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ORIGINAL RESEARCH

Multi-Omics Profiling of the 42-Day Infant Gut as a Pilot Predictor of Atopic Dermatitis at One Year: A Birth Cohort Study in China

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Background: Early-life gut microbiota and metabolism are increasingly linked to immune development and atopic diseases. However, predictive microbial and metabolic markers present during the neonatal period for later atopic dermatitis (AD) remain poorly defined. This study aimed to identify early-life gut microbiome and metabolite signatures associated with the development of AD by one year of age.

Methods: We conducted a prospective birth cohort study in Beijing, China, enrolling 18 infants with fecal samples collected at 42 days of age. Infants were followed for one year and classified into AD (n = 6) or non-AD (n = 12) groups. Fecal samples underwent 16S rRNA gene sequencing and untargeted metabolomic profiling. Key microbial taxa, differential metabolites, and functional pathways were identified and integrated via multi-omics correlation analysis.

Results: While overall microbial diversity was similar between groups, *Staphylococcus* was significantly less abundant in the AD group. *Bifidobacterium* and *Lactobacillus* showed strong correlations with lipid- and amino acid-related metabolites, including linoleic acid and N2-acetyl-L-ornithine. AD infants exhibited reduced levels of linoleic acid and choline phosphate. KEGG analysis revealed enrichment in linoleic acid metabolism, sphingolipid signaling, and AGE-RAGE signaling pathways. Integrated network analysis identified microbial–metabolite modules potentially involved in immune and barrier regulation.

Conclusion: Multi-omics profiling of the infant gut at 42 days identified microbial and metabolic features associated with later AD development. These findings support the gut–skin axis and suggest potential early-life biomarkers for predicting AD risk and informing targeted prevention strategies.

Keywords: gut, atopic dermatitis, pediatric, metabolomics, intestinal, predictors, risk

Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin condition that typically develops in early childhood. It is characterized by red, itchy, and inflamed patches of skin, often appearing on the scalp, face, neck, and body area of skin around joints that touch when the joint bends.[1,2] AD tends to follow a relapsing-remitting chronic course, meaning symptoms can improve temporarily but frequently return, it proves to be a global health burden with a higher incidence rate.[3,4] In infants, AD is positively associated with an increased risk of developing other allergic conditions, that begin

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with AD and food allergies during infancy, and gradually evolve into allergic asthma and allergic rhinitis as the child grows later in life.[5] While the exact cause remains unclear, AD is believed to result from a combination and the complex interaction of genetic, environmental, and immune factors, leading to a weakened skin barrier and increased sensitivity to irritants, allergens, and microbes.[1,2,6] Due to the involvement of multiple factors and the complex interactions of biological processes, AD exhibits high heterogeneity, posing significant challenges in predicting its onset, diagnosing the condition, monitoring its progression, and managing treatment in clinical practice.[7]

Recent studies have emphasized the crucial role of the gut-skin axis in the pathogenesis of AD, suggesting that gut microbiota and their metabolites may significantly influence skin inflammation and immune responses.[8–11]Imbalances in gut microbial composition, also known as dysbiosis, are often observed in individuals with AD and may contribute to the disruption of immune homeostasis, which further highlights the potential of gut microbiota as both a biomarker for early detection and a target for therapeutic interventions.[12–14] While early-life gut microbiome dynamics and their impact on childhood health have been explored in studies spanning from one month to three years of age, data remain limited during the very early postnatal period (~1 month), when the microbiome may exist in a transitional state.[15–18] Few studies have concurrently analyzed early gut microbial-metabolite axes (eg, *Roseburia*-butyrate) alongside skin-barrier parameters (eg, FLG status, *Staphylococcus aureus* colonization) for synergistic prediction. Mechanistic links between transient gut communities and later cutaneous inflammation remain speculative. Given the need to better characterize microbial profiles at this early developmental stage, our study combines longitudinal sampling with multi-omics profiling to capture the maximal predictive signal at early 42 day of birth, identifying candidate microbial-metabolite pairs that may interact with known skin barrier pathways during this early developmental period. Given the dynamic nature of the infant microbiome, early interventions that promote healthy gut colonization may offer an opportunity to reduce AD risk and improve long-term health outcomes.

Despite recent advances, substantial gaps remain in understanding the microbial and metabolic signatures associated with AD onset and progression. Identifying specific microbial taxa or metabolites that precede clinical symptoms could provide predictive models for earlier intervention and improve clinical decision-making. Furthermore, the dynamic nature of the infant microbiome adds complexity to determining consistent biomarkers, emphasizing the need for longitudinal studies that capture microbial and metabolic changes over time. In this context, our study leverages a birth cohort with longitudinal follow-up to investigate the relationship between early microbial and metabolic profiles and the development of AD. By employing 16S rRNA sequencing for gut microbiota profiling and comprehensive metabolomic analysis, we aim to identify biomarkers associated with AD risk.

Materials and Methods

Study Design and Participants

The study complies with the Helsinki Declaration. This prospective birth cohort study was conducted in Beijing, China. Eighteen infants were enrolled and followed from birth to 1 year of age. At 42 days after birth, fecal samples were collected for microbiome and metabolomic profiling. Infants were then categorized into two groups based on whether they developed atopic dermatitis (AD) by 1 year: AD group (n = 6) and non-AD group (n = 12) (Figure 1). AD was diagnosed according to the Hanifin and Rajka (H&R) criteria.[19] The non-AD group in our study consisted of healthy infants without any clinical features or diagnoses of AD at the time of follow-up. The infants in this group did not meet the diagnostic criteria for AD, as outlined by the H&R criteria. Additionally, infants with any other underlying diseases or conditions, such as eczema that did not fulfill the AD diagnostic criteria, were excluded. Furthermore, to ensure that the non-AD group represented a healthy population, we excluded infants whose mothers had conditions such as hypertension, preterm birth, infections, or recent antibiotic use. The mothers' medical history was also considered to avoid confounding factors. Demographic and clinical data were collected, including sex, birth weight, gestational age, delivery mode, feeding type, and family history of allergy. Ethical approval was obtained from the Capital Medical University Daxing Teaching Hospital Ethics Committee (Approval No. 20190614LLKYLX-3-5), and informed consent was obtained from both parents.

