Association of frequent moisturizer use in early infancy with the development of food allergy

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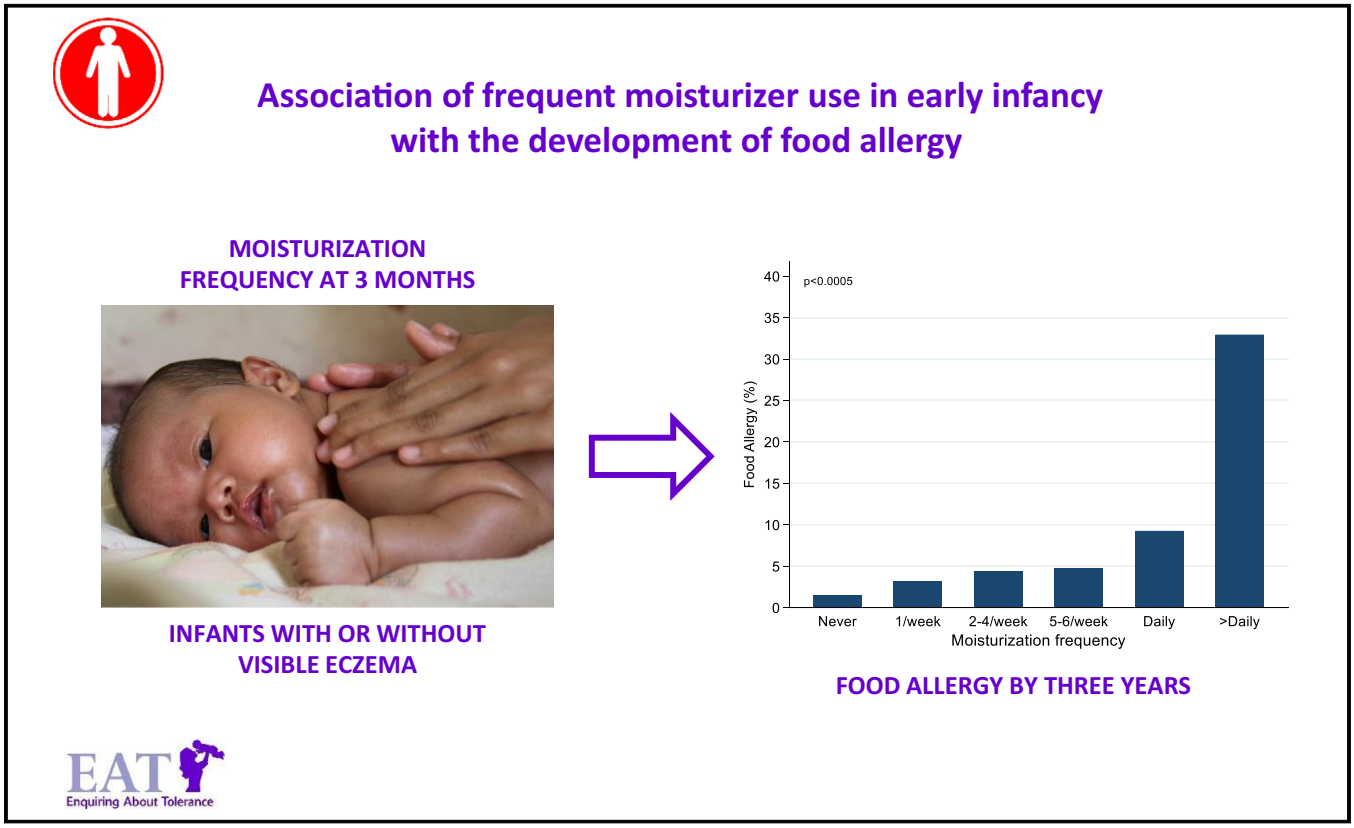
GRAPHICAL ABSTRACT



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Background: Food allergy is thought to develop through transcutaneous sensitization, especially in the presence of skin barrier impairment and inflammation. Regular moisturizer application to infant skin could potentially promote transcutaneous sensitization and the development of food allergy.
Objectives: We tested this hypothesis in the Enquiring About Tolerance (EAT) study population.
Methods: The EAT study was a population-based randomized clinical trial conducted from January 15, 2008, to August 31, 2015, and recruited 1303 exclusively breastfed 3-month-old infants and their families from England and Wales. At enrollment at 3 months, families completed a questionnaire that included questions about frequency and type of moisturizer applied, use of corticosteroid creams, and parental report of dry skin or eczema. Infants were examined for visible eczema at the enrollment visit.
Results: A statistically significant dose-response relationship was observed between parent-reported moisturization frequency at 3 months of age and the subsequent development of food allergy. Each additional moisturization per week was associated with an adjusted odds ratio of 1.20 (95% CI, 1.13-1.27; $P < .0005$) for developing food allergy. For infants with no visible eczema at the enrollment visit, the corresponding adjusted odds ratio was 1.18 (95% CI, 1.07-1.30; $P = .001$) and for those with eczema at the enrollment visit, 1.20 (95% CI, 1.11-1.31; $P < .0005$). Moisturizer frequency showed similar dose-response relationships with the development of both food and aeroallergen sensitization at 36 months.
Conclusions: These findings support the notion that regular application of moisturizers to the skin of young infants may promote the development of food allergy through transcutaneous sensitization. (J Allergy Clin Immunol 2021;147:967-76.)

Key words: *Moisturization, food allergy, allergy prevention, children, eczema, skin barrier, TEWL, filaggrin*

Abbreviations used
AD: Atopic dermatitis
BEEP: Barrier Enhancement for Eczema Prevention
EAT: Enquiring About Tolerance
EIG: Early introduction group
OR: Odds ratio
SAP: Statistical analysis plan
SCORAD: Scoring Atopic Dermatitis
SIG: Standard introduction group
TEWL: Transepidermal water loss

