Metagenomics Analysis of Race and Age influence on the Vaginal Microbiome in Pregnant and Non-pregnant Healthy Women

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Research Article

Keywords: vaginal microbiome, Race, pregnant, non-pregnant

Posted Date: March 24th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-291962/v1

Abstract

Various human body parts are host to many microbial species and have a mutualistic relationship with them. The presence of these microbial species in reproductive tubes plays an essential protective role against the proliferation of harmful organisms and is an important factor in reproductive health. The vaginal microbiota during pregnancy plays a vital role in the health of the mother and the infant. Microbiota imbalance during pregnancy is associated with many complications. As a result, the detection of vaginal microbiota during pregnancy can reduce the risk of these problems. High-throughput culture-independent technologies allow the study of vaginal microbiome on a large scale. This study aimed to compare the vaginal microbiota between pregnant and non-pregnant healthy women of different age or race using the meta-analysis method. The results from 7 articles having 16S rRNA gene sequences, were extracted and analyzed by CLC. Data from 898 pregnant and 702 non-pregnant women showed that the Bacilli, Clostridia, Actinobacteria and Coriobacteria were the dominant classes in pregnancy. The vaginal microbiota in normal non-pregnancy is also predominated by Bacilli. Still, beta diversity maps demonstrated that non-pregnant vaginal microbiome is more variable than that in the pregnant state. This study reveals new insights into age and ethnic effects on the pregnant and non-pregnant vaginal microbiome and found that the microbiome of Chinese women was more distinct than the other races. It was also detected that the relative number of bacterial classes is dramatically lower in women above the age of 35 relative to younger ones.

Introduction

In the human body, various microbial species often coexist with the host. In this relationship, the host provides microbial species with nutritious food to grow and reproduce. On the contrary, a microbial population acts as a barrier against the growth of opportunistic microorganisms, which can cause infection and disease in humans. These microbial populations, called microbiota, play an essential role in the development, physiology, immunity, and nutrition of humans [1]. The entire microbiota, their genomes, and their surrounding biochemical environment are called microbiome [2].

Microbiota of the reproductive tubes plays an important role in reproductive health in women. In healthy women, the vaginal microbial population is predominated by Lactobacillus spp. These microbial species play an important role in vaginal protection against the growth and proliferation of pathogens by the secretion of antibacterial bacteriocins and production of metabolites, such as lactic acid, which reduce vaginal pH [3]. It seems that the lack of Lactobacillus spp. in vaginal microbiota in pregnancy is associated with pregnancy complications, especially preterm birth [4, 5]. Recent studies have shown that although Lactobacillus species are dominant in 60-70% of women, there are also healthy women in whom Gardnerella, Atopobium, Prevotella, Pseudomonas or Streptococcus are dominant. Therefore, the vagina has a very complex ecosystem with heterogeneous microbial distribution [6]. Microbial populations in other body sites are not typically dominated by any single genus [7]. It is known that vaginal microbiota is not always stable. Any internal and external factors such as antibiotic use, vaginal drugs, systemic hormones, contraceptives, douches, sexual intercourse, vaginal sprays, stress levels, and

economic conditions can lead to increased or decreased strains in the microbial vagina and change the normal vaginal fluoride periodically [8–10]. This is to some extent because of the anatomical location and function of the vagina [11]. The vaginal microbiota during a woman's lifespan from birth, puberty, and pregnancy to menopause, also undergoes a combination of changes. Sex steroid hormones appear to play an essential role in the composition and stability of vaginal microbiota [12]. A Microbiome imbalance can lead to many diseases, including bacterial vaginosis (BV). This imbalance during pregnancy is associated with an increased risk of early and late abortion, postpartum infection, postpartum endometriosis, premature delivery, etc. Since preterm birth causes many problems, including increased risk of cardiovascular defects, respiratory syndromes, and increased risk of chronic diseases in adulthood, the detection of the vaginal microbial communities during pregnancy can reduce the risk of birth with these problems [13, 14].

The development of non-culture-dependent techniques, such as the high-capacity sequencing of 16S rRNA genes, has facilitated the comparison of the composition and role of vaginal microbial populations at different times and led to the identification of non-cultivated microbial species [8]. 16S rRNA, as a ubiquitous gene found in all bacteria, is suitable in this regard and has regions of conserved sequences that can be amplified by universal or specific primers. It also has heterogeneous regions that can be used to identify bacteria or to find phylogenetic relationships [15]. These studies show that pregnancy has a significant impact on the vaginal microbiome. Pregnancy is associated with many physiological changes that may lead to changes in the structure and composition of the microbial population in pregnant women, which is different from those of non-pregnant women [13].

This study aimed to evaluate the metagenomic analysis of the vaginal microbiome in pregnant and non-pregnant women. Understanding the vaginal microbiome during pregnancy is an essential step in the diagnosis, prevention, and treatment of adverse pregnancy complications.

