

An Observational Study: Association Between Atopic Dermatitis and Bacterial Colony of the Skin Based on 16S rRNA Gene Sequencing

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Aim: Atopic dermatitis (AD) often accompanies skin infections, and bacterial skin infections often cause persistent and worsening symptoms. In this study, we explored the key changes in the microbiota of AD patients, as well as the effects of different ages and the severity of rash on changes in the microbiota.

Patients and Methods: A total of 95 AD patients and 77 healthy volunteers were recruited. The AD patients were divided into three groups based age and three groups according to the EASI score. Microorganisms collected from the skin were analyzed through 16S rRNA gene sequencing, revealing species diversity via α and β diversity analyses. Species compositions were compared at the phylum and genus levels. The significance of skin microbiota at the genus level was assessed using the random forest algorithm. Finally, the impact of relationships between different microbial communities on the microbial community composition and the pathogenesis of AD was explored using Pearson correlation coefficients.

Results: The species diversity of the skin microbiota in the AD group significantly decreased. Compared with that in the healthy volunteers (HV) group, the bacterial diversity in the two groups of samples significantly differed. *Staphylococcus* dominated the bacterial communities, and as AD symptoms gradually worsened, the abundance of *Staphylococcus* gradually increased. Among all bacterial genera with a relative abundance greater than 1%, *Staphylococcus* showed a negative correlation with other genera, and showed significant consistency in specimens from different age groups.

Conclusion: Changes in the abundance of *Staphylococcus* in the skin bacterial colonies are the main cause of AD. *Brevundimonas*, *Paracoccus*, *Corynebacterium*, and *Veillonella* may serve as characteristic biomarkers for AD. These results indicate that altering the microbiota composition of the skin may aid in the treatment of AD.

Keywords: atopic dermatitis, skin bacterial colony, 16S rRNA gene sequencing

Introduction

Atopic dermatitis (AD) is a common chronic inflammatory itching skin disease that is most common in children but also affects many adults. It is usually associated with allergic diseases such as allergic rhinitis and asthma. It can also cause various mental illnesses, which are related to depression, anxiety, suicidal ideation, attention deficit hyperactivity disorder, decreased quality of life, and sleep disorders,^{1,2} and can have a serious impact on the patient, their family, and society. AD can occur through combination with multiple factors, but the pathogenesis of this disease has not been fully elucidated.

The bidirectional interference between microbiota symbiosis and host immunity is crucial for skin homeostasis, and many chronic inflammatory skin diseases are closely related to the dysregulation of the composition of the colonizing

microbiota.^{3,4} The correlation between the skin microbiota and epidermal barrier dysfunction and T-cell-driven inflammation is a key pathological feature.^{5,6} An increasing number of studies have revealed that AD patients exhibit skin microbiota phenotypes that are different from those of healthy individuals, and these phenotypes change with age and severity of the rash. Oki Suwarsa et al conducted a grouping study on 16 AD patients based on the severity of the disease and identified the distribution of the skin microbiota in moderate and mild AD patients; the authors showed that the diversity of the skin microbiota was relatively low in moderate AD patients.⁷ Baochen Shi PhD et al determined the significant differences in the AD skin microbiota among young children, teenagers, and adults by conducting skin microbiota testing on age groups of AD patients.⁸

However, current research has focused only on the impact of a single factor on the skin microbiota in AD patients, and there have been no large-scale studies on the effects of multiple factors. In fact, AD patients often experience changes in the skin microbiota under the combined influence of multiple factors, such as age and severity. Therefore, additional research is needed to elucidate the influence of multiple factors on the skin microbiota in AD patients. This study aimed to detect colonies on the skin of AD patients and healthy individuals by 16S rRNA gene sequencing, screen for organisms that mediate key changes in colonies, and explore the effects of different age groups and disease severities on changes in microbial communities. This study provides new insights into the relationship between AD incidence and changes in the skin microbiota, as well as into the development of new drugs.

Materials and Methods

Study Subjects

A total of 95 AD patients were recruited at the Guangdong Provincial Hospital of Traditional Chinese Medicine from October 2019 to May 2021; these patients included 34 children (2–12 years old, C group), 20 teenagers (12–18 years old, T group), and 41 adults (18 years or older, A group). According to the EASI score (MILD: ≤ 7 points; MODERATE: 8–21 points; SEVERE: above 22 points),⁹ the AD patients were divided into three groups, 47 in the MILD group, 26 in the MODERATE group, and 22 in the SEVERE group (Table 1). The inclusion criteria for patients were as follows: (1) were diagnosed with AD according to the UK Working Group Williams diagnostic criteria.¹⁰ (2) Patients with a disease course ≥ 1 year. The exclusion criteria for patients were as follows: (1) had received treatment with antibiotics, antifungal glucocorticoids or immunosuppressants within one month or any topical treatments (except for moisturizers) within one week. (2) Patients who were receiving treatment, such as ultraviolet therapy and biological agents. (3) Patients with other skin diseases or clear indications of infection, bone marrow transplantation or gene therapy; pregnant women with severe primary systemic diseases; or patients with mental

Table 1 Grouping of Patients with Atopic Dermatitis (n=95)

