Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial

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Summary

Background Skin emollients applied during early infancy could prevent atopic dermatitis, and early complementary food introduction might reduce food allergy in high-risk infants. The study aimed to determine if either regular skin emollients applied from 2 weeks of age, or early complementary feeding introduced between 12 and 16 weeks of age, reduced development of atopic dermatitis by age 12 months in the general infant population.

Methods This population-based 2×2 factorial, randomised clinical trial was done at Oslo University Hospital and Østfold Hospital Trust, Oslo, Norway; and Karolinska University Hospital, Stockholm, Sweden. Infants of women recruited antenatally at the routine ultrasound pregnancy screening at 18 weeks were cluster-randomised at birth from 2015 to 2017 to the following groups: (1) controls with no specifi advice on skin care while advised to follow national guidelines on infant nutrition (no intervention group); (2) skin emollients (bath additives and facial cream; skin intervention group); (3) early complementary feeding of peanut, cow's milk, wheat, and egg (food intervention group); or (4) combined skin and food interventions (combined intervention group). Participants were randomly assigned (1:1:1:1) using computer-generated cluster randomisation based on 92 geographical living area blocks as well as eight 3-month time blocks. Carers were instructed to apply the interventions on at least 4 days per week. Atopic dermatitis by age 12 months was the primary outcome, based on clinical investigations at 3, 6 and 12 months by investigators masked to group allocation. Atopic dermatitis was assessed after completing the 12-month investigations and diagnosed if either of the UK Working Party and Hanifi and Rajka (12 months only) diagnostic criteria were fulfi The primary effi analyses was done by intention-to-treat analysis on all randomly assigned participants. Food allergy results will be reported once all investigations at age 3 years are completed in 2020. This was a study performed within ORAACLE (the Oslo Research Group of Asthma and Allergy in Childhood; the Lung and Environment). The study is registered at ClinicalTrials.gov, NCT02449850.

Findings 2697 women were recruited between Dec 9, 2014, and Oct 31, 2016, from whom 2397 newborn infants were enrolled from April 14, 2015, to April 11, 2017. Atopic dermatitis was observed in 48 (8%) of 596 infants in the no intervention group, 64 (11%) of 575 in the skin intervention group, 58 (9%) of 642 in the food intervention group, and 31 (5%) of 583 in the combined intervention group. Neither skin emollients nor early complementary feeding reduced development of atopic dermatitis, with a risk difference of 3·1% (95% CI −0·3 to 6·5) for skin intervention and 1·0% (−2·1 to 4·1) for food intervention, in favour of control. No safety concerns with the interventions were identified. Reported skin symptoms and signs (including itching, oedema, exanthema, dry skin, and urticaria) were no more frequent in the skin, food, and combined intervention groups than in the no intervention group.

Interpretation Neither early skin emollients nor early complementary feeding reduced development of atopic dermatitis by age 12 months. Our study does not support the use of these interventions to prevent atopic dermatitis by 12 months of age in infants.

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Research in context

Evidence before this study

Primary prevention of allergic diseases via strengthening of the skin barrier from early infancy has seemed promising. We searched PubMed for clinical trials with no language or date restrictions, using the terms "primary prevention", "atopic dermatitis" or "eczema", "food allergy," and our search yielded 33 different publications. Two pilot studies reported a 30–50% risk reduction of developing atopic dermatitis in about 100 high-risk infants when daily emollients were applied to the skin from a few weeks of age. However, the potential for primary prevention of atopic dermatitis by using emollient in infancy has not been assessed in large infant cohort studies, or in a general population. Furthermore, primary prevention of allergies, based on the hypothesis that reduced skin barrier function could predispose infants to be sensitised to allergens through a broken skin barrier has not been tested in a large population to date. The Enquiring About Tolerance (EAT) trial from the UK is the only large primary prevention study in a general population-based cohort assessing if food allergy could be prevented by introducing common foods from age 3 months. The EAT trial reported no significant reduction in food allergy by age 3 years in the intention-to-treat analyses, although a significant reduction in peanut allergy was observed in the per-protocol analyses, including about a third of the participants in the intervention group. However, no study has yet determined whether combining a potential skin barrier enhancement and early food introduction might prevent allergic diseases.

Added value of this study

The present study is the first factorially designed study to assess whether two intervention strategies (regular use of emollients from 2 weeks of age or complementary introduction of common foods between age 3 and 4 months, or the combination of these strategies) could reduce allergic diseases. This first report addresses the primary outcome of atopic dermatitis by age 12 months. The effect of these interventions on food allergy will be analysed once all children have completed their 3-year assessment.

Regular baths with high concentrations of bath emollient additives did not show any clinical benefit in development of atopic dermatitis by age 1 year in this large general population-based cohort of 2397 infants. Atopic dermatitis was observed in 8% of participants in the control group, 11% in the skin intervention group, 9% in the food intervention group, and 5% in the combined intervention group. Infants of atopic parents were no more likely to benefit from the skin intervention than low-risk infants. Consequently, our study did not support the results of previous studies that suggested regular emollient use in the first 6 months of life could prevent atopic dermatitis in infants. Neither the per-protocol analysis nor the sensitivity analyses supported a beneficial effect of emollient use on atopic dermatitis incidence. The finding that combined interventions seemed to reduce the incidence of atopic dermatitis by age 12 months is novel and was unexpected. However, analyses of these data when the children reach age 3 years will give further insight into the potential effect of combining emollient use and early complementary food introduction on allergy development as well as on atopic dermatitis.

Implications of all the available evidence

Because this large primary prevention study did not show any clinical benefit for use of emollient bath additives in the prevention of atopic dermatitis by age 12 months, we do not recommend this strategy to be implemented as primary prevention advice for the general public.

Introduction

Atopic dermatitis, a chronic inflammatory disease of the skin, affects 5–30% of children[1,2] and has an impact on patient and family quality of life.[3] Most children with atopic dermatitis present with pruritus, dry skin, and eczematous rash before age 1 year;[4] reduced skin barrier function, a pathophysiological hallmark of atopic dermatitis,[5] has been observed in neonates.[6] In addition to anti-inflammatory therapy, emollient use has been the primary strategy in the management of atopic dermatitis because it enhances the skin barrier against irritants and maintains skin moisture.[7–9] Emollients can be applied as leave-on cream or ointments, or used as soap replacement or bath additives. Bath additives have been widely prescribed for many years in infants and young children as additional treatment for dry skin and eczema, despite few studies assessing its efficacy.[10] A pragmatic randomised clinical trial of 483 children with established atopic eczema showed no evidence of clinical benefit of bath oil emollient additives as an addition to standard management.[9] However, the potential of enhancing the skin barrier by emollient bath additives to prevent atopic dermatitis has not been assessed beyond a small open-label pilot study in children with dry skin at age 6 weeks, whose findings indicated that regular bath emollient at a high concentration significantly reduced dry skin, but not atopic dermatitis by age 6 months.[11] Two pilot studies from 2014 showed reduced atopic dermatitis with daily leave-on emollients that were applied to high-risk infants. Horimukai and colleagues[12] defined high-risk infants as those with a parent or sibling with atopic dermatitis, and Simpson as colleagues[13] as those with a parent or sibling with atopic dermatitis, asthma, or allergic rhinitis.

