



Early food intervention and skin emollients to prevent food allergy in young children (PreventADALL): a factorial, multicentre, cluster-randomised trial

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Summary

Background Primary prevention of food allergy by early introduction of allergenic foods seems promising. We aimed to determine whether early food introduction or the application of regular skin emollients in infants from a general population reduced the risk of food allergy.

Methods This 2×2 factorial, cluster-randomised 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 18-week ultrasound examination were cluster-randomised at birth to the following groups: (1) no intervention group; (2) the skin intervention group (skin emollients; bath additives and facial cream; from age 2 weeks to <9 months, both at least four times per week); (3) the food intervention group (early complementary feeding of peanut, cow's milk, wheat, and egg from age 3 months); or (4) combined intervention group (skin and food interventions). Participants were randomly assigned (1:1:1:1) using computer-generated randomisation based on clusters of 92 geographical areas and eight 3-month time blocks. Study personnel performing clinical assessments were masked to group allocation. The primary outcome was allergy to any interventional food at 36 months of age. The primary efficacy analysis was done by intention-to-treat analysis, which included all participants who were randomly assigned, apart from three individuals who withdrew their consent. This was a study performed within ORACLE (the Oslo Research Group of Asthma and Allergy in Childhood; the Lung and Environment). This study is registered as ClinicalTrials.gov, NCT02449850.

Findings We recruited 2697 women with 2701 pregnancies, from whom 2397 newborn infants were enrolled between April 14, 2015, and April 11, 2017. Of these infants, 597 were randomly assigned to the no intervention group, 575 to the skin intervention group, 642 to the food intervention group, and 583 to the combined intervention group. One participant in each of the no intervention, food intervention, and skin intervention groups withdrew consent and were therefore not included in any analyses. Food allergy was diagnosed in 44 children; 14 (2·3%) of 596 infants in the non-intervention group, 17 (3·0%) of 574 infants in the skin intervention group, six (0·9%) of 641 infants in the food intervention group, and seven (1·2%) of 583 infants in the combined intervention group. Peanut allergy was diagnosed in 32 children, egg allergy in 12 children, and milk allergy in four children. None had allergy to wheat. Prevalence of food allergy was reduced in the food intervention group compared with the no food intervention group (risk difference −1·6% [95% CI −2·7 to −0·5]; odds ratio [OR] 0·4 [95% CI 0·2 to 0·8]), but not compared with the skin intervention group (0·4% [95% CI −0·6 to 1·5%]; OR 1·3 [0·7 to 2·3]), with no significant interaction effect ($p=1·0$). Preventing food allergy in one child required early exposure to allergenic foods in 63 children. No serious adverse events were observed.

Interpretation Exposure to allergenic foods from 3 months of age reduced food allergy at 36 months in a general population. Our results support that early introduction of common allergenic foods is a safe and effective strategy to prevent food allergy.

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Introduction

Food allergy is estimated to affect around 3–7% of children younger than 5 years;^{1–3} up to 11% of infants younger than 12 months;⁴ and 1·4–3·8% of children aged

6–10 years.⁴ Diagnosis of food allergies can be challenging. Oral food challenge is currently the gold standard to differentiate between reported and confirmed clinical disease.⁴ IgE-mediated food allergy in early

Research in context

Evidence before this study

Since allergen avoidance in infancy has failed to prevent food allergy, early complementary introduction of allergenic foods was perceived as a more plausible primary prevention strategy. Allergic sensitisation is observed by age 4–6 months in some infants. Before the start of this study (December, 2014), data on the introduction of allergenic foods before 4 months of age for primary prevention of food allergy were scarce. In a systematic review from 2014, Da Silva and colleagues identified one cohort study by Venter and colleagues, who reported reduced food allergy or sensitisation to food when solids were introduced before age 4 months. Additionally, a Swedish randomised trial reported a reduction in allergy symptoms up to age 18 months in children fed cow's milk during the first few days of life, if both parents were atopic. We searched PubMed on Dec 15, 2020, without date or language restrictions, for clinical trials, randomised controlled trials, systematic reviews, and meta-analyses using the search term "primary prevention and ((atopic dermatitis or eczema) or (food allergy))". Our search yielded 201 articles, of which 19 were considered relevant. Additionally, two relevant systematic review and meta-analyses from 2016 and 2020, and one randomised controlled trial published in January, 2021, were included in January, 2021. The Learning Early about Peanut Allergy trial done in 2015, showed that the consumption of peanuts in infants with atopic dermatitis or egg allergy, between age 4 months and 10 months, prevented peanut allergy. In the Enquiring About Tolerance trial, in which multiple allergenic foods were introduced in a general cohort of breastfed infants aged 3 months, no significant reduction in food allergy was identified between 1 and 36 months in the intention-to-treat analysis. However, among the 32% of infants who adhered to the food intervention, food allergy was significantly reduced, indicating that primary prevention through early complementary feeding from age 3 months might be possible. On the basis of 15 intervention trials, a 2016 systematic review and meta-analysis by Lerodiakonou and colleagues concluded with moderate-certainty evidence that the introduction of egg between 4 and 6 months of age reduced childhood allergy to egg, and the introduction of peanut between 4 and 11 months of age reduced childhood allergy to peanut. Two studies reported that early exposure to cow's milk had no significant effect on allergy. The 2020 review by Da Silva and colleagues

based on the same studies specified that early exposure to cooked hen's egg is likely to reduce the prevalence of egg allergy, whereas raw or pasteurised egg might not. Two of the studies found that most infants with egg allergy were already sensitised and allergic by enrolment at age 4–6 months, indicating the need for earlier application of preventive measures. In a 2021 randomised trial, Sakihara and colleagues concluded that cow's milk allergy at age 6 months was significantly reduced after daily exposure to cow's milk between ages 1 and 2 months.

Five randomised controlled trials investigating skin protection as primary prevention of atopic dermatitis were identified, including previous findings from our PreventADALL study. Only one trial reported on food allergy and found no preventive effect of regular emollients applied during the first year of life.

Added value of this study

To our knowledge, no other study has investigated potential additive or synergistic effects of early food allergen introduction and regular emollients to prevent food allergy. The PreventADALL study provides evidence that food allergy at age 36 months might be prevented by the introduction of common foods from age 3 months. The study demonstrated that the food intervention was effective in a general cohort not selected on the basis of atopic risk, suggesting that early feeding of 63 infants might prevent food allergy in one child at age 36 months. In analysis of specific food allergies, the intervention was effective for peanut allergy. There were no safety issues, and breastfeeding rate at 6 months was not affected by early food introduction. Early regular use of skin emollients did not reduce food allergy at 36 months.

Implications of all the available evidence

Collectively, our findings and those of other large randomised controlled trials show that introduction of allergenic foods before age 4 months reduced food allergy in early childhood. Reduced allergy was also observed in the absence of screening for risk of atopic disease. Early complementary feeding seems to be safe and at present is likely to represent a feasible primary prevention strategy to reduce food allergy. We believe that there is sufficient evidence to suggest that food allergy can be prevented by recommending early introduction of allergenic food complementary to regular feeding from age 3 months.

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childhood commonly includes cow's milk, hen's egg, peanut, and wheat.^{2,4} Most infants with allergy to milk, egg, and wheat develop a natural tolerance to these allergens,¹ whereas the development of tolerance is less likely with allergy to peanut and tree nuts.⁵

Primary prevention of food allergy would be of major societal and individual benefit. Regular intake of egg^{6,7} and peanut⁸ from age 4 months might reduce food allergy in infants at increased risk;^{9,10} however, evidence to support early nutritional interventions before age

4 months in infants from the general population remains scarce.^{9,10} In the Enquiring About Tolerance (EAT) study,³ in which 1303 breastfed infants were recruited from the general UK population, no significant reduction in food allergy was observed between 1 and 36 months as a result of the introduction of multiple foods from age 3 months in primary analyses, whereas egg and peanut allergies were significantly less frequent among the 32% of infants who adhered to the intervention.³ Among 504 healthy infants in Japan given cow's milk formula daily between

ages 1 and 2 months, allergy to cow's milk was reduced at 6 months compared with those not given cow's milk formula in the study period.¹¹ Further evidence of the effect of foods introduced before age 4 months is urgently needed.⁹

Atopic dermatitis, a common chronic inflammatory skin disease associated with reduced skin barrier function, is a strong risk factor for subsequent food allergy.^{12,13} The first step in primary prevention of food allergy might be to prevent atopic dermatitis.¹⁴ However, previous studies have shown that application of regular emollients from the first few weeks of life did not prevent atopic dermatitis up to age 2 years¹⁵ in children from a general population,¹⁶ nor in children at high risk of atopic dermatitis.¹⁷

Preventing food sensitisation by improving the infant skin barrier has been proposed.¹³ In a randomised controlled pilot trial of 77 infants at high risk of food allergy given ceramide-dominant emollient twice daily, sensitisation to food allergens was reduced at 12 months in the per-protocol analysis only,¹⁸ whereas in the Barrier Enhancement for Eczema Prevention (BEEP) study,¹⁷ among 1394 infants given daily standard emollients, no reduction in food allergy was identified at age 2 years.¹⁷

The dual allergen exposure hypothesis suggests that food allergen exposure through damaged skin before exposure through the alimentary tract might lead to the development of food allergy.¹⁹ Combining dietary modifications and improved skin barrier function in early infancy to prevent food allergy has therefore been hypothesised,^{13,14,19} but had not been previously investigated in humans before the Preventing Atopic Dermatitis and ALLergies in children (PreventADALL) study.¹⁶ The PreventADALL study is the first large, pragmatic, population-based, randomised clinical trial combining the early introduction of food allergens and regular emollients aiming to prevent atopic dermatitis¹⁶ or food allergy in children. The lack of preventive effect of the interventions on atopic dermatitis at 12 months of age was reported in 2020.¹⁶

In this study, we aimed to determine whether early food or skin interventions prevented food allergy at age 36 months. We also aimed to assess the effect of the interventions on preventing allergy to specific intervention foods, atopic dermatitis, and allergic sensitisation to the intervention foods at age 36 months.

