

## List of Responses

Dear Editors and Reviewers:

Thank you for your letter and the reviewers' comments concerning our manuscript entitled "Different types of fruit intake and colorectal cancer risk: a meta-analysis of observational studies" (ID:82456). Those comments are all valuable and very helpful for revising and improving our paper and provide important guiding significance for our researches. We carefully considered the comments and made corrections that we hope would be approved. Revised portions are marked in red in the paper. The main corrections in the paper and the responses to the reviewer's comments are as follows:

### Responses to the reviewer's comments:

#### Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: It is an exciting article that discusses a hot issue.

**Response:** Thank you for your favorable comments. Currently, the incidence of colorectal cancer (CRC) is high worldwide. It has not only become a time bomb threatening human health, but also caused a heavy economic burden to society. We hope that this study can help people change their dietary habits to reduce the incidence of CRC, thereby making a modest contribution to global public health issues. Thanks again for your comments.

**1. Comment.** Is it easy to know which type of fruit is beneficial for the prevention of CRC.?

**Response:** Thank you very much for your question, and we would answer from the following aspects.

First, from the perspective of researchers, the study process is not easy. After systematically and comprehensively searching four databases, we strictly screened the retrieved literature. Based on a systematic review and meta-analysis of 24 included articles, we drew the final conclusion. Second, from the perspective of clinical practitioners, apart from this study, no other study comprehensively analyzes the association between the intake of different types of fruit and the risk of CRC, so obtaining such information is relatively difficult. Third, it is also relatively difficult for ordinary people. The general population is not very clear about the relationship between fruit and CRC, and they even don't know enough about CRC. They only have a general understanding of fruit, and they have few approaches to obtain relevant information. Therefore, it is not easy for ordinary people to know which type of fruit is beneficial for the prevention of CRC. In summary, the present study may enable clinical practitioners, future researchers, and ordinary people to better develop and use CRC prevention strategies to minimize the incidence of CRC. At last, special thanks to you for your comments.

**2. Comment.** Also, is it easy to know which component in these fruits works against cancer and which can promote ulcers?

**Response:** Thank you for your question. At present, numerous studies have demonstrated the existence of natural anti-cancer substance in fruit. Flavonoids, anthocyanins, apple polysaccharides, and resveratrol, for example, have a surprising anti-cancer effect. In particular, in various in vivo and in vitro experiments, they have been shown to inhibit the growth or migration of cancer cells, regulate intestinal flora, and reduce inflammation. Glucosinolates, indole-3-carbinol, and isothiocyanates in fruits have also been found to have

anti-cancer properties. They can directly inhibit the expression of CYP1A1 (a cytochrome P450 enzyme that catalyzes the metabolic activation of carcinogens) to extinct free radicals, reduce oxidative damage to DNA, inhibit cancer cell growth, and induce cancer cell apoptosis. In addition, fruits are rich in many micronutrients, including carotenoids, folic acid, vitamin C, vitamin E, B vitamins, and minerals, such as selenium, which have antioxidant functions and can prevent oxidative damage to cells and proteins, reduce inflammation and promote ulcer healing. Based on the above explanations, we have rewritten the importance of this research in this article: "This meta-analysis provides further evidence that a higher intake of specific types of fruit is effective in preventing the occurrence of colorectal cancer."

**3. Comment.** And is it a causal effect relationship or just an association? what is the amount of fruit needed, and for how long?

**Response:** Thank you for your question. We think it is an association. Because all the included studies are observational studies, we can only infer an association rather than a casual-effect relationship. To explore the causal-effect relationship between fruit and CRC, intervention research is required. Regarding the amount of fruit intake, we believe that the human body is "oxidized" every day when in a natural state, and the anthocyanins, flavonoids and other substances in fruits can not only resist oxidation but also inhibit adverse cell mutations. Therefore, the time of intake is often not limited. In-depth research on the optimal dose of fruit intake is needed. Thank you again!

**Reviewer #2:**

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: First of all, I would like to thank the editors for granting me this opportunity to review this interesting meta-analysis. In my opinion, a major revision is required though it is a potentially acceptable manuscript.