Infants with atopic dermatitis are also at increased risk of food allergy,[14] asthma, and rhinitis,[4] giving rise to the concept of the atopic march.[15–17] The concept of epicutaneous sensitisation through an impaired skin barrier[18] has been supported by the increased risk of food allergy observed in children aged 2 years with

reduced skin barrier when they were 2 days old, even in the absence of early atopic dermatitis.[19] Therefore, primary allergy prevention should ideally start early and target skin barrier enhancement for reducing atopic dermatitis[20,21] and inducing tolerance to foods through the alimentary tract.[22]

The Preventing Atopic Dermatitis and ALLergies in childhood (PreventADALL) study is the first large, pragmatic, population-based, randomised clinical trial combining two interventions of skin emollient and early complementary feeding aiming to prevent atopic dermatitis by age 12 months and food allergy by age 36 months.[23] The present study primarily aimed to determine if either regular skin emollients or early complementary feeding could prevent atopic dermatitis by age 12 months.

Methods

Study design and participants

The PreventADALL study is an investigator-initiated, 2×2, multicentre, randomised controlled superiority trial done at Oslo University Hospital and Østfold Hospital Trust, Oslo, Norway, and Karolinska University Hospital, Stockholm, Sweden. All women attending the routine 18-week ultrasound pregnancy screening at one of the three sites or in the region of Stockholm between Dec 9, 2014, and Oct 31, 2016, were invited to participate.[23]

All newborn babies of women recruited during pregnancy and born at a minimum gestational age of 35·0 weeks were eligible for randomisation. Exclusion criteria were pregnancy with more than two fetuses; lack of sufficient Scandinavian language skills; plans to move outside a reasonable travel distance within 1 year postpartum; and severe maternal, fetal, or neonatal disease that could potentially influence adherence to the interventions. The study was approved by the Regional Committees for Medical and Health Research Ethics in Norway (2014/518) and Sweden (2014/2242–31/4). Written informed consent was obtained from the mothers at antenatal enrolment and a new written informed consent was obtained from the parents of each newborn before enrolment. The trial design and the baseline characteristics of the participants have previously been published.[23] All follow-up visits were done at the three study sites (appendix pp 12–13).

Randomisation and masking

At the maternity ward of each of the participating hospitals, eligible newborn babies were randomly assigned (1:1:1:1) to the no intervention group, the skin intervention group, the food intervention group, or the combined intervention group, followed by careful appropriate instruction to the parents by trained study personnel. To reduce the risk of intervention contamination across the groups within locally organised well-baby maternity groups, we used computer-generated cluster randomisation based on 92 geographical living area blocks as well as eight 3-month time blocks. All infants born in the same 3-month period and belonging to the same postal code or city area were allocated to the same intervention group (appendix pp 3–4).

The study design did not allow for masking of study participants to the interventions. To limit the risk of observer bias, study personnel who did the clinical follow-up investigations did not have access to the randomisation lists. Furthermore, parents were firmly instructed not to apply any type of emollient bath additives or leave-on emollients within 24 h before each follow-up investigation and all clinical assessments and investigations were done and recorded without knowledge of the group allocation. Hypothesis testing framework and analyses were prespecified in the statistical analysis plan (SAP) before any unmasking of the results.

For the **statistical analysis plan** see https://oslo-universitetssykehus.no/avdelinger/barne-og-ungdomsklinikken/preventadall/SAP_v1.pdf

Procedures

No specific advice on feeding practices or skin care was given to parents of infants in the control group, except following the regular advice from the well-baby clinics and the national guidelines for infant nutrition.[24] In Norway and Sweden, exclusive breastfeeding is generally recommended until age 6 months.

The skin intervention consisted of baths for 5–10 min with added emulsified oil (0·5 dL of bath oil per 8 L of water) and cream applied to the entire face after the bath (Ceridal; GlaxoSmithKline Consumer Healthcare, Philadelphia, PA, USA) on at least 4 days per week, from week 2 to age 8 months. Parents were carefully instructed at the maternity ward on safe baby handling during bathing, including written instructions with illustrations. Flasks of bath oil consisting of paraffinum liquidum and trilaureth-4-phosphate only were produced specifically for the PreventADALL trial by Pharmatech (Østfold, Norway), and were handed out to the participants assigned to the skin intervention together with tubes of Ceridal every 3 months during the clinical investigations from time of birth. Use of soaps was discouraged. The food intervention consisted of complementary feeding introduced between 12 and 16 weeks of age in breastfed or formula-fed babies as follows: peanut butter was given for the first time at the scheduled 3-month clinical follow-up investigation, followed by cow's milk 1 week later, wheat porridge the next week, and finally scrambled eggs in the fourth week of introduction. Parents were instructed to let the infant taste each of the foods from the finger of a parent or from a teaspoon at least 4 days per week and continue to include the foods in the infant's diet to at least 6 months of age (appendix pp 4–7).

Adherence to the interventions was reported as the number of days per week per intervention element in the weekly electronic diaries from age 2–26 weeks, including any deviations from the intervention instruction. Parents of children in all the four groups completed the diaries. Full protocol skin intervention adherence was defined as reported baths with the bath oil additive and the facial

cream for an average of at least 3·5 days per week for at least 16 of the full 25 weeks for which data were available. Additionally, emollients had to be applied for the first time by 4 weeks of age and a sufficient application could not be missed in consecutive weeks.

Food adherence was reported separately for each food. The weekly diary provided the following intake options per interventional food: 0, 1–2, 3–5, or more than 5 days in the past week. For each individual food, full protocol food intervention adherence required intake of each food for a minimum 3–5 days per week for at least 5 weeks. For the overall food intervention, full protocol adherence required full protocol food intervention of at least three of the four foods, and the introduction of at least three of the four foods by week 18. If parents reported adherence in less than 5 of the 8 weeks between age 19–26 weeks, adherence was classified as unknown (appendix pp 7–8, 16).

