Emollients for prevention of atopic dermatitis; 5-year findings from the BEEP randomised trial

Short title: BEEP trial 5 year results

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], Sandra Lawton[5], Tracey H. Sach[6], Joanne R. Chalmers[7], Matthew J. Ridd[8], Carsten Flohr[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[6], Susan Davies-Jones[7], Robert J. Boyle[7,11], Hywel C. Williams [7]

[1]Nottingham Clinical Trials Unit, School of Medicine, University of Nottingham, Nottingham, UK
[2]Skin Research Group, School of Medicine, University of Dundee, Dundee, UK
[3]Department of Dermatology, Ninewells Hospital and Medical School, Dundee,
[4] Population Health Research Institute, St. George's, University of London, London, UK
[5]Rotherham NHS Foundation Trust, UK
[6]Health Economics Group, Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, UK
[7]Centre of Evidence Based Dermatology, School of Medicine, University of Nottingham, Nottingham, UK
[8] Population Health Sciences, University of Bristol, Bristol, UK
[9]Unit for Population-Based Dermatology Research, St John's Institute of Dermatology, Guy's & St Thomas' NHS Foundation Trust and King's College London, UK
[10] Sheffield Children's Hospital, Sheffield, UK
[11]National Heart and Lung Institute, Imperial College London, London, UK
[12]Sheffield Dermatology Research, Department of Infection and Immunity, University of Sheffield, Sheffield, UK
[13]Department of Dermatology, Oregon Health & Science University, Portland, Oregon, USA

*Sara Brown's present affiliations: Centre for Genomic and Experimental Medicine, University of Edinburgh, Edinburgh, UK and Department of Dermatology, NHS Lothian, Edinburgh, UK

Corresponding Author: Prof Hywel C Williams, Centre of Evidence Based Dermatology University of Nottingham, NG7 2RD, UK email: hywel.williams@nottingham.ac.uk

Sources of funding: National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) 12/67/12

Word count: 3891

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/all.15555

Lucy Bradshaw (ORCiD ID: 0000-0001-8382-6040)
Laura A. Wyatt (ORCiD ID: 0000-0002-9817-5356)
Sara J. Brown (ORCiD ID 0000-0002-3232-5251)
Rachel H. Haines (ORCiD ID:: 0000-0001-7924-0602)
Alan A. Montgomery (ORCiD ID: 0000-0003-0450-1606)
Michael R. Perkin (ORCiD ID 0000-0001-9272-2585)
Sandra Lawton (ORCiD ID: 0000-0002-6163-5822)
Tracey H. Sach (ORCiD ID: 0000-0002-8098-9220)
Joanne R. Chalmers (ORCiD ID: 0000-0002-2281-7367)
Matthew J. Ridd (ORCiD ID: 0000-0002-7954-8823)
Carsten Flohr (ORCiD ID: 0000-0003-4884-6286)
Richard Swinden (ORCiD ID: 0000-0001-9877-8301)
Eleanor J. Mitchell (ORCiD ID: 0000-0002-6998-4533)
Nicola Jay (ORCiD ID: 0000-0003-1388-192X)
Hilary Allen (ORCiD ID: 0000-0002-7013-0308)
Michael J. Cork (ORCiD ID: 0000-0003-4428-2428)
Maeve Kelleher (ORCiD ID: 0000-0002-3764-0461)
Eric L. Simpson (ORCiD ID: 0000-0003-0853-0252)
Robert J. Boyle (ORCiD ID: 0000-0002-4913-7580)
Hywel C. Williams (ORCiD ID: 0000-0002-5646-3093)

Declaration of interests

Robert Boyle received personal fees from Cochrane, Wiley, British Society of Allergy and Clinical Immunology for editorial work and from medicolegal firms for expert witness work, outside of the submitted work. Robert's employing institution Imperial College London has a formal research and innovation partnership with Nestlé, who manufacture and market nutritional products for managing food allergy and sponsor infant nutrition research related to eczema and food allergy. Matthew Ridd is Chief Investigator on UK National Institute for Health Research-funded Best Emollients for Eczema (ISRCTN84540529). Carsten Flohr is Chief Investigator of the UK National Institute for Health Research-funded TREAT (ISRCTN15837754) and SOFTER (Clinicaltrials.gov: NCT03270566) trials as well as the UK-Irish Atopic eczema Systemic Therapy Register (A-STAR; ISRCTN11210918) and a Principal Investigator in the European Union (EU) Horizon 2020-funded BIOMAP Consortium (http://www.biomap-imi.eu/). He also leads the EU Joint Program Initiative Trans-Foods and the UK Medical Research Foundation-funded Mind & Skin consortia. His department has received investigator-led funding from Sanofi-Genzyme and Pfizer for skin microbiome work. Carsten Flohr is also Editor of the British Journal of Dermatology Evidence-Based Dermatology Section. Eric Simpson reports personal fees from AbbVie, Amgen, Arena Pharmaceuticals, Aslan Pharma, Boston Consulting Group, Collective Acumen, LLC (CA), Dermira, Eli Lilly, Evidera, ExcerptaMedica, Forte Bio RX, Galderma, GlaxoSmithKline, Incyte, Janssen, Kyowa Kirin Pharmaceutical Development, Leo Pharm, Medscape LLC, Merck, Pfizer, Physicians World LLC, Regeneron, Roivant, Sanofi-Genzyme, Trevi therapeutics, Valeant, WebMD. Eric Simpson also reports grants (or Principal investigator role) from AbbVie, Amgen, Arcutis, Aslan, CorEvitas, Dermavant, Dermira, Eli Lilly, Incyte, Kymab, Kyowa Hakko Kirin, Leo Pharmaceuticals, Pfizer, Regeneron, Sanofi, and TARGET-DERM. These potential conflicts of interest have been reviewed and managed by OHSU. Hywel Williams was director of the NIHR Health Technology Assessment Programme from 2015 to 2020, Tracey Sach was a member of the NIHR Health Technology Assessment Programme Themed calls/general funding/commissioning committees from 2013-2019. Alan Montgomery was a member of NIHR HTA Clinical Trials and Evaluations Funding Committee 2015-2021. HW, TS and AM had no part in the decision making for funding this study. Sara Brown is a Wellcome Trust Senior Research Fellow (106865/A/15/Z and 220875/Z/20/Z); she has also received research funding (but no personal payments) from the British Skin Foundation, Pfizer, Sosei-Heptares and the European Union (EU) Horizon 2020-funded BIOMAP Consortium, outside of the submitted work. Sara receives personal fees from Wiley for editorial work, outside of the submitted work. MK received funding from National Institute of Health (NIHR) for Transitional Research Fellowship for the systematic review of skincare interventions for preventing eczema and food allergy. All other authors declare no competing interests.

