








BMJ Open Relationship between adverse childhood experiences and Alzheimer's disease: a systematic review and meta-analysis protocol

Kayla B Corney ¹, Julie A Pasco ^{1,2,3}, Amanda L Stuart ¹, Emma C West ¹, Shae E Quirk ^{1,4}, Behnaz Azimi Manavi ¹, Lana J Williams ^{1,2}

To cite: Corney KB, Pasco JA, Stuart AL, *et al.* Relationship between adverse childhood experiences and Alzheimer's disease: a systematic review and meta-analysis protocol. *BMJ Open* 2021;11:e049768. doi:10.1136/bmjopen-2021-049768

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online. (<http://dx.doi.org/10.1136/bmjopen-2021-049768>).

Received 08 February 2021
Accepted 19 July 2021



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹IMPACT - Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Deakin University, Geelong, Victoria, Australia

²Barwon Health, Geelong, Victoria, Australia

³Department of Medicine - Western Health, The University of Melbourne, Melbourne, Victoria, Australia

⁴Institute of Clinical Medicine/ Psychiatry, University of Eastern Finland, Joensuu, Finland

Correspondence to

Ms Kayla B Corney;
corneyk@deakin.edu.au

ABSTRACT

Introduction Alzheimer's disease has a high prevalence and a substantial impact on society, as well as the individual. Findings from clinical studies to date, suggest that multiple factors are likely to contribute to the variability seen in the progression of Alzheimer's disease. 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 is exposure to adverse childhood experiences. However, the degree of this association is unknown. This systematic review will examine the literature investigating the associations between adverse childhood experiences and the risk of Alzheimer's disease.

Methods and analysis Articles investigating associations between exposure to adverse childhood experiences and the risk of Alzheimer's disease will be identified systematically by searching CINAHL, MEDLINE and PsycInfo using Ebscohost. No restrictions on date of publication will be applied. The search strategy will be built combining the main key elements of the Population, Exposure, Comparator, and Outcomes inclusion criteria. A meta-analysis is planned and statistical methods will be used to identify and control for heterogeneity, if possible. The development of this protocol was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols.

Ethics and dissemination Only published data will be used for this study, thus, ethical approval will not be required. Findings of the review will be published in a peer-reviewed scientific journal, and presented at national and international conferences.

PROSPERO registration number CRD42020191439.

INTRODUCTION

Healthy cognitive function represents an essential element of successful ageing. Unfortunately, ageing is the predominant risk factor for many diseases that limit the health span.¹ Amid these, Alzheimer's disease (AD) has drawn a lot of attention due to its irreversible and incurable status.^{2,3} AD is the most

Strengths and limitations of this study

- The approach of this review will comprehensively assess the existing literature that investigates associations between adverse childhood experiences and the onset of Alzheimer's disease.
- A rigorous search of multiple databases (ie, 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, extract the data and perform 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.

common form of dementia, affecting approximately 70% of people with the disease, with late-onset AD (≥ 65 years of age) being the predominant form.³ AD typically presents as an 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.^{2,4-6}

Recently, there has been an extensive research into the delineating range of risk factors associated with AD such as smoking, social engagement, education, physical activity, sleep and diet.⁷ Although, notwithstanding the huge research effort, many challengers associated with the development and progression of AD remain unknown.

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open: first published as 10.1136/bmjopen-2021-049768 on 5 August 2021. Downloaded from <http://bmjopen.bmj.com/> on June 12, 2025 at Agence Bibliographique de l'Enseignement Supérieur (ABES).

Nonetheless, distinct pathological changes have been linked to AD, with impairment 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.^{8,9} Moreover, genetic predisposition to AD is very complex. In rare early onset AD, common genes include APP (genes encoding γ -secretase complex), presenilin-1 and presenilin-2 in chromosomes 21, 14 and 1, and in late onset AD, apolipoprotein E series, especially APOE4, is the major genetic risk, with overexpression associated with an increased amyloid burden.^{10–12} 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 in <18 years of age. ACEs include 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).¹³

