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The 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. The search strategy will be built combining the main key elements identified to answer the research question. Additional outcomes of the review will include identifying differences in sex/age of exposure and number/type of adverse childhood experiences. A meta-analysis will be performed, and statistical methods will be used to identify and control for heterogeneity, if possible.

Ethics and dissemination: Only published data will be used for this study, thus, ethical approval will not be required. This protocol is registered with PROSPERO (CRD42020191439). Findings of the review will be published in a peer-reviewed scientific journal, and presented at national and international conferences.

Keywords: Adverse childhood experiences; ACEs: Alzheimer's disease; Dementia; Cognitive decline; Cognitive ageing; Ageing.

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.

- The results of this review may aid in early diagnosis and/or treatment of Alzheimer's disease.

- A potential limitation of this review may be the lack of evidence on the different types of adverse childhood experiences and the onset of Alzheimer's disease, and there may be heterogeneity in available studies.

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 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 the pattern of cortical progression, including apathy, sleep disturbances, impaired spatial and temporal navigations, executive dysfunction, behavioural changes, apraxia, language difficulties, incontinence and high dependency on others [2, 4-6].

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 [7]. 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 [8]. 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 [9-11].

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) [12].

Recently, a growing body of evidence have reported ACEs to be associated with an increased risk for cognitive decline [13-15] and AD [16]. 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 [12, 17-19]. 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, and in turn, increase the risk of AD [12, 17, 19]. For example, recent evidence reports that exposure to early life stress can increase the risk of poor health behaviours such as smoking or misusing 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 [20, 21]. In this view, these mechanisms may contribute to the development 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 [22]. From this prospective, 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 [23-26], 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 [12, 17, 27]. 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 [12, 19, 27-30]. Additionally, sex differences have been reported for adverse childhood experiences and other harmful health outcomes [19, 28-30]. Therefore, the relationship between ACEs and AD may also differ between age and/or sex.

A preliminary search was conducted to determine the nature of the existing literature. To our knowledge, no previous review has synthesised the extent of evidence on what is known regarding ACEs and their relationship with AD. We aim to help close the knowledge gap, by systematically identifying and evaluating the existing literature, providing an indication of the current quality and level of evidence, and provide 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/types of exposures to ACEs and the associated risk of Alzheimer's disease.

Methods

The development of this protocol was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [31].

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 (e.g. sex/nationality).

Exposure: 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. Google Translate may be considered if potentially relevant studies are identified that are published in journals in languages other than English.

Exclusions: Studies that are published in a language other than English, as well as randomized 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. 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 (Table 1).

Table 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")

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 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 included studies will then be performed to identify any further studies.

Data management and selection process: One reviewer (K.B.C) will implement the search strategy, and then import, manage and remove duplicate records using Covidence. Then, two reviewers (K.B.C, E.C.W) 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 (L.J.W) to provide final judgement. Final inclusions will be decided by full-text reading of the articles by two

reviewers (K.B.C, E.C.W) independently, and consensus with the third reviewer (L.J.W). 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 pre-designed 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 (e.g. author/study/year/country)
- Study approach (e.g. aims/design/setting)
- Participant/population information (e.g. age/sex/demographics/sample size)
- Exposure information (e.g. number/type of ACEs/age of exposure)
- Comparator information
- Outcomes (e.g. diagnosis of Alzheimer's disease).

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 adverse childhood experiences. These will be described and reported in the ensuring review.

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).

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.

Reporting and presenting results: The reporting of the findings from the proposed review will adhere to the PRISMA guidelines [31].

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, Odd Ratios (ORs)/Hazard Ratios (HRs) (e.g. 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. The findings will be published in a peer-reviewed scientific journal, and results will be shared at national and international conferences.

Dissemination: This protocol is registered with PROSPERO (CRD42020191439), an international database of health-related systematic review protocols. The findings will be published in a peer-reviewed scientific journal, and results will be shared at national and international conferences.

Ethics: Only published data will be included in this systematic review, therefore ethical approval will not need to be acquired.

Conclusion

To the best of our knowledge, this will be the first review to identify and evaluate the existing evidence regarding the associations between ACEs and the onset of AD. The findings of this review will contribute to the existing literature investigating ACEs and cognitive health, and will add to the evidence base on factors reducing the burden associated with AD.

Footnotes

Patient and Public Involvement: Patients and the public will have no involvement in the design, or conduct, or reporting, or dissemination plans of the research.

Contribution statement: K.B.C, L.J.W and J.A.P planned and designed the study. K.B.C will implement the search strategy, and then import, manage and remove duplicate records using Covidence. K.B.C and E.C.W 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 L.J.W to provide final judgement. Final inclusions will be decided by full-text reading of the articles by K.B.C and E.C.W independently, and consensus with L.J.W. K.B.C will analyse and interpret the data. L.J.W and J.A.P will help supervise the project. K.B.C will report and present the findings. A.L.S, S.E.Q and B.A will provide critical feedback throughout the study. All authors will contribute to the final version of the manuscript.

