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Machine learning elucidates associations between oral microbiota and the decline of sweet taste perception during aging

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Aging-induced deterioration in taste perception can result in loss of appetite and malnutrition in the elderly, posing a substantial challenge to healthy aging. In oral cavity, the oral microbiota, food particles, and taste receptors interact extensively under the flow of saliva. Although it has been hypothesized that oral microbiota may influence taste perception, evidence remains limited. Here we justified this hypothesis and further proposed that specific oral bacterial genera exhibited significant associations with age-related alterations in sweet taste perception. Notable age-related changes in taste perception were observed: the elderly presented significantly higher detection and recognition thresholds for sweet taste acuity compared to the youth. Linking back to the oral microbiota, we identified key bacteria genera *Haemophilus*, *Lachnoanaerobaculum*, *Fusobacterium*, *Aggregatibacter* and *Oribacterium* associated with sweet taste perception via machine learning. Correspondingly, we found several volatile compounds in the oral exhaled breath, especially the endogenous compound isoprene, that significantly correlated with oral bacteria genera and sweet taste sensitivity. Our findings in sweet taste perception-associated bacteria and metabolites can be potential biomarkers of early aging, which provides timely fresh clues for the well-being of the aging population.

Population aging is advancing globally at an unprecedented rate. It is estimated that the proportion of people aged over 60 years will more than double by 2050 according to World Health Organization (WHO)[1]. Besides affecting physical capabilities, aging significantly impairs nutritional and health status, associated with deficits in taste and smell function, which can lead to poor appetite, altered food preferences and choices, and diminished hedonic perception[2–4]. How to mitigate taste perception decline due to aging is a challenging task in enhancing the quality of life for the elderly and propelling healthy aging. Much effort has been taken to unravel the mechanism underlying aging-induced taste perception decline, such as diminished cognition, lower saliva production, swallowing disorders and the disruption of taste bud homeostasis[5,6]. Interestingly, it has been proposed that the oral microbiota played an important role in taste perception given the anatomical proximity to taste receptors[7]. Microbes in oral cavity and even in gastrointestinal tract could potentially exert a direct influence on individuals' eating behaviors and dietary preferences[8,9]. Notably, research has recently revealed novel insights into the association between taste sensitivity and oral microbiota composition[10–12]. For instance, Licandro et al. highlighted the importance of *Streptococcus* and *Prevotella* within the lingual and salivary microbiota for basic taste sensitivity[13]. However, relevant work focusing on elder adults is lacking, and thus the association between age-related changes in taste perception and oral microbiota remains largely unexplored.

Many studies have demonstrated the translocations of the oral microbiota, overcoming physical and chemical barriers to accumulate and colonize in other adjacent or distant tissues, such as nasopharynx, lung and gastrointestinal tract[14–17]. Given this, orally exhaled breath serves as a non-invasive window for observing oral microbiota translocation and assessing overall human metabolism, with many endogenous volatile compounds originating from the metabolism of host-colonizing microorganisms[18]. It is readily obtained and can be a promising avenue for biomarker identification. Previous works have proved that human microbiota could produce volatile compounds such as butyrate, which possess a strong unpleasant odor and are associated with cognitive function in the elderly[19,20]. However, the nexus between oral microbiota and volatile metabolites (volatilome), as well as the potential impact of these in vivo interactions on taste perception,

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requires further investigation. Indeed, human oral microbiota and oral volatilome datasets are inherently complex and highly variable, which can be influenced by numerous factors. Traditional statistical approaches often struggle to capture the intricate, non-linear relationships within these high-dimensional datasets. Therefore, machine learning methods are increasingly used to overcome these challenges and identify informative patterns[21–23].

To fill the knowledge gap regarding the role of oral microbiota in the decline of taste perception, we evaluated the sweet taste threshold in an adult cohort ($n = 140$) formed by the elderly and the youth (Fig. 1). To emphasize the phenotype of taste deterioration, we then selected a core group of 60 participants characterized by higher/lower sensitivity according to the statistics median for the detailed analyses of oral microbiota and oral volatilome. Given the data complexity, we employed machine learning algorithms to efficiently identify key oral microbiota associated with changes in sweet taste perception. This study validated the hypothesis that the decline in taste perception is associated with the oral microbiota and more importantly, pointed out key bacteria genera significantly associated with age-related alterations in sweet taste perception, which offers fresh clues for improving the quality of life for society with aging people as well as flavor optimization strategies for elderly foods.

Results

Sweet taste sensitivity identified the core group

The primary objective of this study is to explore the key oral microbiota associated with age-related alterations in taste perception. Sweet taste was chosen because it serves as a key indicator of energy-rich carbohydrates and is fundamental to human dietary behavior. In this paper, first, we quantified the sweet taste acuity using 3-AFC staircase procedure focused on the detection threshold (DT) and recognition threshold (RT) of sucrose. In total, the elderly showed significantly higher DT and RT values than the youth (Fig. 2A, Table 1). To clarify the oral microbiota associated with alterations in sweet perception, the elderly participants with threshold values above the median ($n = 30$) and the youth participants with threshold values below the median ($n = 30$), named as the core group, were selected for further analysis (Fig. S1). In the core group, we noticed that the DT and RT of the elderly were approximately 15 times and 8 times higher than that of the youth, respectively. Interestingly, we also found significant differences between the DT and RT in the youth ($p < 0.001$), whereas no difference was observed in the elderly ($p > 0.05$). It could be attributed to that, for higher concentrations of sucrose solutions, participants were generally able to easily perceive and accurately recognize the sweet taste. However, the youth exhibited a heightened sensitivity, as they could detect subtle differences between low-concentration sucrose solutions and blank control (pure water), even if they were unable to identify the specific taste. Thus, DT was employed as an important label for individual differences in sweet taste perception for further analyses.

Differences in oral microbiota between youth/elderly core group

To explore the divergence in oral microbiota between the core youth and elderly group, the DNA extracted from unstimulated saliva was analyzed by 16S rRNA gene sequencing. The result revealed a total of 2318 OTUs, with 23 phyla, 52 classes, 115 orders, 198 families, 421 genera, and 984 species. For the α-diversity, there were significant discrepancies regarding the observed species, ace and Chao 1 indices (Fig. 2B). As displayed by principal component analysis (PCA) and principal coordinates analysis (PCoA), although the scatter plots of the two groups did not permit the separation of the youth and elderly individuals, the differences between groups were statistically significant (Fig. 2C–D, $p < 0.01$). Then, the microbial composition and relative abundance were carefully compared. From Fig. 2E–F, regarding the phylum, *Firmicutes* (46.42%), *Proteobacteria* (18.27%), *Bacteroidota* (16.87%), *Actinobacteriota* (7.92%), *Fusobacteriota* (6.23%), *Patescibacteria* (2.60%) were predominant, and the top five genera were *Streptococcus* (27.42%), *Prevotella* (10.53%), *Neisseria* (9.00%), *Haemophilus* (5.76%) and *Rothia* (4.68%).

