The differences of gut microbiota on schizophrenia with obesity and the potential effects of enterotype on metabolic pathways: cross-sectional study

Zhiyong Li
Peking University Sixth Hospital
Yang Shen
Peking University Sixth Hospital
Jiayu Gao
Henan University of Science and Technology
Yichen Huang
Peking University Sixth Hospital
Ye Yuan
Beijing Gene Tangram Technology Co.Ltd,Beijing, China
Meng Zhang
Beijing Gene Tangram Technology Co. Ltd, Beijing, China
Liang Ying (liangying1980@bjmu.edu.cn)
National Clinical Research Center for Mental Disorders,Peking University Sixth Hospital

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Abstract

Background: Recent studies have shown that gut microbiota has a certain influence on the occurrence of obesity. As a special classification of gut microbiota, different enterotypes have various preferences in metabolism. There is a significant risk of obesity in people with schizophrenia. This work proposed that the disorder of gut microbiota in patients with schizophrenia was based on microbial enterotypes, which promoted the increase of BMI.

Methods: 97 schizophrenia patients and 69 matched health controls were recruited. The fresh feces of all subjects were collected to complete 16S rRNA sequence. Statistical analysis was performed using R-3.3.1 and metagenomic data statistical analysis software for identification of enterotypes. The relationships within samples were visualized by principal co-ordinates analysis and significant differences in microbial community composition were detected using analysis of similarities.

Results: The BMI of schizophrenia was significantly higher than that of the controls. Patients with enterotype-P had a higher BMI than the others. There're several differences in the gut microbes of enterotypes-P between patients and controls. Proteobacteria and Firmicutes had significantly higher abundance in patients' group with enterotypes-P. The Bacteroidetes had higher abundance in health controls with enterotypes-P. There're several differences in the metabolic pathways of the microbiota which the enterotype P belonged in different BMI intervals.

Conclusions: The patients with schizophrenia had a significantly higher BMI than health controls. Patients with enterotype-P have a higher risk of BMI. The enterotype-P might affect a variety of metabolic pathways to disrupt the metabolism of glucose and lipid in human body.

Background

Schizophrenia is a chronic mental disorder with a high relapse and mortality rate.[1, 2] As the results of premature cardiovascular disease, suicide, and cancer, the schizophrenia patients have a significantly shorter life span than their peers nearly 25 years.[3, 4] Sudden cardiac deaths are more likely to occur in patients with schizophrenia. Psychiatrists therefore need actively concern on metabolic issues, such as obesity which could significantly increase the risk of cardiovascular diseases, in patients of schizophrenia.[5]

Patients with schizophrenia are at high risk to suffer metabolic disorders. The meta-analysis study pointed out that patients with schizophrenia had problems such as obesity, abnormal blood glucose and lipids, and even metabolic syndrome before receiving antipsychotic medication treatment.[6] In addition, treatment with antipsychotics, especially second-generation antipsychotics, can further aggravate metabolic abnormalities. The research has shown that the drug-naïve first-episode patients may experience significant weight gain and even develop obesity within one month after receiving the

antipsychotics.[7] These factors could adversely affect the compliance of patients under subsequent treatment, the occurrence and development of physical diseases, and long-term prognosis. In addition, obesity also can aggravate brain atrophy.[8] In a study of schizophrenia, it claimed that obesity could be an independent factor affecting the brain health of patients with first-episode schizophrenia, and the aging of the brain appeared earlier than the course of schizophrenia.[9] The results suggest that obesity may be one of the factors that promote and sustain structural changes in the brain of schizophrenia patients, and may ultimately contribute to cognitive decline.[10] Therefore, the schizophrenia associated with obesity urgently need the active attention and intervention.

Dipasquale S *et al*. reviewed 31 studies on the eating patterns of patients with schizophrenia and the patterns effect on metabolism, and indicating that people with schizophrenia prefer a diet high in fat and low in fiber. This unhealthy diet habits led to a high morbidity of metabolic abnormalities.[11] Similar diet habits could also be observed in high-risk individuals for schizophrenia.[12] This unusual diet has a major impact on the gut microbiome. Many studies have shown that the gut microbiota plays an important role in the occurrence and development of obesity.[13, 14] The enterotypes of gut microbiota are most closely determined by diet habits.

