PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The relationship between adverse childhood experiences and Alzheimer's disease: A systematic review and meta-analysis protocol
AUTHORS	Corney, Kayla; Pasco, J; Stuart, Amanda; West, Emma; Quirk, Shae; Azimi Manavi, Behnaz; Williams, Lana

VERSION 1 – REVIEW

REVIEWER	Meng, Xiangfei McGill University
REVIEW RETURNED	09-Aug-2020

GENERAL COMMENTS	Thank you for this review opportunity. The proposed protocol is very interesting in the field of AD. The proposed research aims to explore the relationship between adverse childhood experiences and the onset of Alzheimer's disease. I have several comments or suggestions to make and the research team should assess the feasibility or otherwise of introducing these issues into the study. • Pilot search: How many articles would meet the eligibility criteria of this research topic? It is necessary to have a rough idea of the # of original articles potentially included in the review and meta-analysis. • Eligibility criteria: Why exclude grey literature? Systematic reviews often include grey literature to reduce publication bias. • Search strategy: Both computerized search and manual search should be done to maximize the potential articles. • Articles selection: Often two independent reviewers will separately go over the initial titles->abstracts->full texts and generate a list of articles for group discussions. A third reviewer will go over the inconsistent records and a group discussion of three reviewers will be done for inconsistent records. • Meta-analysis: There is a lack of sufficient details on the proposed meta-analysis in terms of whether fixed-effects/random-effects models, heterogeneity test, publication bias test, moderation and/ or mediation analysis, subgroup analysis by type of adverse experiences, etc.

REVIEWER	Nguyen , Jean-Paul Clinic Bretéché, center
REVIEW RETURNED	17-Aug-2020

GENERAL COMMENTS	The article entitled « The relationship between adverse childhood experiences and Alzheimer's disease: A systematic review and

	meta-analysis protocol" is interesting. Nevertheless, I must make some minor and major remarks. Minor remarks: 1) Introduction, line 21: loss of interest in hobbies is a part of apathy. 2) Introduction line 47: The 10 categories are not well defined. Major remarks: It is an article on the methodology of a systematic review and meta-analysis concerning adverse childhood experiences and their consequences in the future. In that field the article by Hughes K cited in the bibliography already very well describe the methodology and give the results of the meta-analysis. An article based only on the description of the protocol including only a quantitative analysis has not a great interest. As the subject is complex, a qualitative or a mixed (qualitative and quantitative) analysis of the literature would have been interesting. Then, as a qualitative analysis is not well known by most of readers, a precise description of the protocol will be interesting. I suggest reading the articles from Candy B (Using qualitative synthesis to explore heterogeneity of complex interventions. BMC Medical Research Methodology 2011,11: 124) and Snilstveit B (Narrative approaches to systematic review and synthesis of evidence for international development policy and practice. Journal of Development Effectiveness 2012, 4: 409-429). Otherwise, the subject is interesting and an article including the results will certainly be easily accepted.

REVIEWER	Besser, Lilah Florida Atlantic University
REVIEW RETURNED	18-Aug-2020

GENERAL COMMENTS	BMJ Open While the topic of the systematic literature review is interesting and could make a contribution to the literature (I have not seen a review on this topic to date), the protocol as written is severely flawed. If you are given a chance to update the protocol and resubmit, I have provided suggestions for improvement. Abstract: It is mentioned that the protocol IS registered with PROSPERO, but a later section states it WILL BE registered with PROSPERO. Introduction: To give a published protocol substance, an adequate literature review is warranted, including a discussion of the potential causal mechanisms that may relate the exposure and outcome and evidence/references supporting the proposed causal mechanisms. The discussion that no factors have been associated with AD is flawed – physical activity, diet, social engagement, SES/education are all modifiable factors that have been associated with AD. In addition, there is no discussion of the genetic risk factors. Objective/eligibility: It states that the outcome of interest is onset of Alzheimer's disease (AD). Please be clear in how that is defined. In the eligibility section, it states that either Alzheimer's defined based on medical records or ICD clinical diagnoses will be included. However, AD research often focuses on earlier stages of the disease (e.g., preclinical and prodromal). Longitudinal cohort studies focused on AD (and that may be discovered in your review) often employ clinicians/neurologists to determine cognitive status and disease etiology, and technically do not assign an ICD diagnosis code (and cohort studies do not usually collect/reference medical records). What if a study focuses on age of onset of AD as

