International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Early Alzheimer's Disease in China in the Past Ten Years: A Scoping Review Protocol

INPLASY202460069
doi: 10.37766/inplasy2024.6.0069
Received: 18 June 2024
Published: 18 June 2024

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ADMINISTRATIVE INFORMATION

Support - Novo Nordisk (China).

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202460069

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 June 2024 and was last updated on 18 June 2024.

INTRODUCTION

Review question / Objective Review question "What clinical evidence has emerged in terms of epidemiology, disease manifestation, and diagnostic/screening tools in the Chinese early Alzheimer's disease (eAD) population over the past decade? What is the current understanding of the disease among healthcare professionals, patients, and their caregivers?"
Objective This scoping review is to understand the epidemiological characteristics of eAD in the Chinese population, understand the clinical advances in the status and diagnosis of Chinese eAD patients and the development of disease screening tools in the recent ten years, and analyze the understanding of eAD among Chinese academia and the current situation of patients.

Background Alzheimer's disease (AD) is a neurodegenerative disorder characterized by gradual and progressive decline in cognitive function, behavioral abnormalities, and impaired social functioning. According to data from the National Bureau of Statistics of China in 2023, there are 280 million people aged 60 and above in China, accounting for approximately 19.84% of the total population. Due to the rapidly aging of the population, the current epidemiological situation of AD in China appears to be worse than the global average. In 2019, the number of dementia cases worldwide reached 51.6 million, of which China contributed 13 million cases, accounting for about 25.5% of the global total. Furthermore, the standardized prevalence of dementia in China (788.3/100,000) was higher than that in the world (682.5/100,000). At present, there are 9.83 million AD patients in China, and AD has became the fifth leading cause of death in Chinese population. By

2050, China is expected to have half of the world's AD patients, with medical expenses related to AD reaching $1.89 trillion.

According to the draft version of NIA-AA 2023 diagnostic criteria (updated in October 2023), AD can be divided into 7 clinical stages. Stage 1 is characterized by biomarker evidence of the presence of AD in asymptomatic individuals. Stage 2 is transitional decline, which includes subjective cognitive decline (SCD), objectively-defined subtle cognitive decline (Obj-SCD), and neurobehavioral symptoms. These are the earliest detectable clinical symptoms that may be due to AD in cognitively unimpaired individuals. Stage 3 is mild cognitive impairment (MCI) , which is characterized by objective cognitive impairment but is not severe enough to cause significant loss of function and the patient remains independent (does not meet the criteria for dementia). Stages 4 to 6 represent loss of independence and progressive loss of function, with mild, moderate, and severe dementia respectively. Based on projections for patients with different stages of AD in the United States (US), about 2.43 million patients in the US had mild cognitive impairment (MCI) due to AD in 2017, 46.7 million had preclinical AD, and only 1.54 million had advanced disease. No data on the prevalence of AD at different stages were reported in China.

The term eAD , as defined in the 2018 FDA Guidelines for Early Alzheimer's Disease Drug Development, includes AD patients of Stages 1 to 3 that occur before the onset of overt dementia, who may not have dysfunction or even detectable clinical abnormalities, and to use biomarkers that reflect underlying AD pathophysiological change. The International Working Group (IWG) proposed the concept of prodromal AD (pAD) in 2021, including the early symptomatic stage and the pre dementia stage. Unlike the FDA proposed definition, many clinical studies that enrolled eAD patients often included not only those with MCI but also those with early dementia (Stages 3 to 4).11–13 The FDA accepted the study design because relevant approaches for Stage 3 could also be applied to this combination stage with blurred boundaries between Stage 3 and early Stage 4. In this scoping review, eAD will be referred as NIA-AA Stage 1 to 4 , based on FDA eAD guideline and previous clinical trials which recruited eAD patients.

The early stages of AD are particularly important as not only they possess the largest AD population, but also offer the chance to intervene very early in the disease course. Because the pathophysiological changes associated with AD precede the appearance of clinical symptoms, and the progression of AD progressively worsens, intervention in the early stages of the disease can delay or ideally halt/reverse the pathophysiological process before clinical defects become apparent, potentially minimizing the disease burden in patients with AD.