**Response:** Thank the reviewers for their comments and thank the editors for giving us the opportunity to revise the article. We have carefully revised the manuscript according to your suggestions, and the revised parts have been marked in red. Thank you for your review.

**Major Comments:**

**1. Comment.** Although authors' searching strategy seems to be thorough, I would advise to include flavonoid and nobiletin, two of the main compounds in fruit possessing anti-cancer ability in colorectal cancers into the keyword to include more potentially eligible articles to avoid publication bias.

**Response:** Thank you very much for your valuable comments, and we think they are very reasonable. Therefore, we comprehensively searched PubMed, Embase, WOS, and Cochrane Library databases for related articles containing the subject terms and free words of "flavonoid", "nobiletin" and "colorectal cancer" ( for details, please see Appendix 1 and 2 below the letter). The retrieved articles were strictly screened according to the inclusion and exclusion criteria. Unfortunately, we did not find any articles that reported OR/RR with

995%CI of the association between specific fruits and CRC risk to supplement this study. We have attached the search strategy and literature screening flow chart in the supplementary materials. Your professional comments make us more rigorous and meticulous in our future scientific research work. Thanks again.

**2. Comment.** In the section of statistical analysis, I strongly disagree with the use of the fixed-effects model even if the I<sup>2</sup> is less than 50%. The reason is plain and simple: for observational studies, it is inevitable to encounter conceptual heterogeneity even if there is no statistical heterogeneity, especially in observational studies where the assumption that all studies estimate the same underlying effect is rarely justified as population characteristics, exposure, and outcome definitions are highly likely differ across studies. Therefore, using a random-effects model for combining observational studies seems a lot more reasonable. All of which are clearly indicated in the latest Cochrane Handbook for Systematic Reviews of Interventions. As a result the sentence of “Significant heterogeneity was considered when I<sup>2</sup>>50% and p<0.05, and a random-effects model was used, otherwise a fixed-effects model was employed” in the section of statistical methods should be revised.

**Response:** Thank you for your valuable comments, and we strongly agree with the reviewer’s opinions. We have revised this sentence as “Since observational study results are inevitably affected by various sources of heterogeneity such as statistical heterogeneity and conceptual heterogeneity in the real world, we followed the Cochrane Handbook for Systematic Reviews of Interventions and used combined results from random-effects models”. We have to admit that it is more reasonable and

appropriate to use the random-effects model. Thank you again for your suggestions. They are all very important and have guiding significance for my future thesis writing and scientific research work.

**3. Comment.** For assessing non-RCT study, I suggest authors should use ROBINS-I (“Risk Of Bias In Non-randomised Studies - of Interventions”) for cohort studies instead of Newcastle-Ottawa Scale, which is considered outdated after the advent of ROBINS-I.

**Response:** We really appreciate the reviewer's comments. We reviewed the systematic reviews and meta-analyses on related topics published in the past two years. However, we found that NOS scales were mainly used, and ROBINS-I was used less, which may be caused by concerns about ROBINS-I. For example, the complexity of ROBINS-I leads to its low usability; it also causes higher learning costs for clinical practitioners; and it becomes more difficult to use it accurately, which eventually results in compromised evaluation accuracy. Moreover, we chose the older method of NOS because it is more mature and easier to use. Although ROBINS-I is newer than NOS and can better reflect the risk of bias in this study when properly assessed, it has not yet become a widely used assessment tool due to the complexity of its assessment process. ROBINS-I is a good suggestion, but we may still follow our original assessment. The adoption of the new method may wait for an appropriate opportunity. The R&D team of ROBINS-I is also trying to simplify it, and it may be a better choice to use ROBINS-I in the future. Thanks again for your suggestion!

**4. Comment.** As performing a sensitivity analysis based on quality assessment is a common

action and is not associated with selection bias, I advise authors should perform sensitivity analyses based on quality assessment and should delete the following sentence in the section of assessment of study quality in the main text: "To avoid selection bias, no studies were excluded due to these quality criteria."

