

15th of June, 2021

To the Reviewers and the World Journal of Psychiatry (Editor-in-Chief) Rajesh R Tampi, MD.

We would like to thank the reviewers and the editor-in-chief in advance for their comments on our manuscript previously titled "**Healthy Diet, Depression and Quality of Life: A narrative review of biological mechanisms and primary prevention opportunities.**" (Manuscript NO: 65089). These suggestions have served to improve the overall quality of our work and potential interest to the audience of the journal.

In the following pages you will find a point-by-point response to your comments and suggestions for improvement. The reviewers comments can be found in black font, whereas our responses are presented in **blue font**. Furthermore, references are made to the manuscript in various sections. The changes make reference to the document with the changes, indicating page and section as follows (example: **Page 18, Section "Links to other Cardio-metabolic diseases"**).

Sincerely,

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Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: It is an interesting and extensive narrative review with appropriate references. I suggest you to add the following references: - Popa AR, Vesa CM, Uivarosan D, Jurca CM, et al. Cross sectional study regarding the association between sweetened beverages intake, fast-food products, body mass index, fasting blood glucose and blood pressure in the young adults from North-Western Romania. *Rev. Chim. (Bucharest)*, 2019, 70(1): 156-160; - Dimitriu MCT, Pantea-Stoian A, Smaranda AC, Nica AA, Carap AC, Constantin VD, Davitoiu AM, Cirstoveanu C, Bacalbasa N, Bratu OG, Jacota-Alexe F, Badiu CD, Smarandache CG, Socea B. Burnout syndrome in Romanian medical residents in time of the COVID-19 pandemic. *Med Hypotheses*. 2020 Nov;144:109972. doi: 10.1016/j.mehy.2020.109972; - Cotel A, Golu F, Pantea Stoian A, Dimitriu M, Socea B, Cirstoveanu C, Davitoiu AM, Jacota Alexe F, Oprea B. Predictors of Burnout in Healthcare Workers during the COVID-19 Pandemic. *Healthcare (Basel)*. 2021 Mar 9;9(3):304. doi: 10.3390/healthcare9030304.

We appreciate the Reviewer's comments for the benefit of the manuscript and overall interest to the readers of the WJP. The suggested references have been included in the new version of the manuscript on **page 15 section "Links to other Cardio-metabolic diseases"** and **page 19, section "Why a Mediterranean dietary (MD) pattern for the prevention of depression?"**.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: Unipolar depressive disorder (UDD) affects more than 264 million people worldwide and was projected to be the leading cause of disability-adjusted life years lost in 2030, well before the SARS-CoV-2 pandemic. It is imperative for leading economies to implement preventive strategies targeted towards UDD, as consistent policies are currently lacking. Recently established similarities between the aetiological hypotheses of depression and cardiometabolic diseases are shifting paradigms within this field. Hence, it is believed that dietary practices could potentially reduce the incidence of depression; similar to its effects on metabolism. Thus, the aim of this review is to compile current evidence for healthy dietary patterns as suitable contributors to primary prevention strategies against UDD. Most of the well-known biological mechanisms behind depression have been positively associated with healthful diets and dietary patterns, in varying degrees. Interestingly, a common factor is the production and overall effects of inflammatory cytokines such as IL-6, TNF- α , and CRP. These compounds have been associated with depressive symptoms, disturbances in neuroendocrine function, leaky gut, monoamine activity and brain function, but are also a key factor in the development of cardiometabolic diseases. Finally, there is a need to include health related quality of life (HRQoL) as an indicator of physical and mental well-being for its putative associations with depression and suicide risk. In particular, the great potential of the Mediterranean diet (MD) for the prevention of metabolic and cardiovascular diseases is well supported by first-level evidence and it is considered by various organizations as a model healthy eating pattern. In one of the few clinical trials investigating these associations, the PREDIMED trial, individuals with diabetes assigned to a MD supplemented with mixed tree nuts experienced a 41% relative risk reduction of developing depression. Going forward, focusing in clinical trials, using precise nutritional assessments, and identifying nutritional biomarkers that might be related to depression are needed to fully support the implementation of dietary recommendations in the field of psychiatry.

We appreciate the reviewers comments as they add value to manuscript which is of general interest in this developing field. As instructed, we respond on a point-by-point manner to each of the suggestions.

Comments : 1. Literature search and exclusion criteria ?

Although the interest in the field has increased in the past years, substantial research is still lacking. Therefore, our aim was to carry out a narrative review, as stated in our title and the objective, in order to state our general interest and points of view as researchers of the field of Mediterranean diet and UDD. As such, a non-systematic selection of the literature was carried out along with a critical summary of our personal views for the potential prevention of UDD based on dietary interventions and recommendations.

2. What is the clinical utility of the authors findings? The clinical perspective should be confirmed

As mentioned overall within our manuscript, our potential for clinical applications is broad, although limited to speculations based on observational studies. With the up-coming research from the PREDI-DEP trial, these speculations will eventually shift to more robust conclusions and guidelines (**Page 21**).

3. A possible mechanism diagram between Healthy Diet, Depression and Quality of Life could be added

We appreciate this point in particular, as it was lacking in the original manuscript. As mentioned in the section "Why a Mediterranean dietary (MD) pattern for the prevention of depression?" In the new version of the manuscript we have, to the best of our abilities, attempted to summarize these complex mechanisms and their implications with diet and lifestyles.

4. This reference "Decreased level of irisin, a skeletal muscle cell-derived myokine, is associated with post-stroke depression in the ischemic stroke population. Journal of neuroinflammation, 15(1), 1-10." could be added in the revision text.

Point 4. Given the strong relationship with our manuscript we have included the suggested reference to **page 15, section "Links to other Cardio-metabolic diseases"**.

(1) Science editor: Please upload Non-Native Speakers of English Editing Certificate by a native English speaker or a professional editing company.

The English Editing certificate of the manuscript has been uploaded to the journals server. Furthermore, the suggestions made by the editor have been taken into consideration and incorporated into the manuscript. We have included an acknowledgement to the English editor in the corresponding section for their work.

(2) Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of

the World Journal of Psychiatry, 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.

As no further comments were made by the editor-in-chief, we would only like thank the editing team and editors for their suggestions, comments, and remarks as they have much improved the original manuscript. We hope these changes have increased the editors' interest on our manuscript and for the interest on the readers of the *World Journal of Psychiatry*.