Age Grouping	Severity Grouping		
	Severity	n	%
Children (C group) n=34	MILD	21	61.8
	MODERATE	7	20.6
	SEVERE	6	17.6
Teenagers (T group) n=20	MILD	7	35
	MODERATE	7	35
	SEVERE	6	30
Adults (A group) n=41	MILD	19	46.3
	MODERATE	12	29.3
	SEVERE	10	24.4

illness, malignant tumors, or obvious potential immunodeficiency diseases. (4) Asthma patients were diagnosed during acute episodes or those who required hormone maintenance therapy (including systemic and local medication). We also included 77 healthy volunteers (HV group). All AD patients and volunteers signed informed consent forms before participating in the study. For those ages 8 to 18, we also obtained guardian signature. For children under the age of 8, we only obtained a separate signature from their guardians. This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Guangdong Provincial Hospital of Traditional Chinese Medicine (ethics number: BE2019-165-01).

Sampling and Collection of Skin Swabs

Participants were required to avoid using hand sanitizers, antibacterial soap, or skincare products for one week and were advised not to use showers for 24 hours before sample collection. Disposable sterile skin cotton sampling swabs were used to moisten the skin with physiological saline, after which they were subjected to stable pressure on the palmar skin of the forearm (elbow socket). The swab was rubbed back and forth approximately 50 times (approximately 30 seconds), for a collection area of 16 cm². Subsequently, the cotton swab tip samples were stored in test tubes containing sterile buffer solution and transported to the biological resource center for storage at -80°C.

DNA Extraction, PCR Amplification, and Sequencing of the Skin Microbiome

The microbial community DNA was extracted with a MagPure Stool DNA KF Kit B (Magen, China) following the manufacturer's instructions. The quality of all the extracted DNA was detected by a Qubit® dsDNA BR Assay Kit (Invitrogen, USA) and agarose gel electrophoresis.

The V4 variable region of the bacterial 16S rRNA gene was amplified with the common PCR primers 515F (5'-GTGCCAGCMGCCGCGTAA-3') and 806R (5'-GGACTACHVGGGTWTCTAAT-3'). Both forward and reverse primers were tagged with Illumina adapter, pad and linker sequences. PCR enrichment was performed in a 50 µL reaction mixture containing 30 ng of template, fusion PCR primer and PCR master mix. The PCR cycling conditions were as follows: 95°C for 3 minutes; 30 cycles of 95°C for 45 seconds, 56°C for 45 seconds, and 72°C for 45 seconds; and a final extension for 10 minutes at 72°C for 10 minutes. The PCR products were purified using Agencourt AMPure XP beads and eluted in elution buffer. Libraries were analyzed with an Agilent Technologies 2100 bioanalyzer. The validated libraries were sequenced on the Illumina HiSeq 2500 platform (BGI, Shenzhen, China) following the standard Illumina pipelines, generating 2×250 bp paired-end reads.

The original sequencing data were processed to obtain clean data (reads). The sequence splicing software FLASH (fast length adjustment of short reads, v1.2.11) was used to assemble paired reads obtained from dual-end sequencing into a single sequence using overlapping relationships, resulting in tags in the high-variability region. The spliced tags were clustered into OTUs using the software USARCH (v7. 0.1090). The OTU species were annotated and classified, and species abundance maps of the specimens were drawn at the phylum and genus levels.

Data Processing and Statistical Analysis

Intragroup testing of the α diversity of the AD and HV groups was performed to evaluate the abundance and diversity of the two microbial communities. Subsequently, β diversity analysis was conducted based on principal coordinate analysis (PCoA), followed by permutational multivariate analysis of variance (PERMANOVA) to explore potential differences in sample composition between the AD and HV groups. At the phylum and genus levels, species abundance bar charts were created for the AD and HV samples, as well as for the different age groups and disease severities, and differences in key species were compared. Based on the random forest algorithm, the abundance and correlation of the skin microbiota were calculated at the genus level to identify the characteristic bacterial genera that distinguish the AD and HV groups, and probability distribution and receiver operating characteristic (ROC) curve plots were drawn. The Pearson correlation coefficient ($r \geq 0.7$, $p \leq 0.05$) was used to evaluate the correlation between the AD group and different age groups of bacterial genera, and a correlation coefficient matrix was drawn.

Results

Composition of the Bacterial Colony

In total, 172 samples were collected and processed via 16S rRNA sequencing. A total of 12,294,794 reads passing quality control were clustered into 7797 OTUs. There were 1479 unique OTUs for AD patients, 2745 unique OTUs for HV patients, and 3573 OTUs shared by both groups.

Thirty-two phyla and 757 genera were identified. Among the five phyla identified, *Firmicutes* (43.18%), *Proteobacteria* (31.25%), *Actinobacteria* (15.03%), *Bacteroidetes* (4.00%), and *Deinococcus-Thermus* (2.61%) made up more than 96.07% of the total (Figure 1A). At the genus level, the top ten genera which relative abundance >1% on make up 61.02%, including *Staphylococcus* (33.44%), *Enhydrobacter* (7.69%), *Corynebacterium* (5.15%), *Streptococcus* (3.73%), *Propionibacterium* (3.60%), *Acinetobacter* (2.61%), *Deinococcus* (2.30%), *Paracoccus* (1.52%), *Enterococcus* (1.43%), *Sphingomonas* (1.36%) (Figure 1B).