Methods

Study design and participants

The PreventADALL study is an investigator-initiated, 2×2, multicentre, cluster-randomised, controlled superiority trial done at Oslo University Hospital and Østfold Hospital Trust, Oslo, Norway, and Karolinska University Hospital, Stockholm, Sweden. The methods of the PreventADALL trial have been published previously.¹⁶

Briefly, all healthy newborn babies with a minimum gestational age of 35·0 weeks, born to women enrolled in the PreventADALL study during pregnancy between Dec 9, 2014, and Oct 31, 2016, were eligible for randomisation. All pregnant women attending the routine 18-week ultrasound examination at one of the three study sites were invited to participate. Exclusion criteria were pregnancy with more than two fetuses; lack of sufficient Scandinavian language skills; plans to move outside reasonable travel distance within 1 year postpartum; and severe maternal, fetal, or neonatal diseases that could influence adherence to the interventions. Enrolment and all follow-up visits were done at the three study sites. The study was approved by the Regional Committees for Medical and Health Research Ethics in Norway (2014/518) and Sweden (2014/2242–31/4 and 2018/1437–32). Mothers provided written informed consent at antenatal enrolment, and parents signed a new written informed consent before enrolment of their newborn baby.

Randomisation and masking

At the maternity ward of each participating hospital, 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 of the parents by trained study personnel. To reduce the risk of intervention contamination across randomisation groups, we used computer-generated cluster randomisation based on 92 geographical residential areas and eight 3-month time blocks, assigned by a statistician who was not involved in further trial conduct and analyses; outcomes of interest are on the individual participant level only. All infants born in the same 3-month period who belonged to the same residential area were allocated to the same intervention group (appendix pp 4–5). The randomisation was computer generated before study start, but the allocation list was only provided to the study centers every 3 months. From the prespecified allocation list, the newborn infants were allocated to the intervention group after their parents provided written informed consent. Included participants were residents in 80 of the 92 areas, with a mean of 30 participants per geographical area (range 1–191) and 108–385 participants per 3-month time period (appendix p 3), with each of the 736 clusters (residential area per time period) ranging from 0 to 35 participants. All three study sites included participants in all four intervention groups.

The study design did not allow for masking of study participants or their caregivers to the interventions. Study personnel involved in inclusion of the mothers or clinical follow-up investigations, or those included on the expert panel did not have access to the group allocation lists. Furthermore, parents were firmly instructed not to apply any type of emollient bath additives or leave-on emollients 24 h before each follow-up visit, and all clinical assessments and investigations were done and recorded

See Online for appendix

without the study personnel's knowledge of the group allocation. The hypothesis testing framework and analyses were prespecified in the statistical analysis plan before unmasking the intervention groups.

Procedures

The food intervention was chosen based on foods that are commonly associated with sensitisation and food allergy in early childhood. To facilitate feasibility, we limited interventions to three commonly used foods in addition to peanut, since peanut has become a major cause of food allergy.⁹ The foods were introduced between 12 and 16 weeks of age: peanut butter was given for the first time at the 3-month follow-up visit, followed by cow's milk introduced 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, complementary to regular feeding, and to continue to include the food in the infant's diet until at least 6 months of age without any dose restrictions.

The skin intervention was petrolatum-based and consisted of baths for 5–10 min with added emulsified oil (0·5 dL bath oil per 8 L water) and cream applied to the entire face (Ceridal; GlaxoSmithKline Consumer Healthcare, Philadelphia, PA, USA) on at least 4 days per week from age 2 weeks to 8 months. Parents were carefully instructed on safe baby handling during bathing at the maternity ward, 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 given to the participants together with Ceridal at randomisation and subsequently at the 3-month and 6-month clinical follow-up visits, as needed. Use of soaps was discouraged.

No specific advice on feeding practices or skin care were given to the parents of the infants allocated to the no food intervention group and the no skin intervention group. However, parents were encouraged to follow the regular advice from the health centre and the national guidelines for infant nutrition, generally recommending exclusive breastfeeding until 6 months of age (appendix pp 6–7).^{20,21}

The participants attended clinical follow-up visits at 3, 6, 12, 24, and 36 months of age. Additionally, parents were encouraged to contact the study teams for extra consultations in case of suspected reactions to foods or with suspected eczema or other rashes of unknown origin. Further information was collected through electronic weekly diaries from birth until 26 weeks of age, and via electronic questionnaires every 3 months during the first year of life, and subsequently, biannually. For completeness of data, parents of children who did not attend the 36 months (3 years) follow-up visit were contacted by telephone for an interview concerning food exposure, suspected food allergy, eczema, asthma, and rhinitis.

Adherence to the interventions was reported in weekly electronic diaries as the number of days per week per intervention between age 2 and 26 weeks, including any deviations from the intervention instruction. Parents of children in all four randomisation groups completed the diaries. 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. Full protocol adherence to the food intervention required introduction of the food between age 13 and 18 weeks and intake of the food for a minimum 3–5 days per week in at least 5 weeks between age 19 and 26 weeks. Partial adherence required introduction of the food between age 13 and 18 weeks and at least 1–2 days per week in at least 5 weeks between 19 and 26 weeks of age. If parents reported adherence in less than 5 of the 8 weeks between 19 and 26 weeks of age, adherence was classified as unknown. Overall, per-protocol food adherence was defined as full adherence to at least three of four interventional foods.

The use of emollients was recorded by parents of infants in the skin intervention or combined intervention groups only. Full protocol skin intervention adherence was defined as reported baths with the PreventADALL oil additive and the Ceridal facial cream for a mean of at least 3·5 days per week in 16 of the 25 first weeks of life. Emollients had to be applied for the first time by 4 weeks of age and could not be missed in two of three consecutive weeks.

Major protocol deviations were defined as: erroneous enrolment based on eligibility criteria, lack of full protocol adherence (with the exception of possible allergy contraindicating intervention initiation or prompted stopping the intervention based on a clinical decision [including adverse events]), full protocol adherence to an intervention the participant was not allocated to (with the exception of infant milk formula and wheat that might be advised as complementary to regular feeding from age 4 months), and missing data on primary endpoints.

Exposure to the interventional foods during the first year of life was reported in weekly diaries from 2 to 26 weeks of age, and for each 3-month period preceding questionnaires at 6, 9, and 12 months of age. Data were based on what was considered typical for the child per week, and reported in four categories: no intake, less than weekly, 1–3 times per week, and four times or more per week. Additionally, intake of peanut at the 3-month study visit was documented in the clinical visit registration form.

Outcomes

The primary, secondary, and sensitivity outcomes were prespecified in the protocol and statistical analysis plan before analysis and unmasking of the intervention groups.

The primary outcome was food allergy to any interventional food (peanut, milk, wheat, or egg) at 36 months of age, defined as fulfilling the criteria deemed

For the statistical analysis plan see https://oslo-universitetssykehus.no/avdelinger/barne-og-ungdomsklinikken/preventadall/resultater-i-preventadall/PreventADALL_SAP_2021.10.29.pdf

by expert panels (one in Norway and one in Sweden).

At the 3-year follow-up, children were screened for food allergy by a structured parental interview for frequent consumption (≥ 3 times in lifetime) and recent consumption (at least once in the previous month), and possible reactions to any of the four interventional foods (appendix pp 8–9). Children were assessed for allergic sensitisation using a skin prick test for the interventional food allergens and other common food and inhalant allergens (appendix p 8). On the basis of an algorithm used to screen and classify participants in terms of allergy to interventional foods (appendix p 10), participants with insufficient frequent or recent intake or reaction to the food within 2 h of exposure and a positive skin prick test were referred to one of the two expert panels for evaluation (appendix p 10).

The parents of participants who did not attend the 3-year follow-up were contacted by telephone, and were asked the same questions regarding food consumption and possible reactions. In case of suspected allergy, children were encouraged to attend the study centre for an skin prick test or were referred to the relevant expert panel.

