Frequent oil baths and skin barrier during infancy in the PreventADALL study

Eva Maria Rehbinder,1,2 Sabina Wärnberg Gerdin,3,4 Angela Hoyer,3,4 Maria Bradley,5 Karin C. Lødrup Carlsen,2,6 Berit Granum,7 Gunilla Hedlin,3,4 Christine Monceyron Jonassen,8,9 Marissa Leblanc,10,11 Björn Nordlund,3,4 Knut Rudi,12 Håvard O. Skjerven,2,8 Anne Cathrine Staff,2,13 Riyas Vettukattil,6 and Cilla Söderhäll3,4

1Department of Dermatology, Oslo University Hospital, Oslo, Norway 2Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway 3Department of Women’s and Children’s Health, Karolinska Institutet, Stockholm, Sweden 4Astrid Lindgren Children’s Hospital, Karolinska University Hospital, Stockholm, Sweden 5Dermatology Unit, Department of Medicine Solna, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden 6Divisions of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway 7Department of Chemical Toxicology, Norwegian Institute of Public Health, Oslo, Norway 8Center for Laboratory Medicine, Østfold Hospital Trust, Kalnes, Norway 9Department of Virology, Norwegian Institute of Public Health, Oslo, Norway 10Oslo Centre for Biostatistics and Epidemiology; University of Oslo, Oslo, Norway 11Norwegian Institute of Public Health, Oslo, Norway 12Department of Chemistry, Biotechnology and Food Science, Norwegian University of Life Sciences, Ås, Norway 13Divisions of Obstetrics and Gynaecology; Oslo University Hospital, Oslo, Norway

Eva Maria Rehbinder and Sabina Wärnberg Gerdin share first authorship.
Correspondence: Eva Maria Rehbinder. Email: e.m.rehbinder@ous-research.no

Abstract

Background In the general population randomized controlled trial PreventADALL, frequent emollient bath additives from 2 weeks of age did not prevent atopic dermatitis, while the effect on skin barrier function throughout infancy is not established.

Objectives The primary aim of this exploratory substudy was to assess the effect of mineral-based oil baths on transepidermal water loss (TEWL) and dry skin through infancy, and secondarily to explore if filaggrin (FLG) mutations modified the effect.

Methods Overall, 2153 infants were included and randomized to either the ‘Skin intervention’ (SI) group (n = 996) (oil bath 4 times weekly or ‘No skin intervention’ (NSI) group (n = 1158), with TEWL measurements at 3, 6 and/or 12 months of age. Information on FLG mutation status was available for 1683 of these infants. Effects of the skin intervention on TEWL and dry skin through infancy were assessed by mixed-effects regression modelling. Background characteristics and protocol adherence were collected from electronic questionnaires, birth records and weekly diaries.

Results The TEWL (95% confidence interval) was on average 0.42 g m⁻² h⁻¹ (0.13–0.70, P = 0.004) higher in the SI group compared with the NSI group through the first year of life, with significantly higher levels at 3 months (8.6 (8.3–9.0) vs. 7.6 (7.3–7.9)), but similar at 6 and 12 months. Dry skin was observed significantly more often in the NSI group compared with the SI group at 3 months (59% vs. 51%) and at 6 months of age (63% vs. 53%), while at 12 months of age, the difference was no longer significant. At 3 months, the TEWL of FLG mutation carriers was similar to the TEWL in the SI group. No interaction between SI and FLG mutation was found in the first year of life.

Conclusions Infants given frequent oil baths from 2 weeks of age had reduced skin barrier function through infancy compared with controls, largely attributed to higher TEWL at 3 months of age, while the skin at 3 and 6 months appeared less dry in infants subjected to the skin intervention.

Lay summary

Atopic dermatitis (AD) affects approximately 20% of children in industrialized countries. AD causes dry, itchy skin and can increase the chance of infections.

