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Original Communication

Discriminative Gut Microbial Signatures in Hyperuricemia and Overweight Populations Revealed by Metagenomic Sequencing

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Abstract

Background: This cross-sectional study aimed to investigate the relationships between gut microbiota compositional alterations and chronic metabolic disorders by analyzing taxonomic diversity, community structure, and species-level differences in individuals with hyperuricemia (HUA) and a history of being overweight. Our findings offer novel insights into microbiota-targeted therapeutic strategies for managing metabolic diseases. A total of 144 participants were recruited and divided into three diagnostic categories: healthy controls (HL, n = 29), hyperuricemia group (HU, n = 24), and overweight (OW, n = 91). **Methods**: Comprehensive phenotypic profiles and metagenomes were analyzed for fecal samples from the three groups. **Results**: Significant differences were observed in psychological states and microbial ecology between the metabolic disorder groups (HU and OW) and the control group (HL) ($p < 0.05$). Both the overweight individuals and those with HUA presented significant changes in gut microbial composition, with reduced α-diversity indices (Shannon index: HU vs HL Mann–Whitney U = 306; $p = 0.462$; OW vs HL Mann–Whitney U = 1008; $p = 0.040$; richness index: HU vs HL Mann–Whitney U = 307; $p = 0.469$; OW vs HL Mann–Whitney U = 1072; $p = 0.092$) compared to healthy individuals. Moreover, analysis of the linear discriminant analysis effect size (LEfSe) identified four discriminatory species in the HU group (*Alistipes putredinis*, *Mediterraneibacter faecis*, *Streptococcus oralis*, and *Gemella sanguinis*), and five in the OW group (*Pantoea endophytica*, *Pantoea vagans*, *Phocaeicola coprophilus*, *Ruminococcus SGB4421*, and *Klebsiella oxytoca*), representing potential biomarkers for the progression of chronic metabolic diseases. **Conclusion**: This study elucidates the characteristics of overweight individuals and those with HUA in terms of phenotypic features and gut microbiota, providing a theoretical reference for gut microbiota-targeted therapies and lifestyle interventions in chronic metabolic diseases.

Keywords: overweight; hyperuricemia; metagenomics; gastrointestinal microbiome; risk factors; body mass index

1. Introduction

The global epidemic of metabolic disorders, particularly hyperuricemia (HUA) and overweight/obesity (OB), presents escalating public health challenges. Recent epidemiological data reveal alarming trajectories, with overweight prevalence projected to affect over 4 billion adults by 2035 and HUA rates reaching 15% in urban Chinese populations [1,2]. These conditions significantly elevate risks for cardiorenal complications, neurodegenerative disorders, and musculoskeletal pathologies [3,4]. The confluence of genetic predisposition, obesogenic diets, sedentary lifestyles, and circadian disruption creates a perfect storm for metabolic dysregulation.

From a pathogenesis perspective, HUA is a metabolic disorder resulting from disturbed purine metabolism, and an excess production or impaired excretion of uric acid (UA) might be the cause of its development. Most significantly, beyond the purine metabolism, recent findings have indicated that excessive dietary fructose is a potent inducer of hyperuricemia. The characteristic fructose metabolism leads to Adenosine Triphosphate depletion, Adenosine Monophosphate deaminase activation, and hence increased UA production regardless of purine intake [5]. The development of an overweight status relies on the abnormal regulation of energy metabolism. It is determined by an interplay of factors, including genetic predisposition, dietary intake patterns, activity routines [6], and social environment. It is noteworthy that specific similarities in risk factors exist for both metabolic disorders. An unbalanced dietary regimen (e.g., high-purine diet, excessive fructose consumption, excessive alcohol intake, and overconsump-

tion of high-calorie foods) can exacerbate metabolic disturbances through different mechanisms [7,8]. More ominously, environmental changes brought about by socioeconomic development, including Westernization of food composition [9] and physical inactivity, are driving OB-linked conditions to a high-incidence phase. Many complications (e.g., hypertension [10], atherosclerosis, and non-alcoholic fatty liver disease [11]) have become leading public health concerns. Notably, hyperuricemia and metabolic syndrome (MetS) have an intimate bidirectional relationship. Higher serum UA levels have strong associations with the development of MetS components, including hypertension, insulin resistance, and dyslipidemia, in a vicious cycle that accelerates cardiometabolic risk [5].

Recent studies have unveiled the crucial role of the gut microbiota in metabolic regulation [12,13]. The gut microbiota is closely associated with various human health indicators, including blood glucose levels [14], blood lipid levels [15], and inflammatory factors [16]. It plays a significant role in modulating diseases both within and outside the gut, particularly in OB [17], metabolic syndrome [18], and cardiovascular diseases [19]. In the context of HUA, the intestine is responsible for 30% of UA excretion. Disruption of gut microbiota structure can augment systemic inflammatory responses and UA metabolic derangements by regulating intestinal uricase function and increasing intestinal barrier permeability [20].

Furthermore, high-fructose diets have also been found to adversely alter gut microbiota composition and increase intestinal permeability, which in turn could further increase systemic inflammation and cause UA metabolic disorders [5]. For OB and overweight individuals, gut microbiota also modulates the host's energy extraction from food, regulates fat storage, and influences the metabolic pathways of weight maintenance. Dysbiosis of the gut microbiota can disrupt normal metabolic processes and thus be a causative agent of overweight [21]. These findings provide a crucial theoretical basis for microbiota-based interventions in metabolic diseases. Modulating the microbial composition to enhance the host's metabolic phenotype has emerged as a promising research direction.

This investigation employs multi-omics approaches to characterize alterations in the gut ecosystem in individuals with HUA and those who are overweight. By integrating deep metagenomic sequencing with comprehensive phenotyping, we delineate microbiota-host interactions underlying metabolic dysregulation and identify candidate species and lifestyles for targeted modulation.

