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Dementia in China: epidemiology, clinical management, and research advances

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China has the largest population of patients with dementia in the world, imposing a heavy burden on the public and health care systems. More than 100 epidemiological studies on dementia have been done in China, but the estimates of the prevalence and incidence remain inconsistent because of the use of different sampling methods. Despite improved access to health services, inadequate diagnosis and management for dementia is still common, particularly in rural areas. The Chinese Government issued a new policy to increase care facilities for citizens older than 65 years, but most patients with dementia still receive care at home. Western medicines for dementia symptoms are widely used in China, but many patients choose Chinese medicines even though they have little evidence supporting efficacy. The number of clinical trials of Chinese and western medicines has substantially increased as a result of progress in research on new antedementia drugs but international multicentre studies are few in number. Efforts are needed to establish a national system of dementia care enhance training in dementia for health professionals, and develop global collaborations to prevent and cure this disease.

Introduction

Dementia is a leading cause of disability in people older than 65 years worldwide, including China.^{1–3} The number of patients with dementia in China accounts for approximately 25% of the entire population with dementia worldwide,⁴ creating a huge challenge for policy makers, health-care professionals, and family members. In response, over the past 10 years, the Chinese Government and dementia organisations have implemented a series of plans, culminating in the 13th Five-Year Plan to manage this disease, previous iterations of which have improved the access of patients with dementia to health-care services. In particular, the national programme for training dementia doctors, the implementation of new dementia guidelines,^{5,6} and the increased availability of neuroimaging technologies, including MRI and PET,⁷ have enabled earlier and more accurate diagnosis of patients who might previously have been misdiagnosed or overlooked. However, the success of these advances differs between urban and rural areas in China. In rural areas, patients usually have difficulty accessing health services (such as dementia specialist, memory clinics, and imaging facilities) compared with patients in urban areas.⁸ Additionally, advances in diagnostic technology and methods have resulted in changes to diagnostic criteria,^{9–11} which might affect the accuracy of epidemiological studies and the results of clinical trials undertaken before changes to diagnostic criteria. Since the 1990s, more than 100 epidemiological studies have been done in China that have greatly contributed to the knowledge regarding dementia prevalence and incidence.^{12–14} However, other aspects of the disease remain unclear and might limit the understanding of the disease from a national perspective.

In this Review, we highlight the epidemiology, economic burden, health-service system, and clinical trials of Alzheimer's disease and other dementias in China. We also discuss whether Chinese medicines have potential efficacy on dementia and, on the basis of progress and challenges to date, we propose future priorities regarding the care of patients with dementia for policy makers, clinicians, and researchers in China and worldwide. This Review will not include those with other types of dementia, such as frontotemporal dementia, dementia with Lewy bodies, and Parkinson's disease dementia, because the data were generally not available.

Epidemiology
Prevalence

Over the past decade, many studies have focused on the prevalence of dementia in China (appendix pp 3–8). A survey done in 1990 suggested that the prevalence of dementia was 4·60% and Alzheimer's disease was 2·99% in individuals aged 65 years and older.¹⁵ In 2005, the prevalence of Alzheimer's disease was reported to be 3·5% following a large-sample, population-based survey in four regions (with rural and urban areas).¹⁶ Thereafter, many studies were done, but the results showed a broad range for dementia prevalence, from 5·0% to 7·7% for individuals aged 60 years and older and from 2·0% to 13·0% for individuals aged 65 years and older.^{17–24} However, many of these surveys were done in single regions with small sample sizes and might not reflect the actual epidemiology. Two large-sample, multiregion studies have been done, the first in 2014²⁵ and the second in 2019.²⁶ The studies showed that the prevalence of dementia was 5·14% (95% CI 4·71–5·57) in 2014,²⁵ and 5·60% (3·50–7·60) in 2019²⁶ for individuals aged 65 years or older.

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For more on the 13th Five-Year Plan see <http://www.cncaprc.gov.cn/contents/2/179240.html>

See Online for appendix

A meta-analysis of 96 observational studies, published in 2018, reported that the overall prevalence of dementia in Chinese people aged 60 years and older was 5.30% (4.30–6.30).¹³ The prevalence of dementia and Alzheimer's disease was substantially higher in rural populations than in urban populations (6.05% vs 4.40% for dementia and 4.25% vs 2.44% for Alzheimer's disease), probably due to the lower educational level in rural regions.²⁵ Age and sex also affect dementia prevalence.^{12,25,27} A systematic review of 75 observational studies, published in 2013, showed that the prevalence of dementia had doubled at 5-year intervals (from the age of 55 to 99 years) and was higher in women than in men (the ratio of women to men was 1.65).¹² The sex difference in the Alzheimer's disease prevalence was even higher (the ratio of women to men was 2.37),¹² which might be due to hormonal differences and brain development factors.^{28,29} The number of patients with dementia also varies in different geographical areas; the prevalence of dementia is 5.5% in northern China, 5.2% in central China, 4.8% in southern China, and 7.2% in western China, after adjusting for methodological variation, according to a meta-analysis published in 2018 (figure 1).¹³ Moreover, the World Alzheimer Report (2015)³⁰ indicated that the prevalence of dementia in China (which was estimated at 6.19%) is similar to that in most parts of the world (5.50–7.00%), but it is higher than the prevalence in sub-Saharan Africa (5.47%) and central Europe (5.18%), and lower than that reported in Latin America (8.41%) and Southeast Asia

(7.64%) in patients aged 60 years and older.³⁰ The differences in global prevalence might be explained by different dementia survival time, environmental risk factors and genetic factors, and mortality before the onset of dementia.³¹ Moreover, the heterogeneity in research methods, including the use of different diagnostic criteria, can affect results regarding dementia prevalence.^{32,33} Thus, further investigation with a consistent method of diagnosing dementia is needed for confirmation of disease prevalence.