The expert panels initially classified children as having food allergy, probable food allergy, no food allergy, or unclear (appendix p 11). When oral food challenge was

not possible or warranted, diagnostic classification was based on the algorithm used in the BEEP study (appendix p 12).²² Participants classified as having food allergy or probable food allergy were considered to have met the primary outcome. All others were classified as having no allergy to the relevant foods.

Secondary outcomes were allergy to peanut, allergy to cow's milk, allergy to wheat, and allergy to egg at 36 months of age, defined and classified as per the primary outcome.

Additional secondary outcomes were atopic dermatitis at 36 months, defined as fulfilling the UK Working Party²³ or Hanifin and Rajka's²⁴ diagnostic criteria at any time by the age of 36 months, and breastfeeding at age 6 months, reported in questionnaires or weekly diaries.

Sensitivity outcomes were atopic dermatitis at 36 months, defined as fulfilling the UK Working Party²³ or Hanifin and Rajka's²⁴ diagnostic criteria at 36 months of age, and allergic sensitisation to any or each interventional food at age 36 months, defined as an allergen skin prick test mean wheal diameter exceeding that of the negative control by at least 3 mm at the 3-year follow-up visit.

Adverse events were recorded in weekly electronic diaries up to week 26, in electronic questionnaires every 3 months, and in specific adverse events forms up

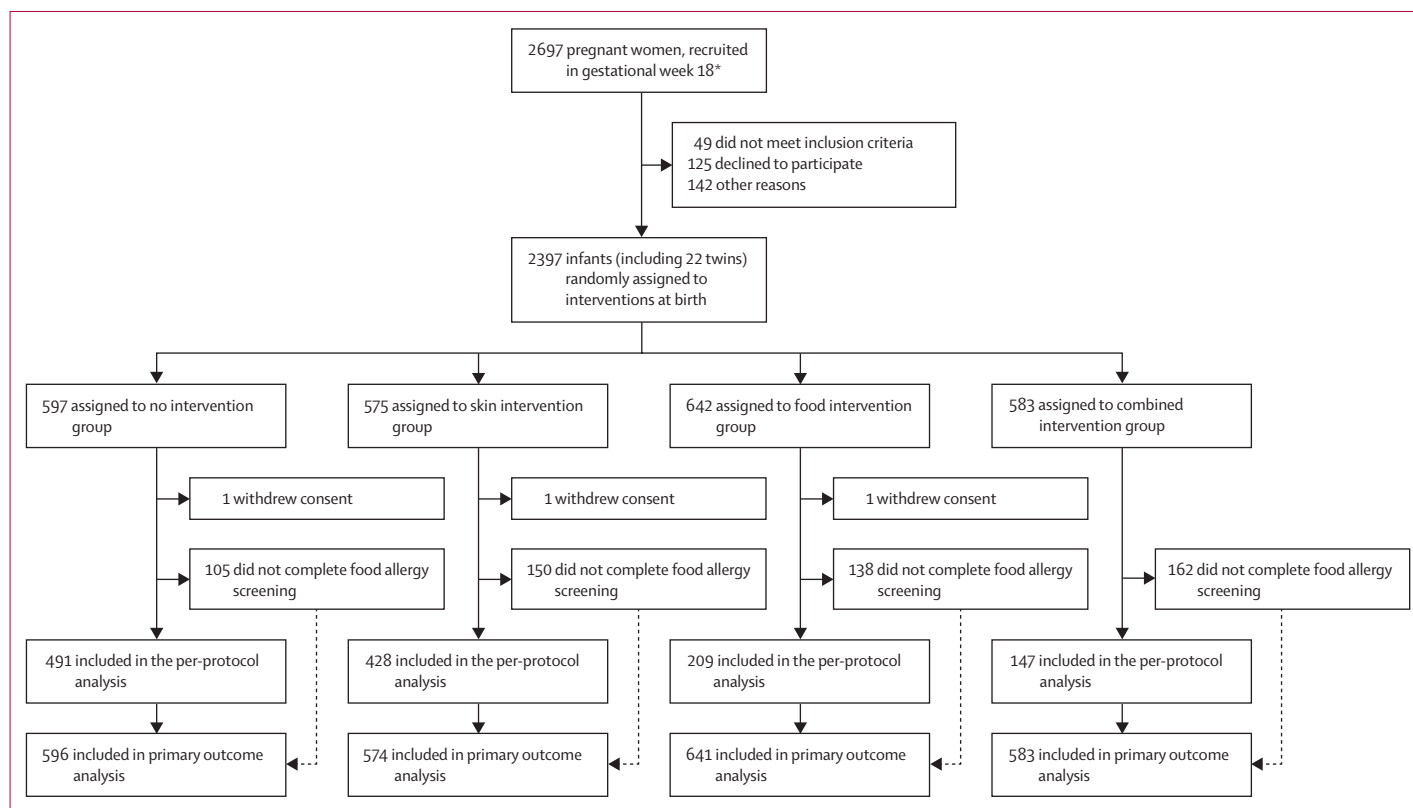


Figure 1: Trial profile

Screening for food allergy at the follow-up study at age 36 months included a structured interview with the caregiver at the clinical visit for 1664 children and by phone for 279 children, and a skin prick test for relevant allergens in children attending the clinics. Complete case analyses were based on children who were screened for food allergy at 36 months of age. *Four women participated twice with two different children and there were 17 twin pregnancies.

to 12 months of age at the discretion of the study personnel.

Statistical analysis

This trial was powered on the basis of the coprimary outcome of atopic dermatitis at 12 months, as previously described.¹⁶ A 30% relative reduction in the probability of atopic dermatitis from 23% in the control group to 16% in the skin intervention only group corresponds to a 7% absolute risk reduction, which was judged to be clinically meaningful. When comparing the intervention group with the no intervention group, 511 participants in each group were required to reject the no intervention effect hypothesis with 80% power. However, the number of participants per group was erroneously multiplied by 4 (for each of the four groups in the 2×2 factorial design) instead of 2 (for each of the two groups at the margins based on the skin care intervention). Therefore, the study had more than 99% power to detect a 30% reduction in atopic dermatitis from 23·2% to 16·2%. No sample size calculation was performed for the food intervention due to insufficient available data. To adjust for potential dropouts, the recruitment target was set at 2700 pregnancies.

For the food allergy outcome, the primary statistical hypothesis testing framework was to test the null hypothesis of no main effect of either intervention and no interaction effect on the primary endpoint using one statistical model in the intention-to-treat population, which included all randomly assigned participants. All hypotheses were tested at the 5% significance level without adjusting for multiplicity.

In masked inspection of the data, we observed 44 children with food allergy at 36 months. Due to the low number of participants meeting the primary outcome, the use of a mixed logistic regression model, with both interventions and their interaction as fixed effects and cluster according to randomisation time period and residential postal code as random effects, might fail to converge or provide incorrect estimates. Furthermore, in the previous analysis at 12 months, the intra-cluster correlations were negligible.¹⁶ We therefore omitted random effects in the primary analysis, although cluster-randomisation was used. Another concern was possible low cell counts in the contingency table. Therefore, before unblinding the statisticians, the unblinded data manager provided the number of children with food allergy in the smallest cell, without unmasking any other information. Based on this result, we decided to use a logistic regression model with food intervention, skin intervention, and their interaction as independent factors for the primary analysis. We present both main effects by treatment (food or skin intervention) and marginal effects by treatment group. We considered the main effects as primary estimates when the p value of the interaction effect was higher than 0·05; otherwise the marginal treatment group effects were considered primary. Missing primary

