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ORIGINAL ARTICLE

Early initiation of short-term emollient use for the prevention of atopic dermatitis in high-risk infants—The STOP-AD randomised controlled trial

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Abstract

Background: Protecting the skin barrier in early infancy may prevent atopic dermatitis (AD). We investigated if daily emollient use from birth to 2 months reduced AD incidence in high-risk infants at 12 months.

Methods: This was a single-center, two-armed, investigator-blinded, randomized controlled clinical trial (NCT03871998). Term infants identified as high risk for AD (parental history of AD, asthma or allergic rhinitis) were recruited within 4 days of birth and randomised 1:1 to either twice-daily emollient application for the first 8 weeks of life (intervention group), using an emollient specifically formulated for very dry, AD-prone skin, or to standard routine skin care (control group). The primary outcome was cumulative AD incidence at 12 months. AD <6 months was diagnosed based on clinical presence of AD. The UK Working Party Diagnostic Criteria were applied when diagnosing AD between 6 and 12 months.

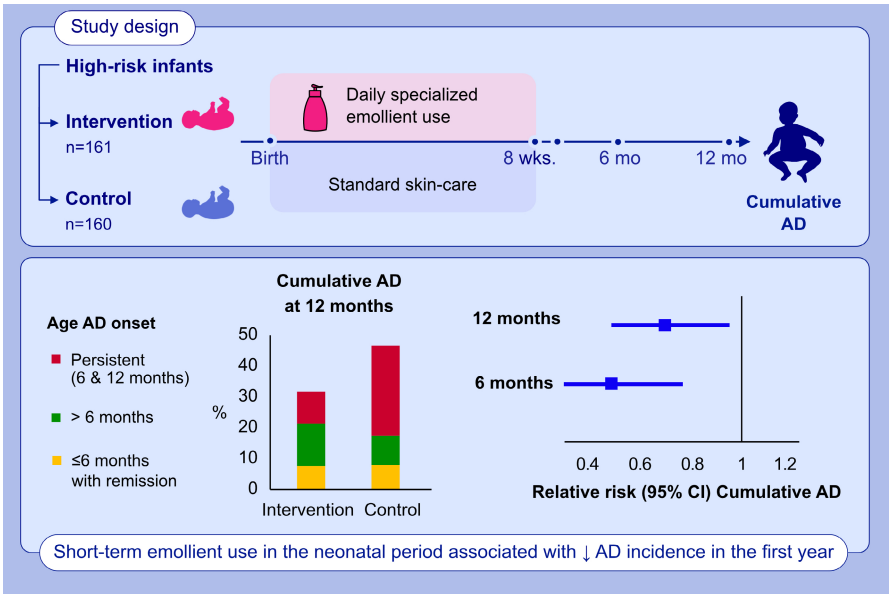
Results: Three hundred twenty-one were randomised (161 intervention and 160 control), with 61 withdrawals (41 intervention, 20 control). The cumulative incidence of AD at 12 months was 32.8% in the intervention group vs. 46.4% in the control group, $p = 0.036$ [Relative risk (95%CI): 0.707 (0.516, 0.965)]. One infant in the intervention group was withdrawn from the study following development of a rash that had a potential relationship with the emollient. There was no significant difference in the incidence of skin infections between the intervention and control groups during the intervention period (5.0% vs. 5.7%, $p > 0.05$).

Abbreviations: AD, Atopic dermatitis; BEEP, The Barrier Enhancement for Eczema Prevention Study; CG, Control group; CI, Confidence interval; CUMH, Cork University Maternity Hospital; FLG, Gene encoding filaggrin; IG, Intervention group; IQR, Inter-quartile range; JJSBF, Johnson & Johnson Santé Beauté France; Lof, Loss-of-function; NMF, natural moisturising factor; OFC, Oral food challenge; PreventADALL, The Preventing Atopic Dermatitis and Allergies in Childhood Study; RCT, Randomized controlled trial; RR, Relative risk; SCORAD, SCORing Atopic Dermatitis; SD, Standard deviation; SPT, Skin prick test; STOP AD, Short-term Topical Application to Prevent Atopic Dermatitis; TEWL, Trans-epidermal water loss; UKWPDC, The UK Working Party Diagnostic Criteria.

Carol Ní Chaoimh and Dhanis Lad should be considered joint first authors.

Conclusions: This study has demonstrated that early initiation of daily specialized emollient use until 2 months reduces the incidence of AD in the first year of life in high-risk infants.

KEYWORDS
atopic dermatitis, emollient, prevention, randomized controlled trial, skin barrier



GRAPHICAL ABSTRACT
This randomized controlled trial investigates if daily emollient use from birth to 2 months can reduce the incidence of AD in high-risk infants. The cumulative incidence of AD at 12 months is 32.8% in the intervention group vs. 46.4% in the control group. A short-term intervention involving early initiation (within 4 days of birth) of daily specialized emollient use until 8 weeks is associated with an approximately 50% and 29% lower risk of cumulative AD at 6 and 12 months, respectively.