	the outcome? Would it be included? What if they focus on AD biomarkers among non-demented participants (e.g., amyloid PET scans or CSF amyloid and t-tau)? What if they include individuals with AD but focus on cognition or longitudinal change in cognition as the outcome? These details needed to be stated. The eligibility section states the review will be inclusive of nationality, but it is not clear if that refers to country of origin of the study or of the participant. On a related note, will you include papers not published in English? Under eligibility, it is mentioned that genetic or neurological disorders that affect cognition will be excluded. AD is such a disease and often co-presents with other pathologies such as Lewy body disease/Parkinson's disease. I think it is okay to exclude other neurodegenerative diseases, but you need to put more thought into explaining why and how. (In life, two or more neurodegenerative diseases are unlikely to be diagnosed, although it is found at autopsy). Search selection: Please provide more detail on the process of searching and selecting. For instance, will you produce a checklist/keywords for each reviewer to use ahead of time. Will they first review titles, then abstracts, then full text? What if they do not agree on whether to include the paper? It would be good to review strong published methods on systematic reviews and use similar methods. Will you be searching titles only or titles and abstracts when querying the databases? This will make a big difference on whether searching for "Alzheimer disease" will actually produce all of the published studies on the topic. Some papers may only discuss "mental health", "dementia", "neurodegenerative disease", "cognitive disorder", and similar terms in the title or abstract, especially if they are focused on multiple outcomes. Assessment of methodological quality: This seems like a gross over-simplification of a quality assessment. A well-designed case-control study may be stronger methodologically than a cohort study. Cohort studies are not necessarily representative but instead can be convenience based. It would be best to find a comprehensive protocol for assessing quality (or provided a lot more detail on the referenced method by Lievense). Issues of selection bias, attrition, information bias, etc. should be evaluated. Main outcome was stated to be: To reach a consensus regarding associations between ACE and onset of AD. It seems that will not be possible if there are few studies published on the topic to date (as one would expect). A more realistic goal would be to identify published papers on the topic, evaluate the quality of evidence to date, and provide suggestions for future research based on the weaknesses of the studies to date/gaps.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Xiangfei Meng, McGill University, Canada

1. *Pilot search: How many articles would meet the eligibility criteria of this research topic? It is necessary to have a rough idea of the # of original articles potentially included in the review and meta-analysis.*

We have now edited accordingly.

Amendments to the text read as follows:

- A pilot search was performed, by testing the search terms and inclusion criteria on MEDLINE, PsycInfo and CINAHL databases. A total of 781 studies was identified (page 7, paragraph 7)

2. *Eligibility criteria: Why exclude grey literature? Systematic reviews often include grey literature to reduce publication bias.*

We have now adapted our eligibility criteria to include grey literature.

Amendments to the text read as follows:

- Grey literature, such as theses and conference presentations will be searched using an adapted search in Google and will be considered for inclusion if shown to meet the eligibility criteria. The Google search may also yield additional relevant journal articles to supplement the database searching. (page 8, paragraph 2)

3. *Search strategy: Both computerized search and manual search should be done to maximize the potential articles.*

The review includes both a computerized and manual search.

Amendments to the text read as follows:

- **Other sources:** Grey literature, such as case studies, theses and conference presentations will be searched using an adapted search in Google and will be considered for inclusion if shown to meet the eligibility criteria. The Google search may also yield additional relevant journal articles to supplement the database searching. A manual search of hand-searching the reference lists of the included studies will then be performed to identify any further studies. (page 8, paragraph 2)

4. *Article selection: Often two independent reviewers will separately go over the initial titles->abstracts->full texts and generate a list of articles for group discussions. A third reviewer will go over the inconsistent records and a group discussion of three reviewers will be done for inconsistent records.*

We have now edited accordingly.

