Received: 27 November 2023 | Revised: 2 February 2024 | Accepted: 23 February 2024

DOI: 10.1111/all.16095

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

LETTER

Neonatal skin dysbiosis to infantile atopic dermatitis: Mitigating effects of skin care

To the Editor,

Patients with atopic dermatitis (AD) harbor *Staphylococcus aureus* in lesional skin, causing dysbiosis, linked to disease flares and progression.[1] The onset of dysbiosis-related AD during infancy remains unclear. To clarify this, we performed a longitudinal microbiome analysis in an interventional cohort study. In total, 177 infants, all of whom received skin care, were included in this study (Figure S1A,B and Table S1). We considered the total amount of moisturizer (TAM) used as an indicator of skincare diligence. At 1 year of age, 13 infants (7.3%) developed AD. Three infants with food allergy (FA) (1.7%) were diagnosed with egg white (EW) allergy, and one of these was also diagnosed with AD. Additionally, 61 infants (34.5%) who neither had AD nor FA were sensitized to EW (EW-AS) (Figure S1B and Table S2). Compared with the healthy group, the EW-AS group received a significantly higher TAM and serum total IgE levels at 1 year of age. In contrast, the infants in the AD group received a relatively lower TAM than the healthy infant group (Table S2). The prevalence rates of vaginal delivery, exclusive breastfeeding, parental allergy history, *FLG* mutations, birth season, and transepidermal water loss (TEWL) levels were similar across groups, potentially due to skincare effects minimizing transepidermal water egress (Table S2).

Concerning skin microbiome, the Shannon diversity and b-diversity indices between healthy and AD groups were similar at all time points (Figure 1A,B and Figure S2). Different from our previous non-intervention cohort study,[2] *S. aureus* abundance at 6 months of age was significantly decreased compared to 1 month regardless of AD development, and the antibiotic use during the perinatal period or the mode of delivery did not affect the bacterial counts (Figure S3). The increased abundance of *Streptococcus* and *Prevotella* OTUs and the decreased abundance of *Cutibacterium* OTU (*Cutibacterium acnes*) at Day 3 after birth were associated with AD development at 1 year of age (Figure 1B,C). Spearman's rank coefficient analysis revealed a negative correlation between the TAM used (TAM 4M, TAM 6M) and the abundance of *Streptococcus* OTU in newborn skin (Figure 1C). In contrast, the abundance of *C. acnes* in newborn skin was positively correlated with TAM (TAM 1yr) and negatively correlated with TEWL levels at 1 year of age (Figure 1C). The correlation between *C. acnes* and the amount of moisturizer used suggests that this bacterium may proliferate by utilizing the essential lipids (cholesterol and ceramides) in the moisturizer as nutrients. These results also imply that skin dysbiosis in newborns increases the risk of AD by 1 year of age, which may be mitigated by skincare.

We also analyzed the microbial composition of healthy and EW-AS groups. We found that infants with EW-AS without AD at 1 year of age had significantly decreased skin microbiome Shannon diversity from 1 to 6 months of age (Figure 2A,B). In Day 3 infant skin, three OTUs (e.g., *Pasteurellaceae*, *Neisseria*, and *Enhydrobacter*) and four genera (e.g., *Corynebacterium*, *Pasteurellaceae*, *Neiserria*, and *Enhydrobacter*) showed relatively higher abundance in the EW-AS group compared with healthy group by LDA (Figure 2C). However, different from AD, the bacteria related to the development of EW-AS were not associated with TAM at any age (Figure 2C).

According to our previous Japanese infant cohort studies, the incidence rates of AD and FA around 1 year of age were between 15.3%–24.6% and 10.9%–12.1%, respectively, and food AS was observed in approximately 40% of the infants.[3,4] However, interestingly, in this skin care intervention study, the incidence rates of AD and FA were much lower, although the incidence rate of food AS was comparable.