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Conflicts of interest: None declared.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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The 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 (PECO) 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. This protocol is registered with PROSPERO (CRD42020191439). Findings of the review will be published in a peer-reviewed scientific journal, and presented at national and international conferences.

Keywords: Adverse childhood experiences; ACEs; Alzheimer's disease; Dementia; Cognitive decline; Cognitive ageing; Ageing.

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, 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.

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 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 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. 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 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 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) [13].

Recently, a growing body of evidence have 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 increase 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 adverse childhood experiences 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 Alzheimer's disease.

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 (e.g. sex/nationality).

Exposure: Any ACEs before 18 years of age is the exposure of interest and includes

- 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 (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. Google Translate may be considered if potentially relevant studies are identified that are published in journals in languages other than English.

Exclusions: Studies that are published in a language other than English, as well as randomized 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 (PECO) 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 (Table 1). A final search syntax for each electronic database is included in the published supplementary file.

Table 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")

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 (K.B.C.) will implement the search strategy, and then import, manage and remove duplicate records using Covidence. Then, two reviewers (K.B.C. and E.C.W.) 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 (L.J.W.) to provide final judgement. Final inclusions will be decided by full-text reading of the articles by two reviewers (K.B.C. and E.C.W.) independently, and consensus with the third reviewer (L.J.W.). 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 pre-designed 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 (e.g. author/study/year/country)
- Study approach (e.g. aims/design/setting)
- Participant/population information (e.g. age/sex/demographics/sample size)
- Exposure information (e.g. number/type of ACEs/age of exposure)
- Comparator information
- Outcomes (e.g. diagnosis of Alzheimer's disease).

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 adverse childhood experiences. 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 (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, 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 possible.

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.

Dissemination: This protocol is registered with PROSPERO (CRD42020191439), an international database of health-related systematic review protocols. The findings will be published in a peer-reviewed scientific journal, and results will be shared at national and international conferences.

Ethics: Only published data will be included in this systematic review, therefore ethical approval is not required.

Footnotes

Patient and Public Involvement: Patients and the public will have no involvement in the design, or conduct, or reporting, or dissemination plans of the research.

Contribution statement: K.B.C., L.J.W. and J.A.P. planned and designed the study. K.B.C. will implement the search strategy, and then import, manage and remove duplicate records using Covidence. K.B.C. and E.C.W. 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 L.J.W. to provide final judgement. Final inclusions will be decided by full-text reading of the articles by K.B.C. and E.C.W. independently, and consensus with L.J.W., K.B.C. will analyse and interpret the data. L.J.W. and J.A.P. will help supervise the project. K.B.C. will report and present the findings. A.L.S., S.E.Q. and B.A. will provide critical feedback throughout the study. All authors will contribute to the final version of the manuscript.

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Conflicts of interest: None declared.

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Adverse childhood experiences and Alzheimer's Disease: A systematic review and meta-analysis protocol

Search Strategy

Medline Complete via EBSCOhost

Search line	Index/keyword/combinations
S1	(MH "Child+")
S2	TI Child*
S3	AB Child*
S4	TI Young*
S5	AB Young*
S6	TI Early*
S7	AB Early*
S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
S9	TI Physical*
S10	AB Physical*
S11	TI Sexual*
S12	AB Sexual*
S13	TI Emotion*
S14	AB Emotion*
S15	S9 OR S10 OR S11 OR S12 OR S13 OR S14
S16	TI Abuse
S17	AB Abuse
S18	TI Neglect
S19	AB Neglect
S20	S16 OR S17 OR S18 OR S19
S21	S8 AND S15 AND S20
S22	(MH "Adverse childhood experiences")
S23	TI Adverse childhood experiences
S24	AB Adverse childhood experiences
S25	(MH "Child abuse+")
S26	TI Child abuse
S27	AB Child abuse
S28	(MH "Child of impaired parents")
S29	TI Child of impaired parents
S30	AB Child of impaired parents

S31	(MH "Divorce")
S32	TI Divorce
S33	AB Divorce
S34	(MH "Domestic violence+")
S35	TI Domestic violence
S36	AB Domestic violence
S37	(MH "Parental death+")
S38	TI Parental death
S39	AB Parental death
S40	AB Parental alcohol abuse
S41	TI Parental alcohol abuse
S42	AB Parental drug abuse
S43	TI Parental drug abuse
S44	AB Parental crime
S45	TI Parental crime
S46	S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45
S47	S21 OR S46
S48	(MH "Alzheimer disease")
S49	TI Alzheimer's disease
S50	AB Alzheimer's disease
S51	(MH "Dementia")
S52	TI Dementia
S53	AB Dementia
S54	S48 OR S49 OR S50 OR S51 OR S52 OR S53
S55	S47 AND S54