Amendments to the text read as follows:

- **Data management and selection process:** One reviewer will implement the search strategy, and then import, manage and remove duplicate records using covidence. Then, two reviewers will independently screen the titles/abstracts according to a predetermined screening checklist. Conflicts at the screening stage between the two reviewers will be resolved through discussion with a third reviewer to provide final judgement. Final inclusions will be decided by full-text reading of the articles by two reviewers independently, and consensus with the third reviewer. A PRISMA flow chart of the selection process and reasons for exclusion at the full-text stage will be reported. (page 8, paragraph 3)

5. *Meta-analysis: There is a lack of sufficient details on the proposed meta-analysis in terms of whether fixed-effects/random-effects models, heterogeneity test, publication bias test, moderation and/ or mediation analysis, subgroup analysis by type of adverse experiences, etc.*

The review has been updated and includes a more detailed description of the meta-analysis.

Amendments to the text read as follows:

- **Quantitative synthesis (meta-analysis)**: Where appropriate, a quantitative synthesis will be performed using random-effects statistical models, given the expected diversity among population. Where possible, Odd Ratios (ORs)/Hazard Ratios (HRs) (e.g. for categorical outcome/diagnosis data) and their 95% confidence intervals (CIs) will be calculated and reported. ns/exposures of ACEs.

If sufficient data is available, we will also consider subgroup analyses of:

- Sex
- Age of exposure
- Number of ACEs
- Type of ACEs.

A statistician will be consulted regarding the appropriateness of assessing risk of bias, heterogeneity, and reporting bias on the included studies. Complete details will be presented in the review. (page 10, paragraph 3)

Reviewer 2: Jean-Paul Nguyen, University Hospital of Nantes, France

6. *Introduction, line 21: loss of interest in hobbies is a part of apathy.*

The review has been updated to include loss of interest in hobbies as part of apathy. Please see Introduction.

Amendments to the text read as follows:

- Including apathy, sleep disturbances, impaired spatial and temporal navigations, executive dysfunction, behavioural changes, apraxia, language difficulties, incontinence and high dependency on others. (page 4, paragraph 1)

7. *Introduction line 47: The 10 categories are not well defined.*

The review now includes a definition of adverse childhood experiences as described by Felitti et al. (1998).

Amendments to the text read as follows:

- One such factor, may be exposure to adverse childhood experiences (ACEs), which refers to "sources of trauma or stress occurring under the age of 18" (add reference). ACEs includes emotional, physical and sexual abuse, emotional and physical neglect, and household challenges, such as domestic violence, substance abuse, mental illness, criminal behaviour and parental loss (death, separation and divorce). (page 4, paragraph 3)

8. *It is an article on the methodology of a systematic review and meta-analysis concerning adverse childhood experiences and their consequences in the future. In that field the article by Hughes K cited in the bibliography already very well describe the methodology and give the results of the meta-analysis. An article based only on the description of the protocol including only a quantitative analysis has not a great interest. As the subject is complex, a qualitative or a mixed (qualitative and quantitative) analysis of the literature would have been interesting. Then, as a qualitative analysis is not well known by most of readers, a precise description of the protocol will be interesting.*

The review has been updated and now includes a quantitative and qualitative synthesis.

To our knowledge, no previous review has focused on ACEs and their relationship with Alzhiemer's disease. The aforementioned paper is a comprehensive systematic review and meta-analysis of ACEs and a number of health outcomes but not Alzhiemer's disease. A systematic review, quality assessment, quantitative and qualitative synthesis will be undertaken.

Amendments to the text read as follows:

- **Qualitative synthesis:** A description of all relevant studies and their methodological quality will be presented (e.g. in tables/text), and a qualitative/narrative summary of the key findings will be reported in text.