This study was a substudy of the large Scandinavian PreventADALL trial, including 2394 infants, recruited from the general population between 2014 and 2016. Children in this trial were allocated randomly to receive either a skin intervention, food intervention, combined intervention, or no intervention. Children were examined at 3, 6 and 12 months of age. The examinations involved an investigation of the skin, to evaluate dry skin and skin barrier function by transepidermal water loss (TEWL) in the outer layers of the skin (higher TEWL suggests decreased skin barrier function). The skin intervention consisted of oil baths at least 4 times per week from 2 weeks of age.
Atopic dermatitis (AD) affects around 20% of children in industrialized countries and is characterized by dry, itchy and inflamed skin susceptible to infections. The skin barrier function is usually impaired, leading to increased transepidermal water loss (TEWL) in both lesional and nonlesional atopic skin. Dry skin is associated with increased TEWL in children, including 3-month-old infants without eczematous lesions, as recently shown in the Preventing Atopic Dermatitis and Allergies in children (PreventADALL) study. Both dry skin and increased TEWL has been found to precede AD, and TEWL also correlates with the severity of AD as well as response to treatment.

Filaggrin (FLG) encodes a skin barrier protein, which is essential for the epidermal differentiation, including the structure and function of the stratum corneum. Loss-of-function mutations in the FLG gene impair the skin barrier function, and is therefore a major risk factor for the development of AD. Around 20–50% of patients with AD carry at least one FLG mutation, compared with 10% in the general population.

The first-line AD treatment consists of improving the impaired skin barrier by moisturization. Although it is well established that leave-on emollients in AD treatment reduce the severity and prevent flares, the effect of emollient bath additives in AD treatment is unclear. Also, the effects of emollients on TEWL are inconsistent; however, they are somewhat favourable for emollients containing humectants, such as urea or ammonium lactate, and when used to treat dry or atopic skin.

Although important in AD treatment, a meta-analysis including 11 randomized controlled trials (RCTs) found that regular emollients from early infancy failed to reduce the risk of AD development in early childhood. The two largest RCTs included in the meta-analysis with negative results using paraffinum liquidum-based emollients were our Scandinavian general population PreventADALL study including 2394 mother–child pairs using oil bath and emollient facial cream and the British Barrier Enhancement for Eczema Prevention (BEEP) study with 1394 high-risk infants using leave-on emollients.

In order to better understand why the skin intervention in the PreventADALL study did not prevent AD, we aimed primarily to assess the effect of the skin intervention on TEWL and dry skin through infancy, and secondarily to explore if the potential effects were influenced by carrying FLG mutations.

Materials and methods

Study design

The present study is an exploratory subanalysis of the PreventADALL study, a Scandinavian multicentre RCT and prospective birth cohort, enrolling 2697 pregnant women from Oslo and Østfold (Norway) and Stockholm (Sweden), and collecting baseline characteristics through electronic questionnaire.

Study population

All 2153 of 2394 randomized infants, with TEWL measured on at least one of the clinical follow-up investigations at 3, 6 and/or 12 months of age were included in the primary analyses, while the secondary aim analysed the 1683 infants who also had information on FLG mutation status (Figure 1).

Randomization and interventions

Randomization was done in a 1:1:1:1 ratio into four groups: no intervention, skin intervention, food intervention or combined interventions. The skin intervention consisted of baths for 5–10 min with added emulsified oil (0.5 mL bath oil per 8 L water) and daily facial cream (Cerital®) on 4–7 days weekly from week 2 through 8 months of age. The bath oil was produced specifically for the PreventADALL trial by Pharmatech (Østfold, Norway), consisting of paraffinum liquidum and tri-laureth-4-phosphate only. The use of emollients was recorded in weekly electronic diaries from 2 weeks to 26 weeks of age, and thereafter in 3-monthly electronic questionnaires. Full-skin intervention adherence was defined as oil baths and...
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2394 mother–child pairs in PreventADALL

Study population of primary aim: 2153 attending the 3, 6 and/or 12 month investigation

Study population of secondary aim: 1683 with additional information on filaggrin mutation status

Figure 1 Study population of the present study, from the Preventing Atopic Dermatitis and Allergies in children (PreventADALL) mother–child birth cohort, where 2701 pregnancies were included.

facial cream for an average of at least 3.5 days per week for at least 16 of 25 weeks, whereas partial adherence to the skin intervention is based on the average number of oil baths only in four categories: ≥ 3.5, 2.5–3.4, 1.5–2.4 and 0.5–1.4 days per week. The food intervention consisted of introducing four foods as small tastes (peanut, cow’s milk, wheat and egg) between 12 and 16 weeks of age and maintaining in the regular diet to at least 6 months of age.

