child up to 21 days old.
- Mothers must be at least 16 years old.
- Consenting adult had the ability to understand English.

Exclusion criteria

- Preterm birth (defined as birth prior to 37 weeks' gestation).
- Sibling (including twin) previously randomised to this trial. If multiple birth, the first-born child was randomised into the trial.
- Child had a severe widespread skin condition that would make the detection and/or assessment of eczema difficult.
- Child had a serious health issue which, at parent or investigator discretion, would make it difficult for the family to take part in the trial.
- Any condition that would make the use of emollient inadvisable or not possible.

Recruitment to the trial came from a variety of sources, including primary and secondary care and advertising. Poster and flyers were displayed at secondary care and primary care sites. If interested in taking part, expectant mothers/parents of the newborn were asked to contact the research team directly. Expectant mothers were identified through antenatal and secondary care clinics in which case relevant healthcare professionals approached parents directly about the study or sent invitation letters. In addition to the general practitioner (GP) surgeries used as sites, GP surgeries in areas with a secondary care site were used as Participant Identification Centres (PICs). In the PICs, invitation letters and information sheets were sent to expectant parents. The trial was also promoted through local radio, television, newspapers, the Mumsnet website and the public display of posters and flyers at venues that families and expectant mothers frequent including nurseries, libraries, supermarkets and Sure Start centres.

Screening and consent

Pregnancy status and family history of atopic disease were checked for parents initially expressing an interest in taking part and, if eligible, the parents were sent the participant information leaflet and a screening visit was arranged. The screening visit took place either in the family home or at the recruiting site, depending on parent preference and was conducted either in the third trimester if the baby had not yet been born or as soon as possible after birth and within 21 days of being born. During the screening visit, the research nurse obtained informed consent and checked eligibility. Consent was also sought for the optional genetic component and for use of samples in potential future research. Parents who consented agreed to their child providing a saliva sample at the 24-month visit for *FLG* genotyping in order to conduct subgroup analysis to explore the effect of emollients on eczema prevention according to genetic risk of atopic disease (*FLG* null mutations).

Outcomes

Full details of definitions and derivation of outcomes are given in the statistical analysis plan (SAP).[47]

Primary outcome

The primary outcome was a diagnosis of AE at 24 months defined as meeting the United Kingdom Working Party (UKWP) Diagnostic Criteria for Atopic Eczema,[4] which assesses signs and symptoms present over the past year, assessed by a trained research nurse blinded to treatment allocation.

Applying the criteria at 24 months was chosen to ensure that any observed effect on reducing AE prevalence could be considered a true preventative effect rather than masking the emergence of mild eczema in the first year due to the use of the emollient.

Secondary outcomes

1. Presence of eczema between birth and 24 months:
   - Any parental report of a clinical diagnosis of eczema.
   - Completion by parents of UKWP Diagnostic Criteria for Atopic Dermatitis at 12 and 24 months.

2. Presence of visible eczema at 24 months (skin examination by researcher).
3. Time to onset of eczema:
   - First parental report of a clinical diagnosis of eczema.
   - First topical corticosteroid and/or immunosuppressant prescription for eczema.

4. Severity of eczema:
   - Eczema Area and Severity Index (EASI)[49] at 24 months.
   - POEM[24] at 12 and 24 months.

5. Presence of other allergic diseases:
   - Parental-reported wheezing and allergic rhinitis between 12 and 24 months.
   - Parental report of a clinical diagnosis of food allergy at 12 and 24 months.
   - Parental report of food allergy at 12 and 24 months. Parents were specifically questioned about cow's milk, egg, peanuts and other nuts plus 'any other food'.
   - Allergic sensitisation at 24 months to any of the following common allergens: milk, egg, peanut, cat, grass pollen, house dust mite (added in protocol version 4.0 after obtaining separate funding).
   - Confirmed diagnosis of food allergy at 24 months to milk, egg, peanut or 'any of milk, egg or peanut' (added in protocol version 4.0 after separate funding obtained). The diagnosis was derived from a combination of parental report, allergic sensitisation and food challenge.

6. Health-related quality of life:
   - Child Health Utility instrument-9 domains (CHU-9D)[50] at 24 months in order to estimate quality-adjusted life-years (QALYs).
   - Parental quality of life measured using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L) at baseline and 24 months in order to estimate change in parental QALYs, if any.

7. Health economic outcomes:
   - Healthcare resource use at 3, 6, 12, 18 and 24 months.
   - Cost-effectiveness and cost–utility at 24 months (combining health resource use and health-related quality-of-life outcomes).

Safety outcomes

1. Number of skin infection events during the first year.
2. Number of infant slippage incidents (slippage in hand and slippages to the floor) that occur within an hour of applying emollient during the first year.

Tertiary outcomes (long-term follow-up)

1. Presence of eczema in the previous year at 36, 48 and 60 months based on parental report of a clinical diagnosis of eczema.
2. Any parental report that in their opinion their child has eczema at 3, 6, 12, 18, 24, 36, 48 and 60 months.
3. Presence of eczema at 36, 48 and 60 months based on completion by parents of UKWP Diagnostic Criteria for Atopic Dermatitis.
4. Severity of eczema at 36, 48 and 60 months as measured by POEM.
5. Presence of other atopic diseases:
   - Parental-reported wheezing, allergic rhinitis and food allergy symptoms at 36, 48 and 60 months.
   - Parental report of a clinical diagnosis of asthma or allergic rhinitis by 60 months.
   - Parental report of a clinical diagnosis of food allergy at 36, 48 and 60 months.

6. Health-related quality of life:
   - CHU-9D at 36, 48 and 60 months in order to estimate QALYs.
   - Parental quality of life: EQ-5D-5L at 36, 48 and 60 months in order to estimate parental QALYs.

7. Health economic outcomes:
   - Healthcare resource use at 36, 48 and 60 months.
   - Cost–utility and cost-effectiveness at 60 months (combining health resource use and health-related quality-of-life outcomes).

8. Cumulative incidence outcomes (not specified in protocol, see below for rationale for addition).
   - Parental report of clinical diagnosis of eczema from the age of 12 to 60 months.
   - Parental report of clinical diagnosis of food allergy by 60 months.

Exploratory outcomes (long-term follow-up, not specified in protocol)

1. Parental report of reaction to egg or nuts by 60 months.
2. Parental report of immediate reaction to egg or nuts by 60 months.

The protocol initially specified the paediatric quality of life (PedsQL)[51] questionnaire to estimate QALYs for the child at 24, 36, 48 and 60 months. This was changed in May 2016 to the CHU-9D questionnaire to reflect the latest research in the area. The Infant Dermatitis Quality of Life questionnaire[52] was also removed as an outcome in May 2016 to reduce the questionnaire burden and also due to BEEP being a prevention trial rather than a treatment trial.

Cumulative incidence tertiary outcomes and exploratory outcomes (not in the protocol) were specified in version 2.0 of the SAP, as a better measure of lifetime experience of eczema and food allergy than single sweeps of 1-year period prevalence. Eczema is a condition that undergoes relapses and remissions – both short term over the course of weeks or months that reflect seasonal influences such as temperature, pollen and humidity (which is adequately captured by enquiring about a one period prevalence) or over the course of years, with some children having eczema which then clears and some getting early eczema which then clears and then returns at different sites. Food allergy can cause only intermittent reactions, often less than once per annum; the condition can be immunologically present for many months or years before a clinical reaction is experienced, especially for allergy to foods which are not widespread components of everyday diets such as tree nuts. The first 12 months were not included

in the tertiary outcome for cumulative incidence of eczema as transient eczematous rashes are common in the first year of life and often reported by parents as 'eczema' but are less likely to be true AE.

Randomisation and blinding

Within 21 days of the birth of the baby, a baseline visit was conducted (either on the phone, via e-mail or face to face) with the research nurse to confirm eligibility and collect baseline data. Babies meeting the eligibility criteria were then randomised by the research nurse via a web-based randomisation system developed and maintained by Nottingham Clinical Trials Unit (NCTU).

The randomisation schedule was based on a computer-generated pseudo-random code using random permuted blocks of randomly varying size created by NCTU and held on a secure University of Nottingham server. Infants were allocated in a 1 : 1 ratio to either emollient and standard skin-care advice (intervention group) or standard skin-care advice only (control group). Randomisation was stratified by recruiting centre and number of immediate family members (parents/siblings) with atopic disease (one, two, or more than two family members with either eczema, asthma or hay fever).

Parents were informed of their child's allocation by staff at NCTU by letter. While it was not possible to blind parents to the treatment allocation, efforts were made to minimise expectation bias by emphasising that information on the effect of emollient in addition to standard skin-care advice was limited.

Research nurses were not informed of the allocation to maintain blinding for the follow-up visit for the primary outcome at 2 years. To reduce the chance of the research nurse being unblinded by the parents at the 2-year visit prior to the skin examination for eczema, the appointment letter reminded parents not to tell the nurse which group they had been assigned to in the first year and skin assessments were conducted first during the visit.

Researchers involved in the food allergy assessment process were also blinded to treatment allocation.

The trial statisticians and health economists remained blinded to treatment allocation until after the initial database lock for the analysis of primary outcome data at 2 years.

Interventions

Skin-care advice

Both groups received advice on general skin care in booklet and video format at the time of randomisation.[47] Skin advice was based on 2006 NICE guidance for postnatal care up to 8 weeks of birth available at the time (since replaced)[53] and updated in 2016)[54] and supplemented with expert opinion from dermatological nursing and skin barrier research expertise (SL and MC). The booklet and video advised to use mild cleansers and shampoos specifically formulated for infants, and to avoid soap, bubble bath and baby wipes. Parents were advised to seek medical advice from their GP if their baby developed any skin problems. Infants in the control group were allocated to skin-care advice alone.

Intervention group

Families in the intervention group were advised to apply emollient (Doublebase Gel® or Diprobase Cream®) at least once daily to the whole body (excluding the scalp) until the child reached 1 year, in addition to skin-care advice described above. These two emollients were chosen based on our pilot work with families from our preceding programme grant for applied research.[42] We were able to establish that the liquid-paraffin-based emollients, Doublebase Gel (Dermal Laboratories Ltd) and Diprobase Cream (Bayer Plc) are popular with parents and do not have any detrimental effects on skin barrier function. Parents in the pilot study also told us that having a choice of emollients was very important to them.

They were also advised to apply emollient after every bath, even if they had already applied the emollient that day. Daily application was advised in order to encourage regular use of emollient several times a week, but since the study was designed to reflect how the intervention might be delivered in normal practice, no prompts or reminders were sent to parents. The skin- care advice booklet and video for the intervention group additionally provided guidance on how to apply emollients correctly by dotting over the skin and using gentle downward strokes rather than rubbing in. The booklet also contained warnings about the skin being slippery after application and the need to clean up spillages from the floor to avoid slipping.

Upon randomisation, the central trial pharmacy sent the families a 500 g container of each emollient by post. Families reordered their preferred emollient during the intervention period (1 year) by contacting the NCTU. Parents were advised to stop applying emollients when their child reached 1 year of age and no further emollients were supplied after this point.

Trial assessments and procedures

Parents were initially contacted by telephone by the NCTU approximately 2 weeks after randomisation to check they have received their skin-care advice pack and web link for the video, and for infants randomised to the intervention group, to check the date that the family started applying the emollient. Parents were also reminded to contact the NCTU if they had any questions or problems (to protect the research nurses from becoming unblinded).

Parents were asked to complete web-based questionnaires at 3, 6, 12, 18, 36, 48 and 60 months to collect information on any skin problems, eczema and other allergy symptoms (including diagnosis, prescriptions and health resource use), feeding, skin-care practices (including emollient use during the intervention period), skin infections, infant slippage incidents within an hour of applying skin-care products, reactions to food and quality of life as detailed in *Table 2* (all questionnaires available at[47]).

TABLE 2 Summary of assessments

	Stuy period							
	Screening/enrolment	**Baseline/ randomisation**	**Post randomisation**					**Final follow-up**
			Months					
Time point	**During pregnancy or up to 21 days post delivery**	**Within 21 days of birth**	**3**	**6**	**12**	**18**	**24**	**36 and 48**	**60**
Enrolment									
Eligibility screen	X								
Informed consent	X								
Family demographic data including history of atopic disease	X								
Baby demographic data		X							
Randomisation		X							
Interventions									
Skin-care advice plus daily emollient			X	X	X				
Skin-care advice alone			X	X	X				

TABLE 2 Summary of assessments (*continued*)

	Stuy period							
	Screening/enrolment	Baseline/ randomisation	Post randomisation					Final follow-up
			Months					
Time point	During pregnancy or up to 21 days post delivery	Within 21 days of birth	3	6	12	18	24	36 and 48	60
Assessments									
Parental-reported skin problems (including eczema)			X	X	X	X	X	X	X
Parental-reported clinical diagnosis of eczema			X	X	X	X	X	X	X
Parental completion of eczema diagnostic criteria (UKWP criteria)					X		X	X	X
Blinded (researcher) assessment of eczema status							X		
Eczema severity (EASI, conducted by blinded researcher)							X		
Eczema severity (parent reported POEM)					X		X	X	X
Parental-reported allergic rhinitis/wheezing symptoms							X	X	X
Parental-reported food allergy symptoms and diagnosis					X		X	X	X
SPT ± oral food challenge if required							X		
Parental-reported skin infections and slippages			X	X	X				
Adherence			X	X	X				
Parent/carer health-related quality of life (EQ-5D-5L)		X					X	X	X
Child health-related quality of life (CHU-9D)							X	X	X
Health resource use			X	X	X	X	X	X	X
Saliva sample collection							X		
Feeding and washing practices questionnaires				X	X		X		
Parental-reported moisturiser use						X	X	X	X
Parental-reported diagnosis of asthma/hay fever									X

SPT, skin prick test.

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Reminders were sent by e-mail after 2 and 3 weeks of non-completion and the questionnaires could be completed up to 4 weeks after the initial e-mail invitation was sent. Paper copies of the questionnaire were sent by post (with pre-paid envelopes) if parents did not wish to complete the questionnaires online. From May 2016, staff at the NCTU also telephoned and/or sent a text message to participants who had not completed the questionnaire after the first reminder and gave participants the opportunity to complete the questionnaire on the phone.

At 24 months, a face-to-face visit with a research nurse took place either in the family home or in clinic according to parent preference. Prior to the first appointment, 28 research nurses were trained in all assessments either by attending an in-person training day or by watching a series of training videos. This included training in diagnosing eczema using the UK diagnostic criteria, the EASI, skin prick test (SPT) and anaphylaxis. After this initial training, nurses used the UKWP Diagnostic Criteria and performed an EASI assessment in clinic with three patients with the local Principal Investigator. Specialist allergy nurses accompanied research nurses at their initial 24 months visits to sign off on proficiency in SPT competency and using an EpiPen (Viatris UK HealthCare Ltd., Potters Bar, Hertfordshire, UK, for anaphylaxis).

After arranging the 24-month visit, the research nurse sent parents an information leaflet and sheet to explain that their child would be offered an allergy test (SPT) at the visit. The nurse then discussed the SPT during the visit and took consent for this if the parents were willing for the child to have the optional allergy test.

During the visit, the research nurse conducted the skin examination for the UKWP Criteria and the EASI and for parents who had given the additional optional consents, collected a saliva sample and conducted a SPT. Parents were also asked to complete the POEM, EQ-5D and CHU-9D questionnaires and another questionnaire to collect information about skin problems, reactions to food, symptoms of allergic rhinitis and wheezing, skin care/washing and other characteristics potentially associated with the development of eczema (e.g. antibiotic use since birth, furry pets, dust mite reduction measures, number of other children in the household and whether the child attends nursery or playgroup), as detailed in *Table 2* (case report form for 24-month visit available at NIHR Funding and Awards[47]). At the end of the visit, nurses recorded if they had become aware of which group the child had been randomised to and if so whether this happened before, during or after the skin examination.

Skin prick testing was carried out following a trial-specific procedure in line with the British Society for Allergy and Clinical Immunology procedures for SPT[55] (*Appendix 2* of protocol v7.0 26 February 2021, see NIHR Funding and Awards[47]). The following allergens were tested; grass pollen mix, dust mite and cat (Allergopharma GmBH & Co., Reinbek, Schleswig-Holstein, Germany), peanut (Inmunotek, Madrid, Spain), fresh skimmed cow's milk and fresh chicken egg. Positive (1% histamine) and negative (0.9% saline) controls were used (Allergopharma GmBH & Co.). The research nurse measured the size of the reactions, and the results were reviewed by the BEEP food allergy team.

If it was not possible to complete a face-to-face visit, data collection was attempted remotely by telephone, text, e-mail or post. If no follow-up with the family was possible at 24 months, the NCTU attempted to collect key minimal data around diagnoses of eczema and food allergy (including number of prescriptions, primary and secondary care visits) from the child's GP.

Children with a positive SPT or history suggestive of food allergy, where further information was needed to confirm a food allergy, were invited for a supervised oral food challenge (*Figure 5*) in an allergy clinic at Imperial College Healthcare National Health Service (NHS) Trust or Sheffield Children's Hospital NHS Trust. A trial-specific food challenge information sheet was sent to parents of children invited to the food challenge and if needed the food allergy team contacted parents to gather more information about the child's food allergy history. Parents who agreed to take part gave consent for their child to have a food challenge to confirm whether their child had a food allergy. Oral food challenges were conducted by experienced allergy nurses blinded to treatment allocation following a trial-specific standard

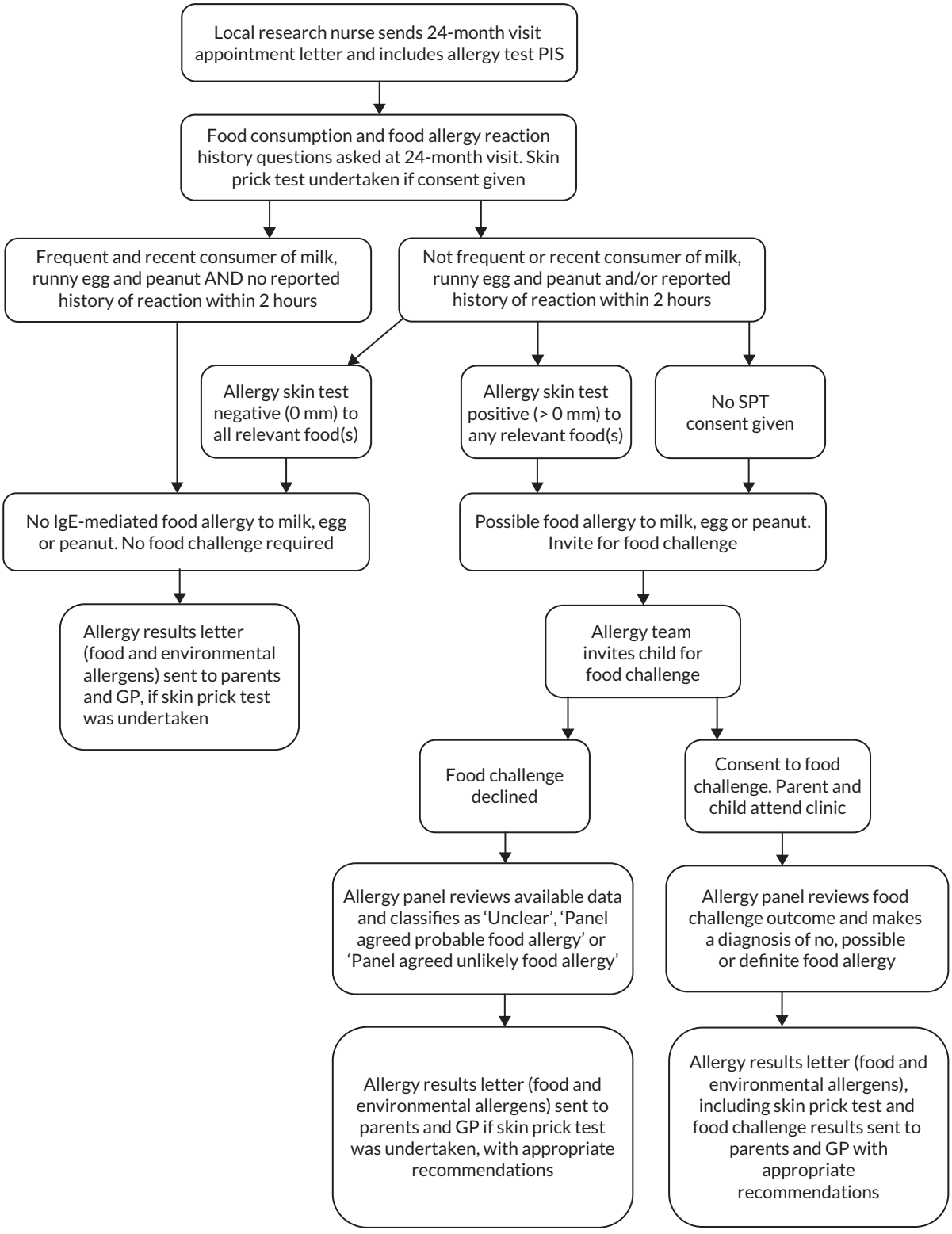

FIGURE 5 Food allergy assessment process.

procedure using incremental doses or a single dose of the relevant food (see *Appendix 3* of protocol v7.0 26 February 2021, see NIHR Funding and Awards[47]). Allergy nurses were able to review SPT results and allergy history as needed to inform clinical decision-making. Trained nurses supported by a consultant paediatric allergist evaluated whether there had been a clinical reaction to the food using modified practical allergy (PRACTALL) and Integrated Approaches to Food Allergen and Allergy Risk Management

criteria.[57,58] Clinical reactions during the food challenge were treated using standard clinical guidelines, with antihistamine, bronchodilator, intramuscular adrenaline or other medications, as needed.

For participants invited to a food challenge where this did not take place, a panel of experienced paediatric allergists agreed allergy status (see *Figure 5*). The panel developed and validated an algorithm to make the food allergy diagnosis.[59] The panel were blinded to treatment allocation and used all available information from the questionnaires and assessments and, where necessary, from secondary care records and direct communication with participants' parents. Following the SPT and food challenge (where applicable), parents and the child's GP were sent a letter summarising the findings and any recommended action by the BEEP food allergy team.

Saliva samples were sent to the Centre for Dermatology and Genetic Medicine at the University of Dundee for deoxyribonucleic acid (DNA) extraction by standard techniques. DNA samples were genotyped for the four most common *FLG* null mutations in the white European population (2282del4, R501X, S3247X and R2447X).[60]

Small tokens of appreciation were sent to all participating families by the NCTU throughout the trial including BEEP branded muslin or bib at randomisation, birthday card and BEEP branded plastic cutlery set or storybook at the child's first birthday and BEEP branded cloth shoulder bag sent at 18 months. At 24 months parents received a £10 voucher either with the invitation letter for the primary follow-up visit or at the visit according to their allocation for the nested SWAT. A £10 voucher was also sent to parents on completion of the 48- and 60-month questionnaire. Parents were also sent trial newsletters every 6 months (from January 2016). The newsletter sent to parents in February 2020 summarised the results for the primary and secondary outcomes up to 24 months.[61]

Trial oversight

An independent Trial Steering Committee (TSC) provided overall supervision of the trial. The TSC had an independent chair and four independent members (parent representative, statistician, consultant dermatologist and paediatric epidemiologist as detailed in *Acknowledgements*). The TSC met at least once a year during recruitment and follow-up for the primary outcome.

Due to the very low medical risk associated with the intervention, there was no separate data monitoring committee for the trial. Safety outcomes were monitored by the TSC during closed sessions of the meetings attended by only the independent members.

Sample size

The sample size was based on assuming 30% of children in the control group would have eczema between 1 and 2 years of age (based on previous epidemiological studies in this high-risk population) and a conservative relative reduction of 30% in the intervention group. This relative reduction was considered conservative as in the pilot study, a 50% reduction in eczema at 6 months was observed [43% developed eczema in the control group (n = 55) and 22% developed eczema in the emollient group (n = 53), 95% CI for RR 0.28 to 0.90]. The anticipated effect size was lower in the main trial due to the more pragmatic study design and the longer-term outcome assessment; however, such a reduction would still have important implications for families and health services.

A total of 1282 children were required to allow this difference to be detected (i.e. 30% of children in the control group, 30% relative reduction to −21% of children in the intervention group) at the 5% significance level (two-sided) with 90% power and allowing for 20% attrition at 24 months.

The protocol specified that the assumptions underpinning the sample size would be checked by independent members of the TSC after approximately 21 months of recruitment (i.e. by checking the percentage of children with eczema in the control group and percentage with follow-up data). However, the original target sample size of 1282 was exceeded prior to this point and the Chief Investigator requested that the sample size review therefore be brought forwards. At this point (July 2016), sites were told to stop consenting women to the trial however randomisation continued for women who consented before this date prior to the birth of their baby. In August 2016, independent members of the TSC were sent details of the follow-up questionnaire completion rate in each group and parental-reported medical diagnosis of eczema in the control group from the questionnaires by a NCTU statistician independent of BEEP. The TSC were asked to advise on whether consent and randomisation should continue. The TSC recommended that consent to the trial should be permanently terminated but randomisation should continue for any women who had consented but had not yet been randomised. The total number of children randomised was expected to be approximately 1400.

Stopping rules and discontinuation

There was no planned interim analysis of treatment efficacy for the primary outcomes. The criteria below (*Box 1*) were specified in the protocol in relation to recruitment and adherence to trigger discussion with the TSC and funder regarding the best course of action.

Statistical methods

Analyses are detailed in the SAP. Version 1.0 of the SAP was finalised prior to database lock and release of treatment allocation codes for analysis of the primary and secondary outcomes at 24 months.[47] Version 2.0 of the SAP was finalised prior to the database lock for the analysis of the tertiary outcomes at 60 months.[47] All analyses were carried out using Stata 15.0 or above (StataCorp LP, College Station, TX, USA), unless otherwise specified.

The main approach for analysis was to analyse participants (children) as randomised regardless of adherence with the allocated intervention using available data (i.e. without imputation for missing data) with sensitivity analysis for key outcomes using multiple imputation for missing data. Estimates of the intervention effect are presented with 95% CIs.

Descriptive analyses

Baseline characteristics were summarised by allocated group to describe the sample recruited and to examine balance between the two groups.

Follow-up completion was summarised in the two groups and baseline characteristics of children with and without primary outcome data in each group compared descriptively. Information collected on

BOX 1 Criteria related to recruitment and adherence to trigger discussion

- ***Recruitment***: If recruitment (as documented in the recruitment plan) was < 50% of the expected rate by 15 months, and strategies to overcome the identified barriers to recruitment had not been successful.
- ***Adherence to the intervention***: If fewer than 90% of families in the intervention group had applied emollient over the majority of their child's body at some stage *and* fewer than 70% were still using emollient at 6 months.
- ***Emollient use by the control group***: If emollient use in the control group exceeded 25% of families at 6 months. This excluded the use of emollients for the *treatment* of eczema and only applied to emollient use that closely reflected the intervention (i.e. regular widespread use in the first year of life, defined as widespread emollient use over the majority of the child's body at least 3 or more days per week).

follow-up questionnaires and at the 24-month visit on characteristics which may be associated with the development of eczema and on the timing of introduction of allergenic foods as well as recent consumption of these foods were summarised by allocated group to inform the interpretation of the results.

Compliance and contamination

Compliance in the intervention group at each questionnaire time point was defined as widespread emollient use over the majority of the child's body at least 3 or more days per week. The 'majority of the child's body' was defined as at least two of the three body areas asked about on the questionnaire (face/neck, arms/legs or trunk). Contamination at each questionnaire time point in the control group was defined as use of a moisturiser or oil at least 3 days per week over most or all of the child's body since the last questionnaire. Compliance in the intervention group and contamination in the control group at each questionnaire time point were tabulated.

Compliance and contamination over the first year of life were described using an ordered categorical variable, as defined in *Table 3*.

Compliance/contamination was summarised for participants with complete data on compliance/contamination (i.e. completed questionnaires at 3, 6 and 12 months) and for all participants using the assumptions for missing data described below.

1. Participants with no reported data on emollient/moisturiser use were categorised as not compliant in the intervention arm and not contaminated in the control arm.
2. If participants missed a questionnaire(s) and went on to complete a subsequent questionnaire, missing emollient/moisturiser use was based on the next subsequent observation carried backwards. For example, if the 6-month questionnaire was missed for a participant in the intervention group and they reported being compliant at 12 months, then it was assumed that they were also compliant at the 6-month time point. The rationale for this was that it was assumed that compliance was likely to decrease over time so that this would be conservative for the intervention group.
3. If participants completed questionnaires initially and missed later questionnaires (e.g. completed at 3, did not complete 6 or 12 or completed at 3 and 6, did not complete 12), then it was assumed that there was no compliance (intervention)/contamination (control) for the later missed questionnaires.
4. Categorisation of compliance/contamination over the first 12 months following randomisation for participants with missing emollient/moisturiser use data then proceeded according to the above table.

Compliance/contamination was summarised according to (1) allocated group and (2) allocated group and whether there was a parental report of eczema diagnosis by a doctor or nurse in the first year (yes, no or unknown).

TABLE 3 Categories of compliance/contamination in the first year of life

Level of compliance in the intervention group/contamination in the control group	Criterion for compliance/contamination met at the following time points
Full	3, 6 and 12 months
Early-onset application	3 months (with neither or only one of 6 or 12 months)
Late-onset application	6 and/or 12 months (but not at 3 months)
None	Compliance/contamination criterion not met at any of 3, 6 or 12 months

Primary outcome

The adjusted RR and difference in risk 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 being stratified by centre and number of immediate family members with atopic disease (one, two or more than two) included as a covariate.

Sensitivity analysis for the primary outcome

The following sensitivity analyses for the primary outcome were performed:

- Analysis repeated including diagnosis of eczema data collected from GP records for participants with missing primary outcome data.
- According to the method of collection of the primary outcome data: between-group estimates for the risk of eczema were calculated separately for outcomes collected during face-to-face visits and outcomes collected by telephone/e-mail/SMS using generalised estimating equations adjusting for stratification variables.
- Analysis repeated replacing 'visible flexural dermatitis' in the UKWP criteria with any visible dermatitis (EASI score of > 0) in the derivation of eczema between 1 and 2 years of age.
- Using multiple imputation for missing primary outcome data (further details described below).
- Repeating the analysis assuming that all participants in the intervention group with missing primary outcome data were eczema free or had eczema and all participants in the control group with missing data had eczema or were eczema free (i.e. best-case and worst-case scenario for intervention).