Manimozhiyan Arumugam *et al*. proposed firstly that human intestinal microorganisms could be divided into three kinds of enterotype, including enterotype-P, enterotype-B and enterotype-R.[15] Among them, the normal population with enterotype-P had a slightly higher BMI than those with other enterotypes. The formation of these enterotypes has no obvious relationship with the age, sex, cultural background and geographic location of the population, but it could be shaped by long-term diet habits.[16, 17] Therefore, this work hypothesized that the disorder of gut microbiota in patients with schizophrenia was based on microbial enterotypes, which affected the increase of BMI.

Taken together, the study will detect the gut microbiota of obese schizophrenia patients to explore the influence of obesity on enterotypes of gut microbiota, and further explore the underlying mechanisms.

Methods

2.1 Subjects

All subjects in this study were required to sign an informed consent form. According to the Helsinki Declaration, the sample collection and data analysis were performed with the approval of the Ethics Committee of the Demobilized Soldiers Kangning Hospital in Liaoning Province.

Referring to previous research standards, all subjects were from Han residents in Huludao, Liaoning Province, China. They had no special religious beliefs or eating habits. 97 schizophrenia patients and 69 matched healthy controls were recruited. All subjects were aged between 18 and 65 years; BMI was between 18 and 35 kg / m^2, and their weight was stable, no significant change in the past three months. The members of patient group were diagnosed as schizophrenia according to the SCID- IV-TR diagnostic manual, and were not accompanied by other types of mental disorders, personality disorders, and mental

retardation; the control group was free of any mental disorders, personality disorders, or mental retardation. According to WHO standards,[18] 18.5 ≤ BMI <25 is considered as normal; BMI ≥ 25 is considered as overweight or obesity.

Based on our previous research,[19] patients with the following conditions were excluded: 1) In addition to obesity, there are physical diseases reported in the literature that can affect the gut microbiota, such as hypertension, diabetes, and digestive diseases; 2) in the last 6 months taking drugs that might affect the gut microbiota, such as antibiotics, glucocorticoids and high-dose probiotics; 3) Medical examinations of the digestive tract, such as gastrointestinal, barium meal, etc. in the last 6 months 4) surgery on the digestive tract and biliary tract in the last 5 years; 5) there are obvious changes in eating habits in the past 3 months; 6) there are obvious restrictions on movement due to physical diseases, such as bedridden.

2.2 Clinical evaluation

For patients who met the inclusion and exclusion criteria, a questionnaire survey was conducted on all subjects using a Case Report Form, including: age, gender, ethnicity, occupation, height, weight, previous medical history, medication history, history of surgery, consumptive history of tobacco and alcohol.

2.3 Collection of stool samples

Patients were firstly instructed to urinate before defecation to prevent urine from diluting or contaminating feces. The feces were drained into a clean container or on a clean urine pad. After defecation, the staff opened the sterile sampling bottle, peeled off the feces with a small spoon which on the inner cover of the sampling bottle, and dug the middle part of the feces. Repeatedly dug feces into the sampling bottle until about 2g samples were collected. The cap of the sampling bottle was then screwed tightly and quickly placed in a container containing liquid nitrogen for transportation. And make sure that it was transferred to -80℃ refrigerator and stored frozen within 1 hour. The samples must be placed in a container filled with liquid nitrogen and attended by a special person no matter a short or long-distance transportation.