The top 30 genera accounted for 92% of the overall abundance at genus-level, which was representative and comprehensive to be used for further exploration (Fig. S2). Considering the weak pattern identification performance of PCA and PCoA, Uniform Manifold Approximation and Projection (UMAP) was employed due to its better flexibility and robustness in dimensionality reduction compared to PCA or PCoA. It can also handle nonlinear and non-Gaussian data while consistently producing stable results across different runs. After applying UMAP, the dimensionality-reduced microbial abundance levels of 30 youth and 30 elderly samples showed an observable clustered distribution, highlighting the significant variances in microbial profiles between the youth and the elderly, which also distinguished samples of high and low sweet detection thresholds (Fig. 3A). Employing LEfSe analysis, a total of 20 characteristic bacterial taxa were identified in the elderly while 33 were identified in the youth (LDA score>3.0, $p < 0.05$, Fig. 3B). Next, differential abundance analysis of oral microbiota found that *Actinomyces*, *Granulicatella*, *Clostridia_UCG-014*, *TM7x*, and *Gemella* were significantly up-regulated in the elderly compared

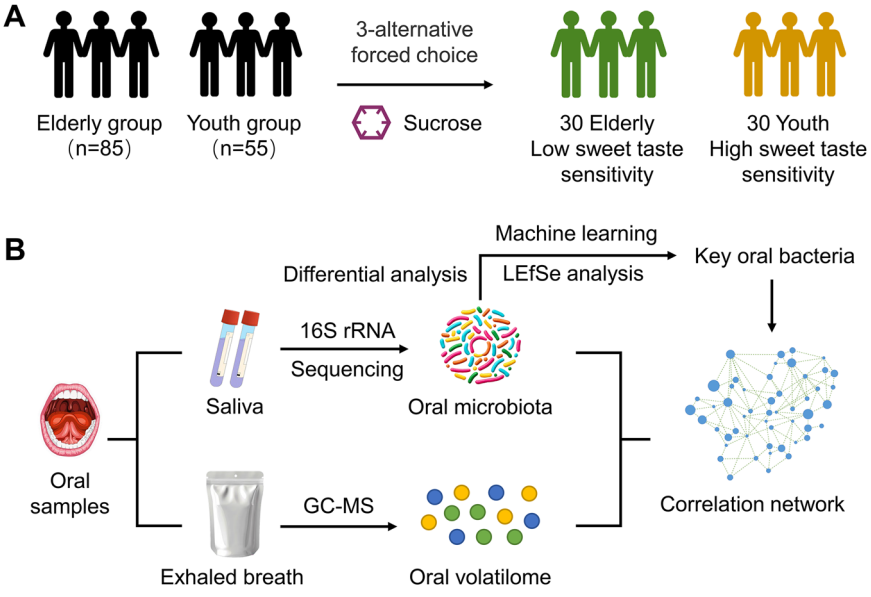

Fig. 1 | Multi-discipline analysis workflow. **A** Sensory test, (**B**) Oral microbiome and volatilome. GC-MS: gas chromatography-mass spectrometry.

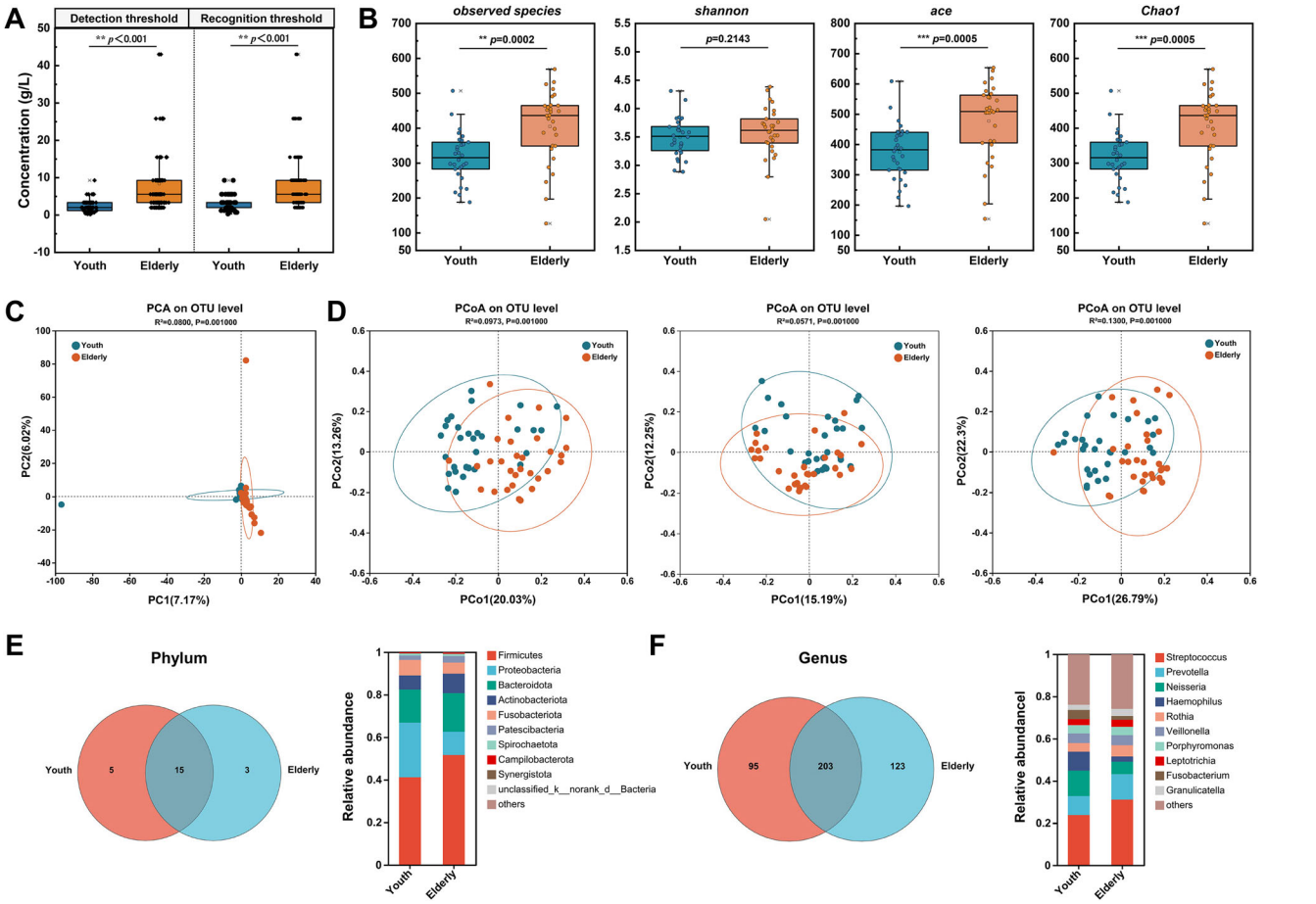

Fig. 2 | Sweet taste perception differences across the youth and the elderly ($n = 140$) and the oral microbiome diversity in the core group ($n = 60$). **A** Sweet taste sensitivity of the youth and the elderly. **B** α-diversity of oral microbiota in the core group. **C** PCA and (**D**) PCoA (left: Bray–Curits distance, middle: unweighted_unifrac distance, right: weighted_unifrac distance) based at OTU level. **E** The Venn diagram (left) and taxonomic distribution (right) of oral microbiota at phylum level. **F** The Venn diagram (left) and taxonomic distribution (right) of oral microbiota at phylum level. Only the top ten taxa were shown at each taxonomic level, and the remaining ones were grouped as 'others'.