In conclusion, we found infants developed AD at the age of 1 year exhibited skin dysbiosis as early as the third day of life. While the

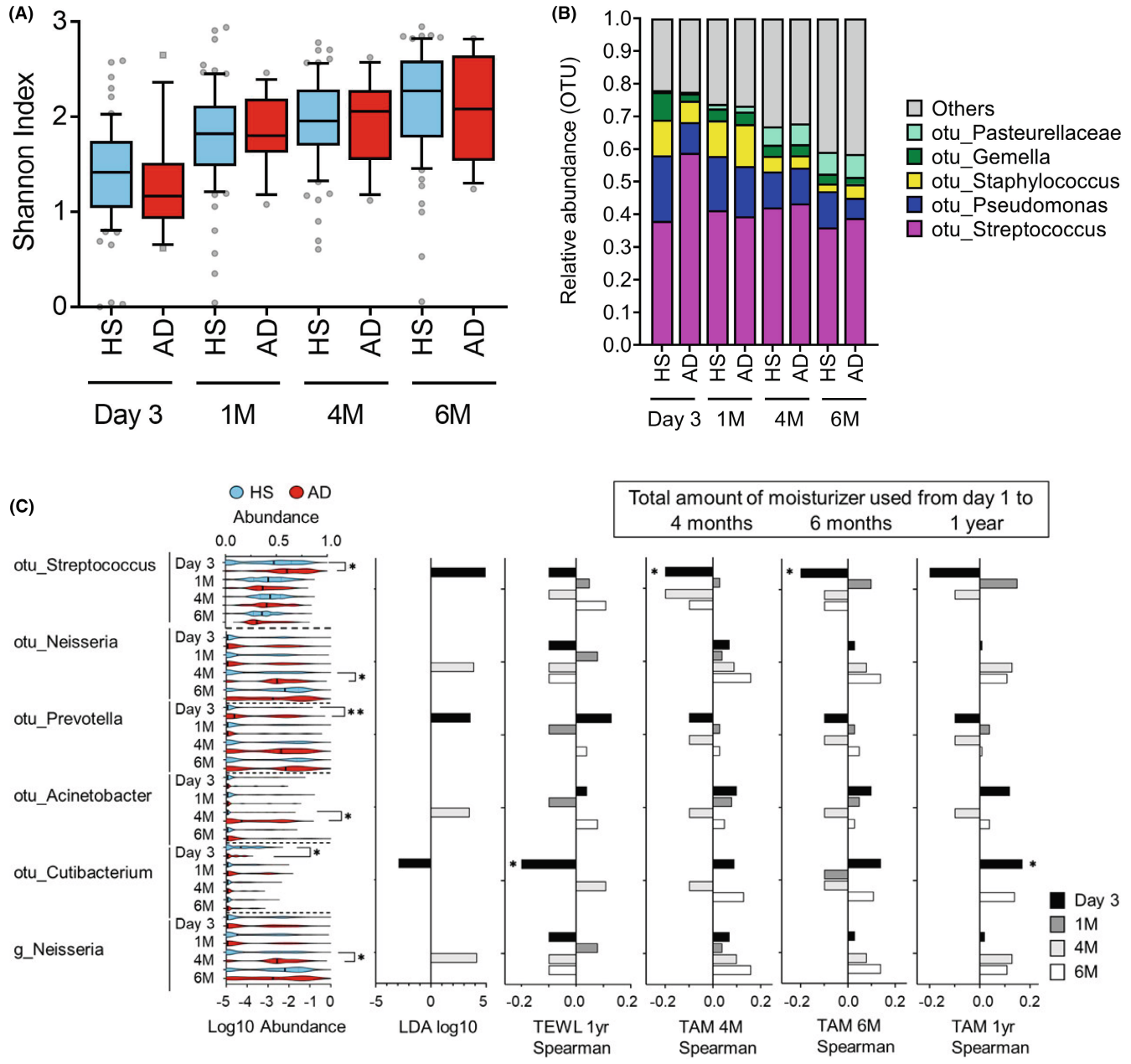

FIGURE 1 Comparison of bacterial diversity, composition, and Spearman's rank coefficient between healthy subjects and infants with AD. (A) Shannon diversity index was compared among HS and AD groups at each infants' age. (B) Relative abundance of major skin microbiota at the OTU level. The label numbers for each OTU were otu00001_Streptococcus, otu00002_Pseudomonas, otu00003_Staphylococcus, otu00004_Gemella, and otu00005_Pasteurellaceae. (C) Bacterial taxa with significant differences between HS and AD groups, as determined by Lefse analysis with absolute value of LDA score ($\log_{10}$) >2, were identified and displayed at OTU and genus levels ($p < .05$). The label numbers for each OTU were otu00001_Streptococcus, otu00013_Neisseria, otu00016_Prevotella, otu00048_Acinetobacter, and otu00049_Cutibacterium. Bacterial abundance of otu00001_Streptococcus was displayed linearly, while abundance of other bacteria was displayed on a $\log_{10}$ scale due to their lower abundance. Comparison of bacterial abundance between HS and AD groups was assessed using the Mann–Whitney *U* test. Correlations between bacterial taxa observed at each infants' age and clinical parameters (TEWL and TAM) were assessed using Spearman's rank correlation analysis. *$p < .05$ and **$p < .01$. HS, healthy subjects; TAM, total amount of moisturizer used; TEWL, transepidermal water loss.

results of our study suggest a potential preventive effect of moisturizer against AD and FA during infancy, a significant limitation that requires further attention is that all patients received intervention in this study and there was no blinding involved. Future randomized trials are warranted to validate the efficacy of moisturizer-based interventions in AD and FA prevention.