1 | INTRODUCTION

Atopic dermatitis (AD), also known as eczema, is a chronic inflammatory skin condition, characterized by dry, red, and itchy skin.[1,2] AD usually begins in infancy and affects up to one-fifth of the children.[3,4] The pathogenesis includes impaired skin barrier function as a significant pathomechanism, along with cutaneous immune dysregulation and microbial disturbances.[5] Supporting this is the consistent evidence that loss-of-function (LoF) mutations in the filaggrin gene (*FLG*), resulting in measurable skin barrier defects, plays a central role in the inherited risk of AD.[6]

Daily emollient use is a cornerstone of AD management.[7] Recently, the spotlight has been on the potential role of emollients in infancy in preventing AD. Prompting this were findings from two small randomised control trials (RCTs) reporting that daily emollient application from birth until 6–8 months reduced AD risk by up to 50%.[8,9] Unexpectedly, these findings were not replicated in two much larger scale studies.[10,11] The Barrier Enhancement for Eczema Prevention (BEEP) trial recruited 1394 high-risk infants and randomised them to either daily emollient application for the first year or to standard skin care advice alone.[10] No evidence of a protective effect of emollient use against AD at 1 or 2 years was found. The Preventing Atopic Dermatitis and Allergies in Childhood (PreventADALL) study involved baths for 5 to 10 min with added emulsified oil and cream applied to the face after the bath on at least 4 days per week from 2 weeks to 8 months and reported no effect on AD prevalence when assessed 4 months later at 12 months. Another RCT where emollient was applied daily to the face only from 0 to 6 months also reported no effect.[12] The data from these three RCTs largely contributed to the conclusion of a recent meta-analysis that skin care interventions probably do not influence AD development.[13] This meta-analysis used an individual participant data approach, excluding studies only providing aggregate data. In contrast, another meta-analysis including more studies found a beneficial effect of emollients in high-risk infants [RR (95% CI: 0.59 (0.43, 0.81))], but only when used up to the point of AD assessment and not when there was an interval between the treatment and the assessment.[14]

The BEEP and PreventADALL studies used petroleum and paraffin-based emollient formulations,[10,11] and while Dissanayake et al. used a more complex ceramide-based emollient, the latter study's intervention involved application to the face only.[12] Data from a small pilot study suggest that emollients with ingredients

specifically designed to repair the skin barrier warrant further investigation.[15] Interventions in BEEP and PreventADALL began at a median age of 11 days and from 2 weeks and continued for 12 and 8 months, respectively.[10,11] Daily emollient application for an extended period in infancy places considerable additional demands on new parents and may not be feasible at a population level, especially if specialized and more expensive emollients are advised. This may be reflected in the low adherence of 27% to the intervention in PreventADALL.[11] We have shown that trans-epidermal water loss (TEWL) increased from birth to 2 months but stabilised thereafter[16] suggesting a shorter intervention period, beginning as soon as possible after birth may represent a more feasible intervention, while targeting a critical period of skin maturation.

This study aimed to investigate if daily emollient use from birth to 2 months can reduce the incidence of AD in high-risk infants.

2 | METHODOLOGY

2.1 | Study design

Short-term Topical Application to Prevent Atopic Dermatitis (STOP AD) was a single-centre, two-armed randomized control trial that postnatally recruited newborn infants at high-risk of AD. Recruitment took place between April 2019 and November 2020 in Cork University Maternity Hospital (CUMH). Parents gave written informed consent prior to participation. Term infants were identified as high-risk if they had at least one parent with a self-reported history of AD, asthma, or allergic rhinitis. Exclusion criteria were pre-term infant (born <37 weeks), admission to the neonatal unit for issues other than feeding, receipt of antibiotics in the maternity hospital, phototherapy, sibling already recruited, other serious health conditions, severe widespread skin condition, or any condition that would make the emollient use inadvisable or not possible (e.g. ankle talipes or hip dysplasia). Participants were not compensated for their participation. The study was conducted in accordance with the Helsinki Declaration and was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals [ref ECM 5 (2) 18/12/18].

2.2 | Randomisation

Infants were randomised (1:1 allocation ratio) within 4 days of birth to either twice-daily emollient application for the first 8 weeks of life (intervention group–IG) or to standard routine skin care advice (control group–CG). Parents and research nurses and staff responsible for recruitment, taking measurements and administering questionnaires were not blinded to study allocation. The sole study doctor (DL) performing AD and food allergy assessments was not involved in recruitment and remained blinded to group allocation throughout the study. Parents in the IG were instructed to apply the emollient AVEENO® Dermexa Fast & Long Lasting Balm (Johnson & Johnson Santé Beauté France, JJSBF) twice daily to the whole body (excluding scalp) for the first 8 weeks, using the familiar, "fingertip" quantitation. The criteria in choosing the study product were that it was commercially available and suitable for use from birth, irritant-free, and that it contained ingredients specifically targeted at improving the skin barrier. The study product, with oat ingredients, fatty acids, and ceramides, developed specifically for very dry itchy skin AD-prone skin, was supplied free to the study by the manufacturer but is publicly available for sale and for use in this age group. IG families were given sufficient moisturizer before they left the maternity hospital. The CG were advised to follow the standard skin care advice given at CUMH, which does not include specific advice on bathing frequency and does not include regular emollient use, unless indicated. Both groups were provided with AVEENO® Baby Daily Care Baby Gentle Wash (JJSBF) to be used at their discretion. Adherence was assessed using questionnaires at 2, 4, and 8 weeks and diaries completed over the intervention period. Adherence to the intervention was defined as using an emollient at least once daily. Contamination in the CG was defined as emollient on four or more days per week. Parents in the IG were asked to return the study product after the intervention period and were advised that they no longer needed to apply emollient daily. Emollient use after the intervention period was at parental discretion in both groups. Advice on emollient use after the intervention was only given if clinically necessary (e.g. in the case of AD).

2.3 | Study visits and procedures

Study visits were at baseline (pre-discharge, within 4 days of birth) and at approximately 2, 4, and 8 weeks and at 6 and 12 months. These involved questionnaires on feeding, health, skin care, and bathing; repeat measurements of weight; TEWL and natural moisturising factor (NMF) and monitoring of skin health.

2.4 | TEWL and NMF measurements

TEWL was measured on the volar forearm using a closed chamber system vapometer (Delfin Technologies, UK) after acclimatization to room conditions for at least 10 min. NMF was measured in vivo, non-invasively, at a depth of 25 ± 3 μm in the stratum corneum of the thenar eminence by Near-Infrared Raman spectroscopy (NMF-scan, RiverD International B.V., Rotterdam, The Netherlands) using a method described previously.[17] Parents were asked not to apply emollient to the measurement areas for 24 h before the assessment.