2.4 16S rRNA amplification of V3-V4 region and Illumina sequencing

Fresh fecal samples were taken from 166 subjects, and all samples were stored in a -80℃ refrigerator until DNA extraction. According to the manufacturer's instructions, PowerSoil DNA kit (MoBio, USA) was used to extract 200 mg feces per sample for DNA extraction. The 16S rRNA (V3-V4) gene marker was amplified using KAPA HiFi HotStart ReadyMix (KAPA, USA). Each DNA sample of the bacterial 16S rRNA gene was amplified with primers 341F (GGACTACHVGGGTWTCTAAT) and 805R (ACTCCTACGGGAGGCAGCAG). Amplification was performed in triplicate by PCR. The amplicons were analyzed on a 1.5% agarose gel electrophoresis, and a band of a desired size was purified using a QIAquick gel extraction kit (QIAGEN, Germany). The products were sequenced on the Illumina HiSeq 2500

platform and submitted to the second-generation sequencing laboratory of the Beijing Institute of Bioinformatics.

2.5 Statistical analysis and bioinformatics analysis

2.5.1 Processing of sequencing data

Raw sequence data was processed and analyzed with QIIME software (Quantitative Analysis of Microbial Ecology, Version 1.9.1) [20]. Separation, ligation, and quality filtering of the forward and reverse sequencing fragments of each sample. Fragments that contain ambiguous characters in the sequence or that contain more than two nucleotide mismatched primers need to be removed. The "open reference" QIIME protocol and other default parameters of the UCLUST method were used to select operational taxonomic units (OTUs). When performing statistical analysis of biological information, to understand the number of bacteria and genus in a sample sequencing result, it was necessary to perform the classification operation and OTU division on all sequences according to the specified similarity (95%, 97%, or 98%, etc.). This study brought together sequences with at least 97% similarity, and used representative sequences from each cluster to identify bacterial taxa from the Greengenes database that was launched on August 13, 2013.[21] OTUs containing less than 2 sequences or an overall relative abundance of <0.00005 were deleted and no further analysis was performed. Because the sequence number of each sample obtained from the sequencing results was variable, the sequence data of each sample was refined into 10,000 sequences to consider the variation in sequencing depth.

2.5.2 Statistical analysis of clinical data

Statistical analysis was performed using SPSS19.0 software. Gender, tobacco and alcohol consumption of all participants were expressed as a proportion or percentage, and the chi-square test was used for the count data. Measurement data, such as age and body mass index (BMI), conformed to the normal distribution for independent sample t test. The study took $P < 0.05$ as statistically significant.

2.5.3 Statistical Analysis of Sequencing Data

Statistical analysis was performed using R-3.3.1 and metagenomic data statistical analysis software.[22] Participants whose gut microbiota mainly predominantly Prevotella was marked as enterotype P, and whose gut microbiota mainly predominantly Bacteroides was marked as enterotype B. Based on this, the subjects could be divided into four groups: patients with enterotype P group (SCH-P), patients with enterotype B group (SCH-B), controls with enterotype P group (HC-P), and controls with enterotype B Group (HC-B). Independent t-test, Welch t-test, and White nonparametric t-test were used in continuous variables. For categorical variables between groups, Pearson's chi-square test or Fisher's exact test were used based on the validity of the hypothesis.

Visualization of the relationship between samples was performed with a principal coordinate analysis (PCoA) based on an unweighted UniFrac distance matrix, and significant differences in the composition

of the microbial community were tested with ANOSIM.[23] All significance tests were two-sided tests, and p <0.05 or adjusted p <0.05 was considered statistically significant.

2.5.4 Gut microbiota abundance

Linear discriminant analysis (LDA) effect size (LEfSe, v1.0) was used to analyze the significant differences in relative abundance of gut microbiota categories related to patients with enterotype P group and controls with enterotype P group.[24] Moreover, the work further compared the differences in metabolic pathways of patients with enterotype P with the body mass index of more than 25kg/m2 (BMI-A group) and less than 25kg/m2 (BMI-N group) . Wilcoxon rank sum test for α = 0.05, and the log value of LDA analysis was set to <2.0.[25]

Results

3.1 Demographic characteristics

According to the inclusion and exclusion criteria, a total of 97 patients with schizophrenia and 69 healthy controls were recruited, and the male to female ratio was 43/54 and 33/36, respectively. There were no statistical differences between the two groups in terms of gender, age, smoking status, and drinking status (P> 0.05). (Table 1.) There were 46 patients in the SCH-P, 51 patients in the SCH-B, 21 patients in the HC-P, and 48 patients in the HC-B.