Materials And Methods

Data Collection: We found 165 case-control studies by exploring keywords in DDBJ, PubMed, and references in relevant meta-analysis and case-control studies. We selected studies containing 16S-related data (fastq or fasta), which could be used as metadata required to establish whether a sample is a case or control. Some data were downloaded from the Sequence Read Archive (SRA) repository and some data were obtained through communication with the authors. In studies where multiple body sites were examined or where multiple samples of each patient were used, we needed the respective metadata to complete the main metadata. We only looked vaginal samples for 16S and thus, studies with other genes, like CPN60, were excluded from our research. In studies with multiple control groups (e.g., non-infectious infertility, female sex worker), only the pregnant and non-pregnant patients were used [16–22]. The study identification and selection process is presented as a PRISMA flowchart (Fig. 1).

16S Processing: Raw data (fasta and fastq) were downloaded and processed using the CLC Genomics Workbench 20.0.4. If required, we de-multiplexed sequences by finding specific matches between the

given barcodes and trimmed primers with a maximum of two mismatches. The paired-end reads were assembled, sequences and quality score data from the fastq and fasta files were extracted. The reverse complement of the reverse read was produced. Finally, the paired-end reads were assembled into a single Contig file. Generally, sequences were quality filtered by trimming at the first base and Q score lower than 8. Nevertheless, some datasets did not deliver such a quality threshold (for instance, the resulting OTU table lacked original samples, or the read depth was significantly lower than in the original article). We aligned the remaining sequences using a customized Greengene bacterial reference database and removed unaligned sequences. To classify the sequences, we used the CLC Microbial Genomics Module 20.1.1 with a cutoff point of 80 and removed non-bacterial sequences. For per dataset, we eliminated samples with reads < 100 and OTUs with read values < 50. Further analysis was done on a random subset of 2000 reads/samples, either using operational taxonomic units (OTUs) clustered with a similarity threshold of 97% or based on taxonomic assignment.

Statistical Analyses: The CLC Microbial Genomics Module 20.1.1 and PERMANOVA analysis were used to evaluate statistical differences in the vaginal microbiome, age, and race during pregnancy and non-pregnancy.

Results

Characteristics of the study population

The present study characterized the vaginal microbial communities in pregnant and non-pregnant women. To this end, 898 pregnant and 702 non-pregnant subjects were analyzed. The age range of the samples was between 15 and 50 years in pregnant and non-pregnant groups and were classified into the age groups of 15-19, 20-25, 26-30, 31-36, and more than 36. The data were also categorized in terms of race. The Pregnant group was divided into Black, Asian, white, Chinese, African American, and American Indian or Alaska native. The non-pregnant group was divided into Black, Asian, white, Chinese, Hispanic, and Puerto Rico. The frequency of bacterial phylum and class in similar groups in terms of age or race was compared between pregnant and non-pregnant women and the following results were obtained.

OTU analysis related to race

Clustering reads at phylum and class levels revealed large fluctuations in the microbiome composition within pregnant and non-pregnant groups depended on the race (figure 2a, 2b, 2d, and 2e) and also distinct differences between these two groups (figure 2c). Firmicutes (81%) were the dominant phylum among all ethnic groups. The vaginal microbiome in pregnant women of Black, Asian, White and African-American races just or mainly composed of Firmicutes. In this group, however, the Chinese female vaginal microbiome has a higher diversity of bacteria at the phylum level and composed of more than 10% of Proteobacteria. This is completely reverse in non-pregnant group in which the Chinese female vaginal microbiome has a lower diversity of bacteria at the phylum level and composed of just Firmicutes and Proteobacteria. Actinobacteria, Bacteroidetes, Fusobacteria and Tenericutes present with different percentage in all other races, but cannot be seen in non-pregnant Chinese women.

At the class level, the most represented class was Bacilli which presents about 80% and 70% in pregnant and non-pregnant groups, respectively. In the pregnant group, the abundance of Bacilli in the races of Black, Asian and White is near 100%. For the American-Indian or Alaska native group, however, this percentage reaches about 50% and for Chinese is about 70%. In the non-pregnant group, this difference is less noticeable and the abundance of Bacilli in the races of Asian and White is near 85% and reaches about 60% in Black, Hispanic, and Puerto Rico. What is interesting in this diagram is the low diversity of bacterial classes in Chinese, so that in this race, most of the bacteria are Bacilli and Gammaproteobacteria. Gammaproteobacteria is the bacterial class that is just seen in Chinese pregnant and non-pregnant group. Clostridia which is the most abundant class after Bacilli in all the races is not seen in Chinese. This is also true in the pregnant group, in which the Chinese do not have Clostridia (figure 2)

Generally, statistical analysis revealed that the difference between microbiome in different races, regardless of pregnancy and non-pregnancy status, is significant (P-value=$3x10^{-3}$(.

In non-pregnant women, the race is effective in the microbiome population, and the differences between different races are statistically significant (P-value=10^{-5}(. But in this group, the microbiome difference among Hispanic, Asian, and black races is not statistically significant. In the population of pregnant women, although race is generally effective in the microbiome population (P-value=10^{-5}(, but a two by two comparison of groups shows that the microbiome of some races are similar, and the difference between them is not statistically significant.