2. Materials and Methods

2.1 Study Design and Participants

Participants were recruited from health examination registers and divided into three groups randomly based on diagnostic criteria (Tables 1,2). The hyperuricemia group (HU, n = 24) was defined as those with more than 420 μmol/L of non-consecutive fasting serum uric acid (SUA) levels (two separate measurements, irrespective of gender and not restricted to body mass index (BMI)), based on the Chinese Guidelines for Hyperuricemia and Gout (2019) [22]. The overweight group (OW, n = 91) comprised subjects with a body mass index (BMI) between 24.0 and 27.9 kg/m^2 as per the Obesity Diagnosis and Treatment Guidelines (2024 Edition) [23] (regardless of their baseline SUA levels). The healthy controls (HL, n = 29) comprised subjects with a BMI of 18.5–23.9 kg/m^2 and free of a history of metabolic diseases. All volunteers provided written informed consent and were excluded in cases of gastrointestinal disease (e.g., Inflammatory Bowel Disease (IBD)), recent antibiotic or probiotic use (within 1 month), cancer, autoimmune disorders, active infection, or pregnancy/lactation. Institutional Review Board of the Naval Special Medical Center approved ethics for this research (Approval No. AF-HEC-017) and the Institute of Food and Nutrition Development, Ministry of Agriculture and Rural Affairs (Approval No. IFNDLLSC20251030).

2.2 Metadata Collection

Questionnaires collected metadata. We can obtain demographic, dietary, environmental, and lifestyle data from the participants using questionnaires. The survey questionnaires assessed populations' age, BMI, diet, living habits, and health status (common health problems, sleep quality, medication, and constitution of Traditional Chinese Medicine).

2.3 Gut Microbiome Analysis

The participants themselves collected the stool samples. The samples were picked up by workers within 15 minutes of defecation and transferred to dry ice, where they were stored at –80 °C until DNA extraction. QIAamp Fast DNA Stool Mini Kit (Qiagen, Hilden, Germany) was used to extract microbiome total DNA from faecal samples according to the manufacturer's instructions. DNA samples were sent to Majorbio (Shanghai, China) for Metagenomics Sequencing. The metagenomics sequencing process has been described elsewhere [24]. Briefly, libraries were constructed using the TruSeq DNA Sample Preparation kit (Illumina, San Diego, CA, USA) and sequenced on an Illumina Hiseq2500 sequencer with paired-end 150-bp sequencing, targeting 4G raw data per sample. Alpha and beta diversity metrics were calculated using VEGAN's diversity function [25]. Linear discriminant analysis effect size (LEfSe) was applied to identify the dissimilarities in bacterial species between groups, based on a combination of the Kruskal-Wallis and pairwise Wilcoxon rank-sum tests, followed by LDA for dimensionality reduction and effect size estimation.

Table 1. Grouping inclusion criteria.

Group	Sample size (n)	Core inclusion criteria	Common exclusion criteria
Healthy control (HL)	29	1. People working at sea 2. BMI: 18.5–23.9 kg/m^2 3. No metabolic diseases	1. Individuals with any of the following conditions: gastrointestinal disorders, severe hepatic or renal impairment, active heart disease, severe cerebrovascular disease, or serious complications of diabetes such as ketoacidosis and hyperglycemic hyperosmolar state; 2. Those currently on other dietary therapies; 3. Use of antibiotics or microbial preparations within the past month.
Overweight group (OW)	91	1. People working at sea 2. BMI: 24.0–27.9 kg/m^2 3. Not limited to SUA levels	
Hyperuricemia group (HU)	24	1. People working at sea 2. Individuals with nonconsecutive fasting SUA levels exceeding 420 μmol/L were measured in two separate sessions	

Note: Data are presented as mean ± standard deviation. HL, healthy control; OW, overweight group; HU, hyperuricemia group; BMI, body mass index; SUA, serum uric acid.

Table 2. Comparison of baseline clinical laboratory parameters and blood pressure among the three groups.

Characteristic	Healthy control (n = 29)	Hyperuricemia group (n = 24)	Overweight group (n = 91)	F value	*p* value
Demographic data					
Age (years)	26.8 ± 3.5	25.6 ± 3.0	27.8 ± 4.7	2.59	0.079
Body mass index (BMI, kg/m²)	22.3 ± 1.2	24.4 ± 2.3	26.3 ± 3.8	17.44	<0.001
Blood routine and inflammation					
Hemoglobin (HB, g/L)	141 ± 8	148 ± 10	149 ± 8	2.53	0.091
Platelet count (PLT, ×10⁹/L)	194 ± 33	205 ± 37	208 ± 38	0.62	0.541
Neutrophil percentage (%)	50.6 ± 7.4	50.3 ± 6.4	48.3 ± 10.1	0.42	0.658
Neutrophil absolute count (×10⁹/L)	2.76 ± 1.12	3.13 ± 0.85	3.12 ± 0.86	0.81	0.449
Liver function					
γ-Glutamyl transferase (γ-GT, U/L)	16.2 ± 3.1	22.2 ± 7.9	22.0 ± 8.0	2.95	0.060
Alanine aminotransferase (ALT, U/L)	18 ± 6	27 ± 28	25 ± 24	0.58	0.563
Aspartate aminotransferase (AST, U/L)	23 ± 6	24 ± 16	22 ± 9	0.29	0.752
Renal function					
Creatinine (CRE, μmol/L)	90.2 ± 8.4	90.2 ± 11.1	90.2 ± 10.3	0.00	1.000
Uric acid (UA, μmol/L)	366 ± 42	477 ± 52	409 ± 77	14.42	<0.001
Blood urea nitrogen (BUN, mmol/L)	6.06 ± 0.94	6.50 ± 1.03	6.09 ± 1.00	1.35	0.268
Blood pressure					
Systolic blood pressure (mmHg)	114.6 ± 14.2	103.0 ± 24.6	112.3 ± 22.9	1.65	0.201
Diastolic blood pressure (mmHg)	77.2 ± 13.3	92.1 ± 19.0	88.1 ± 19.9	2.74	0.072

Note: Data are presented as mean ± standard deviation. BMI, body mass index; HB, hemoglobin; PLT, platelet count; γ-GT, γ-glutamyl transferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRE, creatinine; UA, uric acid; BUN, blood urea nitrogen.