Transepidermal water loss
Skin barrier function was reported as TEWL, which is mean TEWL (g m⁻² h⁻¹) of three performed measurements at each time-point on the left lateral upper arm using an open-chamber DermaLab USB (Cortex, Hadsund, Denmark), noting ambient temperature (room temperature between 20 °C and 25 °C, with windows and doors shut) and humidity, in line with international recommendations and as described in our previous publications.

Dry skin
Dry skin was characterized by the presence of skin scaling and roughness both by visual inspection and palpation at least one of 11 predefined skin locations, including predilection sites for AD in infants, namely the cheeks and extensor surfaces of the extremities, as previously reported. The dry skin evaluation and severity is in line with the principles of the Dry skin/Ichthysis and Severity Index (DASI), but without their score of erythema. Dry skin severity is categorized into mild, moderate or severe dry skin.

Filaggrin analysis
DNA isolated from blood was genotyped using a TaqMan-based allelic discrimination assay (Applied Biosystems, Foster City, CA, USA), as previously described. We defined FLG mutations (‘mutation yes’) as being a carrier of any of the following mutations in the FLG gene: R501X, 2282del4 and R2447X, the most common loss-of-function mutations in the European population.

Exposures
- Skin intervention (SI) includes the skin intervention group and the combined interventions group.
- No skin intervention (NSI) includes the control group and the food intervention group.
- Being an FLG mutations carrier was defined as being a carrier of any of the three mutations: R501X, 2282del4 and R2447X.

Outcomes
- TEWL through infancy, assessed at 3, 6 and 12 months of age, and for sensitivity analysis at each time-point.
- Presence of dry skin through infancy, and for sensitivity analysis, dry skin (1) at any or multiple time-points, (2) as moderate/severe at any time-point and (3) on cheeks and/or extensor surfaces of the extremities at any time-point.

Statistical analysis
Categorical variables are presented as numbers and percentages. Continuous variables are presented as means, SDs and minimum (min) – maximum (max).

The effect of the skin intervention was analysed based on a modified intention-to-treat principle, excluding individuals where the outcome was not assessed. The average effect of the intervention on TEWL (continuous outcome) and dry skin (binary outcome) over time, from 3 to 12 months of age, was assessed using linear and logistic mixed-effects modelling, with the intervention as fixed effect, and participant ID (random intercept) and time-point (random slope) as random effects. Simple linear and logistic regression was used to analyse TEWL and the risk of dry skin, respectively, at each time-point separately. Potential effects of carrying FLG mutations on associations between skin intervention and TEWL and dry skin, respectively, were analysed by adjusting for FLG mutation status and including an interaction term (between skin intervention and TEWL) in the mixed-effects models, with further testing by a three-way-interaction analysis (skin intervention*FLG mutation status*time-point) for the primary outcome (Table S1; see Supporting Information).

No background characteristics were included as potential confounders in adjusted models, as the random assignment to the SI or NSI group provided balanced baseline data in the two groups.

To account for missing data in the primary outcome variables, a sensitivity analysis was performed for TEWL in the study population using multiple imputation with multivariate normal distribution with an upper limit of 20 imputations at each time-point.

Results
The 2153 participants were recruited in Norway (79%) and Sweden (21%), with 53% boys. No significant differences in background characteristics were observed between the 995 infants in the SI and 1158 infants in the NSI groups (Table 1), while they were generally similar in the 241
infants with missing information on TEWL, except for study location, living environment, maternal age and educational level of the caregivers (Table S2; see Supporting Information).

