Dear Editors and Reviewers:

We are very grateful to your time, effort and helpful comments on our manuscript. We have addressed all the comments and detailed all the changes made to the manuscript. Please kindly find the revised manuscript, point-by-point responses as given below.

Point-by-point response letter

Reviewer #1: Reviewer #1:

Scientific Quality: Grade C (Good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)

Specific Comments to Authors:

I congratulate the authors on this vital research, which reveals the significance of genetic factors in establishing the causal link between metabolites and colorectal cancer. “Casual associations between Blood Metabolites and colon cancer” reflects the main subject of the manuscript, and the abstract summarizes the work described. Keywords reflect the focus of the manuscript. The “introduction” section is also written quite adequately and allows even a reader who is not very interested in the subject to understand the study and its reasons. The “Materials and Methods” section is explained in reasonable detail, the language used has been kept simple, and the manuscript meets the requirements of biostatistics. The research objectives achieved and these results may offer fresh insight into the etiology of colorectal cancer and preventive strategies by integrating metabolomics and genomics as stated. Results are interpreted and discussed adequately, encouraging future studies to validate “metabolites & colon cancer association”. Three figures and two tables are all of good quality and appropriately illustrative. However, given the scarcity of studies directly associating these metabolites with colorectal cancer, further experimental and clinical investigations are warranted to validate these findings and elucidate the underlying mechanisms. The manuscript, which is concisely and coherently organized and presented appropriately, cites the latest, influential, and
authoritative references. In conclusion, this study, which employs SNPs identified through GWAS as instrumental variables within a Mendelian randomization study design, has successfully identified several significant blood metabolites associated with colorectal cancer. I have no doubt that this future promising research will be followed, and we will learn more about colorectal cancer and plasma metabolites.

Response: Thank you very much for your positive comments!

(1) Please provide the filled conflict-of-interest disclosure form.
Response: As suggested, we have provided the filled conflict-of-interest disclosure form.

(2) Please provide the Figures cited in the original manuscript in the form of PPT. All text can be edited, including A, B, arrows, etc. All legends are incorrectly formatted and require a general title and explanation for each figure. Such as Figure 1 title. A: ; B: ; C: .
Response: As suggested, we have provided the Figures cited in the original manuscript in the form of PPT. Please refer to the uploaded figures.

(3) Please upload the approved grant application form(s) or funding agency copy of any approval document(s).
Response: As suggested, we have uploaded the approved grant application forms.

(4) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text (and directly before the References).
Response: We have added the “Article Highlights” section at the end of the main text.
(5) LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

Response: As suggested, we have invited a professional English-Edit company to revise our paper. Please find the following edit certificate:
Certificate

Certificate Date: 29/01/2024
Reference: AE-45335
Customer Id: 5554

To Whom it May Concern

This is to certify that the document listed below has been edited for English language by the professional academic editing company Armstrong-Hilton Limited.

- Document Name: Casual associations between Blood Metabolites and colon cancer
- Author(s): Dr. Gangfeng Xiao
- Date: 29/01/2024
- Reference: AE-45335

If you have any questions please contact us at cs@asiaedit.com quoting the reference number above. The authors are free to acknowledge our editing service provided the manuscript has not been altered substantially after the editing.

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