2.5 | Filaggrin genotyping

Buccal swabs for *FLG* genotyping were collected using Isohelix SK-3S swabs and BFX/S1/05/50 pre-filled buccal fix tubes (Cell Projects ltd). Filaggrin genotyping was performed at the A*STAR Skin Research Labs using Microfluidics PCR for full coverage of *FLG* repeat alleles using a method described previously.[18]

2.6 | Atopic dermatitis assessment

Parents were routinely encouraged to report skin concerns to the study team. Suspected cases of AD were reviewed by the blinded investigator at the earliest opportunity. Cases of AD <6 months were diagnosed based on the presence of AD, assessed either in person or via photographs when an in-person assessment was not possible. The UK Working Party Diagnostic Criteria (UKWPDC) were applied when diagnosing AD between 6 and 12 months.[19] AD extent and severity were evaluated (blinded) using SCORing Atopic Dermatitis (SCORAD) for infants ≥6 months.[20] During the high-level COVID-19 restrictions, AD assessments, including SCORADs, were completed remotely by the blinded investigator using photographs and video links (see Appendix S1 for impact of COVID-19 on study). AD cases were treated with a standardized treatment program, which included advice on emollient use and a topical steroid treatment, where required.

2.7 | Food allergy assessment

Parents were advised to introduce common food allergens including egg, dairy, and peanut early during weaning, as per national guidelines. Suspected cases of food allergy were clinically assessed by the blinded investigator and skin prick testing (SPT) was performed, as indicated. Infants also had SPT to egg, dairy, and peanut if they had not safely consumed these foods by 12 months. Where deemed necessary by the allergy team, those with a positive SPT or a reaction suggestive of food allergy were invited for an oral food challenge (OFC).

2.8 | Outcomes

The primary outcome was cumulative incidence of AD at 12 months. Secondary outcomes included AD incidence at 6 months, cumulative incidence of sensitization to food at 12 months, and the evolution of TEWL and NMF between 0 and 12 months.

2.9 | Sample size

The target sample size was 242 ($n = 121$ per group). This would provide 80% power at a 95% confidence level to detect a 50% reduction in cumulative AD at 12 months from 30% to 15%. The expected AD rate of 30% in this high-risk group was based on data from a previous Irish birth cohort study in the same geographical area.[21]

2.10 | Data analysis

Data were analysed based on a "as randomized, complete-case" approach, where those missing an AD outcome were excluded. Groups were analysed for the primary outcome as randomised, regardless of adherence to study allocation. Data were also stratified by *FLG* genotype to determine if there were any differential effects of the intervention between LoF *FLG* mutation carriers and wildtype. Sensitivity per-protocol analyses were conducted based on adherence data from questionnaires and diaries. Using parent-reported emollient data from questionnaires at 2, 4, and 8 weeks, participants in the IG were included in the per-protocol analysis if they reported at least once-daily emollient use at each of the three time-points. CG participants were included if they reported emollient use of <4 days per week at each time-point. In the diary per-protocol analysis, participants in the IG were included if they recorded emollient use on ≥90% of days in the 8-week recording period, equating to >6 days a week. CG participants were included if they used emollient on ≤43% of the days (<4 days a week). Additional sensitivity analyses were conducted including those in the IG who reported emollient use on ≥4 days a week and those who in the CG who used emollient on <4 days a week to more closely align with the adherence definition used in the BEEP study.[10]

3 | RESULTS

3.1 | Recruitment/retention

A total of 3059 infants were screened for eligibility between April 2019 and November 2020, of whom 321 were randomised (161 to intervention and 160 to control), Figure 1. Baseline characteristics were balanced across the groups (Table 1). There were 61 withdrawals (41 intervention and 20 control, 19% attrition), with the majority (80%) occurring before the 2 week visit. The mean (SD) age at randomization was 1.9 (0.9) days.

3.2 | Protocol adherence

The clinical investigator (DL) remained blinded to group allocation throught the study. In the questionnaires, most parents in the IG reported applying emollient at least once daily in the first 8 weeks; 2 weeks: 89%, 4 weeks: 91.7%, 8 weeks: 86.6% (Table 2). Twice-daily application was reported by 63.3% at 2 weeks, 69.2% at 4 weeks, and 73.1% at 8 weeks. Of those in the IG with questionnaires at all three time-points ($n = 114$), 89 (78.1%) reported daily emollient use at all three time-points. Less than 20% of the CG reported emollient use on ≥4 days per week at any of the time-points; 19% at 2 weeks, 17.5% at 4 weeks, and 13.5% at 8 weeks. Of those in the CG with questionnaires at all time-points ($n = 132$), 90 (68.2%) reported using emollients on <4 days per week at all three time-points. There was no significant difference in bathing frequency between the groups over the intervention period (See Appendix S1 and Table S7).

Diaries measuring adherence were returned by 95% (114/120) of the IG and 82.1% (115/140) of the CG. The mean (SD) age that emollient use started in the IG was 3.5 (1.5) days and 41.2% (47/114) reported that they applied emollient at least once on ≥90% of recording days (>6 days/week). A further 41.2% (47/114) reported