Table 1 | Physiological characteristics of the elderly and the youth

Characteristic	Overall		Core group	
	The elderly	The youth	The elderly	The youth
Age (yrs), median (IQR)	67 (64–69)	24 (23–25)	22.8 (22.0–26.3)	24 (23–25)
DT of sucrose (g/L)	8.25 ± 8.58	2.37 ± 1.85	16.64 ± 9.83	1.08 ± 0.65
RT of sucrose (g/L)	9.16 ± 8.55	3.35 ± 2.02	17.19 ± 9.86	1.98 ± 1.01

with the youth, while *Haemophilus*, *Acinetobacter*, *Fusobacterium*, *Aggregatibacter*, *Lachnoanaerobaculum*, *Lautropia*, *Oribacterium*, and *Neisseria* were significantly down-regulated (Fig. 3C).

Machine learning revealed sweet taste perception-associated oral microbiota

We first assessed the classification performance of four candidate machine learning classifiers, and selected LR and linear SVC for hyperparameter tuning given their higher AUC ROC value (Fig. 4A). After hyperparameter optimization via randomized search, LR and linear SVC both achieved robust AUC ROC scores around 0.9 (Fig. 4B). Then, feature importance analysis, with the computed SHAP value for each feature, was performed on trained fine-tuned LR and linear SVC classification models (Fig. 4C–D). Top 10 important features of LR were *Haemophilus*, *Lachnoanaerobaculum*, *Fusobacterium*, *Granulicatella*, *Oribacterium*, *Corynebacterium*, *Aggregatibacter*, *Gemella*, *Campylobacter*, and *Parvimonas* (Fig. 4C). Top 10 important features of linear SVC were *Haemophilus*, *Lachnoanaerobaculum*, *Granulicatella*, *Aggregatibacter*, *Oribacterium*, *Corynebacterium*, *Campylobacter*, *Absconditabacteriales_SR1*, *Gemella*, and *Selenomonas* (Fig. 4D). Among the important features of LR and linear SVC, 7 genera were screened as candidates of key bacterial genera associated with taste perception according to the intersection of differential abundance analysis (Fig. 3C) and feature important analysis (Fig. 4C–D). However, 2 genera (*Gemella* and *Granulicatella*) among the 7 candidates were not characterized in LEfSe and were removed. Finally, we obtained the 5 key bacterial genera associated with sweet taste perception, namely *Haemophilus*, *Lachnoanaerobaculum*, *Fusobacterium*, *Aggregatibacter* and *Oribacterium* (Fig. 4E, Table 2). Then, correlation analysis was carried out to understand the alteration of sweet taste perception-associated oral microorganisms during aging. As shown in Fig. S3, the five key bacterial genera were all negatively

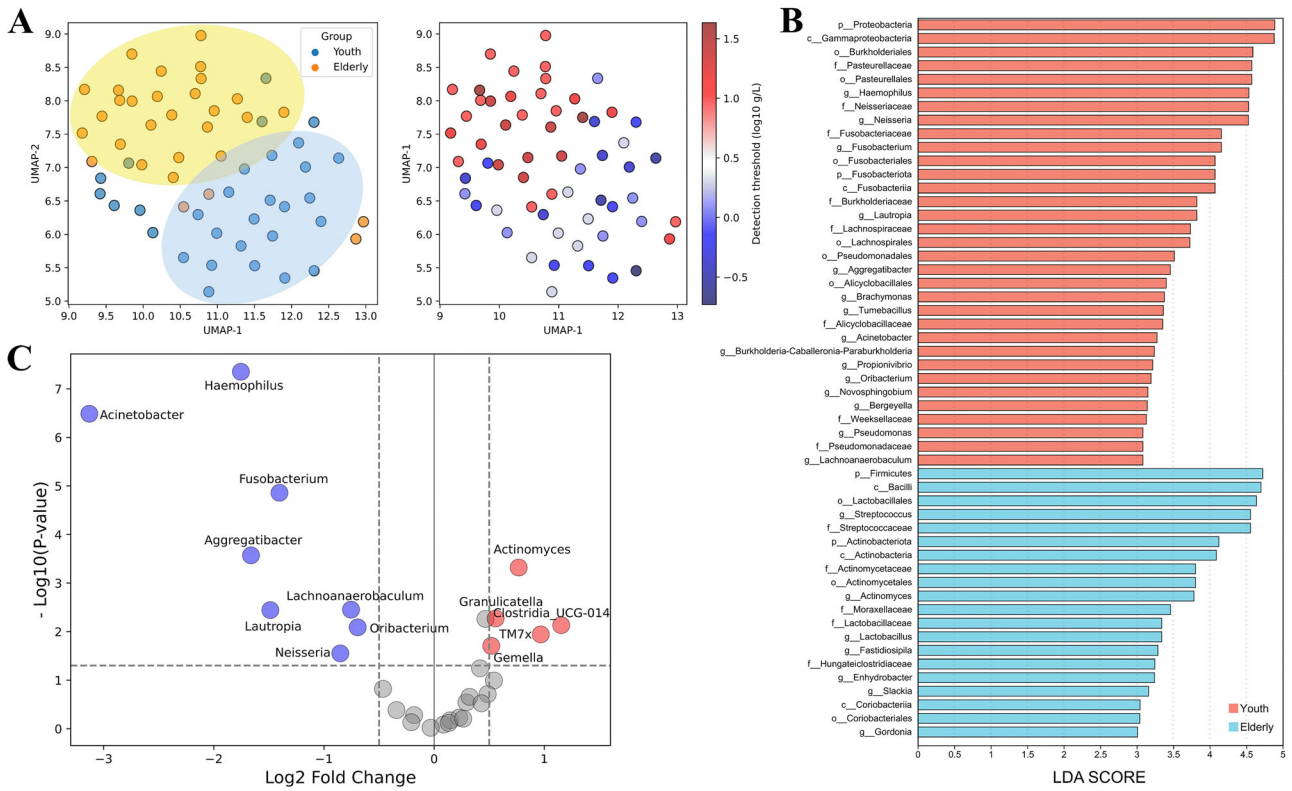

Fig. 3 | The identification of differential oral microorganisms based on relative abundance level. A UMAP biplots of oral microbial abundance with the core group labeled (left) and sweetness detection thresholds labeled (right). **B** LEfSe analysis for oral microbiota (adjusted $p < 0.05$, LDA score>3.0). **C** Differential abundance analysis of oral microorganisms (adjusted $p < 0.05$, log2-fold change>0.5). Blue dots: significantly down-regulated; Red dots: significantly up-regulated. Fold changes were shown as the elderly versus the youth.