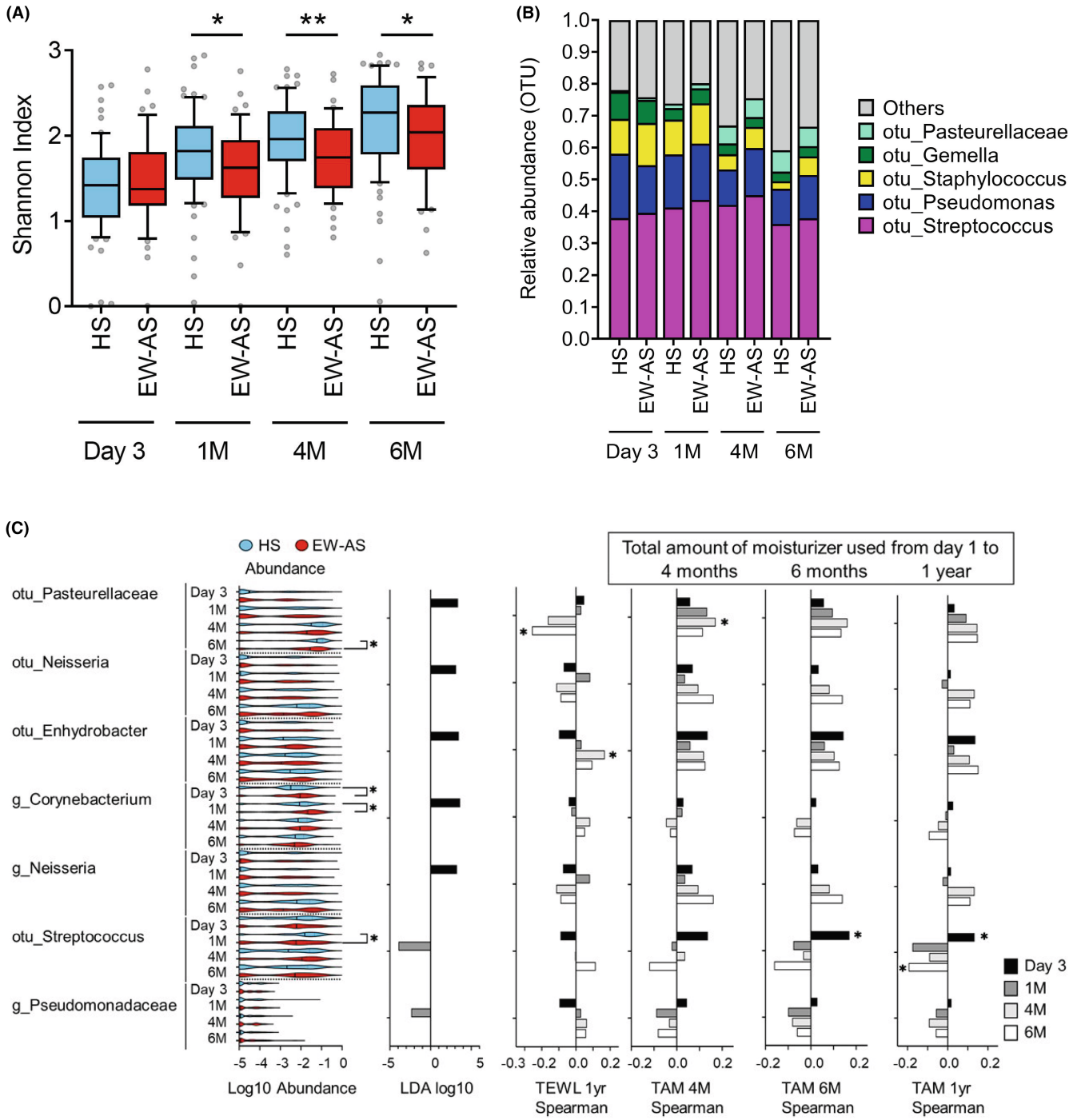

FIGURE 2 Comparison of bacterial diversity, composition, and Spearman's rank coefficient between healthy subjects and infants with EW-AS. (A) Shannon diversity index was compared among HS and EW-AS groups at each infants' age. (B) Relative abundance of major skin microbiota at the OTU level. The label numbers for each OTU were otu00001_Streptococcus, otu00002_Pseudomonas, otu00003_Staphylococcus, otu00004_Gemella, and otu00005_Pasteurellaceae. (C) Bacterial taxa with significant differences between HS and EW-AS groups, as determined by Lefse analysis with absolute value of LDA score ($\log_{10}$) >2 and max abundance >25%, were identified and displayed at OTU and genus levels ($p < .05$). The label numbers for each OTU were otu00005_Pasteurellaceae, otu00013_Neisseria, otu00017_Enhydrobacter, and otu00006_Streptococcus. Bacterial abundance was displayed on a $\log_{10}$ scale. Comparison of bacterial abundance between HS and EW-AS groups was assessed using the Mann–Whitney *U* test. Correlations between bacterial taxa observed at each infants' age and clinical parameters (TEWL and TAM) were assessed using Spearman's rank correlation analysis. EW-AS, Antigen-specific sensitization to egg white. $^{*}p < .05$ and $^{**}p < .01$.

AUTHOR CONTRIBUTIONS