Abstract

Background: The effectiveness of emollients for preventing atopic dermatitis/eczema is controversial. The Barrier Enhancement for Eczema Prevention trial evaluated the effects of daily emollients during the first year of life on atopic dermatitis and atopic conditions to age 5 years.

Methods: 1394 term infants with a family history of atopic disease were randomised (1:1) to daily emollient plus standard skin-care advice (693 emollient group) or standard skin-care advice alone (701 controls). Long-term follow-up at ages 3, 4 and 5 years was via parental questionnaires. Main outcomes were parental report of a clinical diagnosis of atopic dermatitis and food allergy.

Results: Parents reported more frequent moisturiser application in the emollient group through to 5 years. A clinical diagnosis of atopic dermatitis between 12 and 60 months was reported for 188/608 (31%) in the emollient group and 178/631 (28%) in the control group (adjusted relative risk 1.10, 95% confidence interval 0.93 to 1.30). Although more parents in the emollient group reported food reactions in the previous year at 3 and 4 years, cumulative incidence of doctor diagnosed food allergy by 5 years was similar between groups (92/609 (15%) emollients and 87/632 (14%) controls, adjusted relative risk 1.11, 95% confidence interval 0.84 to 1.45). Findings were similar for cumulative incidence of asthma and hay fever.

Conclusions: Daily emollient application during the first year of life does not prevent atopic dermatitis, food allergy, asthma or hay fever.

Trial registration: ISRCTN21528841.

Funding: National Institute for Health and Care Research Health Technology Assessment 12/67/12

Key words: Asthma, atopic dermatitis, food allergy, prevention, rhinitis

Abbreviations: atopic dermatitis (AD), Barrier Enhancement for Eczema Prevention (BEEP), confidence interval (CI), individual patient data (IPD), Patient Oriented Eczema Measure (POEM), relative risk (RR), statistical analysis plan (SAP)

Background

Atopic dermatitis (syn, atopic eczema, eczema) is a global problem affecting around 1 in 5 children (1) and 1 in 20 adults (2, 3). The prevalence of atopic dermatitis (AD) seems to be increasing especially in cities undergoing rapid demographic development (4). Genetic factors such as genes coding for skin barrier proteins and immunological responses appear to be important (5), but the increased prevalence over time, increased risk in smaller families, and migrant studies suggest that environmental factors also play a role (6).

While many effective topical and systemic treatments are available for established AD (7), prevention of AD has remained elusive (8, 9). Most previous preventive strategies focused on allergen reduction during pregnancy and during infancy with little evidence of benefit (10). Some evidence exists for a possible role of probiotics (11), but the exact combination of bacterial strains and timing is still unclear and issues such as selective reporting may have impacted the evidence base. Interest in the role of a defective skin barrier preceding AD development led to the hypothesis that enhancement of the skin barrier from birth might prevent a chain of events resulting in skin inflammation and establishment of AD (12). The risk of atopic dermatitis is strongly associated with mutations in the gene encoding filaggrin - a protein that contributes to skin barrier integrity that suggests an impaired skin barrier as a critical defect in the development of AD (13). Dysfunction in the skin barrier starts soon after birth, making enhancement of the skin barrier a possible target for AD prevention by reducing inflammation from irritants and sensitisation through the skin (14). The “outside-in” hypotheses suggests that there is a complex interplay between epithelial barriers, environmental factors and the immune system in the development of systemic allergic diseases such as AD (15).

Food sensitisation may be initiated through an impaired skin barrier, especially in those with AD, so prevention of AD may also prevent the development of subsequent food allergy (16, 17) . Furthermore, if associated conditions such as asthma and allergic rhino-conjunctivitis truly follow-on from AD in predisposed individuals in the so-called ‘allergic march’ (18), then it might also be possible to prevent such co-morbidities by preventing early onset AD with emollients (16). Two pilot studies had suggested an efficacy signal for preventing AD using such an approach (19, 20). The rationale for the follow-on BEEP (Barrier Enhancement for Eczema Prevention) study was to conduct a definitive large randomised controlled trial to evaluate whether whole body daily emollient application for the first year of life could prevent AD in high-risk children, compared with standard skin care (21). Results for the 2-year primary outcome of AD did not show any protective effect of daily emollient on AD development (adjusted relative risk 0.95 [95% confidence interval (CI) 0.78 to 1.16], p=0.61) (22). Secondary outcomes for AD were consistent with the primary outcome. Parental reported skin infections were more common in the emollient group during the first year (adjusted incidence rate ratio 1.55, 95% CI 1.15 to 2.09). There was also no evidence that emollient reduced the risk of food allergy (adjusted relative risk 1.47, 95% CI 0.93 to 2.33). Other studies have found

similar results on risk of AD (23) but findings are controversial, with some small studies and systematic reviews reporting positive effects (24).

The purpose of the five-year follow-up of children in the BEEP trial was to evaluate the longer-term effects of daily emollient application during infancy on AD and other atopic outcomes up to 5 years of age (21).

Methods

Study design and participants

BEEP was a multicentre, 2-arm, parallel group randomised controlled trial which recruited participants from 12 hospitals and four general practice sites in the UK. The trial was approved by the West Midlands Ethics Committee, UK (14/WM/0162). The protocol (21) and results for the primary outcome at 2 years have been published (22). Briefly, between November 2014 and November 2016 after informed consent from the parent/guardian, term newborns (≥ 37 weeks gestation) at high-risk of developing AD (at least one first-degree relative with parent-reported doctor-diagnosed AD, allergic rhinitis or asthma) were randomised (1:1) to apply emollient all over the body daily for the first year plus standard skin-care advice (emollient) or standard skin-care advice only (control). Standard general skin care advice was provided in booklet and video format at the time of randomisation and included guidance to use mild cleansers and shampoos specifically formulated for infants, and to avoid soap, bubble bath, and baby wipes (22). Randomisation was stratified by recruiting centre and number of first-degree relatives with atopic disease (1, 2, or >2). Participating families were not blinded to group allocation. Parents whose children were allocated to the emollient group were initially sent both Doublebase Gel (Dermal Laboratories, Herts, UK) and Diprobase Cream (Bayer, Berks, UK) and specified which emollient they wanted when reordering. No emollients were supplied after the child reached one year of age. Adherence was assessed by asking parents about emollient use at 3, 6, and 12 months and was deemed satisfactory if emollients were applied at least 3–4 times per week to most of the child's body. We used a similar definition for contamination in the control group.

