Prevention of Alzheimer's Disease in Chinese Populations: Status, Challenges and Directions

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In January 2018, the investigators from Eli Lilly's EXPEDITION3 trial published their negative findings of a large phase 3 trial on the antibody Solanezumab (1). The lacking of statistically significant between-group difference on primary endpoint dampened enthusiasm again, and added the study to a long and growing list of failed trials (including EXPEDITION 1 and EXPEDITION2 from the same company) in the field of AD therapeutics. Without promising disease modifying agents, more and more clinicians and scientists in the field start to believe that prevention is better (and maybe easier) than treatment. In the West, scientists, lobbyists and advocacy groups are working hard in persuading the governments and funding agencies to invest more on efforts related to primary prevention of AD. A major study, the US POINTER will soon be initiated in 2018 in the U.S.

In the East, China is facing unprecedented fast population aging. With the largest elderly population in the World, we can foresee that AD will become a heavy burden to the health care system, families and the society and in the near future. Major policies and public health programs are urgently needed to curb the rising tide, and high quality research must be conducted as the prerequisite.

In this opinion paper, we will highlight the importance of AD and AD prevention in China, summarize existing knowledge on modifiable factors, provide an overview of published and ongoing prevention trials, and discuss AD biomarker research and the role of biomarkers in prevention trial. We also will point out promising future directions and propose the idea of establishing a Consortium for Dementia Prevention in Chinese (CDPC) as a potential forum and platform for the promotion of AD prevention research and practice in China.

AD in China: rising tide in the next 30 years

A key feature of population aging in China is a very rapid increase of the oldest-old. Based on data and projection from the United Nations, in 2015 there were 135.2 million elderly aged ≥ 65 years in China, and 8.5 million of them are oldest-old (as defined as 85 years and above); the figure will become 358.9 million and 47.7 million respectively in 2050 (2). The proportion of oldest-old in the elderly population would increase from 6.3% to 13.3% in three decades. This is critical for AD, as it is well-known that the prevalence and incidence increase exponentially with older age. In the study conducted by Zhang and co-workers, the prevalence of AD for the age group 64-75 years, 75-84 years and ≥ 85 years was 1.2%, 5.7% and 23% respectively (3). Assuming age specific prevalence of AD remains the same, in 2050 China would have over 20 million AD patients.

Table 1. Projected number of AD patients in China, 2050

Age group	Projected Population by UN	AD prevalence based on Zhang report	Number of AD patients in 2050
65-74	167.2 million	1.2%	2.0 million
75-84	144.0 million	5.7%	8.2 million
≥ 85	47.7 million	23%	10.97 million

Total number of AD patients in China, 2050: 21.17 millions

Modifiable risk and protective factors

Prevention is not easy; it requires a good understanding of the natural history of the disease and a complete and comprehensive picture of various factors and markers that could be involved in the process (4). Studies based on the Chinese population have helped in establishing causal relationship between potential

modifiable risk and protective factors.

To our best knowledge, at least 23 population-based prospective studies from 13 cohorts have been published till now to investigate the modifiable risk factors of cognitive disorders (including cognitive impairment, dementia, or Alzheimer's disease) in non-demented or MCI Chinese elderly. These participants were mainly from Mainland China (including Chongqing city, Beijing city, Shanghai city, Taiyuan city, Shandong Province or all over the country), Hong Kong, Taiwan, and Singapore. Three cohorts with larger sample size (over 10,000) and longer follow-up duration (6 to 16 years) are especially notable, including Cohort based on Taiwanese National Health Insurance Research Database (5, 6), Cohort based on All the Elderly Health Centers (EHCs) of the Department of Health in Hong Kong (7, 8), and Chinese Longitudinal Healthy Longevity Survey (CLHLS) in Mainland (9, 10). According to these studies, diabetes, sugar consumption, low vitamin D level were risk factor while education, social engagement, physical exercise, vegetables and fruit intake, and use of traditional Chinese medicine were found to be protective factors associated with incidence of cognitive disorders. In addition, tea consumption (protective), dietary exposure to acrylamide, osteoporosis, smoking, daily alcohol drinking (risky), occupation, cognitive activity (protective), chronic kidney disease, hypertension, plasma leptin level, and hyperlipidemia were also reported in other Chinese-based prospective studies to be associated with risk of cognitive impairment, dementia or dementia progression. The above factors are potential target for prevention trial and prevention programs at population level.