2.4 Statistical Analyses

Raw metagenomic reads were quality filtered with FastP (v0.23.2, OpenGene, https://github.com/OpenGene/fastp) to remove poor-quality bases (Q < 20) and host contamination by mapping against the human reference genome GRCh38/hg38 (Genome Reference Consortium, GCF_000001405.40, https://www.ncbi.nlm.nih.gov/assembly/GCF_000001405.40). High-quality reads were assembled into contigs with MEGAHIT (v1.2.9, Vicuña & Li labs, https://github.com/voutcn/megahit) under a minimum contig length of 500 bp. Open reading frames (ORFs) were predicted using Prodigal (v2.6.3, Oak Ridge National Laboratory, Oak Ridge, TN, USA, https://github.com/hyattpd/Prodigal) and clustered into a non-redundant gene catalog (95% similarity) using CD-HIT v4.8.1 (Li Lab, University of California, San Diego, CA, USA, https://github.com/weizhongli/cdhit/releases/tag/V4.8.1).

Statistical inferences were drawn with SPSS 27.0 (IBM Corp., Armonk, NY, USA) and R 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria, https://www.r-project.org). The continuous variables are expressed as medians (interquartile ranges) and were contrasted using the Kruskal-Wallis test followed by post-hoc Dunn-Bonferroni tests. Comparison of categorical vari-

Table 3. Differences in lifestyle, dietary habits, and physical condition between hyperuricemia and healthy groups [n (%)].

Variable		Hyperuricemia group (n = 24)	Healthy control (n = 29)	χ^2	*p* value
Fruit consumption postprandially	No	18 (75.0)	13 (44.8)	4.382	0.036
	Yes	6 (25.0)	15 (51.7)		
Constipation	No	19 (79.2)	29 (100)	4.202	0.040
	Yes	3 (12.5)	0 (0)		
Depressive state	No Depression	14 (58.3)	28 (96.6)	12.304	0.006
	Mild Depression	3 (12.5)	1 (3.4)		
	Moderate Depression	6 (25.0)	0 (0)		
Lower back pain	No	19 (79.2)	28 (96.6)	3.954	0.047
	Yes	5 (20.8)	1 (3.4)		
Memory decline	No	19 (79.2)	28 (96.6)	3.954	0.047
	Yes	5 (20.8)	1 (3.4)		

Note: The number of valid questionnaires is lower than the total number of participants due to incomplete responses. This discrepancy may affect the interpretation of the data. Data are presented as mean ± standard deviation.

Table 4. Differences in lifestyle, dietary habits, and physical condition between overweight and healthy individuals [example (%)].

Variable		Overweight group (n = 91)	Healthy control (n = 29)	χ^2	*p* value
Exercise in the last three months	No	28 (30.8)	3 (10.3)	3.594	0.032
	Yes	62 (68.1)	25 (86.2)		
Pre-sleep caloric intake	No	18 (19.8)	13 (44.8)	5.461	0.010
	Yes	70 (76.9)	16 (55.2)		
Depressive State	No depression	58 (63.7)	28 (96.6)	9.356	0.009
	Mild depression	8 (8.8)	1 (3.4)		
	Moderate depression	18 (19.8)	0 (0)		
Sleep quality	Very good	34 (37.4)	7 (24.1)	10.188	0.017
	Good	30 (33.0)	19 (65.5)		
	Poor	11 (12.1)	0 (0)		
	Very poor	1 (1.1)	0 (0)		

Note: The number of valid questionnaires is lower than the total number of participants due to incomplete responses. This discrepancy may affect the interpretation of the data. Data are presented as mean ± standard deviation.

ables was done by using the Chi-square or Fisher's exact test. Two-tailed $p < 0.05$ was taken as statistically significant.

3. Results

3.1 Baseline Characteristics of Study Subjects

Comparative analysis revealed varying phenotypic patterns in the study groups (Tables 3,4). HU resulted in major behavioral and physiological deviation from HL, including reduced postprandial intake of fruit (25.0% compliance within 30 minutes versus controls at 15%, $p = 0.036$), elevated frequency of constipation (12.5% vs 0%, $p = 0.040$), and elevated depressive symptomatology (37.5% combined mild/moderate frequency vs 3.4%, $p = 0.006$), and elevated frequency of neuromuscular symptoms such as lower back pain (20.8% vs 3.4%) and loss of memory (20.8% vs 3.4%).

Simultaneously, OW had specific metabolic-behavioral characteristics of decreased physical activity adherence (30.8% sedentary vs 10.3% in controls, $p = 0.032$), pre-sleep caloric consumption (76.9% vs 55.2%, $p = 0.01$), disrupted sleep architecture with 13.2% showing poor/inferior quality and zero such cases in controls, and elevated depressive symptomatology (28.6% vs 3.4%, $p = 0.009$), suggesting coordinated circadian rhythm dysregulation and neuropsychiatric homeostasis.

3.2 Microbial Composition Analysis

At the phylum level, the most dominant phyla in the OW and HU groups and in the normal group were Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. At the species level, the enrichment of *Escherichia coli* (*E. coli*), *Collinsella aerofaciens*, and *Phocaeicola plebeius* occurred in OW and HU individuals compared to HL (Fig. 1). At the relative abundance level in the OW group, *Pantoea endophytica*, *E. coli*, and *Bacteroides stercoris* increased significantly. On the contrary, *Ruminococcus bromii* and *Roseburia inulinivorans* showed a reverse trend. In group HU, *Phocaeicola coprocola* and *Collinsella aerofaciens* were most abundant relative, while *Bacteroides sterco* and *Phocaeicola vulgatus* were least abundant (Fig. 2).