	No intervention (n=596)	Skin intervention (n=574)	Food intervention (n=641)	Combined food and skin interventions (n=583)
Age, years				
Mother	32·5 (4·2)	32·2 (4·2)	32·6 (4·1)	32·5 (4·2)
Father	34·8 (5·5)	34·6 (5·5)	34·8 (5·5)	34·6 (5·4)
Gestational age at birth, days	280·6 (9·7)	279·7 (9·1)	280·2 (9·7)	280·9 (9·3)
Study site				
Oslo (Norway)	394 (66%)	355 (62%)	415 (65%)	371 (64%)
Østfold (Norway)	92 (15%)	99 (17%)	80 (13%)	71 (12%)
Stockholm (Sweden)	110 (19%)	120 (21%)	146 (23%)	141 (24%)
Maternal education				
Preliminary school only (9–10 years of schooling)	3 (0·6%)	4 (0·8%)	4 (0·7%)	5 (0·9%)
High school only	51 (10%)	55 (11%)	61 (11%)	56 (11%)
Higher education for <4 years	168 (31%)	160 (31%)	188 (33%)	174 (33%)
Higher education for ≥4 years	301 (56%)	273 (53%)	310 (54%)	287 (54%)
PhD	15 (3%)	18 (4%)	14 (2%)	13 (2%)
Other	0	2 (<1%)	0	0
Partner education				
Preliminary school only (9–10 years of schooling)	7 (1·3%)	5 (1·0%)	6 (1·1%)	8 (1·5%)
High school only	93 (18%)	99 (20%)	102 (19%)	99 (19%)
Higher education for <4 years	161 (31%)	138 (28%)	170 (31%)	160 (31%)
Higher education for ≥4 years	242 (46%)	221 (45%)	249 (46%)	235 (45%)
PhD	16 (3%)	19 (4%)	15 (3%)	20 (4%)
Other	7 (1%)	8 (2%)	5 (1%)	2 (<1%)
Maternal country of origin				
Norway	381 (70%)	339 (66%)	383 (66%)	340 (63%)
Sweden	107 (20%)	124 (24%)	135 (23%)	126 (24%)
Other Nordic country	10 (2%)	9 (2%)	5 (1%)	4 (1%)
Rest of the world	43 (8%)	42 (8%)	57 (10%)	66 (12%)
Paternal country of origin				
Norway	353 (66%)	338 (68%)	357 (63%)	341 (65%)
Sweden	109 (21%)	115 (23%)	139 (25%)	122 (23%)
Other Nordic country	11 (2%)	6 (1%)	6 (1%)	6 (1%)
Rest of the world	60 (11%)	41 (8%)	61 (11%)	54 (10%)
Sex of infant				
Male	311 (52%)	284 (50%)	347 (54%)	313 (54%)
Female	285 (48%)	290 (50%)	294 (46%)	270 (46%)
Parental relationship status				
Married	239 (44%)	222 (43%)	238 (41%)	234 (44%)
Cohabitants	293 (54%)	277 (54%)	323 (56%)	297 (55%)
Other	11 (2%)	17 (3%)	21 (4%)	7 (1·3%)
Living environment				
City, densely populated	214 (40%)	191 (37%)	229 (40%)	208 (39%)
City, less densely populated	201 (37%)	199 (39%)	204 (35%)	222 (41%)
Suburb	77 (14%)	84 (16%)	100 (17%)	84 (16%)
Village	11 (2%)	11 (2%)	19 (3%)	5 (1%)

(Table 1 continues on next page)

	No intervention (n=596)	Skin intervention (n=574)	Food intervention (n=641)	Combined food and skin interventions (n=583)
(Continued from previous page)				
Countryside, outside village	38 (7%)	29 (6%)	28 (5%)	17 (3%)
Doctor diagnosed allergic diseases				
Maternal asthma	87 (16%)	95 (18%)	114 (20%)	75 (14%)
Maternal atopic dermatitis	124 (23%)	111 (22%)	112 (19%)	84 (16%)
Maternal allergic rhinitis	106 (20%)	107 (21%)	130 (22%)	102 (19%)
Maternal food allergy	72 (13%)	66 (13%)	75 (13%)	68 (13%)
Paternal asthma	76 (14%)	59 (11%)	84 (15%)	60 (11%)
Paternal atopic dermatitis	56 (10%)	52 (10%)	64 (11%)	48 (9%)
Paternal allergic rhinitis	116 (21%)	141 (27%)	136 (24%)	117 (22%)
Paternal food allergy	49 (9%)	52 (10%)	51 (9%)	45 (9%)
Atopy				
Maternal	237 (44%)	209 (41%)	249 (43%)	206 (38%)
Paternal	192 (35%)	188 (36%)	200 (36%)	171 (32%)
Either parent	350 (60%)	330 (59%)	367 (59%)	313 (55%)
Birthweight, g	3584 (484)	3566 (502)	3551 (472)	3583 (473)
Birth length, cm	50.6 (2.1)	50.4 (2.1)	50.4 (2.1)	50.6 (2.0)
Delivery method				
Vaginal delivery	501 (84%)	476 (83%)	539 (84%)	477 (82%)
Caesarean section	95 (16%)	97 (17%)	101 (16%)	104 (18%)
Previous deliveries				
0	362 (61%)	348 (61%)	356 (56%)	363 (62%)
1	177 (30%)	175 (31%)	223 (35%)	171 (29%)
2	49 (8%)	46 (8%)	49 (8%)	44 (8%)
3	5 (1%)	4 (1%)	8 (1%)	3 (<1%)
4	3 (<1%)	0	2 (<1%)	1 (<1%)
≥5	0	0	1 (0.2%)	1 (0.2%)
Twins	2 (<1%)	10 (2%)	6 (1%)	4 (1%)
Children of mothers who participated twice	2 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)
Body-mass index of mother, kg/m ²	24.8 (3.8)	24.8 (3.8)	24.8 (3.6)	24.9 (3.6)
Data are mean (SD) or n (%).				

Table 1: Baseline characteristics

outcome data were imputed with the best-case option of no food allergy, under the assumption that children with food allergy were more likely than not to attend the follow-up investigation because of the opportunity for further investigations at a specialist centre, whereas the reverse might be observed for children without allergic disease. Additionally, sensitivity analyses were done using multiple imputation of different prevalence of food allergy for missing outcomes (appendix p 15).

For complete case analysis, we included all children who were screened for food allergy according to the algorithm shown in the appendix (p 10). For the secondary outcome of peanut allergy, we used logistic regression in the intention-to-treat population. Due to the rarity of egg, milk, and wheat allergy, we used pairwise exact methods with Agresti-Min exact unconditional CIs (Berger-Boos

method, $\gamma=0.000001$) for the risk difference estimates for the corresponding outcomes. These methods do not allow estimation of interaction effects.

For the additional secondary outcomes of atopic dermatitis by age 36 months, which was tested in the intention-to-treat population, and breastfeeding at age 6 months, in all participants who completed the questionnaire, we used mixed-effects logistic regression with the interventions and interaction as fixed effects, and randomisation time period and residential postal code as random effects. For atopic dermatitis, which was tested in the intention-to-treat population, we imputed the so-called best case and for breastfeeding we used multiple imputation with chained equations for missing values separately for each randomisation group using baseline characteristics and outcomes as auxiliary variables.

The primary effect estimate was risk difference, computed from the logistic regression model using the delta method.

All analyses were done with R (version 3.6.0), with the exception of exact tests, which were done in StatXact (version 12). 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 study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We recruited 2697 women with 2701 pregnancies from whom 2397 newborn infants were enrolled between April 14, 2015, and April 11, 2017. Of these infants, 597 were randomly assigned to the no intervention group, 575 to the skin intervention group, 642 to the food intervention group, and 583 to the combined intervention group. One participant in each of the no intervention, food intervention, and skin intervention groups withdrew consent and were therefore not included in any of the analyses (figure 1). Baseline characteristics were similar in the four groups (table 1) and in participants with and without missing primary outcome data (appendix pp 17–19). Overall, 95% of the infants were breastfed at 3 months of age, and the proportion was similar across groups (94–96%). Full protocol adherence was observed in 227 (35%) of 641 infants in the food intervention group and 160 (27%) of 583 infants in the combined intervention group (appendix p 20). The vast majority of infants in the food intervention groups were exposed to the interventional foods before 6 months of age, and the exposure rates were similar in both intervention and non-intervention groups from 6 to 12 months of age (figure 2; appendix pp 21–22). Overall, 1943 children were screened for food allergy by parental interview—1664 at the clinic, of whom 1504 (90%) also had an available skin

prick test, and 279 by telephone interview, with no available skin prick test. Frequent and recent exposure and no clinical reaction or 0 mm skin prick test was reported for 1747 children. Based on reported insufficient exposure or clinical reaction to any interventional food at 36 months, 92 children with a positive skin prick test were referred to the expert panel for evaluation of 117 food allergies, and further information was missing for 104 children without a skin prick test (appendix p 10).

Allergy to any of the interventional foods was diagnosed in 44 children with a total of 48 food allergies: 14 (2.3%) of 596 participants in the non-intervention group, 17 (3.0%) of 574 participants in the skin intervention group, six (0.9%) of 641 participants in the food intervention group, and seven (1.2%) of 583 participants in the combined intervention group (appendix p 23).