Across all samples, a total of 118 classes were detected, but the seven most abundant classes accounted for ~95% of the total relative abundance, bacilli (73%), clostridia (7%), Actinobacteria (4.5%), Corinobacteria (4.5%), Bacteriodia (4%), Fusobacteria (3%), Mollicutes (2%).

OTU analysis related to age

In general, the number of bacterial species decreases dramatically over the age of 36, and the bulk of the microbiome includes only the Bacilli class. (More than 95% in pregnant women and about 90% in non-pregnant women).

After the class of Bacilli, in all age groups in pregnant and non-pregnant women, Clostridia is more common than other bacteria. The frequency of this bacterial class is, on average lower in pregnant than in non-pregnant women in the same age group (figure 3).

In non-pregnant women, the age difference has no effects on the microbial population of the vagina, and it is not statistically significant (p-value=0.28), but Statistical analysis showed that the age of the pregnant mother is effective in the microbial population of the vagina and different age groups have significant microbial population differences (p-value=10^{-5}(. This difference is more evident in the age group of 36-50 years with other groups.

Heatmap analysis

Heatmaps were also constructed, which is a data matrix for visualizing values in the dataset using a color gradient. This gives a good overview of the largest and smallest values in the matrix (figure 4 and 5).

Beta diversity analysis

To elucidate possible similarities in vaginal microbiota community structure between groups of participants, we calculated Euclidean-based distances across the entire population [4]. PCoA (Fig. 6) In PCoA, the first two principal components explained 50 and 18%, respectively, of the variance along the first and second axes, with the pregnant samples visually separated from the non-pregnant. Results consistently showed that the non-pregnant vaginal microbiome is notably different compared to pregnant. Non-pregnant samples had higher variation within the groups.

Discussion

The human vaginal microbiome is affected by factors such as diet, environment, genetic background, and ethnicity [23].

Although the underlying reason behind the microbial changes during pregnancy is still uncertain, a relationship was reported between sex steroid hormone levels and vaginal microbial composition. Forsum et al. showed a relationship between estrogen levels during menstruation and changes in lactobacillus vaginal bacteria [24]. Increasing the estrogen concentration during pregnancy can increase the vaginal mucus thickness and glycogen deposition. Glycogen is the main carbohydrate used by lactobacillus strains hydrolyzed into maltodextrins, maltobiose, and maltose in vaginal fluid by host-encoded α-amylase [25, 26] and resulted in the production of lactic acid in the anaerobic glycolysis, leading to a protective role in reducing vaginal pH [27]. Hormone-induced glycogen production may create a rich medium for bacterial growth in the vagina during pregnancy. Pregnancy also changes the amount and stability of the mucus so that the mucus becomes richer and thicker and the swabs of sampling of pregnant women carry more material than non-pregnant women and may influence judgment about the vaginal microbiome [13, 28]. Comparison of the vaginal microbiota of pregnant versus non-pregnant women showed that normal pregnancy is characterized by Lactobacillus-dominated microbiota [5, 29]. After delivery, the maternal estrogen levels fall and the vaginal microbiota becomes more diverse and can remain in some women for up to one year postpartum [4, 30].

Ghartey et al. in 2014 detected that the microbiome has less diversity and richness in 18-32 weeks' gestation and returned to non-pregnant status in late gestation [20].

A Previous study demonstrated that *L.crispatus* dominant vaginal microbiome is related to *E.coli* growth inhibition, *E.coli* growth in vagina cause neonatal sepsis and chorioamnionitis [20].

Most researchers have studied the vaginal microbiome during a particular period of life or in a specific population and concluded that ethnic diversity and geographical area could affect the vaginal microbiome [31]. Even different ethnicities in one geographical region can result in significant differences in the vaginal bacterium. Genetic and environmental factors, such as diet, are effective in making these differences [32]. Using the meta-analysis method, the present study characterizes the vaginal microbial communities during pregnancy and non-pregnancy in women of different races. Ravel et al. showed that the vaginal microbiome differs in various ethnicities. For example, in Asian and white women, lactobacillus was higher than black and Hispanic [22]. Differences in the microbiome content of different races were also observed in this study. Interestingly, the microbiome of the Chinese was more distinct than the other races, and these findings are consistent with previous studies in the literature.

In Chinese women, the vaginal microbiome variation among women during pregnancy is more significant than that of non-pregnant women [18], and this is completely reverse in other races [12, 13].

Xu et al. stated that the maternal age and the level of FSH hormone were negatively correlated with the relative abundance of Paraprevotella. It was suggested that this bacterium was more commonly found in the vagina of younger women or women with normal ovarian function. Meanwhile, the relative abundances of genera Varibaculum, Streptococcus, and Veillonella were positively related to age, indicating that the colonization of these bacteria in the vagina may increase with female age [33]. In another study Nasioudis et, al. mentioned that there are no statistically significant associations between the relative abundance of any bacterial taxa and maternal age, gestational age at birth, or neonatal gender [34]. However, in this study, it was found that the relative number of bacterial classes is dramatically lower in women above the age of 35 relative to younger ones. As mentioned in the Materials and Methods section, the microbiome of pregnant women over 36 years old is significantly different from other age groups. Since the rate of fetal abnormalities increases with maternal age increasing, and also the increased maternal age is one of the risk factors of pregnancy related complications such as preeclampsia [35], so the authors suggest that the relationship between maternal age, microbiome and factors like fetal abnormalities and pregnancy complications examine more broadly.