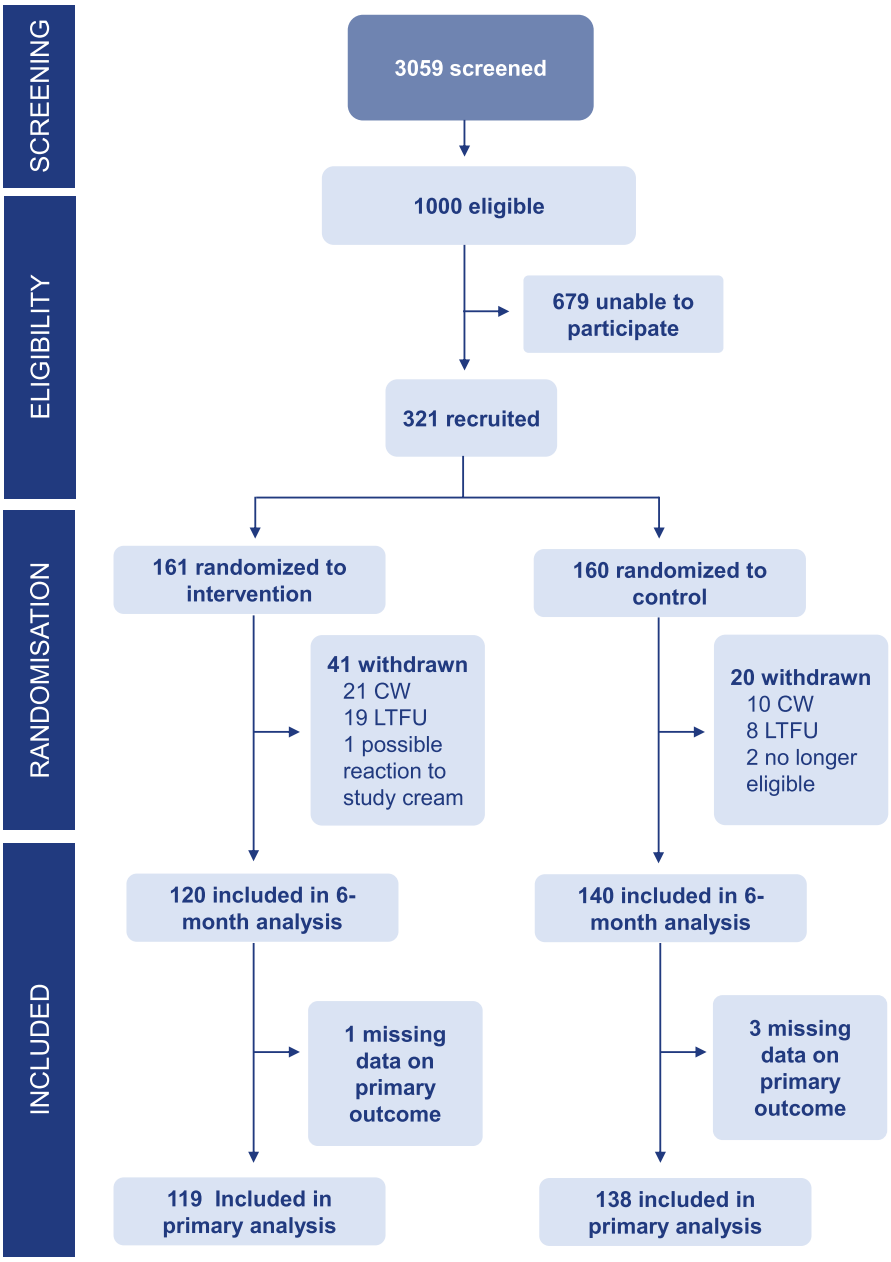


FIGURE 1 Trial profile. *Two infants in the control group were no longer eligible due to receiving phototherapy for jaundice after randomization. The primary outcome was the cumulative incidence of atopic dermatitis at 12 months. CW = Consent withdrawn, LTFU = Lost to follow-up.

emollient use for ≥75% of recording days (>5 days/week). Eighty percent (92/115) of the CG applied an emollient on ≤43% of the recording days (≤3 days a week).

There was no significant difference in the prevalence of regular emollient use (≥4 days a week) between the groups after the intervention period (intervention vs. control: 29.6% vs. 29.7%, $p = 1.000$ at 6 months and 28.4% vs. 25.8%, $p = 0.868$ at 12 months; See Appendix S1 and Tables S1 and S2 for information on bathing frequency and emollient use after the intervention).

3.3 | Safety

No family sought emergency medical assessment related to the study intervention. Parent-reported skin infections during the 8-week intervention period occurred in 5% (6/120) of the IG and 5.7% (8/140) of the CG. One IG infant was advised to stop applying the emollient after developing a rash (erythema on arms, legs, and torso) that had a potential temporal relationship with the emollient and was withdrawn from the study. Two suspected reactions to the study emollient were investigated and confirmed as having no relationship.

3.4 | Primary outcome

The cumulative incidence of AD at 12 months was 32.8% in the IG vs. 46.4% in the CG, $p = 0.036$ [Relative risk (RR) (95% CI): 0.707 (0.516, 0.965), Figure 2]. The point prevalence of AD at 12 months, where the child met the UKWPDC at the assessment, was 20.5% in the IG vs. 38.2% in the CG, $p = 0.003$ [RR (95% CI): 0.536 (0.354, 0.813)].