In intention-to-treat analysis, using best-case imputation of missing data, food allergy was reduced in the food intervention group compared with the no food intervention group (risk difference -1.6% [95% CI -2.7 to -0.5]; odds ratio [OR] 0.4 [95% CI 0.2 to 0.8]), but not compared with the skin intervention group (risk difference 0.4% [95% CI -0.6 to 1.5%]; OR 1.3 [0.7 to 2.3]; figure 3, table 2). Early introduction of allergenic foods in 63 infants was needed to prevent food allergy in one child. In complete-case analyses, the risk of food allergy was lower in the food intervention group than the no food intervention group (risk difference -2.0% [95% CI -3.4 to -0.6]; OR 0.4 [95% CI 0.2 to 0.8]; table 2). Using multiple imputation for missing outcomes, food allergy was significantly reduced in the food intervention group, when the

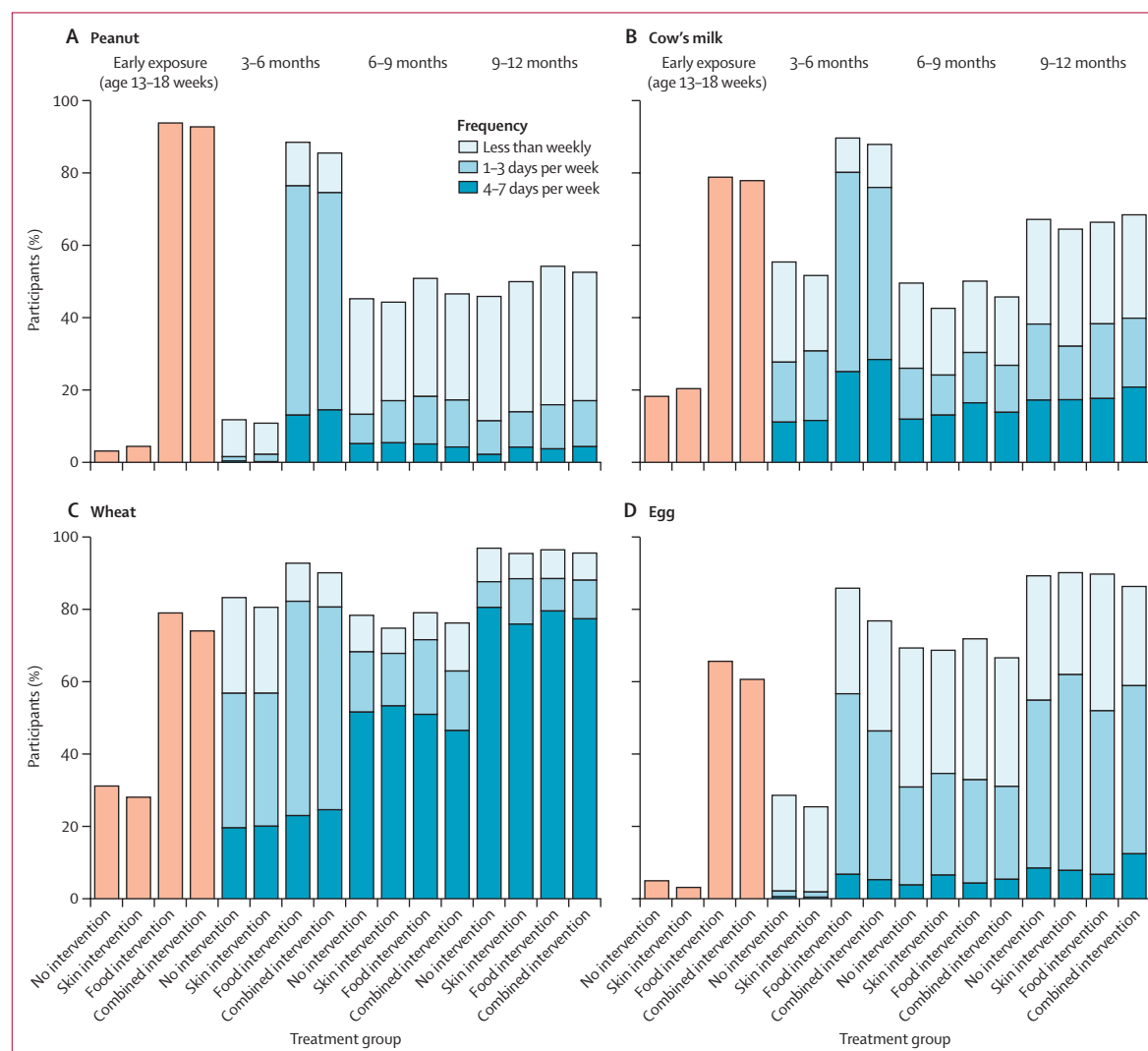


Figure 2: Timing and frequency of exposure to peanut (A), cow's milk (B), wheat (C), and egg (D)

Proportion of participants who had early exposure (aged 13-18 weeks) to each interventional food, as derived from the weekly diaries up to 6 months (orange bars), and frequency of intake per week per interventional food between ages 3 and 6 months, 6 and 9 months, and 9 and 12 months, as reported in questionnaires at age 6, 9, and 12 months (blue bars).

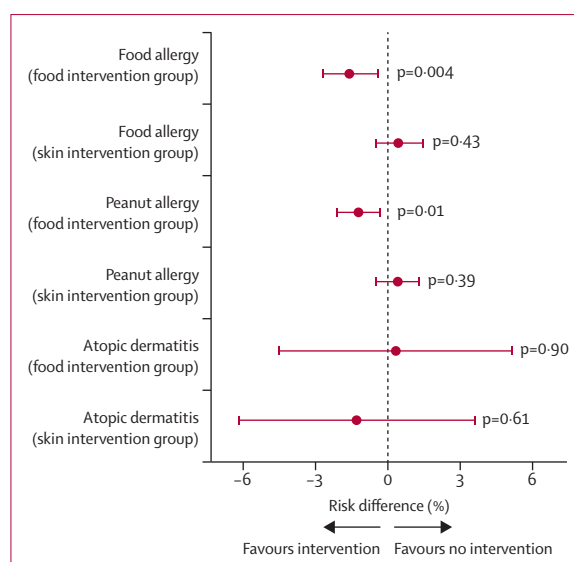


Figure 3: Risk reduction of food allergy for each primary prevention strategy. Error bars show 95% CIs. Food allergies are presented as main effects, whereas atopic dermatitis is presented as a marginal estimate.

prevalence of food allergy was 3.5% or lower (appendix p 25).

When including the food allergy outcomes, mixed models including random effects for the clusters could not be fit due to singularity as a result of the low cell counts. Therefore, it was not possible to report an intra-cluster correlation (ICC) for the primary analysis. For the related sensitivity analysis of allergic sensitisation at age 36 months, we were able to fit a model only accounting for time period and the ICC was 0.005. Marginal estimates by treatment group for all outcomes are presented in the appendix (pp 26–27).

Food allergy was most often diagnosed for peanut, followed by milk and egg. Peanut allergy was diagnosed in 32 children, egg allergy in 12 children, and milk allergy in four children. No infants were diagnosed with wheat allergy in any participant in any group (figures 4, 5, table 2). Peanut allergy was reduced by the food intervention, but not by the skin intervention (figure 3, table 2). The prevalence of specific food allergies by intervention groups and among participants who were fully adherent to the food intervention are shown in figure 4.

Atopic dermatitis at age 36 months was diagnosed in 147 (25%) of 596 participants in the non-intervention group, 136 (24%) of 574 participants in the skin intervention group, 160 (25%) of 641 participants in the food intervention group, and 100 (17%) of 583 participants in the combined intervention group. The main effects model shows an effect of the skin intervention (skin intervention group and combined intervention group) versus no skin intervention (no intervention group and food intervention group) on atopic dermatitis (table 2). However, since the estimated interaction effect was not

negligible ($p=0.047$), the effect of food intervention on atopic dermatitis was modified by the skin intervention such that the results are more appropriately presented as marginal estimates. Neither intervention alone reduced atopic dermatitis development, with a risk difference of -1.3% (95% CI -6.2 to 3.7) for the skin intervention and 0.3% (95% CI -4.5 to 5.2) for the food intervention (appendix pp 26–27). However, in combination, atopic dermatitis was reduced by -7.4% (95% CI -12.1 to -2.7 ; appendix pp 26–27).

No safety concerns with the interventions were identified. The proportion of participants who were breastfeeding at age 6 months was similar in the four groups (85.8–87.9%; table 2; $p=0.40$). In total, 35 participants were admitted to hospital during the first year of life; ten in the non-intervention group, six in the skin intervention group, nine in the food intervention group, and 11 in the combined interventions group. We observed no serious allergic reactions in relation to introduction of interventional foods (appendix pp 28–30), and there were no episodes of choking on the food interventions.

Allergic sensitisation to the interventional foods (appendix p 30) had the same pattern as food allergy (figure 5, table 2; appendix pp 25, 31). Briefly, 21 (4%) of 596 infants in the no intervention group, 18 (3%) of 574 infants in the skin intervention group, nine (1%) of 641 infants in the food intervention group, and eight (1%) of 583 infants in the combined intervention group were sensitised to at least one of the interventional foods (appendix pp 30–31).

Atopic dermatitis at 36 months of age was observed in 103 (17%) of 596 infants in the no intervention group, 90 (16%) of 574 infants in the skin intervention group, 110 (17%) of 641 infants in the food intervention group, and 67 (12%) of 583 infants in the combined intervention group (appendix p 26).

Discussion

In this large, pragmatic, randomised clinical trial, the introduction of peanut, cow's milk, wheat, and egg from 3 months of age, complementary to regular feeding, reduced food allergy at 36 months of age in children from a general population. We were not able to provide evidence that regular emollient baths and facial cream from early infancy reduced food allergy.