Recently, a growing body of evidence has reported ACEs to be associated with an increased risk for cognitive decline^{14–16} and AD.¹⁷ Furthermore, ACEs have shown to be a risk factor for a number of other poor health outcomes, such as inflammation, obesity, depression and smoking, which are known risk factors for AD, and thus, ACEs may also enhance the risk of AD indirectly through other risk factors.^{13, 18–20} Furthermore, previous studies have reported a higher exposure of ACEs can disrupt normal psychosocial development which can lead to an enhanced risk of many poor health outcomes, such as smoking, misusing alcohol, and increased depression and anxiety symptomology, and in turn, increase the risk of AD.^{13, 18, 20, 21} Moreover, recent research has reported that traumatic early life experiences can change stress regulatory functions, leading to later altered stress responses.^{22, 23} Increased stress levels are reported to increase amyloid burden, thus increasing cognitive decline prior to AD progression.²¹ Therefore, ACEs, in conjunction with other biological, psychological and environmental factors that initiate a stress response, could impact the risk of AD.

However, although previous research has reported ACEs to be a risk factor for poor health, few studies have investigated the associations between ACEs and AD. Nevertheless, previous studies have reported a decline in cognition to begin years before clinical signs of AD.²⁴ From this perspective, the risk factors must have occurred before this antecedent period, and thus, ACEs may be a potential factor influencing the onset of AD. In addition, previous evidence reports positive social factors to be protective against AD,^{25–28} which therefore suggests, in reverse conclusion, negative influences of ACEs.

In addition, the relationship between ACEs and AD may vary by age and/or sex, possibly due to age and sex differences in neurological development and stress reactions.^{13, 18, 29} Previous evidence reports the prevalence of

ACEs increases with age, suggesting differences in age stages of a child's development may have unique associations to later adult health.^{13, 20, 29–32} Additionally, sex differences have been reported for ACEs and other harmful health outcomes.^{20, 30–32} Therefore, the relationship between ACEs and AD may also differ between age and/or sex.

To our knowledge, no previous review has synthesised evidence on the extent of knowledge regarding ACEs and their relationship with AD. We aim to identify and evaluate the existing literature, provide an indication of the current quality and level of evidence, and directions for future research on this important and sensitive topic.

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 and type of exposure to ACEs and the associated risk of AD.

METHODS

The development of this protocol was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P).³³

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 cohort, 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 (eg, sex/nationality).

Exposure

Any ACE before 18 years of age is the exposure of interest and includes the following:

- ▶ 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).¹³

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, Diagnostic and Statistical Manual of Mental Disorders, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria and/or National Institute on Aging-Alzheimer's Association workgroup criteria.

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 the journals in languages other than English.

Exclusions

Studies that are published in a language other than English, as well as randomised controlled trials will be excluded.

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. The search strategy will be built combining the main key elements of the Population, Exposure, Comparator and Outcomes inclusion criteria. To develop the search strategy, a list of relevant index terms and key words were derived from the existing, relevant literature and combined using Boolean operators, truncations and explode functions (box 1). A final search syntax for each electronic database is included in the published online supplemental file 1.

In consultation with an academic librarian, the search strategy will be refined, translated accordingly for each database, then pilot tested for MEDLINE Complete, PsycInfo and CINAHL databases. A total of 781 studies were yielded from the preliminary search conducted on 18 September 2020. Complete details regarding the final search strategy and results (including dates searched)

Box 1 Search terms.

("Child*" OR Young* OR Early) AND (Physical* OR Emotion* OR Sexual*) AND (Abuse OR Neglect) OR ("Adverse childhood experiences" OR "Child abuse+" OR "Parental death+" OR "Child of impaired parents" OR "Divorce" OR "Domestic violence+" OR (Parental crime OR Parental alcohol abuse OR Parental drug abuse) AND ("Alzheimer disease" OR "Dementia")

will be presented in the ensuing systematic review and meta-analysis.

Other sources

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. A manual search of the reference lists of included studies will then be performed to identify any further studies.

Data management and selection process

One reviewer (KBC) will implement the search strategy, and then import, manage and remove duplicate records using Covidence. Then, two reviewers (KBC and ECW) 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 (LJW) to provide final judgement. Final inclusions will be decided by full-text reading of the articles by two reviewers (KBC and ECW) independently, and consensus with the third reviewer (LW). A PRISMA flow chart of the selection process and reasons for exclusion at the full-text stage will be reported.

Data collection and extraction

Pertinent data to address the study objectives will be extracted from the included studies. Covidence, as well as a predesigned form will be used to extract the data, and will be pilot tested by two reviewers.