Murine data have demonstrated that food sensitization can occur via transcutaneous food allergen exposure, enhanced by an impaired skin barrier,[1-3] and a recent review of human data concluded that an increasing body of evidence supported the role of a disrupted, inflamed skin barrier as the root cause for the development of food sensitization and allergy.[4] The appreciation that oral consumption of food allergen could induce oral tolerance led to Gideon Lack proposing the dual allergen hypothesis: that in humans, sensitization to food allergen occurs through environmental exposure to allergen through the skin and that oral consumption of food allergen induces immune tolerance.[5] Lack proposed 3 novel interventional strategies to prevent the development of food allergies. The first was that prompt intensive treatment of eczema in early infancy would decrease inflammation in the skin, reduce skin permeability, and prevent allergic sensitization to foods. Evidence to support this has recently emerged in Japan in a retrospective cohort study where early aggressive treatment of eczema in infants with atopic dermatitis (AD) was associated with a significant decrease in later development of food allergies.[6] A randomized trial to validate this finding, the Prevention of Allergy via Cutaneous Intervention (PACI) study is underway (UMIN000028043).[7] The second was that a reduction of food allergens in the child's environment would lead to a reduction in sensitization. The third was that the early introduction of allergenic foods to the infant's diet (in the first 6 months of life) could reduce the development of food allergies through oral tolerance induction. A number of randomized controlled trials have been undertaken and a systematic review of these has confirmed efficacy of early introduction of peanut and egg in preventing allergy developing to these respective foods.[8]

Interestingly, what Lack did not envisage, was the concept of moving from restoring an actively impaired skin barrier, to attempting to prevent the skin barrier becoming impaired in the first place. The Barrier Enhancement for Eczema Prevention (BEEP) study[9] investigated the hypothesis that intensive moisturization from birth would prevent the development of eczema (synonyms: atopic eczema or AD)[10] by enhancing the skin barrier. The BEEP trial recruited newborn infants (n = 1394) from high-risk families.[9] In the intervention arm, families applied a daily emollient (Diprobase cream or DoubleBase gel at parental choice) in the first year of life, plus standard skin care advice, compared with standard skin care advice in the control arm only. The primary outcome was eczema at age 2 years, diagnosed using the UK working party criteria.[11] The study showed that the moisturization intervention did not prevent eczema.[12] At age 2 years, eczema was present in 139 of 598 infants (23%) in the emollient group and 150 of 612 infants (25%) in the control group (adjusted relative risk, 0·95; 95% CI, 0.78-1.16; $P = .61$) and was consistent for other definitions of eczema. In addition, there was a nonsignificant increase in food sensitization and food allergy at 2 years of age in the intervention arm. Confirmed food allergy to milk, egg, or peanut occurred in 7.5% (41 of 547) of the emollient group and 5.1% (29 of 568) of the control group (adjusted odds ratio [OR], 1.47; 95% CI, 0.93-2.33). Sensitization to 1 or more of these foods occurred in 11.9% (58 of 487) of the emollient group and 8.8% (44 of 498) of the control group (adjusted OR, 1.36; 95% CI, 0.94-1.95).

An earlier randomized controlled trial of the application of an emulsion-type moisturizer daily during the first 32 weeks of life to 59 of 118 Japanese infants at high risk for AD found a reduction in the development of eczema (19 infants in the intervention group vs 28 infants in the control group) and the intervention group maintained intact skin for a significantly longer period than the control group did ($P = .012$, log-rank test). Whereas the study reported no statistically significant differences in egg white or ovomucoid sensitization between the 2 groups at 32 weeks of age, ovomucoid sensitization was higher in the intervention group: ≥0.35 kU/L threshold: 19% (9 of 48) in intervention group versus 6.8% (3 of 44) in the control group.[13]

The Enquiring About Tolerance (EAT) study (ISRCTN14254740) is the largest published randomized

controlled trial of the early introduction of allergenic foods and consists of a cohort of 1303 infants, meticulously phenotyped through the first 3 years of life, which also recorded early life moisturization frequency. The EAT cohort provides an opportunity to further assess the relationship between early moisturization and the development of food sensitization and food allergy. In line with the dual allergen hypothesis, we postulated that frequent contact of a parent's hands with their child's skin during moisturizer application might be facilitating the transcutaneous exposure to food allergen, resulting in food allergy developing.

METHODS

Participants

A total of 1303 3-month old infants were recruited from the general population in England and Wales between November 2, 2009, and July 30, 2012. Ethical approval was provided by St Thomas' Hospital Research Ethics Committee and informed consent was obtained from the parents of children enrolled in the study. The Consolidated Standards of Reporting Trials flowchart for the primary outcome of the EAT study is shown in Fig E1 in this article's Online Repository (available at www.jacionline.org). The original trial protocol, final protocol, summary of changes to EAT protocol, original statistical analysis plan (SAP), final SAP, and summary of changes to SAP have been published elsewhere.[14,15] All infants were healthy, exclusively breastfed, and born at term (≥37 weeks' gestation).

In brief, participants were randomized by simple randomization to the standard introduction group (SIG) or early introduction group (EIG). The SIG was asked to exclusively breastfeed to around 6 months of age. Allergenic food introduction beyond this point was at parental discretion. EIG infants continued to breastfeed while sequentially introducing 6 allergenic foods: cow's milk yogurt, then peanut, hard-boiled egg, sesame, and whitefish (cod) in a random order, and finally wheat. By week 6, EIG infants were ideally consuming the required amount of all 6 allergenic foods each week.

Procedures

Clinic visits took place at enrollment and at 1 and 3 years of age at which all children were examined for visible eczema using the UK diagnostic criteria–based photographic protocol of the International Study of Asthma and Allergies in Childhood (ISAAC) phase 2.[16] Disease severity was determined by the Scoring Atopic Dermatitis (SCORAD) index.[17]

Transepidermal water loss (TEWL) was measured with the Biox AquaFlux AF200 closed condenser chamber device (Biox Systems, London, UK) on unaffected skin of the volar aspect of the forearm at 3 and 12 months of age.[18] Venous blood samples were screened for the 6 commonest filaggrin mutations in the UK white population.

The enrollment questionnaire enquired about family member's history of atopic disorders (asthma, eczema, hay fever, and food allergy). It included a detailed section on skin problems and treatments. The latter included a question about current moisturization frequency with the following response categories: never, once a week or less, 2 to 4 times per week, 5 to 6 times a week, daily, or more than daily. The name of the moisturizer was asked and the infant's age when usage had commenced.

All children who had a positive skin prick test to 1 or more of the 6 intervention foods at the 1-year and/or 3-year assessments, or a history of a positive challenge at <1 year of age were considered for a food challenge. The decision to challenge, the timing of challenge, and the type of challenge undertaken were based on the participant's study group and frequency of consumption status.[15] In the EAT study, the primary outcome was allergy, proven by double-blind challenge where possible, to 1 or more of the 6 early introduction foods.

Skin prick testing was performed at 12 months and 36 months of age to the 6 foods and the aeroallergens house dust mite, cat, dog, grass, and tree pollen (Stallergenes, Didcot, UK).