α -Diversity Analysis

α -Diversity analysis was subsequently performed on the bacterial colonies of the samples between the AD group and the HV group. The average Chao1 index and Shannon index were lower in the AD group than in the HV group (Figure 2A and B). The

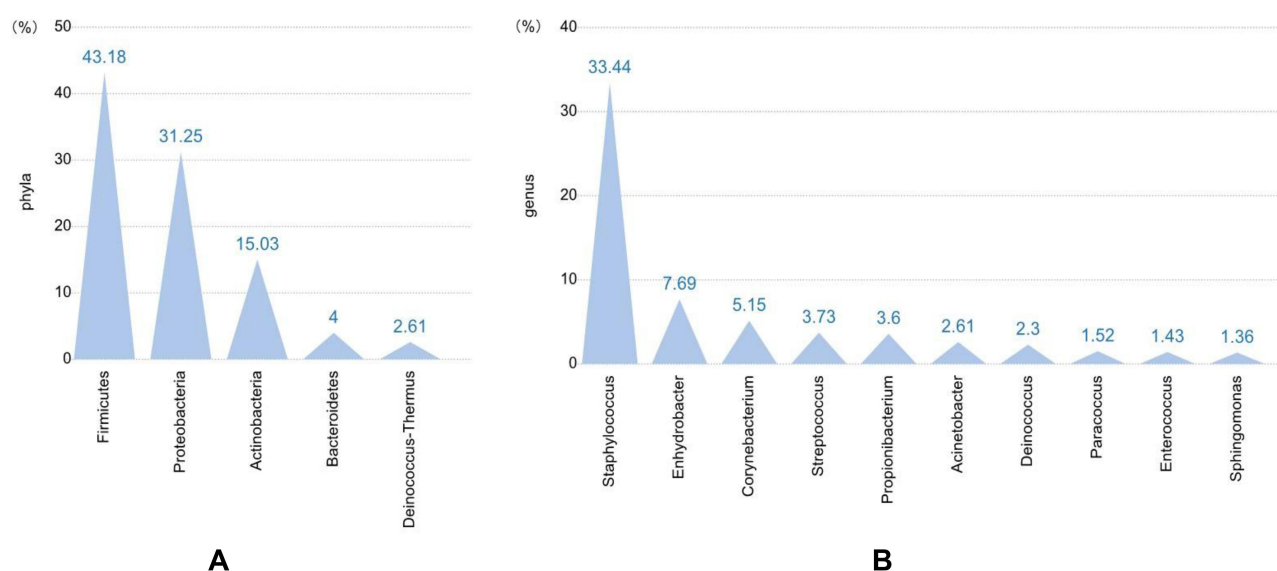


Figure 1 Composition of the bacterial colonies. (A) The five bacterial phyla with the greatest abundance in all samples; (B) the ten bacterial genera with the greatest abundance in all samples.

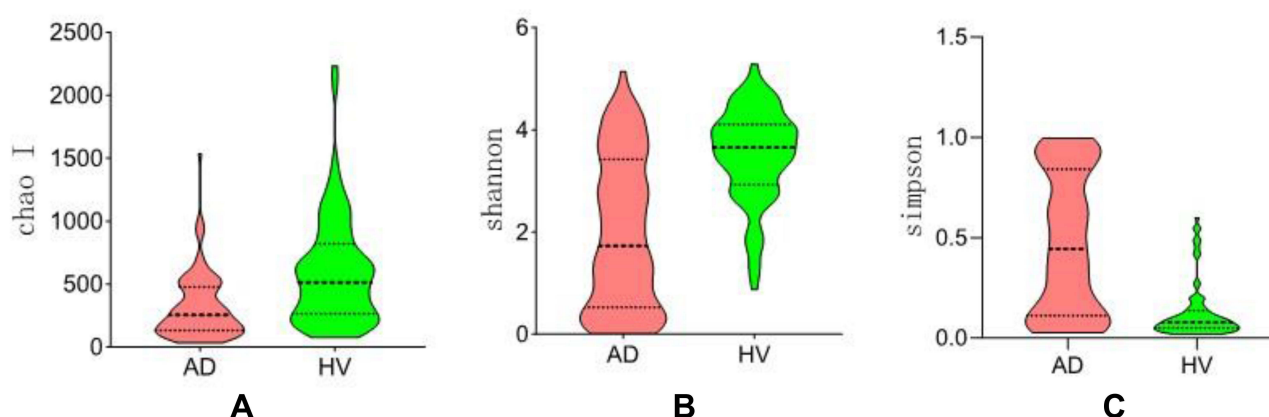


Figure 2 α -Diversity analysis of the AD group and HV group. (A) α -Diversity analysis of Chao I; (B) α -diversity analysis of Shannon; (C) α -diversity analysis of Simpson.

Simpson index was significantly greater in the AD group than in the HV group (Figure 2C). Overall, the analysis revealed that the species richness, colony diversity, and evenness in the skin samples of patients in the AD group were significantly lower than those in the HV group.

β -Diversity Analysis

To explore the potential differences in sample composition between the AD and HV groups, the compositions of the two groups of samples were analyzed via β -diversity analysis. The PCoA results revealed that there was a clear difference between the AD group and the HV group, and the difference was statistically significant ($p < 0.001$) (Figure 3). Therefore, β -diversity analysis revealed significant differences in microbial community composition between the two groups at the genus level, indicating a significant change in bacterial diversity between the two samples.