TABLE 1 Baseline characteristics

	Intervention ($n = 161$)	Control ($n = 160$)
Maternal characteristics		
Age [mean (SD) years]	33.3 (4.4)	34.1 (4.8)
Country of birth (Ireland)	142 (88.2)	139 (86.9)
Ethnicity (white)	156 (96.9)	158 (98.8)
Paternal characteristics		
Age [mean (SD) years]	35.3 (5.7)	35.9 (5.5)
Country of birth (Ireland)	142 (88.2)	143 (89.4)
Ethnicity (white)	157 (97.5)	159 (99.4)
Infant characteristics		
Sex (male)	79 (49.1)	85 (53.1)
Gestational age [mean (SD) weeks]	39.7 (1.1)	39.5 (1.1)
Birth weight [mean (SD) kg]	3.6 (0.4)	3.6 (0.5)
Mode of delivery		
Vaginal	98 (61.3)	103 (64.4)
Caesarean section	62 (38.8)	57 (35.6)
Age randomised [mean (SD) days]	1.9 (1.0)	1.8 (0.8)
Baseline TEWL [median (IQR) gwater/m2/h]	9.31 (7.25, 12.41)	9.25 (7.44, 13.31)
Baseline NMF [median (IQR) g/g protein]	0.32 (0.22, 0.42)	0.33 (0.25, 0.41)
Family history of atopy		
Maternal atopy		
Allergic rhinitis	81 (50.3)	63 (39.4)
Atopic dermatitis	40 (24.8)	56 (35.0)
Asthma	54 (33.5)	63 (39.4)
Any maternal atopy	112 (69.6)	107 (67.3)
Paternal allergy		
Allergic rhinitis	66 (41.8)	75 (47.2)
Atopic dermatitis	43 (27.2)	45 (28.3)
Asthma	56 (35.4)	53 (33.3)
Any paternal atopy	101 (63.9)	107 (67.3)
Two parents with atopic history	52 (32.9)	54 (34.2)
Participant with at least one sibling	87 (54.0)	94 (58.8)
Of which, at least one sibling with		
Allergic rhinitis	20 (23.0)	21 (22.3)
Atopic dermatitis	35 (40.2)	41 (43.6)
Asthma	12 (13.8)	13 (13.8)
FLG genotyping		
FLG wildtype	96/117 (82.1)	113/136 (83.1)
FLG null mutation (one)	21/117 (17.9)	22/136 (16.2)
FLG null mutation (two)	0	1/136 (0.7)

Abbreviations: *FLG* = gene encoding filaggrin, NMF = Natural mositurising factor, TEWL = Transepidermal water loss.

Note: Data are *n* (%) unless stated otherwise.

3.5 | Secondary AD outcome

The cumulative incidence of AD at 6 months was 18.3% in the IG vs. 36.4% in the CG, $p = 0.002$ [RR (95%CI): 0.503 (0.325, 0,779)]. The point prevalence at 6 months was 18.3% in the IG and 35.0% in the CG, $p = 0.004$ [RR (95%CI): 0.524 (0.337, 0813)], Table 3.

Time-to-event survival analysis using the Kaplan- Meier method demonstrates that the IG maintained AD-free skin for a longer period in the first 12 months than the CG ($p = 0.016$, log-rank test, Figure 3). Of those with AD outcome data at 6 and 12 months ($n = 117$ intervention, $n = 137$ control), 7.7% of IG and 8.0% of CG infants were diagnosed at ≤6 months, but no longer met the criteria at 12 months ($p = 1.0$). The prevalence of AD onset between 6 and 12 months was 13.7% and 9.5% in the IG and CG, respectively ($p = 0.397$) and 10.3% vs. 29.2% met the criteria at both 6 and 12 months ($p < 0.001$), (See Figure S1). SCORADs were completed for those ≥6 months at diagnosis ($n = 55$). There was no significant difference in SCORAD total scores at diagnosis between the groups [median (IQR) SCORAD: IG 11.3 (8.0, 18.4), vs. CG 12.3 (7.4, 16.0), $p = 0.888$].

A similar, but non-significant relative risk was observed for the primary outcome in the per-protocol analyses [Questionnaire per-protocol analysis RR (95%) CI: 0.713 (0.501, 1.014), $p = 0.078$; Diary per-protocol analysis RR (95% CI): 0.745 (0.474, 1.173), $p = 0.253$], (See Tables S3–S6).

3.6 | Stratification by *FLG* genotype

Of the 253 with *FLG* genotype data, 17.4% ($n = 44$) had a LoF *FLG* mutation (IG: 17.9%, CG: 16.9%). There were differences in the incidence of cumulative AD between the LoF *FLG* mutation carriers and wildtype groups, with a higher prevalence of AD at 6 (38.6% vs. 26.3%, $p = 0.144$) and 12 months (48.8% vs 38.3%, $p = 0.259$) in *FLG* mutation carriers. When the CG was examined alone, the differences between the mutation and wildtype groups were greater, but remained non-significant while there were no differences in AD incidence at 6 and 12 months between the wildtype and LoF *FLG* groups within the IG (Figure 4A).

The cumulative incidence of AD at 6 and 12 months was lower in the IG vs CG in both the LoF *FLG* mutation and wildype groups; however, the difference at 12 months was not significant for either group (Figure 4B). The effect size (relative risk) at 6 months was greater in the LoF *FLG* mutation group compared with wildtype [RR (95% CI): 0.337 (0.130, 0.873) vs. 0.527 (0.318, 0.871)]. There was a non-significant trend towards a reduced incidence of cumulative AD incidence at 12 months in the IG for both *FLG* groups, with a greater effect size in the LoF *FLG* group [RR (95% CI): 0.524 (0.265, 1.036) vs. 0.722 (0.502, 1.038)].

3.7 | Food allergen sensitization

All infants had been introduced to dairy and almost all had been introduced to egg (99.6%) and peanut (98.0%) by 12 months. Nine

TABLE 2 Parent-reported emollient application frequency at 2, 4, and 8 weeks (questionnaire data)

	Intervention ($n = 120$)			Control ($n = 140$)		
	2 weeks ($n = 118$)	4 weeks ($n = 120$)	8 weeks ($n = 119$)	2 weeks ($n = 137$)	4 weeks ($n = 137$)	8 weeks ($n = 140$)
Never	0	0	0	47 (34.3)	39 (28.5)	34 (24.1)
Occasionally	1 (0.8)	0	0	25 (18.2)	25 (18.2)	25 (17.7)
Once/week	1 (0.8)	0	2 (1.7)	7 (5.1)	9 (6.6)	10 (13.5)
2–3/week	3 (2.5)	3 (2.5)	5 (4.2)	32 (23.4)	40 (29.2)	44 (31.2)
4–6/week	8 (6.8)	6 (5.0)	9 (7.6)	16 (11.7)	17 (12.4)	11 (7.8)
Daily	105 (89.0)	111 (91.7)	103 (86.6)	10 (7.3)	7 (5.1)	8 (5.7)
Twice/day[a]	75 (63.6)	83 (69.2)	87 (73.1)	2 (1.5)	0	0

Note: Data are *n* (%).