A sensitivity analysis was also planned to further adjust for any baseline characteristics with an observed imbalance between groups. However, no important differences between groups in the baseline characteristics were observed so this sensitivity analysis was not conducted.

Multiple imputation was performed using chained equations.[62] The following variables were used in the imputation model:

- Allocated group.
- Randomisation stratification variables: centre, number of immediate family members with atopic disease (one, two or more than two).
- Age of mother, number of other children in household at screening (none, one, two, three or more), any furry pets in the household at screening (yes/no) and baby sex (baseline variables identified as predictive of drop-out by examination only).
- Variables used in subgroup analyses – number of *FLG* null mutations, the number of immediate family members with eczema, water hardness, season of birth and regular use of probiotic supplements during pregnancy.
- Summary of compliance and contamination in the first year of life as per the definitions above (*Table 3*).

The following outcomes were imputed:

- Diagnosis of eczema in the last year at age 2 years (primary outcome).
- Parental report of a clinical diagnosis of eczema at 2 years.
- Parental report of immediate allergy to cow's milk, egg or peanut at 2 years.
- Allergic sensitisation to cow's milk, egg or peanut.
- Food allergy to any of milk, egg or peanut at 2 years.

Forty data sets were imputed and the results of the analyses on the imputed data sets were combined using Rubin rules for multiply imputed data. This analysis assumed that unobserved outcomes are missing at random (MAR) and depend on observed characteristics but not the unobserved outcomes,

since it was considered most plausible that missing outcomes would have been similar to observed outcomes for participants with similar characteristics.

Secondary analysis of the primary outcome

To explore the effect of application of emollient in the first year of life in parents who would comply with the allocated treatment, the complier-average causal effect (CACE) was estimated.[63] CACE models were implemented as latent growth mixture models[64] in MPlus (Version 5.2), with compliance/contamination status included as a training variable for estimating class membership.

Two separate odds ratios (ORs) for the CACE were estimated based on the following definition of compliance:

1. full compliance over the first year of life as per *Table 3* – participants in the control group who met the criteria for full contamination were considered as always-takers
2. compliance within the first 3 months (i.e. in the full compliance or early-onset application categories in *Table 3*) – participants in the control group who met the criteria for full or early-onset contamination were considered as always-takers.

For children with incomplete data on compliance/contamination, the assumptions described above were used to categorise their compliance/contamination.

Subgroup analysis of the primary outcome

Exploratory subgroup analyses were conducted by including appropriate interaction terms in the regression model for the following variables:

1. Number of *FLG* mutations (no *FLG* mutation vs. one or two *FLG* mutations).
2. Number of immediate family members with atopic disease (one, two or more than two).
3. Number of immediate family members with eczema (zero, one, two or more).
4. Season of birth (spring – born in March, April or May, summer, autumn, winter).
5. Water hardness (dichotomised into hard/very hard and moderate/soft).
6. Parental-reported regular use of probiotic supplements during pregnancy (yes/no).

Subgroup analyses one to three were specified in the protocol and subgroup analyses four to six were specified in the SAP prior to database lock for the primary outcome.

The *FLG* subgroup analysis included children whose mother and father were reported to be of white European ethnicity, since the mutations tested are most prevalent in the white European population. Children who were found to have at least one mutation (regardless of ethnicity) were also included in this subgroup analysis but children of other ethnicities without *FLG* mutations were excluded because the genotyping may have been a false-negative result.

Secondary outcomes

For binary secondary outcomes, the adjusted RR and difference in risk were estimated using the analysis model specified for the primary outcome.

Time to onset of eczema was presented descriptively by showing the cumulative percentage of children with eczema at 3, 6, 12, 18 and 24 months in a bar graph and table and presented separately according to: first parental report of a clinical diagnosis of eczema and first topical corticosteroid and/or immunosuppressant prescription for eczema.

Additional analyses were also performed for the main food allergy outcome of confirmed diagnosis of food allergy at 24 months to any of milk, egg or peanut. Sensitivity analyses were conducted using multiple imputation for missing outcomes as described above and repeating the analysis including

panel decisions of 'unclear – possible food allergy' as allergic and 'unclear – food allergy unlikely' as not allergic. The CACE was also estimated for the confirmed food allergy outcome (using methods described above). Exploratory subgroup analyses were conducted by including appropriate interaction terms in the regression model for the following variables: number of *FLG* mutations, number of immediate family members with atopic disease and number of immediate family members with eczema.

Safety outcomes

The adjusted incidence rate ratio for the number of skin infections reported per child was estimated using generalised estimating equations with a negative binomial family and log link with an exchangeable correlation matrix to account for randomisation being stratified by centre and number of immediate family members with atopic disease (one, two or more than two) included as a covariate. Slippage incidents were compared between allocated groups as a binary variable (any slippages reported in the first year/none) using the same analysis model as specified for the primary outcome.

For each questionnaire time point, parental-reported skin infections and slippage incidents since the last questionnaire were also presented descriptively by allocated group and parental-reported emollient/moisturiser use (none/some/widespread over the majority of the child's body at least 3 or more days per week).

Tertiary outcomes

The analysis of the tertiary outcomes was in keeping with the analysis of the primary and secondary outcomes. Analysis was according to randomised group, regardless of adherence with allocation and estimates of the intervention effect are presented with 95% CIs. The main analysis of the tertiary outcomes assumed that missing outcomes were MAR, that, it does not depend on the unobserved outcomes given the observed data.

Analysis of binary tertiary outcomes at 36, 48 and 60 months used mixed-effects logistic regression model, which gives valid inferences when data are assumed MAR.[65] The models included the outcome collected at earlier time points in the trial (i.e. 12 and 24 months where applicable) as dependent variables and adjusted for the randomisation stratification variables, using a fixed effect for the number of immediate family members with atopic disease (one, two, or more than two) and a random effect for the recruiting centre, and a random effect for participant. Models included an allocated treatment-by-time interaction to estimate the between-group difference at each follow-up time point and where technically possible an interaction between number of immediate family members with atopic disease and time. Adjusted risk differences and adjusted risk ratios along with corresponding 95% CIs were obtained using Stata's margins command with standard errors computed using the delta method.[66]

Multiple imputation using chained equations was used to impute missing outcomes collected at 60 months on parental report of a clinical diagnosis of asthma and parental report of a clinical diagnosis of allergic rhinitis and the derived outcomes of parental report of a clinical diagnosis of eczema from the age of 12 to 60 months and parental report of a clinical diagnosis of food allergy by 60 months. The following variables were used in the imputation model: allocated group, randomisation stratification variables (centre, number of immediate family members with atopic disease) and baseline variables identified as predictive of drop-out (by examination only: mothers age at randomisation, number of other children in the household at randomisation, decile of index of multiple deprivation). Fifty data sets were imputed. Between-group effects in each imputed data set were estimated using a mixed-effects logistic regression model including a fixed effect for randomisation stratification variable of number of immediate family members with atopic disease and a random effect for the recruiting centre. The adjusted risk differences and adjusted risk ratios were computed in each imputed data set (computed using the delta method described above) and combined using Rubin rules for multiply imputed data.

To explore the robustness of the results to the MAR assumption, sensitivity analysis was conducted for the tertiary outcomes of parental report of clinical diagnosis of eczema from the age of 12 to 60 months

and parental report of clinical diagnosis of food allergy by 60 months under a missing not at random (MNAR) assumption using controlled multiple imputation.[67] Delta (δ)-based multiple imputation was used to modify the value imputed under a MAR assumption by a fixed amount to explore how the results change if participants with missing outcomes were more likely to have a worse outcome than predicted (based on the MAR assumption). A range of δ values were used in the sensitivity analysis.

Summary of changes to the protocol

A full list of all substantial amendments to the protocol can be found in *Appendix 2*. All amendments were reviewed by the Sponsor before submission to, and approval by, the Research Ethics Committee and/or the Health Research Authority.

Patient and public involvement

Patient and public involvement (PPI) members of the team provided a vital and valuable role throughout the trial. The aim of PPI was to enhance the design of the main trial.

We were fortunate in being able to conduct a thorough pilot trial as part of a programme grant[42] in preparation for this definitive trial. The pilot RCT was similar in design to the main trial and therefore provided the opportunity for meaningful and significant input from parents who had direct experience of a similar eczema prevention trial. Their opinions and feedback during the design of the main trial were therefore largely based on experience rather than hypothetical scenarios and were key in reaching the final design of this main trial. The main areas of input from parents who had participated in the pilot were around the following issues:

1. **Continue applying emollient until the child was 12 months old rather than the 6 months tested in the pilot.** Parental feedback strongly suggested was that this was acceptable, and in fact, many had chosen to do so anyway in the pilot. Therefore, we felt confident that an extended intervention period of 12 months could be introduced to the main trial without high risk to intervention adherence and this was reflected in the continued high adherence rates during months 6–12 of the intervention period.
2. **Restricting choice of emollient to cream/gel formulation only.** Parents reported in the pilot that they liked having a choice of emollient, so it was important to retain this. However, because the cream/gel formulation was the most popular, the decision was made to offer a choice from *within* this emollient type. A group of parents who had participated in the pilot trial participated in a preference study which, along with mechanistic studies, supported the choice of emollient for the main trial.
3. **Number of visits reduced to only screening and 24-month follow-up**. The pilot trial involved multiple visits to the nurse to check the skin for signs of eczema. The feedback from parents was that although they appreciated the support, they often felt the visits were not necessary, especially when there was nothing wrong with their child's skin. Taking this parental feedback into account and to design a large definitive trial that was more practical to deliver, the interim follow-up was conducted via online questionnaires and via contact with the co-ordinating centre over the telephone, coupled with advice to visit the GP if they had concerns about their child's skin. This was a successful approach in terms of making it a viable trial but contacting the higher proportion of non-completers of online questionnaires than anticipated required more resource from the co-ordinating centre. Incentives to complete the questionnaires were introduced part way through the trial to help with completion rates.
4. **Addition of allergic sensitisation (skin prick) tests at the 24-month visit.** As these tests were not done as part of the pilot trial it was essential to get input from parents into the acceptability of these in the main trial. Parents were generally very keen for their child to receive these tests, but

due to funding restrictions, SPTs were introduced part way through the trial recruitment period. As a result, and because of additional concerns raised by families participating in the main trial about the need to travel to the oral food challenge, the SPTs were introduced as *optional and* separate consent was sought.

Further details of how parental input shaped the main trial design are in the pilot study report.[42]

In the early stages of the trial set-up, the Centre of Evidence Based Dermatology (CEBD) patient panel also provided input. The panel comprises of people with lived experience of a wide range of skin diseases but the input into this trial was sought mainly from members who are parents of children with eczema along with some adults with eczema. The panel reviewed and improved the BEEP patient-facing study documentation, including the participant information sheet (PIS), consent forms and the design and content of the online follow-up questionnaires. These were refined as a result of the feedback to ensure they were suitable. As the main trial progressed through the pilot phase, further feedback was sought from both parents and an eczema support group.

Patient and public involvement representatives were involved in promoting and publicising the trial (through local television and radio) alongside the Chief Investigator. In addition, the PPI team were consulted to help modify documentation to increase up-take of the SPT at the 24-month visit and subsequent food challenges. Their advice was sought to help disseminate the important primary outcome findings. We also decided to share the 2-year primary outcome results directly with participating families[61] as our first audience, that is before the main publication in *The Lancet*. Additional PPI colleagues with lived experience of eczema also participated in our 5-year results reveal meeting and were helpful in contextualising the key results on lack of benefit and possible signals of increased minor skin infections and skin sensitisation.

A PPI representative sat on the TSC and attended the meetings throughout the trial and provided key advice on how to balance the key messages for parents and carers.

Chapter 3 Results

Recruitment

Recruitment to the trial took place between 19 November 2014 and 14 July 2016 and the last baby was randomised on 18 November 2016. During this time, 4963 families were assessed for eligibility, and of these 1484 families consented (30%) (*Figure 6*). The main reason families assessed for eligibility did not consent was due to declining (41% of those assessed). After the baby was born, 1395 babies were randomised (94%). Non-randomisation after consent was mainly as a result of no longer being eligible (*n* = 50), mostly as babies were born preterm (*n* = 41). One baby was randomly assigned in error 62 days

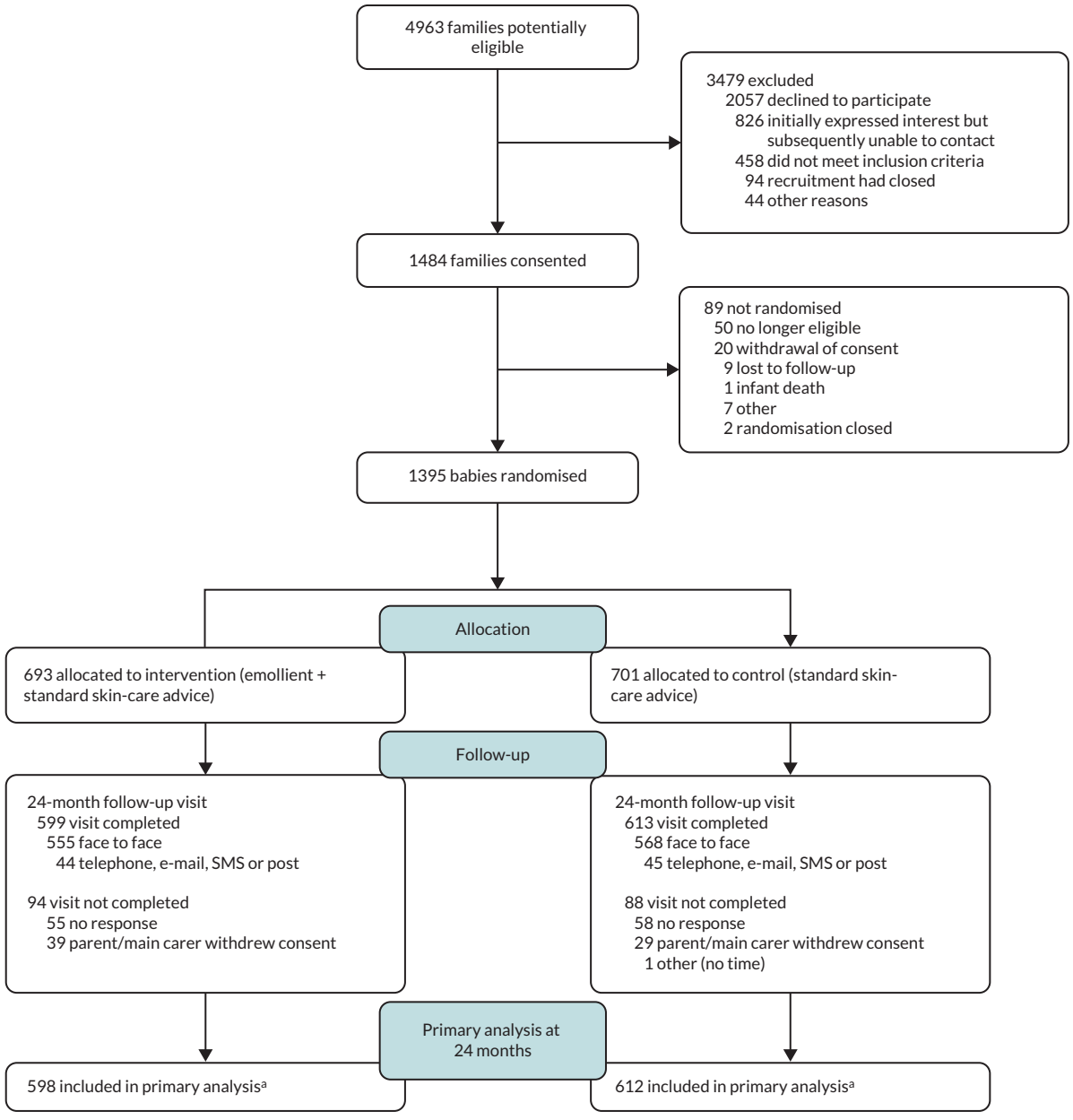

FIGURE 6 Participant flow diagram to 24 months. a, Insufficient data collected to derive primary outcome for two participants (one in each group) at 24 months.

after birth so was not included further. Of the 1394 babies, 693 were randomised to the emollient group and 701 to the control group (randomisation by site presented in *Appendix 3*, *Table 28*). The mean number of days between birth and randomisation was 5.8 [standard deviation (SD) 5.7]. Four babies were randomised more than 21 days after they were born.

Baseline characteristics

Family and baseline baby characteristics were well balanced across groups (*Table 4*). The mean age of the mothers at randomisation was 31 (SD 5.3), 32% of babies were delivered by caesarean section and 82% of babies had at least one first-degree relative with a history of eczema (parent report of doctor diagnosis).

TABLE 4 Baseline characteristics

	Intervention (*n* = 693)	Control (*n* = 701)	Total (*n* = 1394)
Age of mother at randomisation			
Mean (SD)	31.7 (5.3)	31.5 (5.2)	31.6 (5.3)
Minimum, maximum	16, 45	18, 46	16, 46
Singleton pregnancy	690 (100%)	696 (99%)	1386 (99%)
Ethnicity of mother			
White	589 (85%)	601 (86%)	1190 (85%)
Asian	45 (6%)	40 (6%)	85 (6%)
Black	31 (4%)	22 (3%)	53 (4%)
Other	28 (4%)	38 (5%)	66 (5%)
Ethnicity of father			
White	583 (84%)	606 (86%)	1189 (85%)
Asian	45 (6%)	26 (4%)	71 (5%)
Black	30 (4%)	31 (4%)	61 (4%)
Other	26 (4%)	29 (4%)	55 (4%)
Not given	9 (1%)	9 (1%)	18 (1%)
Any furry pets living in house	295 (43%)	302 (43%)	597 (43%)
Maternal antibiotics during pregnancy	210 (30%)	201 (29%)	411 (29%)
Maternal probiotic supplements taken during pregnancy (collected at 6 months)	33/511 (6%)	32/505 (6%)	65/1016 (6%)
Mother has/had a history of eczema (parent report of doctor diagnosis)	348 (50%)	372 (53%)	720 (52%)
At least one first-degree relative with history of eczema (parent report of doctor diagnosis)	563 (81%)	580 (83%)	1143 (82%)
Male infant	374 (54%)	359 (51%)	733 (53%)
Gestation at birth (weeks)			
Median (25th, 75th centile)	40 (39.1, 40.9)	40 (39, 40.9)	40 (39, 40.9)

TABLE 4 Baseline characteristics (*continued*)

	Intervention (*n* = 693)	Control (*n* = 701)	Total (*n* = 1394)
Delivery method			
Vaginal delivery	482 (70%)	472 (67%)	954 (68%)
Caesarean section	211 (30%)	229 (33%)	440 (32%)
No other children living in household at screening	275 (40%)	293 (42%)	568 (41%)
FLG genotype for children with both parents of white ethnicity or with a mutation detected[a]	*n* = 402	*n* = 414	*n* = 816
+/+ (no mutations)	339 (84%)	352 (85%)	691 (85%)
+/− (one *FLG* null mutation)	62 (15%)	60 (14%)	122 (15%)
−/− (two *FLG* null mutations)	1 (< 0.5%)	2 (< 0.5%)	3 (< 0.5%)

a *FLG* genotype obtained from saliva samples at 2-year visit for children whose parents consented to this part of the study. Samples were tested for the four most prevalent *FLG* loss of-function mutations in the white European population. Of the 816 children included in the analysis, 810 had both parents of white ethnicity and a further 6 had parents NOT of white ethnicity but were included in the analysis because a *FLG* null mutation was detected (see *Appendix 3*, *Table 29*). Note in addition a sample was analysed for 155 participants for whom one or both parents were not of white ethnicity but none of the four *FLG* null mutations were detected (see *Appendix 3*, *Table 30*).

Follow-up to 24 months

Follow-up of the infants between 3 and 24 months took place between February 2015 and November 2018. The questionnaires at 3, 6, 12 and 18 months were completed for around 75% at each time point and completion was similar in both groups (*Table 5*). No questionnaires were completed for 14% of participants in both groups (see *Table 5*).

At 24 months, follow-up was completed for 1212 randomised participants (87%, *Figure 6*) and completion was similar in both groups. Most visits (1123 in total) were completed face to face with

TABLE 5 Questionnaire completion at 3, 6, 12 and 18 months

	Intervention (*n* = 693)	Control (*n* = 701)	Total (*n* = 1394)
3 months completed	534 (77%)	524 (75%)	1058 (76%)
6 months completed	530 (76%)	521 (74%)	1051 (75%)
12 months completed	523 (75%)	535 (76%)	1058 (76%)
18 months completed	497 (72%)	512 (73%)	1009 (72%)
Total number of questionnaires completed between 3 and 18 months			
None	99 (14%)	97 (14%)	196 (14%)
One	39 (6%)	45 (6%)	84 (6%)
Two	49 (7%)	51 (7%)	100 (7%)
Three	77 (11%)	87 (12%)	164 (12%)
Four	429 (62%)	421 (60%)	850 (61%)

a research nurse. For 89 participants, where a face-to-face visit was not possible, some data were collected via telephone, e-mail, SMS or post, although for two participants insufficient data were collected to be able to derive the primary outcome. Research nurses completing the skin examination reported becoming aware of which group the child was randomised to (or possibly becoming aware) for 30 participants in the intervention group and 11 participants in the control group. For 12 participants in the intervention group and 6 in the control group, the research nurses reported that this unblinding happened before the examination of the child's skin. Families of infants where no primary outcome data were collected in both groups were more likely to have joined the study after the birth of their baby rather than consenting antenatally, had slightly younger mothers on average when they were born and were more likely to be in a household with other children (see *Appendix 3*, *Table 31*). A slightly greater proportion of girls had primary outcome data collected compared to boys in the intervention group with the opposite observed in the control group (see *Appendix 3*, *Table 31*). The number of family members with a history of atopic disease, delivery method and days between birth and randomisation were similar between infants with and without primary outcome data collected (see *Appendix 3*, *Table 31*).

Of the 1212 infants where the 24-month follow-up visit was completed, SPTs to assess allergic sensitisation were fully completed for 81% in both groups (*Table 6*). Five children were given

TABLE 6 Skin prick test and food allergy assessment completion

	Intervention	Control	Total
Total number of follow-up visits completed	599	613	1212
SPT completion			
Consent to SPT			
No	49 (8%)	58 (9%)	107 (9%)
Yes	508 (85%)	512 (84%)	1020 (84%)
N/A – not face to face[a]	42 (7%)	43 (7%)	85 (7%)
SPT completion			
SPT not done	11 (2%)	7 (1%)	18 (1%)
SPT done	484 (81%)	494 (81%)	978 (81%)
SPT partially done	13 (2%)	11 (2%)	24 (2%)
Food allergy assessment completion			
Food challenge required			
For peanut	76 (13%)	85 (14%)	161 (13%)
For cow's milk	32 (5%)	28 (5%)	60 (5%)
For egg	83 (14%)	73 (12%)	156 (13%)
For at least one of these three foods	133 (22%)	125 (20%)	258 (21%)
Food challenge took place			
For peanut	22 (4%)	19 (3%)	41 (3%)
For cow's milk	5 (1%)	1 (< 0.5%)	6 (< 0.5%)
For egg	24 (4%)	11 (2%)	35 (3%)
For at least one of these three foods	41 (7%)	28 (5%)	69 (6%)

TABLE 6 Skin prick test and food allergy assessment completion (*continued*)

	Intervention	Control	Total
Diagnosis method where food challenge required			
For peanut			
By food challenge	22 (29%)	19 (22%)	41 (25%)
Panel diagnosis – probable food allergy/no food allergy[b]	33 (43%)	40 (47%)	73 (45%)
Panel diagnosis – possible food allergy/food allergy unlikely unclear[c]	21 (28%)	26 (31%)	47 (29%)
n	76	85	161
For cow's milk			
By food challenge	5 (16%)	1 (4%)	6 (10%)
Panel diagnosis – probable food allergy/no food allergy[b]	22 (69%)	22 (79%)	44 (73%)
Panel diagnosis – possible food allergy/food allergy unlikely unclear[c]	5 (16%)	5 (18%)	10 (17%)
n	32	28	60
For egg			
By food challenge	24 (29%)	11 (15%)	35 (22%)
Panel diagnosis – probable food allergy/no food allergy[b]	43 (52%)	45 (62%)	88 (56%)
Panel diagnosis – possible food allergy/food allergy unlikely unclear[c]	16 (19%)	17 (23%)	33 (21%)
n	83	73	156

a Four families where the 24-month visit was initially conducted on the telephone consented to the SPT.
b Panel consensus decision of probable food allergy or no food allergy included in main analysis of confirmed food allergy outcome at 24 months.
c Panel consensus decision of food allergy possible or food allergy unlikely included in sensitivity analysis for the main food allergy outcome at 24 months.

Notes
Children could have food challenges for more than one food.
Percentages for SPT completion and food allergy assessment completion use the number with the 24-month follow-up visit as the denominator. Percentages for diagnosis method for each food use the number requiring a food challenge for the food.

antihistamines after the SPT. No children had a serious allergic reaction to the SPTs requiring the use of an auto adrenaline injector.

Based on the results of the SPTs and/or parent report of consumption and reaction to milk, egg and peanut, 258 children were invited to a food challenge for at least one of the three foods with similar numbers invited in the two groups (see *Table 6*). At least one food challenge took place for 69 children (27%). Similar numbers in each group had food challenges for peanut and cow's milk. Twice as many children in the intervention group had a food challenge for egg compared to the control group (24 vs. 11). There were no incidents of the person completing the food challenge becoming unblinded to the group that the child was randomised to. The main reason that food challenges were not conducted was due to parents being unwilling to participate or due to the travelling distance to the two centres where the food challenges were conducted. For allergy to each food, more than 75% of diagnoses were made by panel consensus due to food challenges not being conducted. For some of these children, the panel made a diagnosis of possible food allergy or food allergy unlikely where there was insufficient information available to make a more definitive diagnosis; these diagnoses were included in a sensitivity analysis for the main food allergy outcome (see *Table 6*).

Adherence with the allocated intervention

For families in the intervention group, 509 (73%) responded to the telephone call at around 2 weeks to check whether they had received the skin-care pack and emollients, and to collect information on the date they started applying the emollient to the infant. Of those responding, the median age that families reported starting to apply the emollient was 11 days after birth [interquartile range (IQR) 7–17], and 452 (89%) reported starting to apply the emollient within 3 weeks of birth.

In the year after randomisation, around half of families in the intervention group reported usually applying the emollient every day (*Table 7*) and emollient was applied at least 3 days per week by 75%. Most families reported usually applying the emollient to the arms/legs and trunk and around three-quarters also reported usually applying it to the face/neck. Emollient was most commonly applied once a day and most families reported usually applying the emollient after bathing or showering their child. The small number of parents who said that they had not used the emollient at all at each time point reported several different reasons for this (see *Table 7*).

Of families with complete data on emollient use at each time point, 88% at 3 months, 82% at 6 months and 74% at 12 months reported using the emollient at least 3 days per week over the majority of the child's body (compliance, *Table 7*). Complete data on adherence over the first year were collected for 442 infants (64%) and of these 311 (70%) infants were considered fully compliant with the intervention (as defined in *Table 3*). Using the conservative assumptions described in the *Statistical methods* section for

TABLE 7 Parental report of study emollient use in the year after randomisation

	3 months	6 months	12 months
Usual frequency of emollient use			
Never	20 (4%)	33 (6%)	58 (11%)
Once or twice a week	34 (6%)	53 (10%)	68 (13%)
3 or 4 days a week	75 (14%)	61 (12%)	74 (15%)
5 or 6 days a week	104 (20%)	84 (16%)	59 (12%)
Every day	299 (56%)	289 (56%)	248 (49%)
n	532	520	507
Emollient usually applied to			
Face/neck	398 (75%)	397 (76%)	351 (69%)
Arms/legs	508 (95%)	480 (92%)	448 (88%)
Trunk	483 (91%)	464 (89%)	427 (84%)
At least two of the areas above	495 (93%)	472 (91%)	438 (86%)
n	533	519	508
Usual number of applications per day			
None	17 (3%)	31 (6%)	50 (10%)
Once	422 (79%)	382 (74%)	362 (72%)
Twice	63 (12%)	68 (13%)	69 (14%)
More than twice	30 (6%)	36 (7%)	25 (5%)
n	532	517	506

TABLE 7 Parental report of study emollient use in the year after randomisation (*continued*)

	3 months	6 months	12 months
Emollient use after bathing/showering child			
Never	21 (4%)	37 (7%)	58 (11%)
Sometimes	40 (8%)	38 (7%)	44 (9%)
Usually	471 (89%)	441 (85%)	406 (80%)
n	532	516	508
Reasons if emollient not used at all			
Prescribed or advised to use a different emollient	3	18	31
Advised to stop applying emollient altogether	1	–	2
Not enough time to apply emollient	4	2	4
Baby didn't like	–	1	4
Ran out of emollient	–	–	2
Other	12	10	14
n[a]	20	31	57
Compliance with intervention (used emollient at least 3 days per week over the majority of the child's body[b]*)*			
No	66 (12%)	92 (18%)	131 (26%)
Yes	466 (88%)	427 (82%)	375 (74%)
n	532	519	506

a No reason given for non-use of emollients in two participants at 6 months and for one participant at 12 months.
b The majority of the child's body defined as applying emollient to two or more of the three body areas asked about (face/neck, arms/legs or trunk).

Note
All questions asked about the time period since birth/the previous questionnaire (e.g. last 3 months at 3 and 6 months, and last 6 months at 12 months).

participants with missing questionnaires, full compliance over the first year in the intervention group was estimated to be 51% (350/693) (see *Appendix 3*, *Table 33*).