Statistical analyses

Nonparametric tests for trend with categorical moisturization frequency were undertaken using the *nptrend* command in Stata 15 (StataCorp, College Station, Tex). Among infants with no visible eczema at enrollment, a sensitivity analysis was done to minimize reverse causation, first, by additionally excluding those with a parent-reported history of the infant ever having had eczema and, second, by additionally excluding those with a parent-reported history of the infant ever having had eczema or having a parent-reported history of dry skin. Univariable and multivariable logistic models were generated with the outcome being food allergy and with moisturization frequency included as a categorical variable in one model and as a continuous variable in another. Variables included in the adjusted models were study group, sex, number of siblings, number of family members with a history of self-reported eczema, ethnicity, eczema severity (SCORAD), filaggrin mutation status, and TEWL. The EAT dataset (ITN900AD) is available through TrialShare (www.itntrialshare.org).

RESULTS

Of the 1303 participants in the EAT study, 1302 were assessed at the enrollment visit at age 3 months for visible eczema, which was present in 24.4% (317 of 1302) and absent in 75.6% (985 of 1302).

Moisturization usage

Of the 985 infants with no visible eczema, 924 had data on moisturization frequency at 3 months and 654 (71%) were being moisturized at least once a week (Table I). Increasing frequency of moisturization was associated with parents reporting their infant having generally dry skin or eczema (despite the absence of visible eczema at the 3-month visit). Excluding infants with a parent-reported history of eczema (n = 5) or parent-reported generally dry skin (n = 174) or both (n = 33) left a group of 712 infants who phenotypically appeared to have healthy skin. Among this group, moisturization rates were still very high, with 66% (469 of 712) being moisturized at least once a week and 16% being moisturized once daily or more.

Those moisturized more frequently had higher filaggrin mutation rates (test for trend, $P = .06$). Moisturization frequency was not associated with the number of first-degree family members with self-reported eczema except in the moisturized more frequently than daily group or the median age when moisturizers had first been applied to the infants' skin (Table I). Corticosteroid cream usage was minimal in the infants with no visible eczema at 3 months of age (overall 3.4%, 31 of 924), and among those who were using it, this was frequently for cradle cap or nappy rash, or as compound preparations including an antifungal agent, presumably for an area of dermatitis of unknown etiology.

Increasing moisturization frequency in infants with visible eczema at 3 months was associated with their eczema severity (SCORAD index). For those with visible eczema at enrollment but never moisturized, the median SCORAD was 7; those moisturized daily, 10.8 ($P = .03$ vs never moisturized group); and those moisturized more frequently than daily, 13.9 ($P < .001$ versus never moisturized group) (Table I). Corticosteroid cream usage was infrequent in infants with visible eczema (11.7%, 35 of 300), with the exception of infants who were moisturized more than daily (35.3%, 19 of 57).

Increasing moisturization frequency at 3 months of age was also associated with higher concurrent TEWL, in infants with and without enrollment eczema, as well as in all enrollment infants combined (Fig 1, right panels).

TABLE I. Moisturization frequency at 3 months and atopy, skin medication usage, and skin barrier characteristics, by visible eczema status at the enrollment (3 month) visit

	Never % (n)	1/wk % (n)	2-4/wk % (n)	5-6/wk % (n)	Daily % (n)	>Daily % (n)	Test for trend
No visible eczema at 3 months (n = 924)	**29.2 (270)**	**24.9 (230)**	**19.4 (179)**	**4.6 (42)**	**18.2 (168)**	**3.8 (35)**	—
Parent-reported generally dry skin	9.6 (26)	16.1 (37)	22.9 (41)	31.0 (13)	39.3 (66)	68.6 (24)	<.001
Parent-reported eczema	1.9 (5)	1.7 (4)	2.8 (5)	0 (0)	7.7 (13)	31.4 (11)	<.001
Filaggrin mutation*	6.7 (16)	7.9 (17)	7.3 (12)	11.9 (5)	9.6 (15)	18.8 (6)	.06
Family members with history of eczema, n *(P value versus Never group)*	0.71	0.79 (.27)	0.79 (.27)	0.64 (.62)	0.85 (.07)	1.17 (.001)	
Age first moisturized (wk), median *(P value versus 1/week group)*	—	3	3 (.55)	4 (.73)	2 (.38)	2 (.82)	
Steroid cream use at 3 mo	1.1 (3)	4.4 (10)	3.4 (6)	0 (0)	4.8 (8)	11.4 (4)	.01
Visible eczema at 3 mo (n = 300)	**10.3 (31)**	**13.3 (40)**	**20.3 (61)**	**8.3 (25)**	**28.7 (86)**	**19.0 (57)**	
SCORAD at 3 mo, median *(P value versus Never group)*	7	7 (.83)	7.2 (.58)	9.1 (.16)	10.8 (.03)	13.9 (<.001)	
Filaggrin mutation*	25.0 (7)	22.9 (8)	15.0 (9)	32.0 (8)	30.4 (24)	18.2 (10)	.74
Family members with history of eczema, n *(P value versus Never group)*	1.23	0.85 (.09)	1.03 (.35)	1.08 (.54)	1.16 (.75)	1.02 (.31)	
Age first moisturized (wk), median *(P value versus 1/week group)*	—	4	4 (.62)	1 (.06)	5 (.35)	4 (.69)	
Steroid cream use at 3 mo	6.5 (2)	2.5 (1)	3.3 (2)	12.0 (3)	9.3 (8)	33.3 (19)	<.001

*Filaggrin mutation data on 848 (no visible eczema) and 282 (visible eczema) participants.

Moisturizer type

The 20 most frequently used moisturizers at the 3-month visit are listed in Table II. Among those without eczema, olive oil predominated, but multiple other food-derived oils also feature in the list: sunflower, almond, coconut, and vegetable oil. Olive oil was also the most frequently used moisturizer in infants with visible eczema, followed by various prescribed moisturizing creams.

Bathing frequency

Bathing frequency and moisturization frequency at 3 months were strongly correlated ($P < .0005$), suggesting that the 2 activities occurred in conjunction for most infants. We have previously shown that bathing frequency at 3 months had a statistically significant independent dose-response relationship with TEWL at 3 months and 1 year and a relationship with visible eczema at 3 months.[19] However, the relationship with TEWL for bathing frequency (change in TEWL per unit increase in weekly bathing frequency: 0.42 g/m^{2}h; 95% CI, 0.24-0.61; $P < .0005$), was weaker than for moisturization frequency (change in TEWL per unit increase in weekly moisturization frequency: 0.63 g/m^{2}h; 95% CI, 0.53-0.73; $P < .0005$).