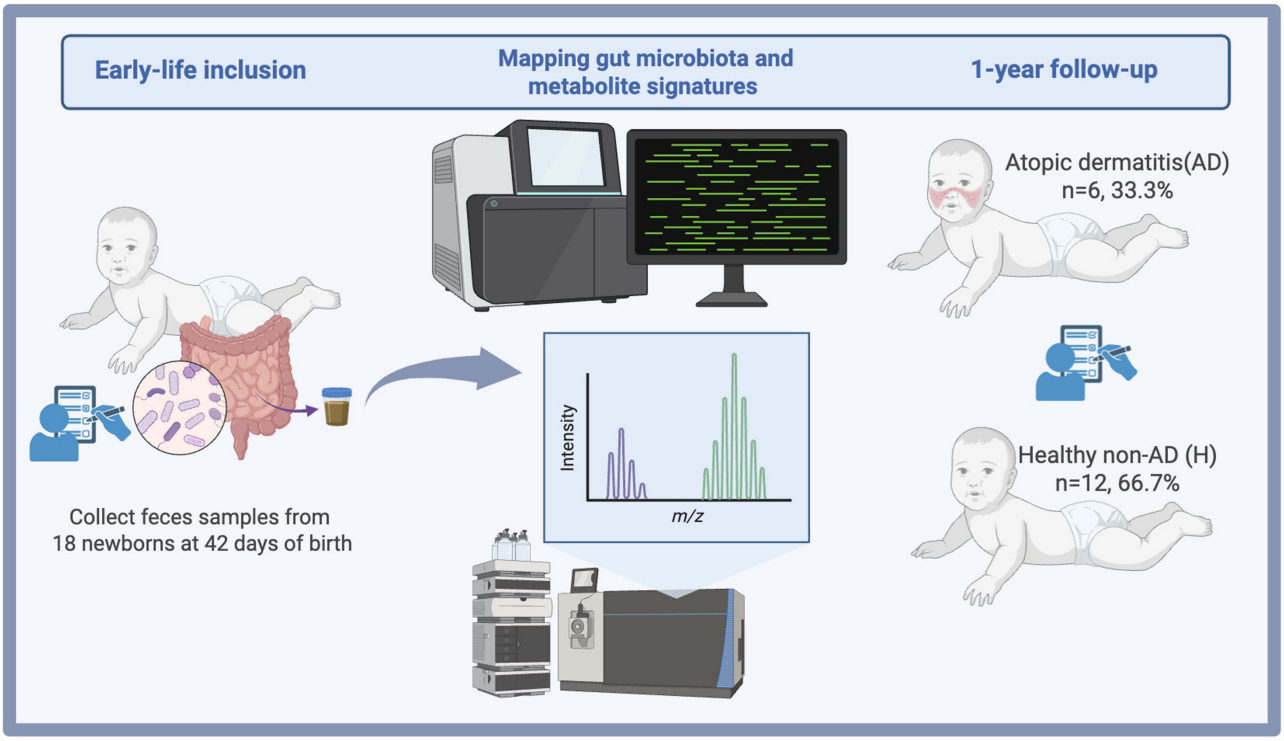

Figure 1 The flowchart of the study. The study enrolled 18 newborns at 42 days of birth, collecting fecal samples to analyze gut microbiota and metabolite signatures. The microbiota was profiled using 16s rRNA sequencing while metabolomics analysis was performed using a Liquid Chromatograph Mass Spectrometer (LC-MS) to explore. A one-year follow-up was conducted to assess health outcomes, with 6 infants (33.3%) developing atopic dermatitis (AD) and 12 infants (66.7%) remaining healthy in the non-AD (H) group.

16S rRNA Gene Sequencing and Microbiome Analysis

Fecal samples were collected at 42 days of age and stored at −80°C within 2 hours. Fecal samples were centrifuged at 13,000 × g for 5 minutes. Bacterial genomic DNA was extracted from the precipitation using the T Guide S96 Magnetic Soil/Stool DNA Kit (Tiangen, Beijing, China), and DNA concentrations were measured using a Qubit 4.0 Fluorometer. The V3–V4 region of the 16S rRNA gene was amplified using primers 338F and 806R, followed by sequencing on the Illumina NovaSeq 6000 platform. Raw reads were quality filtered with Trimmomatic, primer sequences removed with Cutadapt, and paired-end reads merged using USEARCH.[20,21] Chimeras were removed with UCHIME, and OTUs were clustered at 97% similarity. OTUs with relative abundance <0.005% were excluded. Taxonomy was assigned using QIIME2 and the SILVA 132 database.[22,23] Alpha diversity (ACE, Coverage, SOBS) and beta diversity (PCoA, NMDS) were calculated using QIIME2 and R. Group differences were tested using the Wilcoxon rank-sum test. Differential taxa were identified by LEfSe (LDA > 4.0).[24] Redundancy analysis (RDA) was performed using the vegan package in R. For metabolomics analysis, internal standards were used for normalization or quality control. Regarding batch effects, samples were collected at different times but tested in the same batch. To control for batch effects, all samples were processed using the same reagent kits, instruments, and sequencing batches, and were randomized during extraction and library preparation. Normalization for differences in sequencing depth was achieved by rarefaction prior to diversity analysis.