This is the first study to demonstrate a significant reduction in risk of documented food allergy in children aged 36 months after regular exposure to common foods from 3 months of age. Our results are supported by previous findings of allergen-specific risk reduction for peanut⁸ and egg,²⁵ among infants at high risk of food allergy based on the presence of atopic dermatitis^{8,25} or egg allergy,⁸ and for cow's milk among infants not selected by atopic risk.¹¹ Furthermore, the reduced prevalence of food allergy at age 36 months by introducing four common foods between 3 and 4 months

	No skin intervention (n= 1237)	Skin intervention (n=1157)			No food intervention (n=1170)	Food intervention (n=1224)			Intervention interaction (p value)
		n (%)	Risk difference (95% CI)	OR (95% CI)		n (%)	Risk difference (95% CI)	OR (95% CI)	
Food allergy primary analysis									
Intention-to-treat population, best-case imputation	20 (1.6%)	24 (2.1%)	0.4% (−0.6 to 1.5)	1.3 (0.7 to 2.5)	31 (2.6%)	13 (1.1%)	−1.6% (−2.7 to −0.5)	0.4 (0.2 to 0.8)	0.9838
Food allergy sensitivity analyses									
Per-protocol population, no imputation	15/699 (2.1%)	18/575 (3.1%)	1.0% (−0.8 to 2.8)	1.5 (0.7 to 3.0)	31/923 (3.4%)	2/354 (0.6%)	−2.8% (−4.1 to −1.4)	0.2 (0.0 to 0.7)	..
Complete case population, no imputation, including interaction term*	20/994 (2.0%)	24/845 (2.8%)	0.8 (−0.1 to 2.2)	1.4 (0.7 to 2.7)	31/915 (3.4%)	13/924 (1.4%)	−2.0% (−3.4 to −0.6)	0.4 (0.2 to 0.8)	0.9810
Intention-to-treat population, interaction term removed	20 (1.6%)	24 (2.1%)	0.4% (−0.6% to 1.5%)	1.3 (0.7 to 2.3)	31 (2.6%)	13 (1.1%)	−1.6% (−2.7 to −0.5)	0.4 (0.2 to 0.8)	..
Allergy to specific foods									
Peanut	14 (1.1%)	18 (1.6%)	0.4% (−0.5 to 1.3)	1.4 (0.6 to 3.0)	23 (2.0%)	9 (0.7%)	−1.2% (−2.1 to −0.3)	0.4 (0.2 to 0.8)	0.9856
Milk	3 (0.2%)	1 (0.1%)	−0.2% (−0.5 to 0.2)	0.4 (0.0 to 3.4)	3 (0.3%)	1 (0.1%)	−0.2% (−0.6 to 0.2)	0.3 (0.0 to 3.1)	..
Wheat	0	0	0% (−0.2 to 0.2)	..	0	0	0% (−0.2 to 0.2)	..	..
Egg†	6 (0.5%)	6 (0.5%)	0.0% (−0.6 to 0.6)	1.1 (0.3 to 3.3)	7 (0.6%)	5 (0.4%)	−0.2% (−0.8 to 0.4)	0.7 (0.2 to 2.1)	..
Atopic dermatitis									
By 3 years of age	307 (24.8%)	236 (20.4%)	−4.6% (−7.9 to −1.2)‡	0.8 (0.6 to 0.9)	283 (24.2%)	260 (21.2%)	−2.8% (−6.2 to 0.6)	0.8 (0.7 to 1.0)	0.047‡
Present at 3 years of age	213 (17.2%)	157 (13.6%)	−3.6% (−6.6 to −0.7)‡	0.8 (0.6 to 0.9)	193 (16.5%)	177 (14.5%)	−2.0% (−4.9 to 0.9)	0.8 (0.7 to 1.1)	0.136
Allergic sensitisation by skin prick test at age 36 months									
Any interventional food	30 (2.4%)	26 (2.2%)	−0.2% (−1.4 to 1.0)	0.9 (0.5 to 1.7)	39 (3.3%)	17 (1.4%)	−2.0% (−3.2 to −0.7)	0.4 (0.2 to 0.7)	0.8687
Peanut	20 (1.6%)	23 (2.0%)	0.3% (−0.7 to 1.4)	1.6 (0.7 to 3.5)	33 (2.8%)	10 (0.8%)	−2.0% (−3.1 to −0.9)	0.3 (0.1 to 0.6)	0.2106
Milk†	1 (0.1%)	1 (0.1%)	0.0% (−0.3 to 0.3)	1.1 (0.7 to 17.1)	1 (0.1%)	1 (0.1%)	0.0% (−0.3 to 0.3)	1.0 (0.1 to 15.3)	..
Wheat†	2 (0.2%)	4 (0.3%)	0.2% (−0.3 to 0.7)	2.1 (0.4 to 11.7)	5 (0.6%)	1 (0.4%)	−0.3% (−0.8 to 0.1)	0.2 (0.2 to 1.6)	..
Egg	10 (0.8%)	7 (0.6%)	−0.2% (−0.9 to 0.5)	0.7 (0.3 to 2.0)	9 (0.8%)	8 (0.6%)	−0.1 (−0.8 to 0.6)	0.8 (0.3 to 2.2)	..
Breastfeeding at 6 months of age§	934/1088 (85.8%)	764/878 (87.9%)	−0.6% (−4.9 to 3.8)	0.9 (0.7 to 1.2)	852/981 (86.9%)	846/985 (85.9%)	−1.0 (−4.4 to 2.3)	0.8 (0.7 to 1.1)	..

Data are n (%) or n/N (%). Analyses were performed by best-case imputation, unless stated otherwise. Multiple imputation for various food allergies by prevalence are shown in the appendix (p 28). The no food intervention group includes participants assigned to the skin intervention and no intervention. The food intervention group includes participants assigned to the food intervention and combined interventions.*Complete-case analysis included all participants who completed screening for food allergy at age 36 months. †Exact analysis by pairwise exact methods with Agresti-Min exact unconditional CIs. ‡The significant interaction between the interventions on the atopic dermatitis outcomes implies that these outcomes are more appropriately assessed in marginal analyses (appendix pp 17–19). §Denominators for complete-case analysis are reported; however, analysis was performed by multiple imputation by chained equations.

Table 2: Primary, secondary, and sensitivity outcomes, main effects

of age extend the results from the EAT study,³ in which the risk of food allergy between age 12 and 36 months was significantly reduced only among the 32% of participants who were adherent to the multiple food intervention. However, an intention-to-treat subgroup analysis of the EAT study showed that the food intervention significantly reduced food allergy among infants at high risk of developing food allergy.²⁶

In our study, prevalence of food allergy was not reduced among participants in the skin intervention group at 36 months of age. Furthermore, a non-significant increase in food allergy was observed among children randomised to the skin intervention in the BEEP study,¹⁷ and post-hoc analyses of the EAT study showed a positive dose-response relationship between food allergy and reported use of emollients at 3 months of age.²⁷ We are

not aware of other reports on food allergy based on skin interventions for primary prevention at present. However, results from other emollient primary prevention studies are awaited, including studies using more complex formulations, such as emollients containing ceramide.¹⁸

The proportion of children with documented food allergy at 36 months in the no food intervention group (2%) was lower than that among children aged 4 years in the Australian HealthNuts study (4%)¹ and in the no-intervention group of the EAT study (7%).³ Similarly, the proportion of children with food allergy

in the food intervention group in our study was lower than that observed in the early intervention group in the EAT study (0.9% vs 5.5%).³ These differences might partly be explained by the age at which food allergy is determined. Since milk and egg allergies often resolve by age 4 years,¹⁴ the lower food allergy prevalence at 36 months in PreventADALL might reflect the development of natural tolerance in children after 12–24 months of age, whereas the EAT study reported food allergy between 12 months and 36 months of age.³ Notably, peanut allergy, which is less prone to natural tolerance development than egg allergy,¹ was similar in the two studies: 2.0% in children in the no food intervention group in this study and 2.5% in the no-intervention food group in the EAT study.³ The absence of observed allergy to wheat in our study is reassuring, and consistent with the findings of the EAT study.³

The observations that fewer children had peanut allergy with increasing adherence to peanut intake suggests a possible dose-response effect, consistent with the lower prevalence of peanut allergy in groups who consumed 2 g per week compared with less consumption in the EAT study.³ In our intention-to-treat analyses, risk of food allergy was significantly reduced in the food intervention group, indicating that early exposure to even small amounts of allergenic foods might be sufficient to prevent food allergy.

The absolute risk reduction of 1.5% implies that for every 63 children exposed to early feeding, food allergy will be prevented in one child. Since our primary prevention measure is a low-cost, natural intervention with no observed clinically significant side-effects, we consider the effect size to be of clinical significance and relevance.