It is also well established that there is a decline in female fertility as a function of age. M.H. Razi et.al confirmed that the women's age strongly influence outcomes of assisted reproductive technology (ART) treatment [36]. We think this may also be related to microbiome and should be examined.

Regardless of age and race, the difference in the vaginal microbiome in pregnant and non-pregnant women is statistically significant (p-value $=10^{-5}$).

Overall since the vaginal microbiome during pregnancy can affect the neonatal gut microbiota, the microbial infections can be controlled by identifying the vaginal microbiome and its abnormalities [37]. Also, it seems that a healthy human fetus grows in a free-bacterial environment but is exposed to a wide variety of bacteria through the delivery channel at birth. However, many babies are today born by C-section and thus are not exposed to vaginal microbiota. This also diversifies intestinal microbiota, and

since intestinal microbiota affects the balance of energy, metabolism, and resistance to pathogens, the vaginal microbiota can indirectly affect the intestinal microbiota [38].

Extending these studies can lead to discovering biomarkers of reproductive disorders or problems that may occur during pregnancy. We reported the microbial status of the vagina during pregnancy and non-pregnancy. Considering that our women were healthy, this model could be presented as a healthy vaginal model and examined the effect of omission or addition of bacterial strains of the disease. A microbiome core can be considered a sign of health. However, considering one microbiome core does not indicate health properly, and it is better to consider several cores [22]. In general, the vaginal microbiome is very essential, and microorganisms excreted through vaginal secretions should be replaced again [39].

Declarations

Funding

The authors did not receive support from any organization for the submitted work

Conflict of interest

The authors have no conflict of interest.

Ethics approval

This research is a meta-analysis and doesn't involve humans and/or animals.

Consent to participate/publish

This research is a meta-analysis and doesn't involve humans and/or animals.

Availability of data and material

Data sharing not applicable to this article as no datasets were generated during the current study. Raw data were analyzed from other researches which are referenced in the Materials and methods section

Code availability

The CLC Microbial Genomics Module 20.1.1 was used

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Zahra Golestani, Samira Ghaedmohammadi and Najmeh Mozdoori. The first draft of the manuscript was written by Samira Ghaedmohammadi and Najmeh Mozdoori. All authors read and approved the final manuscript.