Data items

Indicative data to be extracted are as follows:

- ▶ Pertinent citation/study details (eg, author/study/year/country).
- ▶ Study approach (eg, aims/design/setting).
- ▶ Participant/population information (eg, age/sex/demographics/sample size).
- ▶ Exposure information (eg, number/type of ACEs/age of exposure).
- ▶ Comparator information.
- ▶ Outcomes (eg, diagnosis of AD).

Outcomes and prioritisation

As per the objectives, the main outcome will be a diagnosis of AD. If sufficient appropriate studies are available, we will examine differences in sex and age of exposure and the number and type of ACEs. These will be described and reported in the ensuing review.

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.³⁴

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.³⁴

Reporting and presenting results

The reporting of the findings from the proposed review will adhere to the PRISMA guidelines.³⁵

Qualitative synthesis

A description of all relevant studies and their methodological quality will be presented (eg, 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/HRs (eg, for categorical outcome/diagnosis data) and their 95% CIs will be calculated and reported. Although a meta-analysis is desired, given that <800 papers were returned on pilot testing the search criteria, and there may be heterogeneity in the available studies, conducting a meta-analysis may not be possible.

If sufficient data are available, we will also consider subgroup analyses of the following:

- ▶ 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.

Ethics and dissemination

Only published data will be included in this systematic review, therefore ethical approval is not required. The findings will be published in a peer-reviewed scientific journal, and results will be shared at national and international conferences.

Contributors KBC, LJW and JAP planned and designed the study. KBC will implement the search strategy, and then import, manage and remove duplicate records using Covidence. KBC and ECW 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 LJW to provide final judgement. Final inclusions will be decided by full-text reading of the articles by KBC and ECW independently, and consensus with LJW. KBC will analyse and interpret the data. LJW and JAP will help supervise the project. KBC will report and present the findings. ALS, SEQ and BA will provide critical feedback throughout the study. All authors will contribute to the final version of the manuscript.

Funding KBC is supported by the Australian Rotary Health/Bing Taylor PhD Scholarship in Dementia. LJW is supported by a NHMRC Investigator grant (1174060). ECW and BA are supported by a Deakin University Postgraduate Research Scholarship (DUPRS).

Disclaimer The funding sources will have no role in the study design, data collection, data analysis, data interpretation, writing of the report or the decision to submit the paper for publication.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Kayla B Corney <http://orcid.org/0000-0003-4789-0007>
 Julie A Pasco <http://orcid.org/0000-0002-8968-4714>
 Amanda L Stuart <http://orcid.org/0000-0001-8770-9511>
 Emma C West <http://orcid.org/0000-0001-9559-7003>
 Shae E Quirk <http://orcid.org/0000-0001-5375-5085>
 Behnaz Azimi Manavi <http://orcid.org/0000-0001-7450-1877>
 Lana J Williams <http://orcid.org/0000-0002-1377-1272>

REFERENCES

- 1 Franceschi C, Garagnani P, Morsiani C, *et al*. The continuum of aging and age-related diseases: common mechanisms but different rates. *Front Med* 2018;5:61.
- 2 Blazer DG, Yaffe K, Liverman CT. *Cognitive aging: progress in understanding and opportunities for action*. Washington, DC: Committee on the public health dimensions of cognitive aging, board on health sciences policy, 2015.
- 3 Thies W, Bleiler L. Alzheimer's disease facts and figures. *J Alzheimer's Assoc* 2013;9:208–45.
- 4 Bahnasy WS, El-Heneedy YA, El-Seidy EA. Sex hormones and alzheimer's disease, in sex hormones in neurodegenerative processes and diseases 2018.
- 5 Buchhave P *et al*. Cerebrospinal fluid levels of β -Amyloid 1–42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. *Arch Gen Psychiatry* 2012;69:98–106.
- 6 Lane CA, Hardy J, Schott JM. Alzheimer's disease. *Eur J Neurol* 2018;25:59–70.
- 7 Baumgart M, Snyder HM, Carrillo MC, *et al*. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. *Alzheimers Dement* 2015;11:718–26.
- 8 Morawe T, Hiebel C, Kern A, *et al*. Protein homeostasis, aging and Alzheimer's disease. *Mol Neurobiol* 2012;46:41–54.
- 9 d'Errico P, Meyer-Luehmann M, Meyer-Luehmann M. Mechanisms of pathogenic tau and A β protein spreading in Alzheimer's disease. *Front Aging Neurosci* 2020;12:265.
- 10 Šimić G, Babić Leko M, Wray S, *et al*. Monoaminergic neuropathology in Alzheimer's disease. *Prog Neurobiol* 2017;151:101–38.
- 11 Theendakara V, Peters-Libeu CA, Spilman P, *et al*. Direct transcriptional effects of apolipoprotein E. *J Neurosci* 2016;36:685–700.
- 12 Shamsi MB, Firoz AS, Imam SN, *et al*. Epigenetics of human diseases and scope in future therapeutics. *J Taibah Univ Med Sci* 2017;12:205–11.
- 13 Felitti VJ, Anda RF, Nordenberg D, *et al*. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The adverse childhood experiences (ACE) study. *Am J Prev Med* 1998;14:245–58.
- 14 Korten NCM, Penninx BWJH, Pot AM, *et al*. Adverse childhood and recent negative life events: contrasting associations with cognitive decline in older persons. *J Geriatr Psychiatry Neurol* 2014;27:128–38.

