PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Continuing Education for the Prevention of Mild Cognitive Impairment and Alzheimer's-Type Dementia: A Systematic Review and Overview of Systematic Reviews.
AUTHORS	Matyas, Nina; Keser Aschenberger, Filiz; Wagner, Gernot; Teufer, Birgit; Auer, Stefanie; Gisinger, Christoph; Kil, Monika; Klerings, Irma; Gartlehner, Gerald

VERSION 1 – REVIEW

REVIEWER	Akio Tada Hyogo University, Dept. Health Science, Japan
REVIEW RETURNED	20-Dec-2018

GENERAL COMMENTS	Overview Studies to investigate the effects of continuing education on the reduction of MCI and of Alzheimer type dementia and the review of evidences concerning this association will help development of clinical practice and prevention of these diseases. I admire their endeavor for this article. However, the literature reviewed are two small to obtain reliable conclusion. Moreover, these two articles used subjects from the same population source, participants of the Tasmanian Healthy Brain Project. The authors have conducted an overview of systematic review articles concerning the intervention effect of leisure on cognitive impairment. I think this work has more possibility to be accepted in the journal, although it may be out of their interest. It is difficult to find definite relationship between review of two articles addressing the preventive effects of continuing education on mild cognitive impairment and Alzheimer's type dementia and overview of systematic reviews concerning the effect of leisure activity on mild cognitive impairment and Alzheimer's type dementia. In other words, the overview of systematic reviews is unnaturally disposed. It is recommended that this article is rewritten as an overview of systematic reviews for the effect of leisure activity on mild cognitive impairment and Alzheimer's type dementia. Special aspects About Di Marco's study and Sajeev's study, the authors provide information only that these studies do not show quantitative analysis. It is insufficient for readers to understand the state of those systematic reviews. How many studies of all studies included in each of those review articles?

	P15 line 298-300 What do two studies (ref no. 48, 49) mean? Are they articles in those systematic reviews? If so, which review article include two studies? Discussion P18 line 357-365 Overall, the discussion of overview of systematic reviews is unsatisfied. Aren't there minor discrepancies between reviews? Line 362-365 The neuroplasticity may be one of the mechanisms in which cognitive function is improved by leisure activity. However, there is no evidence that directly demonstrates the improvement of neuroplasticity by leisure activity in elderly people. Are there evidence that neuroplasticity improves dementia or MCI. The authors must explain more thoroughly.

REVIEWER	Xiaojun Liu Wuhan University, China
REVIEW RETURNED	20-Jan-2019

GENERAL COMMENTS	Mild cognitive impairment (MCI) is considered as an early stage of Alzheimer's disease or other forms of dementia that mainly occurs in older adults. The present systematic review examines the benefits and harms of continuing education on the prevention of MCI or Alzheimer's type dementia. The research targets an interesting research question, and the manuscript is overall well written. I think this is an interesting and useful paper and could potentially be published. Of course, some comments that need to be addressed before the paper could be published. Keywords 1. Too many keywords, five would be more appropriate. Introduction 2. Please update the latest data on MCI (see e.g., The World Alzheimer Report 2018). 3. Line 111 –113 – "…beyond the age of compulsory schooling." Lack of a clear definition. Methods It is well written and consists of detailed information about the quality control. 4. Should the definition of leisure activities be included in the background, not the method? 5. Line 225-227 There is no need to elaborate the meaning of values of HR, OR, RR. Results 6. The results are reported thoroughly. Discussion 7. The discussion can be more concise. 8. Line 340-343 "Cognitive leisure activities..." should be put in the introduction. 9. Line 346-349 "The ongoing Tasmanian Healthy Brain project..." has been referred in outcomes. MINOR ESSENTIAL CHANGES 1. Line 83 –85 – "… was estimated to be 259 billion U.S. Dollars the total global costs for dementia were 818 billion in 2015" Grammar error. 2. Line 91 the abbreviation of mild cognitive disorder is not MCI. 3. Line 108 –109 – "… is associated with a lower risk to develop dementia." Grammar error. 4. Inconsistence in language usage, for example, line 33 "summarize" vs. line 121 "summarise".