Rationale Until 2019, approved AD's treatments were aimed at improving symptoms which would not affect the underlying brain changes that caused symptoms. The fact that there are currently limited treatments for AD indicates that the underlying disease mechanisms are not yet fully understood. Only in recent years, with the continuous development of scientific understanding of AD, it is possible to explore effective treatments for patients with eAD. Two FDA-approved medications, aducanumab and lecanemab, are aimed at changing the underlying biology of the disease by removing beta-amyloid from the brain. Lecanemab, approved by FDA in July 2023, is the only AD treatment to receive full FDA approval in 20 years. Both are investigated in eAD population, and have brought more attention to early interventions in AD clinical practice.

With the approved and upcoming treatments being investigated in the eAD population, the identification of eAD patients will be in great need to bring benefits to patients. However, early diagnosis of AD is a great challenge in China. Varying prevalence rates of AD-related MCI have been reported in different studies as for the changing diagnostic criteria for eAD, with ranges of 0.8% to 6.1% for amnestic MCI among Chinese individuals aged 65 and above. Due to the large population to be screened, the commonly used methods, either invasive (cerebrospinal fluid testing) or expensive (PET scans), could not be widely adopted. In addition, accurate diagnosis of AD remains a problem. Studies have shown that the diagnosis rate of dementia, including AD, in China is only 26.9%, with a high clinical misdiagnosis rate of 76.8%. In the community, about 93% of dementia cases go undetected. These findings suggest that there is a significant gap in proper AD screening and diagnosis in China, which makes early detection more challenging.

The concept of "eAD" is evolving, though with the accumulating evidences on earlier phases of AD population, clinical evidences reported on the population often varies. Relying on data from a single clinical trial may not accurately represent the overall situation. We noted there had been a few systematic reviews , mostly meta-analysis, focusing disease prevalence, risk factors, or diagnostic biomarkers. A scoping review has unique advantages over a meta-analysis or traditional systematic review, in particular a

broader range of research questions that can explore and map the main concepts, theories, sources of evidence, and gaps of research within a field, rather than focusing on specific, narrowly defined research question. This feature makes scoping reviews particularly effective for gathering and organizing evidence on eAD, a concept that is not only newly established, but is also evolving. Conducting a scoping review can draw a preliminary evidence map, provide substantial insights in interpreting existing evidence, such as the epidemiological characteristics of eAD, and better understand the disease burden of eAD in China. However, there is a lack of comprehensive scoping review regarding eAD population, and no scoping review specifically focused on the Chinese population. Thus, reviewing the recent research advances on clinical manifestations, biomarkers, and screening tools related to eAD in the Chinese population could contribute to identify potential biomarkers and screening methods suitable for the Chinese population and lay the foundation for further research. Besides, the scoping review will also analyze the understanding of eAD among Chinese academia and the current situation of patients. In summary, to get a comprehensive picture of the current clinical research status of Chinese patients with eAD, identify the data gap in the field, and lay a foundation for further research, we will conduct a scoping review of eAD in the Chinese population over the past 10 years.

METHODS

Strategy of data synthesis The literature search will include publications from 01 January 2013 to 31 December 2023, covering both Chinese and English literature. Firstly, a preliminary search will be conducted in an English database (Pubmed) and the Chinese database (CNKI) to identify and supplement relevant search terms for the subject matter to ensure a comprehensive search. Secondly, databases of PubMed, EMBASE, Cochrane, Web of Science, CNKI, Wanfang, and CQVIP will be searched based on predefined search criteria. Additional search for conference abstracts in 2022 and 2023 will also be performed, as it is not included in the aforementioned databases . Thirdly, the reference list of the identified literature will be screened and supplemented. The retrieved references will be imported into the reference management web-based tool, EPPI reviewer, to consolidate references from different electronic databases and remove duplicate records.