Table 1. Demographic characteristics of the schizophrenia patients and healthy controls.

Characteristic	Schizophrenia（n=97）	Healthy（n=69）	p-value
Age（mean±SD）	46.93±12.88	46.48±12.24	0.825
Male/Female	43/54	33/36	0.752
Height（mean±SD）	1.70±0.05	1.69±0.07	0.786
Weight（mean±SD）	72.72±9.60	69.43±10.81	0.040*
BMI（mean±SD）	25.26±3.26	24.12±3.02	0.023*
Alcohol intake（ratio%）	16.49	21.74	0.424
Tobacco intake（ratio%）	20.62	23.19	0.706

BMI, body mass index. * p-value < 0.05 was considered statistically significant.

3.2 Distribution of BMI

By comparing the distribution of BMI, the BMI (25.26±3.26 kg/m^2) of the patients group was slightly higher than that of the controls group (24.12±3.02 kg/m^2), and there was a significant difference between the two groups. On the basis of enterotype classification, the BMI of the SCH-P group (25.40±3.27 kg/m^2)

had a tendency to increase compared with others（HC-B, 24.46±3.28 kg/m^2; SCH-B, 25.13±3.28 kg/m^2; HC-P, 23.32±2.17 kg/m^2）. (Figure 1) The distribution ratio of SCH-P group in the high BMI interval increased significantly. The change was statistically significant. The distribution ratio of other groups was more concentrated in the normal range. (Figure 2)

3.3 Microbiota differences between the patients and control enterotype P group

By analyzing the gut microbiota difference and abundance of patients and controls, the abundance of Proteobacteria and Firmicutes in the SCH-P group was significantly higher than that in the HC-P group. The Bacteroidetes in the HC-P group had higher abundance. Among them, the abundance of the Succinivibrio, Gammaproteobacteria, Proteobacteria, Succinivibrionaceae, Aeromonadales, Enterobacteriaceae in the SCH-P group increased most significantly. In the HC-P group, the abundance of Bacteroides_plebeius, Bacteroides, Bacteroidia, Bacteroidetes, Bacteroidales, and Bacteroidaceae was significantly increased. (Figure 3)

3.4 The distribution difference of gut microbiota of enterotype P in schizophrenia group between the weighted and unweighted interval

The subjects with schizophrenia enterotype P were divided into BMI normal group (BMI-H, 18-24.9kg / M2) and BMI abnormal group (BMI-L, ≥25kg / M2) according to body mass index. As seen in Figure 4, the abundance of Firmicutes in the BMI-H group was significantly increased, while the increase of the abundance of Bacteroidetes in the BMI-L group was dominant. (Figure 4)

According to clustering and differential analysis of metabolic pathways in the two groups by LEfSe analysis, there were several differences in the metabolic pathways of the microbiota which the enterotype P belonged in different BMI intervals. BMI-H group had outstanding effects on glycerolipid metabolism, glycerophospholipid metabolism, fat digestion and absorption, and degradation of glycosaminoglycans. (Figure 5) This may affect the body's absorption and metabolism of fat.

Discussion

This study further verified that the proportion of obese patients in schizophrenia was higher than that in the normal population, which was consistent with the results of previous studies.[26, 27] In addition, the gut microbiota of schizophrenia with obesity had certain differences, which was characterized by the enterotype P as the prominent phenotype. The enterotype was characterized by unique digestive functions and a preference for specific food substrates.[28, 29] Among them, the enterotype P is mainly classified by the Prevotella genus, which has abundant hydrolases that can specifically degrade plant fibers, but the ability to decompose lipids and proteolytic fermentation is obviously insufficient. Most of the people with weaker lipid metabolism belong to this kind of enterotype. A high-fiber diet was likely to help enterotype P subjects to control their weight.[28, 29] However, this was contrary to the eating habits of schizophrenia patients. Due to the abnormal metabolism of lipids in the intestine, schizophrenia patients were more prone to chylous diarrhea. In this study, the subjects with high BMI of enterotype P

showed relatively good lipid metabolism, which may due to the environmental adaptation of the gut microbiota under the effect of high fat and high calorie diet in schizophrenia.