REVIEWER	Dr Ingelin Testad University of Stavanger, Department of Health Studies
REVIEW RETURNED	31-Jan-2019

GENERAL COMMENTS	This manuscript is well written and describes the findings from a systematic review of two studies and five systematic reviews of continuing education for older adults (45 years or older) for the prevention of mild cognitive impairment and Alzheimer's disease published between January 1990 and April 2018. An overall comment is to consider the terms/phrases 'Dementing illness' or 'Demented' when referring to people with dementia. It is important to accurately reflect that dementia is an umbrella for the symptoms and that there are many different forms of dementia, each with its own cause. Additionally, from a Patient and Public Involvement perspective, people with dementia and their carers prefers to avoid these terms. Please see for example Dementia Australia 'dementia Language Guidelines'. 2) The abstract should clearly state that the population of interest were adults 45 years or older. The authors may want to consider adding this in the objective part of the abstract, as well as be more precise under the results section, to how many studies were in fact included. It is stated that you identified 4933 citations, and only two of these met the inclusion criteria, this could be more highlighted. 4) Databases searched are identified, identification of the specific search terms used is only in the supplement file and not in the manuscript. The authors may want to consider adding the main search terms in the manuscript. 8) Please consider using World Alzheimer report 2018 on updated numbers on the global and economic impact of dementia, instead of the 2015 report. 10) It is problematic that the two studies found eligible for inclusion is presented in the same table as the systematic reviews, as this makes the presentation of the results unclear. The authors may want to consider adding a few columns in the table and make separate tables for the primary studies and systematic reviews. The table for Primary studies should include: aim, sample size and listing the assessments/measurements used in the studies. The table for Systematic reviews should include: aim, search strategy used in the review (i.e. database(s) used), number of studies included (aside from a separate column on study design), total number of participants. Please see for example Smith et al. 2011 Methodology in conducting a systematic review of systematic reviews of healthcare interventions. 11+12) Based on the sparse results in this review, it is not possible to conclude, which the authors have stated clearly under conclusion. However, this limitation should be stated more clearly and the question whether a conclusion can be drawn at all, should be debated.

VERSION 1 – AUTHOR RESPONSE

Response to reviewer comments

Reviewer #1
Reviewer Name: Akio Tada

Institution and Country: Hyogo University, Dept. Health Science, Japan Please state any competing interests or state 'None declared': None declared

Studies to investigate the effects of continuing education on the reduction of MCI and of Alzheimer type dementia and the review of evidences concerning this association will help development of clinical practice and prevention of these diseases. I admire their endeavor for this article.

However, the literature reviewed are two small to obtain reliable conclusion. Moreover, these two articles used subjects from the same population source, participants of the Tasmanian Healthy Brain Project.

The authors have conducted an overview of systematic review articles concerning the intervention effect of leisure on cognitive impairment. I think this work has more possibility to be accepted in the journal, although it may be out of their interest.

It is difficult to find definite relationship between review of two articles addressing the preventive effects of continuing education on mild cognitive impairment and Alzheimer's type dementia and overview of systematic reviews concerning the effect of leisure activity on mild cognitive impairment and Alzheimer's type dementia. In other words, the overview of systematic reviews is unnaturally disposed. It is recommended that this article is rewritten as an overview of systematic reviews for the effect of leisure activity on mild cognitive impairment and Alzheimer's type dementia.

Response: Our primary research question of interest was whether continuing education has a preventive effect on dementia. Because we suspected that we will not detect much evidence, we included cognitive leisure activities as proxy interventions and chose a mixed methods approach. We outline the rationale in our published protocol (Matyas et al. Systematic Reviews (2017)).

In this manuscript we summarize the results of this study and we feel that the manuscript needs to reflect the approach that we had planned a priori. So even if the systematic review did not yield much, we still think that this gap in knowledge is important information for readers (and funders, potentially). So with all due respect, we would prefer to keep the content of the manuscript as it is and report both, findings of the systematic review and the overview of reviews in one publication.