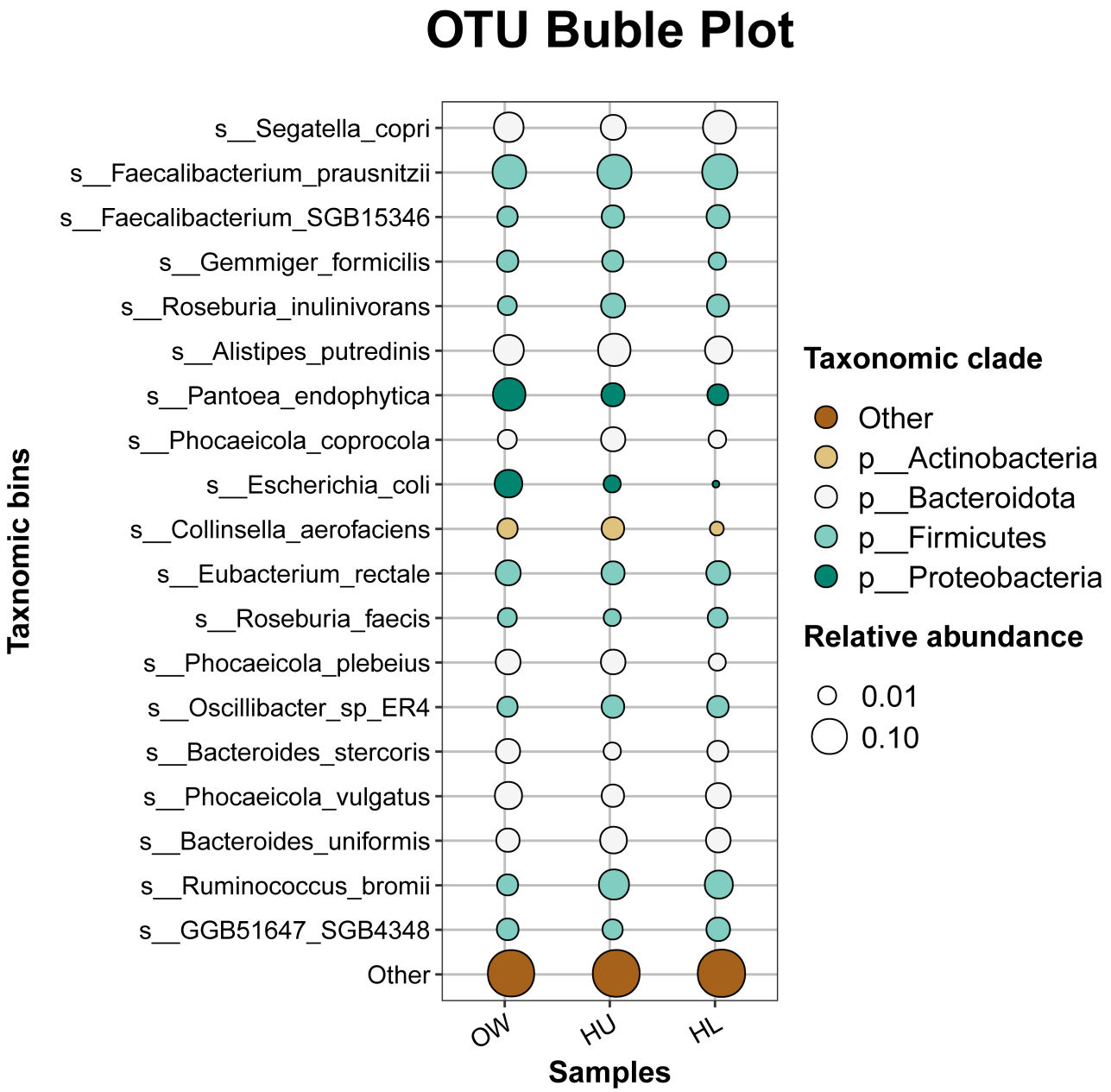

Fig. 1. Bubble plot of gut microbiota in three groups. (Bubble size represents the abundance of gut microbiota) HU (n = 24), HL (n = 29), OW (n = 91). OTUs, Operational Taxonomic Units.

3.3 Microbial Diversity Analysis

α-diversity metrics (Shannon index: HU vs HL 3.24 $\pm$ 0.38 vs 3.31 $\pm$ 0.53, Mann-Whitney U = 306, $p = 0.462$, OW vs HL 3.08 $\pm$ 0.61 vs 3.31 $\pm$ 0.53, U = 1008, $p = 0.040$; Richness: HU vs HL 204.79 $\pm$ 39.78 vs 219.48 $\pm$ 63.73, U = 307, $p = 0.469$, OW vs HL 199.43 $\pm$ 50.53 vs 219.48 $\pm$ 63.73, U = 1072, $p = 0.092$) revealed progressive microbial community simplification in metabolic disorder groups (Fig. 3).

β-diversity analysis further confirmed structural divergence (HU vs HL: PERMANOVA $R^2 = 0.029$, $p < 0.05$; OW vs HL: PERMANOVA $R^2 = 0.016$, $p < 0.01$), with principal coordinates separating HU and HL clusters along PCo1 (10.9% and 9.1% variance explained) from the HL (Fig. 4).

3.4 Microbial Differential Analysis

LEfSe analysis established disease-specific biomarkers: compared to the HL, the HU harbored four unique enrichments of *Alistipes putredinis*, *Mediterraneibacter faecis*, *Streptococcus oralis*, and *Gemella sanguinis*. The OW displayed enteric overgrowth of five differential bacterial species, including *Pantoea endophytica*, *Pantoea vagans*, *Phocaeicola coprophilus*, *Ruminococcus SGB4421*, and *Klebsiella oxytoca* (Fig. 5).