**Response:** Thank you very much for the reviewer's comments, and we strongly agree with your view. We have deleted the sentence "To avoid selection bias, no studies were excluded due to these quality criteria". Furthermore, we conducted sensitivity analysis based on quality assessment. After excluding articles with relatively low quality of evidence (articles with a NOS score of 5-6), we pooled and analyzed the remaining data again. The sensitivity analysis showed that our results were robust. The sensitivity analysis results are shown in supplementary Figure S20 and S21. Sensitivity analysis based on quality assessment could not be performed for other types of fruits due to the small number of relevant studies. Special thanks to you for your constructive comments. Your comments are of great guiding significance to my future research work!

**5. Comment.** In authors' meta-analysis, I would suggest excluding cross-sectional studies because study participants are assessed at a specific time point and the temporal relationship between exposure and outcome can often not be determined.

**Response:** We strongly agree with the reviewer's opinion. We excluded cross-sectional studies and conducted a systematic review and meta-analysis on the remaining data. The specific changes were citrus overall data analysis, subgroup analysis, dose-response analysis, and funnel plot. The specific changes have been marked in red in the manuscript. Thanks

again for your suggestion, and we hope to learn more from you!!

**6. Comment.** Although it is understandable to use adjusted OR/RR for meta-analysis and it is very informative and applaudable to present confounding factors in Table 1, I would suggest authors to also present meta-analysis of unadjusted OR/RR because confounding factors that were adjusted in each study were not identical, which can potentially give rise to a source of between-study variance.

**Response:** Thank you for your rigorous advice, and we strongly agree with your opinion. We have carefully reviewed the 24 included studies. However, we did not find an OR/RR that was not adjusted for confounding factors. Therefore, meta-analysis of unadjusted OR/RR is infeasible. Thank you for your rigorous advices. Your advices are of great guiding significance to my future research work!!

**7. Comment.** Dose response meta-analysis seems solid and sound.

**Response:** Thank you very much for your careful review, and your comments helped us discover an error in this dose-response analysis. What we have placed in this article is the curve result of the linear relationship, but related research shows that the result of the nonlinear relationship is more suitable for explaining such research questions. Therefore, we carefully redraw the dose-response curve after excluding a cross-sectional study. We analyzed and discussed the results in detail based on the new dose-response curve. We sincerely apologize for the inconvenience!

**8. Comment.** Can authors elaborate more on how they attain OR/RR in Table 1? Take Lin et al. 2005 for example, I have a hard time finding the OR of 1.11 (0.71-1.74) in the original paper and I would like to gently ask authors to shed more light on it.

**Response:** Thank you very much for the reviewer's comments. We used the adjusted OR/RR. However, in the actual data extraction, we found that some studies used various models to generate adjusted OR/RR, and the number and type of their correction factors were different. In the study (Lin 2005), model3, which has the most correction factors, was used to generate the adjusted OR/RR. Thank you again for your careful review!

**Minor Comments:**

**1. Comment.** PROSPERO should be spelled out all in capital.

**Response:** Thank you for your reminder, and we have spelled PROSPERO out all in capital. Thanks for your suggestion.

**2. Comment.** English writing should be edited by a native speaker.

**Response:** Thank you for your comments. We have invited a native English speaker to improve the language. The polishing report is provided in the appendix. Thank you for your suggestion!

**Reviewer #3:**

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: .

**Response:** Thanks a lot for your comment.

**Reviewer #4:**

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Dear author, In this manuscript, the author discusses the relationship between different types of fruit consumption and colorectal cancer risk by using previously published studies and carrying out the meta-analysis using statistics. The incidence of colorectal cancer is a serious health problem in the Western world. Though this type of cancer has a survival rate of 91% when diagnosed at the localized stage, preventive measure is much more important. The author makes a good effort to complete this study with a scientific background. The manuscript is written in a good manner and organized properly, however, there are a few corrections to be made before acceptance of the manuscript which is explained in detail below.

**Response:** We gratefully appreciate your constructive comments. We have revised the article based on the issues you pointed out. We sincerely appreciate your enthusiastic work and hope that the revised manuscript can meet your requirements.

**1. Comment.** The title reflects the main subject of the manuscript but there is a mismatch between the title of this manuscript and the study registered in Prospero (study number:

CRD42022354620).