Few multicentre and large-scale studies have been done on the prevalence of mild cognitive impairment in China over the past 10 years (appendix pp 3–8). From 2009 to 2015, six studies that used different diagnostic criteria showed mild cognitive impairment prevalence ranging from 9.70% to 23.30% in Chinese individuals.^{20,34–38} These studies were done in single regions and did not represent the prevalence of mild cognitive impairment on a national scale. Subsequently, a study in multiple regions, which included both urban and rural areas, reported that the prevalence of mild cognitive impairment was 17.9% in urban areas, 25.1% in rural areas, and 20.8% for individuals aged 65 years and older across all of the regions.³⁹ Vascular-related mild cognitive impairment subtypes were the most common (42%), followed by mild cognitive impairment caused by prodromal Alzheimer's disease (29.5%). The strength of this report was the classification of patients with mild cognitive impairment on the basis of the cause of the disease, which highlighted that interventions for vascular risk factors are of vital importance for the prevention of cognitive impairment. The prevalence of mild cognitive impairment was 12.7% for individuals aged 60 years and older⁴⁰ and 14.5% for individuals aged 55 years and older in two meta-analyses.⁴¹ The prevalence of mild cognitive impairment progressively increased with lower educational level, was higher in women than in men, and was higher in rural areas than in urban areas.^{39–41}

Incidence

Few studies have investigated the incidence of dementia and mild cognitive impairment in China (appendix pp 3–8). The incidence of dementia in individuals aged 65 years and older ranged from 17.7⁴² to 24.0⁴³ per 1000 person-years using the same criteria as that of the 10/66 Dementia Research Group in two studies. In 2013, a systematic review of 13 incidence studies reported that the incidence for dementia was 9.87 per 1000 person-years, the incidence of Alzheimer's disease was 6.25 per 1000 person-years, and the incidence of vascular dementia was 2.42 per 1000 person-years for individuals aged 60 years and older.¹² In a multiregion study done in 2016 (using the DSM-IV criteria for the diagnosis of dementia, the NINCDS-ADRDA criteria for Alzheimer's disease, and the NINDS-AIREN criteria for vascular dementia), the incidence for dementia was 12.14 per 1000 person-years, 8.15 per 1000 person-years for Alzheimer's disease, and



Figure 1: The prevalence of dementia in people aged 60 years or older in China¹³
No data from Jilin, Inner Mongolia, Tibet, Qinghai, and Yunnan were included in the study.¹³ The red line marks the border between the different regions of China. The prevalence data in Hong Kong and Taiwan were unavailable for this age range (≥ 60 years).

3·13 per 1000 person-years for vascular dementia among individuals aged 65 years and older.¹⁴ Several studies showed that the incidence of dementia was increasing from 65 years of age in an age-specific manner and is higher in women than in men (appendix p 9).^{14,43,44} Additionally, a report published in 2016 showed that the incidence of dementia was higher in rural areas than in urban areas and greater in northern China than in southern China.¹⁴ However, studies on the incidence of mild cognitive impairment are scarce. One study reported that the incidence of mild cognitive impairment in Chinese individuals aged 65 years and older was 21·7 per 1000 person-years with the 10/66 Dementia Research Group criteria.⁴⁵ In general, these surveys on the incidence of dementia and mild cognitive impairment were done before 2010, and the disease incidence might be higher as a result of the ageing of Chinese society; thus, more studies are needed.

Research on secular trends in the prevalence of dementia in China has rarely been done. A community-dwelling study was done to calculate the prevalence of dementia in Beijing on the basis of mini-mental state examination (MMSE) assessments, and reported a small increase in prevalence from 1·7% in 1986 to 2·5% in 1997.⁴⁶ According to a report from Hong Kong,⁴⁷ the prevalence of clinically diagnosed dementia increased from 0·6% in 2000 to 1·1% in 2004–08 in individuals aged 60 years and older, and from 4·5% in 1995 to 9·3% in 2005–06 in individuals aged 70 years and older. These reports present regional results and might not represent the national situation, but trends have been extrapolated through systemic reviews and meta-analyses. In 2013, a systematic review of 75 prevalence studies analysed the age-specific prevalence of dementia and showed an increase from 1990 to 2000 of at least 16%, and a 43% increase by 2010 for each age stratification.¹² Based on these estimates, another study in 2017 predicted the age-specific prevalence of dementia up to 2030, estimating a potential increase in the number of patients from 2010 (figure 2).^{12,48} According to a meta-analysis, published in 2018, which adjusted for methodological factors (including diagnostic criteria, whole study age range, sampling method, population size and geographical areas), the increasing prevalence of dementia in China from before 1990 (1·90%) to 2010–15 (6·4%) was considerably reduced (from 2·8% before 1990 to 4·9% in 2010–15).¹³ The 2016 Global Burden of Disease study showed that the age-standardised dementia prevalence increased by 5·6% in China from 1990 to 2016, while global prevalence increased by 1·7%.⁴ The increasing prevalence might partly be due to extended lifespan and improved diagnostic criteria, which have resulted in an increased number of people older than 65 years and a higher number of dementia diagnoses. In general, most studies support the expected increase in dementia prevalence in China. Notably, the heterogeneity of research methods might bias the results and explain the scale of the increasing trend.^{32,33,49} A national epidemiological survey