Compared with other enterotypes, enterotype P fecal samples can ferment *in vitro* to produce more short-chain fatty acids, especially the levels of propionate are more prominent.[30] Studies have shown that propionate can inhibit human feeding behaviors by regulating intestinal hormones.[31] In the study of Chambers ES *et al*., propionate was found to significantly promote the release of intestinal hormones such as peptide YY and glucagon-like peptide-1 by human colon cells.[32] The increase of these substances promoted the reduction of energy intake, and long-term supplementation of propionate could effectively reduce weight gain, distribution of adipose tissue in the abdominal cavity, lipid content in liver cells, and prevent deterioration of insulin sensitivity. All of this may improve the status of obesity.[33, 34] Therefore, enterotype changes in patients with schizophrenia may be the greatest efforts for the gut microbiota as a special ecology in the human body to reverse the situation of obesity.

Although this study provided new ideas on the impact of gut microbiota on schizophrenia with obesity, it was subject to sample size and cross-sectional research. The sample size needs to be expanded to strengthen follow-up observations to further clarify the changing of the gut microbiota. Secondly, limited to the 16s rRNA sequencing technique, this study only compared and distinguished the enterotype, and the metabolic function of the gut microbiota of the main enterotype could not be excavated yet. In future research, it should further define the gut microbiota by functional methods such as metabolomics and proteomics. By further exploring the relationship between the types and functions of gut microbiota, it could establish a targeted microbial transplantation strategy, rather than simply destroy and rebuild.

Conclusion

In conclusion, this study found that patients with schizophrenia had a significantly higher BMI than health controls. Patients with enterotype-P had a higher risk of BMI. The enterotype-P might affect a variety of metabolic pathways to disrupt the metabolism of glucose and lipid in human body.

Abbreviations

BMI: Body mass index

SCID-IV-TR: The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders - IV-TR

WHO: World Health Organization

OUT: Optical Transform Unit

LDA: Linear discriminant analysis

PCoA: Principal coordinate analysis

SPSS: Statistical Product and Service Solutions

ANOSIM: analysis ofsimilarities

16S rRNA: 16S ribosomal Ribonucleic Acid

Declarations

Ethics approval and consent to participate

The study was explained to all participants both verbally and in writing, and written informed consent was obtained from each participant. According to the Helsinki Declaration, the sample collection and data analysis were performed with the approval of the Ethics Committee of the Demobilized Soldiers Kangning Hospital in Liaoning Province.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Author contributions

YL designed the study and wrote the protocol. ZYL, JYG and YY managed the literature searches and analyses. ZYL, YCH and MZ undertook the statistical analysis, and YS, ZYL and JYG wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Figures