The sample size for the trial was calculated for the primary outcome of a diagnosis of AD in the last year as defined by the UK working party refinement of the Hanifin and Rajka diagnostic criteria for eczema at age 2 years (25) assessed by research nurses blinded to treatment allocation. The original target sample size of 1282 was based on a *relative* reduction of 30% in the primary AD outcome at the 5% significance level (two-sided) with 90% power assuming 30% of children would have AD in the control group, and 20% dropout. Faster than expected recruitment prompted a review by the Trial Steering Committee (August 2016), who permitted all pregnant mothers who had already given consent by that point to be randomised upon the birth of the baby, resulting in 1394 infants being randomised (693 emollient, 701 control).

Follow-up after the 2-year primary outcome time point was via questionnaires sent to parents at 3, 4 and 5 years, either in an email with link or in the post. Reminders were sent after 2 and then 3 weeks, respectively, if a questionnaire had not been completed. Results for the 2-year primary outcome of AD were published in February 2020, at which point parents were also sent a summary of the results (26).

Outcomes

Long-term follow-up outcomes (defined as tertiary in the protocol) were:

- Presence of AD in the previous year at 3, 4 and 5 years based on parental report of a clinical diagnosis of AD.
- Any parental report that in their opinion their child had AD at 3, 6, 12, 18 months, 2, 3, 4 and 5 years.
- Presence of AD at 3, 4 and 5 years based on parental completion of UK Working Party diagnostic criteria for AD (25)
- Severity of AD at 3, 4 and 5 years as measured by the Patient Oriented Eczema Measure (POEM) (27)
- Presence of other atopic diseases:
    - Parental reported wheezing, allergic rhinitis and food allergy symptoms at 3, 4 and 5 years.
    - Parental report of a clinical diagnosis of asthma or allergic rhinitis by 5 years.
    - Parental report of a clinical diagnosis of food allergy at 3, 4 and 5 years

The questions used for these outcomes are presented in the supplementary materials. A summary of the parental reported outcomes at 2 years are also presented in the supplementary materials.

Two additional long-term outcomes were specified in version 2.0 of the Statistical Analysis Plan (SAP), prior to database lock and unblinding of 3, 4 and 5 year outcome data: parental-report of a clinical diagnosis of AD from the age of 12 months to 60 months and parental report of a clinical diagnosis of food allergy by 5 years. These outcomes were added to capture the lifetime experience and fluctuating nature of AD and food allergy. The first 12 months were not included for AD 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 AD (28).

Health related quality of life and health economic long-term outcomes will be reported separately. No additional long-term safety data was recorded between years 2 and 5 of follow-up.

Statistical analysis

Details of the analyses of the long-term outcomes were added to the SAP (29) by the trial statistician after the analysis of the primary and secondary outcomes at which point, the investigators, trial management, data management, statisticians and participants were aware of the results. Full details of definitions and derivations of the long-term tertiary outcomes are given in version 2.0 of the SAP, which was finalised prior to the database lock for the analysis of the long-term outcomes at 60 months. All analyses were carried out using Stata 17.0 (StataCorp LP, College Station, TX, USA).

Analysis was according to randomised group regardless of adherence with the allocation in the first year. The main analyses made the assumption that missing outcomes were missing at random i.e. did not depend on the unobserved outcomes given the observed data. All analyses adjusted for randomisation stratification variables using a fixed effect for number of immediate family members with atopic disease and a random effect for the recruiting centre.

Analysis of binary long-term outcomes at 3, 4 and 5 years used mixed effects logistic regression models including the outcome collected at earlier time points (i.e. 12 and 24 months where applicable) with 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. Adjusted risk differences and risk ratios along with corresponding 95% confidence intervals (CI) were obtained using Stata's Margins command with standard errors computed using the delta method (30).

Multiple imputation was used to impute missing outcomes collected at 5 years only and the cumulative incidence outcomes. Between group effects in each imputed dataset were estimated using mixed effects logistic regression. Adjusted risk differences and risk ratios were obtained, as described above, and combined using Rubin rules for multiply imputed data. Further details of the multiple imputation model and sensitivity analyses are in the supplementary materials and SAP. Exploratory subgroup analyses for *FLG* genotype was done by including an interaction term in the analysis model for the parental report of clinical diagnosis of AD from the age of 12 months to 60 months.

Results

Follow-up rates and baseline characteristics: Follow-up for the outcomes at 3, 4 and 5 years took place between November 2017 and November 2021. Overall completion was 70% at each time point, however completion was slightly higher in the control group at all time points, particularly at 4 and 5 years (Figure 1).

The baseline characteristics of infants in whom the 5-year questionnaire was completed were similar in the two groups (Table I). Families of infants in both groups in whom the 5-year 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 AD at randomisation (Table I).

Moisturiser use during follow up: At 3 years, parent-reported application of a moisturiser at least 3 times per week over all or most of the child's body in the past year was still increased in the emollient group (139/449, 31%) compared with the control group (94/471, 20%), and differences remained at 4 years (25% vs 18%) and 5 years (22% vs 16%). In both groups and at all time points, this frequent whole body moisturiser use was more common in children with reported AD.

AD outcomes: Diagnosis of AD at 3, 4 and 5 years was consistently slightly higher in the emollient group when compared to the control group, but adjusted differences were small, and none were statistically significant. The lack of difference between emollient and control groups for AD diagnosis was consistent for different methods of defining AD in the last year, including parental report of a clinical diagnosis, UK Working Party Diagnostic Criteria for AD (Table II) and parental opinion of whether their child had developed AD (Table S2). AD of moderate severity or worse as measured by parent-reported symptoms on the POEM was also very similar between the groups at 3, 4 and 5 years (Table II).

Food allergy outcomes: A greater proportion of parents reported a reaction to any food within the previous year at 3 and 4 years in the emollient group than in the control group (3 years 81/430 (19%) emollient, 56/455 (12%) control, adjusted relative risk (RR) 1.37, 95% CI 1.02 to 1.85, Table III). 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 were also slightly higher in the emollient group than in the control group at 3 and 4 years (Table III). At 5 years, all outcomes relating to food allergy were similar between the two groups (Table III).