Untargeted Metabolomic Profiling and Pathway Analysis

Fecal metabolites were extracted using 80% pre-chilled methanol and analyzed using an Orbitrap Q Exactive UHPLC-MS/MS system (Thermo Fisher Scientific) on a Thermo Syncronis C18 column. Data acquisition was conducted in both positive and negative ion modes. Raw data were processed using TraceFinder 3.2 for peak detection, alignment, and quantification. Metabolites were annotated using the mzCloud, HMDB, KEGG, and LIPIDMaps databases. Differential metabolites were selected using VIP > 1, $p < 0.05$. PCA, PLS-DA, volcano plots, and heatmaps were generated using

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metaX and R packages. KEGG pathway enrichment was performed for differential metabolites using hypergeometric analysis (threshold: $x/n > y/N$, $p < 0.05$).

Integrated Microbiome–Metabolome Analysis

Spearman correlation was used to assess relationships between the relative abundance of bacterial genera and differential metabolite intensities. Correlations with $|r| > 0.3$ and $p < 0.05$ were visualized in heatmaps. A subset of strong correlations ($|r| > 0.6$) was selected for KEGG enrichment. A microbe–metabolite interaction network was constructed using Cytoscape.

Statistical Analysis

Continuous variables (eg, birth weight, gestational age) were compared using Student's *t*-test or Wilcoxon rank-sum test, and categorical variables (eg, gender, delivery mode) using Chi-square or Fisher's exact test. Microbiome and metabolomic group differences were analyzed using non-parametric tests. Correlation analyses were performed using Spearman or Pearson methods. All analyses were conducted in R (v3.4.3) or Python (v2.7.6), with $p < 0.05$ considered statistically significant. We used the Benjamini-Hochberg FDR correction for multiple comparisons across all statistical analyses.

Results

Participant Characteristics

The study cohort included 18 participants, comprising 13 females (72.2%) and 5 males (27.8%). The average birth weight was 3.26 ± 0.44 kg, and the mean gestational age was 38.6 ± 1.1 weeks. Half of the participants (9, 50.0%) were delivered vaginally, while the remaining half were delivered via cesarean section. Breastfeeding was the predominant feeding mode, reported in 12 participants (66.7%), with 6 participants (33.3%) receiving mixed feeding. A family history of allergic conditions was noted in 6 participants (33.3%). At the one-year follow-up, 6 participants (33.3%) were diagnosed with atopic dermatitis (AD), with a mean Eczema Area and Severity Index (EASI) score of 4.3 ± 1.3, indicating mild to moderate disease severity. The remaining 12 participants (66.7%) did not exhibit symptoms of AD. Among the 18 participants, 3 participants (16.7%) has a history of AD, 2 participants (11.1%) were from rural, 6 participants (33.3%) were reported gestational diabetes, 2 participants (11.1%) were macrosomia, and none of them has maternal obesity. None of the baby was preterm. Demographic and clinical characteristics of the participants are detailed in Table 1.

Table 1 Demographic and Clinical Characteristics of Study Participants

	Total (n = 18)	**AD Group (n = 6)**	**Non-AD Group (n = 12)**	***P*-Value**
Gender				0.62
Male	5 (27.8%)	1 (16.7%)	4 (33.3%)	
Female	13 (72.2%)	5 (84.3%)	8 (66.7%)	
Birth Weight (kg)	3.26 ± 0.44	3.18 ± 0.25	3.30 ± 0.51	0.60
Gestational Age (weeks)	38.6 ± 1.1	39.2 ± 0.75	38.3 ± 1.2	0.13
Delivery Mode				0.62
Vaginal Delivery	9 (50.0%)	4 (66.7%)	5 (41.7%)	
Cesarean Section	9 (50.0%)	2 (33.3%)	7 (58.3%)	

(*Continued*)

Table 1 (Continued).

	Total (n = 18)	AD Group (n = 6)	Non-AD Group (n = 12)	*P*-Value
Feeding Mode				1.0
Breastfeeding	12 (66.7%)	4 (66.7%)	8 (66.7%)	
Mixed Feeding	6 (33.3.9%)	2 (33.3%)	4 (33.3%)	
Family History of Allergy				0.6
Yes	6 (33.3%)	1 (16.7%)	5 (41.7%)	
No	12 (66.7%)	5 (84.3%)	7 (58.3%)	
EASI in AD Group		4.3 ± 1.3		n/a
History of AD	3 (16.7%)	1 (16.7%)	2 (16.7%)	0.89
Preterm	None			
Rural	2 (11.1%)	1 (16.7%)	1 (8.3%)	0.6
Macrosomia of the Baby	2 (11.1%)	0 (0%)	2 (16.7%)	0.53
Gestational Diabetes	6 (33.3%)	4 (66.7%)	2 (16.7%)	0.11
Obesity of the Mother	None			

Notes: Continuous variables (eg, birth weight, gestational age, sample age) are reported as mean ± SD, while categorical data (eg, gender, delivery mode) are shown as numbers and percentages. EASI, Eczema area, and severity index.

Gut Microbiota Composition and Diversity

Analysis of fecal 16S rRNA sequencing data at 42 days of age revealed no significant differences in alpha diversity indices (ACE, coverage, SOBS) between the AD and non-AD groups (Figure 2B), indicating comparable species richness and evenness. Beta diversity analysis using NMDS also demonstrated no distinct clustering patterns between groups (Figure 2C). However, relative abundance analysis (Figure 2A) revealed notable compositional differences. Wilcoxon rank-sum test identified several genera with differential abundance, with *Staphylococcus* significantly more abundant in the non-AD group ($p = 0.03265$) (Figure 3).