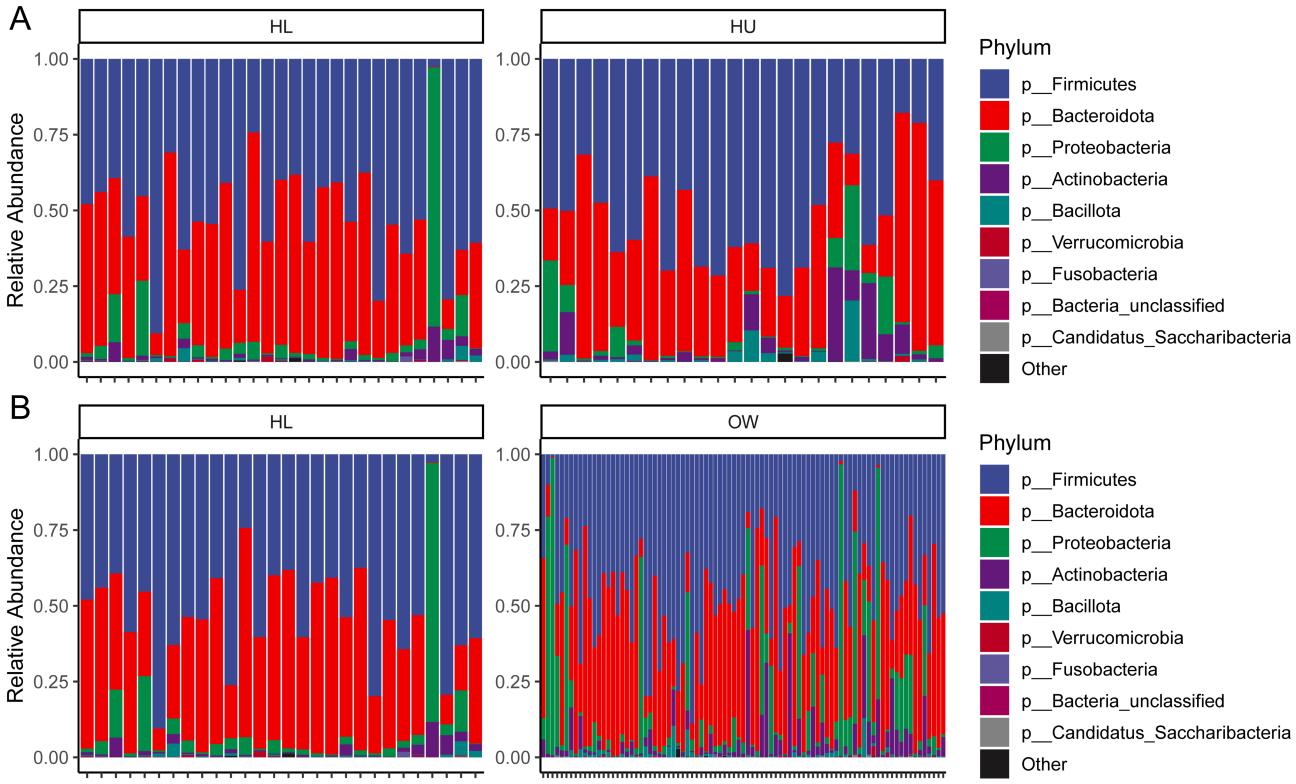

Fig. 2. Comparison of the relative abundance of the top 20 bacterial species across three groups. (A) Relative abundance of gut microbiota phyla (HU, n = 24 vs HL, n = 29). (B) Relative abundance of gut microbiota phyla (OW, n = 91 vs HL, n = 29).

4. Discussion

This study contrasted lifestyle factors and gut microbial ecology between HU, OW, and HL. Clinically, both HU and OW cohorts manifested significant metabolic-psychological comorbidities and lifestyle imbalances relative to HL. Gut microbiota analysis demonstrated reduced biodiversity and altered community structures in both groups, highlighting dysbiosis as a potential pathological nexus.

The present study found that the incidence of constipation, lower back pain, memory decline, and depression was significantly increased in individuals with HUA. The underlying mechanisms may be closely related to gut microbiota dysbiosis. The observed reduction in *Firmicutes phylum* members, key producers of short-chain fatty acids (SCFAs), likely contributes to impaired intestinal motility through diminished neuroenteric signaling [26]. These changes may reduce intestinal motility, thereby affecting defecation function and potentially leading to constipation [27]. Furthermore, dysbiosis-induced disruption of extra-renal UA excretion pathways may facilitate UA crystallization in synovial tissues, potentially explaining the elevated incidence of lower back pain through localized inflammatory responses [28]. Notably, our results suggest that HUA-associated cognitive impairment may involve dual mechanisms of neuroinflammation and oxidative stress [29]. Serum UA deposition in hippocampal regions appears to promote reactive oxygen species (ROS) accumulation [30, 31], while enhancing Tumor Necrosis Factor-alpha (TNF-α) and amyloid beta peptide (Aβ) expression [32]. This proinflammatory milieu may induce dendritic retraction in hippocampal pyramidal neurons through Toll-like receptor 4 (TLR4) activation, ultimately compromising spatial reference memory [33]. These neuropathological processes establish plausible links between sustained HUA and progressive cognitive decline.

Overweight individuals have shown significant changes in physical exercise, pre-sleep caloric intake, sleep quality, and depression. Physical exercise is significantly associated with overweight and OB, and the frequency of physical exercise generally has a negative correlation with body weight [34,35]. Pre-sleep eating is highly likely to lead to weight gain. Maukonen *et al.* [36] found that late eating has a significant impact on hunger and the levels of leptin, ghrelin, and other appetite-regulating hormones, which in turn affect the body's energy metabolism and fat storage mechanisms, promoting weight gain. Poor sleep quality is also a significant contributor to being overweight. Itani *et al.* [37] demonstrated that individuals with less than 6 hours of sleep per day have a 38% higher risk of OB compared to those with normal sleep duration. This is because insufficient sleep disrupts hormonal balance, increasing the secretion of ghrelin—a hormone that promotes appetite—and decreasing the secretion of leptin—a