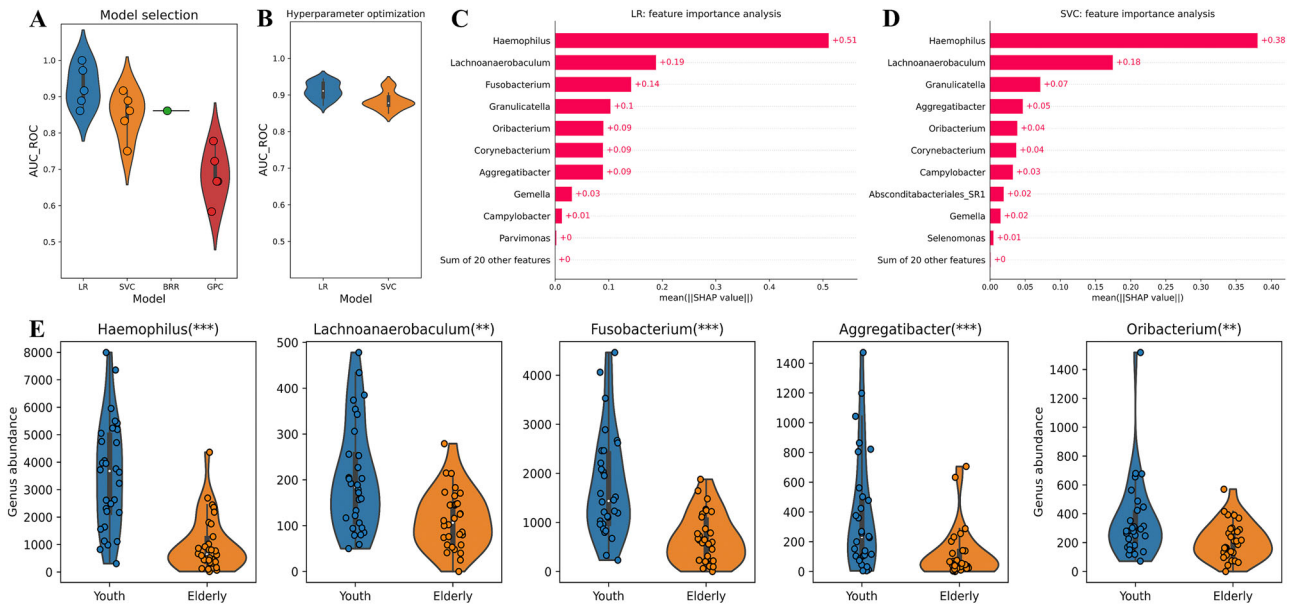

Fig. 4 | Sweet taste perception-associated oral microbiota. A Initial classification performances of LR, SVC, BRR and GPC models. **B** Classification performances of LR and SVC models after hyperparameter optimization. **C** Feature importances of LR, quantified with absolute SHAP values. **D** Feature importances of SVC, quantified with absolute SHAP values. **E** The abundance distributions of sweet taste perception-associated key bacterial genera, including *Haemophilus*, *Lachnoanaerobaculum*, *Fusobacterium*, *Aggregatibacter* and *Oribacterium*.

correlated with the sweetness threshold. It was worth noting that *Haemophilus*, *Lachnoanaerobaculum*, *Fusobacterium*, and *Aggregatibacte* were significantly correlated (| r | >0.3, $p < 0.05$). It is commonly posited that the metabolism of oral bacteria may modulate the concentration of tastants near the taste receptors, thereby exerting an influence on taste perception[24–26]. Additionally, the accumulation of oral microbiota on the tongue can participate in the formation of a thicker physical barrier (biofilm), which will result in a lower taste acuity[27,28].

Inter-microbial Pearson correlation coefficients were computed to investigate potential ecological interactions, revealed by the variance of oral microbial abundance levels across the core group (Fig. 5A). The weighted correlation network of oral microorganisms can be divided into three modules (Fig. 5B). Module 1 was centered around *Haemophilus*, *Prevotella*, and *Selenomonas*. Module 2, which primarily exhibited positive correlations, was centered around *Porphyromonas*, *Treponema* and *Filifactor*. Module 3, characterized by negative correlations, was centered around *Streptococcus*. It can be seen that *Gemella* and *Clostridia_UCG-014*, which were significantly up-regulated in the elderly, primarily acted as activators in the network, while *Haemophilus* and *Neisseria* (the down-regulated taxa) functioned as repressors.

Further, the biological functions of the oral bacteria were predicted based on the 16S rRNA sequencing data combined with PICRUSt2 and KEGG databases. The result showed that bacterial colony function was mainly involved in metabolism (Fig. S4). Diving deeper into the KEGG database at the third level, the functions were primarily related to metabolic pathways, biosynthesis of secondary metabolites, microbial metabolism in diverse environments, biosynthesis of amino acids, and carbon metabolism,

Table 2 | LEfSe analysis for characterized bacterial taxa at genus level

Genus	Mean	LDA	*p*
Haemophilus	4.953309	4.535725	2.47E-07
Fusobacterium	4.645967	4.158566	6.51E-06
Aggregatibacter	3.974804	3.459809	0.000637
Oribacterium	3.947639	3.19602	0.01471
Lachnoanaerobaculum	3.714622	3.082242	0.001269

which supported the previous view that oral microbiota influences taste perception mainly through metabolic activities, in addition to biofilm.

Characteristics of oral volatilome and oral volatilome-microbiota relationships between the core group

The orally exhaled breath is an important source of various volatile byproducts, including volatile metabolites from oral colonizing bacteria and those produced by bacteria that have migrated to other respiratory tissues. For the oral volatilome, 20 elderly individuals were unable to participate in this segment due to practical time conflicts such as work commitments, journeys, dental examinations and other health-related conditions. The withdrawal was not associated with any other underlying reasons. Thus, 10 elderly and 30 youth in the core participants were included in the study. A total of 116 VOCs were successfully detected. The elderly and the youth groups were well-distinguished by dimensionality-reduced oral volatilome, which was strongly consistent and indicative of sweetness detection thresholds (Fig. 6A). The top 30 compounds accounted for 87.1% of the abundance, which was considered representative and used for further analysis (Figs. S5 and S6). Differential abundance analysis of oral volatilome found that butyl acetate and methyl acetate were significantly up-regulated in the elderly, while 2,2,6-trimethyloctane, isoprene, octane, acetone, 2,2,5-trimethylhexane, 2-methylpentane, and 3-methylnonane were significantly down-regulated (Fig. 6B).