Fecal Metabolomic Profiling Reveals Distinct Metabolic Signatures

Untargeted LC-MS-based metabolomics profiling of fecal samples revealed distinct metabolic patterns between the AD and non-AD groups. PCA analysis showed partial separation between groups (Figure 4A). Volcano plot analysis identified multiple significantly altered metabolites, with linoleic acid and choline phosphate being notably downregulated in the AD group (Figure 4B). A heatmap of differential metabolites demonstrated clear clustering between groups (Figure 4C). KEGG pathway enrichment of these differential metabolites (Figure 4D) indicated significant involvement of pathways including linoleic acid metabolism, sphingolipid signaling, and AGE-RAGE signaling.

Microbiota–Metabolite Associations and Functional Implications

Spearman correlation analysis between bacterial genera and differential metabolites using the top 20 core differential fecal metabolites and the top 20 most abundant bacterial genera between the AD and H group revealed strong associations (Figure 5A). Notably, *Staphylococcus*, *Bifidobacterium*, and *Corynebacterium* were significantly correlated with lipid- and amino acid-related metabolites. Zoomed-in views of high-correlation pairs ($|r| > 0.6$) highlighted representative relationships (Figure 5B). KEGG pathway enrichment of core correlated metabolite showed enrichment in glycerophospholipid metabolism, linoleic acid metabolism, and AGE-RAGE signaling (Figure 5C).

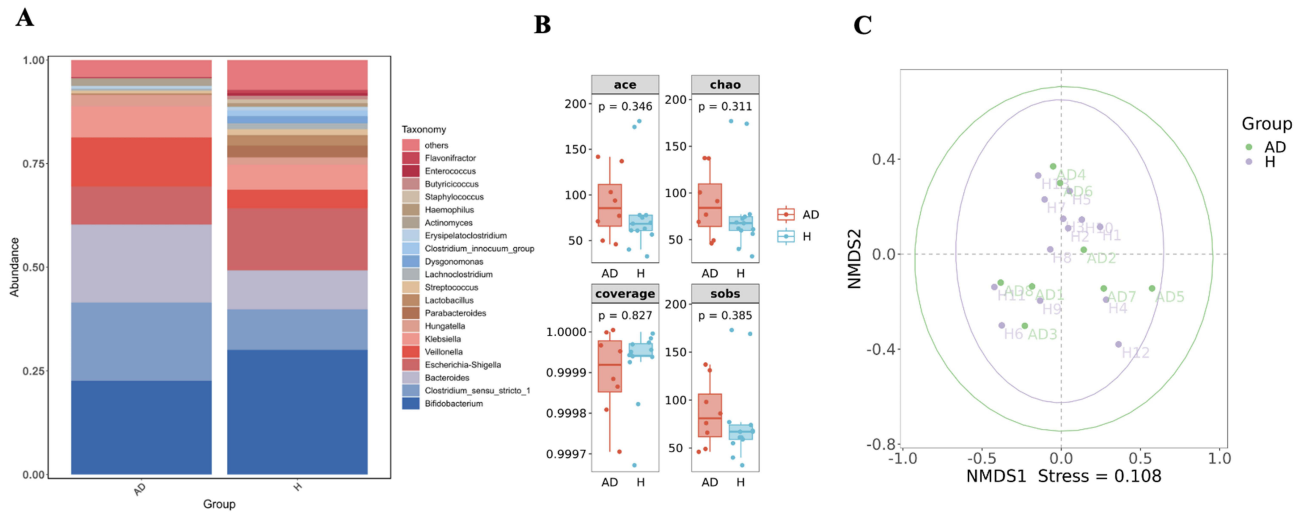

Figure 2 Microbiota Abundance and Diversity Analysis. (**A**) Relative Abundance of Gut Microbiota: Stacked bar plots showing the composition of microbial taxa in atopic dermatitis (AD) and non-AD (H) groups. Each color represents a different genus, with variations in their abundance between the two groups. (**B**) Alpha Diversity Analysis: Boxplots for diversity indices including ACE, coverage, and SOBS. The p-values indicate no statistically significant differences between the AD and non-AD groups, suggesting similar microbial richness and evenness. (**C**) Beta Diversity Analysis via Non-metric multidimensional scaling (NMDS): NMDS plot based on microbial community composition, with stress value = 0.108. Each point represents a sample, color-coded by group (AD vs H), and ellipses indicate group dispersion. No distinct clustering pattern is observed between the two groups, indicating comparable microbial community structures.

