

Impact of Human Microbiome on Polycystic Ovary Syndrome

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Abstract

Polycystic ovarian syndrome (PCOS) is a complex endocrine and metabolic disorder commonly seen in women of reproductive age that is affected by multiple factors, one of which is the intestinal microbiome. However, the specifics of how gut microbes play a role in PCOS are unclear. The purpose of this study is to investigate the transformational changes in gut microbes in PCOS patients and the possible mechanisms by which the intestinal microbiome influences the progression of PCOS. As microbiomes have recently emerged as sources of treatment for various conditions, it is beneficial to understand the role of the microbiome in PCOS to acquire a potential therapeutic method for PCOS patients.

Background

Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder affecting females, typically during their reproductive years. It's characterized by hormonal imbalance, irregular menstrual cycles, ovarian cysts, and often insulin resistance. PCOS affects approximately 1 in 10 women of childbearing age worldwide, making it one of the most common endocrine disorders in this demographic. The exact cause of PCOS remains elusive, but it's believed to involve a combination of genetic and environmental factors. Insulin resistance and hormonal imbalances, particularly elevated levels of androgens, play significant roles in its pathogenesis. Symptoms vary widely and include infertility, weight gain, acne, excess facial or body hair, and mood disturbances which contribute to various physical and mental health issues for women with this condition.¹

Recent research suggests a potential link between PCOS and the human microbiome, particularly intestinal and vaginal microbiomes. Studies have revealed alterations in the gut microbiota composition among women with PCOS compared to healthy controls. These alterations may contribute to inflammation, insulin resistance, and metabolic dysfunction observed in PCOS. Understanding this connection opens avenues for novel therapeutic approaches. Modulating the microbiome through interventions like probiotics, prebiotics, or dietary changes holds promise in alleviating some symptoms of PCOS. For instance, certain probiotic strains have demonstrated the ability to improve insulin sensitivity and reduce inflammation in animal models and small-scale human trials. Additionally, dietary modifications that promote a healthy gut microbiome, such as increased fiber intake and reduced consumption of processed foods, may help manage PCOS symptoms by restoring microbial balance and mitigating inflammation.²

These findings lead us to question the inner workings of the microbial realm: *How do the alterations in the microbiome affect PCOS? Is it possible to reverse some of these effects by treating the microbiomes?* The proposed study is designed to achieve a more pronounced understanding of the interactions between the microbiome and PCOS. This information can be used to determine how the microbiota can be improved in patients to help alleviate and even possibly treat the impacts of PCOS.

Experimental Design and Methods

Researchers in China conducted a study to explore the potential link between gut hormones, gut bacteria, and mental health in women with PCOS. They recruited 48 women aged 17-45 and meticulously divided them into four groups: obese with PCOS (PO), non-obese with PCOS (PN), obese controls (CO), and non-obese controls (CN). This ensured a balanced comparison across weight and PCOS status.

The study employed a multi-pronged approach to gather data. Blood samples collected after overnight fasting (≥ 8 hrs) were analyzed for ghrelin, plasma serotonin, and peptide YY (PYY) using an enzyme-linked immunosorbent assay (ELISA) (FIGURE 3). Other assay methods were used to analyze other hormones such as testosterone, etc. This provided insights into the hormonal profile of each participant. Fecal samples were also collected and frozen until analysis. These samples were examined to identify the composition of gut bacteria using DNA extraction and sequencing, potentially revealing differences between the PCOS and control groups. Finally, mental health questionnaires assessed the participants' emotional state, allowing researchers to evaluate potential connections between PCOS, gut health, and mental wellbeing.

In order to attain the data, the 16sRNA gene was amplified using the following forward and reverse primer sequences:

16S Amplicon PCR Forward Primer = 5'

TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGCTACGGGNGGCWGCAG

16S Amplicon PCR Reverse Primer = 5'

GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGACTACHVGGGTATCTAATCC

As the correlation between the imbalance of gut microbiota and polycystic ovary syndrome is being studied, the V3-V4 region of the 16sRNA gene was amplified. This region is a highly variable region that is known to reveal microbial diverse populations. The primers in the sequence need to be cut out of the sequence so that the important part of the gene can be analyzed.