  Quantitative synthesis (meta-analysis): Where appropriate, a quantitative synthesis will be performed using random-effects statistical models, given the expected diversity among populations/exposures of ACEs. Where possible, ORs (for categorical outcome/diagnosis data) and their 95% confidence intervals (CIs) will be calculated and reported.

  If sufficient data is available, we will also consider subgroup analyses of:
  - Sex
  - Age of exposure
  - Number of ACEs
  - Type of ACEs.

  A statistician will be consulted regarding the appropriateness of assessing risk of bias, heterogeneity, and reporting bias on the included studies. Complete details will be presented in the review. (Page 10, paragraph 2).

Reviewer 3: Lilah Besser, Atlantic University, Florida

9. *Abstract: It is mentioned that the protocol IS registered with PROSPERO, but a later section states it WILL BE registered with PROSPERO.*

The review has been updated with the registered PROSPERO number in all sections.

Amendments to the text read as follows:

- This protocol is registered with PROSPERO (CRD42020191439). (page 10, paragraph 6)

10. *Introduction: To give a published protocol substance, an adequate literature review is warranted, including a discussion of the potential causal mechanisms that may relate the exposure and outcome and evidence/references supporting the proposed causal*

mechanisms. The discussion that no factors have been associated with AD is flawed – physical activity, diet, social engagement, SES/education are all modifiable factors that have been associated with AD. In addition, there is no discussion of the genetic risk factors.

We have now reviewed and updated the introduction as suggested.

Amendments to the text read as follows:

- Recently, there has been extensive research into the delineating range of risk factors associated with AD such as depression, smoking, alcohol, social engagement, education, physical activity, sleep and diet. Although, notwithstanding the huge research effort, many challengers associated with the development and progression of AD still remain unknown. Nonetheless, distinct pathological changes have been linked to AD, with the loss of proteostasis being the primary theory to explain AD, specifically affecting the amyloid and tau proteins, which in turn, causes a cascade of detrimental events. Moreover, genetic predisposition to AD is very complex. In rare early onset AD, common genes include APP (genes encoding γ-secretase complex), presenelin-1 and presenelin-2 in chromosomes 21, 14 and 1, with overexpression resulting in increased Aβ production. In late onset AD, apolipoprotein E series, especially APOE4, is the major genetic risk, as >60% of AD patients harbor the gene, with overexpression associated with increased brain amyloid burden. However, despite this accumulating evidence, current identified factors do not explain the full extent of disease onset. Thus, the role of additional factors needs to be explored further.

  One such factor, may be exposure to adverse childhood experiences (ACEs), which refers to sources of trauma or stress occurring under the age of 18. ACEs includes emotional, physical and sexual abuse, emotional and physical neglect, and household challenges, such as domestic violence, substance abuse, mental illness, criminal behaviour and parental loss (death, separation and divorce). Recently, a growing body of evidence has reported a higher exposure of ACEs can disrupt normal psychosocial development which can lead to an enhanced risk of many poor health outcomes, and in turn, increase the risk of AD. For example, recent evidence reports that exposure to early life stress can increase the risk of poor health behaviours such as smoking or abusing alcohol. Early stressful events can also affect psychological development, increasing the risk of depression. Moreover, recent research has reported that traumatic early life experiences can change stress regulatory functions, leading to later altered stress responses. In this view, these mechanisms may contribute to the development of AD. (page 4, paragraph 2)

11. *Eligibility: It states that the outcome of interest is onset of Alzheimer's disease (AD). Please be clear in how that is defined.*

This section has now been refined. The outcome of interest is the risk of Alzheimer's disease.

Amendments to the text read as follows:

- **Outcomes:** Studies will be eligible if they examine the population/exposure of interest in relation to the risk of AD. For eligibility purposes, the diagnosis of AD must be consistent with an internationally recognised clinical or diagnostic classification system such as the International Classification of Diseases (ICD), Diagnostic and Statistical Manual of Mental Disorders (DSM), National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA criteria), and/or National Institute on Aging–Alzheimer's Association (NIA-AA workgroup criteria). (page 7, paragraph 2)

12. *The eligibility section states the review will be inclusive of nationality, but it is not clear if that refers to country of origin of the study or of the participant. On a related note, will you include papers not published in English?*

This section has now be refined.