YI, NS, and YN conceived the study. YI, NS, and YN designed the study with the help of ST and YK. RA, SN, and YN formed genome sequencing experiments with the help of HT. YI and FI collected all infants' samples with the help of clinical staff at Ichikawa clinic. NI acquired the Illumina sequence data and analyzed the data. RA, SN, NI,

and YN analyzed the data and wrote the manuscript with the help of MF and GN. YY, TI, and TS performed the laboratory work. MK and MA performed *FLG* gene analysis. AT, TN, MF, and GN provided advice. All authors edited the manuscript and approved the final draft.

ACKNOWLEDGEMENTS

We would like to express our gratitude to the nurses at the Ichikawa clinic for their assistance with clinical sample collection. We also thank K. Watanabe and N. Saito for technical assistance. The NGS sample preparation was technically supported by CoMIT Omics Center, Graduate School of Medicine, Osaka University.

FUNDING INFORMATION

This research was supported by JSPS KAKENHI 20H03701 (YN), JSPS KAKENHI JP22H04925 (YN), JSPS KAKENHI 23H02930 (YN), MEXT KAKENHI 16H06279 (HT), JST FOREST JPMJFR200Y (YN), AMED-PRIME JP 18gm6010016h0002 (YN), AMED-CREST 23gm1610004h0003 (YN, HT, AT), AMED 23ek0410105s0101 (YN, HT), National Bioscience Database Center of the Japan Science and Technology Agency (HT), Joint Usage/Research Program of Medical Mycology Research Center, Chiba University (YN/AT and HT), and Institute for Global Prominent Research, Chiba University (HT, AT, and NS).