In the control group, self-directed use of emollients at least 3 days per week to most of the body (contamination) 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 (see *Appendix 3*, *Table 32*).

Washing, feeding and other post-randomisation characteristics between birth and 24 months

Parent report of washing practices at 6, 12 and 24 months in terms of frequency, the products used to wash the child and use of oils in the child's bath water were balanced across the two groups (see *Appendix 3*, *Table 34*). Between 12 and 24 months, just under half of the families in the intervention group and just under 30% in the control group reported using a moisturiser on their child at least 3 days per week to most of the body. This moisturiser use was more common in both groups in children with a parental report of a clinical diagnosis of eczema (see *Appendix 3*, *Table 35*).

At 6 months, parental report of the milk type used to feed their baby since birth and the introduction of solid foods was similar in the two groups (see *Appendix 3*, *Table 36*). Around 40% of babies in both groups had antibiotics in their first year and 50% in their second year of life (see *Appendix 3*, *Table 36*). Other characteristics such as additional children in the household, use of dust mite reduction measures, water softeners fitted in the house and whether the child regularly attended nursery or a playgroup were also similar in both groups (see *Appendix 3*, *Table 36*).

By 24 months, almost all children had eaten foods containing cow's milk and egg and over three-quarters had eaten foods containing peanut (see *Appendix 3*, *Table 37*). The timing of the introduction of these foods was similar in the two groups. The percentage of children who had consumed these three foods recently and frequently at 24 months was also similar in the two groups (see *Appendix 3*, *Table 37*).

Primary outcome: diagnosis of eczema between 12 and 24 months of age

Primary analysis

A diagnosis of eczema between 12 and 24 months, defined as meeting the UKWP Criteria for Atopic Eczema, was present in 139 (23%) of 598 infants in the intervention group and in 150 (25%) of 612 in the control group. The adjusted RR of eczema in the intervention group compared to the control group was 0.95 (95% CI 0.78 to 1.16); *p*-value = 0.61 and adjusted risk difference −1.2% (95% CI −5.9% to 3.6%).

Sensitivity analysis

All sensitivity analyses conducted, including using multiple imputation for missing primary outcome data, were consistent with the primary analysis showing no difference between the two groups in the presence of eczema (*Table 8*).

Secondary analysis

The CACE estimate of the adjusted OR of eczema was 0.78 (95% CI 0.32 to 1.89; *n* = 1210) when compliance was defined as widespread emollient use over the child's body at least 3 or more days per

TABLE 8 Sensitivity analysis for primary outcome of diagnosis of eczema between 12 and 24 months of age

	Intervention	Control	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
Primary analysis				
AE in the previous 12 months using the UKWP Diagnostic Criteria for children under 4 years	139/598 (23%)	150/612 (25%)	0.95 (0.78 to 1.16)	−1.2% (−5.9% to 3.6%)
Sensitivity analyses				
Using data from GP records for participants with no primary outcome data				
AE in the previous 12 months using the UKWP Diagnostic Criteria for children under 4 years or eczema ascertained from GP records	145/624 (23%)	157/639 (25%)	0.95 (0.78 to 1.15)	−1.2% (−5.9% to 3.5%)
According to method of data collection				
For infants with data collected at a face-to-face visit AE in the previous 12 months using the UKWP Diagnostic Criteria for children under 4 years	131/555 (24%)	142/568 (25%)	0.95 (0.77 to 1.16)	−1.3% (−6.3% to 3.7%)

TABLE 8 Sensitivity analysis for primary outcome of diagnosis of eczema between 12 and 24 months of age (*continued*)

	Intervention	Control	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
For infants with data collected via telephone, e-mail, SMS *or post* AE in the previous 12 months using the UKWP Diagnostic Criteria for children under 4 years	8/43 (19%)	8/44 (18%)	1.02 (0.43 to 2.40)	−1.4% (−17.7% to 14.9%)
Replacing the UKWP *criteria definition of visible dermatitis with visible dermatitis anywhere on the body*				
AE in the previous 12 months	147/598 (25%)	161/612 (26%)	0.93 (0.77 to 1.14)	−1.5% (−6.4% to 3.4%)
Using imputation for missing outcome data				
Using multiple imputation model as specified in SAP[a]	23.3% (SE 1.7%)	24.5% (SE 1.8%)	0.96 (0.78 to 1.17)	−1.0% (−5.8% to 3.8%)
Using multiple imputation model including randomisation stratification variables only[b]	23.0% (SE 1.7%)	24.6% (SE 1.7%)	0.94 (0.77 to 1.14)	−1.4% (−6.0% to 3.3%)

SE, standard error.
a See *Statistical methods* section for details of the variables included in the imputation model.
b On checking the imputed values from the multiple imputation model above, it was observed that the percentage of children with each of the food allergy outcomes was higher in the imputed data than in the observed data. Therefore, a simpler multiple imputation model including only allocated group and the randomisation stratification variables with 20 imputations was used to impute the primary outcome and the outcome of food allergy to milk, egg or peanut at 2 years to check the robustness of the results.

week over the first year of life (i.e. full compliance). The CACE estimate of the adjusted OR of eczema based in compliance in the first 3 months was 0.88 (95% CI 0.50 to 1.56; *n* = 1210).

Subgroup analysis

There was no evidence of an interaction effect with allocated group on the risk of eczema according to number of first-degree relatives with atopic disease, number of first-degree relatives with a history of eczema, *FLG* genotype, season of birth, water hardness or regular use of probiotics during pregnancy (see *Figure 7*, see also *Appendix 3*, *Table 38*).

Secondary outcomes

Eczema-related secondary outcomes

There were no differences between the groups in any of the secondary outcomes for eczema, including different definitions of eczema diagnosis (*Table 9*), time to onset of eczema (see *Figure 8*, *Appendix 3*, *Figure 13* and *Table 39*) and severity of eczema (see *Table 9*, *Figure 9* and *Appendix 3*, *Table 40*).

Allergic rhinitis and wheezing at 24 months

The number and percentage of infants with parental-reported allergic rhinitis and wheezing between 12 and 24 months were similar in the two groups (*Table 10*).

Allergic sensitisation at 24 months

There was no evidence of a difference between the two groups in the percentage of infants with allergic sensitisation on SPT overall or to inhalant allergens, and although allergic sensitisation to milk, egg or peanut was more common in the intervention group, the CI for the difference between groups was wide and included the possibility of no effect (adjusted RR 1.36, 95% CI 0.94 to 1.95, *Table 11*).

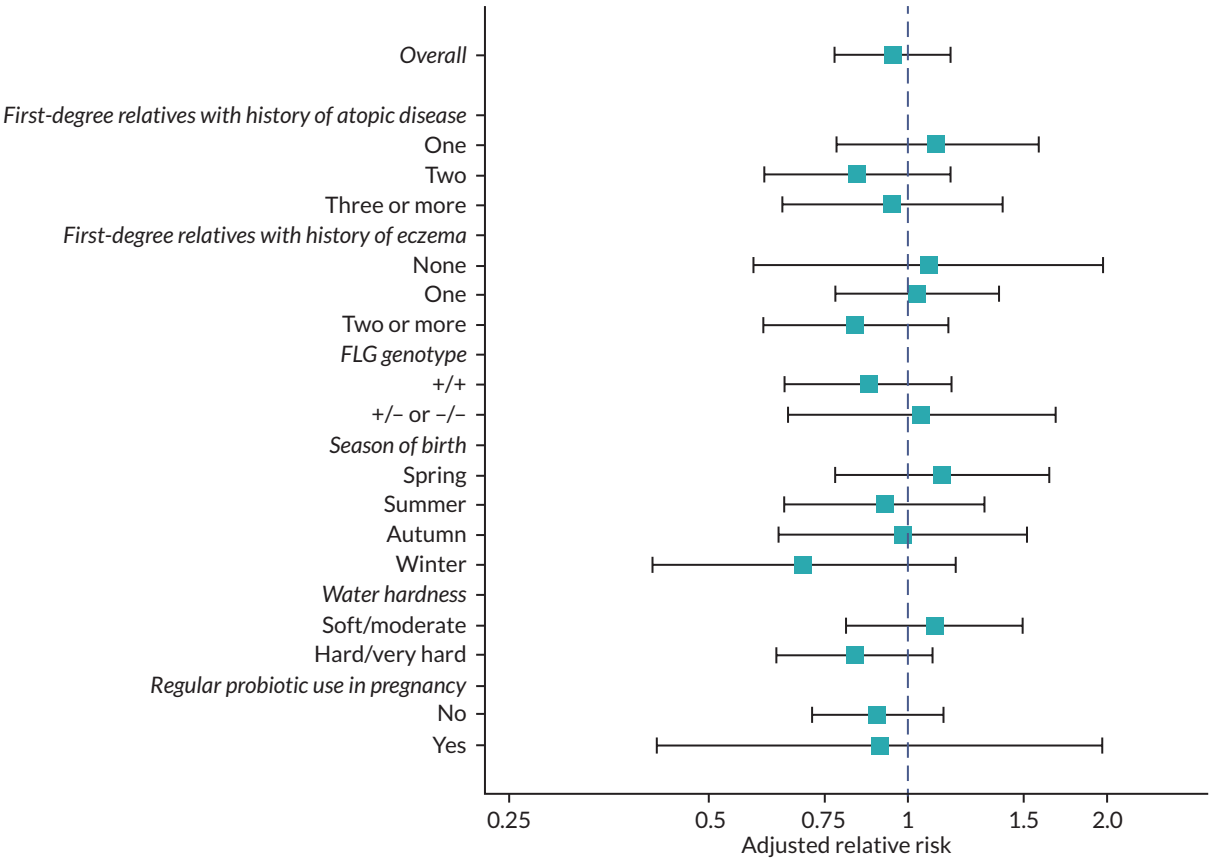

FIGURE 7 Adjusted RR with 95% CIs in each subgroup for primary outcome of diagnosis of eczema between 12 and 24 months.

TABLE 9 Secondary eczema outcomes

	Intervention	Control	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
At 12 months				
Eczema according to UKWP Diagnostic Criteria (parent completion)	103/516 (20%)	107/527 (20%)	0.98 (0.77 to 1.25)	−0.3% (−5.1% to 4.6%)
Moderate/severe/very severe on POEM	52/512 (10%)	49/522 (9%)	1.09 (0.75 to 1.57)	1.0% (−2.5% to 4.6%)
At 24 months				
Presence of visible eczema at 24 months	151/555 (27%)	149/568 (26%)	1.05 (0.86 to 1.27)	1.1% (−4.0% to 6.3%)
Parent report of a clinical diagnosis of eczema between birth and 24 months	266/610 (44%)	282/616 (46%)	0.96 (0.85 to 1.08)	−2.0% (−7.5% to 3.6%)
Eczema according to UKWP Diagnostic Criteria (parent completion[a])	187/599 (31%)	195/612 (32%)	0.98 (0.83 to 1.16)	−0.5% (−5.7% to 4.8%)

TABLE 9 Secondary eczema outcomes (*continued*)

	Intervention	Control	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
Moderate/severe/very severe eczema on EASI	9/553 (2%)	10/567 (2%)	0.93 (0.38 to 2.27)	0.0% (−1.5% to 1.4%)
Moderate/severe/very severe on POEM	58/576 (10%)	51/595 (9%)	1.18 (0.82 to 1.68)	1.7% (−1.6% to 5.0%)

a Questionnaire version, parents not asked questions on visible flexural dermatitis at 2 years.

Parental report of food allergy

For most measures of parental-reported food allergy in the first 2 years, including parental report of a clinical diagnosis of food allergy, there were slightly increased numbers in the intervention group compared with the control group. However, CIs were wide and included the possibility of no difference between the two groups (*Table 12*).

At 12 months, around 20% of parents in both groups reported that their child had had a reaction to at least one food since birth (see *Table 12*). At 24 months, just over 30% of parents reported that their child had had a reaction to at least one food since birth with more immediate reactions (within 2 hours of eating the food) in the intervention group compared to the control group (see *Table 12*). The number of children with a parental report of ever having any reaction to milk, egg or nuts and immediate reactions to milk, egg and peanuts were similar in the two groups at 24 months (see *Table 12*).

Confirmed diagnosis of food allergy

Seventy infants had a confirmed diagnosis of a food allergy to either milk, egg or peanut by either food challenge or panel consensus, which was the predefined main food allergy outcome. There were

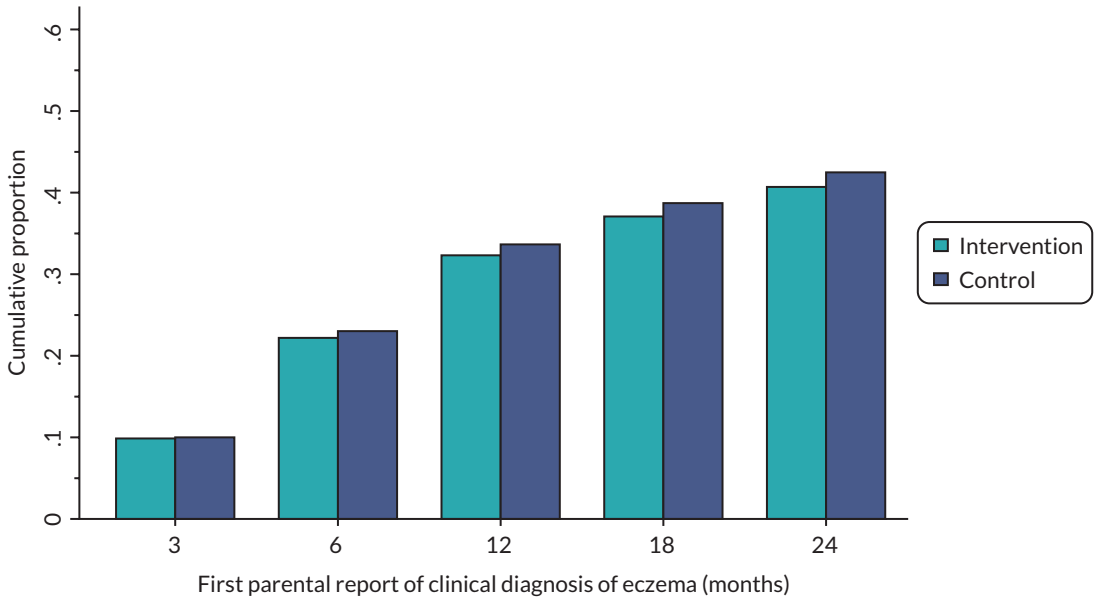

FIGURE 8 Time to onset of eczema based on first parental report of clinical diagnosis of eczema.

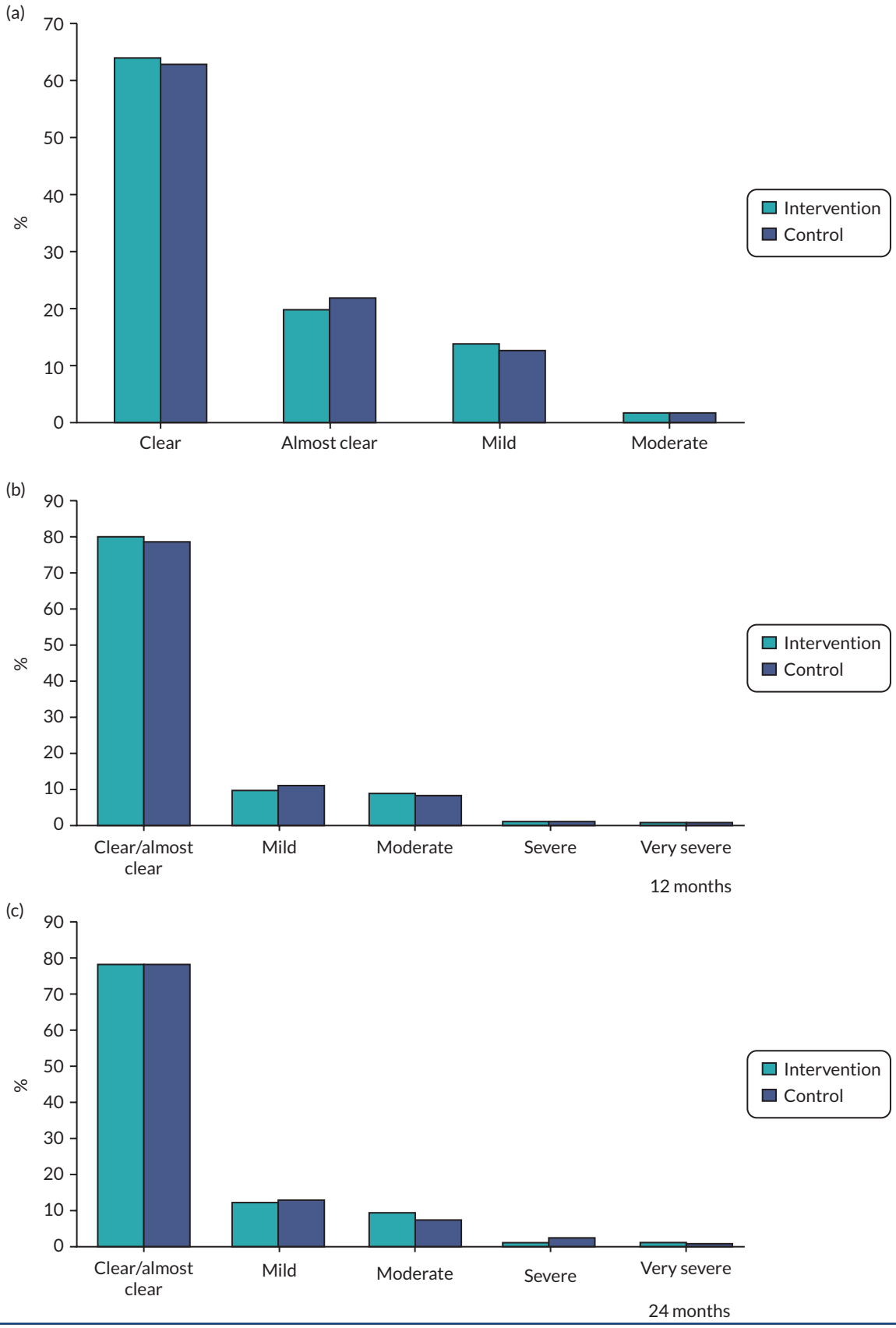

FIGURE 9 Severity of eczema. (a) EASI at 24 months (blinded assessment of severity by research nurse) based on categories in Leshem *et al.*[56] (b) POEM at 12 months (parent-reported severity) based on categories in Charman *et al 2013*. (c) POEM at 24 months. Reproduced from Chalmers *et al.*[1] under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

TABLE 10 Parental-reported allergic rhinitis and wheezing at 24 months

	Intervention (*n* = 572)	Control (*n* = 598)	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
Parental report of allergic rhinitis between 12 and 24 months	174 (30%)	188 (31%)	0.97 (0.82 to 1.15)	−0.8% (−6.2% to 4.5%)
Itchy, watery eyes with the allergic rhinitis	77 (13%)	76 (13%)		
Parental report of wheezing between 12 and 24 months	197 (34%)	191 (32%)	1.07 (0.91 to 1.26)	2.5% (−2.9% to 7.9%)
Number of attacks of wheezing				
None	1 (< 0.5%)	1 (< 0.5%)		
1–3	128 (22%)	130 (22%)		
4–12	52 (9%)	44 (7%)		
More than 12	16 (3%)	16 (3%)		

Note
Parental report of allergic rhinitis and wheezing assessed using a questionnaire completed by parents at the 24-month visit.

TABLE 11 Allergic sensitisation at 24 months

SPT longest wheal diameter	Intervention	Control	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
Cow's milk				
0 mm	461 (94%)	468 (94%)		
1–2 mm	13 (3%)	19 (4%)		
3–6 mm	8 (2%)	6 (1%)		
7 mm	6 (1%)	5 (1%)		
n	488	498		
Egg				
0 mm	435 (89%)	450 (90%)		
1–2 mm	12 (2%)	16 (3%)		
3–6 mm	20 (4%)	17 (3%)		
≥ 7 mm	23 (5%)	16 (3%)		
n	490	499		
Peanut				
0 mm	457 (93%)	468 (93%)		
1–2 mm	15 (3%)	18 (4%)		
3–6 mm	17 (3%)	15 (3%)		
≥ 7 mm	1 (< 0.5%)	1 (< 0.5%)		
n	490	502		

continued

TABLE 11 Allergic sensitisation at 24 months (*continued*)

SPT longest wheal diameter	Intervention	Control	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
Grass pollen				
0 mm	464 (94%)	471 (94%)		
1–2 mm	18 (4%)	18 (4%)		
3–6 mm	10 (2%)	13 (3%)		
≥ 7 mm	–	–		
n	492	502		
Cat				
0 mm	466 (95%)	471 (94%)		
1–2 mm	14 (3%)	16 (3%)		
3–6 mm	11 (2%)	13 (3%)		
≥ 7 mm	1 (< 0.5%)	–		
n	492	500		
Dust mite				
0 mm	432 (88%)	444 (89%)		
1–2 mm	27 (5%)	26 (5%)		
3–6 mm	29 (6%)	26 (5%)		
≥7 mm	5 (1%)	4 (1%)		
n	493	500		
Allergic sensitisation to any allergen (SPT ≥ 3 mm)	88/490 (18%)	74/498 (15%)	1.22 (0.92 to 1.62)	3.1% (−1.5% to 7.7%)
Allergic sensitisation to cow's milk, egg or peanut	58/487 (12%)	44/498 (9%)	1.36 (0.94 to 1.95)	2.9% (−0.9% to 6.8%)
Allergic sensitisation to grass pollen, cat or dust mite	50/492 (10%)	48/499 (10%)	1.07 (0.74 to 1.55)	0.9% (−2.8% to 4.5%)

41 participants with food allergy in the intervention group (7.5%) and 29 in the control group (5.1%) with adjusted RR of 1.47 (95% CI 0.93 to 2.33) (*Table 13*). A greater number of participants in the intervention group were confirmed allergic after a food challenge compared to the control group (15 vs. 6) due to more number of infants in the intervention group being confirmed allergic to egg at the food challenge (12 vs. 3) (see *Appendix 3*, *Table 41*). The number of infants diagnosed as allergic or possibly allergic by panel consensus was similar for each food (see *Appendix 3*, *Table 41*). *Table 13* shows the between-group comparison of food allergy for milk, egg and peanut individually at 24 months as well as sensitivity analysis including infants with a panel consensus decision of food allergy possible or food allergy unlikely.

Results from sensitivity analyses using multiple imputation for missing outcomes of confirmed diagnosis of food allergy were consistent with the main analysis (see *Appendix 3*, *Table 42*). Subgroup analyses for *FLG* genotype and number of first-degree relatives with atopic disease or eczema found no evidence

TABLE 12 Parental-reported food allergy

	Intervention	Control	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
At 12 months				
Parental report of clinical diagnosis of food allergy at 12 months	54/507 (11%)	44/522 (8%)	1.27 (0.87 to 1.85)	2.4% (−1.1% to 6.0%)
Parental report of any food allergy at 12 months	110/505 (22%)	103/523 (20%)	1.11 (0.87 to 1.40)	2.1% (−2.8% to 7.1%)
Reaction to cow's milk	72/508 (14%)	66/525 (13%)		
Reaction to egg	45/507 (9%)	32/525 (6%)		
Reaction to nuts	14/503 (3%)	8/522 (2%)		
Reaction to other food	40/507 (8%)	40/525 (8%)		
Parental report of allergy to cow's milk, egg or nut at 12 months	98/505 (19%)	86/523 (16%)	1.18 (0.91 to 1.53)	3.1% (−1.6% to 7.8%)
At 24 months				
Parental report of clinical diagnosis of food allergy between 12 and 24 months	51/573 (9%)	41/598 (7%)		
Parental report of clinical diagnosis of food allergy at 24 months[a]				
No	421 (73%)	436 (73%)		
Yes	72 (13%)	66 (11%)	1.12 (0.82 to 1.52)	1.5% (−2.8% to 5.7%)
No diagnosis of food allergy reported between 12 and 24 months, not known between birth and 12 months	82 (14%)	97 (16%)		
n	575	599		
Parental report of any food allergy at 24 months	208/574 (36%)	197/597 (33%)	1.10 (0.94 to 1.28)	3.3% (−2.1% to 8.8%)
Reaction to cow's milk	86/575 (15%)	77/598 (13%)		
Reaction to egg	45/575 (8%)	45/598 (8%)		
Reaction to peanut	9/574 (2%)	10/598 (2%)		
Reaction to nuts other than peanut	5/574 (1%)	5/597 (1%)		
Reaction to other food	141/575 (25%)	124/598 (21%)		
Parental report of allergy to cow's milk, egg or nut at 24 months	121/574 (21%)	116/597 (19%)	1.09 (0.87 to 1.36)	1.8% (−2.8% to 6.4%)
Parental report of immediate food allergy to common allergen at 24 months[b,c]	118/574 (21%)	96/597 (16%)	1.28 (1.00 to 1.63)	4.7% (0.2% to 9.1%)
Reaction to cow's milk	61/575 (11%)	46/598 (8%)		
Reaction to egg	44/575 (8%)	41/598 (7%)		
Reaction to peanut	8/574 (1%)	10/598 (2%)		
Reaction to nuts other than peanut	4/574 (1%)	5/597 (1%)		
Reaction to other common food allergen[b]	35/575 (6%)	26/598 (4%)		
Parental report of immediate allergy to cow's milk, egg or peanut at 24 months[c]	98/574 (17%)	83/598 (14%)	1.23 (0.94 to 1.61)	3.3% (−0.9% to 7.4%)

a Nine hundred and ninety-five participants included in analysis model for parent report of clinical diagnosis of food allergy at 24 months. Participants with no diagnosis of food allergy between 12 and 24 months and unknown information between birth and 12 months not included.
b Common food allergens: cow's milk, egg, peanut, other nuts, fish, sesame, wheat, soya and kiwi fruit.
c Immediate food allergy defined as reaction within 2 hours of eating the food.

TABLE 13 Confirmed food allergy at 24 months

	Intervention	Control	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
Main analysis including diagnoses of allergic/not allergic from food challenges and panel consensus				
Allergic to cow's milk[a]	9/571 (1.6%)	8/593 (1.3%)	1.17 (0.45 to 3.01)	0.2% (−1.2% to 1.6%)
Allergic to egg	33/560 (5.9%)	22/581 (3.8%)	1.56 (0.92 to 2.65)	2.1% (−0.4% to 4.6%)
Allergic to peanut	10/555 (1.8%)	8/572 (1.4%)	1.29 (0.51 to 3.25)	0.4% (−1.1% to 1.8%)
Allergic to at least one of milk, egg or peanut	41/547 (7.5%)	29/568 (5.1%)	1.47 (0.93 to 2.33)	2.4% (−0.5% to 5.2%)
Sensitivity analysis also including panel consensus decision of food allergy possible or food allergy unlikely	*n* = 576	*n* = 598		
Allergic to cow's milk[a]	9 (1.6%)	9 (1.5%)	1.04 (0.42 to 2.60)	0.1% (−1.3% to 1.5%)
Allergic to egg	39 (6.8%)	25 (4.2%)	1.63 (1.00 to 2.65)	2.5% (−0.1% to 5.1%)
Allergic to peanut	13 (2.3%)	12 (2.0%)	1.12 (0.51 to 2.45)	0.3% (−1.3% to 2.0%)
Allergic to at least one of milk, egg or peanut	47 (8.2%)	31 (5.2%)	1.59 (1.02 to 2.46)	2.9% (0.0% to 5.7%)

a Unadjusted RR and difference in risk reported for cow's milk. The model including stratification variables did not converge.

of an interaction (see *Appendix 3*, *Table 43*). The CACE could not be estimated when compliance was defined as widespread emollient use over the child's body at least 3 or more days per week over the first year of life due to a problem with the estimation procedure (thought due to the small number with confirmed diagnosis of food allergy). The CACE estimate of the adjusted OR of confirmed food allergy based in compliance in the first 3 months was 1.79 (95% CI 0.62 to 5.14; *n* = 1115).

Safety outcomes

Infant skin infections between birth and 12 months were reported by a slightly greater number of parents in the intervention group than in the control group: 89 in the intervention group (15%) and 67 parents in the control group (11%) with an incidence rate ratio of 1.55 (95% CI 1.15 to 2.09; *Table 14*). The types of skin infections reported by parents were diverse with impetigo and unspecified bacterial, viral or fungal skin infections the most common if known (see *Table 14*).

The number of parents reporting infant slippage incidents within an hour of applying skin-care products to the baby's skin was small (*n* = 26, < 3%) and similar in both groups (see *Table 14*). The trial management team rang parents of children reporting a slippage incident on the questionnaires to find out more about what happened. Of the 20 parents who responded, all confirmed with the trial team that the baby was okay, and that the slippage incident had not caused a serious injury.

Tables showing reported skin infections and slippages according to allocated group and reported emollient use are shown in *Appendix 3*, *Table 44*.

TABLE 14 Parental-reported skin infections and slippages between birth and 12 months

	Intervention	Control	Adjusted difference (95% CI)
Skin infections	*n* = 585	*n* = 585	
Child had at least one skin infection	89 (15%)	67 (11%)	
Number of skin infections reported per child			*Incidence rate ratio*
Mean (SD)	0.23 (0.68)	0.15 (0.46)	1.55 (1.15 to 2.09)
Median (25th, 75th centile)	0 (0, 0)	0 (0, 0)	
Minimum, maximum	0, 9	0, 5	
Type of skin infection			
Child had at least one infection of:			
Impetigo	12 (2%)	7 (1%)	
Folliculitis	2 (< 0.5%)	2 (< 0.5%)	
Boils	1 (< 0.5%)	2 (< 0.5%)	
Other bacterial infection	10 (2%)	12 (2%)	
Other viral infection	19 (3%)	9 (2%)	
Other fungal infection	26 (4%)	14 (2%)	
Other infection	7 (1%)	5 (1%)	
Didn't know	26 (4%)	20 (3%)	
Did not specify	1 (< 0.5%)	1 (< 0.5%)	
Infant slippage incidents	*n* = 584	*n* = 584	
At least one infant slippage incident within an hour of applying skin-care products to the baby's skin	15 (2.6%)	11 (1.9%)	RR: 1.37 (0.63 to 2.97) *Difference in risk:* 0.8% (−0.9% to 2.5%)
Number of questionnaires slippage incidents reported			
One	14 (2%)	11 (2%)	
Two	1 (< 0.5%)	–	

Note
Based on parental reports of infant skin infections and slippages on the 3-, 6- and 12-month questionnaires.
The denominator for skin infections/slippages is children with information provided about skin infections/slippages on a least one of the 3-, 6- or 12-month questionnaires.