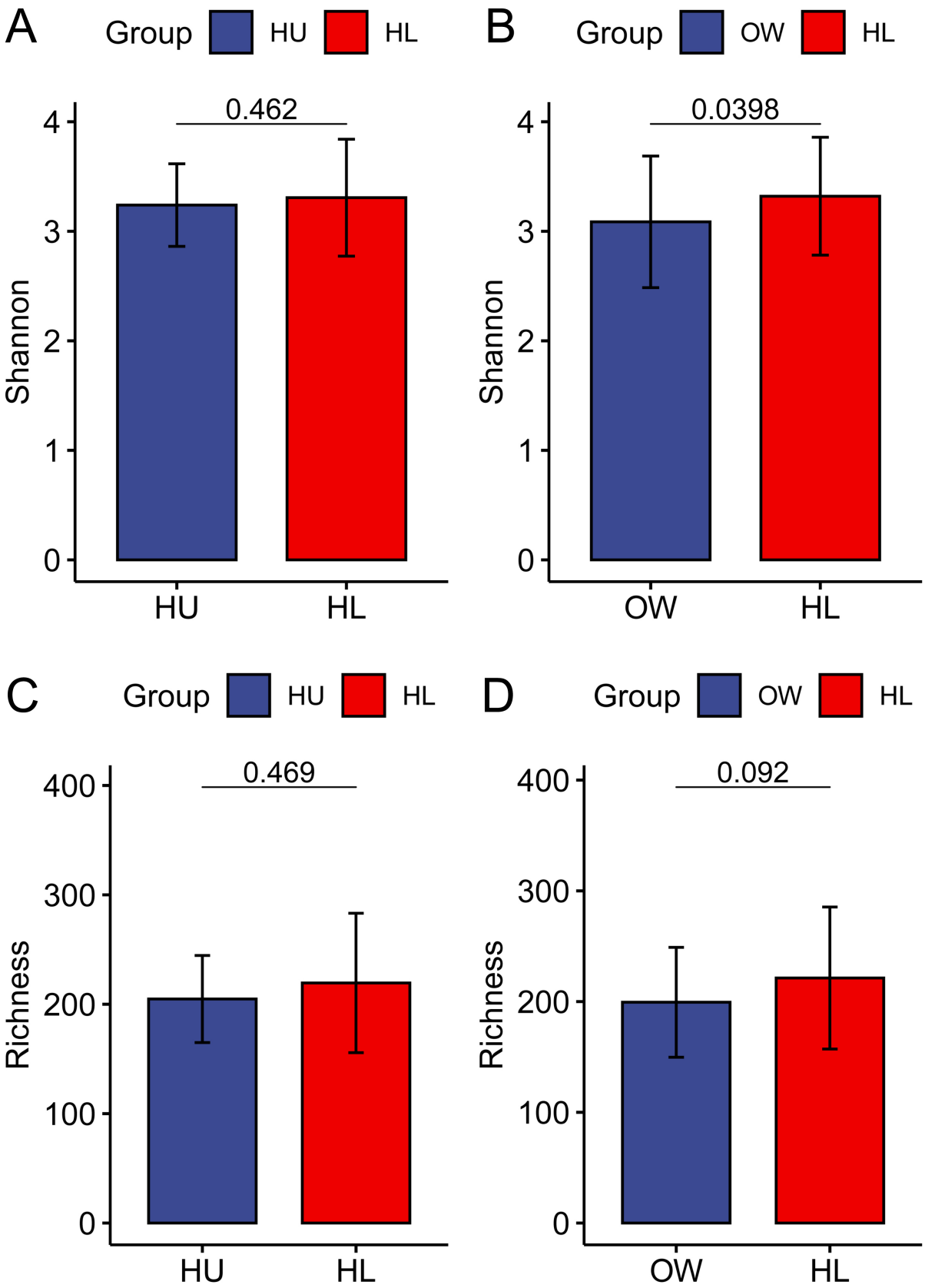

Fig. 3. Alpha diversity differences. (A) Gut microbiota α-diversity richness (HU, n = 24 vs HL, n = 29). (B) Gut microbiota α-diversity richness (OW, n = 91 vs HL, n = 29). (C) Gut microbiota α-diversity Shannon index (HU, n = 24 vs HL, n = 29). (D) Gut microbiota α-diversity Shannon index (OW, n = 91 vs HL, n = 29). Note: A clear statement specifying that the error bars represent the standard error of the mean (SEM).

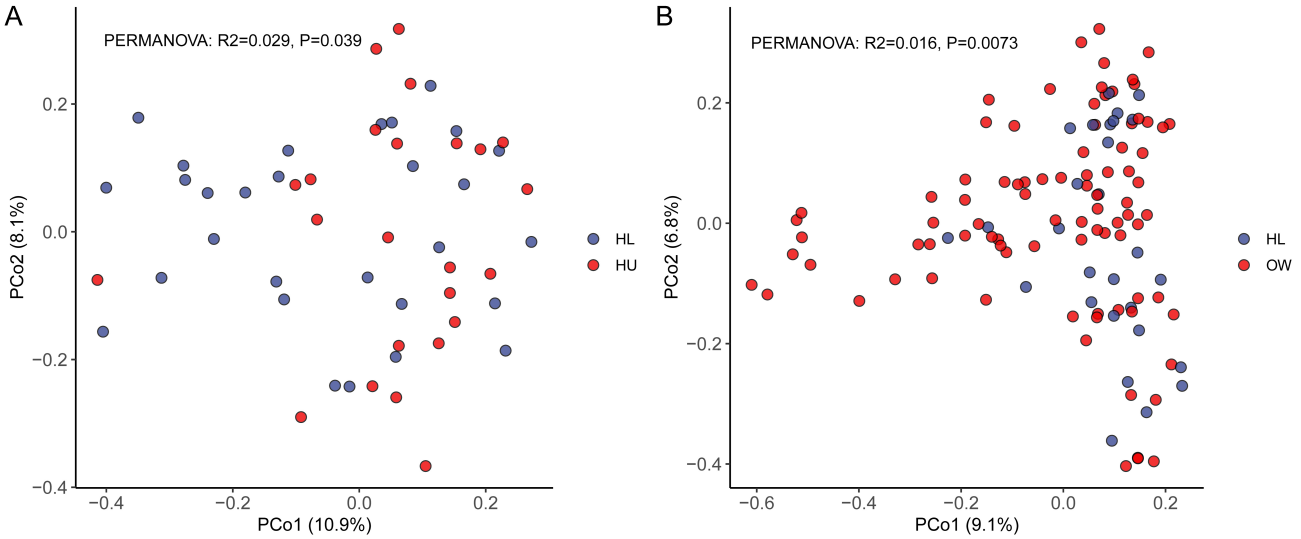

Fig. 4. Beta diversity analysis results. (A) Beta diversity PCoA with PERMANOVA (HL, n = 29 vs HU, n = 24). (B) Beta diversity PCoA with PERMANOVA (HL, n = 29 vs OW, n = 91).

hormone that suppresses appetite, resulting in increased food intake [38]. Notably, this study found that the risk of depression was significantly increased in individuals with HUA and overweight individuals. HUA, as a metabolic disease, may reduce patients' quality of life, which may trigger a range of physiological and pathological changes, including affecting neurotransmitter metabolism and transmission, thereby interfering with normal brain function and increasing the risk of depression [39]. Similarly, being overweight is typically associated with metabolic disorders, and inflammatory cytokines secreted by adipose tissue can affect the balance of the neuroendocrine system, leading to abnormal neuroregulatory functions and can also induce depressive moods [40].