Biomarkers

Biomarkers are important for AD, which can be used in both screening trial participants and evaluating trial outcomes as surrogate markers. Specifically, the biomarker abnormality occurs first in abeta levels which can be either an up-regulation in plasma or a down-regulation in cerebrospinal fluid (CSF) in usually cognitively normal individuals and can be detected by biochemical analysis (11). The next stage of biomarker abnormality was usually amyloid deposition in the brain detected by abeta positron-emission tomography (PET). Subsequently, the changes of biomarkers included neuronal injury, indicated by increased levels of CSF total and phosphorylated tau proteins, and cerebral atrophy revealed by structural magnetic resonance imaging (MRI), as well as neurodegeneration and synaptic dysfunction, detected by reduced fluorodeoxyglucose uptake through PET. The results of biomarker studies showed that they were correlated with different disease stages (12, 13), which thus correlated with and supported the changes in the "abeta hypothesis" (14-17). Furthermore, the detection for blood-based abeta proteins as an AD biomarker was recently highlighted to

be desirable due to its properties in the early stage and up-stream of disease pathology, as well as the minimally invasive and cost-effective features (11).

There have been several researches on AD biomarkers focused on the Chinese population. The results showed that the levels of biomarkers in Chinese population were also associated with different disease stages (18-23). Notably, evidence revealed the relationship of the abeta and tau proteins with AD, as well as the association of plasma inflammatory molecules, e.g. soluble tumor necrosis factor receptors with AD (19, 24). Additionally, a study showed the association of the levels of plasma ceramides with AD (21). The mechanisms of these biomarkers in AD are pending further validation and exploration in different populations.

In summary, the results of biomarkers in Chinese population further supported the previously identified roles of biomarkers in AD, which validated their high-performance values in association with other clinical data at different disease stages. For future directions, it is urgent to further investigate the roles of biomarkers on the system levels in association with the brain pathology and cognitive functions. Collectively, the results from these studies will be useful for future clinical intervention in both prevention and treatment purposes.

Previous studies in China

Although none of previous studies on prevention in China is at the scale comparable with the major prevention trials that have been conducted in western countries (FINGER, MAPT, etc.). Several published studies in China should be noticed as lessons have been learned and experiences have been gained from those important studies. There is now accumulating evidence from clinical trials on prevention of AD or cognitive decline in China, among which, a variety of prevention strategies have been investigated, including pharmacological, cognitive stimulus, physical exercise, nutrition and lifestyle interventions. Some strategies are similar to those of western studies, such as cognitive training (25-31), aerobic exercise (32-35), multi-domain lifestyle (36) and nutritional intervention (37-40), while others are Chinese cultural related interventions. It includes the use of traditional Chinese medicine (TCM) such as Chinese herbs (41-43) and acupuncture or acupressure (44, 45), as well as traditional Chinese sports and pastimes such as Tai chi and Baduanjin (46-49), calligraphy (50), finger exercise (51), etc. Notably, a multi-domain intervention comprised of cognitive training, Tai Chi exercise and psycho-social counselling, has been conducted in healthy elderly people recruited from communities in Beijing. Significant improvement was observed in both cognitive and brain functions in multi-domain intervention group compared to active control group (52-54). Overall, these trials in China have provided potential prevention strategies listed above.

Despite the promising results from the published trials, there are several limitations. First, most of these trials are single-center studies with small sample size and short follow-up periods. Second, most trials published in Chinese medical journals are at high risk of bias associated with inadequate or unclear allocation concealment and lack of blind assessment. Furthermore, nearly all trials measured cognitive performance rather than clinically meaningful endpoint, such as reduction of incidence of Alzheimer's disease as the primary endpoint outcome.