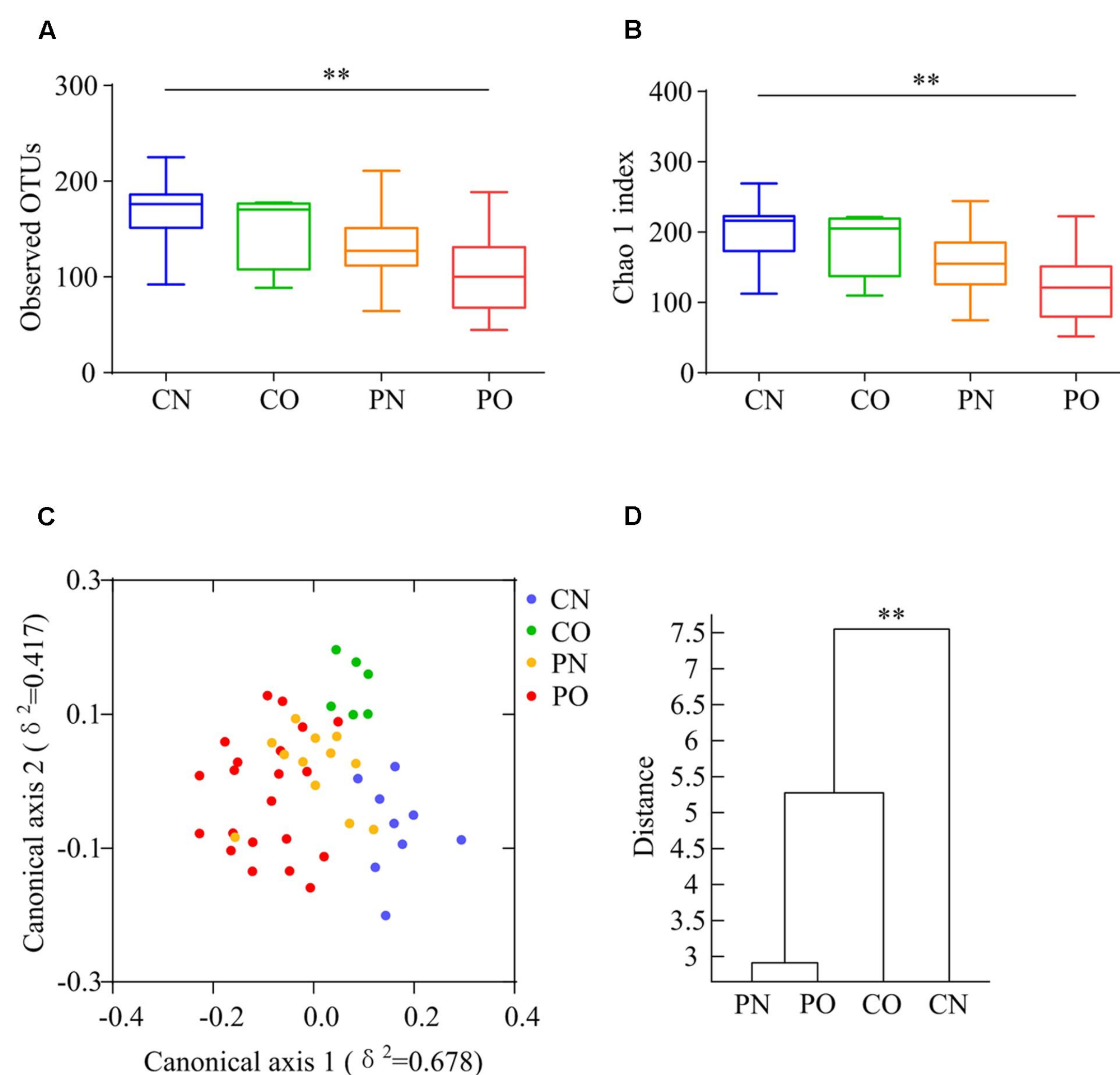


FIGURE 1. Overall structural differentiation of gut microbiota based on distance between four groups.