Special aspects

About Di Marco's study and Sajeev's study, the authors provide information only that these studies do not show quantitative analysis. It is insufficient for readers to understand the state of those systematic reviews. How many studies of all studies included in each of those review articles?

Response: Based on a similar comment of Reviewer 3, we revised Table 1 and split it into two tables. The number of included studies in each review is now summarized in the column termed "N of included studies". We hope that this makes it easier for readers to find this information.

P15 line 298-300 What do two studies (ref no. 48, 49) mean? Are they articles in those systematic reviews? If so, which review article include two studies?

Response: The two references, Akbaraly et al. and Verghese et al., were included in both systematic reviews (DiMarco et al. and Sajeev et al.). Due to similar research questions, some studies were overlapping between the systematic reviews. Of course, both reviews included more than two studies (see 'table 2'). We have highlighted these two primary studies in the results because they represent the studies with the 'best' (HR 0.39 (95%CI: 0.21-0.71) and 'worst' result (HR 0.93 (95% CI: 0.88-0.98) and thus show the range of effect sizes of the included primary studies.

Discussion

P18 line 357-365 Overall, the discussion of overview of systematic reviews is unsatisfied. Aren't there minor discrepancies between reviews?

Response: Thank you for pointing this out. We added text to the Discussion to highlight discrepancies between the two reviews.

Line 362-365 The neuroplasticity may be one of the mechanisms in which cognitive function is improved by leisure activity. However, there is no evidence that directly demonstrates the improvement of neuroplasticity by leisure activity in elderly people. Are there evidence that neuroplasticity improves dementia or MCI. The authors must explain more thoroughly.

Response: We agree with the reviewer, there is no direct evidence that shows the improvement of neuroplasticity by leisure activity in elderly people. Nevertheless, there are studies that demonstrate that leisure activities improve cognitive reserve. Because the concept of neuroplasticity is interrelated with the concept of cognitive reserve, we think that the assumption that we make is reasonable, albeit it is indirect.

We added more text to be clearer about these concepts and the lack of direct evidence.

Reviewer #2
Reviewer Name: Xiaojun Liu

Institution and Country: Wuhan University, China

Please state any competing interests or state 'None declared': None declared

Mild cognitive impairment (MCI) is considered as an early stage of Alzheimer's disease or other forms of dementia that mainly occurs in older adults. The present systematic review examines the benefits and harms of continuing education on the prevention of MCI or Alzheimer's type dementia. The research targets an interesting research question, and the manuscript is overall well written.

I think this is an interesting and useful paper and could potentially be published. Of course, some comments that need to be addressed before the paper could be published.

Keywords

1. Too many keywords, five would be more appropriate.

Response: We deleted two keywords.

Introduction

2. Please update the latest data on MCI (see e.g., The World Alzheimer Report 2018).
Response: Many thanks for pointing this out. We updated the data according to the Alzheimer's disease facts and figures of the Alzheimer Association.

3. Line 111 –113 – "…beyond the age of compulsory schooling." Lack of a clear definition.
Response: We added the age of "16 years and older" in the definition to be more precise.

Methods

It is well written and consists of detailed information about the quality control. **Response: Thank you.**

4. Should the definition of leisure activities be included in the background, not the method?
Response: We still introduce leisure activities and continuing education in the Background. We added definitions to the methods.

5. Line 225-227 There is no need to elaborate the meaning of values of HR, OR, RR. **Response: We deleted this sentence.**

Results

6. The results are reported thoroughly.
Response: Thank you.

Discussion

7. The discussion can be more concise.
Response: We revised the text in the Discussion and made it more concise.

8. Line 340-343 "Cognitive leisure activities..." should be put in the introduction.
Response: We moved the definition of leisure activities to the Introduction. The point that we wanted to make here, was that evidence on leisure activities is the best available evidence that we have. We revised the text in the Discussion and tried to make this point clearer.