[a]"Twice daily" group is a subset of the "Daily" group.

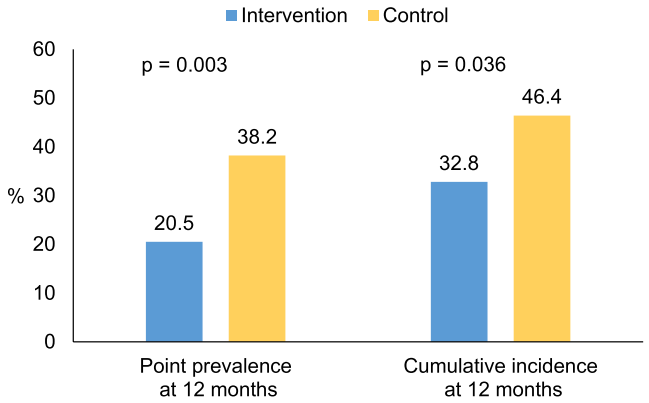


FIGURE 2 Point prevalence and cumulative incidence of AD at 12 months in the intervention and control groups. The point prevalence of AD was calculated based on the number of infants in each group who met the UK Working Party Diagnostic Criteria for atopic dermatitis at 12 months (intervention: 24/117, control: 52/136), as assessed by the blinded investigator. The cumulative incidence of AD was calculated based on the number of infants diagnosed with AD at any point in the first 12 months (intervention: 24/117, control: 52/136). AD = atopic dermatitis.

infants had a positive SPT to at least one food [intervention; 3.3% (4/120), control; 3.6% (5/120), $p = 1.0$].

3.8 | TEWL and NMF evolution

There were no significant differences in TEWL or Thenar NMF between the intervention and control groups at birth, 2, 4, 8 weeks or at 6 and 12 months (See Tables S7 and S8). We also did not observe any early signal in either TEWL or NMF values in those who developed AD in the first 12 months (Tables S9 and S10).

4 | DISCUSSION

In this RCT in high-risk infants, we found that daily emollient use initiated in the first week of life until 2 months is associated with a significant reduction in the cumulative incidence of AD at 12 months. Daily emollient use was associated with a 50% and 29% reduction in the risk of the cumulative incidence of AD at 6 and 12 months, respectively. Similar risk reductions were observed in the per-protocol analyses where only those in the intervention and control groups were included if they used emollients at least once daily and <4 days a week, respectively. However, these were not significant for the primary outcome which may be due to the conservative adherence criteria applied and thus, lower numbers included in the analysis and therefore lower power to detect differences between the groups.

While some AD cases diagnosed before 6 months had resolved by 12 months, there was no difference in transient cases between the groups. As we did not collect longer term data, we cannot exclude the possibility that the intervention may have only delayed the onset of AD beyond 12 months. A recent meta-analysis reported a protective effect of emollients but only when there was no interval between the emollient treatment and AD assessment.[14] However, there was significant heterogeneity between the four studies included in that analysis. In our study, a 29% reduction in the risk of cumulative AD at 12 months was maintained 10 months after the intervention period.

While the study was not powered to detect an effect of the intervention stratified by *FLG* status, we did observe a reduction in AD incidence in both the *FLG* mutation and wildtype groups at 6 months and a trend towards a reduced incidence at 12 months, suggesting that carriers of a *FLG* mutation may benefit more than *FLG* wild type children from early emollient intervention. Indeed, the effect sizes were greater in mutation carriers compared with wildtype. These were not significant at 12 months and would need to be confirmed in a larger group of LoF *FLG* mutation carriers. It may be possible that early emollient use compensates for the additional risk posed by filaggrin deficiency. We have recently shown that thenar NMF measured within days of birth can be used as a surrogate for *FLG* status within days of birth, with the potential to identify a high-risk group that would benefit from targeted intervention.[22] The mechanisms behind the observed protective effect of early emollient use, including the ingredients involved, require investigation.

TABLE 3 Atopic dermatitis outcomes at 6 and 12 months

	Total	Intervention	Control	*p*-value	Relative Risk (95% CI)
Primary outcome					
Cumulative AD at 12 months	103/257 (40.1%)	39/119 (32.8%)	64/138 (46.4%)	0.036	0.707 (0.516, 0.967)
Secondary outcomes					
AD at 12 months					
AD according to the UK Working Party Diagnostic Criteria[a]	76/253 (30%)	24/117 (20.5%)	52/136 (38.2%)	0.003	0.536 (0.354, 0.813)
AD at 6 months					
AD according to the UK Working Party Diagnostic Criteria[a]	71/260 (27.3%)	22/120 (18.3%)	49/140 (35.0%)	0.004	0.524 (0.337, 0.813)
Cumulative AD	73/260 (28.1%)	22/120 (18.3%)	51/140 (36.4%)	0.002	0.503 (0.325, 0.779)

Abbreviations: AD = atopic dermatitis.

[a]Point prevealance.