We next investigated the potential sources and effects of oral volatile compounds in oral microbiota. Pearson correlation coefficients of oral VOC-microorganism were computed (Fig. 7A). The weighted correlation network of oral microorganisms and oral volatile compounds can be divided into five modules, with *Leptotrichia* and *TM7x*, *Streptococcus* and *Lachnoanaerobaculum*, *Atopobium*, *Veillonella*, *Aggregatibacter* as central nodes (Fig. 7B). In the weighted correlation network, there were 18 microbial genera and 24 VOCs, including 15 alkanes, 4 alkenes, 2 ketones, 2 esters, and 1 alcohol. These compounds, especially ketones, esters, and alcohols, can originate from bacterial metabolism such as anaerobic bacterial metabolism and furfural metabolism. Specifically, 2-methylpentane showed a significant positive correlation with *Oribacterium* and *TM7x* in module 1, while isoprene and octane were positively correlated with *Lachnoanaerobaculum* in module 2. Additionally, 2,2,5-trimethylhexane exhibited a significant positive correlation with *Aggregatibacter* and *Lautropia* in module 5. These

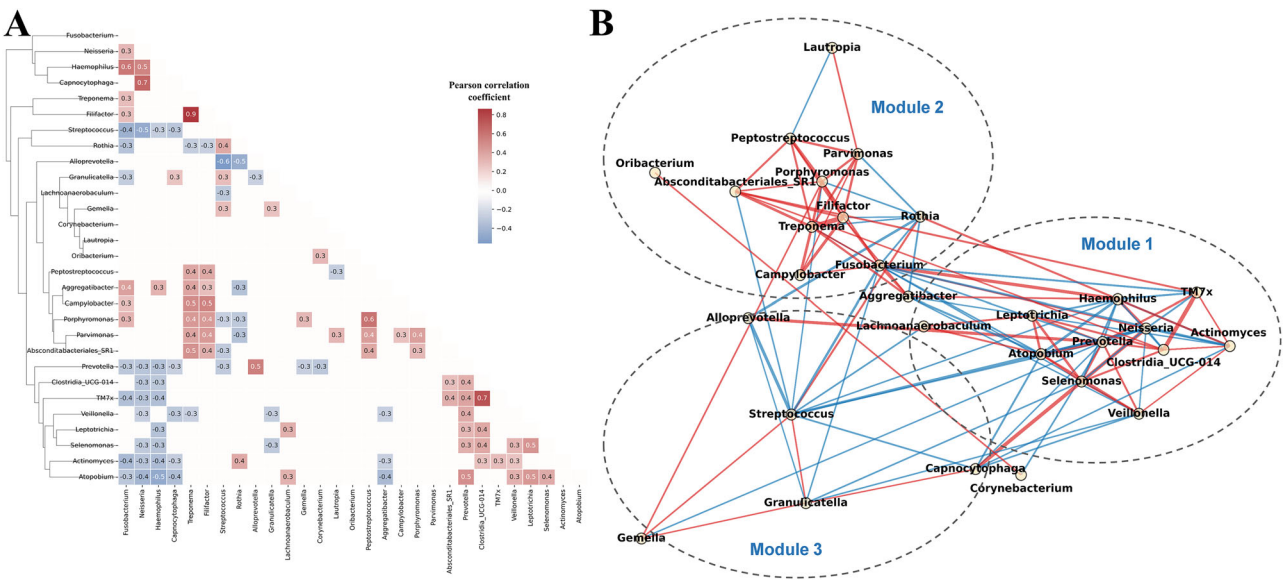

Fig. 5 | The correlation analysis of oral microorganisms. A The hierarchically-clustered heatmap of oral microorganisms (adjusted $p < 0.05$). Non-significant correlation coefficients were not displayed. **B** The weighted correlation network of oral microorganisms. Edge thickness is scaled according to the absolute value of Pearson correlation coefficients. Red line: positive correlation coefficient; Blue line: negative correlation coefficient.

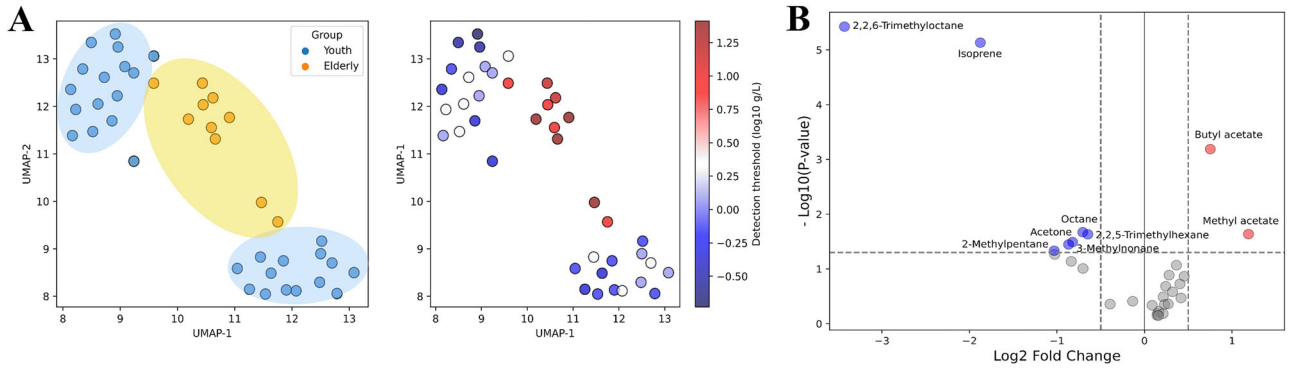

Fig. 6 | The identification of differential oral volatile compounds of the core group. A UMAP biplots of oral volatile compound concentrations with the youth/elderly labeled (left) and flavor detection thresholds labeled (right). **B** Differential abundance analysis of oral volatile compounds (adjusted $p < 0.05$, log2-fold change>0.5). Blue dots: significantly down-regulated; Red dots: significantly up-regulated. Fold changes were shown as the elderly versus the youth.