Microbial Composition and Differential Analysis

Our research revealed significant differences in bacterial abundance in the skin of AD patients compared to that in the skin of healthy individuals in terms of phylum and genus classification, although the main bacteria remained largely unchanged. At the phylum level, the abundance of Firmicutes in the AD group significantly increased compared to that in the HV group, while the abundances of Proteobacteria, Actinobacteria, Bacteroidetes, and Deinococcus Thermus significantly decreased (Figure 4A). At the genus level, the most significant increase was in the abundance of *Staphylococcus* in the AD group (Figure 4B), and Abundance analysis of the different severity and age groups in the AD group revealed that *Staphylococcus* was the dominant genus in the microbial communities equally (Figure 4C and D). At the genus level, there was a significant statistical difference in the abundance of *Staphylococcus* compared to the HV group, while the abundance of *Deinococcus*, *Enhydroactor*, *Sphingomonas*, *Propionibacterium*, *Corynebacterium*, *Acinetobacter*, and *Paracoccus* decreased significantly ($p < 0.001$) (Figure 4E). As AD symptoms gradually worsened, the abundance of *Staphylococcus* gradually increased, with

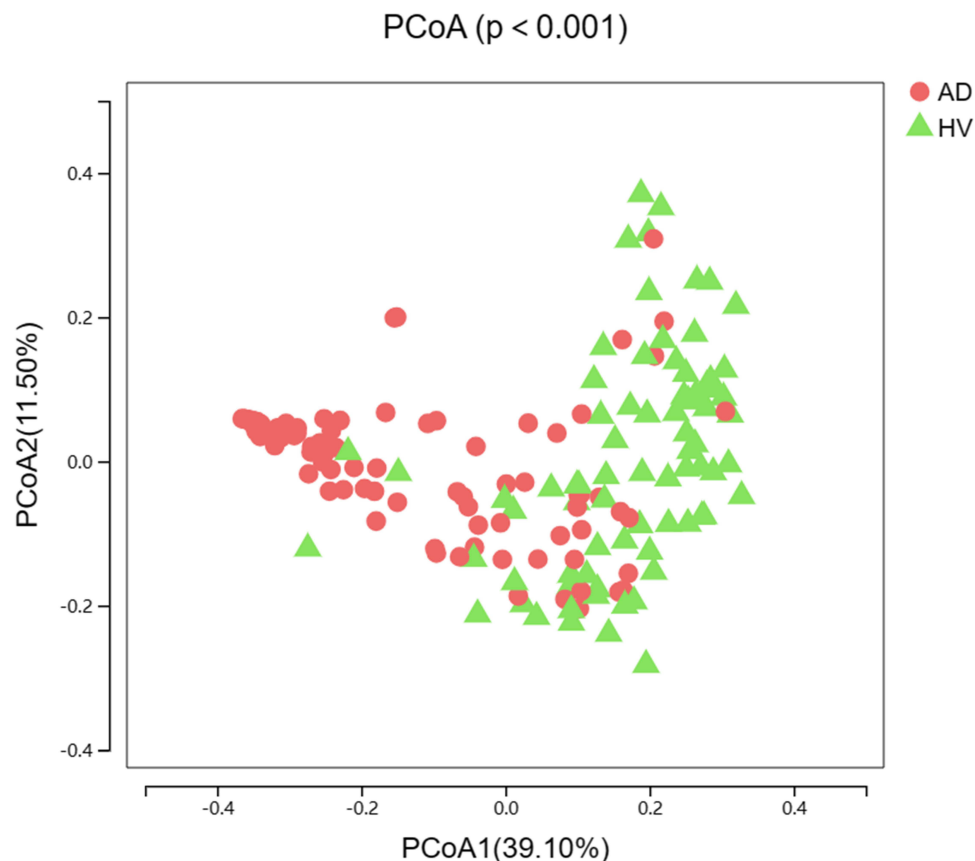


Figure 3 β -Diversity analysis of the microbiota between the AD and HV groups by PCoA.