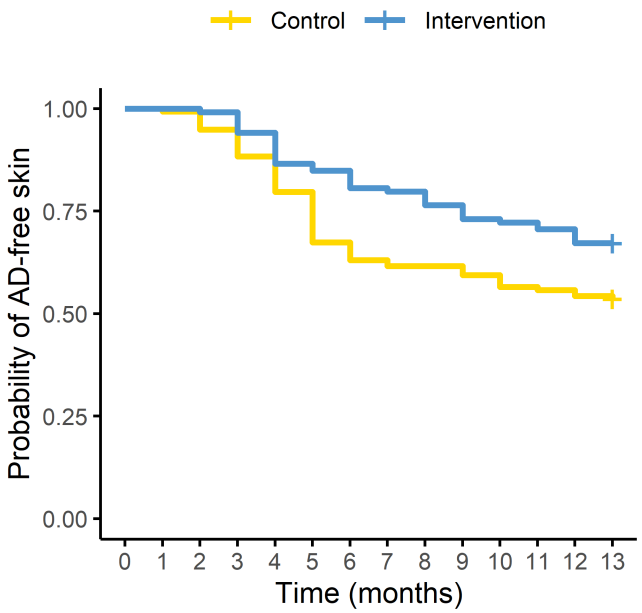


FIGURE 3 Kaplan–Meier plot of the proportion of infants in the intervention and control group without AD during the first 12 months of life. The intervention group maintained AD-free skin for a longer period in the first 12 months than the control group ($p = 0.016$, log-rank test). AD = atopic dermatitis.

Our findings are at variance with recent findings from two large RCTs, where no evidence of a protective effect of emollient use in the first year against AD was found.[10,11] Among the most notable differences between these RCTs and ours was the timing of the intervention. The treatment in STOP AD began within days of birth during a dynamic period of skin maturation and adaption to the dramatic environmental changes of life ex utero. In STOP AD, infants were randomised within 4 days of birth with the IG advised to begin the emollient treatment immediately. In BEEP, the median (IQR) age that emollient use began was 11 days (7, 17) days, with 11% starting emollient application after 3 weeks. In PreventADALL, the intervention began from 2 weeks of age.

The emollients used in BEEP and PreventADALL were basic petroleum and paraffin-based formulations, respectively. The emollient used in this study consists of a formulation with added ceramides developed specifically for very dry itchy skin. Two small studies that also used more complex ceramide-rich emollients reported non-significant trends towards a protective effect against AD.[15,23] Following one of these,[15] a larger scale RCT, the PEBBLES study, involving twice-daily application of the same ceramide-based emollient from 0 to 6 months is ongoing.[24] Here, we showed a reduced risk of AD at 12 months with a short 2-months intervention period, which may represent a more feasible and family friendly strategy for AD prevention.

Our high adherence rates demonstrate the feasibility of implementing a regimen of daily emollient use during the first 2 months of life. Adherence rates using the diaries were lower than reported on the questionnaires but 82.4% still reported using emollients on ≥75% of days equating to over 5 days a week. While infants in this study were followed closely during the intervention period, similar rates of adherence were observed in BEEP, which involved limited contact, but used a less strict definition for adherence (emollient use ≥3 days/week).[10] Only 27% of the IG fully adhered to the protocol in PreventADALL, which may have influenced the absence of a protective effect.[11]

While we did assess food allergy outcomes, this study was not powered to detect a reduction in food allergy risk. Unlike BEEP, where a non-significant increase in food allergy in the IG has been prominently reported (15), we found no difference in the prevalence of food allergy between the groups. While we did not use SPTs to screen for food allergy, almost all infants had tried the most common food allergens—milk, egg, and peanut—by 12 months, so the rate of food sensitization and allergy reported is likely reflective of the true rate in our groups. BEEP reported a higher rate of skin infections in the IG, with suggestions of the possibility of greater pathogen exposure with emollient application.[10] We did not find evidence of an increased risk of skin infections with short-term emollient use.

Despite the reduction of AD risk in the IG, there was no difference in TEWL throughout the first year between the groups. Other studies on emollient use during infancy reported a similar absence of