9. Line 346-349 "The ongoing Tasmanian Healthy Brain project..." has been referred in outcomes.
Response: Thank you. We deleted this sentence in the discussion to avoid redundancy.

MINOR ESSENTIAL CHANGES

1. Line 83 –85 – "… was estimated to be 259 billion U.S. Dollars the total global costs for dementia were 818 billion in 2015" Grammar error.
Response: We corrected this error. And changed the numbers to more up-todate numbers.

2. Line 91 the abbreviation of mild cognitive disorder is not MCI.
Response: We corrected this error.

3. Line 108 –109 – "… is associated with a lower risk to develop dementia." Grammar error.
Response: We corrected this error.

4. Inconsistence in language usage, for example, line 33 “summarize” vs. line 121 “summarise”.

Response: We corrected this inconsistency in the manuscript.

Reviewer #3
Reviewer Name: Dr Ingelin Testad

Institution and Country: Centre for Age Related medicine - SESAM, Stavanger university hospital, Stavanger, Norway. University of Exeter Medical School, University of Exeter, Exeter, United Kingdom. Department of Old Age Psychiatry, Institute of Psychiatry,

Psychology, & Neuroscience, King’s College London, London, United Kingdom
Please state any competing interests or state ‘None declared’: None declared

This manuscript is well written and describes the findings from a systematic review of two studies and five systematic reviews of continuing education for older adults (45 years or older) for the prevention of mild cognitive impairment and Alzheimer’s disease published between January 1990 and April 2018.

An overall comment is to consider the terms/phrases ‘Dementing illness’ or ‘Demented’ when referring to people with dementia. It is important to accurately reflect that dementia is an umbrella for the symptoms and that there are many different forms of dementia, each with its own cause. Additionally, from a Patient and Public Involvement perspective, people with dementia and their carers prefers to avoid these terms. Please see for example Dementia Australia ‘dementia Language Guidelines’.

Response: Thank you for this very important point. We corrected all terms and phrases that were not consistent with the ‘Dementia Language Guidelines’. We fully agree that appropriate language is essential.

2) The abstract should clearly state that the population of interest were adults 45 years or older. The authors may want to consider adding this in the objective part of the abstract, as well as be more precise under the results section, to how many studies were in fact included. It is stated that you identified 4933 citations, and only two of these met the inclusion criteria, this could be more highlighted.

Response: Thank you. We added the information about the population of interest in the objective of the abstract. In addition, we mention that the population of interest is 45 years or older in the key questions and in the Methods.

4) Databases searched are identified, identification of the specific search terms used is only in the supplement file and not in the manuscript. The authors may want to consider adding the main search terms in the manuscript.

Response: The search strategy for our review is quite complex. We are hesitant to add the search strategy to the manuscript because it might reduce the readability of the text. But we are open to this change if the editors of BMJ Open also think that the search strategy should be presented in the main text of the manuscript.

8) Please consider using World Alzheimer report 2018 on updated numbers on the global and economic impact of dementia, instead of the 2015 report.

Response: We updated the data according to the World Alzheimer Report 2018

10) It is problematic that the two studies found eligible for inclusion is presented in the same table as the systematic reviews, as this makes the presentation of the results unclear. The authors may want to consider adding a few columns in the table and make separate tables for the primary studies and systematic reviews.

The table for Primary studies should include: aim, sample size and listing the assessments/measurements used in the studies.

The table for Systematic reviews should include: aim, search strategy used in the review (i.e. database(s) used), number of studies included (aside from a separate column on study design), total number of participants. Please see for example Smith et al. 2011 Methodology in conducting a systematic review of systematic reviews of healthcare interventions.

Response: Thank you for pointing this out. Following your advice, we created two tables instead of one table and added the columns you suggested. We didn't want to create an additional table for outcomes (as suggested by Smith et al.) for the overview of systematic reviews because of our sparse results. We kept the column for outcomes.