**Response:** Thank you very much for your careful check. It is a common phenomenon that Prospero registration is not in line with the title of the manuscript. Because different journals have different requirements for the title, the title has been revised many times during the submission process, but the content is consistent with the registration document. Thanks again for your comment.

**2. Comment.** The abstract summarizes the described work. Sufficient keywords are provided and the introduction covers adequate background information but still, the significance of this study needs to be addressed in brief.

**Response:** We are very grateful for the reviewer's constructive comments. We strongly agree with your opinion, and we have condensed and summarized the significance of this study. Details are shown in the conclusion section of the Abstract: "This meta-analysis provides further evidence that a higher intake of specific types of fruit is effective in preventing the occurrence of colorectal cancer". Thanks a lot for your comments.

**3. Comment.** The method of source retrieval, inclusion, and exclusion criteria are mentioned adequately. The results are discussed in detail and they can serve as a source for further research in this field. The discussion part is elaborate and can be made more concise and clearer.

**Response:** We gratefully appreciate your constructive comments. The Discussion section has been streamlined to present the significance of this study in a clearer and more precise manner. Thanks again for your suggestions, which are helpful for improving the quality of this study!

**4. Comment.** Illustrations and tables are provided adequately, but the referring of the figures in the context is still not properly done. The author has used the proper biostatistics, units, and references. The quality of the manuscript is good and follows PRISMA 2009 Checklist.

**Response:** We gratefully appreciate for your valuable suggestion. We have revised the referring of the figures, and the revisions are marked in red. Special thanks to you for your valuable comments.

**Responds to the editoial office's comments:**

The manuscript has been peer-reviewed, and it' s ready for the first decision.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

I have reviewed the Peer-Review Report, the full text of the manuscript, the relevant ethics documents, and the English Language Certificate, 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.

**Response:** Thank the reviewers for their comments, and thank the editors for giving us the opportunity to revise the article. We would carefully revise the relevant content according to the comments of the reviewers. Thank you very much!

**1. Comment.** Please provide decomposable Figures (in which all components are movable

and editable), organize them into a single PowerPoint file.

**Response:** Thank you very much for your comments. We've provided the decomposable figures and organized them into a single PowerPoint file. The file is provided in the Appendix. Thanks again for your reminder.

**2. Comment.** 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.

**Response:** Thank you for your comments, and we have re-draw the three-line table according to your advice. We hope that the revised table can meet your requirements.

**3. Comment.** 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. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group.

Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. *World J Gastroenterol* 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

**Response:** We really appreciate the reviewer's comments. I have ensured that all diagrams in this study are original (i.e. generated by the author for this article). I have added the copyright information ©the author (s) 2022 to the bottom right of the PowerPoint (PPT) image. Thank you very much for your reminder. We hope that the revisions can meet your requirements.

**4. Comment.** Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

**Response:** We really appreciate the reviewer's comments. We have used the Reference Citation

Analysis (RCA) to supplement and improve the highlights of the latest cutting-edge research results.