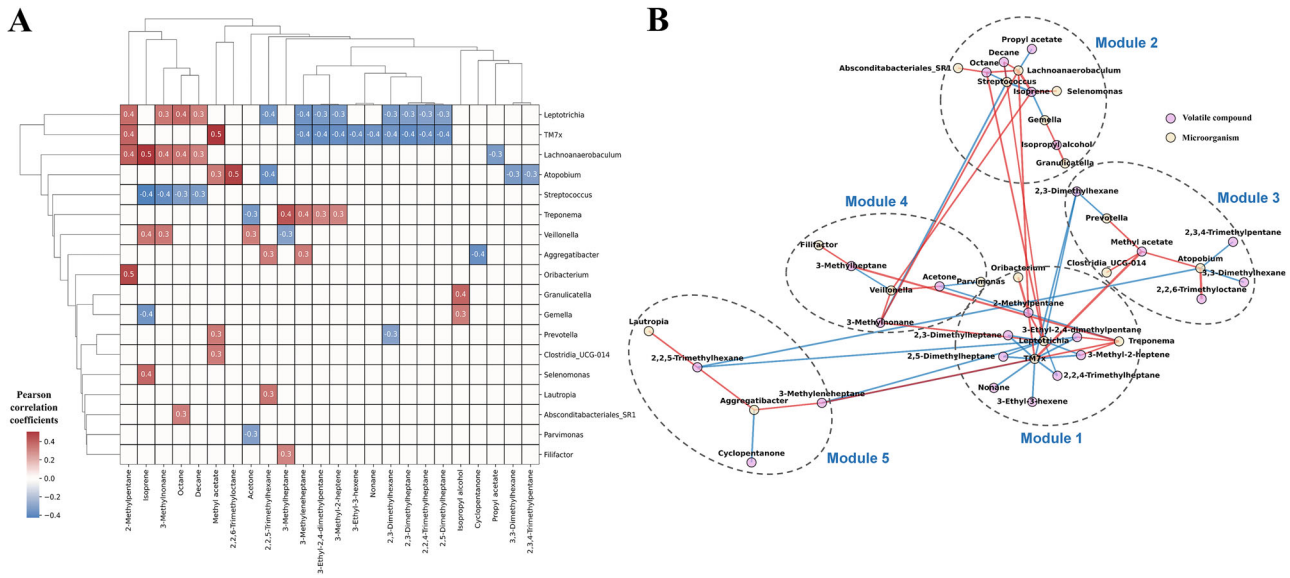

Fig. 7 | The correlation analysis of oral microorganisms and oral volatile compounds. A The hierarchically-clustered heatmap of oral microorganisms and oral volatile compounds (adjusted $p < 0.05$). Non-significant correlation coefficients were not displayed. **B** The weighted correlation network of oral microorganisms and oral volatile compounds. Edge thickness is scaled according to the absolute value of the Pearson correlation coefficients. Red line: positive correlation coefficient; Blue line: negative correlation coefficient.

compounds were all significantly down-regulated in the elderly compared to the youth, suggesting the potential ecological interactions mediated by oral VOCs for the decline of sweet taste perception associated with aging.

Discussion

The decline in taste perception is an important indicator of early aging. In this study, we quantified the fact that the elderly exhibited a marked decline in taste perception compared to the youth via DT and RT. Machine learning combined with statistical analysis further helped us identify five key bacteria genera positively associated with more sensitive sweet taste perception, namely *Haemophilus*, *Lachnoanaerobaculum*, *Fusobacterium*, *Aggregatibacter* and *Oribacterium*. Moreover, lower abundances of several VOCs in the elderly, especially the endogenous compound isoprene, were both significantly correlated with the key bacteria genera and sweet taste threshold. Collectively, taste decline-associated oral bacteria and volatilome can become potential biomarkers for the detection of early aging and/or decline in the perception system.

It is widely recognized that sweet taste brings happiness, and the responses to sweetness in particular influence food choices and acceptability[29,30]. Sweet taste perception, as well as the preference for high-sugar foods, is an innate characteristic of humans[31]. In the sweet taste sensitivity test, it was confirmed that aging people in the elderly showed a significantly lower sweet taste perception ability, i.e., higher sensitivity thresholds. Specifically, the sweetness thresholds in elderly individuals were approximately 2 to 4 times higher than that of youth, which was consistent with previous findings[32–34]. The inevitable decline in sensory acuity among elder adults not only acts as an index of aging but also can lead to reduced pleasure and food intake, which contributes to the condition referred to as anorexia of aging[35].

The region within the oral cavity created an ecological site conducive to the accumulation of saliva, food particles, and microorganisms. As a permanent resident of oral, the salivary microbiota appeared to represent a collective microbiota from various niches within the mouth, which could serve as a valuable source of biomarkers. Indeed, studies that focused on identifying core functional oral microbiota and their association with taste perception over different age groups were scarce and, generally did not apply exhaustive strategies for differential analysis. To our knowledge, this is the first study that applied machine learning algorithms to investigate the oral

microbiota and their role in taste decline with aging. This study demonstrated that the oral microorganisms in the elderly showed greater intragroup variation compared to younger individuals. By integrating LEfSe analysis, differential abundance analysis, and machine learning with the LR and SVC algorithm, five key bacteria genera considered as sweet taste perception-associated were identified at genus level. In the weighted correlation network, the five microbial taxa were distributed across module 1 and module 2. *Haemophilus* and *Lachnoanaerobaculum* were grouped in module 1, while *Fusobacterium*, *Aggregatibacter*, and *Oribacterium* were clustered in module 2. Notably, a significant positive correlation was observed among *Haemophilus*, *Aggregatibacter*, and *Fusobacterium*, indicating a symbiotic relationship. Furthermore, *Haemophilus*, as a common inhabitant of the oral cavity, was detected in all participants and reported to possess certain immunomodulatory effects[36]. As for the genus *Aggregatibacter*, it was designed to encompass species previously classified as *Haemophilus* and *Actinobacillus*, with the latter being famously known for *Actinobacillus actinomycetemcomitans*, one of the major pathogens of periodontitis in adults[37,38]. *Lachnoanaerobaculum* and *Oribacterium* both belonged to the phylum *Firmicutes*, while *Fusobacterium* was classified under the phylum *Proteobacteria*. In this work, correlation analysis further showed that *Haemophilus*, *Lachnoanaerobaculum*, *Fusobacterium* and *Aggregatibacter* were all significantly positively correlated with sweet taste sensitivity. Previous work suggested that the abundances of *Haemophilus*, *Fusobacterium*, and *Oribacterium* were significantly reduced in children with high sugar consumption compared to those with low sugar consumption[39]. *Lachnoanaerobaculum* and *Fusobacterium* have been reported to exhibit a negative correlation with the threshold of salty taste among young adults[11]. Although no significant correlation was found between *Oribacterium* and sweet taste perception, Cattaneo *et al.* described that it was overrepresented in the subjects with greater 6-n-propylthiouracil (PROP), an oral marker for taste sensitivity of a wide range of oral stimuli responsiveness[8]. In a nutshell, the reduction of the five key bacteria genera in the elderly may serve as an indicator for early aging diagnosis.

