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May 17, 2022

Dear Editors:

Thank you very much for your email with the encouraging news regarding our manuscript. We also thank the reviewers for their positive/constructive comments and suggestions, which truly help us to improve the quality of our manuscript. After incorporating the comments and suggestions into the revised manuscript, we would like to re-submit it for the consideration of its publication in *World Journal of Gastroenterology*. The amendments in the revised manuscript are highlighted in yellow. And the specific point-by-point replies to each of the reviewers' comments are marked in red, which are attached below.

Thank you again, and I hope that the revision is acceptable. I am looking forward to hearing from you soon.

Sincerely,

Dr. Jing Lv

Honghui Hospital, Xi'an Jiaotong University

E-mail: [lvjing-1219@163.com](mailto:lvjing-1219@163.com)

## EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

### **(1) Science editor:**

This study report a retrospective study concerning the association between gut microbiota and dyslipidemia in sex subjects. Generally, this is an observational study from a local population study in China. There were many concerns raised by the reviewer, and it would be great that the study could further well address those questions before accept for publication in the journal.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

Thank you so much for your suggestions. We've made the specific point-by-point replies to each of the reviewers' comments, which are marked in red. Please find the detailed information below. The amendments in the revised manuscript are highlighted in yellow, which was uploaded on the Manuscript Submission System. Thank you!

### **(2) Company editor-in-chief:**

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or



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similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Thank you so much for your positive remarks. We appreciated it very much! We've made the amendments according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. The uniform presentation is also used for figures showing the same or similar contents. The amendments are highlighted in yellow in the revised manuscript, which was uploaded on the Manuscript Submission System. The decomposable figures (in which all components are movable and editable) are organized into a single PowerPoint file, which was also uploaded on the Manuscript Submission System. All the figures are original, and the copyright information is added to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Moreover, the tables are prepared according to the guidelines you provided as well. Thank you!

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 75763

**Title:** Associations of gut microbiota with dyslipidemia under sexual dimorphism in subjects from Northwestern China

**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 02537353

**Position:** Editorial Board

**Academic degree:** BSc

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** Italy

**Author's Country/Territory:** China

**Manuscript submission date:** 2022-02-18

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-02-18 07:46

**Reviewer performed review:** 2022-02-23 12:55

**Review time:** 5 Days and 5 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<b>Peer-reviewer statements</b>	Peer-Review: [ <input type="checkbox"/> ] Anonymous [ <input checked="" type="checkbox"/> ] Onymous Conflicts-of-Interest: [ <input type="checkbox"/> ] Yes [ <input checked="" type="checkbox"/> ] No
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## SPECIFIC COMMENTS TO AUTHORS

The aim of the authors was to investigate the associations of GM characteristics with serum lipid profiles under sexual dimorphism in a Chinese population. The topic could be interesting but the manuscript presents different critical points.

Thank you for the comments.

Major revisions:

1) The authors use the characterization of metabolic profile of microbiota the dated database FAPROTAX. Actually there is the PICrust 2 that makes predictions starting from the reads themselves and this brings the prediction closer to reality.

We thank the reviewer so much for the constructive suggestion, which will greatly broaden our horizons in the future studies of GM. Indeed, some studies have utilized PICrust 2 for pathway analysis. Just as the reviewer suggested, PICrust 2 makes predictions starting from the reads themselves and this may bring the prediction closer to reality. However, some of the studies have used FAPROTAX database for function prediction. The Functional Annotation of Prokaryotic Taxa (FAPROTAX) includes updated taxonomies to be consistent with the SILVA release 132 database, and includes specific software for converting taxonomic microbial community profiles (e.g. in the form of an OTU table) into putative functional profiles, based on taxa identified in a sample. The complete database for FAPROTAX integrates various functional annotations for over 4600 taxa, and its output table contains the metabolic assignments of 90 different types of metabolisms. This type of functional inference is a very useful approach to understand the functional differences of microbial communities. In this

study, we've referred to certain authoritative published articles in order to perform the GM data analysis, such as the reference "Louca S, Parfrey LW, Doebeli M. Decoupling function and taxonomy in the global ocean microbiome. *Science* 2016; 353: 1272-1277". Additionally, other utilized literature includes Begrey's Manual of Systematic Bacteriology, The Prokaryotes, and The International Journal of Systematic Bacteriology. Therefore, FAPROTAX was used to obtain information on the functional metabolic patterns of the GM community herein. Nevertheless, we are planning to combine the two results above in the future GM studies, which may refer to the published article "Diversity and function of rhizosphere microorganisms between wild and cultivated medicinal plant *Glycyrrhiza uralensis* Fisch under different soil conditions (*Arch Microbiol.* 2021, 203(6): 3657-3665.)". Thank you again for your precious suggestions.