Tertiary outcomes

Follow-up for the tertiary outcomes

Follow-up for the tertiary outcomes at 36, 48 and 60 months took place between November 2017 and November 2021. Overall completion was 70% at each time point; however, completion was higher in the control group at all time points, particularly at 48 and 60 months (*Table 15*). At least one questionnaire was completed at 36, 48 or 60 months for 77% in the intervention group and 82% in the control group (see *Table 15*). Ninety-two per cent of participants had data for at least one follow-up time point between birth and 60 months (see *Table 15*).

TABLE 15 Questionnaire completion at 36, 48 and 60 months

	Intervention (*n* = 693)	Control (*n* = 701)	Total (*n* = 1394)
36 months completed	478 (69%)	503 (72%)	981 (70%)
48 months completed	467 (67%)	523 (75%)	990 (71%)
60 months completed	467 (67%)	509 (73%)	976 (70%)
Withdrawal of consent after 24 months	3	1	4
Total number of questionnaires completed between 36 and 60 months			
None	156 (23%)	126 (18%)	282 (20%)
One	61 (9%)	52 (7%)	113 (8%)
Two	77 (11%)	86 (12%)	163 (12%)
Three	399 (58%)	437 (62%)	836 (60%)
Total number of follow-ups completed between birth and 60 months			
None	58 (8%)	54 (8%)	112 (8%)
1–3	94 (14%)	82 (12%)	176 (13%)
4–7	198 (29%)	203 (29%)	401 (29%)
All (8)	343 (49%)	362 (52%)	705 (51%)

The baseline characteristics of infants where the 60-month questionnaire was completed were similar in the two groups (see *Appendix 3*, *Table 45*). Families of infants in both groups where the 60-month questionnaire was not completed were more likely to have joined the study after the birth of their baby rather than consenting antenatally, had slightly younger mothers on average, were more likely to be of non-white ethnicity, were more likely to be in a household with other children, lived in areas on average with lower deciles of the Index of Multiple Deprivation and were less likely to have a first-degree relative with a history of eczema at randomisation (*Appendix 3*, *Table 45*). Follow-up completion at 60 months in both groups was slightly higher for participants who did not have eczema based on the primary outcome at 24 months compared to those with eczema (see *Appendix 3*, *Table 46*). Completion rates were similar according to other secondary outcomes at 24 months (see *Appendix 3*, *Table 46*).

Moisturiser use after 2 years

The percentage of parents reporting frequent moisturiser use (at least three times per week) over all or most of their child's body in the previous year remained higher in the intervention group than the control group through to 60 months. In the intervention group, this frequent all-over moisturiser use in the past year was reported by 31% at 36 months (139/449), 25% at 48 months (114/459) and 22% at 60 months (99/448) compared to 20% at 36 months (94/471), 18% at 48 months (90/500) and 16% at 60 months (76/471) in the control group. In both groups and at all time points, this frequent whole-body moisturiser use was more common in children with a parental report of a clinical diagnosis of eczema (see *Appendix 3*, *Table 35*).

Eczema outcomes

Outcomes for eczema in the previous year at 36, 48 and 60 months were slightly higher in the intervention group than the control group; however, adjusted differences were small, and none were statistically significant. This was consistent across the tertiary outcomes for eczema based on parental report of a clinical diagnosis, parental completion of the UKWP Diagnostic Criteria for eczema (see *Table 16*) and parental opinion of whether their child had eczema (see *Appendix 3*, *Table 48*). There was also no difference between groups in the severity of eczema as measured by parent-reported symptoms on the POEM (see *Table 16* and *Appendix 3*, *Table 40*).

TABLE 16 Tertiary eczema outcomes

	Intervention	Control	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
Presence of eczema in the previous year based on parental report of a clinical diagnosis				
36 months	81/469 (17%)	61/493 (12%)	1.31 (0.97 to 1.76)	4.1% (−0.4% to 8.6%)
48 months	50/462 (11%)	46/509 (9%)	1.20 (0.83 to 1.73)	1.9% (−1.9% to 5.7%)
60 months	49/462 (11%)	34/492 (7%)	1.41 (0.94 to 2.12)	3.1% (−0.5% to 6.6%)
Presence of eczema based on completion by parents of UKWP Diagnostic Criteria				
36 months	119/474 (25%)	109/495 (22%)	1.07 (0.87 to 1.33)	1.7% (−3.4% to 6.8%)
48 months	122/458 (27%)	134/511 (26%)	1.01 (0.82 to 1.24)	0.2% (−5.2% to 5.5%)
60 months	137/461 (30%)	132/495 (27%)	1.07 (0.88 to 1.30)	1.9% (−3.7% to 7.5%)
Moderate, severe or very severe eczema according to POEM				
36 months	30/464 (6%)	37/482 (8%)	0.85 (0.55 to 1.31)	−1.2% (−4.4% to 2.0%)
48 months	32/453 (7%)	45/505 (9%)	0.82 (0.54 to 1.23)	−1.6% (−4.9% to 1.7%)
60 months	42/458 (9%)	39/496 (8%)	1.12 (0.76 to 1.66)	1.0% (−2.4% to 4.5%)

Note
The number of participants and observations included in each analysis model are shown in *Appendix 3*, *Table 47*.

Food allergy outcomes

Longer-term food allergy outcomes were also more common in the intervention than control group. Again, CIs were wide and the estimates for most outcomes were compatible with the role of chance. Parental reports of a reaction to any food within the previous year were significantly higher in the intervention group than the control group at both 36 and 48 months (*Table 17*). However, CIs for the difference between groups in parental report of immediate reactions to foods containing cow's milk, egg or nuts and of a clinical diagnosis of food allergy in the previous year at 36 and 48 months were inconclusive (see *Table 17*). At 60 months, all outcomes relating to food allergy were similar between the two groups including parental report of an immediate reaction to any common food allergen (see *Table 17*). Full details of the foods that parents reported their child reacted are presented in *Appendix 3*, *Table 49*.

Wheezing and allergic rhinitis symptoms

At 36 months, fewer parents in the intervention group reported wheezing or whistling in their child's chest in the previous year (adjusted RR 0.79, 95% CI 0.68 to 0.98; *Table 18*). The percentage of parents reporting that their child had been prescribed an inhaler for wheezing was also lower in the intervention group at 36 months (see *Table 18*). At 48 and 60 months, parental reporting wheezing or whistling in the previous year decreased in both groups with CIs including no difference between groups (see *Table 18*). The percentage of parents reporting that their child had been prescribed an inhaler for wheezing was also similar in the two groups at 48 and 60 months (see *Table 18*).

At 36, 48 and 60 months, the percentage of parents reporting that their child had had symptoms of allergic rhinitis in the previous year were similar in the two groups, with approximately a quarter of parents in each group reporting such symptoms at each time point (see *Table 18*).

Cumulative incidence outcomes

By 60 months, the percentage of parents who had reported that their child had had a clinical diagnosis of eczema or food allergy was similar in the two groups (*Table 19*). Thirty per cent of parents had reported a clinical diagnosis of eczema between 12 and 60 months and 15% of parents reported that their child had a clinical diagnosis of food allergy by 60 months.

TABLE 17 Parental report of reactions to foods and clinical diagnosis of food allergy to 60 months

	Intervention	Control	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
Parental report of reaction to any food within the previous year				
36 months	81/430 (19%)	56/455 (12%)	1.37 (1.02 to 1.85)	5.0% (0.3% to 9.7%)
48 months	59/419 (14%)	43/472 (9%)	1.54 (1.08 to 2.20)	5.0% (0.9% to 9.2%)
60 months	52/432 (12%)	49/459 (11%)	1.07 (0.75 to 1.51)	0.8% (−3.4% to 4.9%)
Parental report of immediate reaction to milk, egg or nuts within the previous year[a]				
36 months	40/437 (9%)	26/468 (6%)	1.44 (0.92 to 2.27)	2.7% (−0.6% to 5.9%)
48 months	29/432 (7%)	21/485 (4%)	1.64 (0.97 to 2.76)	2.8% (−0.2% to 5.7%)
60 months	21/429 (5%)	21/453 (5%)	1.05 (0.60 to 1.84)	0.3% (−2.5% to 3.0%)
Parental report of immediate reaction to any common food allergen within the previous year at 60 months[a,b]	30/424 (7%)	23/447 (5%)	1.36 (0.83 to 2.24)	2.0% (−1.2% to 5.2%)
Parental report of a clinical diagnosis of food allergy within the previous year				
36 months	37/407 (9%)	20/422 (5%)	1.55 (0.96 to 2.49)	3.0% (−0.3% to 6.2%)
48 months	26/453 (6%)	17/498 (3%)	1.54 (0.89 to 2.66)	2.1% (−0.6% to 4.7%)
60 months	19/441 (4%)	15/474 (3%)	1.16 (0.64 to 2.11)	0.6% (−1.8% to 3.0%)

a Immediate defined as reaction within 2 hours of eating the food.
b Common food allergens: cow's milk, egg, nuts, fish, sesame, wheat, soya and kiwi fruit.

Note
The number of participants and observations included in each analysis model are shown in *Appendix 3*, *Table 47*.

TABLE 18 Parental-reported wheezing and allergic rhinitis symptoms to 60 months

	Intervention	Control	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
Parental report of wheezing or whistling in the chest in previous year[a]				
36 months	96/449 (21%)	134/472 (28%)	0.79 (0.64 to 0.98)	−6.0% (−11.4% to −0.5%)
48 months	81/456 (18%)	115/501 (23%)	0.84 (0.66 to 1.07)	−3.7% (−8.7% to 1.3%)
60 months	63/459 (14%)	72/490 (15%)	1.00 (0.74 to 1.35)	0.0% (−4.4% to 4.4%)
Parental report of inhaler prescription for wheezing in the previous year				
36 months	52/445 (12%)	79/461 (17%)		
48 months	62/437 (14%)	71/472 (15%)		
60 months	45/446 (10%)	57/467 (12%)		
Parental report of allergic rhinitis symptoms in previous year[b]				
36 months	120/455 (26%)	123/477 (26%)	1.02 (0.83 to 1.25)	0.5% (−5.2% to 6.2%)
48 months	111/453 (25%)	136/498 (27%)	0.91 (0.74 to 1.12)	−2.5% (−8.1% to 3.1%)
60 months	120/457 (26%)	116/485 (24%)	1.10 (0.89 to 1.35)	2.4% (−3.1% to 8.0%)

TABLE 18 Parental-reported wheezing and allergic rhinitis symptoms to 60 months (*continued*)

	Intervention	Control	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
Parental report of itchy, watery eyes with the allergic rhinitis symptoms in the previous year				
36 months	56/458 (12%)	54/480 (11%)		
48 months	64/455 (14%)	68/500 (14%)		
60 months	72/457 (16%)	65/484 (13%)		

a At 36, 48 and 60 months, parents were asked 'In the last year, has your child had any wheezing or whistling in the chest?'
b At 36, 48 and 60 months, the questionnaire asked 'In the last year, has your child had a problem with sneezing or a runny or blocked nose when he/she did NOT have a cold or the flu?'

Note
The number of participants and observations included in each analysis model are shown in *Appendix 3*, *Table 47*.

Similarly, there was no difference between the two groups in the percentage of parents reporting that their child had had a clinical diagnosis of asthma or allergic rhinitis at 60 months (see *Table 19*).

Sensitivity analyses for parental report of a clinical diagnosis of eczema between 12 and 60 months and food allergy by 60 months exploring the impact of a worse outcome in those with missing data were consistent with the main analysis presented in *Table 19* (see *Appendix 3*, *Table 50*).

There was no evidence of an interaction effect with allocated group on the risk of a parental report of eczema between 12 and 60 months according to *FLG* genotype (*Table 20*).

In exploratory tertiary outcomes for parental-reported reactions to egg or nuts by 60 months, 17% (101/597) of parents reported that their child had had a reaction in the intervention group compared to 13% (80/622) in the control group. The percentage of parents reporting that their child had had an immediate reaction to egg or nuts was similar in the two groups (12% intervention, 10% control, see *Appendix 3*, *Table 51*).

TABLE 19 Parental report of clinical diagnoses of eczema, food allergy, asthma and allergic rhinitis by 60 months

	Intervention	Control	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
Parental report of a clinical diagnosis of eczema between 12 and 60 months[a]	188/608 (31%)	178/631 (28%)	1.10 (0.93 to 1.30)	2.8% (−2.3% to 7.8%)
Parental report of clinical diagnosis of food allergy by 60 months[a]	92/609 (15%)	87/632 (14%)	1.11 (0.84 to 1.45)	1.5% (−2.5% to 5.6%)
Parental report that child ever had clinical diagnosis of asthma or allergic rhinitis by 60 months[b]	63/431 (15%)	60/454 (13%)	1.06 (0.77 to 1.47)	0.9% (−4.0% to 5.8%)
Parental report that child ever had clinical diagnosis of asthma	38/431 (9%)	36/456 (8%)	1.08 (0.71 to 1.64)	0.7% (−3.2% to 4.6%)
Parental report that child ever had clinical diagnosis of allergic rhinitis	36/459 (8%)	35/485 (7%)	1.04 (0.67 to 1.63)	0.3% (−3.4% to 4.1%)

a Outcome derived from responses to questionnaires at 12 (food allergy only), 18 (eczema only), 24, 36, 48 and 60 months.
b Collected on 5-year questionnaire.

Note
Adjusted RR and difference in risk estimated after using multiple imputation for missing outcomes to include all randomised participants. See *Statistical methods* for details of the variables included in the imputation model.

TABLE 20 Exploratory subgroup analysis for parental report of a clinical diagnosis of eczema between 12 and 60 months according to *FLG* genotype

	Intervention	Control	Adjusted interaction effect (RR) (95% CI)	Adjusted interaction effect (risk difference) (95% CI)
***FLG* genotype for children with mother and father of white ethnicity and children of other ethnicity with mutation**	*n* = 402	*n* = 414		
+/+ (no mutations)	104/339 (31%)	100/352 (28%)		
+/− (one *FLG* null mutation)	26/62 (42%)	20/60 (33%)	1.15 (0.71 to 1.88)	6.4% (−11.9% to 24.6%)
−/− (two *FLG* null mutations)	1/1 (100%)	1/2 (50%)		

Note
Two groups for *FLG* genotype used in model including interaction effect: +/+ (no mutations) and +/− or −/− (one or two *FLG* null mutations) due to the small number of participants with two *FLG* null mutations. Adjusted interaction effect estimated using generalised estimating equations with the binomial family and log/identity link respectively, with the number of immediate family members with atopic disease (one, two or more than two) included as a covariate and an exchangeable correlation matrix to account for randomisation being stratified by centre.

Chapter 4 Economic evaluation

Introduction

As described elsewhere in this report, the BEEP trial sought to determine if advising parents to apply an all-over-body application of emollient to their child's skin throughout the first year of life in addition to standard infant skin-care advice might prevent the onset of eczema in children at high risk of allergic disease. The trial took a pragmatic, randomised, controlled, parallel group, multicentre assessor-blind design in which parents were advised to follow the skin-care advice for their child at home with minimal clinical contact. One thousand three hundred and ninety-four newborns at high risk of developing eczema were randomly allocated to the intervention or control arm. Standard practice infant skin-care advice was provided to all parents and those randomised to the intervention arm were also given advice to apply emollient daily to the child's entire body surface area for the first year of the child's life. Families were given a choice of two emollients (Doublebase Gel and Diprobase Cream). Diagnosis of eczema between 12 and 24 months of age (defined as meeting the UKWP Diagnostic criteria) was the primary outcome. The methods and results have been published[1] showing no evidence that daily emollient during the first year of life prevents eczema in high-risk children and some evidence to suggest there may be an increased risk of skin infections.

Data on health resource use and quality of life were captured alongside the trial in order to undertake a within trial economic evaluation. Though concerns have been raised in the literature about so-called paradoxical (not clinically effective but yet found cost effective) conclusions between clinical and economic analyses of the same studies,[68] we report the economic results despite the main clinical findings for several reasons. Firstly, the intervention was preventative in nature and when designing the study, we considered it may be possible for emollients not to be found statistically clinically effective yet estimated to be cost-effective. This is because the intervention is relatively cheap and thus even a small insignificant improvement across a lot of people could potentially be deemed cost-effective. Cost-effectiveness, via changes in resource use and costs, may also have been driven by improved secondary outcomes, such as change in severity of eczema, were such differences found. Secondly, Xu *et al.*[69] published a decision tree model estimating the cost-effectiveness of seven moisturisers used in the first 6 months of life to prevent eczema in high-risk individuals. The study concluded that daily moisturisation is a cost-effective preventative strategy that can reduce the burden of eczema. It is therefore important to report the economic evaluation for this preventative strategy based on individual-level data collected alongside the definitive trial in order to add to the evidence base around whether this preventative strategy is cost effective or not. Thirdly, since the data were collected, it is important to analyse and report it so as to help inform any future or related research that might find this analysis relevant. The current level of economic evidence available for interventions aimed at preventing and treating eczema is limited.[70,71] Understanding resource use, costs and quality of life in early life in high-risk children is of value in its own right and is something this study adds to the literature.

The primary objective of this within-trial economic evaluation was to estimate the cost-effectiveness of advice to provide daily all-over-body application of emollient during the first year of life for preventing AE in high-risk children over a 2-year time horizon. A sensitivity analysis is undertaken to estimate the medium-term cost-effectiveness at 5 years using a within-trial analysis.

Methods

Overview of economic analysis

The primary analysis forms the base (or reference) case within-trial economic analysis using individual participant-level data collected over 2 years from the BEEP trial to compare the cost-effectiveness of

providing parents with advice to apply an all-over-body application of emollient daily in addition to standard skin-care advice compared to standard skin-care advice alone. This comparison was chosen to enable us to estimate the additional costs and benefits over usual care. The time horizon was chosen to be consistent with the time points used for the clinical study. The base-case analysis undertakes a cost-effectiveness analysis (CEA) from an NHS perspective in terms of the difference in proportion of cases without eczema. A secondary analysis was undertaken using a cost–utility approach; this was chosen as the secondary analysis due to uncertainties about how best to capture child health utilities especially in the very young.[72–74]

The evaluation was undertaken in line with published guidelines for the economic evaluation of health-care interventions as appropriate.[75–79] After analysis had started NICE published updated guidance,[80] which changed the preferred mapping function to be used in reference case analyses from that published by van Hout *et al.*[81] to that published by Hernandez Alava *et al.*[82,83] Since the analysis started prior to the change in guidelines we have adhered to the earlier guidelines, which for the most part is unchanged, and given the study results is unlikely to be significant in the conclusions reached.[78]

A health economic analysis plan was written and reviewed prior to the trial database being locked, the health economics analysis plan (HEAP) is publicly available.[47]

Identifying and measuring resource use

In keeping with the trial being conducted in the UK, where the NHS provides publicly funded health care, the analysis takes a health service perspective which is also in line with the NICE reference case.[78] Disease-specific (eczema, asthma, and rhinitis) resource use was collected via online or postal paper questionnaires completed by participants at 3, 6, 12, 18 and 24 months. Personal social service (PSS) resource use was not captured explicitly, as it was anticipated that these types of services would not be accessed for the diseases of interest. Since the trial was light touch, in that after recruitment participants only had one face-to-face contact at 2 years, the resource use data collected were limited to NHS resource use relevant to the diseases of interest and did not collect any costs incurred by the family or wider society. This enabled us to keep the respondent burden low while still meeting the requirement of the base case to capture the intervention costs to the NHS and the participant's wider disease-specific resource use of the NHS. Resource use related to food allergies was not collected as this aspect was added to the trial rather than included from the outset. Patient and public involvement members of the research team were involved in the design of the questionnaires.

Valuing costs

The cost of the intervention was estimated using data collected by the NCTU and costed using published unit costs for Doublebase Gel and Diprobase Cream in the prescription cost analysis (PCA).[84] In the trial, the emollients were posted to participants homes but in practice if these were rolled out, people would collect these via repeat prescription from their GP surgery/pharmacy. As a result, these postage costs were not included in the economic evaluation.

Resource use relevant to the NHS perspective was valued using UK unit costs (Great British pounds) for the most current price year available at the start of the analysis (2019–20). Unit costs were identified from published sources and are clearly reported in the *Results* section.

A mean cost (SD) per participant per arm was estimated for 2 years.

Identifying, measuring and valuing outcomes

The primary economic outcome measure was incremental cost per percentage decrease in risk of eczema, a CEA. Secondary analysis reports a cost–utility analysis (CUA) where QALYs are estimated using utility scores obtained from the parental proxy CHU-9D instrument at 24 months. The CHU-9D is a generic preference-based measure of health-related quality-of-life instrument that asks how a child is today on nine questions (worries, sad, pain, tired, annoyed, schoolwork/homework, sleep, daily routine,

activities) each with five response levels (ranging from no difficulty through to a lot or cannot do). We used the additional guidance given to us by the developer of the CHU-9D. This guidance provided extra wording to help parents of younger children understand how to answer questions 6 (schoolwork/homework), 8 (daily routine) and 9 (join in activities) given their child was of pre-school age. Utility ranges from 0.33 (worst health-related quality of life) through to 1 (best health-related quality of life).[50] We also elicited utility scores for the main parent/carer using the EQ-5D-5L at baseline, and 24 months. The EQ-5D-5L is a generic preference-based measure of health-related quality-of-life instrument with five dimensions (mobility, pain/discomfort, usual activities, self-care, anxiety/depression) with five levels ranging from no problems through to unable to or extreme problems. Responses were converted to utility scores using the EQ-5D-5L Crosswalk UK preference weights as this was in line with recommendations at the point analysis started. Utility ranges from −0.594 to 1.[81]

In the CUA, the responses received on the quality-of-life instruments were converted to utility scores using the Stevens, 2012 valuation set for the CHU-9D and UK preference weights published by van Hout *et al.*[81] for parental EQ-5D-5L. Utility values were used to estimate QALYs over 24 and 60 months, using both linear interpolation and area under the curve analysis with and without baseline adjustment.[85] Child utility was assumed to be 1 (perfect health) at baseline, where baseline represented birth, for all participants. This was assumed because such instruments are not appropriate to ask at such a young age and babies were not eligible for inclusion in the study if they had a serious health issue or severe widespread skin condition at birth. The health-related quality of life for the main carer was elicited using the EQ-5D-5L in order to explore whether, if significantly fewer infants developed eczema, there might be any health spillover effects. Parental QALYs were estimated in the same way using baseline, and 24-month utility derived from the EQ-5D-5L. Parental QALYs were not incorporated into the CUA because the appropriate methods to do this are unclear[86] and changes to main parent/carers health resource use and productivity were not also collected.

Economic analysis at primary outcome end point (2 years)

A CEA was planned regardless of what the full clinical results showed in terms of change in eczema cases for the reasons highlighted in the *Introduction* section of *Chapter 4*.

The economic base-case analysis included all randomised participants with complete cost and outcome data available. As the time horizon was 24 months, costs and benefits in months 13–24 were discounted using recommended rates, 3.5% for both.[78]

The main base-case analysis was a CEA, to estimate the incremental cost of preventing an additional case of eczema. Since it is unknown how much decision-makers would be willing to pay to prevent an additional case of eczema, a secondary analysis using the proxy reported CHU-9D to estimate QALYs in a CUA was undertaken and reports incremental cost per QALY as the outcome measure. A cost-effectiveness threshold (λ) of £20,000 (£30,000) per QALY is used in line with NICE guidance.[78]

Mean (SD) resource use and mean (SD) cost per participant are estimated per randomised arm. Mean difference (95% CI) in cost per participant between arms is estimated unadjusted and adjusted [for centre and number of immediate family members with atopic disease (one, two or more than two)]. Mean (SD) utility and mean (SD) QALYs per participant per randomised arm are presented along with mean difference (95% CI) in QALYs between arms unadjusted and adjusted. QALYs for the main carer were also estimated using responses to the EQ-5D-5L and are presented separately.

The unadjusted CEA was analysed using the heabs command[87] in STATA (for which explanatory variables cannot be added to the regression command), while the adjusted analysis used a generalised linear model (GLM) for continuous and binary outcomes assuming costs and outcomes are uncorrelated. The Gaussian distribution was used for the cost GLM model and the binomial for the outcome GLM model.

The identity option is used for the link function for both GLM models. The CUA uses a regression-based approach (seemingly unrelated regression equations).[88]

To determine the level of sampling uncertainty surrounding the mean incremental cost-effectiveness ratios (ICERs) non-parametric bootstrapping was undertaken generating 10,000 estimates of incremental costs and benefits. Cost-effectiveness acceptability curves (CEACs) were also produced, which show the probability that the intervention is cost effective at different values of willingness to pay. STATA MP version 17 was used to conduct the analysis. No subgroup analysis was undertaken as *FLG* mutation was not shown to be important in terms of the clinical effect.[1]

Sensitivity analysis

In the 2-year analysis the cost of emollients was varied in a threshold analysis to explore what cost of emollients would switch the results from cost effective to cost ineffective or vice versa.

The main sensitivity analysis was focused on taking a longer time horizon. It focused on the 5-year economic evaluation, where the primary 2-year CEA and secondary 2-year CUA [see *Economic analysis at primary outcome end point (2 years)*] were repeated using the 5-year data. Disease-specific (eczema, wheezing and rhinitis) resource use was collected via online or postal paper questionnaires completed by participants at 36, 48 and 60 months. The costs are not broken down and reported by individual year (e.g. year 3, 4 and 5) because secondary inpatient stays were collected in a format that did not enable us to see which year they pertained to. As the time horizon was 60 months, costs and benefits in months 13–60 were discounted using recommended rates, 3.5% for both.[89] As part of these analyses, we re-ran the 5-year analysis after removing inpatient hospital costs incurred for wheezing, as it seems unlikely these would have been incurred as a result of having the intervention or not. We did this in order to explore how influential these costs were on the results of the 5-year analysis. In addition, we report the mean utility at 36, 48 and 60 months alongside the mean QALYs at 5 years per participant using the CHU-9D and the EQ-5D-5L for the main carer.

In the base-case economic evaluation, we did not impute missing data; instead, a complete-case analysis was undertaken in line with the clinical analysis. To evaluate the impact of missing data on the cost-effectiveness estimates, multiple imputation was employed for the cost–utility analyses, assuming that the data were MAR and using chained equations to handle the missing cost and outcome data to assess the impact on the conclusions reached.[90] We did not undertake multiple imputation for the cost-effectiveness analyses as we had no baseline costs or effects, and all children were the same age.

There were plans to model the longer-term (i.e. beyond 5 years) costs and benefits of preventing or reducing the severity of eczema if the intervention had been found effective as detailed in the HEAP but this was not undertaken due to the clinical results.

We did not plan to look at the distributional effects, describing how costs and outcomes were distributed across different individuals, as this was not part of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) criteria at the time of writing the HEAP, but given the findings of the clinical study such analysis is unlikely to add much to this study.

This economic evaluation is reported in line with the CHEERS guidance.[77]

Results

The full trial paper[1] provides a detailed description of the final sample size and characteristics at 24 months. Of the 1394 babies randomly assigned to the emollient or control arm at the start of the study, 184 infants and their families either dropped out or were lost to follow-up by the 24-month period. This resulted in a sample of 1210 infants at 24 months: 598 allocated the emollient intervention

alongside standard skin-care advice and 612 allocated standard skin-care advice only. Of these, 598 had complete cost and outcome data in the emollient intervention arm and 610 had this in the control arm (less than % missing) and it is this sample (n = 1208) that is analysed in the base-case CEA at 2 years.

Resource use and costs

Unit costs, together with their source, are presented in *Table 21*.

Intervention resource use and costs

In the 12-month intervention period, the mean number of pots issued per participant in the emollient arm was 4.21 (SD 2.20) (*Table 22*). The associated mean cost of emollients was £28.00 (SD £14.65) per participant in the base case (*Table 23*).

Other health resource use and costs

Resource use between the emollient and control arms was not significantly different (see *Table 22*). *Table 23* reports the disaggregated mean discounted costs per infant for both arms using available case data. In the complete-case analysis, mean cost was £398.23 (SD 1408.39) per child in the emollient arm (n = 598) and £312.16 (SD 1105.04) in the control arm (n = 610). When intervention use was combined

TABLE 21 Unit costs (UK £ sterling, 2019–20)

Resource item	Unit cost (£)	Source (notes)
Intervention		
Doublebase Gel	6.63059	PCA 2020[84]
Diprobase Cream	6.67394	PCA 2020[84]
NHS care		
GP	39.23	PSSRU 2020[91] (9.22 minutes)
Practice nurse	21	PSSRU 2020[91] (0.33 of an hour per patient)
Hospital doctor	85	PSSRU 2020[91] (per half hour)
Hospital nurse	19.8	PSSRU 2020[91] (per 20 minutes)
Health visitor	15.84	PSSRU 2020[91](0.33 of an hour per patient)
Dietician	92	PSSRU 2020[91] (1 hour)
Physiotherapy	82	PSSRU 2020[91] (1 hour)
Pharmacist	12	PSSRU 2020[91] (1 hour)
Paediatric endocrinologist	244	NHS unit costs 2019/2020[89] (1 hour)
Paediatric dermatologist	170	NHS unit costs 2019/2020[89] (1 hour)
Paediatric respiratory medicine	229	NHS unit costs 2019/2020[89] (1 hour)
Paediatric ear nose and throat	124	NHS unit costs 2019/2020[89] (1 hour)
Paediatric clinical immunology and allergy service	247	NHS unit costs 2019/2020[89] (1 hour)
Paediatric ophthalmologist	103	NHS unit costs 2019/2020[89] (1 hour)
Paediatric dentistry	152	NHS unit costs 2019/2020[89] (1 hour)
Hospital admission/overnight stay	1889	NHS unit costs 2019/2020[89]
Medication	Range from 0.74 to 583	PCA 2020[84]

PSSRU, Personal Social Services Research Unit.