Gut dysbiosis is a significant pathophysiological process for the development of gastrointestinal motility and metabolic illness. Reduced gut microbiome diversity could impair regular physiological processes, including intestinal barrier integrity, nutrient metabolism, and absorption, and therefore predispose individuals to long-term metabolic illnesses [41–43]. Le Chatelier *et al.* [44] showed that low bacterial richness individuals had more extensive OB, insulin resistance, dyslipidemia, and a more visible inflammatory phenotype. Alpha diversity of gut microbiota was also reduced in the overweight population in the present study. Intestinal barrier function is compromised when diversity is low, and translocation of lipopolysaccharide (LPS) and other structural elements of bacteria through the intestinal barrier is facilitated. This procedure involves inflammatory processes, leading to insulin resistance, which is one of the most significant pathogenic mechanisms of type 2 diabetes and other chronic metabolic diseases [41]. OB and diabetes are two metabolic diseases characterized by insulin resistance and low-grade inflammation. Comparably, reduced gut microbiota diversity may affect metabolism and nutrient uptake. A loss in diversity can lead to reduced production of SCFAs. Thus, energy metabolism is compromised, promoting the accumulation of overweight and OB, and raising the risk of chronic metabolic disorders, such as diabetes and cardiovascular disease [45].

In the present study, differential analysis revealed a significant enrichment of the bacterial species *Klebsiella oxytoca* in the overweight population, a finding that has been corroborated in previous research. *Klebsiella oxytoca* is a human commensal and an opportunistic pathogen that can cause a variety of infections, including antibiotic-associated hemorrhagic colitis (AAHC), urinary tract infections, and bacteremia [46]. A cross-sectional study in mice has shown that OB impairs the host's defense against *Klebsiella pneumoniae*. This finding is consistent with the observation that diet-induced OB in mice leads to increased bacterial burden and impaired pulmonary clearance of *Klebsiella pneumoniae* [47]. Additionally, an experiment investigating the effects of gut microbiota altered by gastric bypass surgery on energy and metabolic control in diet-induced obese (DIO) mice revealed that these changes can influence metabolic outcomes. The gut microbiota altered by gastric bypass surgery may promote thermogenesis in brown adipose tissue and improve metabolic efficiency by reducing fat accumulation in the body and inhibiting the development of overweight or OB. These effects may be mediated by modulating taurine metabolism and activating the intestinal Farnesoid X Receptor (FXR) and systemic Takeda G-protein-coupled receptor 5 (TGR5) signaling [48].

The present study found that the relative abundance of *Collinsella aerofaciens* was the highest in individuals with HUA, which may reveal a potential link with the occurrence

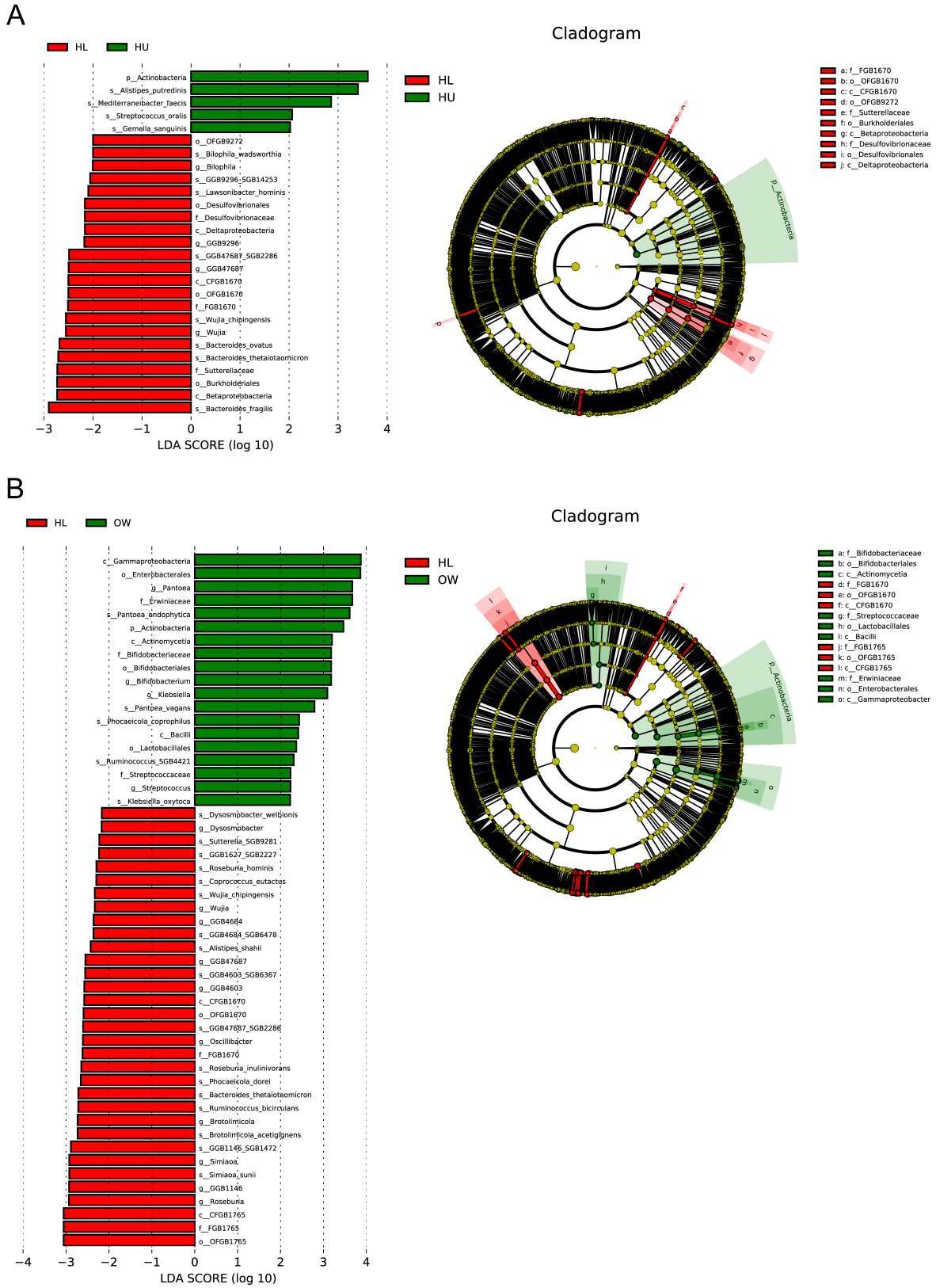

Fig. 5. Gut microbiota biomarkers identified by LEfSe analysis. (A) LEfSe analysis (HL, n = 29 vs HU, n = 24). (B) LEfSe analysis (HL, n = 29 vs OW, n = 91). Note: The circles in the figure represent taxonomic levels from inside to outside, including kingdom, phylum, class, order, family, genus, and species. Each circle at a different level represents a species classification, and the diameter of the circle is proportional to the species' abundance. Yellow indicates no difference, while red and green indicate significant differences, with the species having a higher abundance in the corresponding color-coded group.

of HUA. Some studies have found that an increased abundance of *Collinsella aerofaciens* may lead to the early disruption of intestinal barrier integrity, thereby improving gut permeability and inducing Interleukin-17A (IL-17A) expression [49]. This can promote the translocation of LPS and other bacterial products [50], which, in turn, induces chronic inflammation and increases the risk of HUA [51]. Additionally, the decrease in gut microbial diversity in patients with HUA and the increased abundance of opportunistic pathogens (*E.coli* and *Collinsella aerofaciens*) may lead to elevated UA levels by affecting purine metabolism in the body, thereby promoting the development of HUA and creating a vicious cycle [52].