The reduced prevalence of food allergy among participants in the food intervention group was observed

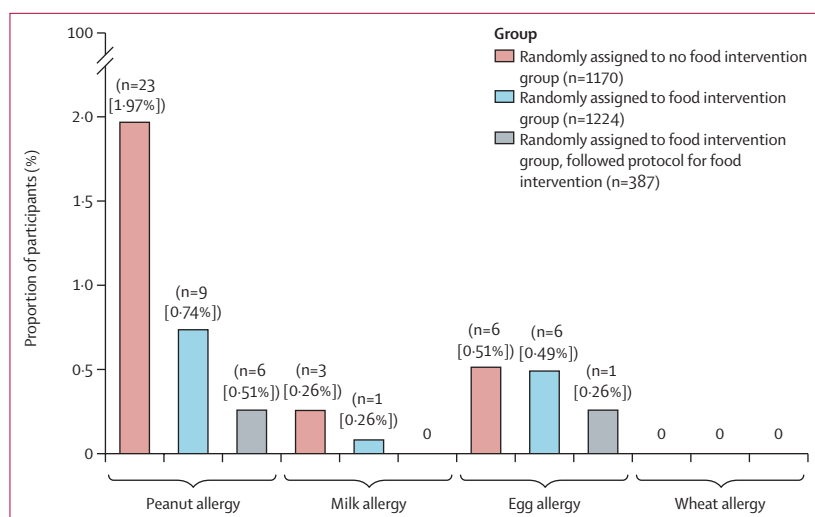


Figure 4: Frequency of food allergy by group allocation and adherence to food intervention

The group of children randomly assigned no food intervention and the group randomly assigned to the food intervention are mutually exclusive. The no food intervention group includes participants assigned to the skin intervention and no intervention. The food intervention group includes participants assigned to the food intervention and combined interventions. Additionally, among the children randomly assigned to the food intervention, the frequency of food allergy is shown among those who were fully adherent for the food intervention (black). No children had an allergy to wheat.

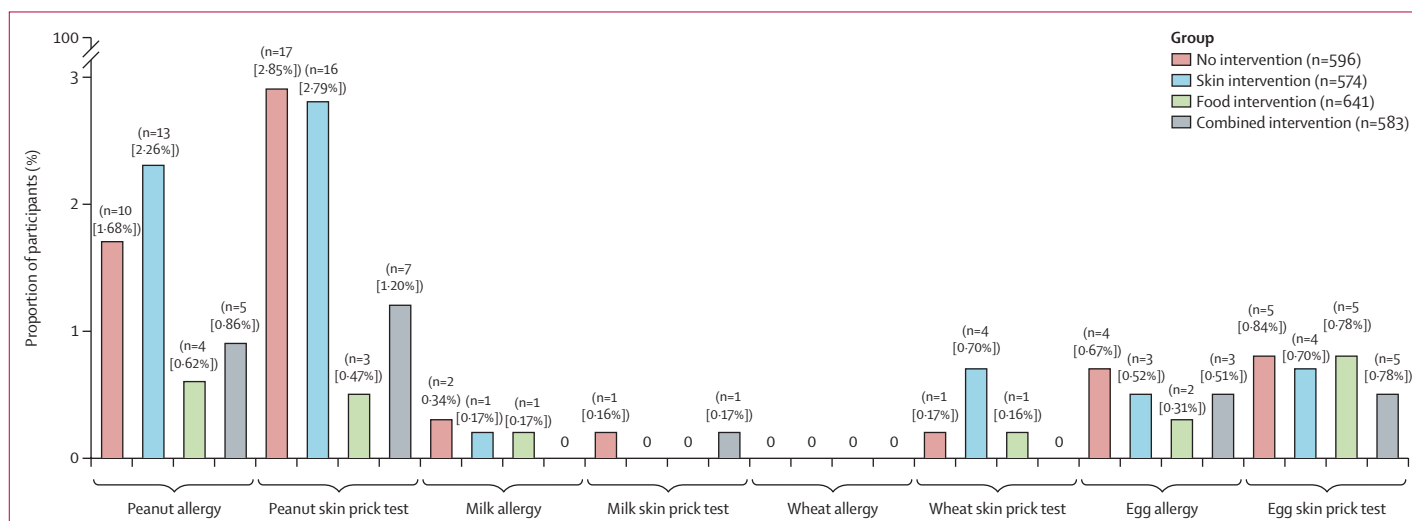


Figure 5: Proportion of children with a diagnosis of allergy and a positive skin prick test for each interventional food by intervention group

A positive skin prick test was defined as mean wheal diameter of 3 mm or larger than the negative control. In one child with documented milk allergy, a skin prick test was not done at 36 months.

for peanut, but not the other specific foods. We are not able to conclude whether early peanut exposure alone would be sufficient to achieve an overall reduction in food allergy, since our intervention consisted of four foods. Although current evidence indicates the development of allergen-specific tolerance, few randomised trials to date have explored immune tolerance through mechanisms other than IgE, and the possibility that broad exposure to allergens might contribute jointly to an overall immune tolerance. The absence of effect of either of the food and skin interventions on atopic dermatitis by 36 months of age is consistent with findings reported at 12 months of age in the PreventADALL study.¹⁶ This result underpins previous conclusions that neither emollients^{16,17,28} nor early feeding^{16,28,29} can be recommended for primary prevention of atopic dermatitis.

The significant interaction effect of the combined interventions on the risk of atopic dermatitis, extending the findings beyond 12 months of age, is surprising, since the principle behind the dual allergen exposure hypothesis is to reduce food allergy, and not atopic dermatitis. No consistent association has previously been reported between the timing of introducing allergenic foods and the risk of developing atopic dermatitis.²⁹ To the best of our knowledge, this study is the first to combine both interventions, targeting the skin and the alimentary tract in parallel to prevent atopic disease. Thus, it is theoretically possible that among a subgroup of susceptible children, for emollients to reduce atopic dermatitis, the absence of allergy development, provided by the food intervention, might be required. Targeting both the skin and the alimentary tract might therefore be appropriate for future primary prevention strategies. At present, the clinical implications of our findings of reduced atopic dermatitis in the combined intervention group are unclear.

Around 95% of the infants in this study were breastfed at the time of introduction to the interventional foods, and all women in the PreventADALL study were encouraged to continue breastfeeding to at least age 6 months, in accordance with national guidelines. A high rate of breastfeeding at 6 months across all randomisation groups shows that the interventions did not negatively influence the natural course of breastfeeding. Thus, a concern that early solid food introduction might cause early cessation of breastfeeding was not confirmed.

The pragmatic approach to assess the primary prevention effects of a low cost and easily accessible food intervention is a strength of the PreventADALL study. The study thus provides evidence for decision makers regarding the benefits and risks of early food introduction in a real world setting among infants of a general population,³⁰ facilitating a broad implementation.

Food allergy was reported at, rather than by age 36 months, consistent with the LEAP study at 60 months of age⁸ and the HealthNuts study at age 4 years (and at age 1 year),¹ but in contrast to the EAT study, which reported food allergy between 1 and 36 months of age.³

Although the resolution of transient food allergy by 36 months was not captured in the PreventADALL study, early introduction of multiple foods in the EAT study did not increase the risk of food allergy between age 1 and 36 months.³ Acknowledging the burden of any food allergy on children and their families, the disease burden might nevertheless increase with duration of the food allergy through childhood. We therefore chose to target food allergy that persisted beyond the first 2 years of life. The diagnosis of food allergy was defined according to strict criteria by highly qualified expert panels. Most cases were based on a positive oral food challenge at one of the three participating hospitals or an anaphylactic reaction within the past 2 years contraindicating an oral food challenge. The highest dose of peanut given in accordance with national recommendations for oral food challenge in young children in Norway was lower than commonly recommended in older children (from approximately 6 years of age); thus a false negative oral food challenge test cannot be ruled out.

The main outcome was based on intention-to-treat analyses by best-case imputation with the risk of underestimating the rate of food allergy. However, robustness of the results was indicated by similar results when using pattern mixture models with increasing food allergy rates, and by complete case-analyses.

To avoid overdiagnosis of food allergy, we believe a conservative approach to correct allergy diagnosis is crucial, since prevalence varies widely between parentally perceived and reported allergy, and objectively documented disease.³¹ Parents had easy access to specialist evaluation of suspected reactions to food in their children through their study participation. We believe this strategy reduced the risk of unidentified food allergy among non-attendees at the 3-year follow-up investigation. Missing outcome data introduce a degree of uncertainty, regardless of analytic strategy, to compensate for the absence of complete data. Data on skin prick tests were available for 90% of the children attending the clinics for the follow-up study, but none of the non-attending children. Some guardians chose to refrain from exposing their child to the discomfort of this procedure, particularly when allergy was not suspected. Sufficient data for further classification were available in all children screened for food allergy, with the exception of 104 infants with reported insufficient exposure or possible reaction. Since children with possible reaction were evenly distributed across the four interventional groups, we consider that the risk of a potential bias on interventional effect estimates by missing food allergy outcome was small. The consistency of the result across analytical approaches and outcomes, using different imputation methods and complete case analysis, strengthens the validity of our findings.

Our study, consistent with the findings of the EAT study,³ found that adherence to the interventions was

lower than anticipated, and, worth noting for future trials, lowest in the combined intervention groups. Although it has been suggested that exposure to low doses of allergenic foods might be inadequate to prevent food allergy,³ we also found a significantly reduced risk of food allergy in the intention-to-treat analysis, which included all randomly assigned participants. Thus, the minimum amount and frequency of exposure to one or more foods to avoid food allergy remains unclear and should be addressed in future studies.

The low prevalence of food allergies other than peanut reduces the power to address the intervention effect on these allergies. Risk differences were subsequently not reported for these individual interventional foods.