Primary outcome: Food allergy

In the 1161 EAT participants evaluable for the primary outcome (89.1% of the 1303 enrolled participants), 74 cases of food allergy developed: 48 in the 284 infants with visible eczema at enrollment (16.9%), and 26 in the 877 infants without visible eczema at enrollment (3.0%). In univariate analysis, a significant dose-response relationship was observed between moisturization frequency and the development of food allergy in infants without visible eczema at enrollment (Fig 1, *A*) , in infants with visible eczema at enrollment (Fig 1, *B*), and in all infants combined (Fig 1, *C*) (for all, $P < .0005$).

Crude and adjusted logistic models were undertaken with moisturization frequency as a categorical variable (Fig 2, left panels), and as a continuous variable (Fig 2, right panels). Despite adjustment for relevant potential confounding variables, the dose-response relationship remained, whether the analysis was undertaken in infants with no visible eczema at enrollment (Fig 2, *A*), in those with visible eczema at enrollment (Fig 2, *B*), or in all infants (Fig 2, *C*). When moisturization frequency was treated as a continuous variable, each additional moisturization per week was associated with an 18% increase in the odds of developing food allergy (adjusted OR [OR_{adj}], 1.18; 95% CI, 1.07-1.30; $P = .001$) for infants with no visible eczema at enrollment; 20% for infants with visible eczema (OR_{adj}, 1.20; 95% CI, 1.11-1.31; $P < .0005$); and 20% for all enrollment infants (OR_{adj}, 1.20; 95% CI, 1.13-1.27; $P < .0005$). In contrast, there was no relationship between 3-month bathing frequency and the development of food allergy in the cohort overall (OR_{adj}, 0.95; 95% CI, 0.83-1.08; $P = .41$) or within those with (OR_{adj}, 1.00; 95% CI, 0.84-1.18; $P = .98$) or without (OR_{adj}, 0.89; 95% CI, 0.73-1.08; $P = .25$) visible eczema at 3 months of age.

An additional analysis was undertaken to assess whether the type of moisturizer (oil- or cream-based) affected the results, but there was insufficient power to identify any formulation-specific effect.

Enrollment (3-month) sensitization

At enrollment onto the EAT study at 3 months of age, infants in the EIG underwent skin prick testing to the 6 early introduction foods: 33 of 652 EIG infants (5.1%) were positive (any wheal size). Blood sampling for specific IgE testing was attempted in all infants in both the EIG and the SIG at enrollment. A positive specific IgE to 1 or more foods (IgE ≥0.35 kU/L) at 3 months was present in 74 of 1170 infants (6.3%) in whom it was possible to obtain blood. We have previously shown that enrollment sensitization at 3 months based on skin prick testing in the EIG[20] or on specific IgE testing in the SIG[21] (and hence independent of the intervention effect) were both strongly predictive of developing

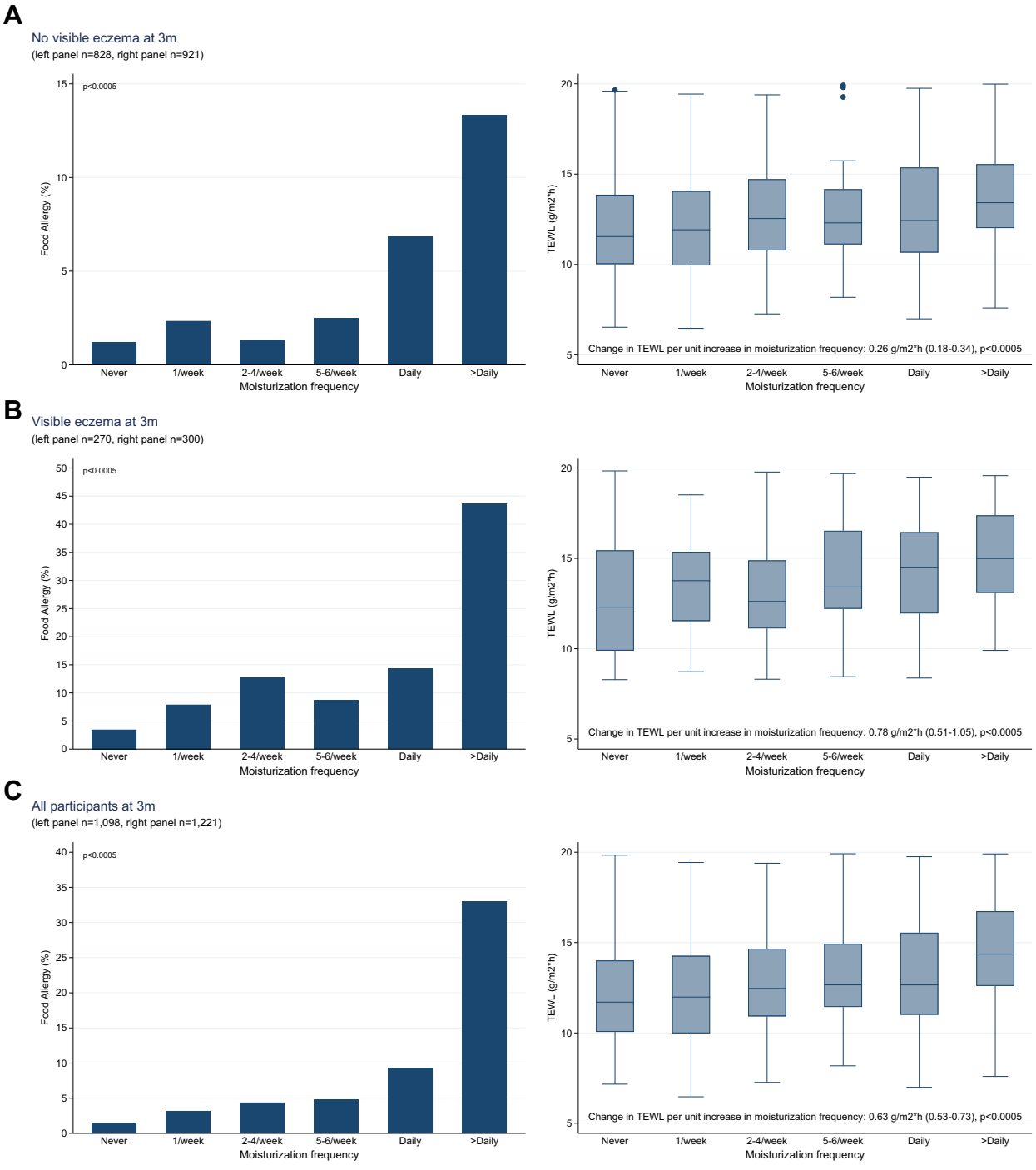

FIG 1. Moisturization frequency at 3 months and food allergy (left panels) and 3 months TEWL (right panels), by visible eczema status at the 3-month visit: no visible eczema **(A)**, visible eczema **(B)**, and all participants **(C)**. Note change of scale of axes between panels. Left-hand panels include participants with (i) visible eczema status at enrollment determined, (ii) enrollment general questionnaire completed including the moisturization frequency question, and (iii) their primary outcome status determined. Right-hand panels include participants with (i) and (ii) as described for the left-hand panels and (iii) TEWL measurement undertaken at enrollment.