11+12) Based on the sparse results in this review, it is not possible to conclude, which the authors have stated clearly under conclusion. However, this limitation should be stated more clearly and the question whether a conclusion can be drawn at all, should be debated.

Response: We substantially revised the Discussion and now point out repeatedly that no real conclusions can be drawn. This is also reflected in our grades of the certainty of evidence which are low or very low throughout all outcomes.

VERSION 2 – REVIEW

REVIEWER	A. Tada Hyogo University, Japan
REVIEW RETURNED	14-Mar-2019

GENERAL COMMENTS	Continuing education is an all-encompassing term within a broad list of post-secondary learning activities and programs. As you described in the article, continuing education activities are structured learning activities offered by educational institutes. These activities are designed to help individuals satisfy learning needs and interests after compulsory schooling, to enrich knowledge, to develop and improve abilities and skills, and to foster personality, social competences, families, networks, health, and professional life. Hence, continuing education may not be suitable for elderly persons who are in the risk of Alzheimer's type dementia and MCI, and research to investigate the effects of continuing education on the reduction of MCI and of Alzheimer type dementia has not been done so much. In the while the effect of leisure activity on the prevention of MCI and of Alzheimer type dementia has been reviewed, the authors have to explain the

	significance of the investigation of continuing education on he prevention of MCI and of Alzheimer type dementia.

REVIEWER	Xiaojun Liu Wuhan University, China
REVIEW RETURNED	04-Mar-2019

GENERAL COMMENTS	The authors have comprehensively addressed the comments that I raised.

REVIEWER	Ingelin Testad University of Stavanger, Department of Health Studies
REVIEW RETURNED	25-Mar-2019

GENERAL COMMENTS	This is a well written paper, that should be published. The questions above where I have replied "NO", refers to research question 4, where no findings were found. As it is, also based on the authors introduction, not likely to find answers to such a broad question in this review, my recomendation would be to leave this out.

VERSION 2 – AUTHOR RESPONSE

Reviewer comments

Reviewer: #2

Reviewer Name: Xiaojun Liu

Institution and Country: Wuhan University, China

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

The authors have comprehensively addressed the comments that I raised.

Response: Thank you.

Reviewer: #1

Reviewer Name: A. Tada

Institution and Country: Hyogo University, Japan

Please state any competing interests or state ‘None declared’: None declared

Continuing education is an all-encompassing term within a broad list of post-secondary learning activities and programs. As you described in the article, continuing education activities are structured

learning activities offered by educational institutes. These activities are designed to help individuals satisfy learning needs and interests after compulsory schooling, to enrich knowledge, to develop and improve abilities and skills, and to foster personality, social competences, families, networks, health, and professional life.

Hence, continuing education may not be suitable for elderly persons who are in the risk of Alzheimer's type dementia and MCI, and research to investigate the effects of continuing education on the reduction of MCI and of Alzheimer type dementia has not been done so much. In the while the effect of leisure activity on the prevention of MCI and of Alzheimer type dementia has been reviewed, the authors have to explain the significance of the investigation of continuing education on the prevention of MCI and of Alzheimer type dementia.

Response: Based on the available evidence, we cannot tell whether continuing education in elderly persons at higher risk for Alzheimer's disease or MCI is effective or not. Any statement for or against effectiveness would be speculation. Therefore, we would prefer to not add additional text addressing this topic. Regarding the significance of leisure activity – we agree with the reviewer that leisure activities are only a surrogate for continuing education. This fact is reflected in our GRADE ratings. We downgraded the certainty of evidence because of indirectness for all outcomes from leisure activities.

Reviewer: #3

Reviewer Name: Ingelin Testad

Institution and Country: Centre for medicine and aging - SESAM, Stavanger University Hospital, Norway; Exeter University, Exeter, UK

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This is a well written paper, that should be published.

The questions above where I have replied "NO", refers to research question 4, where no findings were found. As it is, also based on the authors introduction, not likely to find answers to such a broad question in this review, my recomendation would be to leave this out.

Response: We agree with the editor. Since we have published this question a priori in our protocol, we can't leave it out now.