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

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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.

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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 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.

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.

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), presenelin-1 and presenelin-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)

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]

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")

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.

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