The randomisation resulted in a balance of background characteristics across groups, targeting representation of the general population by inviting all pregnant women attending the national routine ultrasound screening at the relevant study locations to participate in the study. Recruitment was completed in 20 months, and no selection towards atopic parents was intended. However, as expected in such studies, parental atopy was over-represented in our study compared with the general population.

Using a pragmatic study design, our findings indicate that regular exposure to allergenic foods from 3 months of age complementary to regular feeding might be an effective, low-cost, and safe strategy to prevent food allergy in children, even in the absence of screening for risk of allergy. Our study thereby supports the hypothesis that early exposure, rather than avoidance or delayed introduction of allergenic foods, reduces the risk of food allergy. However, the pragmatic design limits insight into identifying possible mechanisms by which the intervention prevents food allergy. Since food allergy represents a significant burden to the child and the family, with a potential to cause acute life-threatening reactions on exposure, it is likely that early food exposure might have an impact on reducing the overall burden of food allergy. However, previous reports of possibly increased rates of aspiration of peanut and other nuts highlights the importance of educating parents about safe introduction of solid foods to the infant diet.³²

Exposure to allergenic foods from 3 months of age reduced the risk of documented food allergy at age 36 months in children recruited from a general population. Our results support that early introduction of common allergenic foods is a safe and effective strategy to prevent food allergy.

Contributors

All authors contributed to the design or clinical follow-up of the PreventADALL study, and to drafting or critically revising the paper. All authors approved the last version before submission. HOS, AL, EMR, AA, K-HC, BG, HKG, GHa, GHe, GHá, LL, KR, ACS, CS, BN, and KCLC conceptualised and designed the study. HOS, AL, EMR, AA, ÅWD, MF, SWG, HKG, GHá, CMJ, LL, C-AOM, CMS, MKS, SGT, SA, HA, BN, and KCLC participated in study conduct or data collection. HOS, AL, RV, EMR, ML, ICO, and KCLC participated in the data

analysis. KCLC and the PreventADALL steering board were responsible for the decision to submit the manuscript. The authors assume responsibility for the completeness and accuracy of the data and analyses, as well as for the fidelity to the study protocol. HOS, ML, RV, AL, and KCLC accessed and verified the data.

Declaration of interests

EMR reports honoraria for lectures from Sanofi Genzyme, Leo Pharma, Novartis, Norwegian Psoriasis and Eczema Association, and the Norwegian Asthma and Allergy Association, outside the submitted work. ML reports personal fees for lectures from Merck Sharp & Dohme. AA reports personal fees from Orion Pharma, Novartis, and MEDA Pharmaceuticals, outside the submitted work. CS has received laboratory material and analytical support from Thermo Fisher Scientific in other research projects. KCLC reports institutional fees for lectures from Thermo Fisher Scientific, and funding for projects as outlined in the financial disclosure of this study. All other authors declare no competing interests.

Data sharing

According to Norwegian legislation, identification of individuals stored in public databases by study code is not permitted, when currently stored in the secure Service for Sensitive Data database at the University of Oslo. Furthermore, the PreventADALL study is ongoing, with data currently being collected and analysed by researchers, pertaining to different research questions within the main framework of the study aims. Data storage is currently approved until 2044. Ethical approval and patient consent did not encompass data sharing, but reasonable requests for anonymous data for meta-analyses can be addressed to the study's Principal Investigator, KCLC (k.c.l.carlsen@medisin.uio.no).

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References

- 1 Peters RL, Koplin JJ, Gurrin LC, et al. The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4-year follow-up. *J Allergy Clin Immunol* 2017; **140**: 145–53.
- 2 Gupta RS, Warren CM, Smith BM, et al. The public health impact of parent-reported childhood food allergies in the United States. *Pediatrics* 2018; **142**: e20181235.
- 3 Perkin MR, Logan K, Tseng A, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med* 2016; **374**: 1733–43.
- 4 Grabenhenrich L, Trendelenburg V, Bellach J, et al. Frequency of food allergy in school-aged children in eight European countries—the EuroPrevall-iFAAM birth cohort. *Allergy* 2020; **75**: 2294–308.
- 5 Savage J, Sicherer S, Wood R. The natural history of food allergy. *J Allergy Clin Immunol Pract* 2016; **4**: 196–203, quiz 204.
- 6 Natsume O, Ohya Y. Recent advancement to prevent the development of allergy and allergic diseases and therapeutic strategy in the perspective of barrier dysfunction. *Allergol Int* 2018; **67**: 24–31.
- 7 Wei-Liang Tan J, Valerio C, Barnes EH, et al. A randomized trial of egg introduction from 4 months of age in infants at risk for egg allergy. *J Allergy Clin Immunol* 2017; **139**: 1621–1628.e8.
- 8 Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015; **372**: 803–13.
- 9 de Silva D, Halken S, Singh C, et al. Preventing food allergy in infancy and childhood: systematic review of randomised controlled trials. *Pediatr Allergy Immunol* 2020; **31**: 813–26.
- 10 Fleischer DM, Chan ES, Venter C, et al. A consensus approach to the primary prevention of food allergy through nutrition: guidance from the American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; and the Canadian Society for Allergy and Clinical Immunology. *J Allergy Clin Immunol* 2021; **9**: 22–43.
- 11 Sakihara T, Otsuji K, Arakaki Y, Hamada K, Sugiura S, Ito K. Randomized trial of early infant formula introduction to prevent cow's milk allergy. *J Allergy Clin Immunol* 2020.
- 12 Tsakok T, Marrs T, Mohsin M, et al. Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immunol* 2016; **137**: 1071–78.
- 13 Brough HA, Nadeau KC, Sindher SB, et al. Epicutaneous sensitization in the development of food allergy: what is the evidence and how can this be prevented? *Allergy* 2020; **75**: 2185–205.
- 14 du Toit G, Tsakok T, Lack S, Lack G. Prevention of food allergy. *J Allergy Clin Immunol* 2016; **137**: 998–1010.
- 15 Kelleher MM, Cro S, Van Vogt E, 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**: 402–18.
- 16 Skjerven HO, Rehinder EM, Vettukattil R, et al. Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial. *Lancet* 2020; **395**: 951–61.
- 17 Chalmers JR, Haines RH, Bradshaw LE, et al. Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial. *Lancet* 2020; **395**: 962–72.
- 18 Lowe AJ, Su JC, Allen KJ, et al. A randomized trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitization: the PEBBLES pilot study. *Br J Dermatol* 2018; **178**: e19–21.
- 19 Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol* 2008; **121**: 1331–36.
- 20 The Norwegian Directorate of Health. Infant nutrition. National professional guideline. <https://www.helsedirektoratet.no/retningslinjer/spedbarnsnaering> (accessed March 23, 2014).
- 21 Swedish Food Agency. National guideline on infant nutrition: good food for babies. 2012. <https://www.livsmedelsverket.se/globalassets/publikationsdatabas/andra-sprak/bra-mat-for-spadbarn/good-food-for-infants-under-one-year-livsmedelsverket.pdf> (accessed March 23, 2014).
- 22 Kelleher MM, Jay N, Perkin MR, et al. An algorithm for diagnosing IgE-mediated food allergy in study participants who do not undergo food challenge. *Clin Exp Allergy* 2020; **50**: 334–42.
- 23 Williams HC, Burney PG, Pembroke AC, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. *Br J Dermatol* 1994; **131**: 406–16.
- 24 Hanifin JM. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* 1980; **92** (suppl): 44–47.
- 25 Natsume O, Kabashima S, Nakazato J, et al. Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETIT): a randomised, double-blind, placebo-controlled trial. *Lancet* 2017; **389**: 276–86.
- 26 Perkin MR, Logan K, Bahnson HT, et al. Efficacy of the Enquiring About Tolerance (EAT) study among infants at high risk of developing food allergy. *J Allergy Clin Immunol* 2019; **144**: 1606–1614.e2.
- 27 Perkin MR, Logan K, Marrs T, et al. Association of frequent moisturizer use in early infancy with the development of food allergy. *J Allergy Clin Immunol* 2021; **147**: 967–976.e1.
- 28 Perrett KP, Peters RL. Emollients for prevention of atopic dermatitis in infancy. *Lancet* 2020; **395**: 923–24.
- 29 Ierodiakonou D, Garcia-Larsen V, Logan A, et al. Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease: a systematic review and meta-analysis. *JAMA* 2016; **316**: 1181–92.
- 30 Califf RM, Sugarman J. Exploring the ethical and regulatory issues in pragmatic clinical trials. *Clin Trials* 2015; **12**: 436–41.
- 31 Pyrhönen K, Näyhä S, Kaila M, Hiltunen L, Läärä E. Occurrence of parent-reported food hypersensitivities and food allergies among children aged 1–4 yr. *Pediatr Allergy Immunol* 2009; **20**: 328–38.
- 32 Peters RL, Koplin JJ, Gurrin LC, et al. The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4-year follow-up. *J Allergy Clin Immunol* 2017; **140**: 145–153.e8.