**Skin intervention and transepidermal water loss**

Infants randomized to the SI group had a significantly higher average TEWL [95% confidence interval (CI)] of 0.4 g m\(^{-2}\) h\(^{-1}\) (0.1–0.7, \(P = 0.004\)) from 3 to 12 months of age (Figure 2a) with an intra-cluster correlation of 0.20 (95% CI 0.16–0.25). The effect was dominated by significantly higher TEWL (95% CI) at 3 months in infants with SI compared with infants in the NSI group [8.6 (8.3–9.0) vs. 7.6 (7.3–7.9); \(P<0.001\)], while TEWL was similar in the two groups at 6 and 12 months of age (Table 2). A dose–response was identified for TEWL at 3 months in relation to degree of adherence to the skin intervention (Figure 2b and Table S3; see Supporting Information). The finding of increased TEWL attributed to the skin intervention was supported by analysis of all four intervention groups (Figure S1; see Supporting Information).

In the analysis of multiple imputation of missing TEWL variables, the TEWL in the NSI and SI groups was similar to the primary analysis (Table S4; see Supporting Information).
Skin intervention and dry skin

On average over time, from 3 to 12 months of age, the infants in the SI group were significantly less likely to have dry skin compared with the infants in the NSI group (odds ratio (OR) 0.71, 95% CI 0.64–0.79). Dry skin was observed in 82% (1771 of 2153) of the infants at any of the three time-points, ranging from 56% (1172 of 2112) at 3 months, to 58% (1171/2112) and 57% (1087/1899) at 6 and 12 months, respectively, with significant differences related to the skin intervention at 3 and 6 months (Table 2). The significantly decreased odds of dry skin at 3 months (OR 0.73, 95% CI 0.61–0.86) and 6 months (OR 0.68, 95% CI 0.57–0.81), as well as at all three time-points (OR 0.66, 95% CI 0.54–0.82), by the skin intervention are presented in detail in Table S5 (see Supporting Information). The skin intervention was not significantly associated with the presence of moderate/severe dry skin through infancy, as shown in Table S6 (see Supporting Information). However, infants randomized to the skin intervention had dry skin observed significantly less often on the cheeks and/or extensors at all three time-points (Table S6).

Skin intervention, transepidermal water loss and dry skin in FLG mutation carriers

No interaction was observed between the skin intervention and FLG mutation status (interaction term P-values 0.505 and 0.211 in the adjusted mixed-effects models with TEWL and dry skin, respectively). Irrespective of the intervention, the 153 infants carrying FLG mutations showed significantly higher TEWL at all three time-points compared with the 1530 infants without an FLG mutation (Table S7; see Supporting Information). Being an FLG mutation carrier did not increase TEWL further when subjected to the skin intervention (Table 2). At 3 months, TEWL in infants in the SI group without FLG mutations was similar to infants in the NSI group with a FLG mutation (Table 2 and Figure 3).

Discussion

In approximately 2000 Scandinavian infants from the PreventADALL study, the TEWL was significantly higher in 3-month-old infants subjected to skin intervention with frequent mineral-based oil baths from 2 weeks of age through 8 months, compared with those without skin intervention. The increase in TEWL was dose-dependent according to adherence to the intervention. At 6 and 12 months the TEWL no longer differed between the intervention groups. Dry skin was significantly less common in infants in the SI group compared with the NSI group. At 3 months, the infants with FLG mutations had a similar TEWL as the infants in the SI group.