TABLE 22 Mean (SD) total NHS resource use (for eczema, rhinitis and wheezing) per infant at 2 years (available case)

	Emollient arm	Control arm	
	Mean ± SD (*n*)	Mean ± SD (*n*)	Mean difference (95% CI)
Intervention	4.21 ± 2.20 (693)	0.00 ± 0.00 (637)	4.21 (4.04 to 4.38)
Doublebase Gel	2.52 ± 2.05 (693)	0.00 ± 0.00 (637)	2.52 (2.36 to 2.68)
Diprobase Cream	1.70 ± 1.54 (693)	0.00 ± 0.00 (637)	1.70 (1.58 to 1.81)
Wider NHS **resource use**			
GP	1.73 ± 3.31 (693)	1.73 ± 2.81 (637)	0.0003 (−0.33 to 0.33)
Practice nurse	0.12 ± 0.53 (693)	0.17 ± 0.80 (637)	−0.06 (−0.13 to 0.02)
Hospital doctor	0.35 ± 1.27 (693)	0.38 ± 1.48 (637)	−0.03 (−0.18 to 0.12)
Hospital nurse	0.02 ± 0.18 (693)	0.03 ± 0.27 (637)	−0.01 (−0.03 to 0.02)
Other health professional	0.14 ± 0.68 (693)	0.18 ± 0.75 (637)	−0.04 (−0.12 to 0.03)
Hospital episode	0.17 ± 1.50 (693)	0.19 ± 1.81 (637)	−0.02 (−0.19 to 0.16)
Medication	3.74 ± 9.84 (693)	3.50 ± 7.71 (637)	0.24 (−0.72 to 1.20)

TABLE 23 Mean (SD) total cost (for eczema, rhinitis and wheezing) per infant at 2 years (£ sterling, 2019–20, unadjusted, available case)

	Emollient arm	Control arm	
	Mean ± SD (*n*)	Mean ± SD (*n*)	Mean difference (95% CI)
Total intervention	28.00 ± 14.65 (693)	0.00 ± 0.00 (637)	28.00 (26.86 to 29.14)
Doublebase Gel	16.69 ± 13.59 (693)	0.00 ± 0.00 (637)	16.69 (15.63 to 17.74)
Diprobase Cream	11.32 ± 10.25 (693)	0.00 ± 0.00 (637)	11.32 (10.52 to 12.11)
Wider NHS **cost**			
GP	67.33 ± 129.01 (693)	67.30 ± 109.54 (637)	0.03 (−12.90 to 12.96)
Practice nurse	2.40 ± 10.89 (693)	3.59 ± 16.77 (637)	−1.19 (−2.70 to 0.32)
Hospital doctor	50.14 ± 207.69 (693)	51.17 ± 226.93 (637)	−1.03 (−24.40 to 22.35)
Hospital nurse	0.40 ± 3.31 (693)	0.56 ± 5.18 (637)	−0.16 (−0.63 to 0.30)
Other health professional (eczema)	6.67 ± 32.99 (693)	10.46 ± 47.42 (637)	−3.79 (−8.15 to 0.58)
Hospital episode	170.32 ± 1106.85 (693)	145.29 ± 950.98 (637)	25.03 (−86.43 to 136.50)
Medication	24.06 ± 83.95 (693)	23.58 ± 79.39 (637)	0.48 (−8.33 to 9.28)
Mean total cost (Int+NHS)	349.32 ± 1314.29 (693)	301.94 ± 1083.61 (637)	47.37 (−82.84 to 177.59)

with other health resource use, the unadjusted mean incremental cost per infant was £86.07 (95% CI £ −57.77 to 229.90; *Table 23*). The difference in total costs between groups largely reflects the cost of the intervention and greater hospital inpatient stays; other NHS costs were not significantly different between groups. The largest component of cost was overnight hospital stays, especially for those infants reporting wheezing.

Outcome measures

Table 24 presents the outcomes for both arms unadjusted on the available-case sample at 2 years. In the complete-case analysis, the proportion of cases without eczema according to the UKWP-AD definition for the emollient arm was 0.7676 (SD 0.4227) (*n* = 598) and 0.7557 (SD 0.4300) for the control arm (*n* = 610) over the 24-month period. In the complete-case analysis, the adjusted incremental difference in proportion of cases without eczema at 2 years was 0.0164 (95% −0.0329 to 0.0656) adjusted or 0.0118 (−0.0359 to 0.0595) unadjusted. Complete responses to the CHU-9D were received from 75.6% (77.3%) of all participants in the intervention (control) arm at 2 years (or 88% of those completing and returning the study questionnaire booklet). Complete responses to the EQ-5D-5L were received from 71.6% to 82.7% (72.5–84.2%) of participants in the intervention (control) arm at baseline and 2 years. The outcomes for the CHU-9D and the EQ-5D-5L are not too dissimilar between the two arms.

Base-case cost-effectiveness analysis at 2 years

Table 25 presents the unadjusted and adjusted results of the CEA in terms of the number of eczema cases diagnosed together with an estimate of the ICER and separately the CEAC for the adjusted

TABLE 24 Mean outcomes to 2 years (unadjusted, available case)

	Intervention (*n* = 693)		Control (*n* = 701)		
	Mean ± SD (*n*)	Missing	Mean ± SD (*n*)	Missing	Mean difference (95% CI)
Child participants					
Proportion without eczema at 24 months (based on UKWP-AD)	0.7676 ± 0.4227 (598)	99	0.7549 ± 0.4305 (612)	89	0.0127 (−0.0355 to 0.0608)
CHU-9D 24 months	0.9349 ± 0.0690 (524)	169	0.9338 ± 0.0685 (541)	160	0.0010 (−0.0071 to 0.0091)
QALYs at 24 months	**1.9030 ± 0.0672 (524)**	**169**	**1.9020 ± 0.0642 (541)**	**160**	**0.0010 (−0.0069 to 0.0089)**
Main carer					
EQ-5D-5L at baseline	0.8560 ± 0.1513 (496)	198	0.8520 ± 0.1580 (508)	193	0.0040 (−0.0152 to 0.0232)
EQ-5D-5L at 24 months	0.9212 ± 0.1417 (573)	120	0.9187 ± 0.1303 (592)	109	0.0024 (−0.0132 to 0.0181)
QALYs – EQ-5D-5L **(parent) (24 months)**	**1.7441 ± 0.2279 (457)**	**236**	**1.7453 ± 0. 2314 (467)**	**234**	**−0.0012 (−0.0308 to 0.0285)**

TABLE 25 Cost-effectiveness and CUA results at 2 years

Analysis (N e, N c)	Incremental cost (UK£) (95% CI)	Incremental effect (95% CI)	ICER	% Cost effective at £20k (£30K)
CEA **base case (CCA, unadjusted)** (598, 610)	86.07 (−57.77 to 229.90)	0.012 (−0.0359 to 0.0600)	£7281 per percentage decrease in risk of eczema	Willingness-to-pay threshold per percentage decrease in risk of eczema unknown.
CEA **base case (CCA, adjusted)** (598, 610)	87.45 (−54.31 to 229.27)	0.0164 (−0.0329, 0.0656)	£5337 per percentage decrease in risk of eczema	
CUA **(CCA,** CHU-9D**, unadjusted)** (524, 542)	81.47 (−80.21 to 243.14)	0.0010 (−0.0069 to 0.0089)	£82,250 per QALY	30% (36%)
CUA **(CCA,** CHU-9D**, adjusted)** (524, 542)	84.28 (−78.36 to 246.93)	0.0010 (−0.0068 to 0.0089)	£82,580 per QALY	29% (36%)

CCA, complete-case analysis.

analysis (*Figure 10*). The incremental difference in cost for the emollient arm (*n* = 598) compared to the control arm (*n* = 610) was £87.45 (95% CI −54.31 to 229.27) (unadjusted this was £86.07, 95% CI £ −57.77 to 229.90). The adjusted incremental difference in proportion without eczema for the emollient arm compared with the control arm was 0.0164 (95% −0.0329 to 0.0656) (unadjusted was 0.012, 95% CI −0.0359 to 0.0600), meaning that the emollient arm had less cases (by a very small margin) of eczema at 24 months. The ICER was £5337 (£7281 unadjusted) per percentage decrease in risk of eczema. The amount decision-makers would be willing to pay per percentage decrease in risk of eczema is unknown, but it can be seen from the CEAC that there is a lot of uncertainty around the probability of the intervention being cost effective, at willingness-to -pay values over £10,000 per percentage decrease in risk of eczema the probability of cost-effectiveness is always < 60 to 72%.

Secondary cost–utility analysis at 2 years

Proxy-reported Child Health Utility instrument-9 domains for the infant

The adjusted incremental difference in cost per infant for the emollient arm (*n* = 524) compared to the control arm (*n* = 542) was £82.28 (95% CI −78.36 to 246.93). The adjusted mean QALYs for infants was very slightly more in the emollient arm, incremental mean difference of 0.0010 (95% CI of −0.0068 to 0.0089), see *Table 25*. This means that the emollient arm was more expensive and slightly more effective than the control arm. The adjusted ICER was £82,580 which, when using a threshold value of £20,000 (£30,000), would not be considered cost-effective.[78] The probability of the intervention being cost-effective at 2 years was 29% (36%) for a threshold value of £20,000 (£30,000) (*Figure 11*).

EuroQol-5 Dimensions, five-level version for the main carer

The adjusted mean difference in the QALYs was close to zero, −0.0012 (95% CI −0.0308 to 0.0285) (see *Table 24*). We did not combine these results into a CUA as we only collected NHS resource use for the infants. However, on average main carers in the emollient arm had slightly lower QALYs than main carers in the control arm.

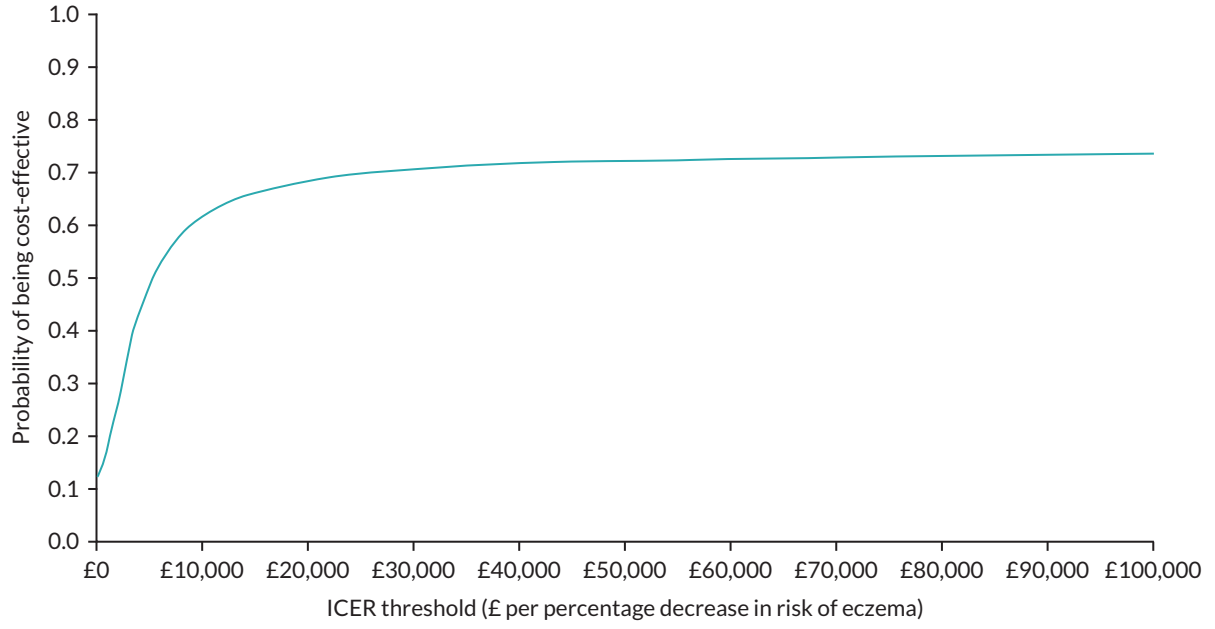

FIGURE 10 Cost-effectiveness acceptability curve for the complete-case adjusted CEA analysis (UKWP-AD) at 2 years.

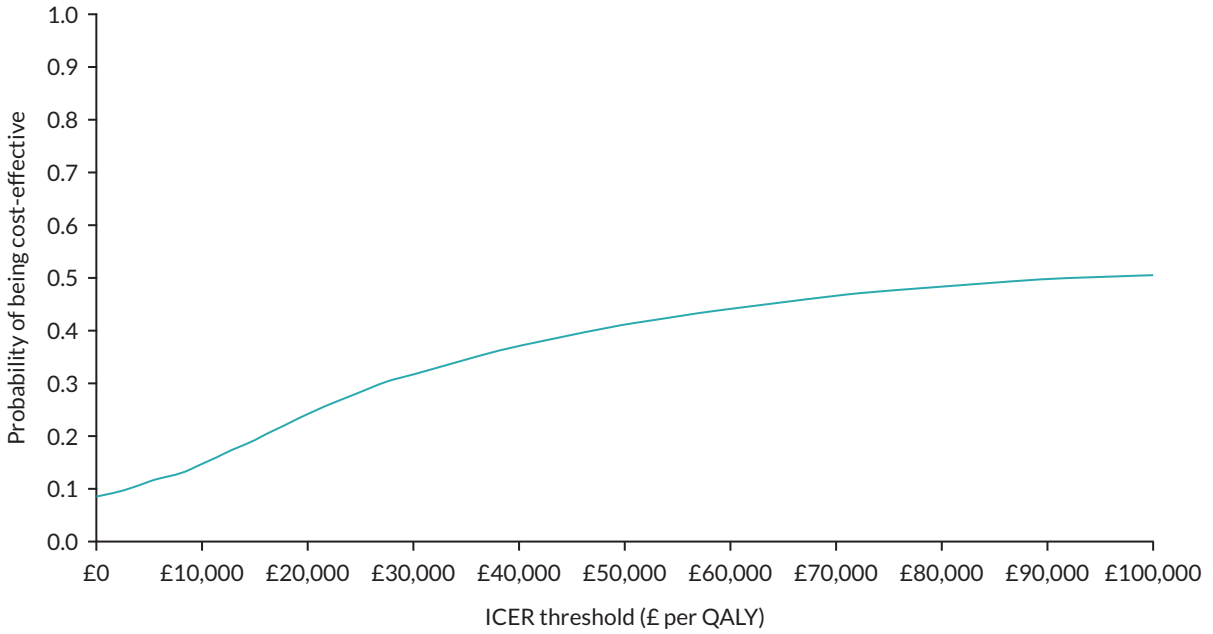

FIGURE 11 Cost-effectiveness acceptability curve for the complete-case adjusted CUA (CHU-9D) at 2 years.

Sensitivity analyses

Cost of emollients

Given we do not know what a decision-maker's willingness to pay per percentage decrease in risk of eczema is, the cost of the emollient was explored in the 2-year adjusted CUA by undertaking a threshold analysis (i.e. the cost of emollients that would switch the intervention from cost-ineffective to cost effective at a willingness to pay of £30,000 per QALY). Doing this, we observed that even at a cost of £0 per emollient item it would not be enough to make this intervention cost-effective unless reduced healthcare use/NHS cost savings could also be found elsewhere.

Cost-effectiveness analysis over 5 years

The complete-case analysis for the CEA at 5 years consisted of 383 (55.3%) children in the intervention arm and 411 (58.6%) children in the control arm and it is this sample that is analysed in the 5-year CEA analysis. In the CUA analysis, this was 354 (36.7%) and 263 (37.5), respectively. Questionnaire response rates declined significantly in years 3–5.

Table 26 reports the mean outcomes per child for both arms for years 3–5 for available case data. The proportion without eczema is slightly higher at 5 years in the control arm, 0.8939 (SD 0.3082) in the intervention arm versus 0.9315 (SD 0.2529) in the control arm [incremental effect −0.0375 (95% CI −0.0732 to 0.0019)], though it should be noted this is based on parental report of a clinical diagnosis of eczema in the previous year unlike at 2 years. The adjusted incremental difference in QALYs (based on proxy report for the CHU-9D) at 5 years for the emollient arm compared with the control was 0.0166 (95% −0.0135 to 0.0467) (unadjusted was 0.0171, 95% CI −0.0138 to 0.0480). Mean QALYs for parental health-related quality of life using the EQ-5D-5L at 5 years was 4.2063 (SD 0.4707) in the intervention arm and 4.1684 (SD 0.5135) in the control arm, with an incremental difference of 0.0379 (95% CI −0.0319 to 0.1077) QALYs (available case). These incremental effects are small, just as they were at 2 years.

The results of the 5-year analysis are shown in *Table 27*. The adjusted incremental cost at 5 years for the emollient arm (n = 383) compared to control (n = 411) was £−106.89 (95% CI −354.66 to 140.88)

TABLE 26 Mean (SD) outcomes to 5 years (unadjusted, available case data)

	Intervention (*n* = 693)		Control (*n* = 701)		
	Mean ± SD (*n*)	Missing	Mean ± SD (*n*)	Missing	Mean difference (95% CI)
Child participants					
Proportion without eczema at 60 months (Parent report of a clinical diagnosis of eczema in the previous year at 60 months)	0.8939 ± 0.3082 (462)	231	0.9315 ± 0.2529 (496)	205	−0.0375 (−0.0732 to 0.0019)
CHU-9D 36 months	0.9283 ± 0.0713 (335)	358	0.9235 ± 0.0671 (350)	351	0.0048 (−0.0056 to 0.0152)
CHU-9D 48 months	0.9337 ± 0.0718 (445)	248	0.9296 ± 0.0754 (480)	221	0.0048 (−0.0056 to 0.0152)
CHU-9D 60 months	0.9398 ± 0.0660 (451)	242	0.9349 ± 0.0696 (472)	229	0.0049 (−0.0039 to 0.0137)
QALYs (CHU-9D) at 60 months	4.424 ± 0.1820 (255)	**438**	4.4053 ± 0.1740 (263)	**438**	0.0181 (−0.0126 to 0.0488)
Main carer					
EQ-5D-5L at 36 months	0.8957 ± 0.1436 (506)	187	0.8931 ± 0.1404 (539)	162	0.0026 (−0.0148 to 0.0200)
EQ-5D-5L at 48 months	0.8813 ± 0.1605 (452)	241	0.8764 ± 0.1666 (491)	210	0.0049 (−0.0160 to 0.0259)
EQ-5D-5L at 60 months	0.8953 ± 0.1504 (452)	241	0.8771 ± 0.1635 (477)	224	0.0181 (−0.0021 to 0.0384)
QALYs (EQ-5D-5L) at 60 months	**4.2063 ± 0.4707 (379)**	**314**	**4.1684 ± 0.5135 (390)**	**311**	**0.0379 (−0.0319 to 0.1077)**

TABLE 27 Five-year sensitivity analysis

Analysis (N e, N c)	Incremental cost (UK£) (95% CI)	Incremental effect (95% CI)	ICER
5-year CEA **(CCA, unadjusted)** (383, 411)	−123.74 (−382.55 to 127.08)	−0.0386 (−0.0776 to 0.0004)	£3312 per percentage decrease in risk of eczema
5-year CEA **(CCA, adjusted)**[a] (383, 411)	−106.89 (−354.66 to 140.88)	−0.0329 (−0.0659 to 0.0002)	£3201 per percentage decrease in risk of eczema
5-year CEA **(CCA, adjusted)**[a] **without inpatient costs due to wheezing** (383, 411)	100.34 (−30.09 to 230.83)	−0.0329 (−0.0658 to 0.0001)	Dominated
5-year CUA **(CCA,** CHU-9D, **unadjusted)** (254, 263)	−336.02 (−670.22 to −1.82)	0.0171 (−0.0138 to 0.0480)	Dominant
5-year CUA **(CCA,** CHU-9D, **adjusted)** (254, 263)	−312.68 (−645.17 to 19.82)	0.0166 (−0.0135 to 0.0467)	Dominant
5-year CUA **(MI,** CHU-9D, **adjusted)** (693, 701)	−49.80 (−306.83 to 207.22)	0.0174 (−0.0045 to 0.0394)	Dominant
5-year CUA **(MI,** CHU-9D, **adjusted) without inpatient costs due to wheezing** (693, 701)	90.92 (−17.06 to 198.90)	0.0173 (−0.0051 to 0.0396)	£5268 per QALY

CCA, complete-case analysis; MI, multiple imputation.
a Site ID was not included in the regression as the model would not converge with it in.

[unadjusted this was £−123.74 (95% CI £−382.55 to 127.08)]. The adjusted incremental difference in proportion without eczema at 5 years for the emollient arm compared with the control was −0.0329 (95% −0.0659 to 0.0002) (unadjusted −0.0386, 95% CI −0.0776 to 0.0004), meaning that the intervention was cost saving but less effective (i.e. associated with slightly more cases of eczema) at 5 years. The adjusted ICER was £3201 (£3312 unadjusted) per percentage decrease in risk of eczema. The amount decision-makers would be willing to pay per percentage decrease in risk of eczema is unknown. It should be noted, however, that the driver for the intervention to be cost saving was the number and cost of inpatient hospital stays incurred as a result of wheezing which were higher in the control group. The control arm had a greater number of participants reporting such costs at 5 years than the intervention arm (22 compared to 7 in the intervention arm) and the control arm had a higher range on the cost incurred than the intervention arm, thus leading the incremental cost to look cost saving for the intervention. When these costs were removed from the analysis, incremental cost became positive (i.e. those in the intervention arm cost more on average) such that since the proportion without eczema was lower in the intervention arm, we would conclude that the intervention is dominated by the control (i.e. we would not recommend the intervention). Such a finding is possible because the costs observed are small and as such a single large cost item can sway the result. It seems quite implausible that the intervention could impact asthma inpatient stays given it was not significantly effective at preventing eczema which would be the first change required in the mechanism of action for it to impact resource use for other atopic diseases.

Table 27 also shows the cost–utility results at 5 years, despite more cases having eczema in the emollient group the intervention was dominant (cheaper and slightly more effective). Dealing with the missing data using multiple imputation did not change this finding. However, incremental costs were higher for the emollient group when high-cost wheezing inpatient stays were excluded, although the ICER was lower than NICE's implicit threshold. It seems likely the CEA is more plausible, although all results reflect the very small values involved.

Discussion

Main findings

In our economic analysis of the main multicentre, pragmatic RCT of high-risk infants, we find no evidence that regular emollient use for the first year of life is cost-effective at 2 years of age. Incremental costs and effects were very small. These results support the findings of the original clinical study.[1] We find that the intervention is more expensive, with potential to prevent only marginally more cases of eczema and generates very slightly more QALYs as measured using the proxy version of the CHU-9D. When the results were adjusted for covariates, the same conclusion held for the primary and secondary outcome measures.

At 5 years almost half the sample had missing cost data. The complete-case CEA found the intervention to be cost saving at 5 years but to have a slightly lower proportion without eczema. However, when inpatient hospital costs for wheezing were removed from the analysis (because < 4% of the sample incurred them and they were associated with high cost), it was found the cost saving of the intervention at 5 years disappeared, and that the CEA was dominated by control (as the intervention was both more costly and less effective).

In the 5-year CUA (as complete case or using multiple imputation) the intervention was found to dominate; the incremental cost was negative indicating the intervention was cost saving and the incremental effect was higher (better quality of life) in the intervention arm. Given the intervention was not clinically effective, the plausibility of these results needs to be questioned. In part, the cost savings found in the 5-year analyses were driven by differences in number and cost of inpatient hospital stays for wheezing between study arms in years 3–5; when these were removed as part of sensitivity analysis, the incremental cost was very small in the CUA. Given there is no evidence the intervention was

clinically effective at preventing eczema, it seems highly unlikely it will have had any impact on wheezing resource use such that the 5-year CUA results are likely to be spurious. That we find this seemingly 'paradoxical'[68] finding at 5 years (particularly in the CUA) is indicative of there being non-significant small incremental costs and effects.

Our results, alongside those of the full trial, have important implications for the existing evidence on whether to use emollients prophylactically in the early years of a high-risk infant's life. This is important to report as a previous economic analysis of emollient use in infants prophylactically[69] reached a different conclusion, that daily emollient use was a cost-effective strategy. Their study was a secondary analysis based on pilot evidence about the effectiveness of emollients, primarily relying on a very large RR estimate of preventing 50% of new eczema cases (n = 108 in complete-case analysis) reported in Simpson et al (2014).[92] Using this estimate along with assumptions over the amount of emollient that would be used and equivalent effectiveness across the seven products compared, the decision tree was reportedly analysed using a CUA approach for a 6-month time horizon. Using data from a larger, definitive study, our results suggest that emollient use as a preventative measure early in life for high-risk infants is not effective or cost-effective taking a 2-year time horizon and this conclusion holds at 5 years given the caveats discussed.

Strengths and limitations

Issues about how to best capture utility for infants and young children for use in economic evaluations are well known.[72–74] In this study, we used the CHU-9D by parental proxy for infants at ages 2, 3, 4 and 5 years old. The CHU-9D is currently validated for children 7 years and upwards[50] and for children aged 5–7 years by parental proxy.[93] We have been unable to find any published studies using the CHU-9D in children under 5 years of age, although the MAGIC trial[94] plans to use the CHU-9D with children as young as 3 years old (Sheffield Clinical Trials Research Unit, 2020). While it is a strength to explore a new approach to add to the growing academic discussion on appropriate HR-QoL measures for young children and infants, it is important to interpret the results tentatively until the use of this instrument in this context is less experimental. Other potential issues such as using parental proxies to value child health also need to be acknowledged.[95]

Response rates to the 36-month questionnaire was comparatively low due to issues distributing this to those first randomised into the study (i.e. the CHU-9D and EQ-5D was inadvertently left out of the questionnaire initially). Completion rates for the questionnaires declined in years 3–5. Together, these may affect the quality and conclusions that can be taken away from the 5-year sensitivity analysis.

The study collected disease-specific resource use but did not capture resource use related to food allergy as this component was not included at the outset of the study. Given the small number of patients who experience clinically diagnosed food allergy and the outcome of the study, this is unlikely to be important. However, it may be appropriate to include resource use related to food allergy in future studies seeking to explore interventions to prevent eczema and other allergic disease.

If a favourable difference in risk had been found at 24 or 60 months and costs and outcomes had not converged at 60 months, a longer-term CEA from birth to 16 years using a model-based analysis would have been undertaken. Given the results, a decision was taken not to develop a longer-term model for this intervention, but future preventative strategies might well benefit from such an approach and from considering a longer time horizon.

Further research

This study is the first we know to have published results using the proxy version of the CHU-9D in children aged as young as 2 years. We did this using the additional guidance developed by the developer of the CHU-9D. We plan to analyse these data further to help inform the design of future studies of

very young children, but in terms of practicality it can be seen in the response rate reported in this chapter that most parents did not have difficulties completing this instrument at 2 years (84% provided complete responses which was not too dissimilar to the completion rate for the main clinical outcome, see *Outcome measures* for further details). There is a need for further research to confirm the validity of the CHU-9D for children and infants aged under 5 years.

Given the results of the clinical and economic study, there is a need for further research looking for potentially preventative strategies that are both effective and cost-effective in order to help reduce the burden of AE.

Conclusions

The daily use of all-over-body application of emollient during the first year of life as described in this study is unlikely to be a cost-effective intervention in preventing AE in high-risk children under 2 years of age if a 2-year time horizon is taken. At 5 years the intervention appears to be cost-effective, but this seemed to reflect the high cost of inpatient hospital stays due to wheezing amongst a small proportion (< 4%) of the sample in a study that shows no clinical benefit for wheezing prevention at 5 years. The 5-year results in this study illustrate what Raftery *et al.*[68] call 'doubly null' results, that is no significant difference in both primary outcome and cost per patient. We seek to avoid 'paradoxical' conclusions at 5 years by exploring and acknowledging the issue (small incremental costs and effects) and factors (such as the differentially high wheezing inpatient costs between arms over years 3–5) that might explain the findings[68] regarding not clinically effective but potentially cost-effective results. Resource allocation decisions should be based on the totality of evidence established by systematic reviews and meta-analysis. Our results add an important contribution to the evidence available to inform any future decisions in this clinical area. Our results also indicate that in terms of practicality it is possible to use the proxy CHU-9D with children as young as 2 years old and further research to explore the validity of this would be useful.

Chapter 5 Discussion

Main findings and interpretation

The overriding finding from BEEP is a lack of any clear benefit from emollients for the prevention of eczema in high-risk children. The findings are remarkably consistent across the range of eczema outcomes used and time points. Results for the main outcomes are robust to sensitivity analyses that account for missing data. In subgroup analysis, there was also no evidence of a difference in the effect of emollients on eczema prevention according to genetic risk of atopic disease, for example, presence of filaggrin gene mutations. No benefit was seen for eczema severity (which could still have been useful in terms of reducing health burden), time to onset of eczema or associated allergic diseases including food allergy, asthma or hay fever. While disappointing, the findings from this study are very important in that they indicate that perhaps skin barrier enhancement using emollients is not an effective pragmatic strategy to prevent eczema and associated diseases, despite earlier interest in this approach. The null result is important because it releases carers from the inconvenience and financial cost of daily emollient application.

Data beyond 2 years

The BEEP study is perhaps a little unusual in that the primary outcome for the 5 years study was elicited at 2 years. The original idea of the 5-year outcome was mainly to collect outcomes on other allergic diseases such as asthma that are potentially difficult to diagnose under the age of 5 years. We also sought to see whether any protective benefits of eczema prevention were transient or sustained as it is unclear from studies on probiotics to prevent eczema whether the benefits diminish over time.[96] The findings of no clinically useful eczema prevention at our primary outcome time point when study children were aged 2 years were upheld in parent-reported 3-, 4- and 5-year data of doctor-diagnosed eczema and other measures. We did not find any evidence of benefit for asthma or hay fever prevention, although we cannot exclude small degrees of benefit. We did not measure additional emollient-related safety outcomes beyond 2 years. None were reported spontaneously from participants for this period. Interestingly, moisturiser use over the body continued at a higher level in the intervention group than in the control group after the 12-month intervention period ceased. Such a 'legacy' effect might be due to routine or a genuine perceived benefit from parents, while some usage would have inevitably reflected the need to use emollients for recently diagnosed eczema.