Adverse events were recorded in weekly electronic diaries up to week 26, in electronic questionnaires every 3 months, and in specific forms by personnel at the discretion of the study personnel (appendix pp 8–9, 14).

Outcomes

The primary outcome was prespecified in the protocol, while the sensitivity analyses were specified in the SAP prior to any analyses and unmasking of the randomisation.

There were two primary outcomes: atopic dermatitis assessed at 12 months of age and food allergy to any intervention allergen assessed at 3 years of age. The primary outcome reported here is atopic dermatitis assessed at 12 months of age. Food allergy will be reported after the 36 month follow-up investigations have been completed in April, 2020.

To increase the likelihood of identifying relevant children with atopic dermatitis, we used two internationally acknowledged diagnostic tools as a basis for our primary outcome measure; the UK Working Party diagnostic criteria[25] used at the 3-month, 6-month, and 12-month follow-up investigations, with the additional use of Hanifin and Rajka[26] diagnostic criteria at age 12 months. The primary outcome of atopic dermatitis was defined as meeting the diagnostic criteria of at least one of these tools at any of the clinical visits up to 12 months of age (appendix p 10).

Exploratory outcomes of asthma (recurrent bronchial obstruction), food allergy to any other allergen, anaphylaxis, or allergic rhinitis will be assessed fi at 36 months of age.

Because children with developing atopic dermatitis might not meet established diagnostic criteria in infancy,

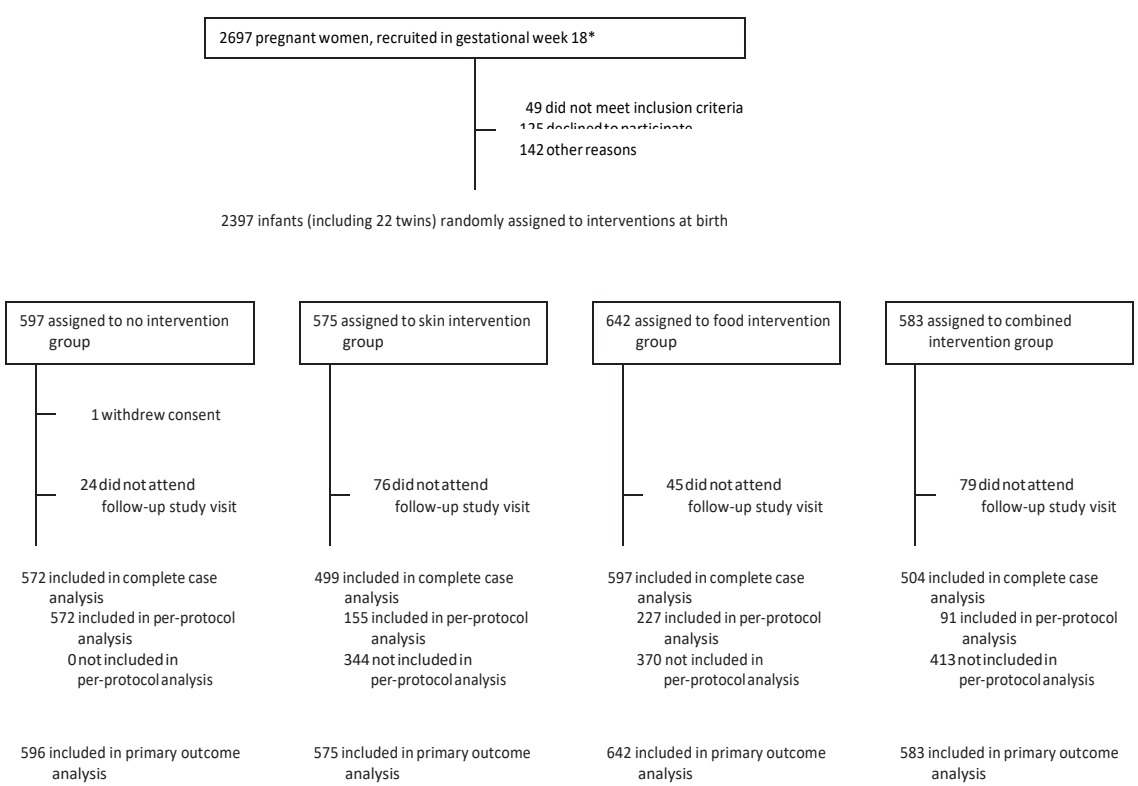

Figure 1: **Trial profile**

*Four women participated twice with different children and 17 extra fetuses from twin pregnancies resulted in 2718 fetuses in womb at 18 weeks. 321 fetuses from 316 mothers were not included.

we used possible atopic dermatitis for the sensitivity analyses outcome. Possible atopic dermatitis was defined as observed eczema (excluding differential diagnoses to atopic dermatitis) and a history or signs of itch at the 3, 6, and 12 month investigations, or reported itchy rash of at least 4 weeks' duration at age 3, 6, 9, or 12 months, assessed via questionnaires. Additionally, the time of onset of eczema observed at any of the investigations was used as an outcome in the sensitivity analysis.

The primary efficacy analyses for all outcomes included all randomly assigned participants. Sensitivity analyses were done on eligible and randomly assigned participants with no major protocol deviations affecting the efficacy (per-protocol set) and with valid outcomes (complete case set).

Two additional post-hoc sensitivity analyses were done using UK Working Party criteria and Hanifin and Rajka as separate atopic dermatitis outcomes.

Major protocol deviations were defined as follows: erroneous enrolment on the basis of eligibility criteria, failure to adhere fully to the protocol with the exception of initiation of a possible allergy contraindicated intervention or cessation of the intervention on the basis of a clinical decision (including adverse event), full protocol adherence to an intervention the participant was not allocated to (with the exception of milk commonly given complementary to or as a supplement for breastmilk, and wheat that might be advised as complementary to breastmilk from age 4 months in Norway and Sweden), and missing data for primary endpoints.

Statistical analysis

A 30% relative reduction of the probability of atopic dermatitis from 23%[27,28] in the no intervention group to 16% in the skin intervention group would correspond to a 7% absolute risk reduction, which was judged to be clinically meaningful. 511 participants in each group were required to reject the no intervention effect hypothesis with 80% power. To adjust for potential dropouts, the recruitment target was set at 2700 pregnancies.

The statistical hypothesis framework of this 2 × 2 factorial trial was to first test the null hypothesis of no main effect of either intervention on the primary endpoint (the omnibus test). If the omnibus test was rejected, both intervention effects could be tested simultaneously under the closed testing principle. All hypotheses were tested at the 5% significance level.