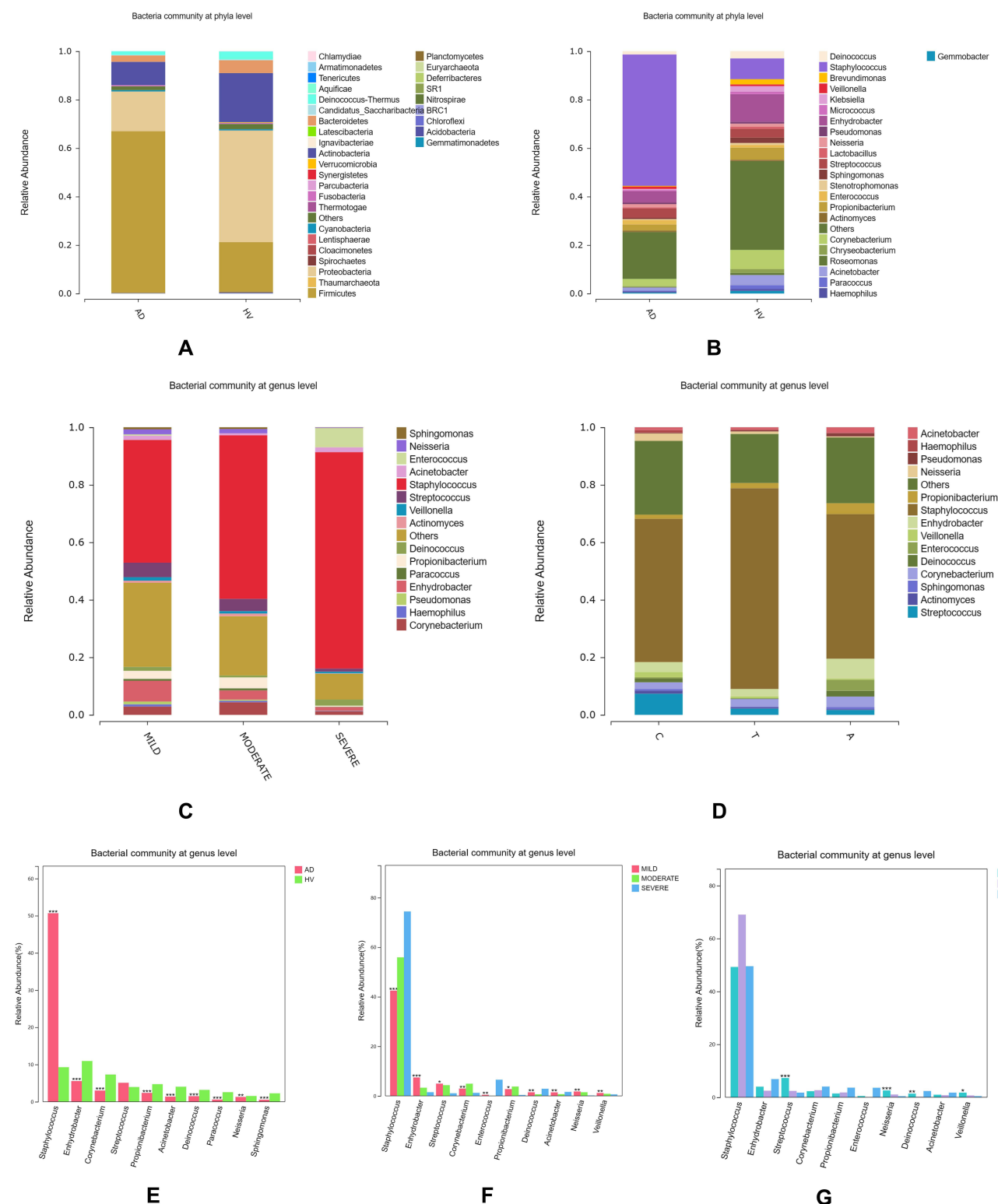


Figure 4 Bacterial composition distribution and comparison of key genera. (A) Bacterial composition distribution at the phylum level in the AD and HV groups. (B) Bacterial composition distribution at the phylum level in the AD and HV groups. (C) Bacterial composition distribution at the genus level in patients with different severity levels in the AD group. (D) Bacterial composition distribution at the genus level in patients from different age groups in the AD group. (E) Comparison of key genus differences between the AD and HV groups. (F) Comparison of key genus differences among samples from patients with different severity levels. (G) Comparison of key genus differences among samples from patients with different severity levels and from patients with different age groups (** p value <0.001 , ** $0.001 \leq p$ value ≤ 0.01 , * $0.01 < p$ value ≤ 0.05).

significant differences observed in the MILD group compared to the other groups (Figure 4F). In terms of age, the abundance of *Staphylococcus* in the skin samples of adolescent AD patients was the highest, and there was no significant difference among the three groups (Figure 4G).

Analysis of Significantly Different Microbial Communities

The importance of the skin microbiota at the genus level was calculated to distinguish the microbiota of the AD and HV groups by the random forest algorithm. There was a significant difference between the two groups, and the model performed well (Figure 5A). The analysis revealed that the 5 bacterial genera with the most significant differences between the two groups were *Staphylococcus*, *Brevundimonas*, *Paracoccus*, *Corynebacterium*, and *Veillonella*. According to the ROC curve, the AUC was close to 0.9, indicating high diagnostic accuracy and value (Figure 5B).