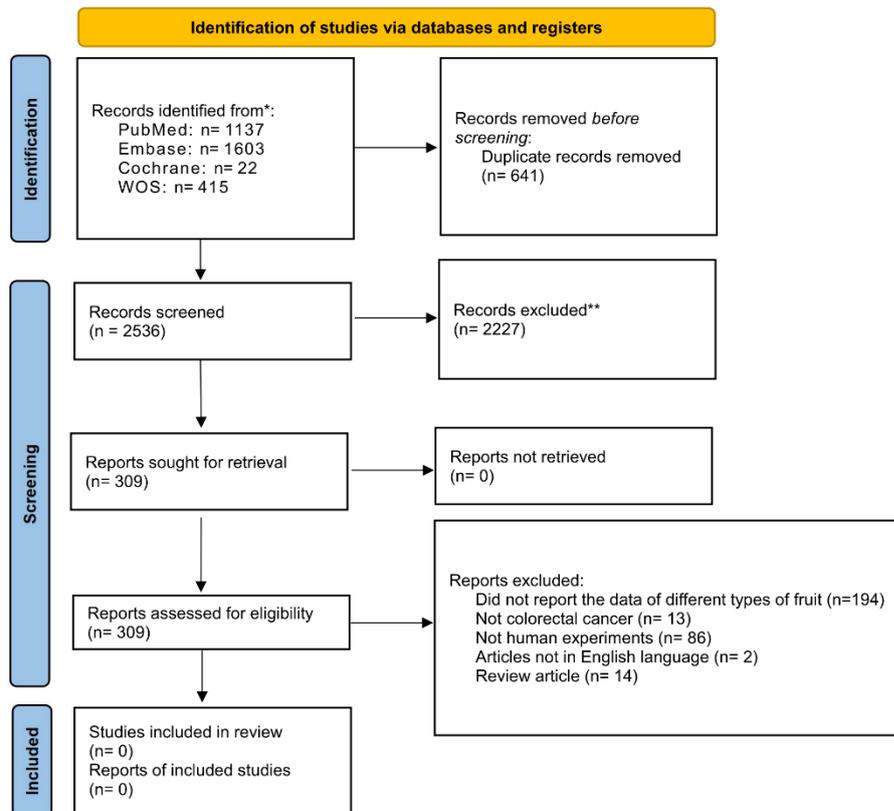
Thank you very much for recommending this practical tool. It will provide a great contribution to my future research and writing. Thanks again for your suggestions!

We tried our best to improve the manuscript and made some changes in the manuscript. These changes did not influence the content and framework of the paper. We did not list the changes here but marked them in red in the revised paper.

We earnestly appreciate for Editors/Reviewers' warm work, and hope that the revision will be approved.

Once again, thank you very much for your comments and suggestions.

## Supplementary Material



Appendix 1. PRISMA flow chart

## Appendix 2. Search Strategy

### 1. Web of science

Search number	Query	Results
#1	(TI=((cancer of colon rectum) OR (cancer of rectum colon) OR (cancer of the colon rectum) OR (cancer of the colon the rectum) OR (cancer of the rectum colon) OR (cancer of the rectum the colon) OR (colo rectal cancer) OR (colo rectal carcinogenesis) OR (colo rectal malignancies) OR (colo rectal malignancy) OR (Colorectal Cancer*) OR (colorectal cancerogenesis) OR (colorectal carcinogenesis) OR (Colorectal Carcinoma*) OR (colorectal malignancies) OR (colorectal malignancy) OR (Colorectal Neoplasm*) OR (Colorectal Tumor*) OR (malignancies of the colon rectum) OR (malignancy of colon rectum) OR (malignancy of the colon rectum) OR (recto colonic cancer) OR (rectocolonic cancer)) OR AB=((cancer of colon rectum) OR (cancer of rectum colon) OR (cancer of the colon rectum) OR (cancer of the colon the rectum) OR (cancer of the rectum colon) OR (cancer of the rectum the colon) OR	265,825