We analysed dichotomous endpoints using mixed effects logistic regression with the interventions and interaction as fixed effects, and randomisation time period and residential postal code as random effects. Missing primary outcome data were imputed with the best-case option, no atopic dermatitis, assuming parents were more likely to attend clinical assessment if the infant had atopic dermatitis. The primary effect estimate was risk difference, computed from the mixed logistic regression model using the delta method. We analysed

	No intervention group (n=596)	Skin intervention group (n=575)	Food intervention group (n=642)	Combined intervention group (n=583)
Age				
Mother, years	32·45 (4·20)	32·16 (4·18)	32·59 (4·07)	32·45 (4·16)
Father, years	34·77 (5·52)	34·58 (5·52)	34·76 (5·50)	34·63 (5·36)
Gestational age at birth, weeks	39·36 (1·65)	39·18 (1·68)	39·17 (1·71)	39·24 (1·65)
Study site				
Oslo, Norway	394 (66%)	355 (62%)	416 (65%)	371 (64%)
Østfold, Norway	92 (15%)	99 (17%)	80 (12%)	71 (12%)
Stockholm, Sweden	110 (18%)	121 (21%)	146 (23%)	141 (24%)
Maternal education				
Preliminary school only (9–10 years)	3/538 (1%)	4/513 (1%)	4/577 (1%)	5/535 (1%)
High school only	51/538 (9%)	55/513 (11%)	61/577 (11%)	56/535 (10%)
Higher education <4 years	168/538 (31%)	160/513 (31%)	188/577 (33%)	174/535 (33%)
Higher education ≥4 years	301/538 (56%)	274/513 (53%)	310/577 (54%)	287/535 (54%)
PhD	15/538 (3%)	18/513 (4%)	14/577 (2%)	13/535 (2%)
Other	0	2 (<1%)	0	0
Partner education				
Preliminary school only (9–10 years)	7/526 (1%)	5/491 (1%)	6/547 (1%)	8/524 (2%)
High school only	93/526 (18%)	99/491 (20%)	102/547 (19%)	99/524 (19%)
Higher education <4 years	161/526 (31%)	138/491 (28%)	170/547 (31%)	160/524 (31%)
Higher education ≥4 years	242/526 (46%)	222/491 (45%)	249/547 (46%)	235/524 (45%)
PhD	16/526 (3%)	19/491 (4%)	15/547 (3%)	20/524 (4%)
Other	7/526 (1%)	8/491 (2%)	5/547 (1%)	2 (<1%)
Maternal country of origin				
Norway	381/541 (70%)	339/515 (66%)	383/580 (66%)	340/536 (63%)
Sweden	107/541 (20%)	125/515 (24%)	135/580 (23%)	126/536 (24%)
Other Nordic country	10/541 (2%)	9/515 (2%)	5/580 (1%)	4/536 (1%)
Other	43/541 (8%)	42/515 (8%)	57/580 (10%)	66/536 (12%)
Paternal country of origin				
Norway	353/533 (66%)	338/501 (67%)	357/563 (63%)	341/523 (65%)
Sweden	109/533 (20%)	116/501 (23%)	139/563 (25%)	122/523 (23%)
Other Nordic country	11/533 (2%)	6/501 (1%)	6/563 (1%)	6/523 (1%)
Other	60/533 (11%)	41/501 (8%)	61/563 (11%)	54/523 (10%)
Sex of infant				
Male	312 (52%)	286 (50%)	350 (55%)	314 (54%)
Female	284 (48%)	289 (50%)	292 (45%)	269 (46%)
Parental relationship status				
Married	227/537 (42%)	211/511 (41%)	231/575 (40%)	226/532 (42%)
Cohabitants	302/537 (56%)	285/511 (56%)	330/575 (57%)	301/532 (57%)
Single	8/537 (1%)	15/511 (3%)	13/575 (2%)	5/532 (1%)
Divorced or separated	0	0	1/575 (<1%)	0
Living environment				
City, densely populated	214/541 (40%)	191/515 (37%)	229/580 (39%)	208/536 (39%)
City, less densely populated	201/541 (37%)	200/515 (39%)	204/580 (35%)	222/536 (41%)
Suburb	77/541 (14%)	84/515 (16%)	100/580 (17%)	84/536 (16%)
Village	11/541 (2%)	11/515 (2%)	19/580 (3%)	5/536 (1%)
Countryside, outside village	38/541 (7%)	29/515 (6%)	28/580 (5%)	17/536 (3%)

(Table 1 continues on next page)

	No intervention group (n=596)	Skin intervention group (n=575)	Food intervention group (n=642)	Combined intervention group (n=583)
(Continued from previous page)				
Maternal asthma	87/541 (16%)	95/515 (18%)	114/580 (20%)	75/536 (14%)
Maternal atopic dermatitis	124/541 (23%)	111/515 (22%)	112/580 (19%)	84/536 (16%)
Maternal allergic rhinitis	106/541 (20%)	107/515 (21%)	130/580 (22%)	102/539 (19%)
Maternal food allergy	72/541 (13%)	66/515 (13%)	75/580 (13%)	68/536 (13%)
Paternal asthma	76/549 (14%)	59/519 (11%)	84/561 (15%)	60/529 (11%)
Paternal atopic dermatitis	56/549 (10%)	52/519 (10%)	64/561 (11%)	48/529 (9%)
Paternal allergic rhinitis	116/549 (21%)	141/519 (27%)	136/561 (24%)	117/529 (22%)
Paternal food allergy	49/549 (9%)	52/519 (10%)	51/561 (9%)	45/529 (9%)
Atopy				
Maternal	219/541 (40%)	187/515 (36%)	227/580 (39%)	182/536 (34%)
Paternal	192/549 (35%)	192/519 (37%)	207/561 (37%)	171/529 (32%)
Either parent	343/506 (68%)	319/471 (68%)	352/522 (67%)	299/490 (61%)
Birthweight, g	3593 (483)	3572 (500)	3556 (469)	3586 (467)
Birth length (crown-rump)	50·59 (2·17)	50·41 (2·24)	50·43 (2·04)	50·59 (2·00)
Delivery method				
Vaginal delivery	503 (84%)	481 (84%)	537 (84%)	478 (82%)
Caesarean section	93 (16%)	94 (16%)	105 (16%)	105 (18%)
Previous deliveries				
0	333/541 (62%)	313/515 (61%)	328/580 (57%)	334/536 (62%)
1	161/541 (30%)	157/515 (30%)	202/580 (35%)	159/536 (30%)
2	42/541 (8%)	41/515 (8%)	41/580 (7%)	37/536 (7%)
3	3/541 (1%)	4/515 (1%)	6/580 (1%)	4/536 (1%)
4	2/541 (<1%)	0	2/580 (<1%)	1/536 (<1%)
5 or more	0	0 (0)	1/580 (<1%)	1/536 (<1%)
Twin pregnancy	2 (<1%)	10 (2%)	6 (1%)	4 (1%)
Participated twice with different children	2 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)
Mother's body-mass index	24·81 (3·76)	24·75 (3·79)	24·81 (3·58)	24·85 (3·59)

Data are mean (SD), n (%), or n/N (%). Diff denominators are because the number of babies diff from the number of parents (eg, twins), or missing data (data from electronic questionnaire to which about 85% of mothers responded).