Wheezing and allergic rhinitis outcomes: At 3 years, 96/449 (21%) parents in the emollient group and 134/472 (28%) parents in the control group reported wheezing or whistling in their child's chest in the previous year (adjusted RR 0.79, 95% CI 0.64 to 0.98). The percentage of parents reporting wheezing or whistling in the previous year decreased in both groups at 4 and 5 years with no difference between groups observed at 5 years (Table IV). Parental report of symptoms of allergic rhinitis were

similar between groups at 3, 4 and 5 years, with approximately a quarter of parents in each group reporting such symptoms in the previous year (Table IV).

Cumulative incidence outcomes: There were no differences between the two groups in the cumulative incidence of a parental report of a clinical diagnosis of AD, food allergy, asthma or allergic rhinitis by 5 years (Table V). By 5 years, 188/608 (31%) parents in the emollient group and 178/631 (28%) parents in the control group had reported a clinical diagnosis of AD since their child was 12 months (adjusted RR 1.10, 95% CI 0.93 to 1.30). Parental report of clinical diagnosis of food allergy by 5 years was reported in 92/609 (15%) parents in the emollient group compared with 87/632 (14%) parents in the control group (adjusted RR 1.11, 95% CI 0.84 to 1.45). Results from sensitivity analyses exploring the impact of a worse outcome in those with missing data were consistent with the main analyses (see Table S3). Subgroup analyses according to *FLG* genotype found no evidence of an interaction (see Table S4). Although safety data was not specifically recorded in the 3 to 5 year follow-up period, no safety concerns such as serious infections or slippages were spontaneously reported during that period.

Discussion

Main findings: This study presents the first long-term follow-up data from an emollient for AD prevention trial documenting AD and other atopic outcomes to 5-years. Consistent with earlier findings from the BEEP trial, we found no evidence for an effect of daily emollient application during the first year of life on longer term AD risk.

Our data also show no clear evidence for an effect of regular emollient application during infancy on risk of other atopic outcomes during the first 5 years of life. Some food allergy outcomes were *increased* in the emollient group, consistent with findings at age 2 years. Food allergy findings were however inconsistent and imprecise with no effect seen in cumulative incidence of parent reported food allergy diagnosis by age 5 years. Similar to AD outcomes, we can be reasonably confident that daily emollient during infancy did not *reduce* food allergy risk. There was also no evidence of a protective effect of emollients for the development of parentally reported wheeze or doctor-diagnosed asthma or allergic rhinitis – perhaps now best considered as co-morbidities rather than sequential development of similar diseases (31-33).

At 2 years, there was no evidence of a difference in the effect of daily emollient on risk of developing AD according to presence of mutations on the gene encoding for *FLG* and findings were similar at 5 years. However, confidence intervals for the interaction effect show a large amount of uncertainty as the trial was not powered to detect interactions.

Although data at 2 years in the BEEP study showed an increase in parental reported physician-diagnosed minor skin infections in the emollient group in the first year (22), no new safety concerns were identified between 2 and 5 years.

*Interpretation in context with other studie*s: Our findings are consistent with another large clinical trial (34) and with the recent individual patient data (IPD) meta-analysis of emollient prevention studies (35). The IPD included 10 trials of 5154 participants and showed that skincare interventions did not change the risk of AD by the age 1-3 years (RR 1.03, 95% CI 0.81 to 1.31; I2 =41%; moderate certainty; 3075 participants, 7 trials). One single centre study (36) has reported a 30% reduction in AD at 12 months following early initiation of daily specialised emollient use until 2 months of age. Other studies using more sophisticated emollients containing ceramides have not shown any benefit for AD prevention (35). Not all emollients are the same in terms of their effects on the skin barrier (37). It is still possible that some emollients could reduce or delay AD development as the role of epithelial barrier disruption in the development of allergic disorders is quite convincing (38). Perhaps barrier enhancement would work in a low-risk rather than high-risk population or perhaps only when combined with enhanced skin care such as reduced bathing and soap avoidance, but the evidence for benefit so far has been disappointing. The

alternative conclusion is that emollient application in early life does not work in terms of preventing AD and that the strongest influences on AD development in high risk children are genetic and in utero programming. Although data on food allergy from BEEP is inconclusive, data from the Enquiring About Tolerance (EAT) trial showed a significant dose-response relationship between parent-reported moisturisation frequency at 3 months of age and the subsequent development of food allergy raising the possibility that that regular application of moisturisers in early life could paradoxically promote food allergy development through transcutaneous sensitisation (39).

Strengths and limitations of this study: Strengths include the long duration of follow-up (up to 5 years since birth) as well as the randomised study design. Follow-up rates of around 70% beyond 2 years are excellent for such a low-contact pragmatic trial, especially given that the lack of benefit for the primary outcome at 2 years had been shared with participants. It is possible that knowledge of the primary outcome results at 2 years could have influenced responses after that point, but it is unlikely that a parent report of AD in their child after 2 years would vary according to their allocation status. Questionnaire completion in the control group was very slightly higher and it is unclear whether this was due to chance or some other factor. Non-responders to long term follow up differed slightly from responders as listed above, but sensitivity analyses assuming non-responders were more likely to have had the outcomes of interest did not change any of the conclusions. Unlike the 2-year primary outcome data for AD that included an objective assessment of the presence or absence of AD using the UK refinement of the Hanifin and Rajka criteria and the Eczema Area and Severity Index measure, follow-up data at 3, 4 and 5 years was based on parental report only, raising the possibility of response bias. Yet it is hard to comprehend why such a response bias should result in such a consistent null result. Furthermore, several alternative outcomes for AD were used including parental report of a clinical diagnosis and completion of a questionnaire-version of the UK diagnostic criteria which has previously been shown to have good validity compared to the face-to-face version (40).

Implications for research: Since application of simple emollients does not appear to prevent AD or associated atopic conditions in high risk families, we suggest that the value of further emollient prevention studies needs to be carefully considered, with a priority given to novel approaches to infant skincare. Around 15 emollient trials are in progress, and ensuring that all are transparently published and contribute to the living IPD meta-analysis is important. Although replicating a systematic review can sometimes be useful, lots more systematic reviews using the same aggregate data and an incomplete list of existing studies are unlikely to be helpful (24, 41). Longer-term data, such as the 5-year data presented in this paper, are useful as are more data on the possible increased risk of skin infections and food sensitisation and allergy in other trials. Other approaches for protecting the skin barrier in early life such as softening domestic water and reducing soap exposure (42) are also needed.