We further focused on the relationship between oral microbiota and oral volatilome. Extensive works have documented the sensory interactions between exogenous odors (from the environment or food) and taste in flavor perception[40–43]. However, the role of endogenous volatile compounds, particularly those produced through the metabolism of human microbiome in taste perception remains unexplored. Through differential abundance analysis, we revealed nine VOCs that were significantly up- and downregulated in the elderly. Among up-regulated compounds, butyl acetate, methyl acetate, acetone, and isoprene have been reported to be related to oral bacteria such as *Porphyromonas gingivalis*[44–46]. The other alkanes were likely products of bacterial fatty acid metabolism and catabolic metabolism, and more likely derived from exogenous gases in the environment. We found that 2-methylpentane was co-located with *Oribacterium* in module 1, isoprene and octane were related to *Lachnoanaerobaculum* in module 2, and 2,2,5-Trimethylhexane was linked to *Aggregatibacter* in module 5. Additionally, most of the downregulated compounds, such as 2-methylpentane, isoprene, 3-methylnonane, and octane, showed significant positive correlations with *Lachnoanaerobaculum*. Among these patterns, isoprene stood out as it was not only a typical endogenous component of exhaled breath but also exhibited a significant negative correlation with the sweetness threshold (Fig. S7). More importantly, isoprene was also positively correlated with *Lachnoanaerobaculum*, one of the five key bacteria genera (Fig. 7). It can be generated through the mevalonate pathway and the 1-deoxy-d-xylulose-4-phosphate/2-C-methylerythriol 5-phosphate pathway (with the latter prevailing in most bacteria), and the decrease in the concentration was correlated with immune activation[47]. These key differential VOCs, together with sweet taste perception-associated oral bacteria can become potential biomarkers for early detection of perception decline in aging people. Interestingly, a distinct clustering of volatilome data within the youth group was observed in Fig. 6A. No significant differences in baseline characteristics were observed between the two subgroups, indicating a hidden substructure within the youth that is worth further investigation.

The causation and mechanisms underlying age-related alterations in taste perception and oral microbiota, and even dietary preferences and host health remain areas of ongoing research. Given the complex host-microbe interactions, the bi-directionality of many of these associations is highly possible. Notably, the synergistic interactions among oral bacteria, rather than the specific relationships of individual species, should be taken into account. More interestingly, recent studies have suggested that gut microbiota can influence the host's taste perception[48,49]. Considering that oral microbiota can enter the gastrointestinal tract through eating and saliva swallowing, the interactions and balance between oral and gut microbiota are potential factors influencing the host taste acuity and diet preference. Besides, we employed 16S rRNA gene sequencing to determine oral microbiota diversity due to its advantages of low cost and high efficiency. However, it is challenging to quantify at species level. Metagenome is recommended to be conducted in the future work. Additionally, there were slight differences in the bacterial metabolic pathways between the youth and the elderly as predicted by PICRUSt2. Higher quality data should be used to further explore the role of oral microbiota metabolism in age-related changes in taste perception, such as integrating metabolomics and proteomics datasets.

In conclusion, this study confirmed the well-acknowledged recognition that elderly individuals exhibited lower sweet taste sensitivities and displayed distinct oral microbiota profiles compared to the youth. We proposed a unique bacteria-VOCs pattern for the elderly with diminished sweet taste sensitivity, which was marked by a reduction in the abundance of specific oral bacterial genera and volatile compounds in exhaled breath. This study offered valuable insights into the interplay among oral microbiota, oral volatilome, and taste perception during aging. With the future work, expectedly, our findings can contribute to enhancing sensory perception and enjoyment of food for the elderly as well as fresh detection methods for early aging.

Methods

Participants

140 individuals were recruited as a function of their age in Apr-Sept 2024 and stratified into two groups: (1) the elderly ($n = 85$) aged 55 to 85 years, recruited from communities in Fangshan District (Beijing, China). (2) the youth ($n = 55$) aged 20 to 30 years, recruited from Beijing Technology and Business University (Beijing, China). Details about the participants (including sex ratio, age and BMI) were given in Table 1 and Table S1. The exclusion criteria were: smokers, pregnancy or lactation, using antibiotics or undergoing specific dental treatments within the past three months.

All experiments were scheduled from 9:00 a.m. to 12:00 a.m. Each participant was asked not to eat or drink (allow water) for 1 h before the experiment. During oral sample collection, no toothpastes or mouthwashes were used to preserve the natural oral microbiome environment. Participants were instructed to rinse their mouths with purified water before and during the sensory evaluation sessions. This study was conducted according to the Declaration of Helsinki and approved by the Scientific Research Ethics Committee of Beijing Technology and Business University (No. 2024-118 and No. 2024-119, approved on 15/04/2024). Informed consent was obtained from all participants.

Sensitivity sensory test for the elderly and the youth

Sweet taste acuity was assessed based on the sensitivity threshold according to ascending three-alternative forced choice (3-AFC)[50], where a lower threshold indicates higher taste sensitivity. In brief, a series of sucrose solutions with varying concentrations, prepared using pure drinking water, served as sweet stimuli. Sucrose concentration levels were determined based on the standards of ISO 3972 with minor modifications[51]. The first sample was always pure water, followed by sucrose solutions in ascending order of concentration: from 2.59 g/L to 33.33 g/L for the elderly with a geometric ratio (R) of 0.6, and from 0.34 g/L to 12 g/L for the youth (R = 0.6) with the addition of 0.14 g/L and 0.24 g/L concentrations. This concentration range was designed to cover inter-individual differences in taste acuity, as well as to

allow for sorting expected individuals with heightened thresholds in the elderly and lower thresholds in the youth. A sample evaluation procedure was performed similarly to the reported work[52] and asked participants to provide their responses as outlined in Table S2. The detection threshold (DT) and the recognition threshold (RT) were calculated by Eq. (1):

$$C = \sqrt{C_n \times C_{n+1}} \quad (1)$$

Where C is the threshold, C_n is the last not correctly identified concentration and C_{n+1} is the next higher correctly identified concentration. If a participant correctly identified the different sample at all 3-AFC test levels, the threshold was calculated as the geometric mean between the lowest concentration and the previous hypothetical lower concentration. Conversely, if a participant failed at the highest concentration, the threshold was calculated as the geometric mean between the highest concentration and the next hypothetical higher concentration, assuming that the series has been extended.

Saliva collection and microbiota analysis

According to the threshold results, individuals with lower sensitivity (the threshold values above the median) among the elderly and those with higher sensitivity (threshold values below the median) among the youth were selected to form the core group for subsequent experiments. Unstimulated whole saliva was collected by direct spitting into 5 mL sterile plastic tubes (Suqian Wuwang Trading Co., LTD, Jiangsu, China), and immediately stored at -80 °C until further analysis. The characterization of salivary microbiota was conducted by 16S rRNA amplicon sequencing. Microbial DNA was extracted by using FastPure Soil DNA Isolation Kit (Magnetic bead) (MJYH, shanghai, China) according to the manufacturer's instructions. The hypervariable region V3-V4 was amplified with the forward primer 338 F (5'-ACTCCTACGGGAGGCAGCAG-3') and reverse primer 806 R (5'-GGACTACHVGGGTWTCTAAT-3'), as previously mentioned[53]. All final PCR products were subjected to electrophoresis on 2% agarose gel and purified with a PCR clean-up kit (Shanghai Majorbio Yuhua Bio-pharm Technology Co., Ltd, China). DNA library for paired-end sequencing was generated on an Illumina PE300 platform (Illumina, San Diego, USA). Data processing and sequence analyses were completed by Majorbio Bio-Pharm Technology Co., Ltd (Shanghai, China) by using standard protocols unless otherwise specified. Sequences exhibiting ≥97% similarity were clustered into the same Operational Taxonomic Unit (OTU), and the OTU table was manually filtered by removing chloroplast and mitochondria sequences. Raw FASTQ files were de-multiplexed using an in-house perl script, and then quality-filtered by fastp version 0.19.6 and merged by FLASH version 1.2.11. Then the optimized sequences were clustered into operational taxonomic units (OTUs) using UPARSE 11 with 97% sequence similarity level, and the OTU table was manually filtered by removing chloroplast and mitochondria sequences. The taxonomy of each OTU sequence was analyzed by RDP Classifier version 2.13 against the 16S rRNA gene database (including Silva v138, RDP v11.5, Greengene v13.5 and HPB) using a confidence threshold of 0.7. To minimize the effects of sequencing depth on alpha and beta diversity analyses, the number of 16S rRNA gene sequences from each sample was rarefied to the minimum sequencing depth across all samples, which still yielded an average Good's coverage of 99.8%, respectively.