Amendments to the text read as follows:

Setting: Participants from general and clinical populations will be eligible.

Language: Worldwide studies that are published in English will be eligible. Google Translate may be considered if potentially relevant studies are identified that are published in journals in languages other than English. (page 7, paragraph 3)

13. *Under eligibility, it is mentioned that genetic or neurological disorders that affect cognition will be excluded. I think it is okay to exclude other neurodegenerative diseases, but you need to put more thought into explaining why and how.*

Reference to these criteria have been removed. For clarity, this section has now been refined to provide greater detail regarding the eligibility criteria.

Amendments to the text read as follows:

- **Eligibility criteria:** Studies will be considered for inclusion according to the following criteria:

  Study designs: Published, peer-reviewed research articles reporting on studies that are longitudinal, case-control and/or cross-sectional observational studies will be eligible.

  Participants: Studies will be eligible if they examine participants who were exposed to any ACE before the age of 18 years. There will be no other restrictions on participant demographics (e.g. sex/nationality).

  Exposure: For this protocol any ACEs before 18 years of age is the exposure of interest and includes [12].

- Emotional/physical/sexual abuse
- Emotional/physical neglect
- Household challenges, such as exposure to domestic/family/intimate violence, substance abuse, mental illness, criminal behaviour and parental loss (death, separation and divorce).

  Comparison: Studies will be eligible if they include an appropriate comparison group, such as participants who were not exposed to any ACEs.

  Outcomes: Studies will be eligible if they examine the population/exposure of interest in relation to the risk of AD. For eligibility purposes, the diagnosis of AD must be consistent with an internationally recognised clinical or diagnostic classification system such as the International Classification of Diseases (ICD), Diagnostic and Statistical Manual of Mental Disorders (DSM), National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA criteria), and/or National Institute on Aging–Alzheimer's Association (NIA-AA workgroup criteria).

  Setting: Participants from general and clinical populations will be eligible.

  Language: Worldwide studies that are published in English will be eligible.

  Exclusions: Studies that are published in a language other than English, as well as randomized controlled trials will be. (page 6, paragraph 4)

14. *Search selection: Please provide more detail on the process of searching and selecting. For instance, will you produce a checklist/keywords for each reviewer to use ahead of time. Will they first review titles, then abstracts, then full text? What if they do not agree on whether to include the paper? Will you be searching titles only or titles and abstracts when querying the databases?*

This section has now be refined.

Amendments to the text read as follows:

- **Search strategy:** An electronic search will be performed in three research databases (CINAHL, MEDLINE Complete and PsycInfo) using the Ebscohost platform to identify relevant studies. To develop the search strategy, a list of relevant Index terms and key words was derived from the existing, relevant literature, and combined using Boolean operators, truncations, and explode functions (Table 1).

  In consultation with an academic librarian, the search strategy was further refined, translated accordingly for each database, then pilot tested for MEDLINE Complete, PsycInfo and CINAHL databases. A total of 781 studies were found. Complete details regarding the search strategy and results (including dates searched) will be presented in the ensuing systematic review and meta-analysis.

  Other sources: Grey literature, such as case studies, theses and conference presentations will be searched using an adapted search in Google and will be considered for inclusion if shown to meet the eligibility criteria. The Google search may also yield additional relevant journal articles to supplement the database searching. A manual search of hand-searching the included studies will then be performed to identify any further studies.