	(colo rectal cancer) OR (colo rectal carcinogenesis) OR (colo rectal malignancies) OR (colo rectal malignancy) OR (Colorectal Cancer*) OR (colorectal cancerogenesis) OR (colorectal carcinogenesis) OR (Colorectal Carcinoma*) OR (colorectal malignancies) OR (colorectal malignancy) OR (Colorectal Neoplasm*) OR (Colorectal Tumor*) OR (malignancies of the colon rectum) OR (malignancy of colon rectum) OR (malignancy of the colon rectum) OR (recto colonic cancer) OR (rectocolonic cancer)) OR AK=((cancer of colon rectum) OR (cancer of rectum colon) OR (cancer of the colon rectum) OR (cancer of the colon the rectum) OR (cancer of the rectum colon) OR (cancer of the rectum the colon) OR (colo rectal cancer) OR (colo rectal carcinogenesis) OR (colo rectal malignancies) OR (colo rectal malignancy) OR (Colorectal Cancer*) OR (colorectal cancerogenesis) OR (colorectal carcinogenesis) OR (Colorectal Carcinoma*) OR (colorectal malignancies) OR (colorectal malignancy) OR (Colorectal Neoplasm*) OR (Colorectal Tumor*) OR (malignancies of the colon rectum) OR (malignancy of colon rectum) OR (malignancy of the colon rectum) OR (recto colonic cancer) OR (rectocolonic cancer)))	
#2	(TI=((2 Phenyl Benzopyran*) OR (2 Phenyl Chromene*) OR (Bioflavonoid*) OR (flavonoid derivative) OR (Flavonoid*)) OR AB=((2 Phenyl Benzopyran*) OR (2 Phenyl Chromene*) OR (Bioflavonoid*) OR (flavonoid derivative) OR (Flavonoid*)) OR AK=((2 Phenyl Benzopyran*) OR (2 Phenyl Chromene*) OR (Bioflavonoid*) OR (flavonoid derivative) OR (Flavonoid*)))	143,969
#3	(TI=((Nobiletin) OR (hexamethoxyflavone)) OR AB=((Nobiletin) OR (hexamethoxyflavone)) OR AK=((Nobiletin) OR (hexamethoxyflavone)))	1, 687
#4	#2 OR #3	144,995
#5	#1 AND #4	646
#6	#1 AND #4 and Meeting or Review Article or Editorial Material or Patent or Book or Retracted Publication (Exclude Document Types)	463
#7	TI=(Animal OR Rat OR Mouse OR Mice OR Pig OR canine OR gene OR DNA OR RNA OR rabbit)	5,286,476
#8	#6 NOT #7	415

## 2. Cochrane (Date Run: 05/02/2023 17:36:18)

ID	Search	Hits
#1	('cancer of colon rectum' OR 'cancer of rectum colon' OR 'cancer of the colon rectum' OR 'cancer of the colon the rectum' OR 'cancer of the rectum colon' OR 'cancer of the rectum the colon' OR 'colo rectal cancer' OR 'colo rectal carcinogenesis' OR 'colo rectal malignancies' OR 'colo rectal malignancy' OR 'Colorectal Cancer*' OR 'colorectal cancerogenesis' OR 'colorectal carcinogenesis' OR 'Colorectal Carcinoma*' OR 'colorectal malignancies' OR 'colorectal malignancy')	19267

	OR 'Colorectal Neoplasm*' OR 'Colorectal Tumor*' OR 'malignancies of the colon rectum' OR 'malignancy of colon rectum' OR 'malignancy of the colon rectum' OR 'recto colonic cancer' OR 'rectocolonic cancer'):ti,ab,kw	
#2	MeSH descriptor: [Colorectal Neoplasms] explode all trees	10857
#3	('2 Phenyl Benzopyran*' OR '2 Phenyl Chromene*' OR 'Bioflavonoid*' OR 'flavonoid derivative' OR 'Flavonoid*'):ti,ab,kw	1792
#4	MeSH descriptor: [Flavonoids] explode all trees	2894
#5	('nobiletin' OR 'hexamethoxyflavone'):ti,ab,kw	15
#6	(#3 OR #4) OR #5	3796
#7	(#1 OR #2) AND #6	25
#8	('Animal' OR 'Rat' OR 'Mouse' OR 'Mice' OR 'Pig' OR 'canine'):ti,ab,kw	28729
#9	#7 NOT #8	22