a subsequent food allergy. Using either measure, moisturization at 3 months was associated with the early emergence of food sensitization: in the EIG, OR_{adj} for being skin prick test–positive at 3 months of age to any of the EAT study early introduction foods, for each unit increase in weekly moisturization frequency, was 1.10 (95% CI, 1.01-1.20; $P = .04$); and in the total study population, OR_{adj} for being specific IgE positive at 3 months of age to any of the EAT study foods, for each unit increase in weekly moisturization frequency, was 1.11 (95% CI, 1.03-1.18; $P = .003$).

TABLE II. Top 20 products most frequently used as moisturizers on infants with and without visible eczema at the 3-month visit

	No visible eczema at 3 mo				Visible eczema at 3 mo		
	Moisturizer	Frequency	% (Cumulative %)		Moisturizer	Frequency	% (Cumulative %)
1	Olive oil	151	23.1 (23.1)	1	Olive oil	49	18.2 (18.2)
2	Johnson's baby oil	74	11.3 (34.5)	2	Diprobase	27	10.0 (28.3)
3	E45	39	6.0 (40.4)	3	Doublebase	22	8.2 (36.4)
4	Johnson's baby lotion	36	5.5 (45.9)	4	Aqueous cream	18	6.7 (43.1)
5	Oilatum	29	4.4 (50.4)	5	Oilatum	15	5.6 (48.7)
6	Aqueous cream	27	4.1 (54.5)	6	Aveeno	14	5.2 (53.9)
7	Diprobase	18	2.8 (57.3)	7	Epaderm	13	4.8 (58.7)
8	Sunflower oil	16	2.5 (59.7)	8	E45	12	4.5 (63.2)
9	Aveeno	15	2.3 (62.0)	9	Johnson's baby oil	12	4.5 (67.7)
10	Almond oil	13	2.0 (64.0)	10	Cetraben	11	4.1 (71.8)
11	Epaderm	13	2.0 (66.0)	11	Johnson's baby lotion	6	2.2 (74.0)
12	Coconut oil	12	1.8 (67.8)	12	Coconut oil	5	1.9 (75.8)
13	DoubleBase	12	1.8 (69.7)	13	Hydromol	5	1.9 (77.7)
14	Sudocrem	12	1.8 (71.5)	14	Sunflower oil	5	1.9 (79.6)
15	Cetraben	9	1.4 (72.9)	15	Dermol	4	1.5 (81.0)
16	Baby oil	8	1.2 (74.1)	16	Emulsifying ointment	3	1.1 (82.2)
17	Neal's yard baby oil	8	1.2 (75.3)	17	Baby lotion	2	0.7 (82.9)
18	Vegetable oil	8	1.2 (76.6)	18	Boots baby moisturiser	2	0.7 (83.6)
19	Vaseline	6	0.9 (77.5)	19	Boots baby oil	2	0.7 (84.4)
20	Weleda calendula lotion/oil	6	0.9 (78.4)	20	Burt's bees lotion	2	0.7 (85.1)

None of the items listed were trilipid/ceramide-containing products.

Sensitivity analysis

A sensitivity analysis was undertaken to mitigate the possibility that in those infants with no visible eczema at enrollment, reverse causality might be affecting the relationship between moisturization frequency and the emergence of food allergy. The odds of developing food allergy for each additional moisturization per week remained significant both in infants with no visible eczema at enrollment and no parent-reported eczema (OR_{adj}, 1.16; 95% CI, 1.03-1.30; $P = .01$) and in infants with no visible eczema at enrollment and no parent-reported eczema or generally dry skin (OR_{adj}, 1.16; 95% CI, 1.01-1.33; $P = .04$).

Of the 1303 infants enrolled onto the EAT study at 3 months of age, 1129 (87%) had at least 1 first-degree relative (mother, father, or sibling) with parent-reported eczema, hay fever, or asthma. Of the 74 cases of food allergy that occurred in the EAT study, 73 were within this high-risk group. Repeating the analyses undertaken in this paper, but restricted to this high-risk group, analogous to the BEEP study participants, yielded very similar results (data not shown).

Food and aeroallergen sensitization

With regard to the development of food and aeroallergen sensitization, as assessed by skin prick testing at the 36-month clinical visit, statistically significant dose-response relationships were seen between increasing moisturization frequency and sensitization rates in infants without visible eczema (Fig 3, *A*), in those with visible eczema (Fig 3, *B*), and in all infants (Fig 3, *C*). Particularly for the latter, a dose-response relationship with both food and aeroallergen sensitization was notable (both relationships, $P < .0005$).

Eczema development

There was no evidence that increased moisturization frequency at enrollment in infants with no history of eczema or generally dry skin or visible eczema at the 3-month visit, protected against the development of eczema at the 12-month or 36-month visit (Fig 4).

DISCUSSION

In this analysis of a well-phenotyped cohort of infants participating in the EAT study, we confirm a positive association between early moisturization and the development of food allergy and sensitization, with a dose-dependent relationship with moisturization frequency. This relationship was present both in infants with and without eczema at the enrollment visit.

That such a relationship was present among infants with eczema might simply be attributed to a dose-response relationship between severity of eczema, known to be strongly associated with food allergy, and frequency of moisturization. However, the analysis adjusted for eczema severity, as well as filaggrin mutation status. Most compelling is that the relationship was present even in infants without visible eczema. This too might be refuted on the grounds that eczema is a waxing and waning condition and that some of these infants might have already had eczema without it being present at the 3-month enrollment visit or have had a propensity to dry skin that would ultimately evolve into overt eczema. However, the dose-response relationship persisted even when infants whose parents reported a history of eczema or a history of dry skin were excluded.