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Figures

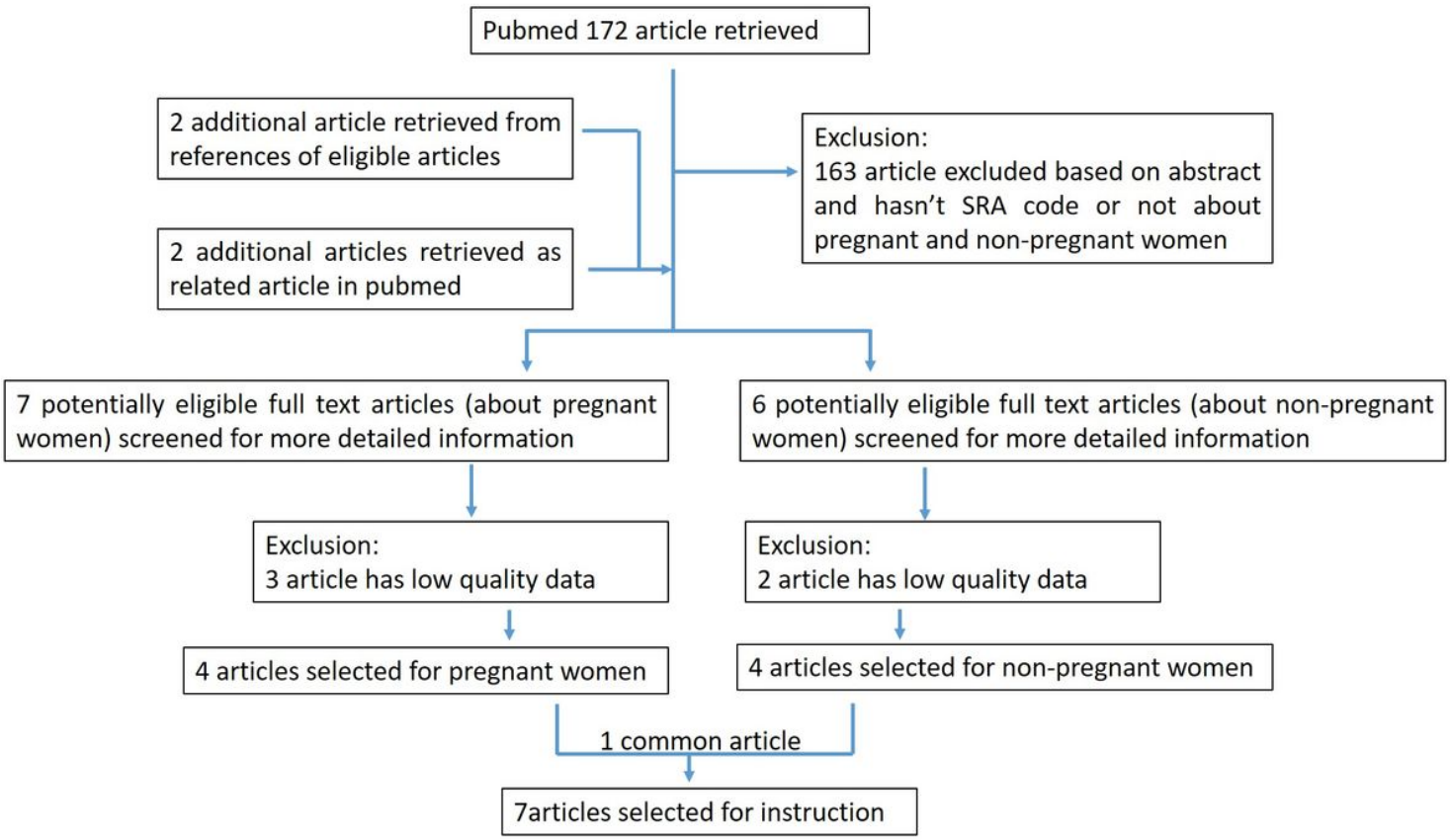

Figure 1

PRISMA study selection flowchart for meta-analyses of the pregnant and non-pregnant vaginal microbiome.

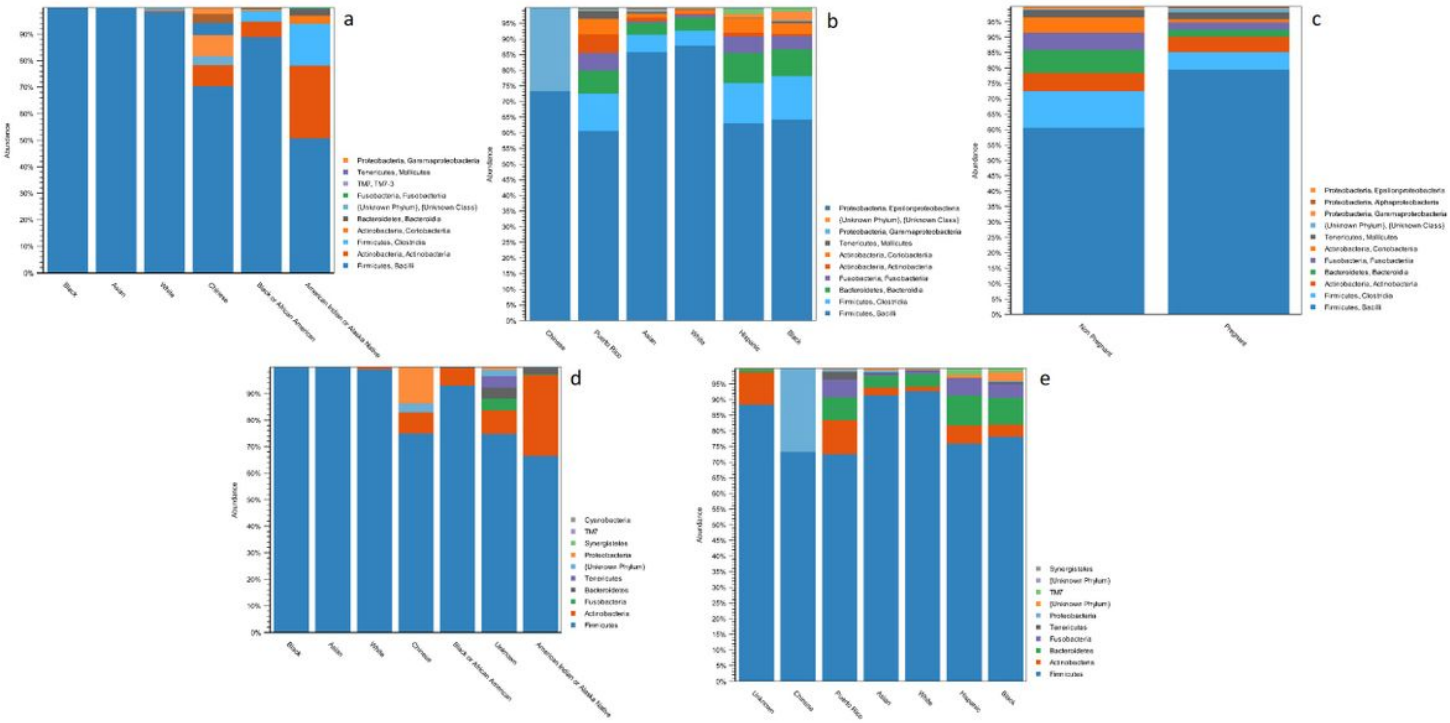

Figure 2

Taxonomic profile of samples. Taxa were clustered at class and phylum level within pregnant (a and d) and non-pregnant women (b and e) and between these two groups (c).