In patients with HUA, the abundance of four specific bacterial species (*Alistipes putredinis*, *Mediterraneibacter faecis*, *Streptococcus oralis*, and *Gemella sanguinis*) is remarkably higher compared to controls. *Streptococcus oralis* is a chief human colonizer of the oral cavity and upper respiratory tract and one of the top HUA community species. It is a key regulator of the mucosal immune response's response to the microbiota. *Streptococcus oralis* might regulate inflammation by inhibiting the activity of Nuclear Factor kappa B (NF-κB) and inhibiting Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) transcriptional activity by its metabolites, thereby regulating the inflammatory and metabolic pathway. This regulatory function acts as a connector between the host metabolic and immune systems, acting as an intermediary between the two [53]. When the *Mediterraneibacter genus* has been investigated in different research studies, it was found that *Mediterraneibacter tenuis* is highly prevalent in RA gut microbiota of patients, and it shows a significant positive correlation with RA clinical indicators, like erythrocyte sedimentation rate (ESR) and interleukin-10 (IL-10) levels. *Mediterraneibacter tenuis* can enhance inflammatory reactions, promote the activation of pro-inflammatory signaling pathways, and lead to decreased IL-10 levels and increased IL-17A levels, thereby disrupting intestinal immune homeostasis in mouse models [54]. *Mediterraneibacter faecis* is a Gram-positive, strict anaerobic coccus. To date, there are no definite reports of an intimate relationship between *Mediterraneibacter faecis* and HUA or IBD pathogenesis [55]. *Gemella sanguinis* is a Gram-positive coccus and opportunistic pathogen that can be found on the mucous membranes of the oral cavity, gastrointestinal tract, and genitourinary tract in healthy individuals. Underlying heart disease and oral disease are risk factors for infection with *Gemella morbillorum*, not *Gemella sanguinis*. The bacterium can cause infections through oral contamination, leading to severe conditions such as sepsis, endocarditis, and meningitis [56]. Some research has shown that when *Gemella genus* strains isolated from patients with pulp necrosis were planted in germ-free mice, the production of interleukin-12 (IL-12) and interferon-γ (IFN-γ) was inhibited [57]. HUA is characteristically associated with low-grade chronic inflammation, which can alter the oral cavity or gut mucosal barriers, making it easier for *Gemella sanguinis* to penetrate the blood and thereby leading to an increase in *Gemella sanguinis* counts.

It must be mentioned that one of the main limitations of this study is that our findings are directly derived from an overweight population with hyperuricemia. The results may therefore not apply to patients with other chronic metabolic diseases, such as diabetes mellitus or dyslipidemia, that do not exhibit these specific characteristics.

5. Conclusion

The decrease in gut microbial α-diversity and compositional structure variations (β-diversity modifications) is significantly related to the chronic metabolic disease pathogenesis and development (overweight and HUA). Investigating further their associations may help explain the pathogenesis of chronic metabolic diseases and provide a theoretical basis for the development of new diagnostic methods and therapeutic tools. Conversely, studying the single mechanisms of action of bacterial species associated with overweight and HUA, such as *E. coli* and *Collinsella aerofaciens*, in the gut microbiota is promising for identifying new targets for the prevention and treatment of these diseases.

Abbreviations

Aβ, Amyloid beta; AAHC, Antibiotic-associated hemorrhagic colitis; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body Mass Index; BUN, Blood Urea Nitrogen; CRE, Creatinine; DIO, Diet-induced obese; E. coli, Escherichia coli; ESR, Erythrocyte sedimentation rate; FXR, Farnesoid X Receptor; γ-GT, γ-Glutamyl transferase; HB, Hemoglobin; HL, Healthy Control; HUA, Hyperuricemia; HU, Hyperuricemia Group; IBD, Inflammatory Bowel Disease; IFN-γ, Interferon-gamma; IL-10, Interleukin-10; IL-12, Interleukin-12; IL-17A, Interleukin-17A; LEfSe, Linear Discriminant Analysis Effect Size; LPS, Lipopolysaccharide; NF-κB, Nuclear Factor kappa B; OB, Obesity; ORFs, Open Reading Frames; OW, Overweight Group; PLT, Platelet Count; PPARγ, Peroxisome Proliferator-Activated Receptor Gamma; RA, Rheumatoid Arthritis; ROS, Reactive Oxygen Species; SCFAs, Short-Chain Fatty Acids; SUA, Serum Uric Acid; TGR5, Takeda G-protein-coupled receptor 5; TLR4, Toll-like receptor 4; TNF-α, Tumor Necrosis Factor-alpha; UA, Uric Acid.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request. All data reported in this paper will also be shared by the lead contact upon request.

Author Contributions

TC: Data curation, Formal Analysis, Visualization, Writing – original draft, Writing – review & editing. YG: Data curation, Formal Analysis, Visualization, Writing – original draft, Writing – review & editing. DoL: Formal Analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. DaL: Formal Analysis, Validation. SX: Formal Analysis, Writing – review & editing, Language polishing and revision. DanL: Funding acquisition, Conceptualization, Supervision. CZ: Funding acquisition, Conceptualization, Validation. FW: Conceptualization, Validation, Funding acquisition, Supervision. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the Institutional Review Board of the Naval Special Medical Center (Ethic Approval Number: AF-HEC-017), and the Institute of Food and Nutrition Development, Ministry of Agriculture and Rural Affairs (Ethic Approval Number: IFNDLLSC20251030). All of the participants provided signed informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used DeepL and Deepseek in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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