Therefore, further evidence from larger and longer multi-center trials is needed to confirm long-term effectiveness and establish the individualized optimum design or dose of feasible, affordable, and safe interventions. Notably, Chinese cultural related interventions combined with new technology will hold great promise for preservation of cognitive function among the Chinese elderly.

Emerging new studies

As noted above, there are growing evidence on trainable protective factors and modifiable risk factors of cognitive decline and dementia. Therefore from a population-based perspective, it is imperative to conduct multi-domain intervention targeting at those risk and protective factors to prevent or delay the onset of dementia. The Finnish FINGER study has demonstrated for the first time in a randomized controlled trial that an intensive multidomain lifestyle intervention among older at-risk individuals may help prevent cognitive decline. Multidomain intervention to prevent and delay dementia is still in its infancy in China. Inspired by the FINGER study, China-FINGER was recently initiated. The China-FINGER aims to test whether a multidomain intervention program sensitive to Chinese lifestyle and socialcultural factors will prevent cognitive decline and delay dementia among elderly people in both rural and urban areas. The intervention program consists of multiple components: (1) lifestyle and nutritional guidelines; (2) intellectual and social activities; (3) physical exercise; (4) regular monitoring and management of major cardiometabolic risk factors. The rural and urban parts of China-FINGER are organized by multidisciplinary research teams from Shangdong Provincial Hospital led by Yifeng Du, and from Institute of Psychology, Chinese Academy of Sciences led by Juan Li, in collaboration with senior researchers from Karolinska Institute (Chengxuan Qiu and Miia Kivipelto). This pioneering national multidomain intervention program is supported by Chinese Ministry of Science and Technology, Chinese National Science Foundation, Chinese Academy of Sciences and Beijing Municipal Science & Technology Commission.

There are also new studies on novel single intervention approaches. In Singapore, Lei Feng and colleagues are

currently conducting a large scale RCT to assess the efficacy and biological mechanisms of choral singing in preventing cognitive decline among community-living elderly who are at high risk of dementia (ClinicalTrials.gov Identifier NCT02919748). Square dancing has become the most popular leisure activity among Chinese elderly women, and it has been estimated to have over 100 million elderly practitioners in mainland China (55). In Beijing, a team led by Juan Li in Chinese Academy of Sciences is conducting a RCT trial (ChiCTR-IOR-17011668) to assess how Square dancing, a culturally adapted aerobic dance, could enhance cognitive health and hippocampal plasticity for community-dwelling older adults. Another example of such novel single intervention study is a collaborative project on the potential role of Chinese ink painting in AD prevention. This study is a collaboration between Singapore, Shanghai and Boston. The trial will be conducted in both Singapore (site PI: Lei Feng) and Shanghai (site PI: Chunbo Li) using identical study protocols. AD biomarkers will be measured in MGH (Lab PI: Can Zhang). Another study, Tea for Alzheimer's Prevention (TAP) trial, is also being planned in Singapore. The study is based on growing evidence of cognitive benefits of tea drinking (56-61) and will involve collaborators from the Europe (Bruno Vellas) and the U.S. (Can Zhang).

More importantly, research findings should be translated into community-based programs to benefit the population. Such a community-based program, the Singapore Dementia Prevention Program (DPP) (62) has been established by Ee-Heok Kua and a group of academics, practitioners and volunteers; the program aims to apply evidence-based interventions in the community through collaborations with various senior activity centers and voluntary welfare organizations. Such community-based programs could be established in China in the near future.

Future directions

We project that there are over 20 million AD patients in China by 2050. With this rising tide, we urge that more high-quality research should be funded and conducted in the next decade to guide policymaking and public health measures. Findings from those studies will enable the design and implementation of effective prevention programs at population level. To curb the emerging dementia epidemic in China and other major Chinese populations, we propose to form the Consortium for Dementia Prevention in Chinese (CDPC). This Consortium will serve as platform for the sharing of information, protocols and data, and as a forum for the communication of new ideas and the conceptualization of large collaborative studies. We invite colleagues who are focusing on larger prospective cohort studies and interventional trials in AD, dementia, mild cognitive impairment and cognitive aging to join the Consortium.

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