

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The association of magnesium intake with type 2 diabetes and total stroke: an updated systematic review and meta-analysis
AUTHORS	Zhao, Binghao; Zeng, Lianli; Zhao, Jiani; Wu, Qian; Dong, Yifei; Zou, Fang; Gan, Li; Wei, Yiping; Zhang, Wenxiong

VERSION 1 - REVIEW

REVIEWER	Claudio Pedone Università Campus Bio-Medico di Roma. Rome, Italy.
REVIEW RETURNED	22-Aug-2019

GENERAL COMMENTS	<p>This meta-analysis evaluates the association of magnesium intake and incident diabetes mellitus or ischemic stroke. The author used a standard methodology that seems appropriate for the subject matter. The results are confirmatory of the accepted knowledge that magnesium intake is associated with a reduced risk of incident diabetes mellitus and cardiovascular events. Most of the discussion, however, overstretch this findings as if causation is implied. For example, in the discussion (lines 340 ff) they state that "Enhancing magnesium intake seemed to be more effective for North American and European individuals to get lower stroke risk". This statement is not supported by the data: due to their observational nature, it is not possible to infer that since higher intake is associated to lower risk, then enhancing the intake would lower the risk. That would be true only if magnesium deficiency was causally related to the outcome. Similarly, at lines 344 ff the authors state that "[...] the correction of magnesium deficiencies and enhancement of magnesium intake appears to be useful [...]". Once again, that would be true if magnesium was causally related to T2D or stroke, which is not demonstrable in observational studies. Other examples are scattered throughout the discussion, that should be thoroughly revised in order to avoid any statement implying a causal role of magnesium intake.</p>
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REVIEWER	Asst. prof. Dario Rahelic, MD, PhD, FACE, FACN, FRCP Edin. Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Merkur University Hospital, School of Medicine, University of Zagreb, Croatia
REVIEW RETURNED	11-Sep-2019

GENERAL COMMENTS	<p>The goal of this paper is commendable in that the question of whether magnesium intake can reduce incidence of type 2 diabetes and stroke is of high importance. The paper has the potential to be an important contribution to the literature.</p> <p>However, in its present form there are few unanswered questions to truly evaluate the significance of the findings. For example, the following basic question was not clearly answered – what defines high vs. low magnesium intake. Furthermore, FFQs and SFFQs can be used for magnesium intake estimation, but for accurate magnesium intake estimation should be used magnesium specific food questionnaire and/or food records. That should be addressed in Study limitations section.</p> <p>Was there a minimum study duration to be included? Were studies only included if they tested high vs. low magnesium intake or would one or the other be ok? Please clarify. Thank you.</p> <p>Instead of term low magnesium level I suggest to use term low serum concentration.</p> <p>In line 325 there is ... RR was0.98 That should be corrected.</p> <p>In conclusion section, recommendation regarding magnesium intake dose, in order to decrease incidence of diabetes or stroke, should be given.</p>
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VERSION 1 – AUTHOR RESPONSE

Responds to the Reviewer's comments

Reviewer #1:

1. Response to comment: Most of the discussion, however, overstretch this findings as if causation is implied. For example, in the discussion (lines 340 ff) they state that "Enhancing magnesium intake seemed to be more effective for North American and European individuals to get lower stroke risk". This statement is not supported by the data: due to their observational nature, Similarly, at lines 344 ff the authors state that "[...] the correction of magnesium deficiencies and enhancement of magnesium intake appears to be useful [...]". Once again, that would be true if magnesium was causally related to T2D or stroke, which is not demonstrable in observational studies. Other examples are scattered throughout the discussion, that should be thoroughly revised in order to avoid any statement implying a causal role of magnesium intake.

Response: The authors were sorry for the inappropriate writing and overstretching some findings in Discussion section. The examples are like "Enhancing magnesium intake seemed to be more effective for North American and European individuals to get lower stroke risk"; like "the correction of magnesium deficiencies and enhancement of magnesium intake appears to be useful"; and other sentences displayed throughout the discussion. The most important point is that we can not get conclusions reflecting causality based on observational cohort studies, however, randomized trials will help to imply or establish a causal role.

Changes: Authors would be more cautious to describe our findings and let the readers carefully interpret these conclusions. The reasons would also be addressed in the limitation part. Overall, the authors would thoroughly revise the discussion and try to avoid statements implying a causal role of magnesium intake.

Reviewer #2:

1. Response to comment: However, in its present form there are few unanswered questions to truly evaluate the significance of the findings. For example, the following basic question was not clearly answered – what defines high vs. low magnesium intake

Response: We apologized for some unanswered questions. At this time, amount of magnesium intake was key points in the included studies. Because most eligible articles provided magnesium intake as categorized variable in a specified amount form (some articles provided five categories and some other studies provided three categories). They deemed the lowest intake as references and gave hazard ratio (HR) data for other different intakes vs. the lowest intake to show potential association of increasing magnesium intake and type 2 diabetes (T2D)/stroke incidence. However, amount of magnesium intake varied across the eligible studies, to mostly decrease heterogeneity in our study, the authors uniformly used the HR data of the highest intake level vs. the lowest intake level. Consequently, high vs. low magnesium intake meant the highest level vs. the lowest level. The HR data was used by us for statistical convenience. We would address it in the Methods section.