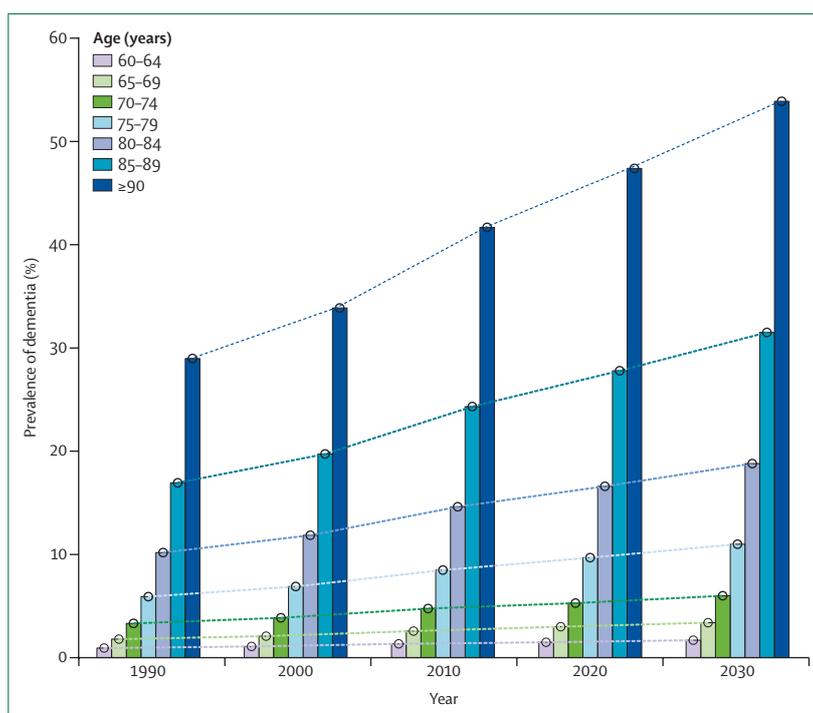


Figure 2: Estimated age-specific prevalence of dementia from 1990 to 2030 in China

The age-specific prevalence of dementia in China is shown with the data from 1990 to 2010 estimated by a systematic review,¹² and the 2020 to 2030 predictions by Xu and colleagues.⁴⁸

with standardised screening methods and diagnostic criteria must be designed to identify the secular trend for the prevalence of dementia in China.

Health economics

Dementia poses a heavy burden on patients and their families. In 2006, a study of 67 patients with Alzheimer's disease in Shanghai reported that the cost of this disease per person-year was US\$2384.⁵⁰ However, this study might have underestimated indirect costs by only including the time spent on caregiving in the analysis, while ignoring the lost productivity and income of non-professional caregivers. Another study of 146 patients with dementia in Shandong estimated that the cost of dementia was approximately \$5900 per person-year in 2010.⁴⁸ This study also suggested that the national annual cost of dementia (including direct medical costs [eg, goods and services for the diagnosis and treatment of the disease], direct non-medical costs [eg, travel costs], and indirect costs [eg, loss of productivity]) was \$47·20 billion in China alone in 2010, according to a prevalence-based bottom-up approach. Notably, the national annual costs were estimated on the basis of small samples from single province studies; thus, the estimates might not represent the general burden of dementia in China.⁴⁸ In 2015, a multicentre survey of 3098 patients with dementia reported that the total cost of care was \$19 144 per person-year.⁵¹ The national annual cost of Alzheimer's disease was \$167·74 billion, with direct medical costs (such as

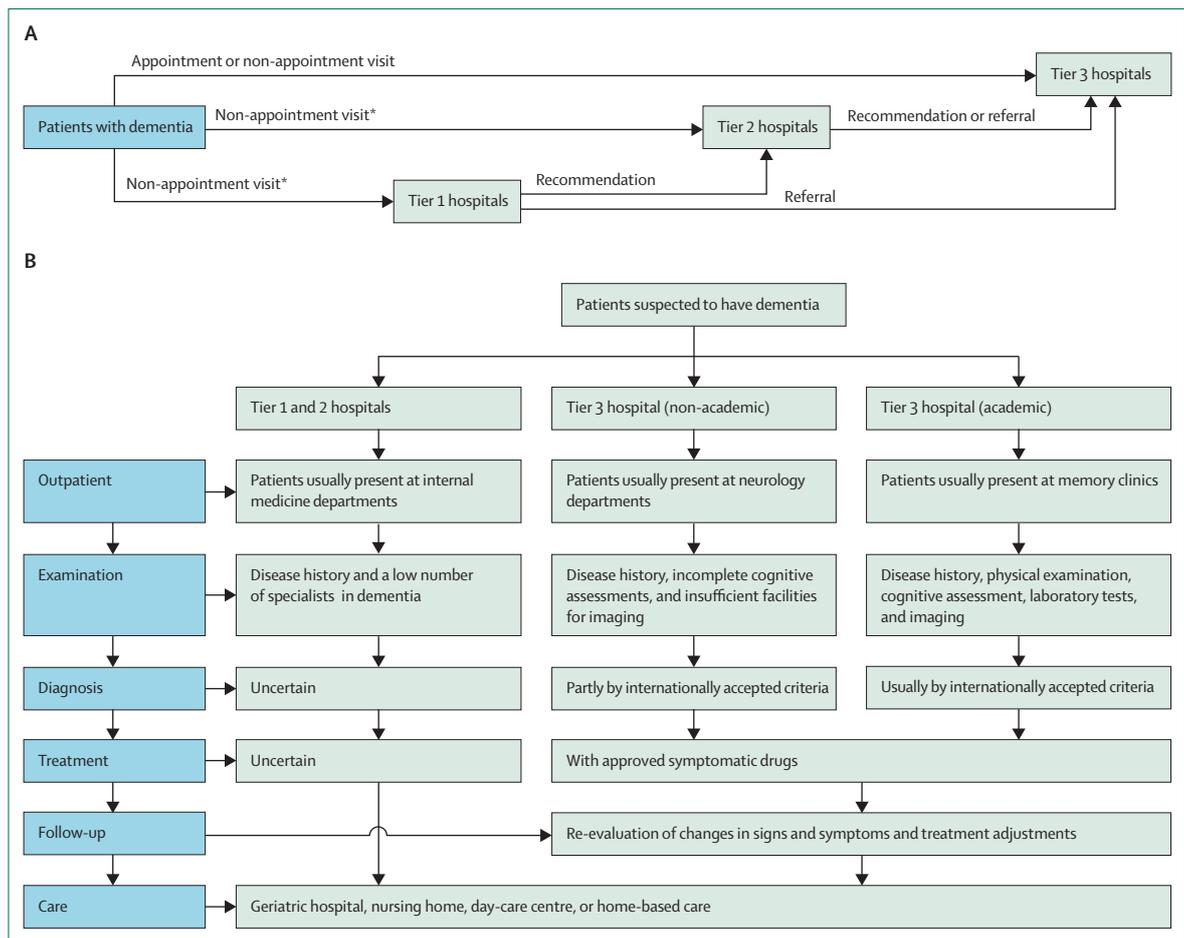


Figure 3: Common of the health-care route (A) and diagnosis, treatment, and follow-up pathways (B) for patients with dementia in the Chinese health-care system