Two-thirds of EAT study infants with no history of eczema or dry skin were being actively moisturized, as frequently as daily or more and a number of respondents mentioned that it was for baby massage. Moisturization as part of baby skin care is frequently recommended: in a survey of all UK maternity and neonatal units, more than one-half (52.1%) recommended oil for baby skin care. Of those recommending oil, 81.6% recommended olive oil to moisturize the skin, whereas 69.4% suggested its use for baby massage.[22] Consistent with these findings, in the EAT study, the most commonly used product for moisturization was olive oil,

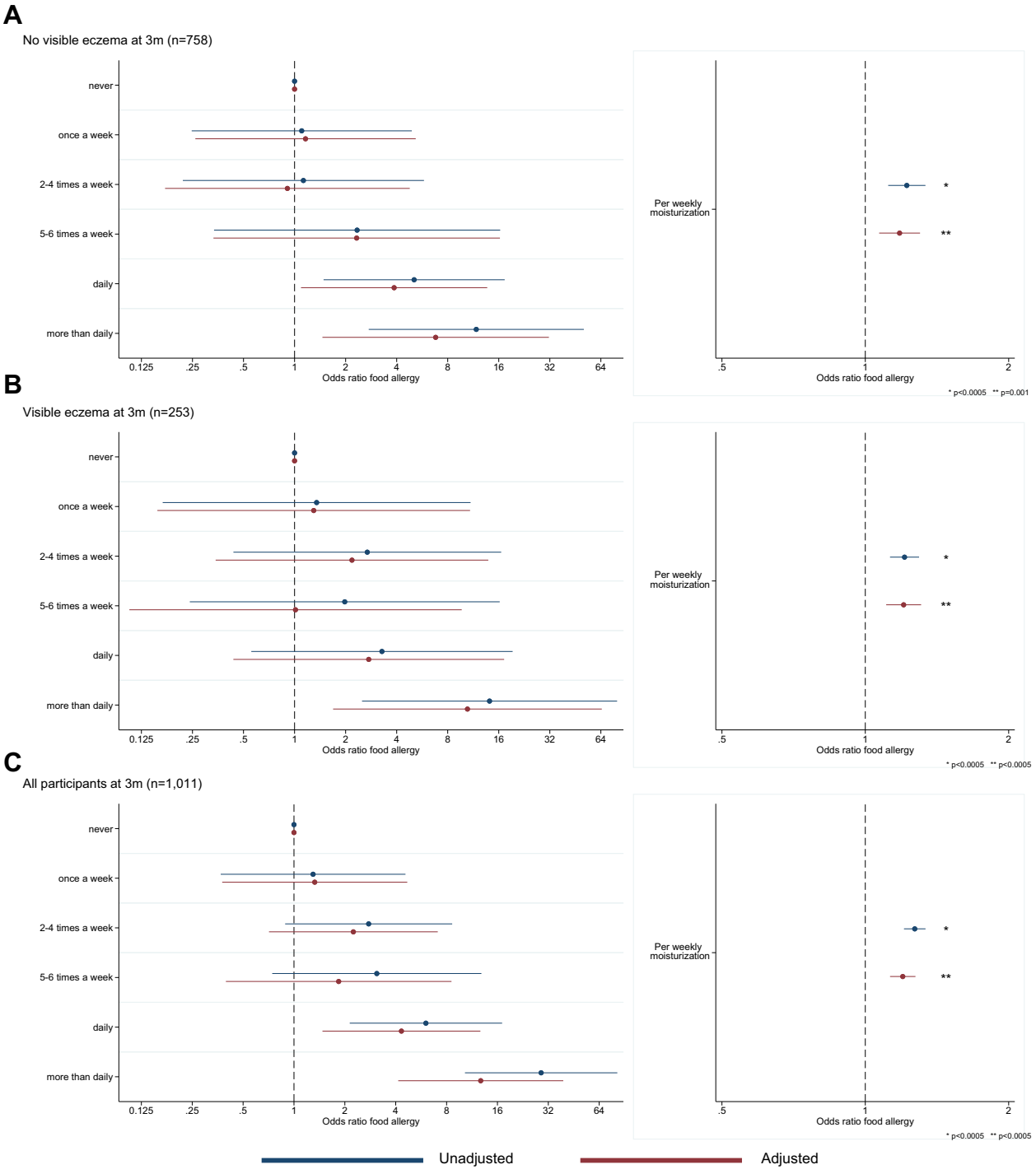

FIG 2. Moisturization frequency at 3 months and food allergy (crude and adjusted analysis), by visible eczema status at the 3-month visit: no visible eczema **(A)**, visible eczema **(B)**, and all participants **(C)**. Left-hand panels show the results for moisturization frequency as a categorical variable, with the never moisturized category as baseline (OR, 1.0). Right-hand panels show the results for moisturization frequency treated as a continuous variable with the OR shown being for each unit increase in weekly moisturization frequency. Crude (unadjusted) analysis restricted to participants with complete covariate data. Adjusted analysis was adjusted for study group, sex, number of siblings, number of family members with history of eczema, ethnicity, eczema severity (SCORAD) **(B** and **C)**, filaggrin mutation status, and TEWL.

in both infants with and without visible eczema at the 3-month visit.

There are 2 possible explanations for our findings: moisturizers might be facilitating the passage of food allergens across the skin barrier, or moisturizers might be damaging the skin barrier and allowing the passage of the food allergen. Moisturizers are known to facilitate the passage of substances across the skin. For example, in a murine model, moisturizers