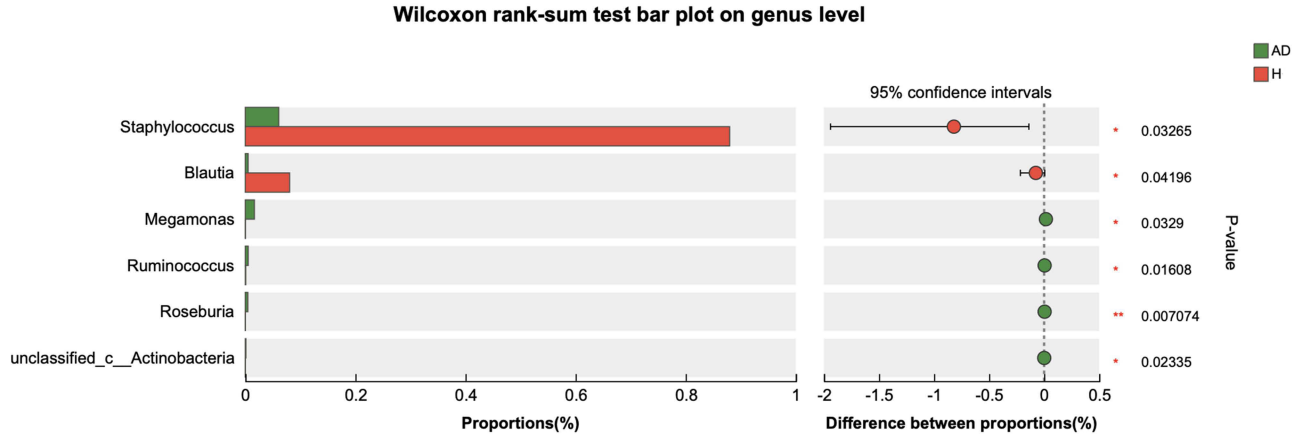

Figure 3 Wilcoxon Rank-Sum Test Bar Plot on Genus Level Comparing Gut Microbiota between AD and H Groups. *Staphylococcus* is significantly more abundant in the healthy control (H) group compared to the atopic dermatitis (AD) group (p = 0.03265). *P < 0.05, **P < 0.01. Other genera, including *Blautia* and *Ruminococcus*, also display notable differences between the groups, with varying levels of abundance, but *Staphylococcus* stands out as the most significant finding. Full taxonomic classifications are as follows: *Staphylococcus* (*Phylum Bacillota*; *Class Bacilli*; *Order Caryophanales*; *Family Staphylococcaceae*; *Genus Staphylococcus*); *Blautia* (*Phylum Bacillota*; *Class Clostridia*; *Order Eubacteriales*; *Family Lachnospiraceae*; *Genus Blautia*); *Megamonas* (*Phylum Pseudomonadota*; *Class Gammaproteobacteria*; *Order Aeromonadales*; *Family Succinivibrionaceae; Genus Megamonas*); *Ruminococcus* (*Phylum Bacillota*; *Class Clostridia*; *Order Eubacteriales*; *Family Ruminococcaceae*; *Genus Ruminococcus*); *Roseburia* (*Phylum Bacillota*; *Class Clostridia*; *Order Eubacteriales*; *Family Lachnospiraceae*; *Genus Roseburia*); *Unclassified Actinobacteria* (*Phylum Actinobacteria*; *Class unclassified*; *Order unclassified*; *Family unclassified*; *Genus unclassified*).

Microbe–Metabolite Interaction Network

A correlation network was constructed to visualize significant relationships between microbial genera and differential fecal metabolites (Figure 6). Microbial nodes are shown in green, and metabolite nodes in orange. Edges represent positive or negative correlations between taxa and metabolites. Key genera such as *Staphylococcus*, *Bifidobacterium,* and *Lactobacillus* showed strong connections with metabolites including linoleic acid, N2-acetyl-L-ornithine, and palmitoyl-carnitine. The network revealed distinct microbe–metabolite interaction modules present at 42 days of age.