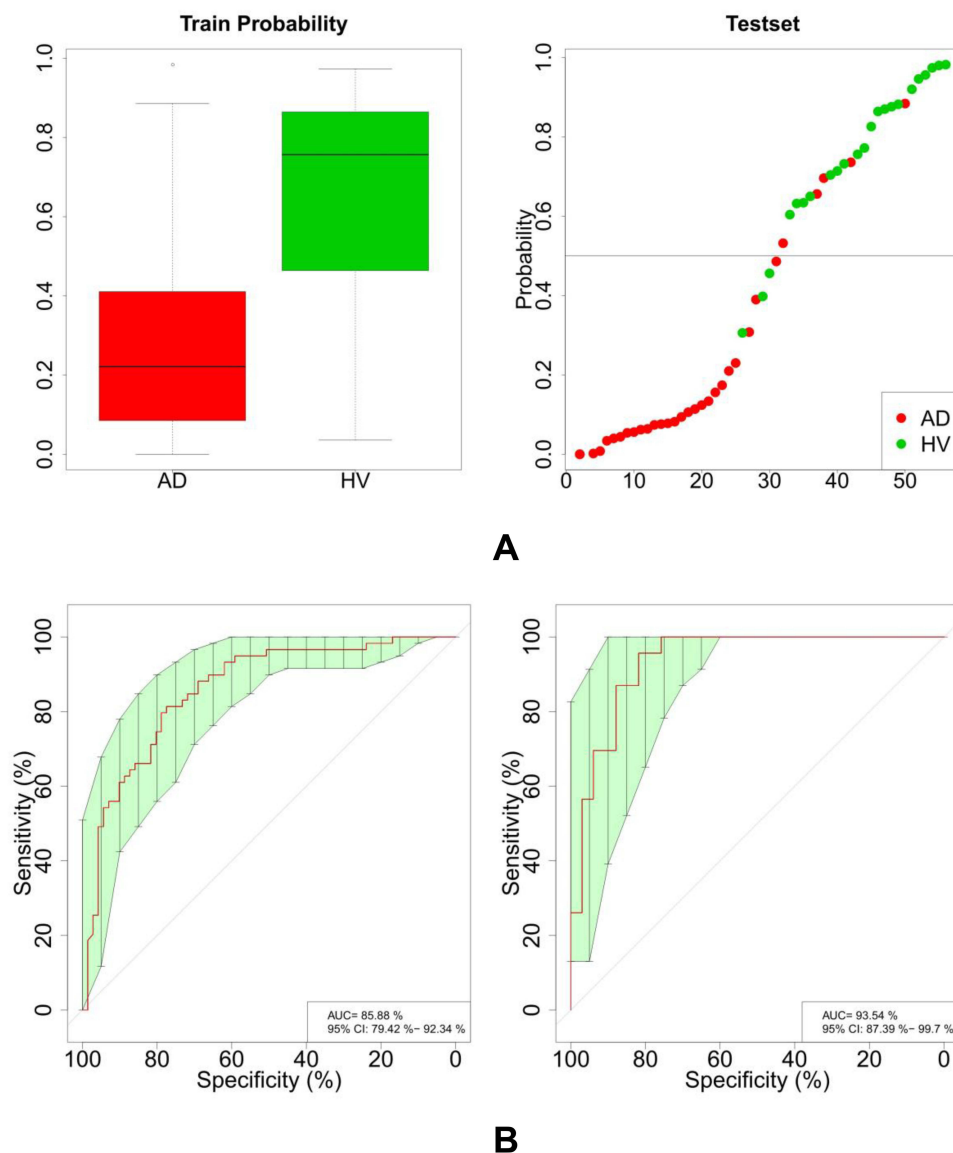


Figure 5 Random forest/ROC curve. **(A)** The probability map of the training set on the left and the distribution map of the test set on the right. The greater the distance between the two box plots in the training set was, the greater the difference between the groups. The test distribution chart shows that if two groups can be distinguished by a line on the vertical axis of 0.5, this indicates a significant difference between the groups and a good model effect. **(B)** The ROC curve of the training set is on the left, and the ROC curve of the testing set is on the right. In the ROC curve, the point closest to the upper left corner has higher sensitivity and specificity, with the least false positives and false negatives; AUC (area under the ROC curve) refers to the area under the ROC curve (area under the red line in the figure). The larger the AUC is, the better, indicating a higher diagnostic value of the test. The green range represents the 95% confidence interval of the model. 1) AUC $\approx$ 1.0: the most ideal inspection indicator; 2) AUC between 0.7 and 0.9: high experimental accuracy; 3) AUC=0.5: The test has no diagnostic significance.

Bacterial Correlation Analysis

To explore the impact of interrelationships between different microbial communities on microbial community composition and the pathogenesis of AD, Pearson correlation coefficients ($r \geq \pm 0.7, p \leq 0.05$) were used to evaluate the correlation between genera (relative abundance $> 1\%$) (Figure 6). Among all the bacterial genera with a relative abundance greater than 1% in the AD samples, an extreme situation occurred, with *Staphylococcus* showing a negative correlation with the other main bacterial genera. Correlation analysis between different age groups of AD patients also revealed significant consistency. In the AD group, there was a significant positive correlation between *Neisseria* and *Streptococcus*, which was also present in the children and teenagers. In the adult AD patient group, the correlation coefficient between bacterial genera was lower than that between the children and teenager groups.

Discussion

AD often accompanies skin infections, and skin bacterial infections are often an important cause of persistent and worsening symptoms. There have been few studies on the changes in microbiota from healthy skin to AD skin based on multiple dimensions of age and severity.