  Data management and selection process: One reviewer will implement the search strategy, and then import, manage and remove duplicate records using covidence. Then, two reviewers will independently screen the titles/abstracts according to a predetermined screening checklist. Conflicts at the screening stage between the two reviewers will be resolved through discussion with a third reviewer to provide final judgement. Final inclusions will be decided by full-text reading of the articles by two reviewers independently, and consensus with the third reviewer. A PRISMA flow chart of the selection process and reasons for exclusion at the full-text stage will be reported. (page 7, paragraph 6)

15. *Assessment of methodological quality: This seems like a gross over-simplification of a quality assessment. A well-designed case-control study may be stronger methodologically than a cohort study. Cohort studies are not necessarily representative but instead can be convenience based. It would be best to find a comprehensive protocol for assessing quality (or provided a lot more detail on the referenced method by Lievense). Issues of selection bias, attrition, information bias, etc. should be evaluated.*

The review has been updated with a more detailed description of the assessment of methodological quality from Lievense et al.

Amendments to the text read as follows:

Assessment of methodological quality of included studies: Assessment of methodological quality of individual studies will be performed using a modified version of the methodological scoring system by Lievense, Bierma-Zeinstra [32]. This method has been undertaken and published in several reviews by the authors [33, 34] and protocols [35, 36] Appropriately reflecting optimal study designs, each of the eligible studies will be scored based on the methodological assessment criteria of study population, assessment of risk factor, assessment of outcome, study design, and analysis and data presentation (table 2) [32]. The methodology of eligible studies will be scored using the predetermined criteria as follows: positive (1) or negative (0). (Page 10, paragraph 5)

Table 2.

Methodological quality assessment criteria, modified from Lievense et al. [32]

Item	Criteria	C/CC/CS
	Study population	
1	Uniform point (selection before disease was present)	C/CC/CS
2	Case and controls drawn from then same population	CC
3	Participation rate >80% for cases/cohort	C/CC/CS
4	Participation rate >80% for controls	CC
	Assessment of risk factor	
5	Exposure assessment blinded	C/CC/CS
6	Exposure measure identical for cases and controls	CC

7	Exposure assessed prior to outcome	C/CC/CS
	Assessment of outcome	
8	Outcome assessed identically in studied populations	C/CC/CS
9	Outcome assessed reproducibly	C/CC/CS
10	Outcome assessed according to validated measures	C/CC/CS
	Study design	
11	Prospective study design used	C/CC
12	Follow up time >12 months	C
13	Withdrawals <20%	C
	Analysis and data presentation	
14	Appropriate analysis techniques used	C/CC/CS
15	Adjust for at least age and sex	C/CC/CS

C, applicable to cohort studies; CC, applicable to case-control studies; CS, applicable to cross-sectional studies.

16. *Main outcome was stated to be: To reach a consensus regarding associations between ACE and onset of AD. It seems that will not be possible if there are few studies published on the topic to date (as one would expect). A more realistic goal would be to identify published papers on the topic, evaluate the quality of evidence to date, and provide suggestions for future research based on the weaknesses of the studies to date/gaps.*

We have now revised the rationale and objectives.

Amendments to the text read as follows:

- **Objectives**

  The primary objective is to conduct a systematic review and meta-analysis of published observational studies that examine the associations between ACEs (occurring before the age of 18 years) and the risk of AD in adulthood. Where feasible, the secondary objectives are to examine potential differences between sex/age and number/types of exposures to ACEs and the associated risk of Alzheimer's disease. (page 6, paragraph 2)

VERSION 2 – REVIEW

REVIEWER	Besser, Lilah Florida Atlantic University
REVIEW RETURNED	16-Mar-2021

GENERAL COMMENTS	Your revisions have adequately addressed my prior concerns, but I would suggest a minor revision to acknowledge that the proposed meta analysis is desired but might not be possible given that <800 papers were returned upon pilot testing your search criteria in the 3 databases. Amongst those, you will likely end up with <20 papers with heterogeneous methods and outcomes/exposures that will make it impossible to perform a meta analysis.