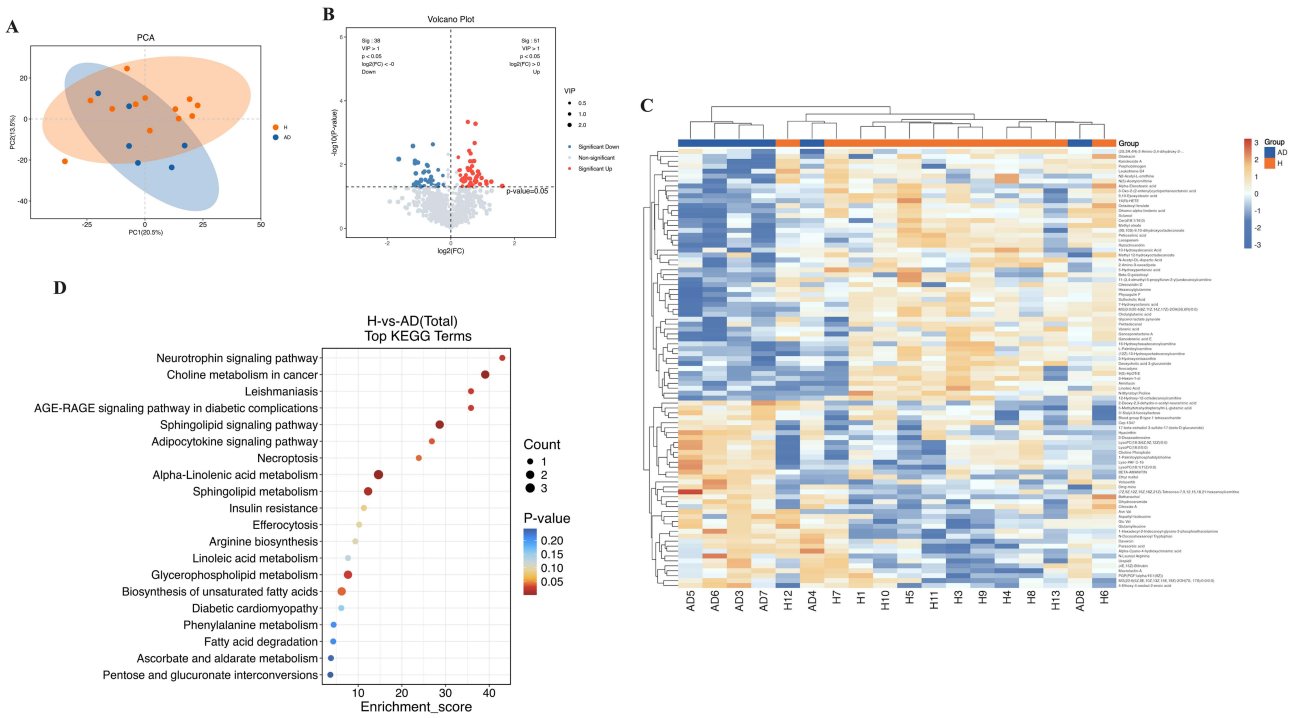

Figure 4 Differential Metabolite Profiles and Pathway Enrichment between AD and non-AD Groups. (**A**) Principal Component Analysis (PCA): PCA plot showing the distribution of metabolomic profiles in fecal samples at 42 days of age. Each point represents one sample, with orange and blue indicating the AD and non-AD groups, respectively. The partial separation suggests distinct metabolic patterns between groups. (**B**) Volcano Plot: Differential metabolite analysis between the AD and non-AD groups. Metabolites with |log2FC| > 0.2, VIP > 1, and p < 0.05 were considered significant. Red dots represent upregulated metabolites in AD, blue dots represent downregulated metabolites, and gray dots are non-significant. (**C**) Heatmap of Differential Metabolites: Z-score-normalized intensity values of differential metabolites across all samples. Hierarchical clustering reveals distinct patterns in metabolite abundance between AD and non-AD individuals. (**D**) KEGG Pathway Enrichment: Bubble plot displaying the enriched metabolic pathways among the differential metabolites. Bubble size corresponds to the number of mapped metabolites, while color represents the p-value for pathway enrichment.

Discussion

In this prospective birth cohort study, we characterized gut microbiota and metabolite profiles at 42 days of age in relation to the later development of AD at one year. Through a multi-omics approach integrating 16S rRNA gene sequencing and untargeted metabolomics, we identified distinct microbial and metabolic features that may serve as early-life predictors of AD. Our findings provide additional support for the gut–skin axis hypothesis and highlight potential targets for early intervention. Although alpha and beta diversity of the gut microbiota were not significantly different between infants who developed AD and those who did not, taxonomic profiling revealed differences at the genus level. *Staphylococcus* was found to be significantly more abundant in the non-AD group. While *Staphylococcus aureus* (*S. aureus*) is a well-established pathogen in active AD lesions, early colonization by non-pathogenic *Staphylococcus* species may play a beneficial role in immune maturation.[25,26] This is supported by evidence that early microbial exposure and colonization are critical for the development of immune tolerance.[27,28] Interestingly, although the pathogenic role of *S. aureus* on the skin in driving AD has been well documented, its function in the gut remains poorly understood.[29,30] In our study, *Staphylococcus* was significantly less abundant in the feces of infants who developed AD. While we did not achieve species-level resolution, this observation raises the possibility that gut-colonizing *Staphylococcus*, including potentially *S. aureus*, might have distinct roles in mucosal immune education during early life. This contrasts with its pro-inflammatory role on the skin and suggests that its function may be compartment-specific. *Staphylococcus* may act differently in the gut vs skin because the abundant skin commensal *Staphylococcus epidermidis* (*S. epidermidis*) has been reported to contribute to skin barrier integrity. *S. epidermidis* secretes a sphingomyelinase that acquires essential nutrients for the bacteria and assists the host in producing ceramides, the main constituent of the epithelial barrier that averts skin dehydration and aging.[31,32] Further studies using strain-level or metagenomic approaches will be essential to clarify the identity and role of gut *Staphylococcus* in allergic disease risk. The reduced

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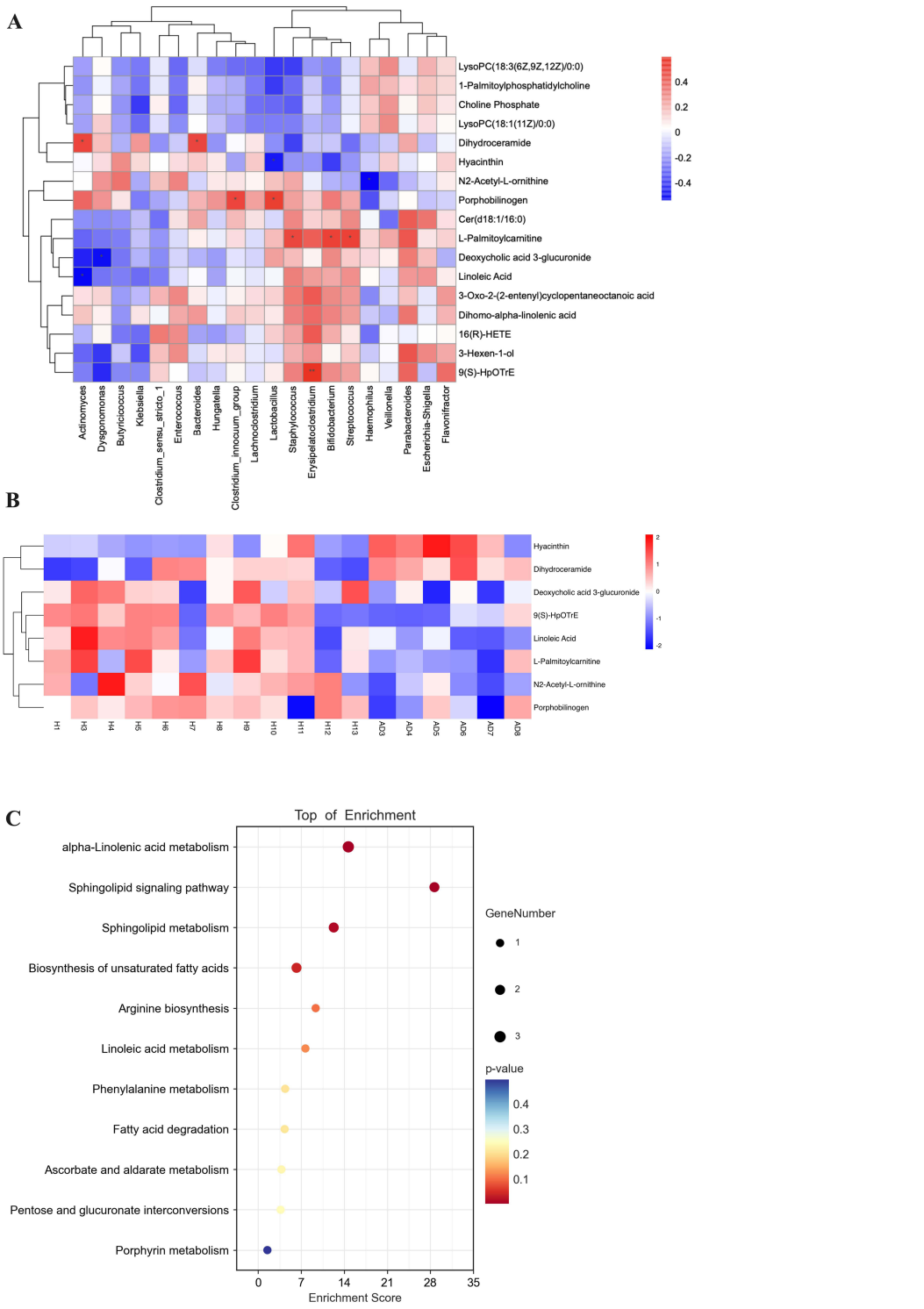