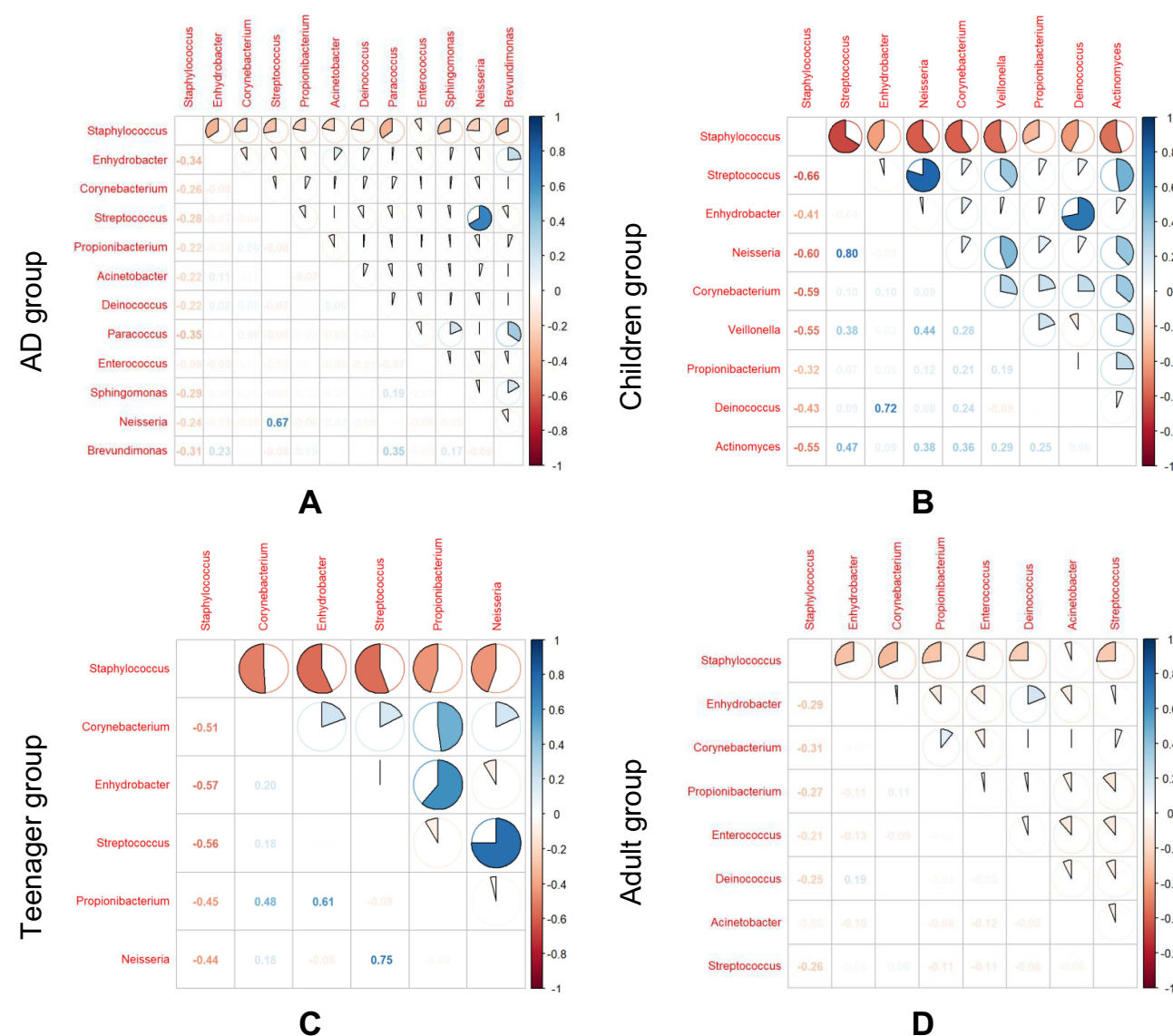


Figure 6 Microbial correlation matrix diagram. Matrix diagram of pairwise Pearson correlations between the bacterial genera with a relative abundance $> 1\%$ in the (A) AD group and healthy group and (B), (C), and (D) each age group for AD patients. Blue represents a positive correlation, red represents a negative correlation, and the darker the color is, the stronger the correlation.

In this study, it was found that changes in the abundance of *Staphylococcus* play an important role in the onset of AD. In samples from AD patients in different age groups and severity groups, the abundance of *Staphylococcus* increased compared to that in the healthy population, showing consistency.

Staphylococcus species are a group of gram-positive cocci that are commonly detected in AD patients and include *Staphylococcus aureus* and *Staphylococcus epidermidis*.¹¹ *Staphylococcus aureus* often colonizes inflammatory skin lesions in AD patients, and its carrier rate may range from 30% to 100%.¹² In the present study, the α -diversity of the bacteria detected in the AD group decreased, and in the analysis of microbial community correlation, *Staphylococcus* was negatively correlated with the other main bacterial genera in all age groups. AD inflammation is considered to be dominated by a single *Staphylococcus aureus* infection,^{13,14} and extensive infection with *Staphylococcus aureus* leads to a decrease in species richness, colony diversity, and evenness. However, the current explanation for this common phenomenon is still through research on the coadaptation of *Staphylococcus aureus* and AD skin,¹⁵ and there have been no reports of *Staphylococcus aureus* directly affecting other bacterial communities, leading to a decrease in species diversity. In this study, the abundance of *Staphylococcus* was positively correlated with the severity of AD and gradually increased as symptoms worsened. Among them, *Staphylococcus aureus* completes adaptation through continuous mutation during the colonization process.¹⁶ Arwa Al Kindi et al reported that *Staphylococcus aureus* is unique to the genus *Staphylococcus*, as it can induce rapid release of constitutive IL-33 from human keratinocytes, independent of the Toll-like receptor pathway.¹⁷ Moreover, *Staphylococcus aureus* can also express stimuli that stimulate mast cell δ -Toxins and damage keratinocyte α -Toxins, phenolic soluble regulatory proteins that stimulate the release of cytokines from keratinocytes, protein A that triggers the inflammatory response of keratinocytes, and superantigens that trigger the expansion of B cells and cytokine release, damage the normal skin barrier, and further promote the progression of atopic dermatitis.^{4,12} The total IgE concentration is positively correlated with the enrichment of *Staphylococcus aureus*.^{18–20} IL-1 β , TNF- α , IL-6 and IL-33 in a model of keratinocyte infection induced by *Staphylococcus aureus* inhibited the expression of fatty acid elongation enzymes (ELOVL3 and ELOVL4), thereby disrupting the skin barrier in AD patients.²¹ Similarly, *Staphylococcus epidermidis* can directly or indirectly affect the skin barrier function of AD patients through various molecular-level interactions, thereby affecting the severity of the disease.^{22–24}