Table 1: **Baseline characteristics**

time-to-event endpoints using a Weibull regression model assuming non-informative interval censoring with regular observation times.

All analyses were done with R version 3.6.0. A registered steering committee designed and oversaw the trial, and the study is registered at clinicaltrials.gov, NCT02449850.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

We recruited 2697 women with 2701 pregnancies from whom 2397 newborn infants were enrolled from April 14, 2015, through to April 11, 2017, and randomly assigned to either the no intervention group (n=597), skin intervention group (n=575), food intervention group (n=642), or the combined intervention group (n=583). consent and was not included in the intention-to-treat data analyses for the primary outcome (figure 1).

Baseline characteristics were similar for the four groups (table 1). Most infants (1825 [76%] of 2397) attended all three study visits up to age 12 months, and 2172 (91%) of 2397 attended at least one visit.

Overall, bath oil additive was used on at least 4 days per week in 497 (43%) of 1158 infants assigned to a skin intervention, facial cream on at least 4 days per week in 514 (44%), and 316 (27%) were fully protocol adherent for use of both emollients. Between age 13 weeks and 18 weeks, peanut butter was introduced to 966 (79%) of 1225 infants assigned to food intervention, cow's milk to 838 (68%), wheat to 820 (67%), and egg to 677 (55%). 431 (35%) were fully protocol adherent up to week 26 for peanut butter, 530 (43%) for cow's milk, 543 (44%) for wheat, and 289 (24%) for egg. Full protocol adherence to the overall food intervention was reported in 387 (32%). Details on adherence to both interventions for all four groups are presented in table 2.

Data for the primary endpoint were missing in 24 (4%) of 596 infants in the no intervention group, 76 (13%) of 575 in the skin intervention group, 45 (7%) of 642 in the food intervention group, and 79 (14%) of 583 in the combined intervention group.

Other protocol deviations included four infants who were erroneously informed that they were randomly assigned to the skin intervention and were subsequently fully protocol adherent to the skin intervention. Additionally, eight infants not allocated to the food intervention were fully protocol adherent for introduction of peanut or egg, or both.

Atopic dermatitis was observed in 48 (8%) of 596 infants in the no intervention group, 64 (11%) of 575 in the skin intervention group, 58 (9%) of 642 in the food intervention group, and 31 (5%) of 583 in the combined intervention group. The primary hypotheses that either skin intervention or food intervention reduced atopic dermatitis were not confirmed, with a risk difference of 3·1% (95% CI −0·3 to 6·5) for skin intervention and 1·0% (−2·1 to 4·1) for food intervention, in favour of control (figure 2). A significant interaction was recorded between the interventions (p=0·0026; table 3 and appendix p 19). The intra-cluster correlation coefficient (ICC) was 0·002.

In the per-protocol as well as complete case sensitivity analyses, no superiority of skin or food intervention was found (table 3). In analyses for which missing outcome was addressed by multiple imputation, the risk of atopic dermatitis was significantly increased in the skin intervention group with a risk difference of 5·9% (2·0 to 9·7). Post-hoc sensitivity analyses using the primary outcome

as atopic dermatitis based on the UK Working Party diagnostic criteria alone (n=136) and Hanifin and Rajka diagnostic criteria alone (n=134) supported the primary atopic dermatitis outcome (table 3).

Possible atopic dermatitis was observed in 90 (15%) of 596 in the no intervention group, 94 (16%) of 575 in the skin intervention group, 101 (16%) of 642 in the food intervention group, and 69 (12%) of 583 in the combined intervention group. Compared with the no intervention group, we found no clinically meaningful risk differences for possible atopic dermatitis in the skin intervention group (1·3% [95% CI –2·9 to 5·4]) or the food intervention group (0·6% [–3·4 to 4·7]; table 3, figure 2).

The symptoms of possible atopic dermatitis presented earlier in infants with the skin intervention than they did in those without the skin intervention, and infants in the combined interventions group had delayed presentation of disease (table 3).

No significant interaction effect of parental atopy was found with the skin intervention (p=0·4) or the food interventions (p=0·8).

Food allergy will be assessed at age 3 years and probably reported mid-2020, while asthma, allergic rhinitis, and allergic sensitisation to allergens other than the interventional food allergens will be reported in separate publications.

Reported skin symptoms and signs, including itching, oedema, exanthema, dry skin, and urticaria were no more frequent in the skin, food, and combined intervention groups than in the no intervention group (figure 3). Graphical presentation of reported symptoms and signs are shown by organ system in the appendix (pp 17–18). Nine participants stopped applying the facial cream to infants at a median age of 9 weeks, and eight stopped using the bath oil additives at a median age of 11·5 weeks because of infantile folliculitis or acne (n=2), seborrhoea (n=3), worsening of atopic dermatitis (n=6), and unspecific skin reactions (n=6). Two participants stopped the peanut intervention after the first intake after a suspected, and later verified, peanut allergy. 17 participants stopped the milk intervention because of suspected (n=10) and verified allergy (n=7). No participants stopped the wheat introduction. Nine participants stopped the egg intervention because of suspected (n=1) and verified egg allergy (n=8).

One slippage accident, not causing injury, was reported in the skin intervention group. Hospital admissions (n=36) and observed impetigo (n=9) were infrequent and evenly distributed across the randomisation groups (appendix pp 23–24).