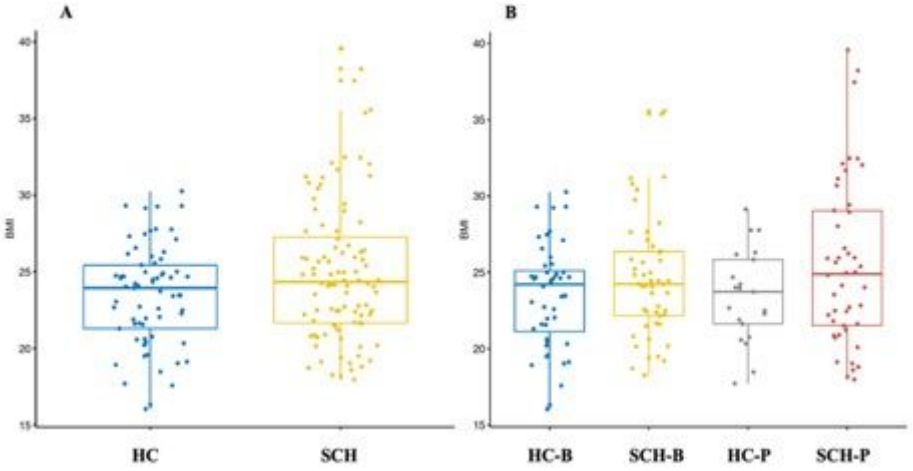

Figure 1

Box-plot (A) Independent sample t-test was conducted for the two groups. BMI of schizophrenia was significantly higher than the healthy controls. (B) All subjects were divided into four groups based on the enterotypes. Through analysis of variance, it found that BMI of schizophrenic patients with Prevotella-type showed an increasing trend.

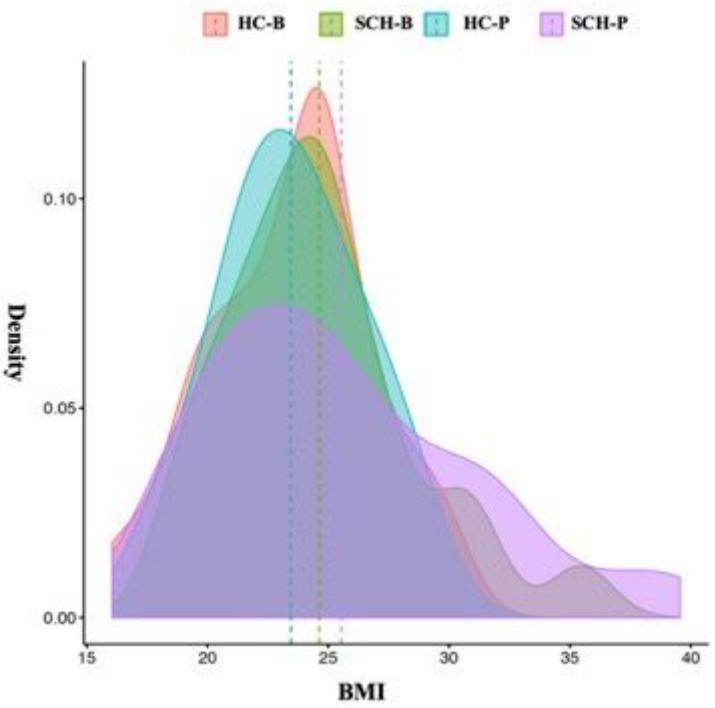

Figure 2

The chi-square test showed that the number of Prevotella-type subjects in the SCH group was significantly higher than that in the healthy controls. The normal distribution showed that schizophrenia with Prevotella-enterotype have a higher BMI.