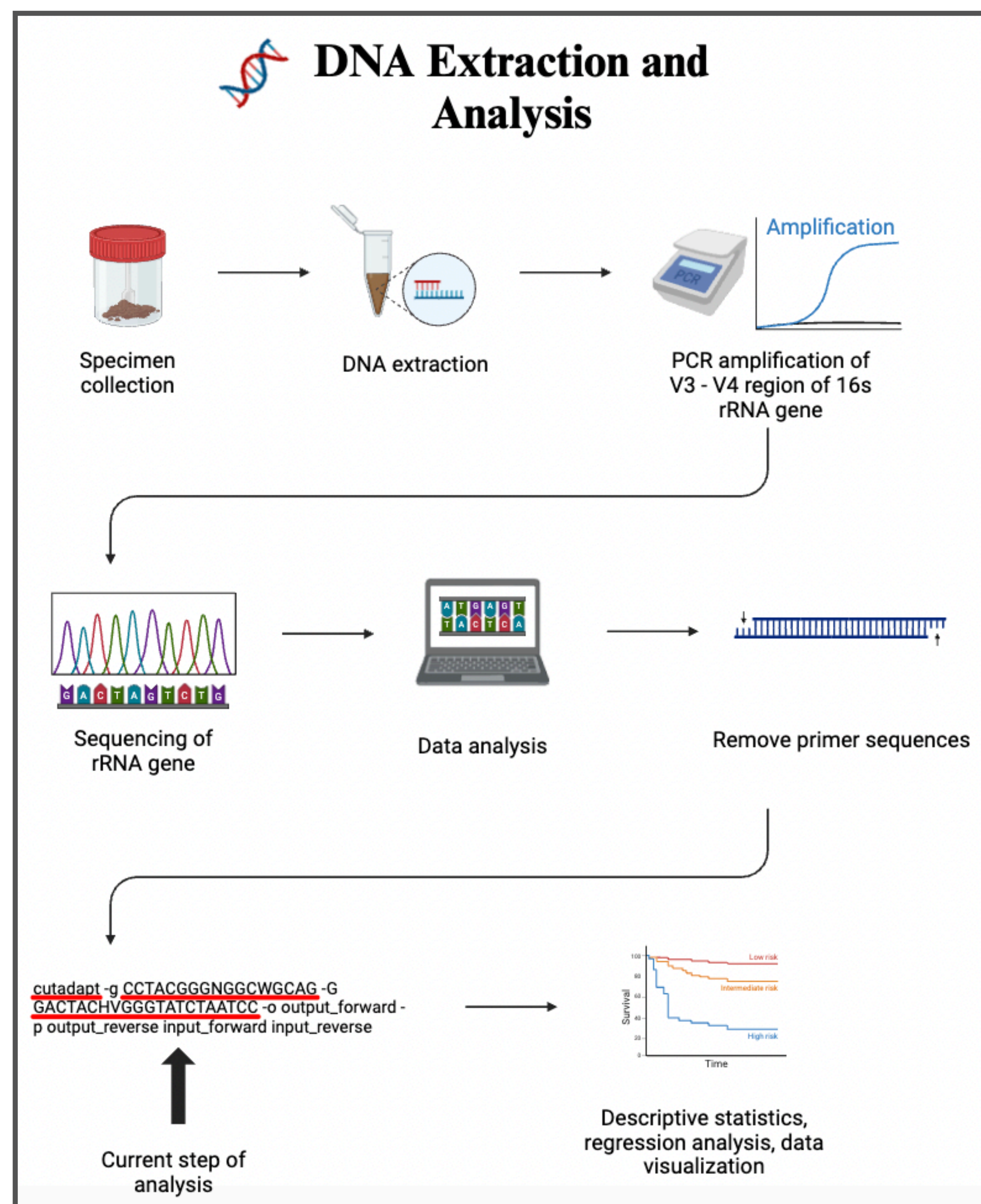


Figure 3. Process of obtaining and analyzing data to determine impact of gut microbiome on PCOS