CONFLICT OF INTEREST STATEMENT

S. Tanaka and Y. Koyano are affiliated with Natural Science Co., Ltd. They were not involved in data collection nor the analysis of data for this paper. This conflict of interest statement was agreed upon by all authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in DDBJ at https://ddbj.nig.ac.jp, reference number PRJDB 16177.

Reika Aoyama[1]
Seitaro Nakagawa[1,2,3]
Yoko Ichikawa[4]
Naohiro Inohara[3]
Yuriko Yamazaki[1,5]
Tomoka Ito[1]
Takashi Sugihira[2]
Michihiro Kono[6]
Masashi Akiyama[7]
Hiroki Takahashi[8,9]
Akiko Takaya[8,9,10]
Fumitaka Ichikawa[11]
Taiji Nakano[12]
Seiko Tanaka[13]
Yutaka Koyano[13]
Manabu Fujimoto[1]
Gabriel Núñez[3]
Naoki Shimojo[14]
Yuumi Nakamura[1,5]

[1]*Department of Dermatology, Integrated Medicine, Graduate School of Medicine, Osaka University, Osaka, Japan*
[2]*Department of Cutaneous Immunology and Microbiology, Graduate School of Medicine, Osaka University, Osaka, Japan*
[3]*Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan, USA*
[4]*Department of Pediatrics, Ichikawa Clinic, Fukushima, Japan*
[5]*Cutaneous Allergy and Host Defense, Immunology Frontier Research Center, Osaka University, Osaka, Japan*
[6]*Department of Dermatology and Plastic Surgery, Akita University Graduate School of Medicine, Akita, Japan*
[7]*Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[8]*Medical Mycology Research Center, Chiba University, Chiba, Japan*
[9]*Plant Molecular Science Center, Chiba University, Chiba, Japan*
[10]*Department of Infection Control Science, Graduate School of Pharmaceutical Sciences, Chiba University, Chiba, Japan*
[11]*Department of Obstetrics and Gynecology, Ichikawa Clinic, Fukushima, Japan*
[12]*Department of Pediatrics, Graduate School of Medicine, Chiba University, Chiba, Japan*
[13]*Natural Science Co., Ltd., Tokyo, Japan*
[14]*Center for Preventive Medical Sciences, Chiba University, Chiba, Japan*

Correspondence
Yuumi Nakamura, Cutaneous Allergy and Host Defense, Immunology Frontier Research Center, Osaka University, Osaka, Japan.
Email: ymatsuoka@derma.med.osaka-u.ac.jp

Reika Aoyama, Seitaro Nakagawa, and Yoko Ichikawa should be acknowledged as joint first authors, and Naoki Shimojo and Yuumi Nakamura as joint senior authors

ORCID

Reika Aoyama https://orcid.org/0000-0002-0703-3281
Taiji Nakano https://orcid.org/0000-0001-7499-1204
Yuumi Nakamura https://orcid.org/0000-0001-6256-8302

REFERENCES

1. Kong HH, Oh J, Deming C, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res*. 2012;22(5):850-859.
2. Nakamura Y, Takahashi H, Takaya A, et al. *Staphylococcus* Agr virulence is critical for epidermal colonization and associates with atopic dermatitis development. *Sci Transl Med*. 2020;12(551):eaay4068.
3. Dissanayake E, Tani Y, Nagai K, et al. Skin care and synbiotics for prevention of atopic dermatitis or food allergy in newborn infants: a 2 ×2 factorial, randomized, non-treatment controlled trial. *Int Arch Allergy Immunol*. 2019;180(3):202-211.

4. Tanabe H, Sakurai K, Kato T, et al. Association of the maternal microbiome in Japanese pregnant women with the cumulative prevalence of dermatitis in early infancy: a pilot study from the Chiba study of mother and child health birth cohort. *World Allergy Organ J*. 2019;12(10):100065.

SUPPORTING INFORMATION

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