To our knowledge this is the first RCT that demonstrates an increased TEWL at 3 months in infants subjected to a skin intervention consisting of paraffinum liquidum bath oil and face cream. Our finding is partly supported by a substudy from the Irish observational birth cohort BASELINE study of 1500 children, showing that TEWL at 2 months of age was significantly higher in infants with frequent emollient baths and leave-on emollients from 2 days of age compared with three groups with less treatment.26 In the BASELINE study, the group with frequent bath emollient and infrequent leave-on emollient did not have a significantly higher TEWL compared with the infrequent bath/leave-on emollient group. Because the skin intervention in the present study was bath emollient at least 4 days per week, and as we also found a dose–response effect on TEWL, the amount of emollient used per week might be important for skin barrier function. Although the BASELINE study measured TEWL at 2, 6, 12 and 24 months, only TEWL at 2 months was reported.26 In contrast to our findings, a German study with 60 individuals aged 0.5–85 (mean 40) years with clinically dry skin and similar TEWL at enrolment observed a significant decrease in TEWL after 28 days of bathing with 1 mL of soy bean oil per 5 L of water every second day.20 In a review by Wilborn et al., inconsistent TEWL results were found in 15 of 42 studies with different skincare regimes in neonates and infants.23 In partial support of our findings, a study including 115 British healthy newborns randomized to direct application of either sunflower oil, olive oil or no intervention found similar TEWL between the groups at 4 weeks. However, in both oil groups the organization of lipids throughout the stratum corneum was significantly impaired, which is associated with decreased skin barrier function.35
Our finding of reduced skin barrier function at 3 months in the skin intervention group is also supported by studies reporting increased TEWL from leave-on emollients,\textsuperscript{18,23,24} however, it is difficult to directly compare studies using different emollients, as they can have varying effects on the skin barrier due to their diverse compositions. A substudy from the British EAT cohort observed that increasing the moisturizing frequency in 1221 infants at 3 months of age was associated with higher concurrent TEWL,\textsuperscript{24} and half of the emollients used were oils, olive oil being the most common (20%), followed by oils containing paraffinum liquidum (10%). A German pilot study, including 50 infants at high risk for AD, found no difference in TEWL at 6 and 12 months between the intervention group applying daily emollient containing a prebiotic \textit{Vitreocilla filiformis} lysate and the controls.\textsuperscript{25}

In contrast to our findings, a Japanese study including 227 neonates comparing moisturizing skincare (bathing every 2 days and using lotion daily) to daily bathing without lotion (controls), found a significantly lower face TEWL at 3 months in the intervention group compared with the controls.\textsuperscript{22} A German study including 64 neonates in four similar-sized groups with the intervention done twice-weekly (bathing with wash gel, bathing and cream, bathing with wash gel plus cream, and bathing with water) found significantly lower TEWL at 8 weeks of age in the intervention groups with cream compared with the group bathing with water only.\textsuperscript{26} In both the above-mentioned studies, the bathing frequency in the intervention groups was considerably lower than in our study.

Our finding that infants subjected to the skin intervention had lower prevalence of dry skin than the control group is in line with the Norwegian pilot study\textsuperscript{27} preceding the
PreventADALL study, using a similar skin intervention. The skin intervention from 6 weeks of age reduced xerosis at 6 months in the 24 infants having regular mineral-based oil baths compared with the 32 controls. Some of the studies in the review by Wilborn et al. included dry skin as one of their outcomes, and in contrast to our findings most of these studies did not find any difference in dry skin prevalence between the intervention groups; however, all these studies had different designs, different interventions and much shorter follow-up periods compared with our study. The finding that the skin intervention in our study reduced the appearance of dry skin on the cheeks and/or extensor surfaces of the extremities is novel, and somewhat contradictory to our previous findings of increased TEWL among infants with dry skin, especially on the cheeks and extensors. It is peculiar that the oil bath intervention seems to improve the appearance of dry skin, thereby masking the reduced skin barrier function seen as increased TEWL.

There are many studies on the effect of emollients on the dysfunctional skin barrier presenting as eczema lesions and dry skin seen in patients with AD. The majority of these show reduction in AD severity and reduction of flares when leave-on emollients are used, but dry skin was not included as an outcome. In the British BATHE study, including 482 children between 1 and 11 years with AD, the intervention group using emollient bath additives regularly for 12 months did not identify any difference in AD severity, in support of our findings. A review by Lodén from 2012, including 11 studies investigating the effect of leave-on moisturizers on clinically dry skin, found a positive effect on dryness in all the studies, but all the moisturizers contained humectants such as urea or ammonium lactate.