Note. Apply equivalent subjects; Search modes - Boolean/Phrase; AB= search in abstract field; TI = search title field; MH = Index Term field

APA PsycInfo via EBSCOhost

Search line	**Index/keyword/combinations**
S1	TI Child*
S2	AB Child*
S3	TI Young*

S4	AB Young*
S5	TI Early*
S6	AB Early*
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6
S8	TI Physical*
S9	AB Physical*
S10	TI Sexual*
S11	AB Sexual*
S12	TI Emotion*
S13	AB Emotion*
S14	S8 OR S9 OR S10 OR S11 OR S12 OR S13
S15	TI Abuse
S16	AB Abuse
S17	TI Neglect
S18	AB Neglect
S19	S15 OR S16 OR S17 OR S18
S20	S7 AND S14 AND S19
S21	(DE "Childhood Adversity")
S22	TI Childhood Adversity
S23	AB Childhood Adversity
S24	(DE "Child Abuse+")
S25	TI Child Abuse
S26	AB Child Abuse
S27	(DE "Parent child relations")
S28	TI Parent child relations
S29	AB Parent child relations
S30	(DE "Divorce")
S31	TI Divorce
S32	AB Divorce
S33	(DE "Domestic violence")
S34	TI Domestic violence
S35	AB Domestic violence
S36	(DE "Parental death+")
S37	Parental death
S38	Parental death
S39	AB Parental alcohol abuse
S40	TI Parental alcohol abuse
S41	AB Parental drug abuse
S42	TI Parental drug abuse

S43	AB Parental crime
S44	TI Parental crime
S45	S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR 32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44
S46	S20 OR S45
S47	(DE "Alzheimer's disease")
S48	TI Alzheimer's disease
S49	AB Alzheimer's disease
S50	(DE "Dementia+")
S51	TI Dementia
S52	AB Dementia
S53	S47 OR S48 OR S49 OR S50 OR S51 OR S52
S54	S45 AND S53

Note. Apply equivalent subjects; Search modes - Boolean/Phrase; AB= search in abstract field; TI = search title field; DE = Index Term field

Cinahl complete via EBSCOhost

Search line	**Index/keyword/combinations**
S1	(MH "Child+")
S2	TI Child*
S3	AB Child*
S4	TI Young*
S5	AB Young*
S6	TI Early*
S7	AB Early*
S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
S9	TI Physical*
S10	AB Physical*
S11	TI Sexual*
S12	AB Sexual*
S13	TI Emotion*
S14	AB Emotion*
S15	S9 OR S10 OR S11 OR S12 OR S13 OR S14
S16	TI Abuse
S17	AB Abuse
S18	TI Neglect
S19	AB Neglect
S20	S16 OR S17 OR S18 OR S19
S21	S8 AND S15 AND S20

S22	(MH "Adverse childhood experiences")
S23	TI Adverse childhood experiences
S24	AB Adverse childhood experiences
S25	(MH "Child abuse+")
S26	TI Child abuse
S27	AB Child abuse
S28	(MH "Child of impaired parents")
S29	TI Child of impaired parents
S30	AB Child of impaired parents
S31	(MH "Divorce")
S32	TI Divorce
S33	AB Divorce
S34	(MH "Domestic violence+")
S35	TI Domestic violence
S36	AB Domestic violence
S37	(MH "Parental death+")
S38	TI Parental death
S39	AB Parental death
S40	TI Parental alcohol abuse
S41	AB Parental alcohol abuse
S42	TI Parental drug abuse
S43	AB Parental drug abuse
S44	TI Parental crime
S45	AB Parental crime
S46	S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45
S47	S21 OR S46
S48	(MH "Alzheimer disease")
S49	TI Alzheimer's disease
S50	AB Alzheimer's disease
S51	(MH "Dementia+")
S52	TI Dementia
S53	AB Dementia
S54	S48 OR S49 OR S50 OR S51 OR S52 OR S53
S55	S47 AND S54

Note. Apply equivalent subjects; Search modes - Boolean/Phrase; AB= search in abstract field; TI = search title field; MH = Index Term field

Google Advanced search

Search line	Index/keyword/combinations
S1 All these words	Adverse childhood experiences Alzheimer's disease Dementia
S2 This exact word or phrase	"Adverse childhood experiences" "Alzheimer's disease"
S3 Any of these words	Child OR Young OR Early OR Physical OR Emotion OR Sexual OR Abuse OR Neglect OR Divorce OR Domestic OR violence OR Parental OR death OR crime OR alcohol OR drug

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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