The keywords and MeSH terms of Alzheimer's disease used are Alzheimer* and Alzheimer disease. To further confine the research population to eAD, the following keywords will be included: early, mild cognitive impairment, MCI, mild neurocognitive disorder, aMCI, amnestic mild cognitive impairment, early AD, mild AD, prodromal AD, pre-dementia, early dementia, Mild Dementia, mild cognitive dysfunction, mild cognitive decline, preclinical AD, subjective cognitive decline, subjective cognitive impairment, subtle cognitive impairment, possible AD, probable AD. Keywords including China, Chinese, People's Republic of China, Republic of China, Hong Kong, Hongkong, Taiwan, Macau, and Macao were added as the scoping review will focus on eAD in Chinese population. Four English databases (PubMed, EMBASE, Cochrane, and Web of Science) and 3 Chinese databases (CNKI, Wanfang, and CQVIP) will be searched for peer-reviewed articles published between 01 January 2013 and 31 December 2023. For papers in Chinese, only articles published in high-quality journals will be considered (ie, Chinese Core Journals). Non-human studies and articles focusing on AD treatment using the keywords treatment, therapy, Huperzine, medicine, traditional Chinese medicine, pharmacy, acupuncture, lecanemab, animal, cellular, and vitro in the title and mouse, mice, rat, rats, rabbit, and rabbit in title/abstract will be excluded. Based on different databases searched, the keywords will be supplemented with appropriate thesaurus terms.

An example of the search conducted in PubMed is as follows: ((((("Alzheimer*" [Title/Abstract] OR "Alzheimer disease" [MeSH Terms]) AND ("early" [Title/Abstract] OR "mild cognitive impairment"[Title/Abstract] OR "MCI" [Title/Abstract] OR "mild neurocognitive disorder"[Title/Abstract] OR "aMCI"[Title/Abstract] OR "amnestic mild cognitive impairment" [Title/Abstract] OR "Early AD"[Title/Abstract] OR "Mild AD"[Title/Abstract] OR "Prodromal AD"[Title/Abstract] OR "Pre-Dementia"[Title/Abstract] OR "Early Dementia"[Title/Abstract] OR "Mild Dementia"[Title/Abstract] OR "Mild Cognitive Dysfunction"[Title/Abstract] OR "Mild Cognitive Decline"[Title/Abstract] OR "preclinical AD"[Title/Abstract] OR "subjective cognitive decline"[Title/Abstract] OR "subjective cognitive impairment"[Title/Abstract] OR "subtle cognitive impairment"[Title/Abstract] OR "possible AD" [Title/Abstract] OR "probable AD"[Title/Abstract])) AND ("China"[All Fields] OR "Hong Kong"[All Fields] OR "Taiwan"[All Fields] OR "Macau"[All Fields] OR "Chinese"[All Fields] OR "People's Republic of China"[All Fields] OR "Republic of China"[All Fields] OR "Hongkong"[All Fields] OR "Macao"[All Fields]) AND (2013:2024[pdat])) NOT ("Treatment"[Title] OR "therapy"[Title] OR" Huperzine" [Title] OR "medicine" [Title] OR

"Traditional Chinese medicine" [Title] OR "pharmacy" [Title] OR "acupuncture" [Title] OR" lecanemab" [Title])) NOT (Animal*[Title] OR cellular[Title] OR vitro[Title] OR mouse[Title/Abstract] OR mice[Title/Abstract] OR rat[Title/Abstract] OR rats[Title/Abstract] OR rabbit[Title/Abstract] OR rabbits[Title/Abstract]).

Eligibility criteria The eligibility criteria studies will be based on the Participants, Concept, Context (PCC) framework.

Participants：eAD patients

Concept

All studies will be related to one of the following aspects:

1. Epidemiological characteristics of eAD in the Chinese population.
2. Recent advances in clinical manifestations, biomarkers, and screening/diagnostic tools related to eAD in the Chinese population.
3. The current understanding and response to eAD among healthcare professionals, patients, and society.

Context

This review aims to capture studies conducted in Chinese populations in the past decade, and patients from China including Chinese Mainland, Taiwan, Hong Kong, and Macau are all included.