A study on *Staphylococcus* in the skin of AD patients across different age groups showed that the abundance of *Staphylococcus* was relatively higher in the teenage group compared to the control group, although there was no significant difference in the abundance of the *Staphylococcus* genus among the three groups. This may be linked to the high proportion of severe AD cases in the teenage group. Notably, teenagers are highly self-aware, often have minimal contact with doctors, and tend not to adhere fully to their medication plans, sometimes devising their own topical treatments.²⁵ Therefore, it is crucial to enhance disease awareness and education among the adolescent atopic dermatitis population.

In terms of significantly different bacterial genera, *Staphylococcus*, *Brevundimonas*, *Paracoccus*, *Corynebacterium*, and *Veillonella* were identified as significantly different bacteria. Among them, *Staphylococcus* and *Veillonella* were significantly increased in the AD group, while the rest were significantly decreased. *Staphylococcus aureus* is the cause of most bacterial skin infections,^{26,27} and *Staphylococcus epidermidis* is also a common cause of numerous skin infections,²⁸ making it difficult to use *Staphylococcus* as a biomarker to characterize AD. At present, many studies have shown that *Corynebacterium spp.* have significant differences in their AD skin microbiota^{29,30} and that it has a certain effect on maintaining skin homeostasis.³¹ Yoojin Chun et al reported that a greater abundance of *Corynebacterium* in the nasal epithelium is associated with nonallergenicity in pets and decreased expression of inflammatory genes.³² However, there is currently no research on the correlation between *Corynebacterium spp.* and the severity of AD or on the correlation between *Brevundimonas spp.*, *Paracoccus spp.*, *Veillonella spp.*, and AD. Whether these significantly different bacterial communities can be used to characterize the specificity of AD patients still needs further exploration.

Compared to oral probiotics regulating the gut microbiota to improve AD symptoms, direct treatment of the skin surface microbiota is more intuitive and convenient. In traditional treatment, oral and systemic antibiotics are often used to inhibit the growth of opportunistic pathogens such as *Staphylococcus aureus*, but the accompanying drug resistance also exacerbates the difficulty of treatment. *Staphylococcus aureus* can constantly spread within the environment on the surface of the patient's skin¹⁵ and rapidly develop antibiotic resistance, occurring almost as soon as new therapeutic drugs are developed.³³ At present, increasing research is targeting the diversity of the microbiota in the skin of AD patients, and some scholars have started using topical probiotics to improve the skin condition of AD patients.³⁴ Teruaki Nakatsuji et al applied the healthy skin-colonizing

bacterium *Staphylococcus hominis* A9 (ShA9), which can kill *Staphylococcus aureus* on the skin and inhibit the expression of the inflammatory toxin *Staphylococcus aureus*, on AD patients.³⁵ Teruaki Nakatsuji et al applied coagulase-negative *Staphylococcus* (CoNS) to the skin of AD model mice and AD patients and observed a decrease in the colonization of *Staphylococcus aureus*.³⁶ In this study, there was a negative correlation between *Staphylococcus* and various common skin-specific bacteria in the skin microbiota of AD patients in different age groups, indicating a possible inhibitory relationship between the two bacteria. This approach will provide us with ideas to further explore topical drugs containing one or more colonizing bacteria that can act on the skin surface of AD patients, inhibit the growth of *Staphylococcus* by increasing the abundance of colonizing bacteria, and reduce the severity of the disease.

Conclusion

In summary, AD patients and healthy individuals exhibit different microbial characteristics on their skin, which vary with age and severity. Among these bacteria, *Staphylococcus* plays a dominant role in the entire process of AD onset. This study was based on second-generation 16S rRNA sequencing technology, and the classification of microbial communities was limited to only the genus level. We look forward to further research to determine the impact of changes in bacterial species on AD. This study identified significant differences in the skin microbiota between AD patients and healthy individuals, which can provide a basis for the next step in identifying characteristic biomarkers of AD. At the same time, there may be an inhibitory relationship between *Staphylococcus* and most skin-colonizing bacteria, which will provide opportunities for the development of new drugs.

Data Sharing Statement

The sequence dataset has been deposited on the NCBI Sequence Reads Archive (SRA) Database (Accession Number: PRJNA1075284).

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Disclosure

The authors declare no conflicts of interest related to the publication of this work.

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