	No intervention group (n=596)	Skin intervention group (n=575)	Food intervention group (n=642)	Combined intervention group (n=583)
Adherence to skin intervention				
Emollient bath additive				
At least 0·5 day	0	361 (63%)	0	369 (63%)
At least 1·5 days	0	332 (58%)	0	343 (59%)
At least 2·5 days	0	282 (49%)	0	298 (51%)
At least 3·5 days	0	242 (42%)	5 (1%)	255 (44%)
At least 4·5 days	2 (<1%)	186 (32%)	3 (<1%)	192 (33%)
At least 5·5 days	1 (<1%)	75 (13%)	1 (<1%)	80 (14%)
Ceridal facial cream				
At least 0·5 day	2 (<1%)	343 (60%)	4 (1%)	357 (61%)
At least 1·5 days	2 (<1%)	333 (58%)	4 (1%)	322 (55%)
At least 2·5 days	1 (<1%)	286(50%)	4 (1%)	280 (48%)
At least 3·5 days	1 (<1%)	256 (45%)	3 (<1%)	258 (44%)
At least 4·5 days	1 (<1%)	208 (36%)	3 (<1%)	218 (37%)
At least 5·5 days	1 (<1%)	127 (22%)	1 (<1%)	140 (24%)
Emollient bath additive and Ceridal facial cream (full protocol adherence*)	1 (<1%)	155 (27%)	3 (<1%)	161 (28%)
Adherence to food intervention†				
Peanut				
Introduced week 13–26	68 (11%)	54 (9%)	529 (82%)	437 (75%)
Introduced early (week 13–18)	17 (3%)	19 (3%)	495 (77%)	409 (70%)
At least partial adherence‡	7 (1%)	10 (2%)	343 (53%)	249 (43%)
Full protocol adherence	2 (<1%)	3 (1%)	251 (39%)	180 (31%)
Cow's milk				
Introduced week 13–26	314 (53%)	250 (43%)	519 (81%)	436 (75%)
Introduced early (week 13–18)	103 (17%)	98 (17%)	454 (71%)	384 (66%)
At least partial adherence‡	56 (9%)	59 (10%)	356 (55%)	280 (48%)
Full protocol adherence	33 (6%)	33 (6%)	299 (47%)	231 (40%)
Wheat				
Introduced week 13–26	472 (79%)	390 (68%)	537 (84%)	447 (77%)
Introduced early (week 13–18)	176 (30%)	135 (23%)	455 (71%)	365 (63%)
At least partial adherence‡	124 (21%)	83 (14%)	367 (57%)	276 (47%)
Full protocol adherence	94 (16%)	61 (11%)	317 (49%)	226 (39%)
Egg				
Introduced week 13–26	162 (27%)	123 (21%)	497 (77%)	381 (65%)
Introduced early (week 13–18)	28 (5%)	15 (3%)	378 (59%)	299 (51%)
At least partial adherence‡	16 (3%)	6 (1%)	276 (43%)	198 (34%)
Full protocol adherence	4 (1%)	1 (<1%)	174 (27%)	115 (20%)
Full overall protocol adherence (to at least three foods)	3 (1%)	1 (<1%)	227 (35%)	160 (27%)

Data are n (%). *Full protocol skin intervention adherence was defined as baths with the bath oil additive and the Ceridal facial cream on at least an average of 4 days per week in the best 16 of the 25 weeks, emollients applied for the first time by 4 weeks of age, and no consecutive weeks of reported no use. †For each food, full protocol intervention adherence required intake of each food for a minimum of 3–5 days per week for at least 5 weeks. Full overall protocol food intervention adherence required full protocol food intervention of at least three of the four foods, and the introduction of at least three of the four foods by week 18. If parents reported adherence in less than 5 of the 8 weeks between 19 and 26 weeks, adherence was classified as unknown. ‡Partial adherence was defined as food introduced in week 13–18 and given at least 1–2 days per week (calculated from weeks 19–26) and not meeting fully adherent criteria.

Table 2: **Adherence to the interventions**

Discussion

In this large, randomised, primary prevention pragmatic clinical trial in a general infant population, development of atopic dermatitis by age 12 months was not prevented by regular use of bath oil additives and face-emollient cream on at least 4 days per week from 2 weeks of age, nor by early complementary feeding introduced from age 12 weeks. The effects of interventions were not influenced by parental atopy.

Our novel finding that atopic dermatitis was not prevented by emollient bath additives and emollient facial cream from age 2 weeks is in contrast to the significant preventive effects of daily leave-on emollient cream reported in two previous, smaller studies of high-risk infants in Japan (n=118)[12] and in the US and the UK (n=124).[13] Our results did not document beneficial effects of the skin intervention in intention-to-treat or per-protocol analyses. Additionally, the confidence intervals of the main effect estimates exclude a clinically meaningful benefit of 7%, implied by the power calculation. The results are robust to different handling of adherence to the interventions and missing data. The sensitivity analyses using other atopic dermatitis endpoints support our findings.

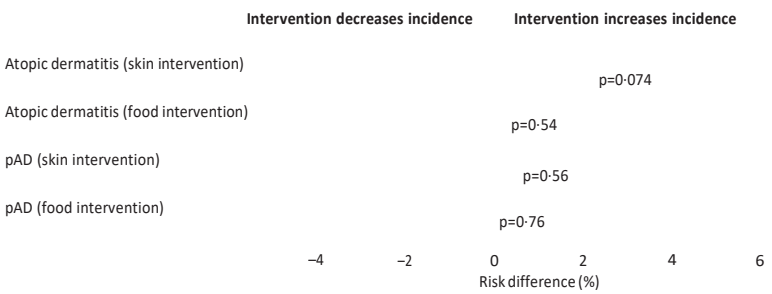

Figure 2: **Risk reduction of atopic dermatitis for each primary prevention strategy**
pAD=possible atopic dermatitis.

The reason for the difference between our result and two previous pilot studies showing significantly reduced atopic dermatitis and observed risk reduction in high-risk infants using daily leave-on emollients[12,13] is unclear. The skin intervention using highly concentrated emollient additives[8,9,29,30] should be sufficient to improve the skin barrier, as shown by the reduced transepidermal water loss observed especially in young children using baths with 1 mL of oil added per 5 L of water.[30] In this large trial it was not feasible to measure the newborn skin barrier function at the maternity ward before starting the skin intervention to assess the potential effect on the barrier function. Our findings are supported by the absence of reduction in symptoms or signs of atopic dermatitis from including bath oil additives in a pragmatic, randomised, open-label trial from 96 general practices in the UK of 483 children with atopic dermatitis.[9] We anticipated an atopic dermatitis prevalence of approximately 23%,[28] in which case a 7% risk difference, corresponding to applying the intervention to 14 infants to prevent one case of atopic dermatitis, would be clinically meaningful. Although the power calculation assumed a higher prevalence than our observed atopic

