PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of Dietary Inflammatory Index(DII) and Depression in the elderly over 55 years in Northern China: analysis of data from a multicentre, cohort study
AUTHORS	Li, Ruiqiang; Zhan, Wenqiang; Huang, Xin; Zhang, Zechen; Zhou, Meiqi; Bao, Wei; Huang, Feifei; Ma, Yuxia

VERSION 1 – REVIEW

REVIEWER	Salama, Amany Pharos University, Nutrition and food safty
REVIEW RETURNED	28-Sep-2021

GENERAL COMMENTS	The subject of Systemic inflammation is a hot topic in nutrition & NCDs; yet you need to elaborate more on its effect & relation to depression as well as on the DII used. In the method section you better add an appendix of the DII used to allow the study to be repeated. On page 7 the 1st paragraph contains repetition. Some abbreviations are not expanded when 1st mentioned. In page 12 of discussion; the paragraph starting with "As we all know" needs some rephrasing & grammatical checking.

REVIEWER	Feizi, Awat Isfahan University of Medical Sciences, Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran
REVIEW RETURNED	30-Sep-2021

GENERAL COMMENTS	Authors investigated the association of DII with depression in adults over 55 in China, The following points are suggested point by point Abstract In methods section it is needed to explain or express the tool used for measuring depression, which method was used for computing DII, also, study design name. Results section needs major concerns, incidence is not correct term in this study, also the first and last sentence are repetitive. The second sentence is irrelevant and do not scientifically sound make sense. What is PCR? Where it has been introduced previously? Introduction Should be expanded through presenting the reasons and mechanism of affecting mood by inflammation.

	How about the DII history? More relevant literature should be presented about the association between DII and mental disorders. Please explain the novelty and necessity of your study. The study objective should be explained more complete and correct, population? Depressive outcomes is not correct term for your study, you only studied depression. Methods First and second subsections needs some corrections, tow times you said about informed consent! You can combine these two subsections. Please present more explanation about the main study, sampling process (more) inclusion and exclusion criteria for your current secondary study? Whether you included people with other psychological disorders? These pints clear your study population for your paper's readers. For all instruments used for evaluating depression, food, please present their psychometric properties (validity and reliability) in Chines population with relevant reference. Which cut point was used by you for considering people as depressed? How you evaluated physical activity by yes/no?! if you used energy adjusted DII, why you considered it as confounder, it is incorrect approach and data analysis results affected severely by that. Statistical analysis: I have some important suggestion, I saw the results, the results for subgroup analyses by BMI are not reliable in some categories because of low sample size? I suggest to do it in three subgroups as normal, overweight, obese. Also, subgroup analysis by gender is recommended due to dependence of depression as well as inflammation to the gender. Other minor points: finally, you used SD or SEM?! Please explain the process of model fitting in logistic regression, each model contains which confounding variables? Which version of R was used? Results Very important points The above suggested points in statistical analysis subsection are necessary for completing results section. You should compare the variables in table 1, between depressed and non-depressed people You should compare the nutrients used for constructing DII between depressed and non-depressed people. For this and above comment, you should provide separate tables. Please footnote the used statistical test below table 1, and for two new suggested tables in above previous comment. How about the p-trend in table 2? Discussion The authors cited few relevant studies for comparing their results with previous ones particularly among elderly people. After conducting new analysis by gender, discussion should be reconsidered. Limitations should be expanded to some other points such as unreliableness of some confounders such as diabetes, hypertension,… that are only based on the report from participants.

VERSION 1 – AUTHOR RESPONSE

Responses to the comments of Reviewer #1

Recommendations to Dr. Amany Salama, Pharos University

Additional comments :

1.The subject of Systemic inflammation is a hot topic in nutrition & NCDs; yet you need to elaborate more on its effect & relation to depression as well as on the DII used.

Response:

Thank you very much for your valuable comments on this article. Based on your suggestion, we have made corresponding changes in the manuscript.