*An appointment is not needed to access these health-care centres. A shows the routes available for seeing a doctor, which emphasises the relationship among the three hospitals tiers. B shows the management pathways available to patients with dementia, which emphasises the different diagnostic and treatment modalities. As defined by the National Health Commission of the People's Republic of China tier 3 hospitals act across districts, provinces, and cities, with the term academic indicating if a hospital is affiliated with a medical school or university; tier 2 [secondary] hospitals are regional or district hospitals, which have a role across several communities; and tier 1 [primary] hospitals are community hospitals.

For more on the **National Health Commission of the People's Republic of China** see <https://www.hqms.org.cn/>

outpatient costs) accounting for 32.5% of the total, direct non-medical costs (such as health-care equipment) accounting for 15.6% of the total, and indirect costs (such as monetary loss due to the inability of the patient and informal caregivers to work) accounting for 51.9% of the total. Moreover, this study showed that the Alzheimer's disease costs in China accounted for 1.47% of the gross domestic product (GDP), whereas the worldwide Alzheimer's disease costs accounted for 1.09% of the global GDP, indicating that the burden of Alzheimer's disease, in terms of socioeconomic costs, was greater in China than the worldwide average.⁵¹ Based on this study, the annual total costs associated with dementia will be \$248.71 billion in 2020, \$507.49 billion in 2030, \$1.00 trillion in 2040, and \$1.89 trillion in 2050 in China (appendix p 2); on a global scale, these costs will be \$1.33 trillion in 2020, \$2.54 trillion in 2030, \$4.83 trillion in 2040, and \$9.12 trillion in 2050.⁵¹

Diagnosis

In China, patients with dementia usually visit neurologists rather than psychiatrists because of concerns about negative stigma.⁵² Thus, the neurology department is the primary setting where patients usually receive their diagnosis. A flowchart of the health-care system highlights the differences between tier 1, 2, and 3 hospitals (as defined by the National Health Commission of the People's Republic of China, tier 3 [tertiary] hospitals act across districts, provinces, and cities, with the term academic indicating if a hospital is affiliated with a medical school or university; tier 2 [secondary] hospitals are regional or district hospitals, which have a role across several communities; and tier 1 [primary] hospitals are community hospitals; figure 3); the differences between dementia diagnosis and treatment in rural and urban areas are illustrated in case studies (panel 1). In general, the diagnosis of dementia differs between the various hospital

levels.⁵³ First, at academic hospitals in medical universities, trained dementia specialists working in memory clinics make a diagnosis according to the International Classification of Diseases tenth edition, the DSM-IV-R or DSM-5, and the Chinese dementia guidelines.^{5,6,11} Thus, a diagnosis is determined by standard procedures. Second, in the non-academic tier 3 hospital settings found in average-sized and large cities (populations >500 000), doctors who diagnose patients who are cognitively impaired are usually neurologists without specialised training in dementia. Thus, a diagnosis is determined by standard procedures and personal experience. Third, in county hospitals that do not have memory clinics and dementia specialists, diagnoses are typically determined by internists with little experience regarding dementia, resulting in high proportions of incorrect and missed diagnoses. Finally, the number of diagnoses vary greatly between hospitals with and without memory clinics.⁵³ Only 0·10% of neurology outpatients are diagnosed with dementia in hospitals without memory clinics, whereas 0·41% are diagnosed with dementia in hospitals with memory clinics. In addition to the shortage of dementia specialists, the other barriers to diagnosing dementia are the stigma associated with dementia;⁵² the belief that a patient is showing a normal ageing process;⁵⁴ inconsistent versions or cutoff scores for neuropsychological tests, such as the MMSE, in different areas in China;^{4,55} the costs of certain advanced techniques to assist with the diagnosis, such as PET, which are not fully covered by health insurance; and refusal of invasive diagnostic examinations, such as lumbar puncture and brain pathological examinations, by patients and their families.⁵⁶

Clinical management and care

The number of patients with dementia in China is estimated to be 10–11 million individuals aged 60 years and older or 9–10 million patients aged 65 years and older;^{13,26,57} more than 60% of patients with dementia have Alzheimer's disease, and approximately 70–80% of them have not received treatment.^{12,25,53} Not receiving treatment is a substantial problem that occurs because of economic difficulties and low awareness of this disease among patients and their families.⁵³ Although patients with vascular dementia constitute the second largest population of people with dementia in China (2·49 million people aged 65 years and older),^{25,57} no treatment data for this population are available. In China, there are approximately 11·8 million patients who have had a stroke, 9·5 million of whom have had cognitive impairments after their stroke.^{58,59} However, the symptoms of dementia can be misdiagnosed as symptoms of the stroke itself and, as a result, patients diagnosed with vascular dementia after a stroke might not receive specific treatment. Overall, China is estimated to have approximately 31 million patients with mild cognitive impairment, with mild cognitive impairment caused by Alzheimer's disease accounting for more than 9 million patients.^{39,57} The

Panel 1: Case study: Alzheimer's disease diagnosis and treatment differences in rural and urban hospitals

Mrs A, a 66-year-old woman with 8 years of education, is a housewife living with her husband in a village in Shanxi Province, China. Beginning in the summer of 2015, Mrs A (then aged 63 years) had difficulties recalling events, she always forgot to take her keys when she left the house, and always forgot to add salt to the pan when she cooked. Her husband thought that she was getting old and that her forgetfulness was caused by normal ageing; thus, he did not take her to the doctors. 2 years later, in 2017, her husband found that she was speaking less often and had difficulties using appropriate words, was frequently angry and agitated for no reason, and had difficulty falling asleep.