- 15 Richards M, Wadsworth MEJ. Long term effects of early adversity on cognitive function. *Arch Dis Child* 2004;89:922–7.
- 16 Ritchie K, Jaussent I, Stewart R, *et al.* Adverse childhood environment and late-life cognitive functioning. *Int J Geriatr Psychiatry* 2011;26:503–10.
- 17 Norton MC, Smith KR, Østbye T, *et al.* Early parental death and remarriage of widowed parents as risk factors for Alzheimer disease: the Cache county study. *Am J Geriatr Psychiatry* 2011;19:814–24.
- 18 Danese A, Moffitt TE, Harrington H, *et al.* Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. *Arch Pediatr Adolesc Med* 2009;163:1135–43.
- 19 Chapman DP, Whitfield CL, Felitti VJ, *et al.* Adverse childhood experiences and the risk of depressive disorders in adulthood. *J Affect Disord* 2004;82:217–25.
- 20 Tani Y, Fujiwara T, Kondo K. Association between adverse childhood experiences and dementia in older Japanese adults. *JAMA Netw Open* 2020;3:e1920740.
- 21 Burke SL, O'Driscoll J, Alcide A, *et al.* Moderating risk of Alzheimer's disease through the use of anxiolytic agents. *Int J Geriatr Psychiatry* 2017;32:1312–21.
- 22 De Bellis MD, Zisk A. The biological effects of childhood trauma. *Child Adolesc Psychiatr Clin N Am* 2014;23:185–222.
- 23 Fink DS, Galea S. Life course epidemiology of trauma and related psychopathology in civilian populations. *Curr Psychiatry Rep* 2015;17:31.
- 24 Shea TB. While I still remember: 30 years of Alzheimer's disease research. *JAD* 2018;62:1049–57.
- 25 Lemche E. Early life stress and epigenetics in late-onset Alzheimer's dementia: a systematic review. *Curr Genomics* 2018;19:522–602.
- 26 Khondoker M, Rafnsson SB, Morris S, *et al.* Positive and negative experiences of social support and risk of dementia in later life: an investigation using the English longitudinal study of ageing. *JAD* 2017;58:99–108.
- 27 Mortimer JA, Ding D, Borenstein AR, *et al.* Changes in brain volume and cognition in a randomized trial of exercise and social interaction in a community-based sample of non-demented Chinese elders. *JAD* 2012;30:757–66.
- 28 Evans IEM, Martyn A, Collins R, *et al.* Social isolation and cognitive function in later life: a systematic review and meta-analysis. *JAD* 2019;70:S119–44.
- 29 Hughes K, Bellis MA, Hardcastle KA, *et al.* The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Health* 2017;2:e356–66.
- 30 Chartier MJ, Walker JR, Naimark B. Separate and cumulative effects of adverse childhood experiences in predicting adult health and health care utilization. *Child Abuse Negl* 2010;34:454–64.
- 31 Flaherty EG, Thompson R, Dubowitz H, *et al.* Adverse childhood experiences and child health in early adolescence. *JAMA Pediatr* 2013;167:622–9.
- 32 Flaherty EG, Thompson R, Litrownik AJ, *et al.* Effect of early childhood adversity on child health. *Arch Pediatr Adolesc Med* 2006;160:1232–8.
- 33 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- 34 National Institute of Health. National heart, lung and blood Institute quality assessment tool for observational cohort and cross-sectional studies. Available: <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>
- 35 Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.