REVIEWER	Nguyen , Jean-Paul Clinic Bretéché, center
REVIEW RETURNED	21-Mar-2021

GENERAL COMMENTS	The article entitled « The relationship between adverse childhood experiences and Alzheimer's disease: A systematic review and meta-analysis protocol" is still interesting. Nevertheless, I still must make some remarks. Page 4 line 17: I do not understand how this study may aid in early diagnosis or treatment of Alzheimer's disease. It can help for the prevention by being extremely strict with management of modifiable risk factors. Following this idea anxiety merit more attention. It may be a consequence of adverse childhood experiences and treatment by anxiolytic agents has been suggested as a potential moderator of AD risk in older adults (Burke SL, O'Driscoll J, Alcide A, Li T. Moderating risk of Alzheimer's disease through the use of anxiolytic agents. Int J Geriatr Psychiatry. 2017 Dec;32(12):1312-1321. doi: 10.1002/gps.4614. Epub 2016 Nov 2. PMID: 27805724; PMCID: PMC5441966). Page 5 line 24: Sleep disturbances and incontinence are not part of "cognitive domain". Page 5 line 33: The list of risk factors discussed in reference 7 is not correct. In that article, the role of depression and alcohol as risk factors is not proved. Page 5 line 45: The loss of proteostasis is never mentioned in reference 8. For the authors of that article the primary theory to explain AD is an impairment of APP (Amyloïd βPrecursor Protein) metabolism. Authors must take care when citing reference. Page 13 line 26: The methodology which will be used for qualitative analysis is not detailed. I suggest the authors to describe the qualitative methodology used to evaluate the literature as in the article by Micklitz Katrin (Micklitz K, Wong G, Howick J. Mindfulness-based programmes to reduce stress and enhance well-being at work: a realist review. BMJ Open. 2021 Mar 19;11(3):e043525. doi: 10.1136/bmjopen-2020-043525. PMID: 33741667).

VERSION 2 – AUTHOR RESPONSE

Reviewer 1: Dr. Lilah Besser, Florida Atlantic University

17. *Your revisions have adequately addressed my prior concerns, but I would suggest a minor revision to acknowledge that the proposed meta-analysis is desired but might not be possible given that <800 papers were returned upon pilot testing your search criteria in the 3 databases. Amongst those, you will likely end up with <20 papers with heterogeneous methods and outcomes/exposures that will make it impossible to perform a meta-analysis.*

The review has been updated.

Amendments to the text read as follows:

Page 12, line 13: Quantitative synthesis (meta-analysis): Where appropriate, a quantitative synthesis will be performed using random-effects statistical models, given the expected diversity among populations/exposures of ACEs. Where possible, Odd Ratios (ORs)/Hazard Ratios (HRs) (e.g. for categorical outcome/diagnosis data) and their 95% confidence intervals (CIs) will be calculated and reported. Although a meta-analysis is desired, given that <800 papers were returned upon pilot testing the search criteria, and there may be heterogeneity in the available studies, conducting a meta-analysis may not be likely.

If sufficient data is available, we will also consider subgroup analyses of:

- Sex
- Age of exposure
- Number of ACEs
- Type of ACEs.

Reviewer 2: Jean-Paul Nguyen, Clinic Bretéché

18. *Page 4 line 17: I do not understand how this study may aid in early diagnosis or treatment of Alzheimer's disease. It can help for the prevention by being extremely strict with management of modifiable risk factors. Following this idea anxiety merit more attention. It may be a consequence of adverse childhood experiences and treatment by anxiolytic agents has been suggested as a potential moderator of AD risk in older adults (Burke SL, O'Driscoll J, Alcide A, Li T. Moderating risk of Alzheimer's disease through the use of anxiolytic agents. Int J Geriatr Psychiatry. 2017 Dec;32(12):1312-1321. doi:10.1002/gps.4614. Epub 2016 Nov 2. PMID: 27805724; PMCID: PMC5441966).*

We have now revised the strengths and limitations, and updated the rationale.

Amendments to the text read as follows:

Page 4, line 1: Strengths and Limitations

- The approach of this review will comprehensively assess existing literature that investigates associations between adverse childhood experiences and the onset of Alzheimer's disease.