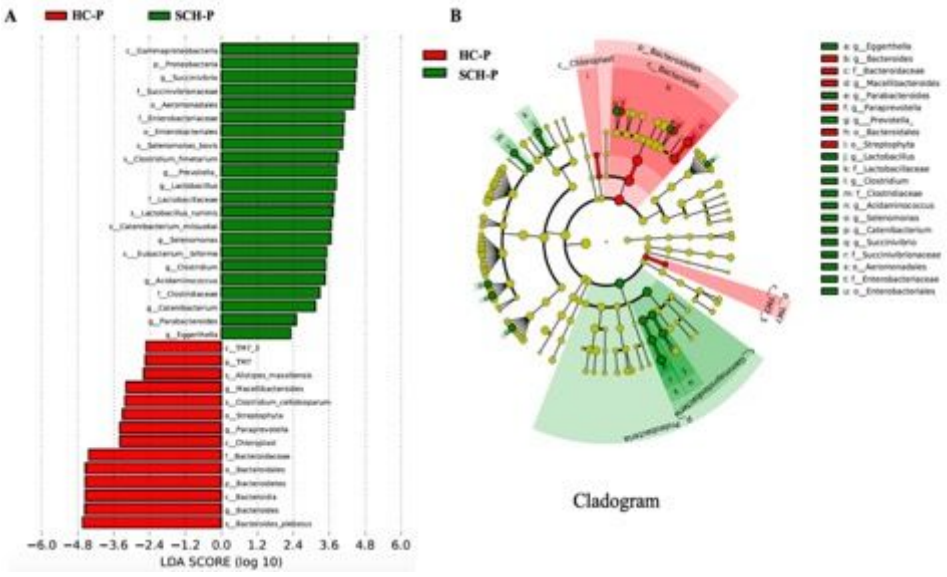

Figure 3

Differently abundant taxa identified using LEfSe analysis. (A) Visualization of only taxa meeting an LDA threshold ≥2. (B) LEfSe Cladogram showed the most differentially abundant taxa between the two groups. Taxa enriched for healthy with Prevotella-enterotype in red; schizophrenia with Prevotella-enterotype enriched taxa in green. The brightness of each dot was proportional to its effect size.

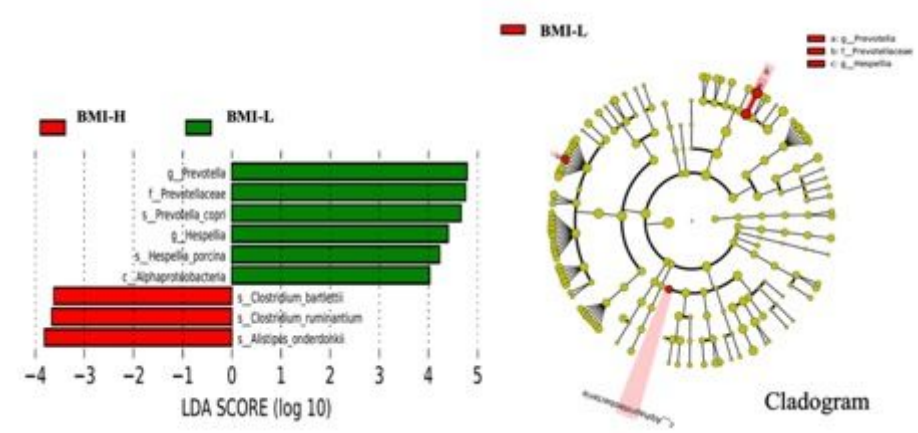

Figure 4

Differently abundant taxa identified using LEfSe analysis. (A) Visualization of only taxa meeting an LDA threshold 2. (B) LEfSe Cladogram showed the most differentially abundant taxa between the two groups. Taxa enriched for body mess index above 25kg/m2 in red and below 25kg/m2 in green. The brightness of each dot was proportional to its effect size.

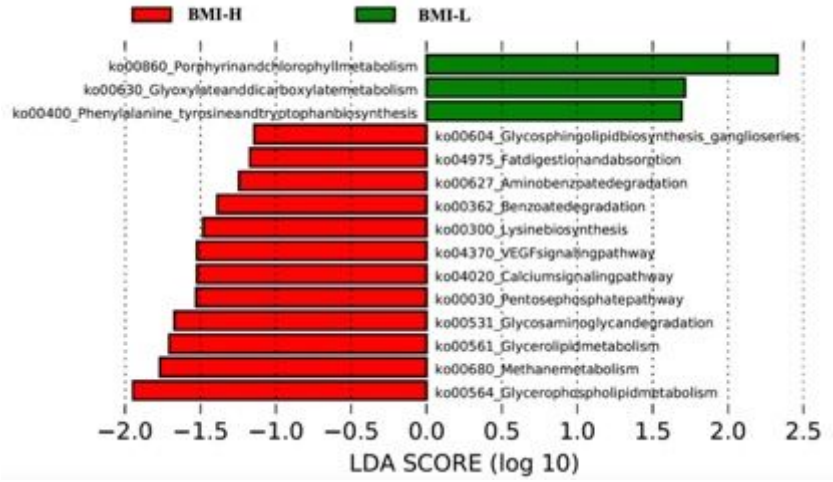

Figure 5

Pathway clustering analysis based on LefSe classification showed that gut microbiota in different weight ranges expressed different metabolic pathways. The gut microbiota of patients with high BMI can express more pathways related to disordered glucose and lipid metabolism.