### 3. Embase

No.	Query	Results	Date
#11	#10 AND 'Article'/it	1603	5-Feb-23
#10	#9 NOT #7	3309	5-Feb-23
#9	(#1 OR #2) AND #8	4094	5-Feb-23
#8	#3 OR #4 OR #5 OR #6	206777	5-Feb-23
#7	'animal':ti,ab,kw OR 'rat':ti,ab,kw OR 'mouse':ti,ab,kw OR 'mice':ti,ab,kw OR 'pig':ti,ab,kw OR 'canine':ti,ab,kw	3644589	5-Feb-23
#6	'nobiletin'/exp	1425	5-Feb-23
#5	'nobiletin':ti,ab,kw OR 'hexamethoxyflavone':ti,ab,kw	1076	5-Feb-23
#4	'flavonoid'/exp	192424	5-Feb-23
#3	'2 phenyl benzopyran*':ti,ab,kw OR '2 phenyl chromene*':ti,ab,kw OR 'bioflavonoid*':ti,ab,kw OR 'flavonoid derivative':ti,ab,kw OR 'flavonoid*':ti,ab,kw	84321	5-Feb-23
#2	'colorectal cancer'/exp	371603	5-Feb-23
#1	'cancer of colon rectum':ti,ab,kw OR 'cancer of rectum colon':ti,ab,kw OR 'cancer of the colon rectum':ti,ab,kw OR 'cancer of the colon the rectum':ti,ab,kw OR 'cancer of the rectum colon':ti,ab,kw OR 'cancer of the rectum the colon':ti,ab,kw OR 'colo rectal cancer':ti,ab,kw OR 'colo rectal carcinogenesis':ti,ab,kw OR 'colo rectal malignancies':ti,ab,kw OR 'colo rectal malignancy':ti,ab,kw OR 'colorectal cancer*':ti,ab,kw OR 'colorectal cancerogenesis':ti,ab,kw OR 'colorectal carcinogenesis':ti,ab,kw OR 'colorectal carcinoma*':ti,ab,kw OR 'colorectal malignancies':ti,ab,kw OR 'colorectal malignancy':ti,ab,kw OR 'colorectal neoplasm*':ti,ab,kw OR 'colorectal tumor*':ti,ab,kw OR 'malignancies of the colon rectum':ti,ab,kw OR 'malignancy of colon rectum':ti,ab,kw OR 'malignancy of the colon rectum':ti,ab,kw OR	219410	5-Feb-23

	'recto colonic cancer':ti,ab,kw OR 'rectocolonic cancer':ti,ab,kw		
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#### 4. PubMed

Search number	Query	Results
13	#11 NOT #12	1,137
12	review[Publication Type]	3,107,928
11	#9 NOT #10	1,241
10	"Animal"[Title/ Abstract] OR "Rat"[Title/Abstract] OR "Mouse"[Title/Abstract] OR "Mice"[Title/Abstract] OR "Pig"[Title/Abstract] OR "canine"[Title/Abstract]	2,904,938
9	(#1 OR #2) AND #8	1,733
8	(#3 OR #4) OR (#5 OR #7)	147,632
7	nobiletin[MeSH Terms]	0
6	nobiletin[MeSH Terms] - Schema: all	0
5	"nobiletin"[Title/ Abstract] OR "hexamethoxyflavone"[Title/ Abstract]	861
4	Flavonoids[MeSH Terms]	120,443
3	"2 Phenyl Benzopyran*"[Title/Abstract] OR "2 Phenyl Chromene*"[Title/Abstract] OR "Bioflavonoid*"[Title/Abstract] OR "flavonoid derivative"[Title/Abstract] OR "Flavonoid*"[Title/Abstract]	61,285
2	colorectal neoplasms[MeSH Terms]	232,586
1	"cancer of colon rectum"[Title/Abstract] OR "cancer of rectum colon"[Title/Abstract] OR "cancer of the colon rectum"[Title/Abstract] OR "cancer of the colon the rectum"[Title/Abstract] OR "cancer of the rectum colon"[Title/Abstract] OR "cancer of the rectum the colon"[Title/Abstract] OR "colo rectal cancer"[Title/Abstract] OR "colo rectal carcinogenesis"[Title/Abstract] OR "colo rectal malignancies"[Title/Abstract] OR "colo rectal malignancy"[Title/Abstract] OR "Colorectal Cancer*"[Title/Abstract] OR "colorectal cancerogenesis"[Title/Abstract] OR "colorectal carcinogenesis"[Title/Abstract] OR "Colorectal Carcinoma*"[Title/Abstract] OR "colorectal malignancies"[Title/Abstract] OR "colorectal malignancy"[Title/Abstract] OR "Colorectal Neoplasm*"[Title/Abstract] OR "Colorectal Tumor*"[Title/Abstract] OR "malignancies of the colon rectum"[Title/Abstract] OR "malignancy of colon rectum"[Title/Abstract] OR "malignancy of the colon rectum"[Title/Abstract] OR "recto colonic cancer"[Title/Abstract] OR "rectocolonic cancer"[Title/Abstract]	146,552