Evaluation at the local county hospital

In August, 2017, Mrs A's husband took her to a local county hospital, and an internist saw her. After talking with Mrs A and her husband, the internist measured her blood pressure and ordered a brain CT; her blood pressure was 140/100 mm Hg, and the CT scan did not reveal any abnormalities. The internist diagnosed Mrs A with neurosis and hypertension and prescribed amlodipine besilate, Gamma oryzanol, and vitamin B1. Despite taking these medications for 3 months, Mrs A's condition continued to worsen. She sometimes forgot what she had said or done, she kept asking her husband the same questions, and when she went to the market she often missed items on her shopping list.

Evaluation at an academic hospital in Beijing, China

Mrs A had a daughter living and working in Beijing, who asked her father to bring Mrs A to Beijing. On Dec 13, 2017, Mrs A went with her daughter and husband to the memory clinic at an academic hospital. A dementia specialist assessed Mrs A, spoke with her and her family, checked the medical records brought from the county hospital, and ordered a blood pressure test. The specialist also ordered neuropsychological tests, including a minimal state examination (MMSE), the Montreal Cognitive Assessment (MoCA), activities of daily living (ADL) scale, the Clinical Dementia Rating (CDR) scale, the Neuropsychiatric Inventory (NPI), and the Hachinski Ischaemic Index (HIS). Laboratory examinations, including thyroid hormone, folic acid, vitamin B12, and *Treponema pallidum* antibody tests, and MRI examination were done. The patient's blood pressure was 140/90 mm Hg, her MMSE score was 19, MoCA score was 18, ADL score was 30, CDR score was 1, NPI score was 18, and HIS score was 1, and her laboratory results were within the normal range. An MRI scan revealed mild bilateral hippocampal atrophy. The specialist asked that she be hospitalised with continued use of amlodipine besilate tablets. PET scans were done, which showed widespread deposition of amyloid β , and the specialist diagnosed Mrs A with mild Alzheimer's disease and prescribed her donepezil. Additionally, the specialist enrolled Mrs A in a computer-based cognitive training programme. Mrs A stayed in hospital for 7 days before being discharged. The specialist advised Mrs A's family to monitor her medicine intake, provided instructions about memory training at home, and asked her to come back in 6 months for a follow-up visit.

Follow-up visit

On June 10, 2018, Mrs A returned to the specialist at the academic hospital with her husband and daughter. Her husband told the specialist that Mrs A's temper had become better, and she did not miss items at the market or forget to salt food as often as before. The specialist requested that Mrs A complete the MMSE, MoCA, and CDR, and undergo an MRI examination; her MMSE score was 20, MoCA score was 19, and CDR score was 1, and the MRI scan revealed mild bilateral hippocampal atrophy. The specialist retained the diagnosis of mild Alzheimer's disease, prescribed the same medications, and told her to persist with her memory training at home. Since that visit, Mrs A's condition has remained stable. Her daughter occasionally goes to the academic hospital to buy donepezil and sends it by post to Mrs A because it is not available at local hospitals.

Panel 2: Dementia organisations

In China, the major organisations involved in Alzheimer's disease and related cognitive diseases include:

- The Cognitive Disorder Committee of the Neurology Branch of the Chinese Medical Association, which is led by the China Association for Science and Technology and the National Health Commission of the People's Republic of China; the Committee's main function is to organise meetings and academic communications
- The Committee for Cognition Impairment Disorders of the Neurology Branch of the Chinese Medical Doctor Association, which is led by the Ministry of Civil Affairs of the People's Republic of China and the National Healthy Commission of the People's Republic of China; the Association is responsible for the training of dementia doctors and formulating standards and guidelines
- The China Association for Alzheimer's disease, which was launched in 2015 and is led by the Ministry of Civil Affairs; The China Association for Alzheimer's disease is mainly responsible for popular science, publicity, and education regarding dementia
- Alzheimer's Disease China was approved in 2002 by Alzheimer's disease International; Alzheimer's disease China is the only branch of Alzheimer's Disease International in China, and its main functions involve patient education

We acknowledge that the list does not provide a comprehensive account of all dementia-related organisations in China.

For more on the **Cognitive Disorder Committee of the Neurology Branch of the Chinese Medical Association** see <http://www.cmancn.org.cn/>

For more on the **Committee for Cognition Impairment Disorders of the neurology branch of the Chinese Medical Doctor Association** see <http://www.cmda.net/>

For more on the **China Association for Alzheimer's disease** see <http://www.caad.org.cn/>

For more on **Alzheimer's Disease International** see <https://www.alz.co.uk/>

importance of early diagnosis and treatment for individuals in the predementia stage (in which the patient has symptoms or subjective cognitive decline, but does not meet the criteria for dementia diagnosis) is also gradually becoming recognised, but most patients with mild cognitive impairment are not diagnosed or treated. Taken together, China has approximately 50 million patients with dementia and mild cognitive impairment and this patient population has a large effect on society.