	No intervention group (n [%])	Skin intervention group		Food intervention group		Combined intervention group		Intervention interaction* (p value)
		n (%)	Risk difference† (95% CI)	n (%)	Risk difference† (95% CI)	n (%)	Risk difference† (95% CI)	
Atopic dermatitis primary analysis								
Intention-to-treat population, best case imputation	48/596 (8%)	64/575 (11%)	3·1% (–0·3 to 6·5)	58/642 (9%)	1·0% (–2·1 to 4·1)	31/583 (5%)	–2·7 (–5·6 to 0·1)	0·0026
Atopic dermatitis, sensitivity analyses								
Per-protocol population, no imputation	48/572 (8%)	16/155 (10%)	1·9% (–3·4 to 7·2)	26/227 (11%)	3·1% (–1·7 to 7·8)	5/91 (5%)	–2·9% (–8·1 to 2·3)	0·10
Complete cases, no imputation	48/572 (8%)	64/499 (13%)	4·4% (0·7 to 8·1)	58/597 (10%)	1·3% (–2·0 to 4·6)	31/504 (6%)	–2·2% (–5·3 to 0·9)	0·0017
Intention-to-treat population, multiple imputations	53/596 (9%)	85/575 (15%)	5·9% (2·0 to 9·7)	67/642 (10%)	1·5% (–1·9 to 4·9)	51/583 (9%)	–0·2% (–3·8 to 3·6)	0·0086
Intention-to-treat population, best case imputation, adjusted for sex and parental atopy	48/596 (8%)	64/575 (11%)	3·1% (–0·2 to 6·4)	58/642 (9%)	0·9% (–2·2 to 4·0)	31/583 (5%)	–2·5% (–5·4 to 0·3)	0·0037
UK working party only, best case imputation	29/596 (5%)	43/575 (7%)	2·6% (–0·2 to 5·4)	42/642 (7%)	1·7% (–0·9 to 4·2)	22/583 (4%)	–1·0% (–3·4 to 1·3)	0·0051
Hanifin and Rajka only, best case imputation	37/596 (6%)	43/575 (7%)	1·3% (–1·6 to 4·1)	36/642 (6%)	–0·6% (–3·2% to 2·0)	18/583 (3%)	–3·1% (–5·5 to –0·7)	0·026
Possible atopic dermatitis								
Intention-to-treat population, best case imputation	90/596 (15%)	94/575 (16%)	1·3% (–2·9 to 5·4)	101/642 (16%)	0·6% (–3·4 to 4·7)	69/583 (12%)	–3·3% (–7·2 to 0·6)	0·068
Time to possible atopic dermatitis‡								
Intention-to-treat population, no imputation	..	..	0·64 (0·46 to 0·91)	..	0·84 (0·60 to 1·18)	..	1·29 (0·86 to 1·93)	0·0013

*p value of the no interaction between interventions test from the mixed logistic regression model. †Risk differences versus no intervention are computed from the mixed logistic regression model by the delta method. ‡Data presented as time to event ratio (95% CI). The time to event ratios versus no intervention are computed from the accelerated failure time parametrisation of the Weibull regression model. Values below 1 should be interpreted as shorter time to event, values above 1 as longer time to event.

Table 3: **Primary and sensitivity outcomes**

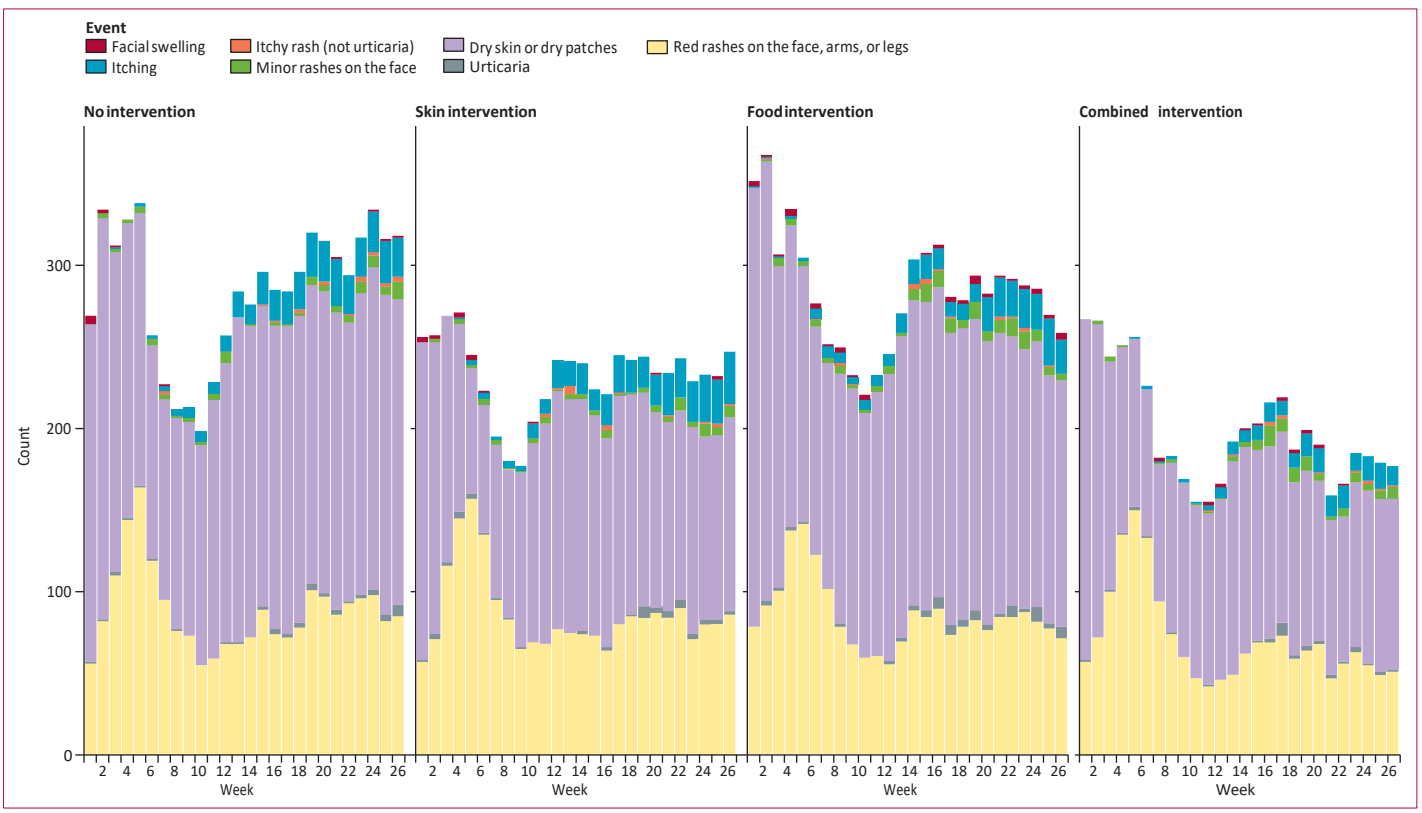

Figure 3: **Skin signs and symptoms for each intervention group reported by parents in weekly diaries**

dermatitis prevalence, limited statistical power is unlikely to explain the absence of an observed beneficial effect in our study. The results in this large randomised controlled trial in a general infant population did not verify results from two small pilot studies in high-risk infants, in line with other examples of clinical trials showing beneficial effects in a selected population, but not when tested in a large population.[31] On the basis of our analysis of the interaction between the interventions and parental atopy, we did not find support for the notion that regular skin emollient is effective to reduce atopic dermatitis among high-risk infants.