At genus level, dimensionality reduction via Uniform Manifold Approximation and Projection (UMAP)[54] was applied to observe the distribution of oral microbial abundance for the youth/elderly. Differential abundance analysis was performed, using PyDESeq2[55], to find out significantly up/down-regulated microorganisms in the elderly, in comparison to the youth (as the reference group). The p and log2-fold change cutoffs were 0.05 and 0.5. For correlation network analysis, pairwise Pearson correlation coefficients (r) were computed for each genus-genus. Only significant correlations ($p < 0.05$) were used to construct weighted correlation networks. Nodes in networks were clustered using Clauset–Newman–Moore greedy modularity maximization[56] for the largest modularity, and then networks were visualized as undirected graphs by the network[57] in force-directed layouts. The *p-values* in differential abundance analysis and correlation analysis were all corrected for multiple testing using the Benjamini and Hochberg method[58]. From phylum to genus levels, the linear discriminant analysis effect size (LEfSe) analysis was applied to identify differential bacterial populations. Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt2) combined with the Kyoto Encyclopedia of Genes and Genomes (KEGG) database was used to predict biological functions based on OTU representative sequences.

Classification of the youth/elderly based on genus-level abundance

Logistic regression (LR), linear support vector machine (SVC), Bayesian ridge regression (BRR) and Gaussian process classifiers (GPC) were chosen as candidate classification models for age groups (i.e., elderly and youth), all implemented with scikit-learn[59]. The area under receiver operating characteristic curve (AUC ROC) was used to evaluate the classification accuracy in this study. First, 5-fold cross validation was used to select classification models (with hyperparameters untuned) of relatively high accuracy. Then, hyperparameter optimization was performed on selected classification models using randomized search with 5-fold cross validation. In each 5-fold cross-validation, the dataset was randomly divided into training and test sets with a 7:3 ratio. The details of hyperparameter optimization can be found in supplementary material (Table S3 and Supplementary Data).

With trained fine-tuned classification models, feature importance analysis was performed by computing the SHAP value[60] for each feature (microorganisms). The SHAP value, which originally quantifies each player's contribution in cooperative game theory, assigns each feature an importance score for the classification of age groups.

Quantification of oral volatilome in exhaled breath

Oral volatilome quantification was carried out by gas chromatography-mass spectrometry (GC-MS)-based non-targeted metabolomics. One sample of the morning breath was collected from each participant. Briefly, breath samples were collected by letting participants exhale into commercial aluminum-foil-based air sampling bags (2 L volume, BKMAMLAB, Hunan, China) under the guidance of laboratory personnel, following a method similar to that reported by Roslund K et al.[46]. Subsequently, the exhaled breath sample of each sampling bag was transferred to Tenax TA tubes (Shimadzu, Japan) at a constant flow (0.15 L/min) using the mini-pump MP-W5P (Shimadzu, Japan) with a total volume of 0.8 L. This process was completed within 24 h. Then, the tubes were sealed and stored at 4 °C for further GC-MS analysis within 3 days. GC-MS (GCMS-TQ8050 NX, Shimadzu Corporation, Japan) combined with a thermal desorption system (TD-30R, Shimadzu Corporation, Japan) was used to determine volatile organic compounds (VOCs) in exhaled breath. In the TD system, the compounds were desorbed at 250 °C for 5 min with a desorption flow rate of 60 mL/min and adsorbed on a cold trap with a temperature of −20 °C. Then the compounds were re-desorbed at 260 °C for 2 min and transferred to the GC inlet. The temperature of inlet and interface was 250 °C. Chromatographic separation was performed on the SH-Rxi-624MS capillary column (30 m × 0.25 mm × 1.4 μm, Shimadzu Corporation, Japan) under the following temperature program: an initial hold at 35 °C for 5 min, followed by a ramp at 5 °C/min to 150 °C and subsequently increased the ramp rate to 30 °C/min until 260 °C, and a final hold for 5 min. Helium carrier gas was used at a column flow of 2 mL/min and a split ratio of 10:1. Electron ionization (EI) source was equipped and undertaken at 250 °C. The acquisition mode of data was Q3 scan mode with a mass scan range of 30–350 m/z at a scan speed of 0.3 s/scan velocity. Data processing was performed using GCMSsolution software (Shimadzu, Japan). The qualitative identification of compounds was conducted by using the National Institute of Standards and Technology NIST20 Mass Spectral Library, ensuring a similarity index greater than 70. Moreover, retention indices (RI), calculated from n-alkanes, were employed to assist in the qualitative

analysis. Compounds with an RI deviation of 50 or less were provisionally identified, finally providing qualitative results. Normalization of peak area helped to quantify the abundance of different compounds in each exhaled breath sample. Further, the dimension reduction and differential abundance analysis of oral volatilome used the same methods as in Section "Machine learning revealed sweet taste perception-associated oral microbiota". Compound-microorganism Pearson correlation coefficients were computed, and the construction of a weighted correlation network followed the same procedure as in Section "Machine learning revealed sweet taste perception-associated oral microbiota".

Statistical analysis

Results were expressed as mean ± standard deviation unless otherwise stated. Statistical analysis was performed by Python 3.8.10, OriginPro 2018 software and IBM SPSS Statistics 25.0. Nonparametric comparisons between groups were performed by Mann-Whitney U tests for non-normally distributed data. For principal component analysis (PCA) and principal coordinates analysis (PCoA) analyses, Adonis was used to assess the significant changes in community between groups. Correlations across datasets were conducted by Pearson correlation analysis. $p < 0.05$ was considered significant.

Data availability

The raw sequencing reads were deposited into the NCBI Sequence Read Archive (SRA) database (Accession Number: PRJNA1206801). Other data are available upon reasonable request for academic use.

Code availability

Code are available upon reasonable request for academic use.

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Author contributions

Conceptualization H.N., S.Q., H.Z. and Y.W.; investigation H.N., S.Q., and W.L.; methodology H.N., L.W., and X.Z.; data curation H.N., S.Q.; writing-original draft H.N. and S.Q.; writing-review and editing H.Z. and Y.W.; funding acquisition H.Z.; project administration H.Z. and Y.W. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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