Figure 5 Correlation and Functional Enrichment Analysis of Gut Microbiota–Metabolite Interactions. (**A**) Heatmap of Spearman Correlations between Core Differential Metabolites and Dominant Bacterial Genera. Spearman correlation heatmap displaying relationships between the top 20 core differential fecal metabolites and the top 20 most abundant bacterial genera between the AD and H group. Red indicates positive correlations; blue indicates negative correlations. Several genera, such as *Bifidobacterium*, *Staphylococcus*, and *Corynebacterium*, were significantly associated with lipid- and amino acid-related metabolites. *P < 0.05, **P < 0.01. (**B**) Zoomed-in Heatmap of Strong Metabolite–Microbiota Associations. Enlarged view highlighting representative metabolite–bacteria correlations with strong coefficients (|r| > 0.6). These featured associations underscore candidate microbial drivers of metabolic signatures potentially linked to AD development. (**C**) KEGG Pathway Enrichment of Correlated Core Differential Metabolites. KEGG pathway enrichment analysis of the strongly correlated metabolites identified. The bubble plot illustrates enriched biological pathways, with bubble size indicating the number of matched metabolites and color denoting enrichment significance. Enriched pathways included linoleic acid metabolism, glycerophospholipid metabolism, and AGE-RAGE signaling in diabetic complications, which may mediate early immune and epithelial dysfunction in infants at risk of AD.

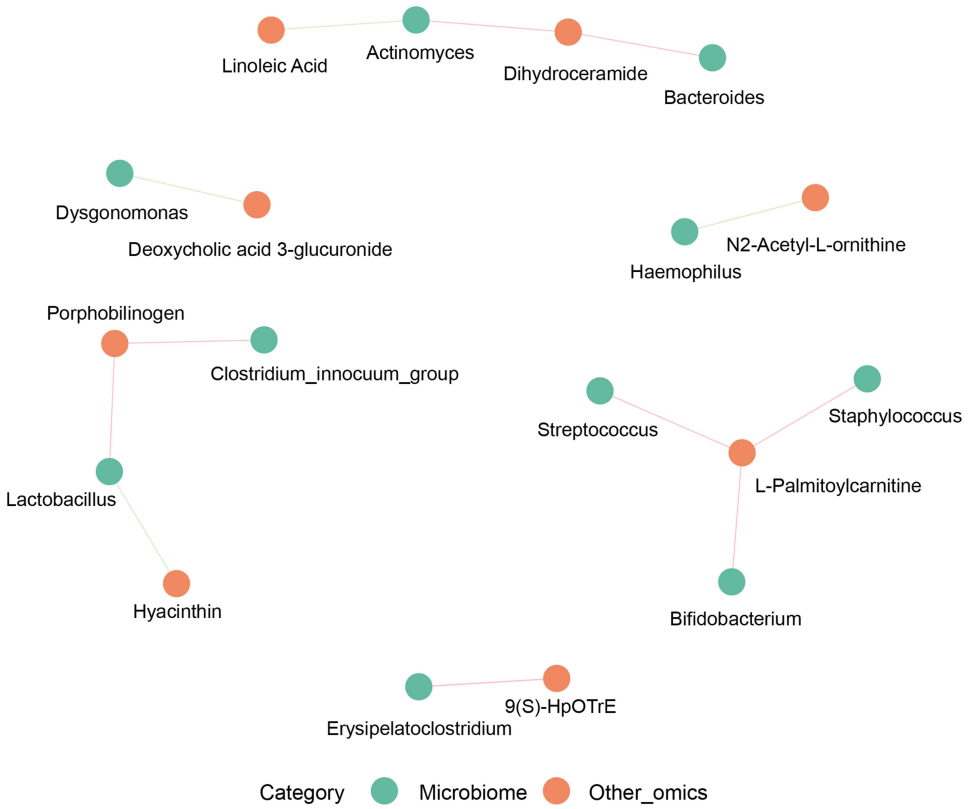

Figure 6 Correlation Network of Gut Microbiota and Differential Fecal Metabolites. Network plot illustrating significant Spearman correlations ($p < 0.05$) between dominant bacterial genera and key differential metabolites identified at 42 days of age. Microbial nodes are shown in green, and metabolite nodes in Orange. Edges represent positive or negative correlations between taxa and metabolites. Highly connected microbial nodes, including *Staphylococcus*, *Bifidobacterium*, and *Lactobacillus*, show interactions with metabolites involved in lipid metabolism (eg, linoleic acid, palmitoylcarnitine) and amino acid metabolism (eg, N2-Acetyl-L-ornithine), indicating possible microbiota-driven modulation of metabolic pathways relevant to AD development.

abundance of *Staphylococcus* in the AD group may reflect impaired microbial succession or environmental factors that limit exposure to commensal skin or maternal microbes.