Memory clinics and health professionals

In China, memory clinics represent a novel and disease-specific management model that integrates medical resources, such as clinical, neuropsychological, imaging, and biological diagnostic techniques, with pharmacological and non-pharmacological treatments for cognitive disorders.⁶ Staff at the memory clinics include dementia specialists, neuropsychological evaluators, and nurses. These facilities comprise consulting rooms (independent diagnostic rooms), neuropsychology evaluating rooms, imaging facilities (such as radiology departments), laboratories for blood and CSF tests, and lumbar puncture rooms. Approximately 10% of tier 3 hospitals have memory clinics and dementia centres. According to the Neurology Branch of the Chinese Medical Doctor Association, China has 2340 tier 3 hospitals with 96000 neurologists and approximately

2000 active dementia specialists in different related organisations (panel 2). In China, a dementia specialist is defined as having a qualification as an associate chief physician or above, with clinical practice experience treating cognitive disorders over the past 5 years, more than 1 year of learning experience in the dementia centre of a major national academic hospital, and the ability to independently diagnose dementia.⁶ Doctors who cannot fulfil these criteria but still engage in dementia treatment are referred to as dementia doctors who do not have professional training. The low number of memory clinics and dementia doctors in neurology, psychiatry, or geriatric departments and hospitals represents a major problem. In 2018, the government approved plans for the Cognitive Disorders Committee of the Neurology Branch of the Chinese Medical Doctor Association to establish a programme that would train dementia specialists at dementia centres in national academic hospitals and to mitigate the shortage of dementia doctors in China.

Treatment

Care accounts for more than half of the cost of dementia treatment in China.⁵¹ The major challenge associated with the treatment of patients with dementia in China is a poorly developed care system, which is further affected by low levels of public awareness regarding dementia, inadequate knowledge, poor education among caregivers, and a high cost.⁶⁰ Most patients with dementia receive informal care at home, with formal care only available to patients with mild symptoms and from high-income families.⁶¹ The sources of caregiving in China include government-owned and private institutions for long-term care, community-based care, such as day-care centres and nursing homes, and home-based dementia-specific services provided by a professional caregiver, all of which are still in the initial stages of development.^{54,61-63} In a national survey of 1355 patients with dementia, only 27 (2.0%) received formal care in hospitals or nursing homes, with the remaining 1328 patients cared for by family members and other non-professionals at home.⁵³ Most family caregivers and paid caregivers do not have the required knowledge and skills to adequately care for someone with dementia.⁵⁴ Due to the insufficiency of the care system and the scarcity of effective treatments for patients, an undue burden has been placed on caregivers, which has been ignored over the past several decades.⁴ The burden and stressors on Chinese caregivers are severe and multidimensional, especially in terms of guilt and personal strain, as indicated by the 22-item Zarit Burden Interview.⁶⁴ Stressors might directly relate to caregiving demands (ie, the burden due to the physical, cognitive, or behavioural functions of a patient), or they might relate to role strains, family conflicts, and pressure from the social environment.⁵² Notably, caregivers' burden might not only affect a caregiver's physical and mental health but also hinder the delivery of optimal care to the patient.⁶⁵ Thus, the development of a successful

	Drug type	Trial phase	Condition	Participants		Length of intervention (weeks)	Follow-up (weeks)	Diagnostic criteria	Estimated completion date
				Number of patients	Age of patients (years)				
Chinese medicines									
TMBCZG tablet; NCT03230071	Multitarget	2	Vascular dementia	160	55–80	24	4	NINDS-AIREN	June, 2020
SailuoTong capsule; NCT03789760	Multitarget	3	Vascular dementia	500	40–75	52	NA	DSM-5 and NINDS-AIREN	April, 2022
Ginkgo biloba dispersible tablet; NCT03090516	Multitarget	2/3	Alzheimer's disease	240	50–85	12	NA	NIA-AA	March, 2018
Innovative Chinese compounds*									
AD-35; NCT03790982	Multitarget	2	Alzheimer's disease	480 to ensure 240 patients are included after drop outs	50–75	52	NA	NINCDS-ADRDA	July 30, 2021
Butylphthalide soft capsule; NCT02993367	Multitarget	2/3	Vascular cognitive impairment no dementia	200	40–65	24	NA	MMSE \geq 24 and normal or slightly impaired activities of daily living	July, 2019
Butylphthalide soft capsule; NCT03804229	Multitarget	3	Vascular dementia	700	50–80	52	NA	DSM-5, DSM-IV, and NINDS-AIREN	February 1, 2022
Octohydroaminoacridine succinate tablet; NCT03283059	Cholinesterase inhibitor	3	Alzheimer's disease	600	50–85	54	NA	NIA-AA	February 16, 2020
Huperzine A; NCT02931136	Cholinesterase inhibitor	4	Mild cognitive impairment	300	55–85	52	NA	Activities of daily living	December, 2025
International novel compounds									
Gantenerumab and solanezumab; NCT01760005	Monoclonal antibodies to amyloid β	2/3	Alzheimer's disease	490	18–80	208	NA	Having an Alzheimer's disease-causing mutation or an autosomal dominant Alzheimer's disease family history; and CDR 0–1 (inclusive)	March, 2021
Elenbecestat; NCT03036280	β -secretase inhibitor	3	Alzheimer's disease	950	50–85	96	12	Mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease, MSM \geq 24, CDR 0.5, and clinical dementia rating Memory Box \geq 0.5	Nov 21, 2023
Crenezumab; NCT03114657	Monoclonal antibody to amyloid β	3	Alzheimer's disease	750	50–85	100	52	NIA-AA	May 31, 2019
Gantenerumab; NCT03444870	Monoclonal antibody to amyloid β	3	Alzheimer's disease	760	50–90	104	50	NIA-AA	March 2, 2023

Ongoing clinical trials with more than 150 patients. All the studies listed recruited men and women. TMBCZG=TianMaBianChunZhiGanPian. NINDS-AIREN=National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences. NA=not available. DSM-5=Diagnostic and Statistical Manual of Mental Disorders, 5th edition. NIA-AA=National Institute on Aging and Alzheimer's Association. NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association. MMSE=mini-mental state examination. DSM-IV=DSM, 4th edition. CDR=clinical dementia rating. *Innovative Chinese compounds are compounds that were initially identified or synthesised by Chinese scientists.