Health economics

The economic evaluation results are consistent with the clinical findings of the study and finds that at 2 years the use of emollients to prevent eczema is unlikely to be cost-effective. The results at 5 years, if read uncritically, could be interpreted as suggesting the intervention is cost-effective over this longer period. However, incremental costs and effects were small in both the 2- and 5-year analyses. In addition, the costs in the 5-year analysis were largely driven by the small number of participants who incurred inpatient hospital costs due to wheezing and which were unequally distributed between the two study arms. Given the findings elsewhere in this report do not find evidence of benefit for asthma, or indeed hay fever, it seems unlikely these costs were related to the intervention. When they were excluded in a sensitivity analysis the CEA results suggest that the intervention is dominated by control (i.e. the intervention is both more costly and less effective than control).

Possible signals of harms?

Given that the combination of greasy emollients and water in the bathroom is a recipe for very slippery surfaces, one of our main concerns with the use of emollients was slippages. Thankfully, slippages were not common, and none were serious. More importantly, they were similar in intervention and control group and mainly due to non-study emollients for eczema or general skin-care use.

The finding of increased parental report of doctor-diagnosed skin infections in the intervention group is an area of concern. Although none were serious, they nevertheless represent a nuisance to the infant and parents and may involve healthcare contact. Interpretation of the skin infection data is challenging though as the range of skin infections was quite wide and not coherent with the sort of specific infections such as folliculitis due to *S. aureus* that one would normally associate with eczema or occlusion of the skin with emollients.[39] Although we recorded parental report of doctor-diagnosed skin infection, we did not verify these reports or diagnoses with the doctors concerned and whether such infections were confirmed by laboratory investigations. Ideally, more specific investigation of skin infections should be undertaken in ongoing and future emollient prevention studies.

Skin sensitisation and food allergy outcomes; although funded separately, the results of this aspect of the BEEP warrant some brief discussion as food allergy and eczema are so inextricably linked.[97] Our hope was that successful prevention or postponement, of eczema onset might lead to prevention of food allergy, since early-onset IgE-mediated food allergy is thought to be directly caused by early-onset eczema.[98] BEEP trial findings showed no prevention or postponement of eczema, and a possible increase in IgE-mediated food allergy. Food allergy is less common than eczema, so the trial was not adequately powered to detect changes in food allergy prevalence. This means there is significant uncertainty about food allergy outcomes. While most food allergy outcomes, including the a priori defined main food allergy outcome, showed increased food allergy or sensitisation in the intervention group, CIs were wide and, for most analyses, included the possibility of no effect. If emollient application increases risk of IgE-mediated food allergy, then this may be an important mediating factor in the relationship between eczema and food allergy. Although no statistically significant increase in food allergy was seen across most estimates provided by the BEEP study (whether reported at 2, 3, 4 and 5 years or cumulative incidence), there is some uncertainty which ideally needs to be resolved by combining results with other studies. Stimulated by concerns of emollients possibly increasing sensitisation to food allergens and causing food allergy, some members of this team investigated the relationship between frequency of emollient use and food allergy in the enquiring about tolerance study population and found a dose–response relationship between frequency of emollient application and subsequent food allergy.[99] Although this finding was based on observational data, the relationship between emollient use and transcutaneous sensitisation to foods clearly requires further investigation. Other work supports the concept of transcutaneous sensitisation to foods, and this process could potentially be enhanced by the use of lipid-rich emollient, by rubbing the skin and by environmental traces of food allergens on parent hands or infant skin.[100] A European Union project called TRANS-FOODS, led by BEEP co-investigator Carsten Flohr, is building on these BEEP findings to try to understand how transcutaneous sensitisation to foods might be prevented.[101]

Although the possibility of harms as a result of emollients used in early life seems low, small degrees of harm affecting a large population of healthy children can add up to a considerable absolute burden and attention to such concerns become a significant issue for public health intervention studies on otherwise healthy children.

Equality, diversity and inclusion

The majority of participants were recruited via secondary care sites, with the remainder via GP surgeries. While sites were mainly in Central/Northern England and London, it is unlikely that any population

were systematically excluded from taking part by virtue of where they lived in the country or how they were approached.

The majority of children had mothers of white ethnicity (see *Table 4*, 85%), which reflects the overall mix of ethnicity the UK.[102] The high proportion of mothers (52%) or other first-degree relatives (82%) with a history of eczema reflect the inclusion criterion of 'first degree relative with parental-reported doctor diagnosis of eczema, allergic rhinitis or asthma'.

No information was collected directly from mothers on their educational or economic status, but deprivation indices derived from participant's home postcodes included a reasonable range (from 3 to 9).

We were conscious of the fact that severity assessment of eczema involves scoring the intensity of erythema (redness) which is traditionally underestimated in darker skin tones.[103] During our face-to-face training that included tests images, we took measures to ensure that all research nurses were aware of the need to upgrade erythema scores by 1 point as per the EASI guidance by including several images of darker skins in the training material.[104] The quality control test[105] for determining the presence of visible flexural dermatitis which the nurses had to pass in order to undertake the physical assessments also included images of darker skin.

The interpretation of genetic test results is affected by the prevalence of genetic variants in different populations. The most prevalent *FLG* null mutations have been established in the white European population and other ethnicities have population-specific mutations.[34,106,107] To maximise inclusivity in this study we welcomed DNA collection from all participants and all samples were genotyped.

The composition of the BEEP study team was diverse with a range of content expertise from medical (dermatology, paediatrics and primary care) and nursing backgrounds. The team ethos was to always include the important contribution of trial managers, co-ordinators and administrators in emergent publications, and allow opportunities for methodologists such as statisticians (who are rarely afforded an opportunity to be first author) to lead on some publications such as this monograph. The study also allowed the development of early career investigators (such as Maeve Kelleher) who then led on funded parallel projects such as the Cochrane Individual Patient Data meta-analysis of similar studies and also Stella Lartey, who is new to the UK, who benefited from having the opportunity to gain skills in undertaking an economic evaluation in a UK context.

Patient and public involvement

Our trial was unusual for a NIHR Health Technology Assessment (HTA) Programme trial as it was the only study that successfully applied to the specific HTA call at the time to undertake definitive trials as a result of feasibility work carried out in a NIHR Programme Grants for Applied Research (PGfAR) project. Most of the critically important PPI work for the BEEP trial was undertaken in a specific eczema prevention workstream in our PGfAR award entitled 'Setting priorities and reducing uncertainties in the prevention and treatment of people with skin diseases'. PPI in this eczema prevention workstream defined the choice of intervention, duration of the intervention period and nature of follow-up and contact and is described briefly in the methods section of this report and in full elsewhere.[42]

Additional PPI work throughout the trial was critical in informing the way in which the add-on food allergy study and genetics substudy could be offered to participants resulting in both being offered as *optional* studies with a short additional consent procedure that resulted in excellent uptake. In addition, PPI colleagues helped to design, advertise and promote the study and to comment on and disseminate the study results as described in our methods section. It was also very beneficial to have a PPI member in the TSC as they provided an important and varied perspective throughout the trial, and in particular when disseminating the results to parents at 24 and 60 months in order to balance the positive aspects

of the key study message (one less thing to do) versus the signal of possible harm (increased minor skin infections). There were no negative experiences of working with parents, carers and patients as PPI colleagues before and during the BEEP study. Although the whole team was disappointed that emollients did not prevent eczema in the BEEP study, our PPI colleagues were remarkably accepting and objective about the finding and enthusiastic about the need to disseminate our important findings.

Throughout the trial we have received positive feedback from the families and the level of engagement and enthusiasm is evidenced by the high retention rate, particularly for the longer-term follow-up at 36, 48 and 60 months. There were no negative experiences communicated to us from parents and carers who participated in the BEEP study which we suspect is due to the thorough PPI work and preparation undertaken in the proceeding Programme Grant for Applied Research.

Findings in context

The BEEP trial results contrast with the BEEP feasibility study[92] where a signal on a preventive effect on eczema was found. It should be pointed out that the BEEP feasibility study was designed to test feasibility issues and was one-tenth of the size of the main BEEP trial. Reasons for the difference are unclear but could be due to chance or the fact that the outcome in the BEEP feasibility study was measured at 6 months when irritant dermatitis is more common.

Another large independent eczema prevention trial was conducted in Scandinavia (Preventing Atopic Dermatitis and ALLergies in children – PreventADALL) around the same time as BEEP and its primary outcome results for eczema were published alongside the BEEP trial in *The Lancet* in 2020. PreventADALL[108] was a factorial cluster trial of 2397 newborns that included a skin-care intervention (bath additives and facial cream) and a food intervention (early complementary feeding of peanut, cow's milk, wheat and egg) as well as both or neither with two primary outcomes: eczema at 12 months and food allergy at 36 months. That study found that neither the skin intervention nor food intervention reduced eczema development, with a risk difference of 3.1% (95% CI −0.3% to 6.5%) for the skin intervention and 1.0% (95% CI −2.1% to 4.1%) for food intervention, in favour of control. No safety concerns were identified.

The most important overall summary of contextual evidence to frame the BEEP study comes from the Cochrane living review of skin-care interventions to prevent eczema that includes traditional aggregate-based data and individual participant data (IPD), funded by the NIHR through the Research for Patient Benefit programme and a personal fellowship award to MK.[109] Up to July 2020, the review identified 33 trials that included 25,827 participants. Information on one or more of the review's specified outcomes was available in 17 studies that included 5823 participants. Eleven trials with 5217 participants, 10 of which provided IPD, were included in one or more meta-analysis. The review found that risk of eczema by 1–2 years of age was not decreased by interventions for skin barrier enhancement in infancy, with a pooled risk ratio from 7 trials and 3075 participants of 1.03, 95% CI 0.81 to 1.31 (classified as moderate-certainty evidence). Time to onset of eczema was also not earlier for those receiving the intervention, with a pooled hazard ratio from 9 trials and 3349 participants of 0.86, 95% CI 0.65 to 1.14 (classified as moderate-certainty evidence). Interestingly, the skin infections signal from BEEP was also found in other studies, with a pooled increased relative risk of skin infection over the intervention period from 6 trials and 2728 participants of 1.34, 95% CI 1.02 to 1.77 (classified as moderate-certainty evidence). Only one trial (the BEEP study) provided data on food allergy outcomes.

The review failed to find any evidence that specific subgroups based on age, intervention duration, hereditary risk, *FLG* mutation, or classification of intervention type for risk of developing eczema are more likely to benefit from the skin-care interventions. The study also undertook a trial sequential analysis that indicates that further studies of similar interventions are unlikely to change the conclusion that emollients do not reduce eczema risk by more than 30%, although the sequential analysis was

inconclusive for a RR reduction of 20%. The review also included studies which used more sophisticated emollients containing ceramides. The review concluded that skin-care interventions in early life are probably not effective for preventing eczema, and probably increase risk of skin infection, whereas the effects of such interventions on food allergy risk remain uncertain. The review also compared findings from aggregate studies versus those obtained from IPD and found that, although IPD did not significantly change the overall primary outcome risk estimates, certainty of evidence and safety outcomes were significantly different using IPD compared to aggregate data. In addition, subgroup and adherence analyses are only possible with IPD demonstrating the added value of using an IPD approach to meta-analysis.[110]

An update of the review has recently been accepted for publication in the Cochrane Library. This update was planned in order to include the food allergy outcome data from the largest similar trial, PreventADALL. At the timing of the updated review, no new relevant studies with eczema outcomes were published in time to be included, so the eczema outcome at 1–3 years did not change. For food allergy, skin-care interventions during infancy may increase the risk of IgE-mediated food allergy by 1–3 years of age (RR 2.53, 95% CI 0.99 to 6.49; low-certainty evidence; 976 participants, 1 trial) but may not change risk of allergic sensitisation to a food allergen by age 1–3 years (RR 1.05, 95% CI 0.64 to 1.71; low-certainty evidence; 1794 participants, 3 trials). Pre-planned sensitivity analysis assessing food allergy by oral food challenge or investigator assessment showed similar findings (RR 1.45, 95% CI 0.98 to 2.15; low certainty evidence; 2081 participants, 2 trials). The additional results from in this Cochrane review analysis consolidate the results for food allergy diagnosed in this way that were shown in the BEEP study.

Another systematic review on the same topic using aggregate data concluded that emollients do prevent eczema in high-risk children and that the significant protective benefit is only evident where emollients were used continuously to the point of eczema outcome assessment but not when treatment was stopped before eczema assessment.[111] However, that review has been criticised for registering the review retrospectively with limited public record of pre-planned eligibility criteria, outcomes and analysis, including subgroup analyses.[112] That review also failed to include three eligible trials that were included in the Cochrane review rendering it an unreliable source of evidence for informing clinical practice.

Following the update of the Cochrane IPD meta-analysis, the 3-year results for the Scandinavian PreventADALL study has been published.[113] These showed that neither the skin-care intervention nor early complementary feeding of peanut, cow's milk, wheat and egg from age 3 months had any influence on AD (eczema) diagnosis at 36 months. The study found early complementary feeding reduced food allergy (risk difference −1.6%, 95% CI −2.7% to −0.5%; OR 0.4, 95% CI 0.2 to 0.8) but not in the skin intervention group (risk difference 0.4%, 95% CI −0.6% to 1.5%; OR 1.3, 95% CI 0.7 to 2.3), with no evidence of an interaction effect (p = 0.98).

Study strengths and limitations

The strengths of the BEEP trial can be considered using the population, intervention, comparator, outcome framework. Participants were representative of babies born across the UK who would normally be considered at high risk of developing eczema and associated atopic disorders. The intervention was chosen to be acceptable in a previous feasibility study and was shown in pre-study experiments not to paradoxically damage the skin barrier as some emollients have been shown to do.[114] The intervention was simple and cheap and adherence to the intervention was good, especially for study with only two face-to-face contacts with the study team (baseline and at 2 years). Participants in the control group followed standard best advice for infant skin care, and contamination rates with emollients were low (< 20% as specified in our stop/go criteria for study progression). Outcomes were robust and included family reported as well as objective outcomes on the presence of eczema and eczema severity

with objective outcomes measured by trained assessors blinded to allocation status. Unblinding of intervention status prior to skin examination was minimal (12 in the intervention group and 6 in the control group). As some debate exists over the validity of diagnostic criteria for eczema in early life,[115] a range of eczema outcomes were used that showed consistent lack of a preventive effect. Timing of the outcome was also conducted well away from the emollient intervention period in order to avoid any potential inflation of emollient benefit due to the mild anti-inflammatory effect of the emollient concealing mild eczema. The long duration of follow-up meant that any later benefits of emollient prevention could be picked up. Additional data from the add-on genetic study provided useful insights into whether filaggrin gene mutations are an important consideration for disease stratification in such studies. The add-on food allergy study also provided useful data on the feasibility and prevalence of SPT sensitivity to common food allergens in the UK community setting and resulted in a novel pragmatic method of confirming food allergy for those not able to travel to regional test centres for oral food challenges.[59]

In terms of study design, BEEP conforms to a relatively pragmatic design when considered using the PRECIS-2 (PRagmatic Explanatory Continuum Indicator Summary) tool.[116] The large sample size had sufficient power to exclude a moderate reduction of eczema incidence. Various sensitivity analyses have confirmed the stability of the main conclusions. The effects of missing data on the study conclusions have also been thoroughly explored. The independence of the BEEP study from any commercial influence from emollient manufacturers is also a study strength. Risk of bias for the BEEP study has been rated independently in a Cochrane review[109] as low risk of bias for randomisation process, deviations from intended interventions, missing outcome data, outcome measurement and selection of reported results for the eczema outcomes.

The BEEP study has also generated several useful spin-off publications that have contributed to thinking about the design and conduct of eczema prevention trials including how to define an incident case,[6] an algorithm for diagnosing IgE-medicated food allergy,[59] a SWAT to explore strategies for enhancing follow-up in RCTs,[117] an overview of methodological considerations for eczema prevention studies,[32] and the value of hyperlinear palms in evaluating *FLG* mutations.[118]

Study limitations include the risk that BEEP used the 'wrong' emollients. Not all emollients are the same. Some exhibit different physiological effects on skin barrier function in adults with eczema in terms of epidermal water loss, hydration, natural moisturising factor levels and response to irritant challenges.[119] Alternatively, it may be that it is critically important to start emollients immediately after birth. Although we were pleased that families started reporting using emollient at a median of 11 days after birth (IQR 7–17 days), one single-centre industry-funded study[120] has suggested preventive benefit of eczema at 12 months as a result of twice-daily specially formulated emollients applied for 8 weeks of life when started early (63% within 2 weeks). Perhaps the intervention was not intense enough and rather than an 'advice to use' study, an efficacy study whereby emollient application was supervised and measured accurately might have shown benefit. However, such a study would not have been practical and unlikely to be translated into everyday practice. It is also worth pointing out that based on strong user feedback from our BEEP feasibility study, parents wished to have a choice of emollients for the BEEP main study. This meant that the BEEP study used two emollients which might have had slightly different barrier enhancement properties.[44] We were however unable to explore this in a meaningful sensitivity analysis as parents initially received both types of emollients and then chose which emollient they preferred when reordering. Perhaps we were wrong to ignore various forms of transient irritant eczemas that emerge in the first year of life during the intervention period, although other studies that have measured such skin findings at 3, 6 and 12 months have not found any benefit from emollients.[108] As mentioned in the introduction, it is likely that eczema represents a range of distinct phenotypes with different disease trajectories and severity, but such variation is unlikely to affect the interpretation of this study which evaluates the prevention of new onset eczema that corresponds to a well-defined phenotype depicted by the UK diagnostic criteria for eczema. The strongest predictors of eczema onset and subsequent severity are family history of atopic disease and filaggrin gene mutations. Both

were explored in subgroup analyses in this study with neither showing evidence of benefit in such subgroups. Although contamination in our control was considered low (< 20%), perhaps such a degree of contamination was sufficient to mask a small preventive effect. The results of the CACE analysis (with compliance defined as widespread emollient use at least 3 days per week) were consistent with the main analysis of no difference; however, the CIs for the CACE estimate were wider. Due to the pragmatic low-contact efficient study design, we inevitably used parental report for many of the outcomes such as skin infections and allergic diseases at 3, 4 and 5 years. Such unmasked outcome assessment is perhaps a potential source of information bias. We mitigated such bias by mainly asking for parental report of doctor-diagnosed skin infections or allergic disease. We would also argue that capturing parental report of such illnesses are important as not all families who are used to dealing with eczema will necessarily take a child with mild disease to a healthcare professional. Studies comparing parental report of the UK diagnostic criteria for eczema have also shown them to be equally valid when compared with research nurses' assessed findings.[121] The findings from parental reports were also consistent with findings from the research nurse assessors for eczema presence and eczema severity who were masked from intervention or control status at the 2-year primary outcome assessment. Information bias as a result of enthusiasm for the intervention is also perhaps more likely to have resulted in a positive benefit for eczema prevention, whereas the study showed consistent null effects regardless of the timing and choice of outcome. The trial was not powered to detect interaction effects in subgroup analysis meaning that there is considerable uncertainty in the interaction effects (shown through wide 95% CIs) between subgroups and the effect of the intervention including for presence of *FLG* mutations.

Although the spread of our centres was reasonable representative of English cities and towns, we could have been more inclusive by considering translation of written materials at the study outset. Although the proportion of mothers of white ethnicity in BEEP is broadly reflective of the UK, we could have done more to reach out to under-represented groups using such frameworks as INCLUDE that appeared towards the end of this study.[122]

Recommendations for clinical practice

Based on the findings of the BEEP study and the emerging evidence from other similar studies, summarised in an ongoing living systematic review that uses individual patient data meta-analysis, emollients cannot be recommended for primary prevention of eczema. Small benefits cannot be excluded, but the burden of applying whole-body emollients daily for the first year of life is considerable, and uncertainty exists about possible signals of harm in terms of skin infections and food allergy.

The use of emollients for eczema prevention should not be confused with use of emollients for eczema treatment. Emollients should continue to be used as part of standard treatment for eczema along with topical corticosteroids and calcineurin inhibitors and systemic therapies for more severe disease. In addition to treating the symptoms of dry skin associated with eczema, emollients may contribute to reducing flares (secondary prevention).[123] A recent NIHR HTA study suggests that there is little difference between the efficacy of emollient types (creams, ointments, gels or lotions) for eczema treatment in the community but patient and carer preference for each formulation varies.[124]

Recommendations for future research – specific and general

Apart from the PreventADALL study, emollient prevention studies to date have focused on barrier enhancement in early life to prevent eczema in high-risk children on the basis that the preventive fraction is likely to be higher in this group when compared to others. The assumption that potential preventive benefits are likely to be higher in high-risk babies may be untrue, as it is possible that babies born to high-risk families inherit such a strong deviation in immunological responses that any potential benefit of barrier enhancement is overcome by the inherited prevailing immunological dysfunction.

Studies evaluating emollients for the prevention of eczema in all (including lower risk children) may be useful to provide a complete the picture. Such a study (the CASCADE trial)[125] is underway in the USA recruiting around 1250 infant/parent dyads from community settings in Oregon, Colorado, Wisconsin and North Carolina. Future studies should describe and define the phenotype of eczema that develops in the infants participating in prevention studies using well-established diagnostic criteria for defining incident cases[6] and by describing the severity and trajectory of such cases once they develop. Many transient irritant forms of eczema may develop in the first year of life most of which probably do not develop into eczema,[7] so care should be taken in following up such cases to see if they evolve into persistent eczema. Candidate emollients tested in future studies should ideally be tested for their skin barrier properties on infant skin. Measurement of eczema should also be done well away from the intervention period, for example, 1 year after the intervention has ceased as in the BEEP study, in order to avoid masking any potential mild eczema by the use of emollients.

With around 33 similar studies published or in progress, we suggest that enough studies on emollients for eczema prevention in high-risk families have now been set up and/or completed. Large independent high-quality studies are always welcome, but the addition of a lot of smaller studies is unlikely to help as indicated by the trial sequential analysis illustrated in the ongoing Cochrane IPD review. The priority must be to try and include all existing eczema prevention studies in that Cochrane review in some form – preferably individual patient data rather than aggregate data. We predict that there could be a degree of publication bias from some studies funded by companies with a vested interest in showing a positive outcome that claim that specially formulated emollients containing ceramides or natural moisturising factors are useful in preventing eczema. Although such emollients have not appeared to work so far, we cannot exclude the possibility that such newer specialised formulations could work, and we look forward to seeing the authors share their individual patient data of all registered and non-registered trials with the living Cochrane IPD review on this topic. Some degree of heterogeneity of effects between studies is expected since not all emollients are the same. Other studies should also link their choice of emollient to functional studies of the skin barrier. Attention to measuring and pooling potential harms of daily emollients during infancy should be encouraged in all similar future studies, with more refined collection and verification of the types and severity of skin infection. Experimental studies on the role of whole-body emollients as a vehicle for inducing skin sensitisation should also be considered.

In general terms, investing in research to prevent eczema and associated diseases is important given the burden of disease in the UK and worldwide and concerns about increasing prevalence. The variation in eczema prevalence between different environmental settings and variable genetic penetrance indicates that there are important environmental determinants, which may be modifiable. Given the disappointing results of BEEP and other trials on the strategy of skin barrier enhancement in early life using moisturisers, future eczema prevention research might concentrate on strategies to reduce potentially harmful interventions such as frequent bathing, exposure to hard water and/or use of wash products[126] or future molecular mechanisms led by personalised medicine to improve skin barrier formation and function.[127] Other areas warranting further investigation are interventions which might influence early immune development, including nutritional and microbial interventions during pre or postnatal life.[128] There is already some supportive evidence for probiotics during pregnancy/lactation – however the data are heterogeneous and potentially selectively reported, so the probiotic evidence may potentially be clarified through a high-quality individual patient data meta-analysis.[128]

Chapter 6 Conclusions

Despite a compelling rationale and promising early indications of a possible benefit of emollients as a means of preventing eczema from developing in babies born to families with allergic disease, the BEEP study found no evidence to support a clinically useful benefit for emollients when used in this way. The BEEP study found no evidence that advice to use daily emollients for the first year of life can prevent eczema when defined in a range of ways, nor did emollients reduce the severity distribution of eczema or time to onset. The study did not show any other benefits in terms of prevention of associated conditions including food allergy, asthma and hay fever up to the age of 5 years. The intervention delivered in this study is unlikely to be considered cost effective.

Some uncertainty exists around possible harms of emollients used in the first year of life including a possible increase in food allergy and increased parental report of doctor-confirmed skin infections; these uncertainties need to be explored in future studies. The findings of the BEEP study are consistent with other studies that form part of an ongoing living systematic review and meta-analysis.[129]

Based on the BEEP study and other similar studies, advice to use daily emollients for the first year of life cannot be recommended as a method to prevent eczema and associated atopic diseases. This is a useful scientific finding as the burden of applying daily emollients for the first year of life is considerable, so it is one less thing for busy parents to do when coping with allergic disease in the family. Parents often feel guilty for not doing all they can to prevent 'passing on' eczema to their newborn child, so not applying emollients from birth is one less thing for parents to feel they should have done. Apart from testing earlier initiation of emollients and/or more potent skin barrier enhancers as a means of primary prevention, the addition of a lot more 'me too' studies is unlikely to be helpful. Enough research has been set up and conducted on emollients for preventing eczema. The emphasis should be on encouraging those leading existing skin barrier prevention studies to measure potential harms as well as benefits, and to share their individual patient data with the living systematic review in order to add precision to the outcome estimates and to explore the full range of interventions in different populations over the world. Future prevention of eczema should concentrate more on preventing potentially harmful skin-care practices during infancy and on identifying interventions that can influence the course of early skin barrier and immune development.

Additional information

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Lucy E Bradshaw (https://orcid.org/0000-0001-8382-6040**)** (Medical Statistician) contributed to the conception and design of the trial and the acquisition, analysis and interpretation of the data; was responsible for statistical analysis; drafted, reviewed and edited the final report; and was a member of the Trial Management Group (TMG).

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

The study protocol, SAP and HEAP are available on the trial website and the NIHR journals library. All other related documents are available on request to Prof. Hywel C Williams as chief investigator of the BEEP trial, at any point.

Ethics statement

The trial was approved by the NRES Committee West Midlands – Solihull (REC reference 14/WM/0162) on 9 June 2014 prior to the start of recruitment.

Information governance statement

The University of Nottingham is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, the University of Nottingham is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: https://www.nottingham.ac.uk/governance/records-and-information-management/contact.aspx.

Disclosure of interests

***Full disclosure of interests*:** Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the report publication page of NIHR Journals Library at https://doi.org/10.3310/RHDN9613.

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

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Bradshaw LE, Haines RH, Thomas KS, Chalmers JR, Irvine AD, Williams HC, Brown SJ. Clinical examination for hyperlinear palms to determine filaggrin genotype: a diagnostic test accuracy study. *Clin Exp Allergy* 2021;**51**:1421–28. https://doi.org/10.1111/cea.14025. Epub 18 October 2021. PMID: 34608691.

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Appendix 1 Distribution of primary and secondary care recruitment sites

Secondary care recruiting sites	Principal investigator	Recruiting staff
Nottingham University Hospitals NHS Trust[a]	Prof. Hywel Williams	Susan Davies-Jones, Jim Thornton, Barbara Maston, Victoria Maddox, Faye Shelton, Catherine Thorne
Portsmouth Hospital NHS Trust	Dr Bronwyn Hughes	Andrew Gribbin, Sharon McCready, Zoe Garner, Amanda Hungate, Emma Glasspool, Rachel Watson
Harrogate and District NHS Foundation Trust	Dr Alison Layton	Louise Wills, Elizabeth Marshall, Joyce Guy, Christine Morgan
Sherwood Forest Hospitals NHS Foundation[a]	Dr Michael Yanney	Caroline Moulds, Lisa Foster, Yvette Girvan, Victoria Moore, Andrea Palfreman
Burton Hospitals NHS Foundation Trust	Dr Mansoor Ahmed	Stephanie Boswell, Claire Prince, Jane Radford, Clare Mewies, Claire Backhouse, Elizabeth Kemp
Derby Hospitals NHS Foundation Trust[a]	Dr Adam Ferguson	Elaine Coulborn, Melody McGregor, Coral Smith, Vanessa Unsworth, SallyAnn Bell, Jill Smith, Liane Hufton
University Hospitals of Leicester NHS Trust[a]	Dr Karen Harman	Dr Ingrid Helbling, Suzanne Foxon, Simal Patel, Jackie Philps, Esther Rook
York Teaching Hospital NHS Foundation Trust	Dr Calum Lyon	Anna Clayton, Jill Green, Jessica Scott, Richard Furnival, Samantha Roche, Holly Alcock, Sian Sturdy
Sheffield Teaching Hospitals NHS Foundation Trust[a]	Prof. Michael Cork	Heather Chisem, Hilary Rosser, Alyson Barber, Sarah Besley, Emma Steel, Sarah Senbeto, Pauline Bayliss, Carolyn Clark
Imperial College Healthcare NHS Trust[a]	Dr Robert Boyle	Anna Bosanquet, Batia Gourin
Guy's and St Thomas's NHS Foundation Trust	Dr Carsten Flohr	Nikeeta Gurung, Annette Briley, Claire Singh, Rebecca Williams, Shelley Carter, Elodie Lawley
University of Bristol[a]	Dr Matthew Ridd	Kingsley Powell, Lyn Liddiard, Anna Gilberston
Primary care recruiting sites		
Francis Grove Surgery	Dr Katharine Broad	Nina Walters, Sarah Buttinger, Rachel Joy
Streatham Common Group Practice	Dr Kirsty Rankin	Dr Ruth Robinson, Ellen Trendell
Clapham Park Group Practice	Dr Mydhili Chellappah	Dr Dina Saleh
The Park Group Practice	Dr Mita Patel	Jayshireen Singh

a Also used GP surgeries as PICs.