To the best of our knowledge, our finding of similar TEWL at 3 months between infants with or without FLG mutations subjected to frequent oil baths in a general unselected infant population is novel. While TEWL in infants with FLG mutation was not affected when subjected to frequent oil baths, it was significantly increased in infants without FLG mutations and reached the same level as for mutation carriers not subjected to the skin intervention. A British study by Flohr et al. found higher TEWL in FLG mutation carriers at 3 months of age, but the study did not include any emollient treatments.

Regarding clinical implications, the findings in the present study support that regular mineral-based emollients as a preventive measure do not improve the skin barrier function, which may be one of the reasons why the skin intervention in the PreventADALL study did not prevent AD. We have demonstrated that mineral oil bathing increases TEWL in a dose–response pattern at 3 months and thus may transiently even worsen the skin barrier function. The impaired skin barrier may facilitate penetration of allergens, as demonstrated in the BEEP study where emollients increased the risk of allergic sensitization, and in the EAT study, where increasing use of emollients, oils in particular, increased the risk of food allergy. However, we need to highlight that the amount of mineral oil used in our intervention was considerably higher than other oil bath intervention studies where an increase in TEWL was not found. It can be hypothesized that at considerably lower oil dosage, the skin barrier may not be affected. Based on our results, we cannot advise against adding a few mL of mineral oil to the bath water, but we may suggest that frequent oil bathing of infants is not advisable. And there is certainly no evidence of a positive effect. It is also important to keep in mind that in the first few months of life the skin goes through a physiological maturation and there is no evidence that any skincare product, including bath oil, may be beneficial for the maturation process of healthy skin.

The strengths of our study are: a large, prospective RCT from a general population; high follow-up rates (89.1%, 84.4% and 79.7% at the 3-, 6- and 12-month investigations, respectively); stringent skin assessment by trained personnel as well as standardized TEWL measurements in most of the participants (79.3%, 77.7%, and 58.7%, at 3, 6 and 12 months, respectively); and close monitoring of adherence to the skin intervention. Most of the study participants originate from the Nordic countries, limiting the generalizability. Another considerable limitation is the low full protocol adherence of 32% for the skin intervention. However, 50% and 58% were able to perform oil baths for an average of at least 3.5 days per week, or 2.5 days per week, respectively.

In conclusion, in the general population-based PreventADALL study, the skin intervention comprising of mineral-based bath oil several times per week transiently increased TEWL at 3 months of age in a dose-dependent manner independent of FLG mutation status. Surprisingly, the appearance of any dry skin was less common in the infants subjected to the skin intervention compared with the infants with no skin intervention, especially at 3 and 6 months of age. The findings of the skin intervention leading to reduced skin barrier function may partly explain why AD by the age of 12 months was not prevented by the skin intervention.

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Conflicts of interest
E.M.R. has received honoraria for lectures from Leo Pharma, Novartis, Norwegian Asthma and Allergy Association, Norwegian Psoriasis and Eczema Association, and Sanofi Genzyme. K.C.L.C. reports that her institution has received an honorarium from Thermo Fisher Scientific for symposium presentation. C.M.J. has received honoraria for lectures from the Norwegian Medical Association outside the submitted work and M.L. reports personal fees from MSD. All other authors declare no conflicts of interest.

Data availability
The data underlying this article cannot be shared publicly because the study is still ongoing and due to the privacy of individuals that participated in the study. The data may be shared on reasonable request to the corresponding author.

Ethics statement
The study was conducted according to the guidelines of the Declaration of Helsinki, and was approved by the Regional Committee for Medical and Health Research Ethics in Norway (2014/518) and the Swedish Ethical Review Authority in Stockholm (2014/518) and the Swedish Ethical Review Authority in Norway (2018/1437-32), and registered at https://www.clinicaltrials.gov, NCT02449850 (https://clinicaltrials.gov/study/NCT02449850). Informed written consent was obtained from all mothers at enrolment, and from individuals that participated in the study. The data may be shared on reasonable request to the corresponding author.

Supporting Information
Additional Supporting Information may be found in the online version of this article at the publisher’s website.

References
Oil baths and skin barrier in infancy, E.M. Rehbinder and S. Wärnberg Gerdin et al.