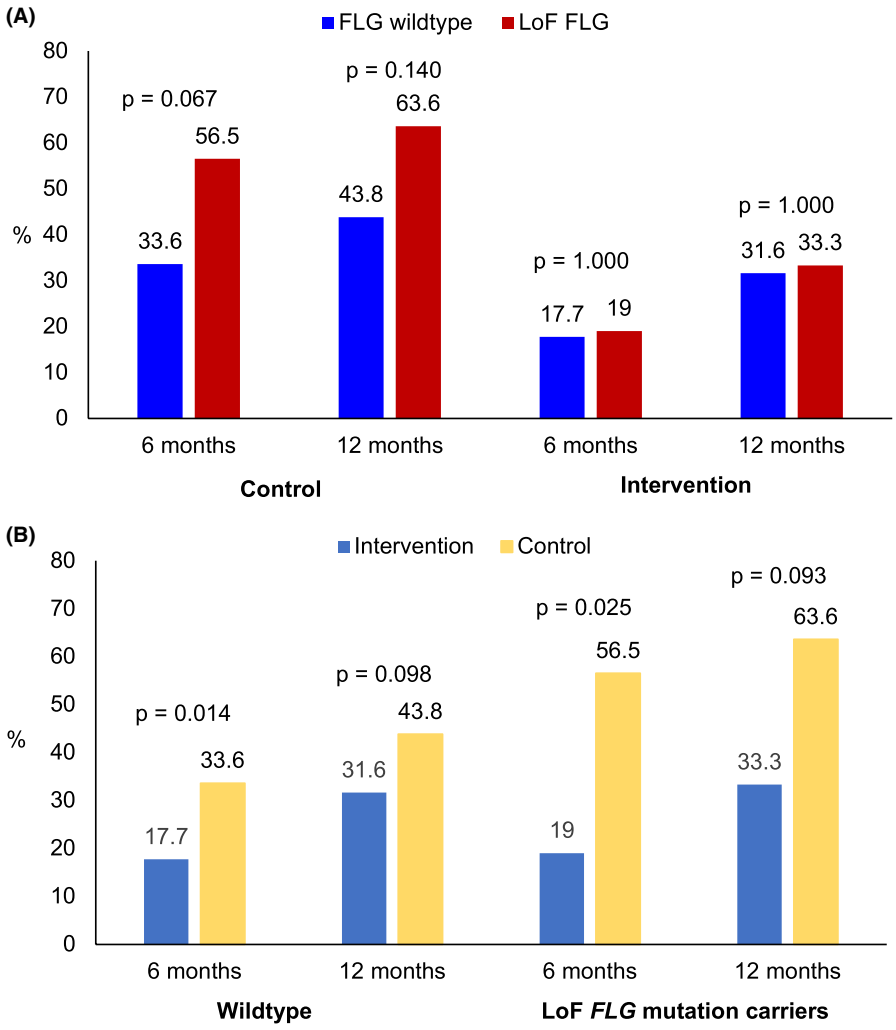


FIGURE 4 (A, B) Cumulative incidence of AD at 6 and 12 months in a LoF *FLG* mutation carriers and wildtype stratified by study treatment (B) intervention and control groups stratified by *FLG* status. The cumulative incidence of AD was calculated based on the number of infants diagnosed with AD at any point in the first 6 and 12 months. There was a non-significant trend towards a reduced incidence of cumulative AD incidence at 12 months in the intervention group for both *FLG* groups, with a greater effect size in the LoF *FLG* group [RR (95% CI): 0.524 (0.265, 1.036) vs. 0.722 (0.502, 1.038)]. LoF = Loss-of-function, *FLG* = gene encoding filaggrin, AD = atopic dermatitis.

an effect of the intervention on TEWL.[15,23] TEWL measurements are influenced by environmental factors and more crucially for infants, subject-specific parameters including stress and crying.[25] This may have affected our ability to detect differences between the groups.

The major strength of this study is the initiation of emollient use within days of birth in the IG. Other strengths include the close follow-up of infants, a high rate of adherence in the IG, and a low rate of contamination in the CG and the 10 months interval between the end of the intervention and the 12 months AD assessment, with no differences in the frequency of emollient use between the IG and CG after the intervention period.

This was a single centre study and, thus, findings may not be generalizable to broader populations. Another limitation is that in response to the COVID-19 pandemic, many AD diagnoses were made remotely. To mitigate this, detailed information and photographs were collected when making a diagnosis. SCORAD assessments were also completed remotely, which may have affected assessments of AD severity. However, as a significant portion of the SCORAD total severity score is rated subjectively by parents, it is less likely to be affected by remote assessment. Validated diagnostic criteria could not be applied when diagnosing earlier onset AD (<6 months), where cases were diagnosed based on presence of AD lesions. However, of the 73 infants diagnosed with AD ≤6 months, 71 (97.3%) met the UKWPDC at 6 months. The prevalence of cumulative AD in this group was higher than expected based on the rates among infants with parental history of atopy in an Irish birth cohort.[21] A possible explanation for this is the a priori recruitment of high-risk infants and the close monitoring of skin health in this study. Only a third (32.1%) of those eligible for this study were recruited. One of the main reasons for the refusal to participate was the demanding follow-up schedule involved, particularly during the intervention period that started before going home with their newborn baby, suggesting that more motivated individuals were recruited. We also had a higher rate of withdrawals in the first 2 weeks of life, particularly in the intervention group, mainly due to withdrawal of consent and not due to early onset of AD by this time. This is a consideration in assessing the feasibility of advising daily emollient use in the early postnatal period to a more general population. Due to pandemic restrictions, we were unable to complete systematic assessment of moisturizer consumption in the intervention group.

We have demonstrated that early initiation of daily specialized emollient use until 2 months reduces the incidence of AD in the first year of life in high-risk infants. The mechanisms behind this

are unclear, but analysis of microbiome diversity and inflammatory biomarkers in a subgroup of this study is ongoing and may provide further information. While several recent studies do not support a protective effect of emollient use in infancy, future studies should examine the use of more complex emollients directed at enhancing the skin barrier in various populations and ethnicities, while identifying a treatment window that is both effective and acceptable to parents.

AUTHOR CONTRIBUTIONS

Carol Ní Chaoimh and Dhanis Lad—substantial contributions to design, lead contributions to acquisition, interpretation and analysis of data, drafting and revising the manuscript. Claudio Nico, Gerwin J. Puppels, X.F.Colin C, and John E. Common—substantial contributions to analysis and interpretation of data and in revising the manuscript. Deirdre M Murray—substantial contribution to study supervision and safety data interpretation and revising manuscript. Alan D. Irvine and Jonathan O'B. Hourihane—lead contributions to the conception and design, substantial contribution to acquisition, interpretation of data, supporting contribution to drafting, and revising manuscript. JOBH is guarantor of this work. All authors have seen and approved the submitted manuscript.

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CONFLICT OF INTEREST

The emollient used in this study was provided by its manufacturer Johnson and Johnson Santé Beauté France (JJSBF) as benefit-in-kind. JJSBF did not have any role in the trial design. JJSBF provided funding for a sub-study within this study, which includes the analysis of the microbiome and inflammatory biomarkers in a subgroup of the study. This is separate from the study's primary funding source. CNC, DL, DM, XFCCW, and JEC declare no conflicts of interest. CN and GJP are employees of RiverD International B.V., which produced the NMF-scan. GJP is the managing director and a shareholder of RiverD International B.V. JO'BH receives research funding, speaker fees, and consultancy fees from Aimmune Therapeutics, research funding and speaker fees from DBV Technologies, and research funding from Clemens von Pirquet Foundation and Temple St Hospital Foundation. ADI is a consultant/on the advisory board for AbbVie, Novartis, Regeneron, Sanofi Genzyme, Pfizer, Eli Lilly, Amgen, Benevolent AI, LEO, Arena. A patent application has been submitted by Johnson & Johnson based on these results, with JO'BH and ADI named as inventors.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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