Inclusion Criteria

1. Diagnosed with AD based on established diagnostic criteria, and identified to be in the early stages of AD (NIA-AA Stage 1 to 4 or equivalent). Diagnostic criteria include, but not limited to, NIA-AA, AAMI, FDA, IWG-2, Petersen criteria, Matthews criteria, or diagnoses made by clinicians based on various measurements.
2. Data available for the group of Chinese eAD patients
3. Articles published in Chinese or English between 01 January 2013 and 31 December 2023

Exclusion Criteria

1. MCI or dementia caused by non-Alzheimer's etiologies, such as stroke, type 2 diabetes, Parkinson's disease, Lewy body dementia, or frontotemporal dementia, etc.
2. Studies related to AD treatments, which aim to investigate whether interventions, including drug treatment and non-drug treatment, could improve prognosis or alleviate symptoms of AD patients.
3. Case reports, study protocols, editorials, commentaries, review articles including systematic reviews, consensus, guidelines, conference abstracts published before or in 2021, texts, opinion papers.
4. Non-clinical studies including basic researches on animals, cells, or molecular level.

Types of evidence sources

This scoping review will consider published, peer-reviewed primary clinical studies written in English or Chinese. Clinical studies, such as experimental, descriptive and epidemiological study designs including randomized controlled trials, nonrandomized controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case-control studies, and analytical or descriptive cross-sectional studies will be considered for inclusion. Conference abstracts in 2022 and 2023 are eligible. Individual case reports, conference abstracts before or in 2021, review papers including systematic reviews, editorials, comments papers, text, and opinion papers are not eligible.

This proposed scoping review will be conducted in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews, and will be reported according to PRISMA Extension for Scoping Reviews (PRISMA-ScR).

Source of evidence screening and selection 1. After the search is completed, all the Chinese and English citations will be compiled and uploaded into EPPI Reviewer. Duplicate records of literatures will be eliminated.
2. Two independent reviewers will then pilot-test the screening process by reviewing titles and abstracts for adherence to the inclusion criteria.
3. Twenty-five titles/abstracts are randomly selected for pilot screening test, and title/abstract screening will only start when 85% or higher conformance is achieved. Two independent reviewers will screen based on title/abstract and reasons for exclusion will be recorded.
4. Two independent reviewers will thoroughly assess the full text of the selected citations against the inclusion criteria. Reasons for excluding full text records will be documented and included in the final scoping review. The pilot screening test will also be conducted during the evaluation of the full text of the selected citations, following the same process and criteria as the title/abstract screening.

In the event of any disagreement between the reviewers at any stage, a third reviewer will be consulted to resolve the issue. A fourth reviewer will act as quality control during the whole evidence screening and selection phase. The complete results of the search and the study inclusion process will be reported in the final scoping review, accompanied by a PRISMA flow diagram.

Data management Data extraction will be completed using a data extraction form. The

retrieved information will be cross-checked. Any disagreement will be discussed and a third reviewer will be involved if necessary. If a study was published more than once, the most informative and complete study will be extracted. If important variables/ information are missing, attempts will be made to contact the authors of the included studies. The extracted data will include information on participants, study methods, concept, context, and key findings related to the outcome measurement relevant to the review question. General information including publication year, study site, province/city, study design, and sample size are planned to be extracted. Patient characteristics like gender, age, educational level, income level, confirmed diagnosis, criteria for diagnosis, disease stages, time from onset of symptoms to diagnosis, and disease manifestations will be collected. Other outcomes including morbidity, disease prevalence, risk factors, biomarkers, sensitivity and specificity of screening tools, and other relevant information will also be extracted. Any necessary adjustments during the data extraction process will be thoroughly explained in the comprehensive scoping review. Efforts will be made to contact authors for clarification on any missing, ambiguous, or incomplete data. Due to the nature of the scoping review, critical appraisal and bias analysis will not be performed.

Reporting results / Analysis of the evidence The PRISMA diagram will be used to illustrate the review process and delineate stages at which studies are excluded along with the relevant reasons. The charted data will be synthesized in a narrative manner, with dimensions plotted according to the results of thematic grouping when the manuscript is discussed.

Language restriction Only articles published in Chinese or English will be included in the review.

Country(ies) involved The scoping review is carried out in China.

Keywords early alzheimer's disease; eAD; Chinese; mild cognitive impairment; MCI; early dementia.

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