Implications for clinical practice: Evidence up to 5 years plus combined evidence from other emollient prevention studies do not support a preventative effect on AD or associated allergic diseases, and cannot be recommended. Asking parents to apply

emollient all over a baby's body daily for the first year of life is a significant undertaking, so producing evidence to show that it is not beneficial is helpful in reducing burden on families. Daily emollients for a whole year can also represent a significant socio-economic burden for families and their use risks over-medicalising otherwise healthy children. The potential signals of possible adverse effects can also not be ignored. An increase in parental report of skin infections in the emollient group at 2 years in the BEEP study, was also noted in other studies including the IPD meta-analysis (RR 1.34, 95% CI 1.02 to 1.77; I2 =0%; moderate certainty; 2728 participants, 6 trials). Although the reported skin infections were very diverse and none of the infections were serious, they can lead to morbidity, unnecessary antibiotic use and increased healthcare consultations. The food allergy data from BEEP at 2 years was inconclusive (adjusted RR 1.47, 95% CI 0.93 to 2.33) but data from observational studies suggest that frequency of emollient use in infancy is associated with increased risk of food allergy (39). Concerns regarding increased skin infections and food allergy are therefore both additional reasons why emollient use for AD prevention should not be recommended.

Conclusion: This study presents follow-up of infants participating in the BEEP randomised controlled trial up to 5 years and, consistent with other previously published outcome data at 2 years, does not show any effect in preventing or delaying atopic dermatitis occurrence or its severity. There was also no benefit with regard to a potential prevention of other atopic diseases. Healthcare professionals including dermatologists, paediatricians, allergologists and general practitioners should be aware that intense moisturisation from birth cannot be recommended for AD prevention or other atopic diseases. Research efforts need to explore other ways of enhancing the skin barrier in early life as a means to prevent AD and associated conditions.

References

1. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. J Allergy Clin Immunol. 2009;124(6):1251-8 e23.
2. Abuabara K, Yu AM, Okhovat JP, Allen IE, Langan SM. The prevalence of atopic dermatitis beyond childhood: A systematic review and meta-analysis of longitudinal studies. Allergy. 2018;73(3):696-704.
3. Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL, et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. Allergy. 2018;73(6):1284-93.
4. Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR. Is eczema really on the increase worldwide? J Allergy Clin Immunol. 2008;121(4):947-54.e15.
5. Brown SJ. Atopic Eczema: How Genetic Studies Can Contribute to the Understanding of this Complex Trait. The Journal of investigative dermatology. 2022;142(4):1015-9.
6. Williams HC. Atopic eczema - we should look to the environment. BMJ. 1995;311(7015):1241.
7. Ständer S. Atopic Dermatitis. The New England journal of medicine. 2021;384(12):1136-43.
8. Williams HC, Chalmers J. Prevention of Atopic Dermatitis. Acta dermato-venereologica. 2020;100(12):adv00166.
9. Bawany F, Beck LA, Järvinen KM. Halting the March: Primary Prevention of Atopic Dermatitis and Food Allergies. J Allergy Clin Immunol Pract. 2020;8(3):860-75.
10. Foisy M, Boyle RJ, Chalmers JR, Simpson EL, Williams HC. Overview of Reviews The prevention of eczema in infants and children: an overview of Cochrane and non-Cochrane reviews. Evid Based Child Health. 2011;6(5):1322-39.
11. Garcia-Larsen V, Ierodiakonou D, Jarrold K, Cunha S, Chivinge J, Robinson Z, et al. Diet during pregnancy and infancy and risk of allergic or autoimmune disease: A systematic review and meta-analysis. PLoS medicine. 2018;15(2):e1002507.
12. Paller AS, Spergel JM, Mina-Osorio P, Irvine AD. The atopic march and atopic multimorbidity: Many trajectories, many pathways. J Allergy Clin Immunol. 2019;143(1):46-55.
13. Brown SJ, Elias MS, Bradley M. Genetics in Atopic Dermatitis: Historical Perspective and Future Prospects. Acta dermato-venereologica. 2020;100(12):adv00163.
14. Lowe AJ, Leung DYM, Tang MLK, Su JC, Allen KJ. The skin as a target for prevention of the atopic march. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2018;120(2):145-51.
15. Sugita K, Soyka MB, Wawrzyniak P, Rinaldi AO, Mitamura Y, Akdis M, et al. Outside-in hypothesis revisited: The role of microbial, epithelial, and immune interactions. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2020;125(5):517-27.
16. Tsakok T, Marrs T, Mohsin M, Baron S, du Toit G, Till S, et al. Does atopic dermatitis cause food allergy? A systematic review. J Allergy Clin Immunol. 2016;137(4):1071-8.
17. Tham EH, Rajakulendran M, Lee BW, Van Bever HPS. Epicutaneous sensitization to food allergens in atopic dermatitis: What do we know? Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2020;31(1):7-18.
18. Maiello N, Comberiati P, Giannetti A, Ricci G, Carello R, Galli E. New Directions in Understanding Atopic March Starting from Atopic Dermatitis. Children (Basel, Switzerland). 2022;9(4).

19. Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WH, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. J Allergy Clin Immunol. 2014;134(4):818-23.
20. Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. J Allergy Clin Immunol. 2014;134(4):824-30 e6.
21. Chalmers JR, Haines RH, Mitchell EJ, Thomas KS, Brown SJ, Ridd M, et al. Effectiveness and cost-effectiveness of daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children (The BEEP trial): protocol for a randomised controlled trial. Trials. 2017;18(1):343.
22. Chalmers JR, Haines RH, Bradshaw LE, Montgomery AA, Thomas KS, Brown SJ, et al. Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial. Lancet (London, England). 2020;395(10228):962-72.
23. Kelleher MM, Cro S, Cornelius V, Lodrup Carlsen KC, Skjerven HO, Rehbinder EM, et al. Skin care interventions in infants for preventing eczema and food allergy. The Cochrane database of systematic reviews. 2021;2(2):Cd013534.
24. Kelleher MM, Cro S, Phillips R, Williams HC, Lowe AJ, Boyle RJ. Correspondence to " Emollients in infancy to prevent atopic dermatitis: A systematic review and meta-analysis". Allergy. 2022;77(6):1931-3.
25. Williams HC, Burney PG, Pembroke AC, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. The British journal of dermatology. 1994;131(3):406-16.
26. BEEPTrial. The BEEP Study, Participant Newsletter - Results Edition 2019 [Available from: https://www.nottingham.ac.uk/research/groups/cebd/documents/researchdocs/beep-parentsresultsnewsletterweb.pdf]
27. Spuls PI, Gerbens LAA, Simpson E, Apfelbacher CJ, Chalmers JR, Thomas KS, et al. Patient-Oriented Eczema Measure (POEM), a core instrument to measure symptoms in clinical trials: a Harmonising Outcome Measures for Eczema (HOME) statement. The British journal of dermatology. 2017;176(4):979-84.
28. Endre KMA, Landrø L, LeBlanc M, Gjersvik P, Lødrup Carlsen KC, Haugen G, et al. Diagnosing atopic dermatitis in infancy using established diagnostic criteria: a cohort study. The British journal of dermatology. 2022;186(1):50-8.
29. BEEPTrial. A randomised controlled trial to determine whether applicatoin of emollient from birth can prevent eczema in high risk children (BEEP Trial) - Statistical Analysis Plan 2022 [Available from: https://www.nottingham.ac.uk/research/groups/cebd/documents/researchdocs/0935-beep-sap-final-v2.0-20220106-signed.pdf]
30. Norton EC, Miller MM, Kleinman LC. Computing Adjusted Risk Ratios and Risk Differences in Stata. The Stata Journal. 2013;13(3):492-509.
31. Maiello N, Giannetti A, Ricci G, Cinicola B, Carello R, Indolfi C, et al. Atopic dermatitis and atopic march: which link? Acta bio-medica : Atenei Parmensis. 2021;92(S7):e2021525.
32. Custovic A, Custovic D, Kljaić Bukvić B, Fontanella S, Haider S. Atopic phenotypes and their implication in the atopic march. Expert review of clinical immunology. 2020;16(9):873-81.
33. Williams H, Flohr C. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. J Allergy Clin Immunol. 2006;118(1):209-13.
34. Skjerven HO, Rehbinder EM, Vettukattil R, LeBlanc M, Granum B, Haugen G, et al. Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial. Lancet (London, England). 2020;395(10228):951-61.
35. Kelleher MM, Cro S, Van Vogt E, Cornelius V, Lodrup Carlsen KC, Ove Skjerven H, et al. Skincare interventions in infants for preventing eczema and food allergy: A cochrane systematic review and individual participant data meta-analysis. Clin Exp Allergy. 2021;51(3):402-18.

36. Chaoimh CN, Lad D, Nico C, Puppels GJ, Wong XFCC, Common JE, et al. Early initiation of short-term emollient use for the prevention of atopic dermatitis in high risk infants – the STOP AD randomised controlled trial. Allergy. 2022;Accepted(Epub ahead of print. PMID: 35997592).
37. Danby SG, Andrew PV, Taylor RN, Kay LJ, Chittock J, Pinnock A, et al. Different types of emollient cream exhibit diverse physiological effects on the skin barrier in adults with atopic dermatitis. Clinical and experimental dermatology. 2022.
38. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? Nature reviews Immunology. 2021;21(11):739-51.
39. Perkin MR, Logan K, Marrs T, Radulovic S, Craven J, Boyle RJ, et al. Association of frequent moisturizer use in early infancy with the development of food allergy. J Allergy Clin Immunol. 2021;147(3):967-76.e1.
40. Fleming S, Bodner C, Devereux G, Russell G, Campbell D, Godden D, et al. An application of the United Kingdom Working Party diagnostic criteria for atopic dermatitis in Scottish infants. The Journal of investigative dermatology. 2001;117(6):1526-30.
41. Williams HC. Are Dermatology Systematic Reviews Spinning Out of Control? Dermatology (Basel, Switzerland). 2021;237(4):493-5.
42. Jabbar-Lopez ZK, Ezzamouri B, Briley A, Greenblatt D, Gurung N, Chalmers JR, et al. Randomized controlled pilot trial with ion-exchange water softeners to prevent eczema (SOFTER trial). Clin Exp Allergy. 2022;52(3):405-15.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project number 12/67/12). The funder had no role in the study design, collection, analysis and interpretation of data; in the writing or the report; and in the decision to submit the article for publication.

The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, or the Department of Health.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Access to the data will be subject to review of a data sharing and use request (available from ctu@nottingham.ac.uk) by a committee including the CI and sponsor, and will only be granted upon receipt of a data sharing and use agreement. Any data shared will be pseudoanonymised which may impact on the reproducibility of published analyses.

The study protocol, statistical analysis plan and health economics analysis plan are available on the trial website: https://www.nottingham.ac.uk/research/groups/cebd/projects/1eczema/beep-maintrial.aspx.

Author contributions

HCW conceived of the trial and was the Chief Investigator. HCW, JRC, RJB, RHH, LEB, AAM, KST, SJB, MJR, SL, ELS, MJC, THS, CF, EJM, SDJ, NJ, and MP all contributed to the conception or design of the trial. JB, LAW, EJM, RHH, RS and ST supported the conduct of the trial, including acquisition of the data. RJB led on the

food allergy outcomes and NJ, MK, HA and MRP contributed to this. AAM and LEB were responsible for the statistical analysis. THS was the health economist with STL. MJC provided expertise in emollients and the skin barrier. SJB was responsible for the genetic analysis. ELS, KST, MJR, SJB, SL, SDJ and CF all contributed clinical experience of eczema and/or eczema trials.

The manuscript was drafted by HCW, LAW, RJB and LEB; all other authors critically reviewed and revised the manuscript. All authors have approved the final version.

Acknowledgements

Research nurse support was provided by the NIHR Clinical Research Networks. The trial was developed with and supported by the UK Dermatology Clinical Trials Network (UK DCTN) and designed in collaboration with and managed by the Nottingham Clinical Trials Unit (NCTU). Grace Holt (NCTU) independently validated the analysis for the UKWP AD tertiary outcome. The majority of the genetic analysis work was undertaken by SJB whilst at the Skin Research Group, School of Medicine, University of Dundee. During this time SJB also worked clinically at the Ninewells Hospital and Medical School, Dundee. UKDCTN is grateful to the British Association of Dermatologists and the University of Nottingham for financial support of the Network.

We would like to thank the parents and infants who took time to participate in this trial, and the patients who contributed to trial design by providing helpful feedback at different stages of trial development.

We would like to thank the independent members of the Trial Steering Committee: Sarah Meredith, (Chair, Medical Research Council Clinical Trials Unit), Angela Crook (Statistician, Medical Research Council Clinical Trials Unit), Paula Beattie (Dermatologist, Royal Hospital for Sick Children, Glasgow), Kirsty Logan (Paediatric Epidemiologist, King's College London) and Emma Thomas (patient representative). Michael Perkin (St. George's, London) was previously an independent member of the TSC prior to becoming part of the team involved in the food allergy assessment.