Table: Ongoing randomised, controlled clinical trials of Chinese medicines, innovative Chinese compounds, and international novel compounds for the treatment of dementia in China

care system is crucial. Since the integration of the National Working Commission on Ageing into the work remit of the National Health Commission of the People's Republic of China in 2018, more efforts and strategies have been developed, including the establishment of the three-tier long-term care system to facilitate long-term care for all who need it.⁶⁶ This system includes home care, community care, and institutional care, and will benefit patients with dementia.

Medication for dementia in China includes US Food and Drug Administration (FDA) approved drugs and Chinese medicines. The first-line medications for dementia include cholinesterase inhibitors, such as donepezil and rivastigmine, and the NMDA receptor antagonist memantine. However, a report based on a national multicentre study done from 2009 to 2010 showed that only 23.6% of patients with dementia receive pharmacological treatment. Additionally, cholinesterase inhibitors are prescribed to

Panel 3: Priorities in Alzheimer's disease and other dementias

The challenges facing treatment of Alzheimer's disease and other dementias in China include the increasing prevalence of dementia, the heavy economic burden of the disease, the uneven health service, a poorly developed health-care system, and the slow progress in drug development. Here, we highlight effective strategies that could improve this situation.

National surveillance system

Most epidemiological studies on dementia in China in the past few decades were based on single regions, small sample sizes, and inconsistent diagnostic criteria, which do not reflect the situation for the whole country. The establishment of a national surveillance system by the Chinese Government to monitor the epidemiology of the disease among people older than 65 years across the country is urgently needed. This system should monitor the incidence and prevalence, economic costs, and risk and protective factors of dementia. Based on these data, primary and secondary prevention strategies could be established.

Dementia specialists and memory clinics

A high proportion of patients with dementia have no access to appropriate diagnosis and treatment because of the low number of dementia specialists and memory clinics, as well as the low awareness of dementia in the general population. A national project to train health professionals at dementia centres in national academic hospitals, to build more memory clinics in tier 3 hospitals, and to enhance public awareness for seeking dementia-related medical services is imperative. A national hospital-based cohort study should be initiated to refine the diagnostic criteria and procedures for clinical studies and trials.

Dementia care

Long-term care systems for patients with dementia have not yet been established in China.⁶⁶ Accordingly, specific strategies should be implemented to improve this situation, including training for informal caregivers in home settings and increased investment and better availability of institutional and community-based care facilities. Professional and psychosocial support for patients with dementia and family caregivers is needed and should be emphasised. Guidelines for the home care and professional care of patients with dementia should be developed. Research on improving the dementia care system is essential.

Chinese medicine

Chinese medicine is based on a philosophy of a balanced yin and yang.⁹³ Therefore, Chinese medicine aims to re-establish the dynamic balance of bodily functions. Chinese medicine compounds for dementia can be potentially successful because they might have multiple antidementia components. However, their safety and efficacy should be tested and confirmed by domestic and international clinical trials.

Clinical trials platform

An increasing number of clinical trials in China have been done over the past 10 years, but only a few represent an international collaboration because of an inability to meet criteria set by international requirements. Stronger measures should be taken to build more international clinical trial centres and platforms in China that are administered by a committee composed of Chinese and international experts, and monitored by an independent organisation. The enrolment of patients with dementia should conform to criteria consistent with internationally accepted standards. In particular, quality control must be emphasised throughout all procedures to ensure the accuracy of the results. For international clinical trials, more efficient and smoother channels should be formed to encourage involvement by international companies.

19.7% and memantine to 4.1% of patients with Alzheimer's disease.³³ Other medications given to patients with dementia include various adjuvants, primarily aniracetam and nicergoline (12.4%) and traditional

Chinese medicines (5.3%).⁵³ Because the prescription of the cholinesterase inhibitors, memantine, adjuvants, and Chinese medicines are symptom driven and the effects are modest, traditional Chinese medicines have drawn increasing attention over the past 10 years. Chinese medicines can be classified as either Chinese formulated products or herb decoctions. Chinese formulated products, which include pills, granules, and capsules, are manufactured with certain proportions of ingredients in accordance with the Chinese Pharmacopoeia monograph.⁶⁷ The Yizhi Kangnao pill, Congrong Yizhi capsule, and Tianzhi granule, are available for purchase over the counter at pharmacies.^{68–70} Herb decoctions, which contain multiple herbs, are usually formulated by traditional Chinese medicine practitioners on the basis of assessment of the patient, and they are usually taken orally after being decocted in water; well-known medications include the Qifuyin and Ditan decoctions.⁷¹ However, the efficacy of most Chinese formulated products and herb decoctions has not been tested in international randomised controlled trials, which will require further efforts in the future.

Clinical trials

Over the past 10 years, the number of clinical trials done in China investigating dementia treatments has increased. 28 clinical trials (involving ≥ 150 patients in total) have been done or are ongoing, including four phase 4 trials, 14 phase 3 trials, four phase 2/3 trials, and six phase 2 trials (table; appendix pp 10–12). In general, these trials can be classified into four categories: first, conventional drugs, such as the rivastigmine patch and cilostazol; second, traditional Chinese medicines, such as the SaiLuoTong capsule and Ginkgo biloba dispersible tablets; third, innovative Chinese compounds (compounds that were first identified or synthesised by Chinese scientists), such as butylphthalide soft capsules and huperzine A; and finally, international novel compounds, such as LY450139 and lanabecestat. Notably, an increasing number of international compounds are being introduced into the Chinese clinical trial pipeline, such as elenbecestat. Additionally, China has joined the international multidomain intervention trials and is conducting the multimodal interventions to delay dementia and disability in rural China⁹⁴ study, which aims to investigate the effect of multimodal interventions on cognition patients aged 60–79 years. However, such trials are scarce in China. More multidomain intervention trials and international collaborations are needed.