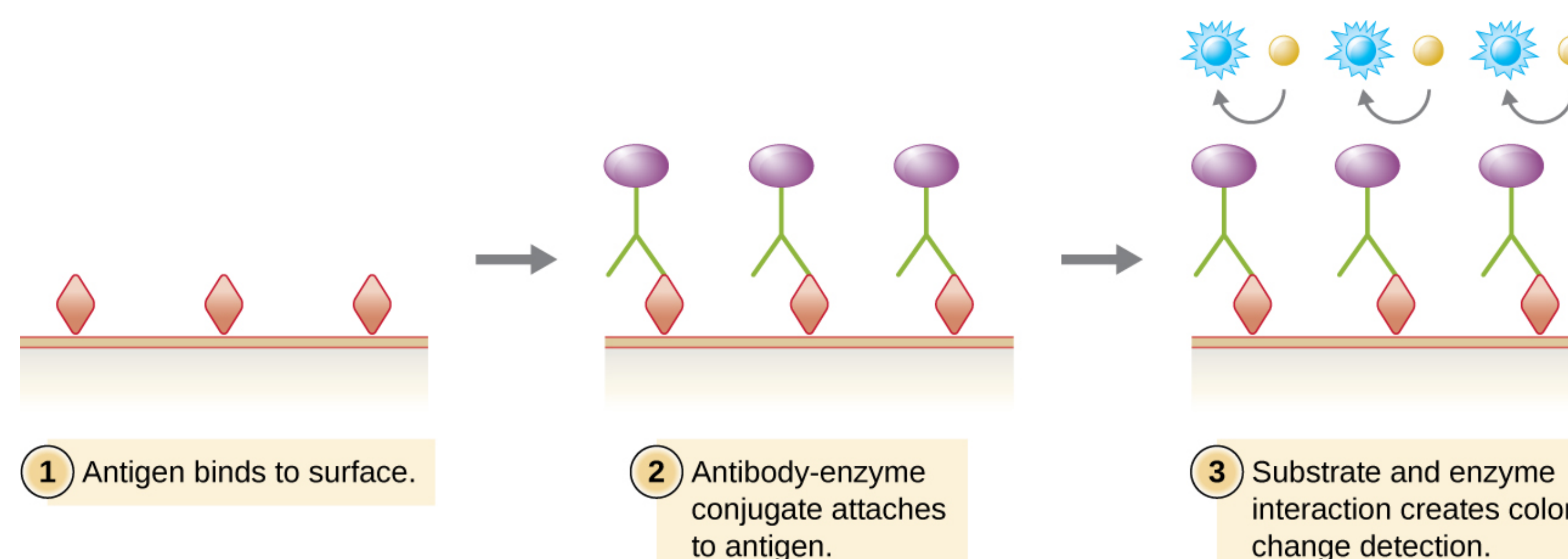


FIGURE 4. ELISA procedure used to analyze blood samples after fasting.

Results

Compared to women without PCOS, women with PCOS showed significantly higher levels of testosterone and hirsutism score. PO group also had increased levels of metabolic parameters and SDS value than PN group, indicating that excess weight aggravated the metabolic abnormalities in women with PCOS. The level of serotonin was significantly higher in CN group than the other three groups. The level of ghrelin was lower in women with PCOS compared with women without PCOS, and it was also lower in obese women with PCOS compared with non-obese women with PCOS. PYY showed a significant decrease in PO group compared with CN and CO groups, while PN group was also decreased compared to CN and CO and it was higher than the PO group. Both PCOS patients and obese individuals possessed abnormal levels of the mediators of the brain-gut axis.²

According to observed OTUs and the Chao1 index, CN group owned the highest richness, followed by CO and PN group, and PO group showed the lowest richness of gut microbiota. The gut microbiota composition of CO group was more similar with that of PN and PO groups, rather than CN group. The overall composition of the gut microbiota was disrupted in PCOS.²

OTU4 belonging to genus *Bacteroides* was enriched in PO group than CN and CO groups ($P < 0.01$ and $P < 0.05$, respectively), with PN group falling in between them. The average relative abundances of 21 OTUs were higher in CN group than PO group ($P < 0.05$), which mostly belonged to the genera *Akkermansia*, *Bacteroides*, *Clostridium* IV, *Lactobacillus*, *Oscillibacter*, or unclassified genera from family *Ruminococcaceae*, while in CO and PN groups, the abundances of these OTUs were lower than CN group but were higher than PO group. Five OTUs were enriched in CO group, which belonged to the genera *Collinsella*, *Paraprevotella*, *Slackia*, and unclassified genera from class *Clostridia* and kingdom *Bacteria*. OTU7 belonging to *Bacteroides* showed decreased abundance in CO group, compared with the other three groups (Figure 2).²