2. Response to comment: Furthermore, FFQs and SFFQs can be used for magnesium intake estimation, but for accurate magnesium intake estimation should be used magnesium specific food questionnaire and/or food records. That should be addressed in Study limitations section
Response and changes: FFQ and SFFQ are highly acknowledged questionnaires applied in nutritional researches and nutritional epidemiology studies/trials. As this reviewer suggested there was still a limitation that magnesium specific food questionnaire should be appropriated used instead of FFQ and SFFQ. Actually, this was a limitation of incorporated primary studies rather than this pooled study, however, the authors would address them in Study limitations section in the revised manuscript.

3. Response to comment: Was there a minimum study duration to be included?

Response: Many thanks to your comments. In fact, there was a minimum study duration in our study, where the authors ruled that eligible studies should have at least one year duration period if they provided the follow-up period data.

Some included studies (Kao et al 1999, Kirii et al 2010, Sluijs et al 2013, Sluijs et al, 2014) did not provide their follow-up information, but they did meet the selection criteria, so the authors included these studies after consideration. That's why we did not address the follow-up information in selection criteria of the initial manuscript edition.

Changes: The authors would address a minimum study duration of one year in selection criteria in the revised manuscript. Special conditions would also be further explained and addressed.

4. Response to comment: Were studies only included if they tested high vs. low magnesium intake or would one or the other be ok?

Response: In our study, most of the eligible studies deemed magnesium intake amount as categorized variable, for other studies with continuous intake reported as category data reported with a range, we assigned mid-point category of the lower and upper bound to the relative risk (RR) in these studies, and we used other methods to achieve the adjacent interval. In fact, we mainly used the HR data of the highest magnesium intake vs. the lowest intake provided by these authors to uniformly get a pooled result.

Consequently, only studies testing the highest intake vs. the lowest intake of magnesium and providing the HR data were specially selected. Studies with only one result reported were not OK.

5. Response to comment: Instead of term low magnesium level I suggest to use term low serum concentration

Response: We really appreciate your instructions. However, after a rigorous discussion with the key members of the author list, we regarded it seemed not appropriate to use "low serum concentration" instead of low magnesium level.

Because the authors mainly focused on magnesium intake level rather than the serum magnesium concentration level. Intake level and serum level are two varied concepts, which is to say taking more dietary or total magnesium dose not totally equal to high serum concentration. There are complex

metabolism procedures during that process from magnesium intake to converting into serum magnesium.

6. Response to comment: In line 325 there is ... RR was 0.98 That should be corrected
Response and changes: Thank you, the sentence has been re-written. "RR was 0.98"

7. Response to comment: In conclusion section, recommendation regarding magnesium intake dose, in order to decrease incidence of diabetes or stroke, should be given

Response and changes: We apologized for not giving proper recommendations regarding concrete magnesium intake dose. We conducted dose-response analyses in the manuscript and yielded the RR was 0.94 for 100mg/day increment for T2D and 0.98 for 100mg/day increment for total stroke. However, from the plots given by dose-response analysis, there was no RR cut-off point because the decreasing trend was going on. We found RR was decreased a bit quickly with any slightly decreased at approximately 260 mg/day for T2D and 350 mg/day for total/ischemic stroke. The lower range of this distribution kept elusive.

Overall, the authors are afraid that a clear intake dose of magnesium to decrease incidence of T2D or stroke could not be reasonably recommended based on current evidence.

We have addressed these results in dose-response analysis. We are sorry for not giving concrete magnesium intake dose, and further clinical trials involving different magnesium dose are required.

VERSION 2 – REVIEW

REVIEWER	Claudio Pedone Università Campus Bio-Medico di Roma
REVIEW RETURNED	04-Dec-2019

GENERAL COMMENTS	The authors have satisfactorily addressed my issues. The English language, however, should be further improved.
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REVIEWER	Asst. prof. Dario Rahelic, MD, PhD, FACE, FACN, FRCP Edin. Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Merkur University Hospital, School of Medicine, Univeristy of Zagreb, Croatia
REVIEW RETURNED	18-Dec-2019

GENERAL COMMENTS	The goal of this paper is commendable in that the question of whether magnesium intake can reduce incidence of T2D and stroke is of high importance. The paper could be an important contribution to the literature. Issues which have been addressed in previous review were corrected, so I suggest to accept the manuscript for publication.
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VERSION 2 – AUTHOR RESPONSE

Responses to the Reviewer's comments

Reviewer #1:

1. Comment: The authors have satisfactorily addressed my issues. The English language, however, should be further improved.

Response: We apologize for the grammatical errors in the initial manuscript; we have sought help from a professional language editing service (American Journal Experts [AJE]) and improved the academic writing and language quality of the revised manuscript. We hope these minor errors have not affected your consideration of our paper.

Thank you again for your helpful comments.

Reviewer #2:

1. Comment: The goal of this paper is commendable in that the question of whether magnesium intake can reduce incidence of T2D and stroke is of high importance. The paper could be an important contribution to the literature. Issues which have been addressed in previous review were corrected, so I suggest to accept the manuscript for publication.

Response: We are very grateful for your recognition of the importance of our study.