Tables

Table I: Baseline characteristics according to allocated group and follow-up at 5 years

Table II: Parental reported presence of AD and severity of AD at 3, 4 and 5 years

Table III: Parental report of reactions to foods and clinical diagnosis of food allergy at 3, 4 and 5 years

Table IV: Parental reported wheezing and allergic rhinitis symptoms at 3, 4 and 5 years

Table V: Parental report of clinical diagnoses of AD, food allergy, asthma and allergic rhinitis by 5 years

Figures

Figure 1: Participant flow diagram

Table I: Baseline characteristics according to allocated group and follow-up at 5 years

	Emollient – completed 5-year questionnaire (n = 467)	Emollient – did not complete 5-year questionnaire (n = 226)	Control – completed 5-year questionnaire (n = 509)	Control – did not complete 5-year questionnaire (n = 192)
Age of mother at randomisation – mean [sd]	32.5 [4.6]	30.2 [6.2]	32.2 [4.9]	29.7 [5.6]
Parental-reported number of first-degree relatives with atopic disease				
1	179 (38%)	75 (33%)	191 (38%)	62 (32%)
2	192 (41%)	108 (48%)	214 (42%)	82 (43%)
3 or more	96 (21%)	43 (19%)	104 (20%)	48 (25%)
At least one first degree relative with history of AD (parent-report of doctor diagnosis)	388 (83%)	175 (77%)	428 (84%)	152 (79%)
Ethnicity of mother				
White	413 (88%)	176 (78%)	449 (88%)	152 (79%)
Asian	28 (6%)	17 (8%)	29 (6%)	11 (6%)
Black	11 (2%)	20 (9%)	7 (1%)	15 (8%)
Other	15 (3%)	13 (6%)	24 (5%)	14 (7%)
Number of other children in household at screening				
0	199 (43%)	76 (34%)	232 (46%)	61 (32%)
1	195 (42%)	91 (40%)	200 (39%)	71 (37%)
2	55 (12%)	40 (18%)	56 (11%)	40 (21%)
3 or more	18 (4%)	19 (8%)	21 (4%)	20 (10%)

	Emollient – completed 5-year questionnaire (n = 467)	Emollient – did not complete 5-year questionnaire (n = 226)	Control – completed 5-year questionnaire (n = 509)	Control – did not complete 5-year questionnaire (n = 192)
Decile of English index of multiple deprivation 2015, median [25th, 75th centile]	7 [4, 9]	4 [3, 7]	6 [4, 9]	4 [2, 7]

Other ethnicities include mixed ethnicity, Middle Eastern and south American.

Table II: Parental reported presence of AD and severity of AD at 3, 4 and 5 years

	Emollient	Control	Adjusted relative risk (95% CI)	Adjusted difference in risk (95% CI)
Presence of AD in the previous year based on parental report of a clinical diagnosis of AD				
3 years	81/469 (17%)	61/493 (12%)	1.31 (0.97 to 1.76)	4.1% (-0.4% to 8.6%)
4 years	50/462 (11%)	46/509 (9%)	1.20 (0.83 to 1.73)	1.9% (-1.9% to 5.7%)
5 years	49/462 (11%)	34/492 (7%)	1.41 (0.94 to 2.12)	3.1% (-0.5% to 6.6%)
Presence of AD based on completion by parents of UK Working Party Diagnostic Criteria for AD				
3 years	119/474 (25%)	109/495 (22%)	1.07 (0.87 to 1.33)	1.7% (-3.4% to 6.8%)
4 years	122/458 (27%)	134/511 (26%)	1.01 (0.82 to 1.24)	0.2% (-5.2% to 5.5%)
5 years	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 AD according to POEM				
3 years	30/464 (6%)	37/482 (8%)	0.85 (0.55 to 1.31)	-1.2% (-4.4% to 2.0%)
4 years	32/453 (7%)	45/505 (9%)	0.82 (0.54 to 1.23)	-1.6% (-4.9% to 1.7%)
5 years	42/458 (9%)	39/496 (8%)	1.12 (0.76 to 1.66)	1.0% (-2.4% to 4.5%)

POEM=Patient-Oriented Eczema Measure
Adjusted relative risk/difference in risk estimated using a mixed effects logistic regression model using all available outcome data (including time points prior to 3 years) adjusting for randomisation stratification variables and including a random effect for participants. The number of participants and observations included in each analysis model are shown in Table S1.

Table III: Parental report of reactions to foods and clinical diagnosis of food allergy at 3, 4 and 5 years

	Emollient	Control	Adjusted relative risk (95% CI)	Adjusted difference in risk (95% CI)
Parental report of reaction to any food within the previous year				
3 years	81/430 (19%)	56/455 (12%)	1.37 (1.02 to 1.85)	5.0% (0.3% to 9.7%)
4 years	59/419 (14%)	43/472 (9%)	1.54 (1.08 to 2.20)	5.0% (0.9% to 9.2%)
5 years	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[1]				
3 years	40/437 (9%)	26/468 (6%)	1.44 (0.92 to 2.27)	2.7% (-0.6% to 5.9%)
4 years	29/432 (7%)	21/485 (4%)	1.64 (0.97 to 2.76)	2.8% (-0.2% to 5.7%)
5 years	21/429 (5%)	21/453 (5%)	1.05 (0.60 to 1.84)	0.3% (-2.5% to 3.0%)
Parental report of a clinical diagnosis of food allergy within the previous year				
3 years	37/407 (9%)	20/422 (5%)	1.55 (0.96 to 2.49)	3.0% (-0.3% to 6.2%)
4 years	26/453 (6%)	17/498 (3%)	1.54 (0.89 to 2.66)	2.1% (-0.6% to 4.7%)
5 years	19/441 (4%)	15/474 (3%)	1.16 (0.64 to 2.11)	0.6% (-1.8% to 3.0%)

1 - Immediate defined as reaction within 2 hours of eating the food

Adjusted relative risk/difference in risk estimated using a mixed effects logistic regression model using all available outcome data (including time points prior to 3 years) adjusting for randomisation stratification variables and including a random effect for participants. The number of participants and observations included in each analysis model are shown in Table S1.