2) Usually and rightly to define the metabolic profile the microbiota studies evaluate the fecal SCFA, why the authors did not define the SCFA signature in stool of patients.

Thank you for your advice. This is a very good suggestion. In the gut, microbial enzymes produce short-chain fatty acids (SCFAs), which are important GM-dependent metabolites. Anaerobic bacteria are uniquely capable of digesting complex carbohydrates, or dietary fiber, with one primary product being SCFAs. There is significant heterogeneity with respect to dietary fiber and SCFA production, of which butyrate, propionate, and acetate are the most abundant. Both butyrate and propionate have low systemic concentrations whereas acetate levels are higher. In addition to being metabolic substrates, SCFAs act as signaling molecules, notably through the G-protein coupled receptors GPR43/FFAR2 and GPR41/FFAR3, and GPR43 protects against diet-induced-obesity in mice. Furthermore, the microbiota increases peptide YY (PYY) production through GPR41. Butyrate and propionate have also been shown to activate PPAR $\gamma$ , and SCFA-induced activation of PPAR $\gamma$  modulates lipid metabolism through

increased energy expenditure, reduced body weight and decreased liver triglyceride accumulation. SCFAs in the gut exert their systemic effects in different parts of the body, which are important for host metabolism, intestinal immune homeostasis, energy production, gluconeogenesis, lipogenesis and cholesterol synthesis. This might provide a novel perspective on the molecular mechanisms involved in the development of dyslipidemia. However, whether the SCFAs is one of the causes responsible for the pathogenesis of dyslipidemia has not been proved. Therefore, as you suggested, it is very critical to evaluate the metabolic profiles of SCFAs, and the signature of SCFAs should be defined in the stool samples of patients. In our research group, we are doing a series of studies about GM and metabolic diseases, such as osteoporosis, hypertension and dyslipidemia. At this very moment, another part of our research is doing the GM-derived metabolite-related analysis with dyslipidemia on the same subjects to acquire more information of the interplay between GM and lipid metabolism. Thereafter, the aim of this study was to investigate the associations of GM features with serum lipid profiles based on gender differences in a Chinese population. That is to say, the mechanism exploration of GM dysbiosis in dyslipidemia will be introduced in our future study, and we will submit another manuscript mainly describing SCFAs-related data. We totally agree with your advisements and thanks a lot!

3) The discussion is very long and verbose, please short it and focused on very important points.

Thank you for your question. In the discussion part, we first introduced the background of this study briefly, and compared our data with previous researches accordingly, then discussed the limitations of this study finally. In consideration of your suggestion, we've shortened the discussion part, and focused on very important points of our data. The amendments are highlighted in yellow in the revised manuscript. Thank you again.



4) The number of enrolled patients is low for the conclusions of the authors.

We thank the reviewer for the comments. Indeed, there are several limitations in the current study, and the sample size was relatively small to make certain general conclusions. We've discussed the limitations of this study in the manuscript. However, our results truly indicated that the GM distribution and composition in different dyslipidemia subgroups changed in both females and males, suggesting a complex interactivity between GM and distinct lipid metabolisms. In addition, our results further support previous researches from another perspective, and may provide new evidence for GM analysis in dyslipidemia based on gender differences. Nevertheless, more studies are required to determine which specific taxa have the potential to ameliorate dyslipidemia, and to draw definite conclusions. We will conduct the research with a larger sample size as a validation group to support the results herein, and investigate the underlying biological functions of the key GM in dyslipidemia, including the mechanism exploration as well. Thank you.

#### Minor Revisions:

1) Please specify in the section Study Design "206 adult individuals" the number of patients and Healthy controls. In addition, please define how you have enrolled the Healthy controls.

Thank you for your question. As you suggested, it's necessary to specify the details of the recruited individuals. However, the first step of the participant recruitment was as follows: we consecutively screened 206 potentially eligible participants from the outpatient clinics at Honghui Hospital, Xi'an Jiaotong University, without detecting their serum lipid levels. That is to say, we could not group these individuals at this point. Therefore, we added the numbers of females and males herein, which is highlighted in





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yellow in the revised manuscript. Then, we finally selected 142 eligible participants (73 females and 69 males) after exclusion, including 81 dyslipidemia patients and 61 controls, and the detailed grouping information is shown in Figure 1. In addition, individuals usually go to the outpatient clinics (including Physical Examination Center) for annual physical examination in China, and these individuals could become the source of controls. Thereafter, we've add such detailed information in this section, which are highlighted in yellow. Please refer to the revised manuscript. Thank you for your questions.

2) Please replace subjects with patients.

Thank you for your question. We've modified the information accordingly in the revised manuscript, which are highlighted in yellow. Thank you.