Systemic inflammation is becoming an important factor in the etiology of mental illnesses such as depression and anxiety. Approximately one-quarter of patients with major depression (MDD) show evidence of systemic inflammation. Moreover, some studies have shown that chronic low-grade inflammation of the whole body can affect monoaminergic and glutamate neurotransmission, which may adversely affect the cognitive function of patients with bipolar disorder or major depression. However, before the first episode of depression, whether various pro-inflammatory cytokines are abnormally elevated remains unclear. Some studies have shown that the association between diet and mental health disorders may be mediated by the inflammatory properties of diet. The current treatment of depression is not considered to be effective in all cases. So far, there are few nutritional programs in the guidelines for the treatment of depression. Recently, due to the pro-inflammatory and anti-inflammatory properties of nutrients, people are paying more and more attention to the protective and regulating effects that diet may have in common mental disorders (including depression). However, there are limited data on the role of dietary inflammation potential in this regard. The long-term unhealthy diet leads to a decline in the quality of the diet, which may create a pro-inflammatory environment in the human body, thereby creating conditions for the occurrence and development of various chronic inflammatory diseases. DII, as a tool that can assess the potential of dietary inflammation, provides the possibility to test this hypothesis.

2.In the method section you better add an appendix of the DII used to allow the study to be repeated.

Response:

Thank you for your suggestion. Based on your suggestion, we have made corresponding changes in the manuscript.

$$Zscore = [(\text{daily mean intake} - \text{global daily mean intake})/\text{st andard deviation}]$$
$$Zscore^1 = Zscore \rightarrow (\text{converted to a percentile score}) \times 2 - 1$$
$$DII = \sum Zscore^1 \times \text{the inflammato ry effect score of each dietary component}$$

On page 7 the 1st paragraph contains repetition.

Some abbreviations are not expanded when 1st mentioned.

In page 12 of discussion; the paragraph starting with "As we all know" needs some rephrasing & grammatical checking.

Response:

Thank you for your suggestion. We revised the manuscript accordingly based on your suggestions.

For all instruments used for evaluating depression, food, please present their psychometric properties (validity and reliability) in Chines population with relevant reference. Which cut point was used by you for considering people as depressed?

Response:

Thank you for your suggestion. Beck Depression Inventory (BDI), Hamilton Depression Inventory (HAM-D), Epidemiological Research Center Depression Inventory (CES-D), Patient Health Questionnaire 9 (PHQ-9), Cornell Dementia Depression Inventory (CSDD) and Zung Self-rated Depression Scale (SDS) are widely used self-report screening tools for depression. However, these scales are not specifically designed for the elderly, and some problems arise when applied to the elderly. First of all, the answer format is too complicated for the elderly to answer. For example, some scales have multiple choices for each question, requiring the participant to choose the one that is closest to the actual situation. Other scales require participants to estimate how often each description occurs.

Second, the physical symptoms that may be caused by other physical diseases are not unique to depression. A scale that includes problems related to physical symptoms, such as decreased appetite or sleep disturbance, can overestimate the prevalence of depressive symptoms. Considering these

problems, Brink and Yesavage developed the Geriatric Depression Scale (GDS), which is a 30-item screening questionnaire designed for the elderly. None of the 30 items are physical symptoms, thus avoiding the confusion of physical symptoms with physical disorders common in the elderly. The 30-item GDS (GDS-30) is validated and used in multiple languages around the world and is a reliable and effective screening tool, although the factor structure differs for different language versions. A systematic review reported that the sensitivity of the pooled GDS-30 study was 0.753 and the specificity was 0.770.

The criteria for judging depression in the study are as follows: 0-10 points indicate no depression, 11-20 points indicate mild depression, and 21-30 points indicate severe depression.

Responses to the comments of Reviewer #2

Recommendations to Dr. Awat Feizi, Isfahan University of Medical Sciences

Additional comments：

Introduction

Should be expanded through presenting the reasons and mechanism of affecting mood by inflammation.

Response:

Thank you for your suggestion. Based on your suggestion, we have made corresponding changes in the manuscript.

Meanwhile, inflammation has important physiological effects on mood and behavior. Kynurenine metabolism is hypothesized to be a pathway connecting inflammation and depression, partly because of the effect of kynurenine metabolites on the neurotransmission of glutamate in the central nervous system. Some studies have shown that inflammation may affect the interconnection of the hypothalamus with areas important for cognition and emotion, and it may cause the hypothalamus-pituitary-adrenal (HPA) axis to be dysregulated and affect the monoaminergic system.

How about the DII history? More relevant literature should be presented about the association between DII and mental disorders.