Since 2003, no US FDA-approved drugs that stop or slow the progression of Alzheimer's disease have been introduced.^{72,73} The most probable reason is the single-target mechanisms of these drugs and the fact that Alzheimer's disease is a complex disease that involves a variety of pathophysiological changes.^{74,75} Chinese medicines might have the potential to overcome this issue because of the incorporation of multiple anti-Alzheimer's

disease components that have multiple physiological targets.⁷⁶ Active compounds, such as baicalein, tanshinone IIA, curcumin, ginsenoside Rb1, and ginkgolides B, have been shown to have anti-Alzheimer's disease activities both in vitro and in vivo through reductions in amyloid- β concentration and tau phosphorylation,⁷⁷⁻⁷⁹ antioxidant function, and anti-inflammatory actions.^{80,81} A systematic review of 16 trials⁸² suggested that Chinese medicines could be potential candidates for the treatment of Alzheimer's disease, but the efficacy of Chinese medicines needs to be validated in randomised controlled trials.

Several studies have investigated the ability of Chinese medicines to treat vascular-related cognitive impairment. In animals, Chinese medicines, such as ginkgo biloba extract, ginseng, and crocetin, had neuroprotective effects and improved learning and memory in animal models of vascular dementia.⁸³⁻⁸⁸ In a phase 2, randomised, double-blind, placebo-controlled clinical trial that enrolled 281 patients, a modern Chinese medicinal compound, DL-3-n-butylphthalide, was shown to be safe and effective at improving cognitive and global functioning (measured with the 12-item Alzheimer's disease assessment scale-cognitive subscale [ADAS-cog], the clinician's interview-based impression of change plus caregiver input [CIBIC-plus], and the mini-mental state examination [MMSE]) in patients with subcortical vascular cognitive impairment with no dementia.⁸⁹ In a phase 2, randomised, controlled, double-blind clinical trial (340 participants), SaiLuoTong was shown to improve memory, orientation, language, executive functions, and daily activities (measured with the Vascular Dementia Assessment Scale-cognitive subscale [VaDAScog] and Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change [ADCS-CGIC]) for patients with vascular dementia.^{90,91} Taken together, these studies provide evidence that Chinese medicines might be effective in treating vascular cognitive impairment and might inspire further clinical trials for the treatment of Alzheimer's disease.

Conclusions and future perspectives

The prevalence of dementia has increased in China since 1990,^{4,13} but more studies with larger samples and national coverage are needed to confirm this result. Both the annual cost per person and the percentage of the national GDP that dementia accounts for exceeds the global averages,^{51,92} imposing a heavy economic burden on China, which affects the rest of the world. The health service has been improved (through professional training and with new diagnostic technology), but the improvements are not equal between urban and rural areas.⁸ A three-tier long-term care system is under development, which is still far from meeting the needs of people with dementia.⁶⁶ Only a few international multicentre clinical trials are taking place, and a small amount of clinical research has investigated Chinese medicines. Therefore, strong actions should be taken to address the challenges outlined in this Review in a timely manner.

Search strategy and selection criteria

In this Review, we searched for the terms "dementia", "Alzheimer's disease", "vascular dementia", "mild cognitive impairment", "epidemiology", "prevalence", "incidence", "burden", "diagnosis", "dementia care", "treatment", "medication", "Chinese traditional medicine" or "Chinese medicine", "prevention", "clinical trial", "China", and "Chinese" in the PubMed, China National Knowledge Infrastructure (CNKI) and WanFang databases for literature published between Jan 1, 2008, and May 31, 2019, except for some key references that were published before this period. We only considered literature published in English and Chinese. We acquired more than 700 studies in total, and the search included original articles, meta-analyses, and systematic reviews, as well as annual reports and websites of the National Bureau of Statistics of China and the National Health Commission of the People's Republic of China. We selected publications by the following criteria: including Chinese patients, internationally accepted diagnostic criteria of dementia, and more than 1000 patients for studies (except clinical trials), and meta-analyses or systematic reviews with more than 20 studies. For clinical trials, we searched for studies that enrolled at least 150 patients in China on the website ClinicalTrials.gov and extracted the details of these trials (eg, drug, NCT number, phase, study design, population, and diagnostic criteria). The final reference list was generated in terms of the relevance to these topics, in addition to the aforementioned inclusion criteria.

On the basis of thematic workshops, a literature review, and consultations with a variety of clinicians and researchers, we propose the next steps and future priorities of dementia care in China (panel 3): first, a national surveillance system should be established to monitor the incidence and prevalence and the risk and protective factors of dementia to support the infrastructure of primary and secondary prevention strategies; second, a national project to train dementia specialists, to build more memory clinics, and to enhance public awareness urgently needs to be initiated; third, building more care facilities, training professional caregivers, and alleviating the physical and mental burden of caregivers should be encouraged; fourth, the safety and efficacy of Chinese medicine for dementia should be tested and confirmed by randomised controlled trials; and finally, open and transparent clinical trial centres should be established for domestic and international trials, using consistent criteria for diagnosis as well as rigorous quality control.

Contributors

JJ, LJ, and SG conceived and designed the Review. MQ, YF, TZ, YL, and QQi searched and selected publications and extracted the data. JJ, LJ, MQ, YF, TZ, CW, YT, FW, and QQi participated in writing the first draft of the manuscript. JJ, SG, LJ, MQ, YF, TZ, YL, and QQi interpreted the data. FW, QQu, SS, Y-JW, YD, JiZ, JuZ, BL, and CZ oversaw data quality control. JJ, LJ, MQ, YF, TZ, YL, QQi, JuZ, CW, YT, CZ, FW, YQ, SS, Y-JW, YD, JiZ, BL, and QQu revised the first manuscript. LJ, MQ,

YF, and TZ contributed to the creation of figures. LJ and MQ generated tables. JJ, SG, LJ, MQ, YF, TZ, and YL contributed to the writing of the revised and final version of the manuscript. All authors in this project have read the manuscript and approved the final draft.

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