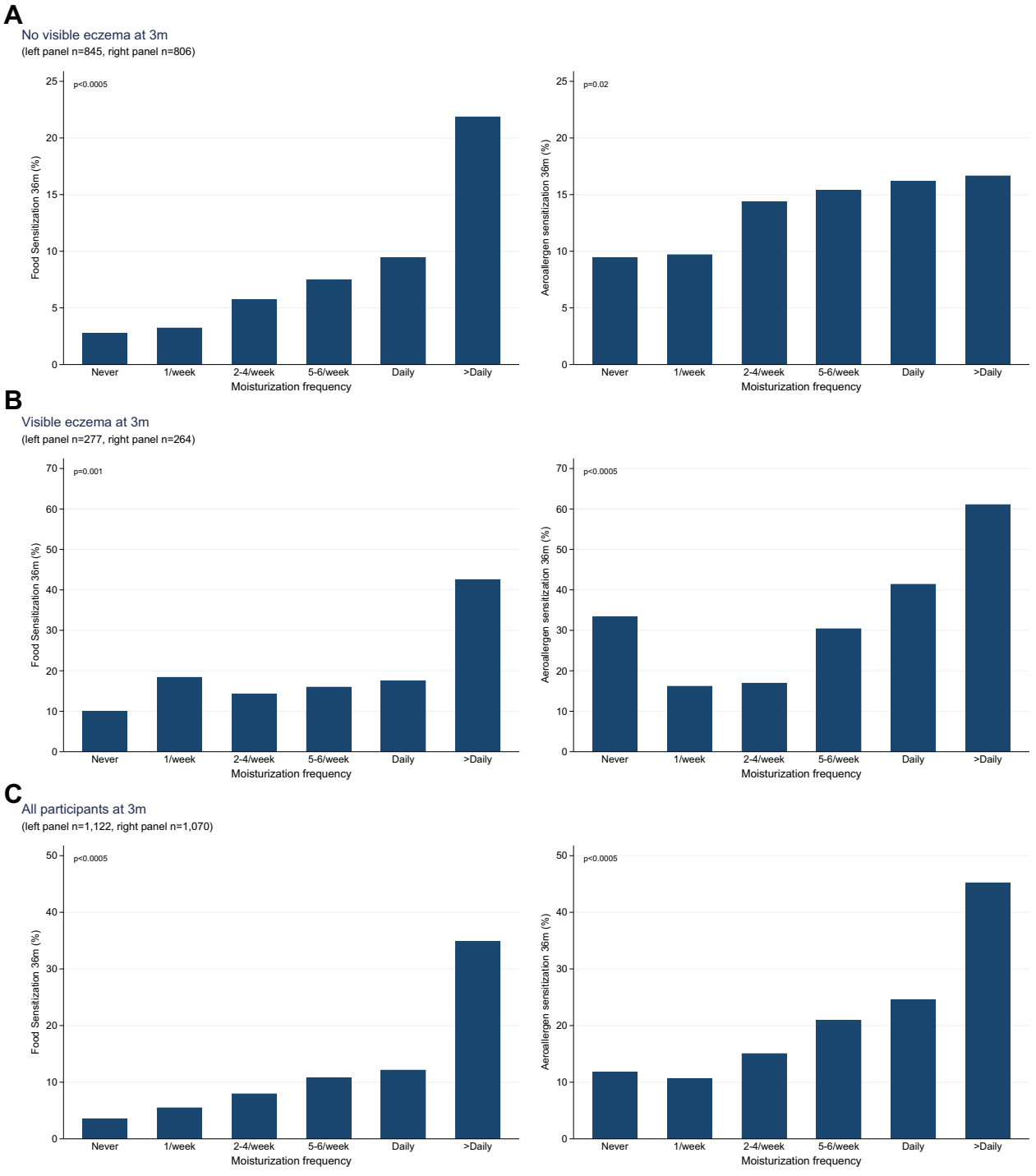

FIG 3. Moisturization frequency at 3 months and food (left panels) and aeroallergen (right panels) sensitization at 36 months, by visible eczema status at the 3-month visit: no visible eczema **(A)**, visible eczema **(B)**, and all participants **(C)**. Note change of scale of axes between panels.

increased the penetration of a model chemical, the herbicide 2,4-dichlorophenoxyacetic acid, with the more effective moisturizers having a greater effect on 2,4-dichlorophenoxyacetic acid absorption.[23] Thus transfer of allergenic proteins from the parent's hands to their infant could be occurring when they are applying moisturizer to their infant's skin. With regard to the second explanation, previous research has shown that olive oil (and other vegetable oils) may impede the development of the lamellar lipid structures of the permeability barrier from birth. The investigators concluded that it was difficult to support the use of sunflower or olive oils on babies' skin.[24] The detergent, sodium lauryl sulfate, historically a common ingredient in soaps, shampoos, and other skin care products, has also been shown to disrupt the skin barrier.[25] Hence the dose-response relationship observed between increasing moisturizing frequency and increasing levels of TEWL at 3 months

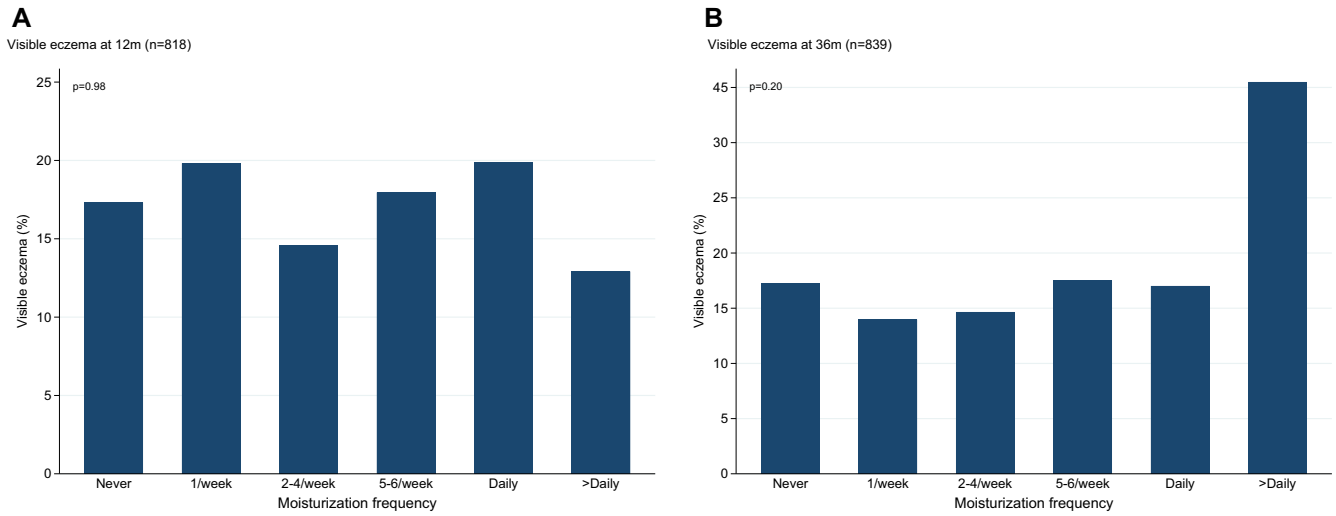

FIG 4. Moisturization frequency at 3 months and the development of visible eczema at 12 months **(A)** and 36 months **(B)**, among infants with no visible eczema at the 3-month visit. Note change of scale of axes between panels.

of age might simply be reflecting a dose-dependent adverse effect of the moisturizer on the skin barrier. The 2 explanations are not mutually exclusive, and it may be that a combination of both explanations is responsible for our findings.