Additionally, *Bifidobacterium* and *Lactobacillus* were found to be correlated with key fecal metabolites, reinforcing their role in immune development. These genera are widely recognized as pioneer taxa in the infant gut and have been implicated in promoting mucosal immune tolerance, inducing regulatory T cells, and modulating inflammation via their metabolic outputs.[27,33–35] Their observed association with lipid- and amino acid-related metabolites in our study, such as palmitoylcarnitine and N2-acetyl-L-ornithine, suggests a functional link between microbial metabolic output and host immunometabolism pathways. Palmitoylcarnitine, a representative long-chain acylcarnitine, plays a role in mitochondrial β-oxidation, and previous studies have reported lower levels of such acylcarnitines in individuals with food allergy and atopic dermatitis, implying impaired fatty acid metabolism.[36] Our findings add to this by showing a potential microbial influence, especially from *Bifidobacterium* on acylcarnitine levels, suggesting that gut microbes may modulate lipid oxidation pathways critical to immune regulation. These interactions likely contribute to shaping the early-life immune landscape and may influence susceptibility to allergic inflammation. Given that *Bifidobacterium* and *Lactobacillus* are commonly used as probiotics, their identification in this network also highlights their potential as microbiota-based targets for early intervention in infants at risk of atopic dermatitis. Our untargeted metabolomic analysis revealed that multiple metabolites involved in lipid metabolism, amino acid metabolism, and immune signaling were significantly altered in infants who developed AD. Notably, linoleic acid and choline phosphate were significantly reduced in the AD group. Linoleic acid is a critical fatty acid involved in skin barrier integrity and is often reduced in both lesional and non-lesional AD skin.[37] Choline derivatives are known to influence phospholipid metabolism, membrane stability, and inflammatory responses.[38] These findings suggest that key metabolic pathways involved in epithelial barrier formation

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and immune modulation may be disrupted before the clinical onset of AD. Our KEGG pathway enrichment analysis further supported this by revealing significant enrichment in linoleic acid metabolism, sphingolipid signaling, and AGE-RAGE signaling pathways, biological processes known to mediate oxidative stress responses, skin inflammation, and innate immune activation. Together, these data imply that dysregulated immunometabolism in early infancy may create a pro-inflammatory and barrier-impaired state, increasing vulnerability to atopic disease development. The integrated microbiome–metabolome analysis further elucidated potential microbial drivers of metabolic changes. By correlating bacterial genera with significantly altered metabolites, we identified several microbial–metabolic modules that may underpin early immune or epithelial dysfunction. For example, *Bifidobacterium* showed strong positive correlations with lipid-related metabolites such as palmitoylcarnitine, while *Lactobacillus* and *Corynebacterium* were associated with amino acid derivatives such as N2-acetyl-L-ornithine. These relationships suggest the functional roles of gut microbes in modulating metabolite pools relevant to AD pathogenesis. The constructed network highlighted several hub genera, supporting the concept that early microbial colonization patterns shape host metabolic output and immune development.

This study has several limitations. First, the sample size was small, and the number of participants in the AD and non-AD groups was unbalanced, which inevitably limits the statistical power and generalizability of the findings. While our study was designed as a pilot, future validation in larger and independent cohorts is needed. Second, although we collected detailed perinatal and demographic information—including gestational age, delivery mode, feeding type, family history of allergy, macrosomia, and gestational diabetes—the sample size was not sufficient to adjust for potential confounding factors in a robust way. These variables are known to influence the infant gut microbiome and may have affected the results. Third, due to ethical considerations, no blood samples or skin biomarkers (such as IgE levels or FLG mutation status) were collected from infants at baseline. As a result, we were unable to explore direct links between gut features and systemic immunological parameters. Fourth, the use of 16S rRNA sequencing limited our ability to resolve bacterial identities at the species or strain level. Fifth, although we selected the 42-day time point based on its relevance to early immune development, the infant gut microbiome is still highly dynamic at this stage, and a single time point may not capture the full picture of microbial succession or metabolite shifts over time. Despite these limitations, our findings provide a useful foundation for understanding early-life gut features associated with AD development and suggest directions for future mechanistic and longitudinal studies.

Nevertheless, our study provides meaningful insights given its setting in China, where cohort-based, early-life gut microbiome research related to AD remains limited. By integrating microbiome and metabolomic data from a prospective Chinese birth cohort, our findings contribute region-specific evidence to the growing body of literature on early-life predictors of AD, and may help inform preventive strategies that are culturally and geographically relevant.

Conclusion

In summary, using integrated microbiome and metabolome profiling at 42 days of age, we identified specific bacterial genera and fecal metabolites—particularly those involved in lipid metabolism and immune signaling—that may serve as early indicators of AD risk, suggesting that distinct gut microbial and metabolic signatures are already present in early infancy among children who later develop atopic dermatitis. The small cohort limited statistical power and generalizability, and external validation in larger, independent cohorts is needed in the future study. Despite these limitations, these findings reinforce the importance of the gut–skin axis in early immune development and provide a pilot foundation for future predictive and preventive strategies. Early-life gut profiling holds promise as a non-invasive tool to identify infants at risk for allergic diseases and to inform microbiota-targeted interventions during critical windows of immune programming.

Ethical Approval Statement

The study was approved by the ethical committee of Capital Medical University Daxing Teaching Hospital, Beijing, China (No.20190614LLKYLX-3-5).

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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