- A rigorous search of multiple databases (i.e. CINAHL, MEDLINE and PsycInfo) to ensure a comprehensive review will be conducted.
- This review will be guided by robust guidelines, and a validated tool will be used to assess the quality of included articles to minimise bias.
- Two independent reviewers will perform the screening process, extraction of data and quality assessment.
- A potential limitation of this review may be the lack of evidence on the different types of adverse childhood experiences and the risk of Alzheimer's disease, and there may be heterogeneity in available studies.

Page 6, line 9: Previous studies have reported a higher exposure of ACEs can disrupt normal psychosocial development. This can lead to an enhanced risk of poor health outcomes, such as increased depression and anxiety symptomology and lifestyle ?choices such as smoking and misusing alcohol, which in turn, could increase the risk of AD. Moreover, recent research has reported that traumatic early life experiences can change stress regulatory functions, leading to later altered stress response. Increased stress levels are reported to increase amyloid burden, thus increasing cognitive decline prior to AD progression. Therefore, ACEs, in conjunction with other biological, psychological and environmental factors that initate a stress response, could impact the risk of AD.

19. *Page 5 line 24: Sleep disturbances and incontinence are not part of "cognitive domain".*

We have now reviewed and updated the introduction as suggested.

Amendments to the text read as follows:

Page 5, line 7: AD typically presents as episodic memory impairment, which gradually progresses to interfere with daily activities. Memory impairment is usually followed by other cognitive domain declines which vary according to disease progression, including apathy, impaired spatial and temporal navigations, executive dysfunction, behavioural changes, apraxia, language difficulties, and high dependency on others.

20. *Page 5 line 33: The list of risk factors discussed in reference 7 is not correct. In that article, the role of depression and alcohol as risk factors is not proved.*

We have now reviewed and updated the introduction as suggested.

Amendments to the text read as follows:

Page 5, line 12: Recently, there has been extensive research into the delineating range of risk factors associated with AD such as smoking, social engagement, education, physical activity, sleep and diet.

21. *Page 5 line 45: The loss of proteostasis is never mentioned in reference 8. For the authors of that article the primary theory to explain AD is an impairment of APP (Amyloïd βPrecursor Protein) metabolism.*

These references have now been revised and updated.

Amendments to the text read as follows:

- Morawe, T., et al., *Protein homeostasis, aging and Alzheimer's disease.* Mol Neurobiol, 2012. **46**(1): p. 41-54.
- d'Errico, P. and M. Meyer-Luehmann, *Mechanisms of Pathogenic Tau and Abeta Protein Spreading in Alzheimer's Disease.* Front Aging Neurosci, 2020. **12**: p. 265.

22. *Page 13 line 26: The methodology which will be used for qualitative analysis is not detailed. I suggest the authors to describe the qualitative methodology used to evaluate the literature as in the article by Micklitz Katrin (Micklitz K, Wong G, Howick J. Mindfulness-based programmes to reduce stress and enhance well-being at work: a realist review. BMJ Open. 2021 Mar 19;11(3):e043525. doi:10.1136/bmjopen-2020-043525. PMID: 33741667).*

The quality assessment tool has been revised and updated.

Amendments to the text read as follows:

Page 11, line 18: Assessment of methodological quality of included studies: Assessment of methodological quality of individual studies will be performed by two independent reviewers, and consensus with the third reviewer using the US National Heart, Lung and Blood Institute 14-item checklist for observational cohort and cross-sectional studies. The methodology of eligible studies will be scored using the predetermined criteria as follows: good, fair or poor, with a rating of poor translating to a high risk of bias.

National Institute of Health., *National Heart, Lung and Blood Institute quality assessment tool for observational cohort and cross-sectional studies.* Available from https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

VERSION 2 – REVIEW

REVIEWER	Nguyen , Jean-Paul Clinic Bretéché, center
REVIEW RETURNED	08-Jun-2021

GENERAL COMMENTS	Authors made corrections adequately to my suggestions.