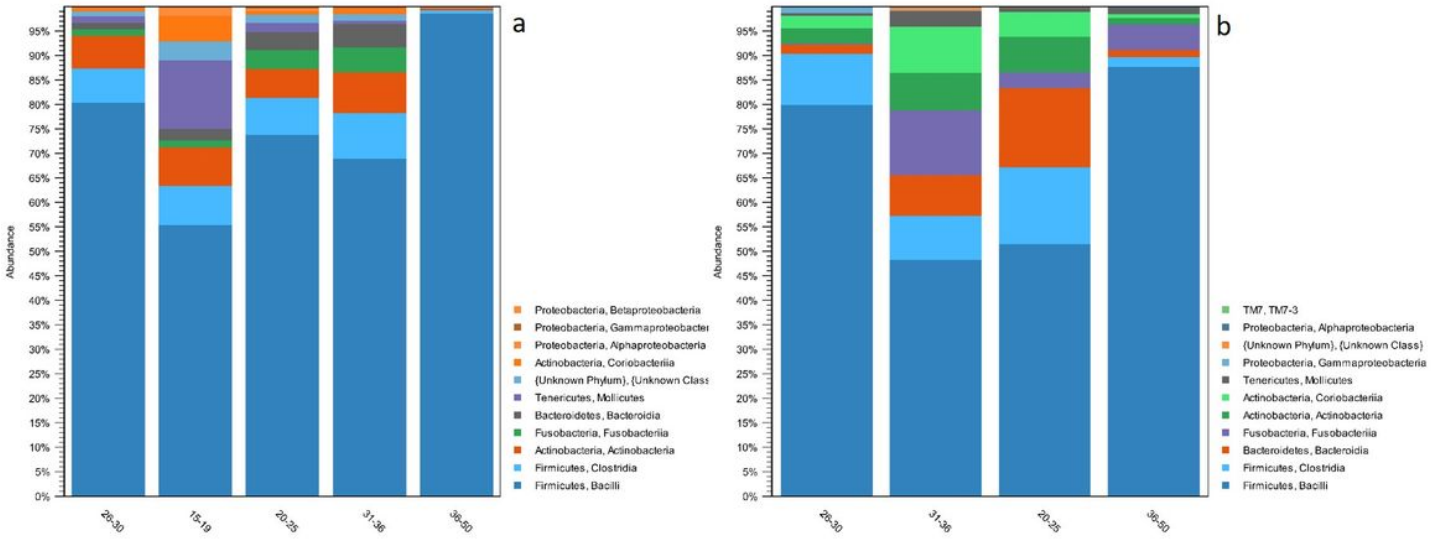

Figure 3

Taxonomic profile of samples. Taxa were clustered at class and phylum level within pregnant (a) and non-pregnant women (b).