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 75763

**Title:** Associations of gut microbiota with dyslipidemia under sexual dimorphism in subjects from Northwestern China

**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 02623966

**Position:** Editorial Board

**Academic degree:** MD, MSc, PhD

**Professional title:** Attending Doctor, Research Scientist

**Reviewer's Country/Territory:** Greece

**Author's Country/Territory:** China

**Manuscript submission date:** 2022-02-18

**Reviewer chosen by:** Xin Liu (Online Science Editor)

**Reviewer accepted review:** 2022-04-13 12:15

**Reviewer performed review:** 2022-04-13 12:16

**Review time:** 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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<b>Peer-reviewer statements</b>	Peer-Review: [ <input type="checkbox"/> ] Anonymous [ <input checked="" type="checkbox"/> ] Onymous Conflicts-of-Interest: [ <input type="checkbox"/> ] Yes [ <input checked="" type="checkbox"/> ] No
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#### **SPECIFIC COMMENTS TO AUTHORS**

It is an interesting manuscript. Authors succeed to present their data in a clear way adding information to the existing literature. Therefore, I have no corrections to do and the manuscript can be published unaltered.

Thank you very much for your positive remarks. We appreciate it very much!

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 75763

**Title:** Associations of gut microbiota with dyslipidemia under sexual dimorphism in subjects from Northwestern China

**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 00053786

**Position:** Editorial Board

**Academic degree:** FAASLD, MD, PhD

**Professional title:** Research Scientist

**Reviewer's Country/Territory:** Mexico

**Author's Country/Territory:** China

**Manuscript submission date:** 2022-02-18

**Reviewer chosen by:** Xin Liu (Online Science Editor)

**Reviewer accepted review:** 2022-04-11 13:26

**Reviewer performed review:** 2022-04-20 16:45

**Review time:** 9 Days and 3 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

<b>Peer-reviewer statements</b>	Peer-Review: [ <b>Y</b> ] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [ <b>Y</b> ] No
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## **SPECIFIC COMMENTS TO AUTHORS**

Guo L et al. present a retrospective study concerning the association between gut microbiota and dyslipidemia in male and female subjects from Northwestern China. The study may be of interest to the medical-hepatologist community in regards to the sex differences shown in the features of the gut microbiota community and dyslipidemia.

**Thank you very much for your positive remarks. We appreciate it very much!**

However, there are several concerns that need to be amended.

1) The term sex dimorphism is not correct. Commonly, sex dimorphism is about traits that are only seen in one sex but not in the other. In general, any dyslipidemia was not exclusive to one sex or the other, and dysbiosis is present in both sexes. Therefore, the title and other parts of the text should read: sex differences or gender differences where the term sex dimorphism was originally written. For example, the new title can be: Sex differences in the association of gut microbiota with dyslipidemia in subjects from Northwestern China.

**Thank you for your advice, and we totally agree with your advisement. We've gone through the manuscript again and made such kind of modifications in the revised manuscript, which are highlighted in yellow. Thank you again!**

2) a) Add the time of patient recruitment when this study was carried out.

**Thank you for your question. As you suggested, it's necessary to specify the details of the recruited individuals. We've add the time of patient recruitment "From July 2018 to January 2020" in the "Study design" section, and highlighted it in yellow in the revised**

manuscript. Thank you!

b) The total number of patients was 142 subjects, 81 subjects and 61 controls. Please clarify this data in the text of the methodology section.

Thank you for the detailed information. We've added the numbers of patients and controls in the "Study design" section, and highlighted it in yellow in the revised manuscript. Thank you again.

3) Discussion: In regards to the functional analysis of the metabolic pathways that were differentially activated in the study patients, it would be of great value that the authors discuss the influence of diet in the subjects vs controls, and between genders because diet composition influences GM diversity. These findings have implications for the management of obesity-related chronic diseases. Can the authors add some information about the local diet or changes in the local diet that may lead to the prevalence of dyslipidemia?

We thank the reviewer for the constructive comment. This is quite a good suggestion, and we couldn't agree more. Just as the reviewer pointed, the dietary habit and composition may influent GM characteristics significantly. However, we didn't collect the detailed dietary information from the participants in this study, which indeed was a limitation of this study. We have added this point as a study limitation in the discussion. Generally, all the participants in this study were recruited near Xi'an (a central city in northwestern China), and we assumed that the overall dietary composition may not obviously differ among the residents herein. In future study, we will definitely consider the influences of dietary and other factors on GM, as the reviewer suggested. We hope that more researchers will focus on this field to give more clues or suggestions, and multi-center studies in different areas could provide more evidence. Moreover, we will



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also continue to work on this area for sure. I hope that our replies are useful. Thank you again!