Table IV: Parental reported wheezing and allergic rhinitis symptoms at 3, 4 and 5 years

	Emollient	Control	Adjusted relative risk (95% CI)	Adjusted difference in risk (95% CI)
Parental report of wheezing or whistling in the chest in previous year				
3 years	96/449 (21%)	134/472 (28%)	0.79 (0.64 to 0.98)	-6.0% (-11.4% to -0.5%)
4 years	81/456 (18%)	115/501 (23%)	0.84 (0.66 to 1.07)	-3.7% (-8.7% to 1.3%)
5 years	63/459 (14%)	72/490 (15%)	1.00 (0.74 to 1.35)	0.0% (-4.4% to 4.4%)
Parental report of allergic rhinitis symptoms in previous year				
3 years	120/455 (26%)	123/477 (26%)	1.02 (0.83 to 1.25)	0.5% (-5.2% to 6.2%)
4 years	111/453 (25%)	136/498 (27%)	0.91 (0.74 to 1.12)	-2.5% (-8.1% to 3.1%)
5 years	120/457 (26%)	116/485 (24%)	1.10 (0.89 to 1.35)	2.4% (-3.1% to 8.0%)

Adjusted relative risk/difference in risk estimated using a mixed effects logistic regression model using all available outcome data (including time points prior to 3 years) adjusting for randomisation stratification variables and including a random effect for participants. The number of participants and observations included in each analysis model are shown in Table S1.

Table V: Parental report of clinical diagnoses of AD, food allergy, asthma and allergic rhinitis by 5 years

	Emollient	Control	Adjusted relative risk (95% CI)	Adjusted difference in risk (95% CI)
Parental report of a clinical diagnosis of AD between 12 and 60 months[1]	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 5 years[1]	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 5 years[2]	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%)

1 – Outcome derived from responses to questionnaires at 12 (food allergy only), 18 (AD only), 24, 36, 48 and 60 months

2 – Collected on 5 year questionnaire

Analysis used multiple imputation for missing outcomes and included all randomised participants (693 emollient and 701 control). See supplementary materials for further details of the multiple imputation model. Adjusted relative risk/difference in risk estimated in each imputed dataset for food allergy, asthma and allergic rhinitis outcomes using a mixed effects logistic regression model adjusting for randomisation stratification variables (using fixed effect for of number of immediate family members with atopic disease and a random effect for the recruiting centre) and for the AD outcome, due to convergence problems with the mixed effects logistics regression models in some of the imputed datasets, using generalised estimating equations with the Binomial family and log/identity link respectively, with an exchangeable correlation matrix to account for randomisation being stratified by centre and number of immediate family members with atopic disease (1, 2, or more than 2) included as a covariate. Estimates were combined using Rubin's rules.

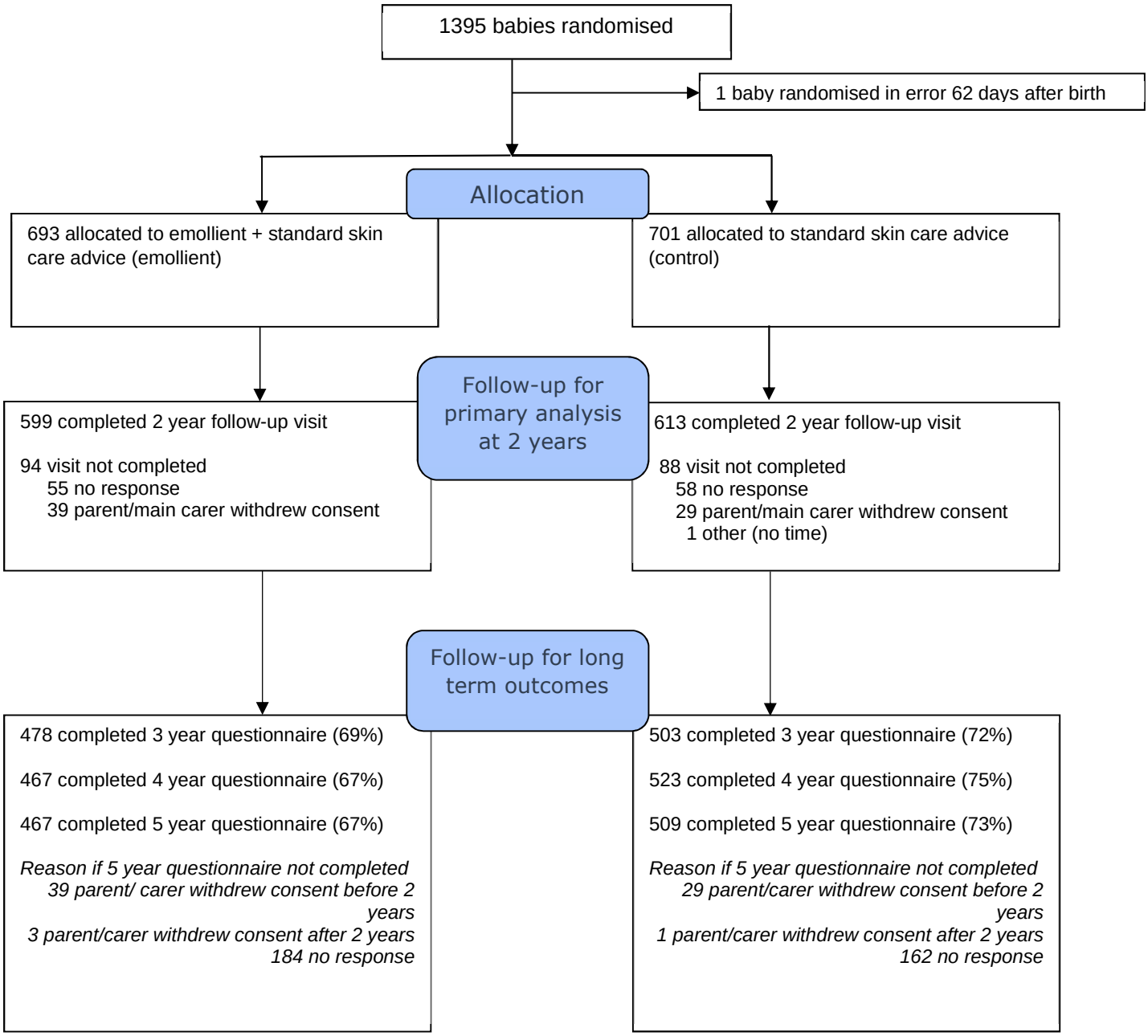

Figure 1_Bradshaw et al.