FIGURE 12 Geographical distribution of recruitment sites within the UK.

Appendix 2 Summary of changes to the protocol after the start of the trial

Protocol	Date	Summary of changes
V2.1[a]	15 October 2014	Clarification on inclusion and exclusion.
V2.2	13 November 2014	Updates include eligibility, both inclusion and exclusion criteria, details about the Skin Care Video, information to be collected 2 weeks post randomisation, questionnaire collection and timing.
V3.0	12 October 2015	Recruiting sites and PICs send text message to potential participants informing them of the trial and where to get further information. At the 2-week follow-up, the co-ordinating centre would like to text participants that have not responded to phone calls and/or e-mails. Addition to the inclusion criteria which states that mothers must be aged ≥ 16 years.
V4.0	20 May 2016	Addition of food allergy outcome and tests, including SPT at 24 months' visit and the option of a Food Challenge after 24-month visit
V5.0	26 October 2016	Sample size revision proposed by TSC. Protocol and Information sheet updates to clarify procedures and safety around food allergy testing, and an additional letter for nurses to inform GP's that the child was seen for a 24-month visit.
V6.0	2 August 2017	Documents amended to attempt to increase retention rate at 24 months' visit
V6.1	8 November 2017	Update to the BEEP Trial SPT Working Practice Document and clarification and added completion instructions on 36-, 48- and 60-month questionnaires.
V6.2	8 October 2019	Update to wording in the long-term follow-up questionnaire reminder e-mails and letters, now that the results of the main BEEP study are known. Wording has been amended to reflect the results and other minor wording updates. Addition of tertiary end point that will be collected in the 60-month follow-up questionnaire.
V7.0	26 February 2021	Update to tertiary outcomes to clarify that eczema diagnosis will be analysed at 36, 48 and 60 months. Addition of a further verification of medical records: parental report of food allergy data highlighted discrepancies requiring further verification of the medical records. Two new letters created to give parents the option to opt out of this further level of data verification, and a second to request the records from the GP, if the parent does not opt out. Update to the location of the long-term storage of the collected saliva samples: Professor Sarah Brown changed affiliation, which required the samples to be moved to her new lab, in order to ensure their continued safe storage. Update to the letters and e-mails that parents receive with the last questionnaire at 60 months: in an attempt to further increase completion rates.

a The first protocol approved by the Research Ethics Committee on 9 June 2014 was v2.0.

Appendix 3 Additional results tables

TABLE 28 Randomisation by recruiting centre

Site	Intervention (*n* = 693)	Control (*n* = 701)	Total (*n* = 1394)
Sheffield	103 (15%)	102 (15%)	205 (15%)
Imperial College	97 (14%)	97 (14%)	194 (14%)
Nottingham	95 (14%)	94 (13%)	189 (14%)
Burton	93 (13%)	95 (14%)	188 (13%)
Derby	54 (8%)	54 (8%)	108 (8%)
Portsmouth	47 (7%)	48 (7%)	95 (7%)
King's Mill	43 (6%)	46 (7%)	89 (6%)
Guy's and St Thomas	38 (5%)	39 (6%)	77 (6%)
Leicester	36 (5%)	36 (5%)	72 (5%)
Harrogate	34 (5%)	34 (5%)	68 (5%)
Bristol GP surgeries	27 (4%)	27 (4%)	54 (4%)
York	19 (3%)	19 (3%)	38 (3%)
London GP surgeries	7 (1%)	10 (1%)	17 (1%)

TABLE 29 Ethnicity information for six participants for whom one or both parents were not of white ethnicity and a *FLG* mutation was detected

	Father's ethnicity			
Mother's ethnicity	White	Black Caribbean	Other Asian[a]	Total number
White	0	2	1	3
Indian	1	0	0	1
Other Asian[a]	0	0	1	1
Mixed race	1	0	0	1
Total number	2	2	2	6

a Non-Chinese.

TABLE 30 Ethnicity information for 155 participants for whom one or both parents were not of white ethnicity and a DNA sample was analysed, but none of the four *FLG* null mutations were detected

Mother's ethnicity	*n* (%)
White[a]	36 (23%)
Indian	20 (13%)
Pakistani	12 (8%)
Bangladeshi	1 (1%)
Black Caribbean	9 (6%)
Black African	13 (8%)
Black (other)	3 (2%)
Chinese	12 (8%)
Other Asian (non-Chinese)	11 (7%)
Mixed race	22 (14%)
Other	16 (10%)
Total	**155**

a The ethnicities of fathers included 4 Indian, 2 Pakistani, 4 Black Caribbean, 3 Black African, 1 black (other), 2 Chinese, 10 mixed race, 6 other and 4 not known.

TABLE 31 Baseline characteristics according to primary outcome data collection and randomised group

	Intervention – no primary outcome (*n* = 95)	Intervention – primary outcome collected (*n* = 598)	Control – no primary outcome (*n* = 89)	Control – primary outcome collected (*n* = 612)
Screening visit				
Prior to birth	47 (49%)	382 (64%)	41 (46%)	398 (65%)
After birth	48 (51%)	216 (36%)	48 (54%)	214 (35%)
Age of mother at infant randomisation				
Mean (SD)	29.6 (6.6)	32.1 (5.0)	28.8 (5.6)	31.9 (5.0)
Minimum, maximum	16, 43	18, 45	20, 39	18, 46
Ethnicity of mother				
White	78 (82%)	511 (85%)	77 (87%)	524 (86%)
Asian	7 (7%)	38 (6%)	4 (4%)	36 (6%)
Black	4 (4%)	27 (5%)	5 (6%)	17 (3%)
Other	6 (6%)	22 (4%)	3 (3%)	35 (6%)
Mother took oral antibiotics during pregnancy				
No	56 (59%)	418 (70%)	62 (70%)	435 (71%)
Yes	37 (39%)	173 (29%)	27 (30%)	174 (28%)
Not known	2 (2%)	7 (1%)	–	3 (< 0.5%)

TABLE 31 Baseline characteristics according to primary outcome data collection and randomised group (*continued*)

	Intervention – no primary outcome (*n* = 95)	Intervention – primary outcome collected (*n* = 598)	Control – no primary outcome (*n* = 89)	Control – primary outcome collected (*n* = 612)
Total number of first-degree relatives with atopic disease				
1	31 (33%)	223 (37%)	30 (34%)	223 (36%)
2	48 (51%)	252 (42%)	37 (42%)	259 (42%)
3 or more	16 (17%)	123 (21%)	22 (25%)	130 (21%)
Total number of first-degree relatives with history of eczema				
0	20 (21%)	110 (18%)	21 (24%)	100 (16%)
1	35 (37%)	279 (47%)	42 (47%)	310 (51%)
2 or more	40 (42%)	209 (35%)	26 (29%)	202 (33%)
Boy	58 (61%)	316 (53%)	39 (44%)	320 (52%)
Girl	37 (39%)	282 (47%)	50 (56%)	292 (48%)
Number of other children in household at screening (including non-full blood siblings)				
0	33 (35%)	242 (40%)	28 (31%)	265 (43%)
1	34 (36%)	252 (42%)	35 (39%)	236 (39%)
2	20 (21%)	75 (13%)	15 (17%)	81 (13%)
3 or more	8 (8%)	29 (5%)	11 (12%)	30 (5%)
Delivery method				
Vaginal delivery	62 (65%)	420 (70%)	63 (71%)	409 (67%)
Caesarean section	33 (35%)	178 (30%)	26 (29%)	203 (33%)
Days between birth and randomisation				
Median (25th, 75th centile)	2 (1, 8)	4 (1, 9)	4 (1, 9)	3 (1, 9)

TABLE 32 Parental report of use of (non-trial) emollients in the control group during the first year (contamination)

Note that the questionnaires asked about applying moisturisers to the baby's skin or used oil for baby massage

a. All children

	Control
3 months	
Applied moisturiser to baby's skin or used oil for baby massage at least 3 days per week over most or all of the child's body during the past 3 months	
No	407 (79%)
Yes	110 (21%)
n	517

continued

TABLE 32 Parental report of use of (non-trial) emollients in the control group during the first year (contamination) (*continued*)

	Control
6 months	
Applied moisturiser to baby's skin or used oil for baby massage at least 3 days per week over most or all of the child's body during the past 3 months	
No	370 (72%)
Yes	143 (28%)
n	513
12 months	
Applied moisturiser to baby's skin or used oil for baby massage at least 3 days per week over most or all of the child's body during the past 6 months	
No	376 (72%)
Yes	144 (28%)
n	520
b. Excluding children with eczema (i.e. those that may have been using emollients for treating eczema)	
3-month questionnaire and no reported eczema	*n* = 457
Applied moisturiser to baby's skin or used oil for baby massage at least 3 days per week over most or all of the child's body during the past 3 months	
No	375 (82%)
Yes	82 (18%)
6-month questionnaire and no reported eczema at 3 or 6 months	*n* = 372
Applied moisturiser to baby's skin or used oil for baby massage at least 3 days per week over most or all of the child's body during the past 3 months	
No	310 (83%)
Yes	62 (17%)
12-month questionnaire and no reported eczema at 3, 6 or 12 months	*n* = 324
Applied moisturiser to baby's skin or used oil for baby massage at least 3 days per week over most or all of the child's body during the past 6 months	
No	275 (85%)
Yes	49 (15%)

Note
Report of eczema on a questionnaire defined as a response of 'yes' to 'In the last xx months (with xx = 3 months on the 3 and 6 month questionnaires and 6 months on the 12 month questionnaire), has your baby been diagnosed with eczema by a doctor or a nurse?'

TABLE 33 Summary of adherence and contamination during the first year

a. For children with complete data

	Intervention (*n* = 442)	Control (*n* = 439)
Level of compliance in the intervention group/contamination in the control group		
Full	311 (70%)	56 (13%)
Early-onset application	86 (19%)	38 (9%)
Late-onset application	17 (4%)	85 (19%)
None	28 (6%)	260 (59%)

Note
Early-onset application is during the first 3 months, late-onset application is application at 6 and/or 12 months (but not at 3 months).

b. For children with complete data by allocated group and parental report of eczema in the first year

	Intervention – no report of eczema in first year (*n* = 294)	Intervention –eczema reported in first year (*n* = 148)	Control – no report of eczema in first year (*n* = 280)	Control – eczema reported in first year (*n* = 159)
Level of compliance in the intervention group/contamination in the control group				
Full	223 (76%)	88 (59%)	24 (9%)	32 (20%)
Early-onset application	42 (14%)	44 (30%)	21 (8%)	17 (11%)
Late-onset application	11 (4%)	6 (4%)	25 (9%)	60 (38%)
None	18 (6%)	10 (7%)	210 (75%)	50 (31%)
If eczema reported, compliance/contamination prior to questionnaire that eczema was first reported				
No		12 (8%)		106 (67%)
Yes		136 (92%)		53 (33%)

Note
Report of eczema in the first year based on the response to 'In the last xx months (with xx = 3 months on the 3 and 6 month questionnaires and 6 months on the 12 month questionnaire), has your baby been diagnosed with eczema by a doctor or a nurse?' on the 3-, 6- and 12-month questionnaires.

c. For all children

	Intervention (*n* = 693)	Control (*n* = 701)
Level of compliance in the intervention group/contamination in the control group		
Full	350 (51%)	74 (11%)
Early-onset application	153 (22%)	59 (8%)
Late-onset application	21 (3%)	90 (13%)
None	169 (24%)	478 (68%)

Note
See *Statistical methods* section for details on assumptions used for children with incomplete data on compliance/contamination.

TABLE 34 Frequency of bathing/showering child throughout the study

a. 6 months

	Intervention	Control	Total
Bath/shower frequency			
Less than once a week	14 (3%)	9 (2%)	23 (2%)
Approx. once a week	86 (17%)	104 (20%)	190 (18%)
Approx. every other day	210 (41%)	191 (37%)	401 (39%)
Every day or most days	207 (40%)	207 (41%)	414 (40%)
n	517	511	1028
Products used to wash child			
Water only	168 (32%)	156 (31%)	324 (32%)
Wash product only	258 (50%)	256 (51%)	514 (50%)
Emollient only	35 (7%)	39 (8%)	74 (7%)
Something else only	17 (3%)	31 (6%)	48 (5%)
Wash product and emollient	18 (3%)	12 (2%)	30 (3%)
Wash product and something else	15 (3%)	9 (2%)	24 (2%)
Emollient and something else	2 (< 0.5%)	1 (< 0.5%)	3 (< 0.5%)
Other	4 (1%)	2 (< 0.5%)	6 (1%)
n	517	506	1023
Regularly used oils in the child's bath water			
No	475 (92%)	452 (89%)	927 (91%)
Yes	41 (8%)	54 (11%)	95 (9%)
n	516	506	1022

b. 12 months

	Intervention	Control	Total
Bath/shower frequency			
Less than once a week	4 (1%)	7 (1%)	11 (1%)
Approx. once a week	64 (13%)	59 (11%)	123 (12%)
Approx. every other day	181 (36%)	201 (38%)	382 (37%)
Every day or most days	260 (51%)	256 (49%)	516 (50%)
n	509	523	1032
Products used to wash child			
Water only	148 (29%)	123 (24%)	271 (26%)
Wash product only	266 (52%)	303 (58%)	569 (55%)
Emollient only	39 (8%)	40 (8%)	79 (8%)
Something else only	27 (5%)	22 (4%)	49 (5%)

TABLE 34 Frequency of bathing/showering child throughout the study (*continued*)

	Intervention	Control	Total
Wash product and emollient	10 (2%)	15 (3%)	25 (2%)
Wash product and something else	11 (2%)	16 (3%)	27 (3%)
Emollient and something else	3 (1%)	2 (< 0.5%)	5 (< 0.5%)
Other	3 (1%)	2 (< 0.5%)	5 (< 0.5%)
n	507	523	1030
Regularly used oils in the child's bath water			
No	446 (89%)	456 (88%)	902 (89%)
Yes	57 (11%)	60 (12%)	117 (11%)
n	503	516	1019

c. 24 months

	Intervention	Control	Total
Bath/shower frequency			
Less than once a week	3 (1%)	2 (< 0.5%)	5 (< 0.5%)
Approx. once a week	53 (9%)	52 (9%)	105 (9%)
Approx. every other day	244 (43%)	256 (43%)	500 (43%)
Every day or most days	271 (47%)	286 (48%)	557 (48%)
n	571	596	1167
Products used to wash child			
Water only	83 (15%)	97 (16%)	180 (15%)
Wash product only	381 (67%)	374 (63%)	755 (65%)
Emollient only	43 (8%)	42 (7%)	85 (7%)
Something else only	15 (3%)	26 (4%)	41 (4%)
Wash product and emollient	24 (4%)	32 (5%)	56 (5%)
Wash product and something else	13 (2%)	18 (3%)	31 (3%)
Emollient and something else	4 (1%)	3 (1%)	7 (1%)
Other	6 (1%)	2 (< 0.5%)	8 (1%)
n	569	594	1163
Regularly used oils in the child's bath water			
No	528 (92%)	540 (91%)	1068 (91%)
Yes	44 (8%)	56 (9%)	100 (9%)
n	572	596	1168

TABLE 35 Parental report of moisturiser use between 12 and 60 months (post intervention)

a. Overall

	Intervention	Control
18 months		
Used moisturiser at least 3 days per week over most or all of the child's body during the past 6 months		
No	251 (52%)	372 (74%)
Yes	236 (48%)	129 (26%)
n	487	501
24 months		
Used moisturiser at least 3 days per week over most or all of the child's body during the past 6 months		
No	322 (56%)	423 (71%)
Yes	250 (44%)	173 (29%)
n	572	596
36 months		
Used moisturiser at least 3 days per week over most or all of the child's body during the past year		
No	310 (69%)	377 (80%)
Yes	139 (31%)	94 (20%)
n	449	471
48 months		
Used moisturiser at least 3 days per week over most or all of the child's body during the past year		
No	345 (75%)	410 (82%)
Yes	114 (25%)	90 (18%)
n	459	500
60 months		
Used moisturiser at least 3 days per week over most or all of the child's body during the past year		
No	349 (78%)	395 (84%)
Yes	99 (22%)	76 (16%)
n	448	471

b. By allocated group and parental report of a clinical diagnosis of eczema

	Intervention – no report of eczema	Intervention – eczema reported[a]	Control – no report of eczema	Control – eczema reported[a]
18 months				
Used moisturiser at least 3 days per week over most or all of the child's body during the past 6 months				
No	185 (62%)	64 (35%)	253 (88%)	116 (56%)
Yes	114 (38%)	117 (65%)	35 (12%)	93 (44%)
n	299	181	288	209

TABLE 35 Parental report of moisturiser use between 12 and 60 months (post intervention) (*continued*)

	Intervention – no report of eczema	Intervention – eczema reported[a]	Control – no report of eczema	Control – eczema reported[a]
24 months				
Used moisturiser at least 3 days per week over most or all of the child's body during the past 6 months				
No	229 (69%)	93 (39%)	278 (86%)	145 (53%)
Yes	102 (31%)	148 (61%)	46 (14%)	127 (47%)
n	331	241	324	272
36 months				
Used moisturiser at least 3 days per week over most or all of the child's body during the past year				
No	187 (79%)	123 (58%)	227 (92%)	150 (67%)
Yes	50 (21%)	89 (42%)	20 (8%)	74 (33%)
n	237	212	247	224
48 months				
Used moisturiser at least 3 days per week over most or all of the child's body during the past year				
No	203 (84%)	142 (65%)	230 (91%)	180 (73%)
Yes	39 (16%)	75 (35%)	22 (9%)	68 (27%)
n	242	217	252	248
60 months				
Used moisturiser at least 3 days per week over most or all of the child's body during the past year				
No	188 (88%)	161 (69%)	213 (93%)	182 (75%)
Yes	26 (12%)	73 (31%)	15 (7%)	61 (25%)
n	214	234	228	243

a Parental report of clinical diagnosis of eczema up to and including each time point.

TABLE 36 Post-randomisation information

a. Collected at 6 months

	Intervention (*n* = 530)	Control (*n* = 521)
Best description of how baby fed between birth and 6 months		
Breast milk only	179 (35%)	190 (37%)
Formula milk only	90 (17%)	75 (15%)
Mainly breast milk with occasional formula	82 (16%)	86 (17%)
Mainly formula with occasional breast milk	32 (6%)	26 (5%)
Combination feeding (mixture of breast milk and formula)	38 (7%)	45 (9%)
Breast milk only for a while then moved over to formula	96 (19%)	88 (17%)
Other	1 (< 0.5%)	–
n	518	510

continued

TABLE 36 Post-randomisation information (*continued*)

	Intervention (*n* = 530)	Control (*n* = 521)
Introduced solid foods by 6 months		
No	41 (8%)	24 (5%)
Yes	476 (92%)	484 (95%)
n	517	508
Mother had antibiotics while breastfeeding[a]		
No	316 (74%)	304 (70%)
Yes	110 (26%)	129 (30%)
Could not remember	1 (< 0.5%)	2 (< 0.5%)
n	427	435
Number of courses of antibiotics		
Median (25th, 75th centile)	1 (1, 2)	1 (1, 2)
Minimum, maximum	1, 7	1, 40
n	105	127
Didn't know/didn't complete	5	2
Mother regularly took probiotics while breastfeeding[a]		
No	395 (93%)	407 (94%)
Yes	28 (7%)	24 (6%)
n	423	431
Baby given regular probiotic supplement between birth and 6 months		
No	496 (96%)	499 (98%)
Yes	20 (4%)	8 (2%)
n	516	507

a Tabulated for babies who were not fed using formula milk only between birth and 6 months.

b. Collected at 12 months

	Intervention (*n* = 523)	Control (*n* = 535)
Baby had antibiotics between birth and 1 year		
No	309 (61%)	311 (59%)
Yes	193 (38%)	212 (40%)
Could not remember	6 (1%)	1 (< 0.5%)
n	508	524
Number of courses of antibiotics		
Median (25th, 75th centile)	1 (1, 2)	1 (1, 2)
Minimum, maximum[a]	0, 16	1, 90
n	184	201
Didn't know/didn't complete	9	11

a One participant responded as 'yes' to 'Over the last year, has your baby had any antibiotics?', then responded as '0' to 'If yes, how many courses?'.

TABLE 36 Post-randomisation information (*continued*)

c. Collected at 24 months

	Intervention (*n* = 599)	Control (*n* = 613)
Baby had antibiotics between 1 and 2 years		
No	297 (52%)	303 (51%)
Yes	266 (47%)	281 (47%)
Could not remember	9 (2%)	12 (2%)
n	572	596
Number of courses of antibiotics		
Median (25th, 75th centile)	1 (1, 2)	1 (1, 2)
Minimum, maximum	1, 18	1, 12
n	265	278
Didn't know	1	3
Baby had antibiotics between birth and 2 years		
No	190 (33%)	195 (33%)
Yes	342 (59%)	347 (58%)
No/could not remember at 24 months, no information at 12 months	46 (8%)	58 (10%)
n	578	600
Additional children in house since baby born		
No	518 (91%)	539 (90%)
Yes	54 (9%)	57 (10%)
n	572	596
Number of other children in household at 24 months		
0	203 (36%)	225 (38%)
1	257 (45%)	249 (42%)
2	78 (14%)	83 (14%)
3 or more	33 (6%)	38 (6%)
n[a]	571	595
Family has any furry pets that live entirely or partly in the house		
No	355 (62%)	335 (56%)
Yes	217 (38%)	261 (44%)
n	572	596
Type of furry pet		
Dog	119 (21%)	134 (22%)
Cat	99 (17%)	139 (23%)
Other	35 (6%)	39 (7%)
Furry pets introduced into house since baseline	25/572 (4%)	43/596 (7%)

continued

TABLE 36 Post-randomisation information (*continued*)

	Intervention (*n* = 599)	Control (*n* = 613)
Attempted to reduce dust mites in 2 years since birth		
No	361 (63%)	418 (70%)
Yes	211 (37%)	178 (30%)
n	572	596
Dust mite reduction measures used:		
Used special mattress covers	86 (15%)	84 (14%)
Regular mattress vacuuming	76 (13%)	72 (12%)
Removed carpets	29 (5%)	24 (4%)
Used vacuum cleaner with high-efficiency filters	125 (22%)	112 (19%)
Used dust mite killing spray	4 (1%)	8 (1%)
Other	18 (3%)	19 (3%)
Water softener fitted in house		
No	555 (97%)	573 (96%)
Yes	17 (3%)	21 (4%)
n	572	594
When fitted:		
Fitted before child born	10	11
Fitted within first year	4	2
Fitted after first year	3	8
Child regularly attends nursery or playgroup		
No	144 (25%)	137 (23%)
Yes	428 (75%)	459 (77%)
n	572	596
Age in months when child first had solids		
Median (25th, 75th centile)	6 (5, 6)	6 (5, 6)
Minimum, maximum	2, 12	3, 18
n	572	595
Water hardness[b]		
Soft	132 (19%)	135 (19%)
Moderate	180 (26%)	176 (25%)
Hard	342 (50%)	349 (50%)
Very hard	33 (5%)	36 (5%)
n	687	696
Decile of English index of multiple deprivation 2015[b] (decile 10 = least deprived)		
Median (25th, 75th centile)	6 (3, 9)	6 (3, 8)
n	680	688

a Note for two infants, the parents indicated that there were more children in the household compared to when the baby was born but did not say how many.
b Collected by NCTU using postcode on database in March 2018.

TABLE 37 Timing of introduction of allergenic foods and recent consumption at 24 months

	Intervention	Control
Child ever eaten food containing cow's milk		
No	6 (1%)	5 (1%)
Yes	569 (99%)	593 (99%)
n	575	598
Had at least 60 ml of cow's milk in last 3 months		
No	40 (7%)	33 (6%)
Yes	512 (93%)	539 (94%)
n[a]	552	572
Had at least 60 ml of cow's milk more than 3 times		
No	22 (4%)	23 (4%)
Yes	530 (96%)	549 (96%)
n[a]	552	572
Age in months the first time they had food containing cow's milk		
Median (25th, 75th centile)	6 (1, 7)	6 (1, 7)
Minimum, maximum	0, 22	0, 22
n	566	591
Before 4 months	189 (33%)	212 (36%)
Between 4 and 6 months	233 (41%)	224 (38%)
Between 7 and 12 months	129 (23%)	144 (24%)
Between 13 and 24 months	15 (3%)	11 (2%)
After 24 months/never eaten	6 (1%)	5 (1%)
n	572	596
Child ever eaten food containing egg		
No	10 (2%)	8 (1%)
Yes	565 (98%)	590 (99%)
n	575	598
Had at least four teaspoons of runny egg in last 3 months		
No	240 (44%)	238 (42%)
Yes	307 (56%)	333 (58%)
n[a]	547	571
Had at least four teaspoons of runny egg more than three times		
No	223 (41%)	213 (37%)
Yes	325 (59%)	358 (63%)
n[a]	548	571

continued

TABLE 37 Timing of introduction of allergenic foods and recent consumption at 24 months (*continued*)

	Intervention	Control
Age in months the first time they had food containing egg		
Median (25th, 75th centile)	7 (6, 9)	7 (6, 9)
Minimum, maximum	4, 21	1, 24
n	562	587
Before 4 months	–	1 (< 0.5%)
Between 4 and 6 months	251 (44%)	244 (41%)
Between 7 and 12 months	284 (50%)	319 (54%)
Between 13 and 24 months	27 (5%)	23 (4%)
After 24 months/never eaten	10 (2%)	8 (1%)
n	572	595
Child ever eaten food containing peanut		
No	138 (24%)	146 (24%)
Yes	436 (76%)	452 (76%)
n	574	598
Had equivalent of one teaspoon of peanut butter in last month		
No	345 (62%)	363 (63%)
Yes	213 (38%)	215 (37%)
n[a]	558	578
Had equivalent of one teaspoon of peanut butter more than three times		
No	246 (44%)	271 (47%)
Yes	312 (56%)	307 (53%)
n[a]	558	578
Age in months the first time they had food containing peanut		
Median (25th, 75th centile)	12 (8, 14)	12 (8, 14)
Minimum, maximum	3, 24	3, 25
n	434	450
Before 4 months	1 (< 0.5%)	1 (< 0.5%)
Between 4 and 6 months	62 (11%)	63 (11%)
Between 7 and 12 months	245 (43%)	251 (42%)
Between 13 and 24 months	126 (22%)	134 (22%)
After 24 months/never eaten	138 (24%)	147 (25%)
n	572	596
Child ever eaten food containing nuts other than peanut		
No	109 (19%)	112 (19%)
Yes	465 (81%)	485 (81%)
n	574	597

TABLE 37 Timing of introduction of allergenic foods and recent consumption at 24 months (*continued*)

	Intervention	Control
Age in months the first time they had food containing nuts other than peanut		
Median (25th, 75th centile)	12 (10, 18)	12 (12, 18)
Minimum, maximum	4, 26	4, 24
n	462	484
Before 4 months	–	–
Between 4 and 6 months	36 (6%)	35 (6%)
Between 7 and 12 months	278 (49%)	261 (44%)
Between 13 and 24 months	147 (26%)	188 (32%)
After 24 months/never eaten	110 (19%)	112 (19%)
n	571	596

a Questions about frequent and recent consumption of foods were added to the CRF in May 2017. For participants with 24-month visits completed prior to May 2017, it was attempted to collect these data retrospectively otherwise this information is unknown.

TABLE 38 Subgroup analysis for primary outcome of eczema between the age of 1 and 2 years

	Intervention	Control	Adjusted interaction effect (RR) (95% CI)	Adjusted interaction effect (risk difference) (95% CI)
Number of first-degree relatives with atopic disease				
1	51/223 (23%)	46/223 (21%)		
2	53/252 (21%)	65/259 (25%)	0.76 (0.47 to 1.22)	−6.3% (−16.9% to 4.3%)
3 or more	35/123 (28%)	39/130 (30%)	0.86 (0.51 to 1.44)	−3.8% (−17.4% to 9.8%)
Number of first-degree relatives with history of eczema				
0	19/110 (17%)	16/100 (16%)		
1	69/279 (25%)	75/310 (24%)	0.96 (0.49 to 1.88)	−0.5% (−12.7% to 11.7%)
2 or more	51/209 (24%)	59/202 (29%)	0.78 (0.39 to 1.55)	−5.9% (−19.0% to 7.3%)
FLG genotype for children with mother and father of white ethnicity and children of other ethnicity with mutation[a]				
+/+ (no mutations)	66/339 (19%)	79/352 (22%)		
+/− (one *FLG* null mutation)	22/62 (35%)	20/60 (33%)	1.20 (0.70 to 2.09)	5.1% (−12.6% to 22.9%)
−/− (two *FLG* null mutations)	1/1 (100%)	1/2 (50%)		
Season of birth				
Spring	47/183 (26%)	38/169 (22%)		
Summer	43/172 (25%)	51/185 (28%)	0.82 (0.49 to 1.37)	−6.1% (−18.8% to 6.6%)

continued

TABLE 38 Subgroup analysis for primary outcome of eczema between the age of 1 and 2 years (*continued*)

	Intervention	Control	Adjusted interaction effect (RR) (95% CI)	Adjusted interaction effect (risk difference) (95% CI)
Autumn	30/137 (22%)	35/156 (22%)	0.87 (0.49 to 1.54)	−4.0% (−17.0% to 9.0%)
Winter	19/106 (18%)	26/102 (25%)	0.62 (0.32 to 1.18)	−11.0% (−25.2% to 3.1%)
Water hardness				
Soft/moderate	66/270 (24%)	60/274 (22%)		
Hard/very hard	71/323 (22%)	90/334 (27%)	0.76 (0.50 to 1.14)	−7.0% (−16.6% to 2.6%)
Parental report of regular use of probiotic supplements during pregnancy				
No	107/457 (23%)	121/463 (26%)		
Yes	9/31 (29%)	9/30 (30%)	1.01 (0.45 to 2.27)	0% (−23.6% to 23.5%)

a Two groups for *FLG* genotype used in model including interaction effect: +/+ (no mutations) and +/− or −/− (one or two *FLG* null mutations) due to the small number of participants with two *FLG* null mutations.