Response:

The Dietary inflammatory index (DII) was developed and verified by researchers at the University of South Carolina in Columbia to assess the inflammatory potential of an individual's diet. The initial DII score was based on the results of articles published from 1950 to 2007 that assessed the impact of specific foods on specific inflammatory markers (specific inflammatory markers include IL-1β, IL-4, IL-6, IL-10, TNF-α and CRP), significantly increase IL-1β, IL-6, TNF-α or CRP, or decrease IL-4 or IL-10 to "+1", which is pro-inflammatory; significantly reduce IL-1β, IL-6, TNF -α or CRP, or increase IL-4 or IL-10 to "-1", which is an anti-inflammatory effect. In 2014, South Carolina researchers improved the DII score from 2007 to 2010, and the improved scoring system applied 45 food parameters.

The relationship between diet, inflammation and mental health is of increasing interest, and the link between diet and mental health disorders may be mediated by the inflammatory properties of diet. [14,15] As a tool to assess the potential of dietary inflammation, the relationship between DII and mental disorders is worthy of discussion and research. Moreover, a study has shown that people with the lowest levels of DII have a lower risk of being at the highest levels of mental health disorders.

Please explain the novelty and necessity of your study.

Response:

Although the number of patients with depression has increased in recent years, compared with other developed countries, there are relatively few studies on depression in China. Therefore, it is urgent to explore the relationship between DII and depression risk in the Chinese elderly. The Dietary Inflammatory Index (DII) is a tool used to quantify the dietary inflammation potential of an individual's diet. Its goal is to assess the impact of diet-related inflammation on health outcomes. Thus, the purpose of this work was to examine the association between the inflammatory potential of habitual diets and depression. Moreover, the use of DII as an indicator to directly and reasonably connect the three of nutrition, inflammation and depression, may have clinical and public health significance for the development of new nutritional psychiatric methods to promote good mental health.

The study objective should be explained more complete and correct, population? Depressive outcomes is not correct term for your study, you only studied depression.

Response:

Thank you very much for your suggestion. Based on your suggestion, we have made corresponding changes in the manuscript.

Thus, the purpose of this work was to examine the association between the inflammatory potential of habitual diets and depression.

Methods

First and second subsections needs some corrections, two times you said about informed consent! You can combine these two subsections. Please present more explanation about the main study, sampling process (more) inclusion and exclusion criteria for your current secondary study? Whether you included people with other psychological disorders? These pints clear your study population for your paper's readers.

Response:

Thank you very much for your suggestion. Based on your suggestion, we have made corresponding changes in the manuscript.

Participants came from the Community Cohort Study of Nervous System Diseases (CCSNSD) project under the National Key Research and Development Program, the National Key Research and Development Program, and the Precision Medicine Project Nervous System Disease Cohort Research (CCSNSD) project. The project is undertaken by the Institute of Nutrition and Health of the Chinese Center for Disease Control and Prevention, in cooperation with the Center for Disease Control and Prevention. The project uses a multistage random cluster sampling method to draw samples. The protocol of this study was reviewed and approved by the Institutional Review Board of the National Institute for Nutrition and Health (No. 2017020, November 6, 2017).

In allusion to subjects recruited in the CCSNSD cohort, the samples eligible for inclusion were (1) 55 years old and older, (2) resident population living in the sampled community, (3) absence of clinically diagnosed depression, (4) be able to perform a normal depression assessment, (5) completed data of sociodemographic characteristics, disease history, and food frequency questionnaire (FFQ). We excluded subjects because of (1) no depression assessment results, (2) lack of baseline status such as education and physical activities, (3) nutrient deficiency, (4) abnormal energy intake, (5) people with other psychological disorders. Finally, a total of 2022 participants were involved in the analysis.

Results

You should compare the nutrients used for constructing DII between depressed and non-depressed people. For this and above comment, you should provide separate tables.

Response:

Thank you very much for your suggestion. Based on your suggestion, we have made corresponding changes in the manuscript.

Statistical analysis: I have some important suggestion, I saw the results, the results for subgroup analyses by BMI are not reliable in some categories because of low sample size? I suggest to do it in three subgroups as normal, overweight, obese. Also, subgroup analysis by gender is recommended due to dependence of depression as well as inflammation to the gender.

Response:

We have changed the BMI to three subgroups of normal, overweight, and obese. At the same time, due to the dependence of depression and inflammation on gender, we conducted a supplementary analysis of subgroups by gender.

Other minor points: finally, you used SD or SEM?! Please explain the process of model fitting in logistic regression, each model contains which confounding variables? Which version of R was used?