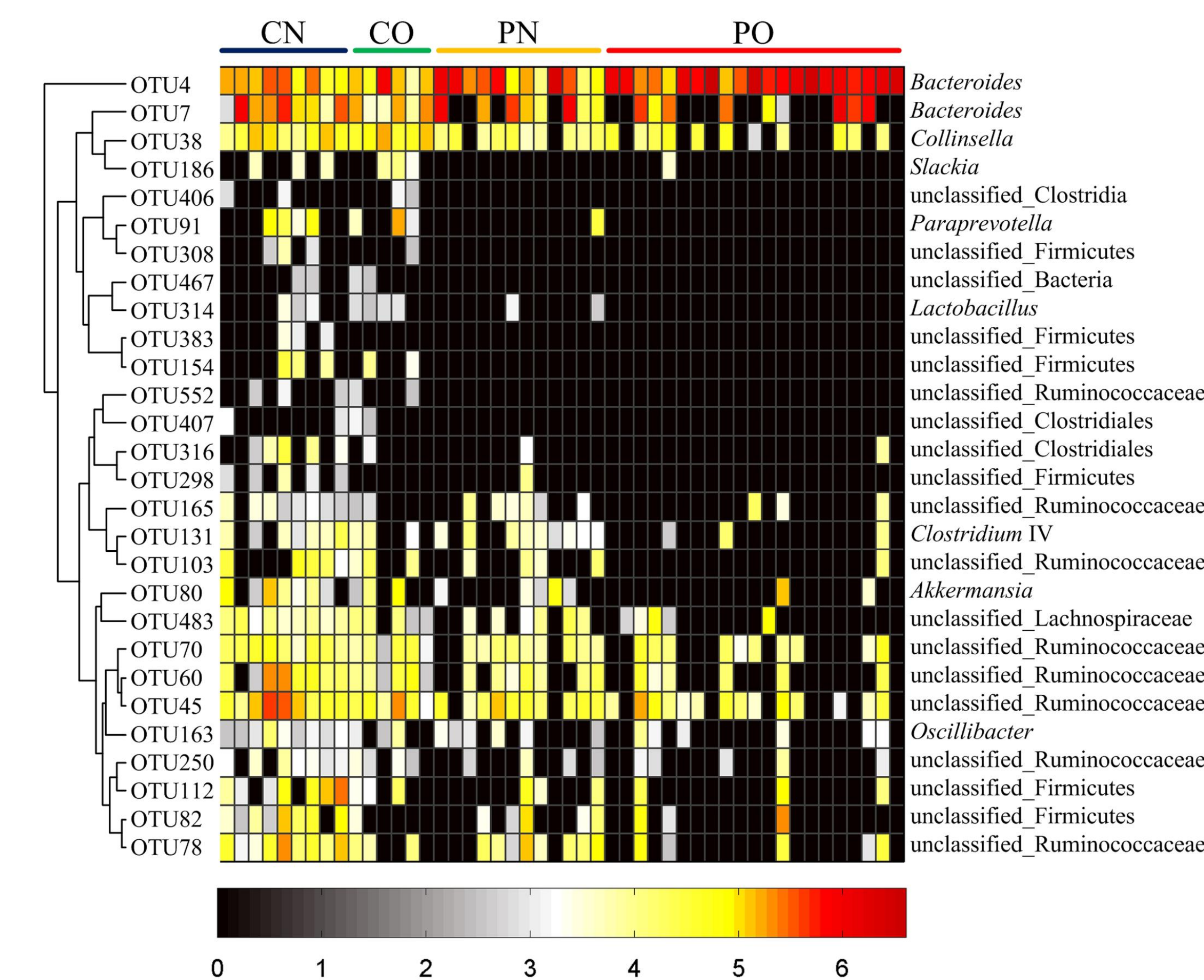


FIGURE 2. Heat map of the relative abundances of 28 key OTUs related to the alteration of gut microbiota between the four groups.

Conclusion

The study investigated the link between gut bacteria and PCOS in women. They found that the gut bacteria composition differed in women with PCOS compared to healthy controls, regardless of weight. This difference was similar to what's seen in obesity. The gut bacteria imbalance was linked to PCOS symptoms like hormone levels and metabolism. The study also looked at gut hormones that affect appetite and mood, finding lower levels in PCOS patients. Certain gut bacteria may influence these gut hormones. Overall, the study suggests gut bacteria may play a role in PCOS and warrants further investigation into the mechanisms behind these impacts and how treatments can be designed that target improving the microbiome to improve PCOS symptoms.

Currently, logistical and computational errors have prevented the obtaining of data to compare and validate the results from the study. Efforts are being put into determining how to simultaneously run the cutadapt command for all the data acquired. This will allow for a more comprehensive analysis that will shed more light on the relationship between the gut microbiome and PCOS symptoms.

References

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- [2] Wang L; Zhou J; Gober HJ; Leung WT; Huang Z; Pan X; Li C; Zhang N; Wang L; "Alterations in the Intestinal Microbiome Associated with PCOS Affect the Clinical Phenotype." *Biomedicine & Pharmacotherapy = Biomedicine & Pharmacotherapie*, U.S. National Library of Medicine, pubmed.ncbi.nlm.nih.gov/33171400/.