Another novelty in our study is the factorially designed 2×2 intervention targeting the skin and the alimentary tract to prevent atopic dermatitis and food allergy. Because there was no previous hypothesis that early introduction of specific foods could modify a skin intervention to reduce development of atopic dermatitis, the present study tested the two hypotheses—that either the skin intervention or the food intervention would prevent atopic dermatitis. The food intervention was primarily implemented to target food allergy prevention, predefined to be first assessed at age 36 months (in 2020). Therefore, the significant interaction between the food and skin intervention was unexpected and could represent a chance finding. Furthermore, the risk difference estimates and corresponding confidence intervals between the group with combined intervention and no intervention excludes a clinically meaningful difference. The potential role of combined interventions will be further investigated once all children have reached age 36 months, as the study design did not include interim analyses before the main outcome assessments.

The interventions seemed to be safe, with a similar proportion of hospital admissions across the groups and reported skin symptoms or signs. For the approximately 100 000 baths with added bath oil emollient, we had one reported slippage accident, but with no consequences to the infant. This is likely to be a result of vigilant safety teaching of both parents. All infants were recruited from a general population of pregnant women, with atopic dermatitis seen more often in infants with parental allergy.[25] The randomisation procedure was chosen to account for location as well as seasonality and ensured balanced background characteristics in the four groups. The outcomes were based on standard atopic dermatitis diagnostic tools[32] applied during clinical follow-up visits by assessors masked to the randomisation groups. In line with other studies,[12,13,33] we focus on primary prevention interventions in the fi 6 months of life. However, we extended the observation period to age 1 year, compared with age 6 months in the two pilot studies.[12,13]

Intervention contamination across groups is unlikely to influence the results, with the per-protocol analyses pointing in favour of control, rather than the intervention. The bath emollient additive was produced especially for the study and provided only to participants in the skin intervention group. However, parents could have used other emollients or started early food introduction in the control group. Although recruitment was non-selective among pregnant women at the study hospitals, the participating mothers had a higher socioeconomic status than the population average. However, no such differences were evident between the randomisation groups.

A strength of the study was the close follow-up of the participants with clinical visits at 3, 6, and 12 months, as well as weekly electronic diaries and extensive questionnaires every 3 months to assess adherence to the interventions, symptoms, signs, and adverse events.

Because intention-to-treat analysis estimates the effect of an intervention under realistic conditions (ie, the combined effect of adherence and intervention assignment), this is the most relevant estimate for the effect of primary prevention advice relating to use of skin emollients and early complementary feeding regimens.

In a clinical setting, atopic dermatitis can be diagnosed on the basis of observed eczema, itch, and an atopic predisposition, often without using internationally validated diagnostic criteria. This proximate approach in diagnosing atopic dermatitis could, in part, explain variation in atopic dermatitis prevalence across studies.[2] The prevalence of atopic dermatitis in the present study based on the no intervention group varied from 8% according to the validated criteria to 15% according to the loosely defined criteria of possible atopic dermatitis. The lower prevalence than in our estimation might be because of careful monitoring of the skin and appropriate advice given to all participants, regardless of assignment group.

The calculation of the food adherence would have been more precise by recording in the weekly diaries the exact number, rather than categories of days for which the intervention was used. Another limitation of our study was the low full protocol adherence of 27% in the skin emollient group and 32% in the early complementary feeding group. However, this degree of adherence reflects real life settings, in a study with highly educated, highly motivated parents,[23] in whom adherence patterns are presumed to be no lower than in a general population. Low adherence was also the case in therapeutic studies on childhood atopic dermatitis[9] as well as in primary prevention of food allergy.[33] When planning the study, we assumed that bathing the baby for most days of the week,[11] as well as introducing foods from the family's regular diet—in contrast to the more complex diet in the EAT study[33]—would not be too demanding. However, our study proved otherwise for a large part of the study population, suggesting that any additions to regular infant care are challenging. Nevertheless, 43% of participants in our trial showed full protocol adherence to the emollient bath additive, irrespective of the facial emollient cream, and in the early complementary feeding group, 55% of infants were introduced to egg and 79% to peanut before age 18 weeks.

Early skin emollient therapy or early complementary feeding did not prevent atopic dermatitis development up to age 1 year in infants from a general population. Our findings are in line with the barrier enhancement for eczema prevention (BEEP) study,[34] which reported no reduction in atopic dermatitis by two years among 1394 high-risk infants using daily emollient leave on creams for the first year of life.[34] Therefore, we cannot recommend these interventions as primary prevention strategies.

Contributors

All authors contributed to the design or clinical follow-up of the PreventADALL study, as well as having contributed to drafting or critically revising the paper. All authors approved the final version before submission. HOS, KCLC, EMR, BN, BG, GHa, GHe, CS, ACS, K-HC, LL, BJM, KR, IS, GHå, KDS, AA, KESB, OCLC, HKG, KH, IK, and LSN participated in the conception and design of the study. CMJ, HOS, KCLC, EMR, BN, LL, AA, KESB, OCLC, HKG, KH, IK, LSN, JUH, KMAE, PAG, C-AOM, CMS, SGT, MRV, and JW participated in conducting the study, data collection, or both. ML, RV, ICO, HOS, KCLC, and EMR did the data analysis. The authors assume responsibility for the accuracy and completeness of the data and analyses, as well as for the fidelity of the report to the study protocol, reported in the appendix.

Declaration of interests

EMR has received honoraries for presentations from Sanofi Genzyme, Novartis, MEDA, and Omega Pharma. KCLC has received honoraria for presentation from Thermo Fisher Scientific. All other authors declare no competing interests.

Data sharing

Data are stored at the Service for Sensitive Data database at the University of Oslo. The PreventADALL study is an ongoing study that has been approved for data collection until 2044.

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