## Round 2

List of Responses Dear Editors and Reviewers: Thank you for your letter and the reviewers' comments concerning our manuscript entitled "Different types of fruit intake and colorectal cancer risk: a meta-analysis of observational studies" (ID:82456). Those comments are all valuable and very helpful for revising and improving our paper and provide important guiding significance for our researches. We carefully considered the comments and made corrections that we hope would be approved. Revised portions are marked in the paper. The main corrections in the paper and the responses to the reviewer's comments are as follows: 1. Comment. The authors have revised their manuscript appropriately, significantly enhancing the quality of their article. I would like to congratulate authors on their significant contribution. However, I regret that I still disagree with the authors using NOS as the mainstay tool for quality assessments. According to Cochrane Handbook Chapter 25, ROBINS-I is recommended when assessing non-RCT studies. The underlying rationale for its use resides in the fact that the evaluations of non-RCT studies are facilitated by attempting to emulate a hypothetical pragmatic randomized trial. This is of utmost importance as researchers are passionate for the possible use of non-RCT studies to provide evidence with regard to the comparative effectiveness of given interventions because conductions of RCT are expensive, time consuming, and may not reflect real world experience with healthcare interventions (Ann Intern Med 2009;151:203-5). Of note, NOS tool is not designed to evaluate non-RCT studies in this manner so it is main reason why it is considered outdated with the advent of ROBINS-I. I speculate that what the authors referred to regarding the low usability of ROBINS-I is a conclusion from a recent paper by Zhang et al. (J Evid Based Med. 2021;1-11.) suggesting that appraising studies with the use of ROBINS-I is time-consuming and advanced training in epidemiology is mandatory, which is true as it would be difficult to use it without experts in both methodology and subject-related content. However, it should not be the reason against using it. Although it may not affect the ultimate meta-analysis results regardless of using NOS or ROBINS-I in this study, it would be more appropriate

to use ROBINS-I than otherwise in terms of solid and sound methodology and I still suggest authors revise the quality assessment section in accordance with the strictest methodology.

**Response:**

I would like to thank the reviewers for their patience and guidance. Admittedly, the emergence of ROBINS-I is a milestone for the evaluation of the quality of NRSI. ROBINS-I is a more suitable bias risk assessment tool for NRSI. It is applicable to various types of non-randomized research in the evaluation of intervention effects, and it is also a domain evaluation tool. The ROBINS-I tool includes 7 evaluation domains, which are divided into pre-intervention, during-intervention, and post-intervention. Based on your suggestion, we have replaced the original quality evaluation tool with ROBINS-I. After consulting an experienced reviewer, another researcher and I independently assessed the quality of all included studies. Any disagreements were discussed mutually, and then the experienced reviewer assisted in the final determination. The detailed quality evaluation is as follows: Based on the ROBINS-I tool, we identified all studies as having moderate risk of bias. Most of the problems found were regarding confounding and missing data. There was a moderate bias in the classification of interventions in five studies and a moderate bias in the selection of participants in five studies. Among all observational studies, Bias due to deviations from intended interventions, outcomes measurement bias and selection of reported results were considered low. Risk of bias assessment results are summarized in Table 3. Furthermore, sensitivity analysis was performed based on the quality assessment results. All revisions are marked in red in the manuscript. Thanks again for your suggestions, and I hope to learn more from you!

2. Comment. Your manuscript has been checked by CrossCheck. Please read the attached CrossCheck report for details. Our editorial policy states the overall similarity should be less than 30%, the overlapped section should

be less than 5% in single papers, including author's own work. Response: Thank you for your reminder. We have revised the overlapped section, and the similarity meets the above criteria. We hope our revisions can get your approval. Thank you again for your hard work! I would like to extend my deep respect to you! We tried our best to improve the manuscript and made some changes in the manuscript. These changes did not influence the content and framework of the paper. We did not list the changes here but marked them in red in the revised paper. We earnestly appreciate for Editors/Reviewers' warm work, and hope that the revision will be approved. Once again, thank you very much for your comments and suggestions.