The next-generation trilipid skin barrier creams, containing ceramides, cholesterol, and free fatty acids, which aim to mimic the skin's natural pH and lipid composition, may not influence food sensitization development in the same way. A recent small pilot randomized controlled study comparing 12 weeks of daily application of a triplipid cream (EpiCeram; Primus Pharmaceuticals, Scottsdale, Ariz) versus a paraffin-/petrolatum-based cream (Aveeno; Johnson & Johnson, New Brunswick, NJ) found that the triplid cream decreased total IgE and increased total IgG4, as well as increasing total and peanut-specific IgG_4/IgE ratios.[26] Furthermore, a separate small study found that EpiCeram reduced TEWL much more markedly than Aveeno did.[27]

The association between moisturization and food allergy development in infants with no visible eczema is consistent with our previous observation in the EAT cohort that skin barrier impairment can be present in the absence of clinical eczema: TEWL measured at 3 months was elevated in filaggrin mutation carriers unaffected by eczema.[28]

The route of exposure that is most relevant for the development of sensitization to aeroallergens is not known.[29] However, epicutaneous house dust mite application in a murine model has been shown to result in house dust mite sensitization developing.[30]

Strengths and limitations

The primary outcome in the EAT study, food allergy, was robustly diagnosed. In the EAT study, of the 74 participants who developed a food allergy, 70 were diagnosed based on double-blind, placebo-controlled food challenges (and 4 on a history of a skin prick test reaction of 5 mm or more). Eczema diagnoses were made using validated tools and infants had measures of skin barrier function performed (TEWL) and their filaggrin mutation status evaluated. The principal limitation is that we lack any mechanistic data to explain the finding.

Conclusions

The observation has been made that the increased availability and use of baby skin care products has coincided with the increased prevalence of eczema.[24] Given the strong link between the development of eczema and food allergy, this raises the possibility that the use of such products might have contributed to the levels of food allergy that are currently seen. Taken together, our findings and those of prior studies suggest that emollients may facilitate transcutaneous sensitization to both food and aeroallergens. These findings are potentially of great significance, and further research is required to understand the mechanism of action. To be determined are whether moisturizers facilitate food and aeroallergen uptake; whether moisturizers become contaminated by these allergens from the hands or the environment; and whether the effects are limited to certain types of moisturizer or to specific susceptible individuals. It is important that planned and future studies of moisturizer use in infancy aimed at preventing eczema also measure food allergy outcomes that can be combined with other studies in an ongoing individual patient meta-analysis.[31] In the interim it would seem sensible that before moisturizers are applied, hands are washed thoroughly, and that careful consideration be given to the frequency of moisturizer application and the type of moisturizer used in infant skin care.

We would like to thank the parents and children of the EAT study for taking part.

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Clinical implications: Frequent skin moisturization in early life might promote the development of food allergy, most likely through transcutaneous sensitization.

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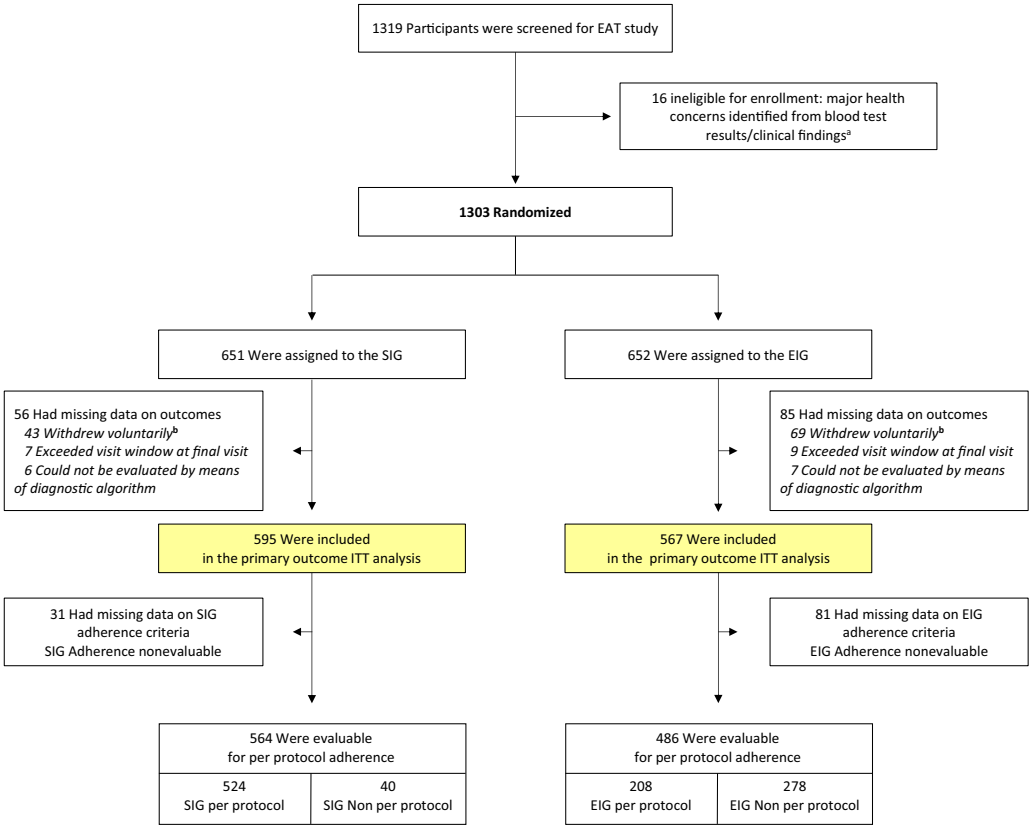

FIG E1. EAT enrollment and randomization. Baseline visits occurred when participants were 3 months of age. The primary outcome for the EAT study was challenge-proven food allergy to 1 or more of the 6 early introduction foods between 1 and 3 years of age. [a]Eight infants randomized to each group were found to have significant health issues either on blood testing or the clinical examination at the enrollment visit, rendering them ineligible for enrollment: conditions included severe vitamin D deficiency, severe iron deficiency, severe failure to thrive, familial hypercholesterolemia, congenital stridor, epidermolysis bullosa, and cartilage hair hypoplasia syndrome. [b]Forty-three participants in the SIG and 69 participants in the EIG withdrew voluntarily from the study. Reasons given were as follows: concerns about the blood tests (SIG 0, EIG 2), emigration (SIG 10, EIG 12), expenses (SIG 1, EIG 1), family health issues (SIG 3, EIG 0), family issues (SIG 2, EIG 4), no reason given (SIG 11, EIG 16), lost contact with family (SIG 15, EIG 28), too far to travel for study assessments (SIG 0, EIG 1), and unhappy participating in the study (SIG 1, EIG 5). *ITT*, intention-to-treat.