Note
p-values for interaction effect between subgroup and allocated group (using model for RR, *n* = 1210 unless other stated): 0.51 for number of first-degree relatives with atopic disease, 0.58 for number of first-degree relatives with history of eczema, 0.51 for *FLG* genotype in two categories (*n* = 816), 0.53 for season of birth, 0.18 for water hardness (*n* = 1201) and 0.98 for use of probiotic supplement during pregnancy (*n* = 981).

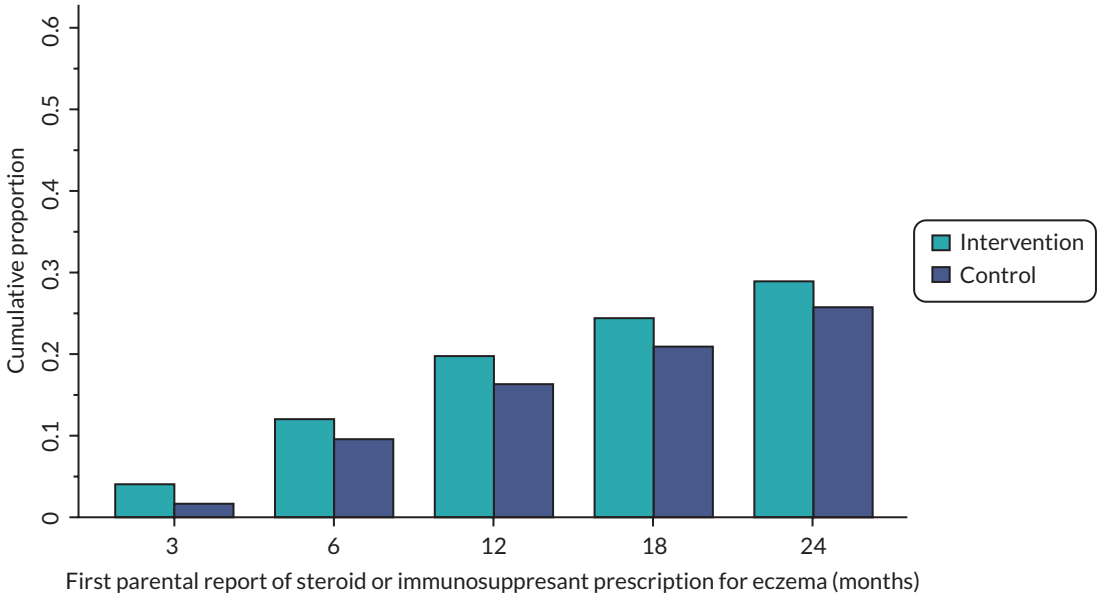

FIGURE 13 Time to onset of eczema based on first parental report of a topical corticosteroid and/or immunosuppressant prescription for eczema AND a parental report of a clinical diagnosis of eczema.

TABLE 39 Time to onset of eczema

a. Based on first parental report of a clinical diagnosis of eczema

	First parental report of a clinical diagnosis of eczema[a]		Total with parental report of a clinical diagnosis of eczema[b]	
	Intervention	Control	Intervention	Control
3 months	60/534 (11%)	60/518 (12%)	60/594 (10%)	60/584 (10%)
6 months	73/477 (15%)	75/462 (16%)	133/591 (23%)	135/578 (23%)
12 months	61/406 (15%)	67/409 (16%)	194/594 (33%)	202/596 (34%)
18 months	25/335 (7%)	29/325 (9%)	219/588 (37%)	231/593 (39%)
24 months	24/391 (6%)	26/385 (7%)	243/594 (41%)	257/601 (43%)

a Numerator is number of children with first parental report of clinical diagnosis of eczema at time point. The denominator is the number of children where questionnaire completed at time point i with no clinical diagnosis of eczema reported at a previous time point.
b Numerator is the number of children with first parental report of a clinical diagnosis of eczema at or before time point *i*. The denominator is number of children with parental report of a clinical diagnosis of eczema at or before time point *i* + children whose parents responded that the child had never had a diagnosis of eczema at 24 months + children whose parents responded as no about clinical diagnoses of eczema on all questionnaires up to and including time point *i* (if 24-month follow-up not completed).

b. Based on first parental report of a topical corticosteroid and/or immunosuppressant prescription for eczema AND a parental report of a clinical diagnosis of eczema

	First parental report of a topical corticosteroid and/or immunosuppressant prescription for eczema[a]		Total with parental report of a topical corticosteroid and/or immunosuppressant prescription for eczema[b]	
	Intervention	Control	Intervention	Control
3 months	25/534 (5%)	11/518 (2%)	25/594 (4%)	11/584 (2%)
6 months	46/510 (9%)	45/508 (9%)	71/583 (12%)	56/568 (10%)
12 months	43/455 (9%)	39/480 (8%)	114/571 (20%)	95/574 (17%)
18 months	24/397 (6%)	24/428 (6%)	138/562 (25%)	119/566 (21%)
24 months	27/447 (6%)	29/484 (6%)	165/568 (29%)	148/573 (26%)

a Numerator is number of children with first parental report of a topical corticosteroid and/or immunosuppressant prescription for eczema at time point i (and a parental report of a clinical diagnosis of eczema at or before time point *i*), denominator is number of children where questionnaire completed at time point *i* with no topical corticosteroid and/or immunosuppressant prescription for eczema reported at a previous time point.
b Numerator is the number of children with a parental report of a topical corticosteroid and/or immunosuppressant prescription for eczema before or at time point i (and a parental report of a clinical diagnosis of eczema at or before the time point where topical corticosteroid and/or immunosuppressant prescription for eczema reported). The denominator is the numerator + children with no parental report of a clinical diagnosis of eczema by time point *i* (derived as table as per table above) + children with a parental report of a clinical diagnosis of eczema by time point *i* whose parents did not report a topical corticosteroid and/or immunosuppressant prescription for eczema on all questionnaires up to and including time point *i*.

TABLE 40 Severity of eczema (EASI and POEM)

a. Summary of EASI at 24 months

	Intervention (*n* = 553)	Control (*n* = 567)
Severity of eczema[a] – *n* (%)		
Clear	355 (64%)	357 (63%)
Almost clear	112 (20%)	125 (22%)
Mild	77 (14%)	75 (13%)
Moderate	9 (2%)	10 (2%)
Severe	–	–
Very severe	–	–
Summary statistics		
Mean (SD)	0.6 (1.8)	0.6 (1.7)
Median (25th, 75th centile)	0 (0, 0.5)	0 (0, 0.5)
Minimum, maximum	0, 20.5	0, 16.4
n	553	567

a Based on categories in Leshem *et al.*[56]

Note
EASI assessed by research nurse at face-to-face visit.

b. Summary of POEM at 12, 24, 36, 48 and 60 months

	Intervention	Control
12 months		
Severity of eczema[a] – *n* (%)		
Clear/almost clear	409 (80%)	414 (79%)
Mild	51 (10%)	59 (11%)
Moderate	44 (9%)	42 (8%)
Severe	7 (1%)	6 (1%)
Very severe	1 (< 0.5%)	1 (< 0.5%)
Summary statistics		
Mean (SD)	1.8 (4.1)	1.7 (3.8)
Median (25th, 75th centile)	0 (0, 1)	0 (0, 1)
Minimum, maximum	0, 28	0, 26
n	512	522
24 months		
Severity of eczema[a] – *n* (%)		
Clear/almost clear	451 (78%)	466 (78%)
Mild	67 (12%)	78 (13%)
Moderate	50 (9%)	42 (7%)
Severe	7 (1%)	9 (2%)
Very severe	1 (< 0.5%)	–
Summary statistics		
Mean (SD)	1.9 (3.9)	1.9 (4.0)

TABLE 40 Severity of eczema (EASI and POEM) (*continued*)

	Intervention	Control
Median (25th, 75th centile)	0 (0, 2)	0 (0, 2)
Minimum, maximum	0, 26	0, 24
n	576	595
36 months		
Severity of eczema[a] – *n* (%)		
Clear/almost clear	368 (79%)	384 (80%)
Mild	66 (14%)	61 (13%)
Moderate	27 (6%)	31 (6%)
Severe	3 (1%)	6 (1%)
Very severe	0	0
Summary statistics		
Mean (SD)	1.6 (3.4)	1.5 (3.5)
Median (25th, 75th centile)	0 (0, 2)	0 (0, 1)
Minimum, maximum	0, 24	0, 22
n	464	482
48 months		
Severity of eczema[a] – *n* (%)		
Clear/almost clear	359 (79%)	407 (81%)
Mild	62 (14%)	53 (10%)
Moderate	31 (7%)	35 (7%)
Severe	0	10 (2%)
Very severe	1 (< 0.5%)	0
Summary statistics		
Mean (SD)	1.6 (3.3)	1.7 (3.9)
Median (25th, 75th centile)	0 (0, 2)	0 (0, 1)
Minimum, maximum	0, 28	0, 23
n	453	505
60 months		
Severity of eczema[a] – *n* (%)		
Clear/almost clear	357 (78%)	401 (81%)
Mild	59 (13%)	56 (11%)
Moderate	41 (9%)	36 (7%)
Severe	1 (< 0.5%)	2 (< 0.5%)
Very severe	0	1 (< 0.5%)
Summary statistics		
Mean (SD)	1.7 (3.3)	1.5 (3.5)
Median (25th, 75th centile)	0 (0, 2)	0 (0, 0.5)
Minimum, maximum	0, 17	0, 27
n	458	496

a Based on categories in Charman *et al.*[25]

TABLE 41 Food allergy at 24 months: summary of diagnoses

	Intervention	Control
Cow's milk		
Not allergic based on parental report and/or SPT	544 (94%)	570 (95%)
Not allergic confirmed by OFC	4 (1%)	1 (< 0.5%)
Allergic confirmed by OFC	1 (< 0.5%)	–
Allergic by panel consensus	8 (1%)	8 (1%)
Not allergic by panel consensus	14 (2%)	14 (2%)
Unclear – possible food allergy	–	1 (< 0.5%)
Unclear – food allergy unlikely	5 (1%)	4 (1%)
n	576	598
Egg		
Not allergic based on parental report and/or SPT	493 (86%)	525 (88%)
Not allergic confirmed by OFC	12 (2%)	8 (1%)
Allergic confirmed by OFC	12 (2%)	3 (1%)
Allergic by panel consensus	21 (4%)	19 (3%)
Not allergic by panel consensus	22 (4%)	26 (4%)
Unclear – possible food allergy	6 (1%)	3 (1%)
Unclear – food allergy unlikely	10 (2%)	14 (2%)
n	576	598
Peanut		
Not allergic based on parental report and/or SPT	500 (87%)	513 (86%)
Not allergic confirmed by OFC	16 (3%)	16 (3%)
Allergic confirmed by OFC	6 (1%)	3 (1%)
Allergic by panel consensus	4 (1%)	5 (1%)
Not allergic by panel consensus	29 (5%)	35 (6%)
Unclear – possible food allergy	3 (1%)	4 (1%)
Unclear – food allergy unlikely	18 (3%)	22 (4%)
n	576	598
Overall classification		
OFC allergic	15 (3%)	6 (1%)
Allergic by panel consensus	26 (5%)	23 (4%)
Panel consensus possible allergy	6 (1%)	2 (< 0.5%)
Passed OFC	24 (4%)	15 (3%)
Panel consensus allergy unlikely	23 (4%)	28 (5%)
Not allergic by panel consensus	39 (7%)	51 (9%)
Not allergic based on parental report and/or SPT	443 (77%)	473 (79%)
n	576	598

OFC, oral food challenge.

TABLE 42 Sensitivity analysis for confirmed food allergy at 24 months to any of milk, egg or peanut using multiple imputation for missing outcomes

	Intervention (*n* = 693)	Control (*n* = 701)	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
Allergic to at least one of milk, egg or peanut				
Using multiple imputation model as specified in SAP[a]	9.6% (SE 1.4%)	6.5% (SE 1.2%)	1.49 (0.94 to 2.36)	3.1% (−0.5% to 6.7%)
Using multiple imputation model with randomisation stratification variables only[b]	7.6% (SE 1.1%)	5.1% (SE 1.0%)	1.49 (0.93 to 2.36)	2.5% (−0.3% to 5.3%)

SE, standard error.
a See *Statistical methods* section for details of the variables included in the imputation model.
b On checking the imputed values from the multiple imputation model above, it was observed that the percentage of children with each of the food allergy outcomes was higher in the imputed data than in the observed data. Therefore, a simpler multiple imputation model including only allocated group and the randomisation stratification variables with 20 imputations was used to impute the primary outcome and the outcome of food allergy to milk, egg or peanut at 2 years to check the robustness of the results.

TABLE 43 Subgroup analysis for confirmed food allergy at 24 months to any of milk, egg or peanut

	Intervention	Control	Adjusted interaction effect (RR) (95% CI)	Adjusted interaction effect (risk difference) (95% CI)
Number of first-degree relatives with atopic disease				
1	14/207 (7%)	9/208 (4%)		
2	17/234 (7%)	14/244 (6%)	0.81 (0.28 to 2.35)	−0.9% (−7.2% to 5.3%)
3 or more	10/106 (9%)	6/116 (5%)	1.16 (0.32 to 4.12)	1.8% (−6.4% to 10.0%)
Number of first-degree relatives with history of eczema				
0	6/103 (6%)	2/95 (2%)		
1	21/255 (8%)	12/289 (4%)	0.73 (0.13 to 4.06)	0.4% (−6.3% to 7.1%)
2 or more	14/189 (7%)	15/184 (8%)	0.33 (0.06 to 1.86)	−4.3% (−12.0% to 3.3%)
FLG genotype for children with mother and father of white ethnicity and children of other ethnicity with mutation[a,b]				
+/+ (no mutations)	14/325 (4%)	12/344 (3%)		
+/− (one *FLG* null mutation)	8/59 (14%)	4/56 (7%)	1.57 (0.40 to 6.17)	5.6% (−5.6% to 16.8%)
−/− (two *FLG* null mutations)	0/1 (0%)	0/2 (0%)		

a Two groups for *FLG* genotype used in model including interaction effect: +/+ (no mutations) and +/− or −/− (one or two FLG null mutations) due to the small number of participants with two FLG null mutations.
b Unadjusted estimates are reported for *FLG* genotype as the model including stratification variables did not converge.

Note
p-values for interaction effect between subgroup and allocated group: 0.83 for number of first-degree relatives with atopic disease (*n* = 1115), 0.21 for number of first-degree relatives with history of eczema (*n* = 1115) and 0.52 for *FLG* genotype in two categories (*n* = 787).

TABLE 44 Parental-reported safety outcomes at each questionnaire time point according to allocated group and reported emollient/moisturiser use

	Intervention – no emollient use	Intervention – some emollient use	Intervention – widespread regular[a] emollient use	Control – no emollient/ moisturiser use	Control – some emollient/ moisturiser use	Control – widespread regular[a] emollient/ moisturiser use
3 months	*n* = 20	*n* = 46	*n* = 466	*n* = 298	*n* = 109	*n* = 110
At least one skin infection	0	2/46 (4%)	20/466 (4%)	6/298 (2%)	9/107 (8%)	5/110 (5%)
Number of skin infections						
Median (25th, 75th centile)	–	2 (1, 3)	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)
Minimum, maximum	–	1, 3	1, 2	1, 2	1, 1	1, 2
Slippage incident involving infant within an hour of applying skin care products to the baby's skin	0	2/46 (4%)	3/464 (1%)	1/289 (< 0.5%)	0	0
6 months	*n* = 33	*n* = 59	*n* = 427	*n* = 264	*n* = 106	*n* = 143
At least one skin infection	2/33 (6%)	4/59 (7%)	28/426 (7%)	7/262 (3%)	1/105 (1%)	14/140 (10%)
Number of skin infections						
Median (25th, 75th centile)	1 (1, 1)	1 (1, 1)	1 (1, 1.5)	1 (1, 1)	1 (1, 1)	1 (1, 1)
Minimum, maximum	1, 1	1, 1	1, 7	1, 2	1, 1	1, 3
Slippage incident involving infant within an hour of applying skin care products to the baby's skin	1/33 (3%)	1/57 (2%)	1/422 (< 0.5%)	1/260 (< 0.5%)	1/105 (1%)	0
12 months	*n* = 58	*n* = 73	*n* = 375	*n* = 268	*n* = 108	*n* = 144
At least one skin infection	9/58 (16%)	4/73 (5%)	32/375 (9%)	12/268 (4%)	6/108 (6%)	15/144 (10%)
Number of skin infections						
Median (25th, 75th centile)	1 (1, 1)	1 (1, 1.5)	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 2)
Minimum, maximum	1, 4	1, 2	1, 3	1, 2	1, 1	1, 2
Slippage incident involving infant within an hour of applying skin care products to the baby's skin	1/57 (2%)	0	7/368 (2%)	2/262 (1%)	0	5/144 (3%)

a Widespread regular emollient/moisturiser use defined as emollient/moisturiser use over the majority of the child's body at least 3 or more days per week since the previous questionnaire.

TABLE 45 Baseline characteristics according to questionnaire completion at 60 months and randomised group

	Intervention – did not complete 60-month questionnaire (*n* = 226)	Intervention – completed 60-month questionnaire (*n* = 467)	Control – did not complete 60-month questionnaire (*n* = 192)	Control – completed 60-month questionnaire (*n* = 509)
Screening visit				
Prior to birth	125 (55%)	304 (65%)	103 (54%)	336 (66%)
After birth	101 (45%)	163 (35%)	89 (46%)	173 (34%)
Age of mother at infant randomisation				
Mean (SD)	30.2 (6.2)	32.5 (4.6)	29.7 (5.6)	32.2 (4.9)
Minimum, maximum	16, 45	20, 44	18, 43	18, 46
Ethnicity of mother				
White	176 (78%)	413 (88%)	152 (79%)	449 (88%)
Asian	17 (8%)	28 (6%)	11 (6%)	29 (6%)
Black	20 (9%)	11 (2%)	15 (8%)	7 (1%)
Other	13 (6%)	15 (3%)	14 (7%)	24 (5%)
Number of first-degree relatives with atopic disease				
1	75 (33%)	179 (38%)	62 (32%)	191 (38%)
2	108 (48%)	192 (41%)	82 (43%)	214 (42%)
3 or more	43 (19%)	96 (21%)	48 (25%)	104 (20%)
Number of first-degree relatives with history of eczema				
0	51 (23%)	79 (17%)	40 (21%)	81 (16%)
1	87 (38%)	227 (49%)	88 (46%)	264 (52%)
2 or more	88 (39%)	161 (34%)	64 (33%)	164 (32%)
Boy	125 (55%)	249 (53%)	96 (50%)	263 (52%)
Girl	101 (45%)	218 (47%)	96 (50%)	246 (48%)
Number of other children in household at screening (including non-full blood siblings)				
0	76 (34%)	199 (43%)	61 (32%)	232 (46%)
1	91 (40%)	195 (42%)	71 (37%)	200 (39%)
2	40 (18%)	55 (12%)	40 (21%)	56 (11%)
3 or more	19 (8%)	18 (4%)	20 (10%)	21 (4%)
Delivery method				
Vaginal	154 (68%)	328 (70%)	128 (67%)	344 (68%)
Caesarean	72 (32%)	139 (30%)	64 (33%)	165 (32%)
Days between birth and randomisation				
Mean (SD)	5.7 (6)	5.8 (5.6)	5.5 (5.8)	5.8 (5.6)
Median (25th, 75th centile)	3 (1, 9)	4 (1, 9)	3 (1, 8.5)	4 (1, 9)

continued

TABLE 45 Baseline characteristics according to questionnaire completion at 60 months and randomised group (*continued*)

	Intervention – did not complete 60-month questionnaire (*n* = 226)	Intervention – completed 60-month questionnaire (*n* = 467)	Control – did not complete 60-month questionnaire (*n* = 192)	Control – completed 60-month questionnaire (*n* = 509)
Decile of English Index of Multiple Deprivation 2015 (1 = most deprived)				
Mean (SD)	4.9 (2.8)	6.3 (2.7)	4.6 (2.9)	6.3 (2.6)
Median (25th, 75th centile)	4 (3, 7)	7 (4, 9)	4 (2, 7)	6 (4, 9)

TABLE 46 Questionnaire completion at 60 months according to outcomes at 24 months and randomised group

	Intervention	Control
Diagnosis of eczema between 12 and 24 months of age (defined as meeting the UKWP Diagnostic criteria, *primary outcome*)		
No	357/459 (78%)	385/462 (83%)
Yes	102/139 (73%)	115/150 (77%)
Parental report of clinical diagnosis of eczema between birth and 2 years		
No	259/344 (75%)	277/334 (83%)
Yes	203/266 (76%)	225/282 (80%)
Parental report of any food allergy at 24 months[a]		
No	292/366 (80%)	329/400 (82%)
Yes	159/208 (76%)	161/197 (82%)
Parental report of immediate food allergy to common allergen at 24 months[b]		
No	359/456 (79%)	414/501 (83%)
Yes	92/118 (78%)	76/96 (79%)
Confirmed food allergy to at least one of milk, egg or peanut		
No	402/506 (79%)	453/539 (84%)
Yes	33/41 (80%)	18/29 (62%)

a Reported a reaction to food containing cow's milk, egg or nuts or any other food.
b Immediate food allergy defined as reaction within 2 hours of eating cow's milk, egg, peanut, other nuts, fish, sesame, wheat, soya and kiwi fruit.

TABLE 47 Number of observations and participants included in analysis of tertiary outcomes

	Intervention (*n* = 693)	Control (*n* = 701)
Table 16		
Presence of eczema in the previous year based on parental report of a clinical diagnosis	4052 observations 632 participants	4171 observations 643 participants
Presence of eczema based on completion by parents of UKWP Diagnostic Criteria	2507 observations 619 participants	2640 observations 637 participants

TABLE 47 Number of observations and participants included in analysis of tertiary outcomes (*continued*)

	Intervention (*n* = 693)	Control (*n* = 701)
Moderate, severe or very severe eczema according to POEM	2463 observations 612 participants	2600 observations 633 participants
Table 17		
Parental report of reaction to any food within the previous year	1855 observations 596 participants	1983 observations 622 participants
Parental report of immediate reaction to milk, egg or nuts within the previous year	1872 observations 596 participants	2004 observations 622 participants
Parental report of immediate reaction to any common food allergen within the previous year at 60 months	1867 observations 596 participants	1997 observations 622 participants
Parental report of a clinical diagnosis of food allergy within the previous year	2381 observations 609 participants	2514 observations 632 participants
Table 18		
Parental report of wheezing or whistling in the chest in previous year	1936 observations 596 participants	2061 observations 623 participants
Parental report of allergic rhinitis symptoms in previous year	1937 observations 595 participants	2058 observations 623 participants

TABLE 48 Any parental report that in their opinion their child had eczema at 3, 6, 12, 18, 24, 36, 48 and 60 months

Selected 'eczema' in response to 'In the last xx months (with xx = 3 months on the 3 and 6 month questionnaires and 6 months on the 12 month questionnaire), has your baby/child suffered from any of the following skin problems?'[a]	Emollient	Control	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
3 months	91/530 (17%)	107/523 (20%)	0.83 (0.65 to 1.06)	−3.5% (−8.0% to 1.0%)
6 months	160/523 (31%)	155/517 (30%)	1.01 (0.85 to 1.21)	0.4% (−4.9% to 5.8%)
12 months	189/514 (37%)	186/528 (35%)	1.03 (0.88 to 1.20)	0.9% (−4.7% to 6.6%)
18 months	173/489 (35%)	183/506 (36%)	0.99 (0.84 to 1.16)	−0.3% (−6.1% to 5.4%)
24 months	189/591 (32%)	193/607 (32%)	1.01 (0.86 to 1.19)	0.2% (−5.0% to 5.4%)
36 months	169/474 (36%)	168/493 (34%)	1.03 (0.87 to 1.21)	1.0% (−4.8% to 6.8%)
48 months	154/459 (34%)	162/513 (32%)	1.06 (0.89 to 1.26)	1.9% (−3.8% to 7.5%)
60 months	168/460 (37%)	151/499 (30%)	1.18 (0.99 to 1.39)	5.4% (−0.3% to 11.1%)

a At 3 and 6 months, the questionnaire asks about the last 3 months, at 12, 18, 24 months, the questionnaire asks about the last 6 months and at 36, 48 and 60 months asks about the last year. Analysis model included 8226 observations (4040 intervention, 4186 control) from 1278 participants (632 intervention, 646 control).

TABLE 49 Parental-reported food allergy symptoms at 36, 48 and 60 months

	Intervention	Control
36 months		
Parental report of reaction within the previous year		
Reaction to cow's milk	35/460 (8%)	26/487 (5%)
Reaction to egg	27/447 (6%)	14/476 (3%)
Reaction to nuts	13/451 (3%)	11/480 (2%)
Reaction to other food	33/441 (7%)	25/469 (5%)
Parental report of immediate reaction within the previous year[a]		
Reaction to cow's milk	19/460 (4%)	13/486 (3%)
Reaction to egg	18/445 (4%)	12/476 (3%)
Reaction to nuts	11/449 (2%)	10/480 (2%)
48 months		
Parental report of reaction within the previous year		
Reaction to cow's milk	21/453 (5%)	17/502 (3%)
Reaction to egg	16/443 (4%)	12/496 (2%)
Reaction to nuts	14/451 (3%)	8/496 (2%)
Reaction to other food	22/430 (5%)	17/477 (4%)
Parental report of immediate reaction within the previous year[a]		
Reaction to cow's milk	9/453 (2%)	9/501 (2%)
Reaction to egg	12/442 (3%)	10/495 (2%)
Reaction to nuts	12/449 (3%)	5/493 (1%)
60 months		
Parental report of reaction within the previous year		
Reaction to cow's milk	18/455 (4%)	16/482 (3%)
Reaction to egg	14/440 (3%)	8/463 (2%)
Reaction to nuts	6/452 (1%)	14/479 (3%)
Reaction to other food	26/452 (6%)	21/480 (4%)
Parental report of immediate reaction within the previous year[a]		
Reaction to cow's milk	9/454 (2%)	7/480 (1%)
Reaction to egg	11/438 (3%)	7/462 (2%)
Reaction to nuts	5/451 (1%)	11/476 (2%)
Reaction to other common food allergen	14/448 (3%)	4/475 (1%)
Total number of times child reacted to any food in the previous year		
None	387 (89%)	417 (91%)
One	10 (2%)	15 (3%)
Two	8 (2%)	11 (2%)
More than two	29 (7%)	15 (3%)
n	434	458

TABLE 49 Parental-reported food allergy symptoms at 36, 48 and 60 months (*continued*)

	Intervention	Control
Unusually runny or frequent poos or blood/slime in poo for a month or longer within the previous year		
No	420 (95%)	450 (95%)
Yes	22 (5%)	23 (5%)
n	442	473
Stomach pains or been unusually irritable for more than a month within the previous year		
No	421 (95%)	457 (97%)
Yes	22 (5%)	15 (3%)
n	443	472
Prescribed low-allergy formula milk within the previous year		
No	441 (100%)	474 (100%)
Yes	2 (< 0.5%)	0
n	443	474

a Immediate defined as reaction within 2 hours of eating the food.

TABLE 50 Sensitivity analysis for missing data for key tertiary outcomes using delta-based multiple imputation

a. Parental report of clinical diagnosis of eczema from the age of 12–60 months

	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
Main analysis assuming MAR	1.10 (0.93 to 1.30)	2.8% (−2.3% to 7.8%)
Sensitivity analysis [exp(δ) = 1.2][a]	1.11 (0.94 to 1.31)	3.1% (−2.1% to 8.2%)
Sensitivity analysis [exp(δ) = 1.5]	1.11 (0.94 to 1.31)	3.2% (−2.0% to 8.4%)
Sensitivity analysis [exp(δ) = 2.0]	1.11 (0.94 to 1.31)	3.3% (−1.9% to 8.5%)

a Based on 49 imputed data sets, model failed to converge in 1 imputed data set.

Note
Sensitivity analysis under a MNAR assumption conducted using delta (δ)-based multiple imputation used to modify the value imputed under a MAR assumption by a fixed amount to explore how the results change if participants with missing outcomes had better/worse outcomes than predicted (based on the MAR assumption). δ represents the difference in the log-odds of the outcome for participants where the outcome is missing compared to participants where the outcome is non-missing, for example if exp(δ) = 1.2, OR for eczema in participants with missing data compared to non-missing data is 1.2.

b. Parental report of a clinical diagnosis of food allergy by 60 months

	Adjusted RR (95% CI)	Adjusted difference in risk (95% CI)
Main analysis assuming MAR	1.11 (0.84 to 1.45)	1.5% (−2.5% to 5.6%)
Sensitivity analysis [exp(δ) = 1.2]	1.12 (0.86 to 1.46)	1.7% (−2.3% to 5.7%)
Sensitivity analysis [exp(δ) = 1.5]	1.12 (0.86 to 1.46)	1.8% (−2.3% to 5.9%)
Sensitivity analysis [exp(δ) = 2.0]	1.13 (0.87 to 1.46)	1.9% (−2.3% to 6.1%)

TABLE 51 Exploratory tertiary outcome of parental report of any/immediate reaction to egg or nuts by 60 months

	Intervention	Control
Parental report of reaction to egg or nuts		
No	496 (83%)	542 (87%)
Yes	101 (17%)	80 (13%)
n	597	622
If yes, reaction reported to[a]:		
Egg only	68 (67%)	46 (57%)
Nuts only	19 (19%)	21 (26%)
Egg and nuts	14 (14%)	13 (16%)
Parental report of immediate reaction to egg or nuts		
No	522 (88%)	559 (90%)
Yes	74 (12%)	63 (10%)
n	596	622
If yes, reaction reported to[a]:		
Egg only	52 (70%)	37 (59%)
Nuts only	14 (19%)	15 (24%)
Egg and nuts	8 (11%)	11 (17%)

a Percentages use the number with a parental report of reaction/immediate reaction to egg or nuts as the denominator.

EME
HSDR
HTA
PGfAR
PHR

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