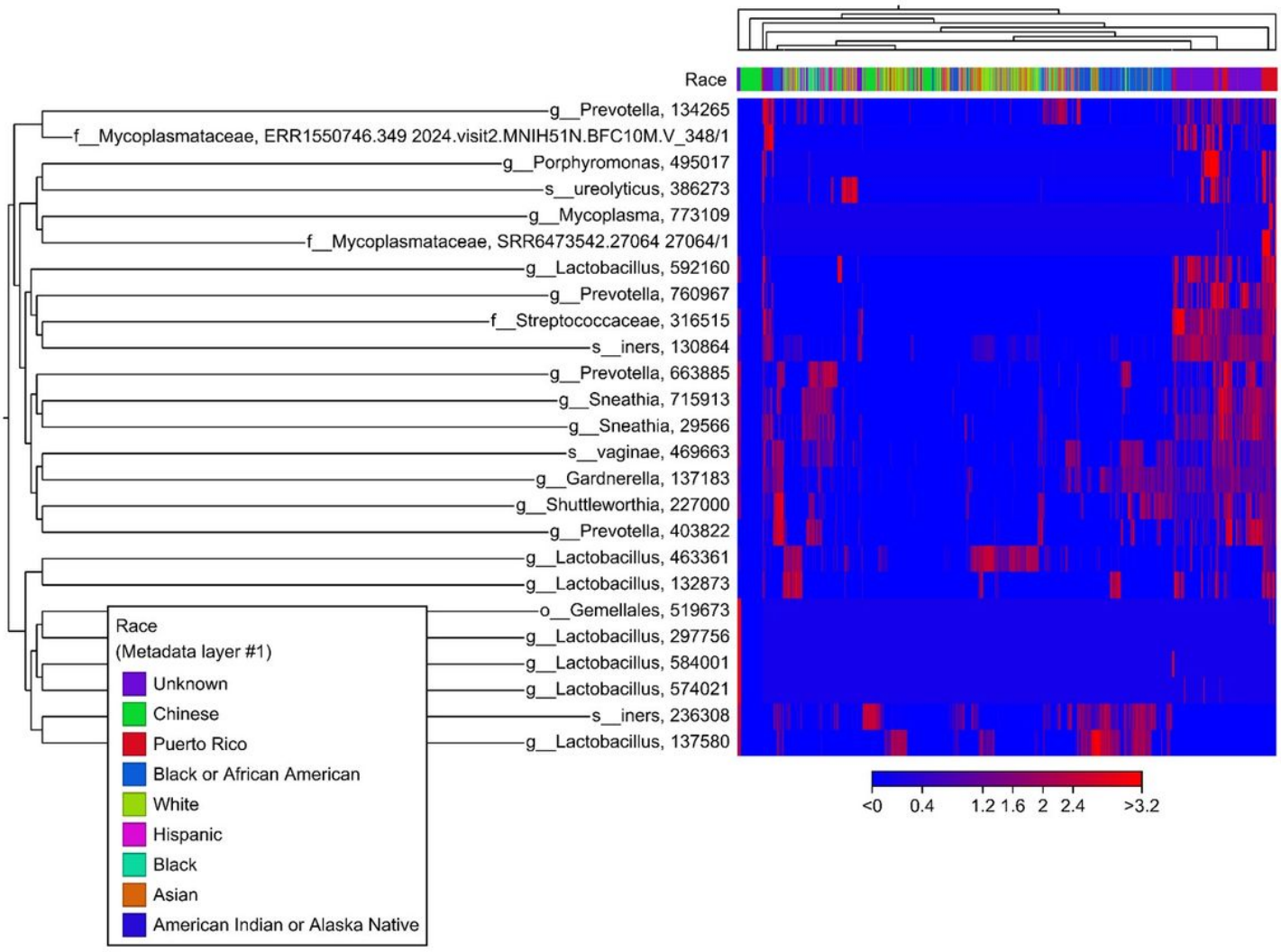

Figure 4

Heatmap of microbial taxa relative abundance identified in the vaginal microbiota of pregnant and non-pregnant women of different races.