Response:

Thank you very much for your suggestion. We used SEM and described it in the statistical method. We noted the confounding variables contained in each model in the logistic regression model table.

How you evaluated physical activity by yes/no?! if you used energy adjusted DII, why you considered it as confounder, it is incorrect approach and data analysis results affected severely by that.

Response:

Thank you very much for your suggestion. The study used the International Physical Activity Questionnaire (IPAQ)-a short form to estimate the level of physical activity and sitting time. The amount of physical activity (MET hours/week) is calculated as follows: the designated MET level for high-intensity activity is 8.0 MET, for moderate-intensity activity is 4.0 MET, and walking is 3.3 MET. An activity level equal to or greater than 10.0 MET hours/week is considered to meet the 150-minute weekly physical activity guidelines. According to this standard, we divided physical activity into

vigorous intensity and moderate intensity, and made corresponding changes in the table. We also removed the energy from the adjustment confounding factors and re-adjusted the results.

Statistical analysis: I have some important suggestion, I saw the results, the results for subgroup analyses by BMI are not reliable in some categories because of low sample size? I suggest to do it in three subgroups as normal, overweight, obese. Also, subgroup analysis by gender is recommended due to dependence of depression as well as inflammation to the gender.

Response:

Thank you very much for your suggestion. We have regrouped BMI and regrouped BMI as normal, overweight, and obese. At the same time, conduct subgroup analysis by gender.

Other minor points: finally, you used SD or SEM?! Please explain the process of model fitting in logistic regression, each model contains which confounding variables? Which version of R was used?

Response:

Thank you very much for your suggestion. Our results use SEM, and the confounding variables included in each model in logistic regression are supplemented in the methods and results. Statistical analyses were all performed with R 3.6.0 sofware (R: A Language and Environment for Statistical Computing, {R Core Team}, R Foundation for Statistical Computing, Vienna, Austria, 2018, https://www.R-project.org).

Results

Very important points

The above suggested points in statistical analysis subsection are necessary for completing results section.

You should compare the variables in table 1, between depressed and non-depressed people

You should compare the nutrients used for constructing DII between depressed and non-depressed people. For this and above comment, you should provide separate tables.

Please footnote the used statistical test below table 1, and for two new suggested tables in above previous comment.

How about the p-trend in table 2?

Response:

Thank you very much for your suggestion. We compared the variables in Table 1 between depressed and non-depressed people, and we added the comparison of the nutritional components used to construct DII between depressed and non-depressed people. At the same time, we made footnotes to the statistical tests used under Table 1, and added footnotes to the two new tables. Meanwhile, the P-trend in Table 2 is added.

Discussion

The authors cited few relevant studies for comparing their results with previous ones particularly among elderly people.

After conducting new analysis by gender, discussion should be reconsidered.

Limitations should be expanded to some other points such as unreliableness of some confounders such as diabetes, hypertension,… that are only based on the report from participants.

Response:

Thank you very much for your suggestion. We have added the results of previous related studies in the manuscript discussion to compare with our results, especially in the elderly. At the same time, the content of depression of different genders has been added. Finally, the limitations in the manuscript increase the unreliability of some confounding factors such as diabetes and hypertension.

VERSION 2 – REVIEW

REVIEWER	Feizi, Awat Isfahan University of Medical Sciences, Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran
REVIEW RETURNED	26-Nov-2021

GENERAL COMMENTS	Dear author Some points are essential for improving your work You should compare the variables between depressed and non-depressed participants (as categories of your dependent variable) , you did not address this point. This may affect your confounders in logistic regression analysis. You should do subgroup analysis by gender, as stated both predictor (DII) and mental status (Depression) are highly dependent to gender.

VERSION 2 – AUTHOR RESPONSE

Responses to the comments of Reviewer #2

You should compare the variables between depressed and non-depressed participants (as categories of your dependent variable) , you did not address this point. This may affect your confounders in logistic regression analysis.

Response:

Thank you for your suggestion. Our Supplementary Table 1 in the Supplementary Materials compares the differences in variables (as categories of dependent variables) between depressed and non-depressed participants.

You should do subgroup analysis by gender, as stated both predictor (DII) and mental status (Depression) are highly dependent to gender.

Response:

Thank you for your suggestion. We performed subgroup analyses by sex in Supplementary Table 3 in the Supplementary Material and added possible reasons for the difference in the Discussion.

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in BMJ Open.

We shall look forward to hearing from you at your earliest convenience.