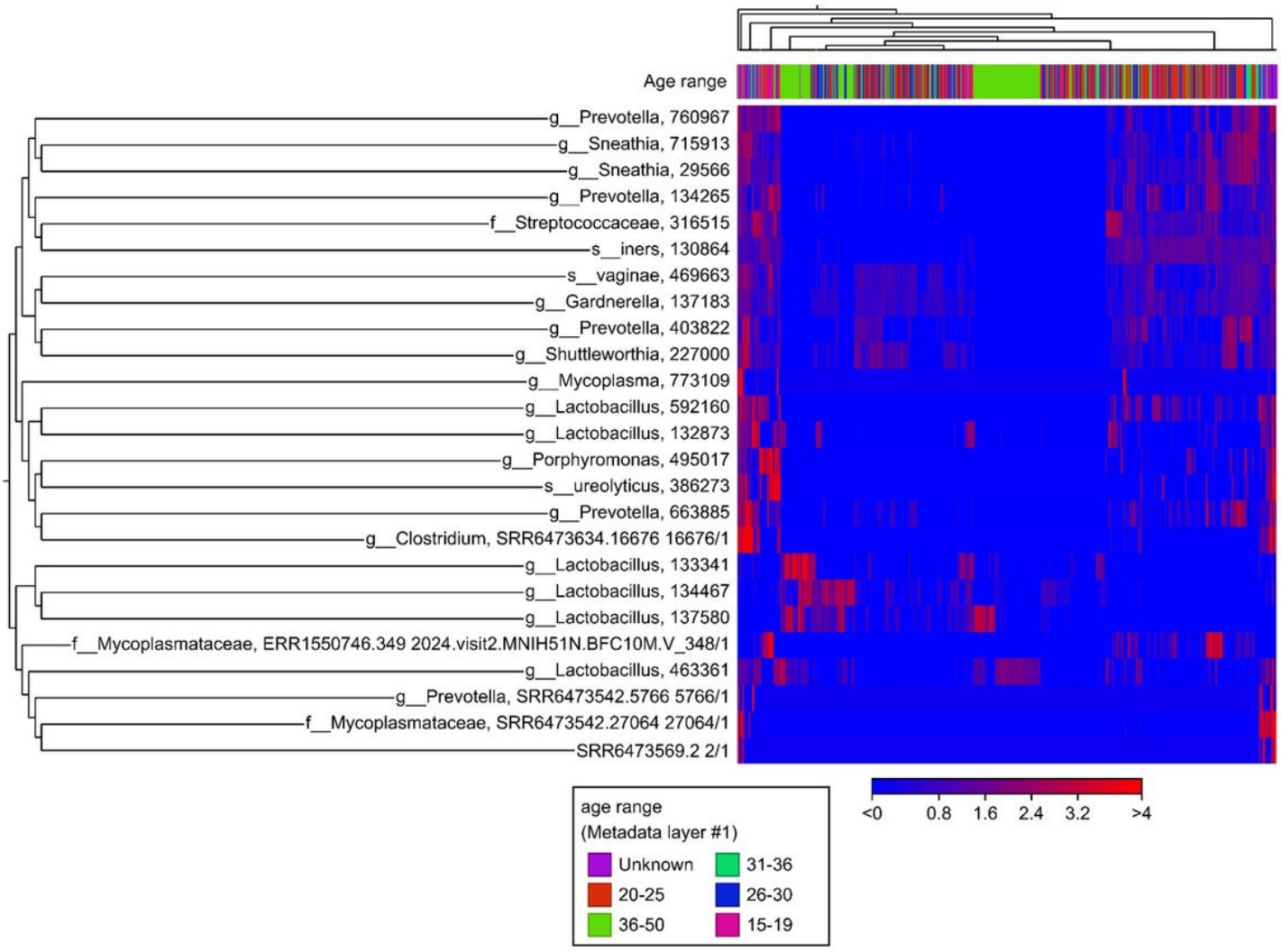

Figure 5

Heatmap of microbial taxa relative abundance identified in the vaginal microbiota of pregnant and non-pregnant women of different ages.

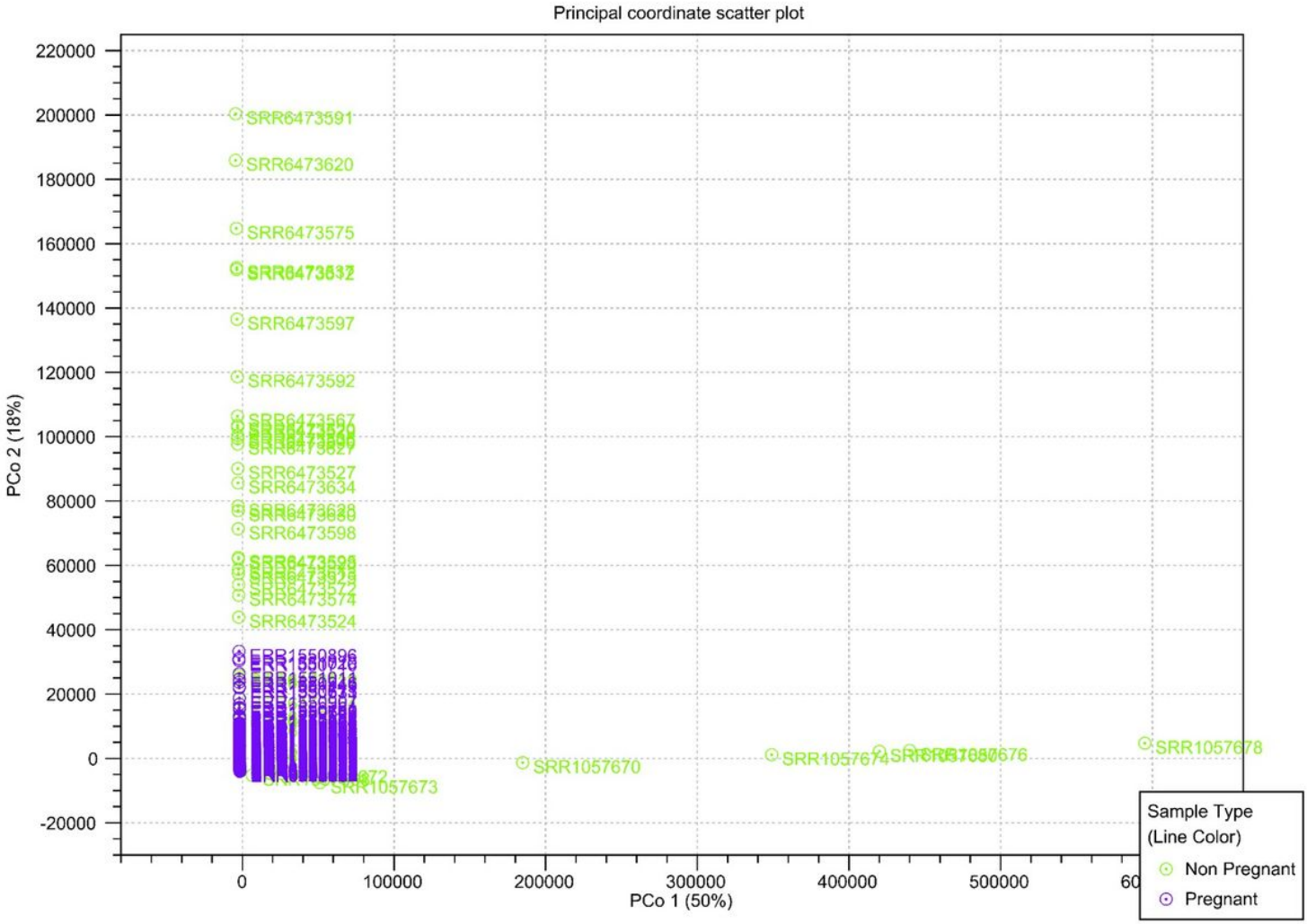

Figure 6

Euclidean principal coordinates analysis (PCoA) plot comparing sample distribution for the different groups