What are the Prevalence and Risk Factors of Alzheimer's Disease in China and the United States?

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Abstract. Dementia, especially Alzheimer's dementia, which occupies more than 60% of total dementia cases, has become one of the most significant health problems in the world due to its increasing global prevalence, irreversible pathology, and rising social and economic costs. In this research, the author compared Alzheimer's disease (AD) prevalence in China and the United States and found the common pattern of its epidemiology. Apart from the quantitative analysis, this research also identifies the pathophysiological, socio-environmental, and other risk factors of Alzheimer's disease by qualitative desk research. It was found that the risk factors related to or controlled by genes such as Single Nucleotide Polymorphisms (SNPs) have more influential effects on Alzheimer's disease onset than the socio-environmental factors. Some socio-environmental factors such as level of education reflecting the brain activity of a person are also correlated with Alzheimer's disease prevalence. This disease is caused by an interplay of numerous factors, so there needs to be further investigations into its mechanisms as well as the combination therapy.

1 Introduction

Dementia is one of the dominating causes of dependence, disability, and mortality for the elder aged more than 65 that has become a challenge to the healthcare systems around the world. With one new case every 3 seconds, the number of confirmed cases would double every 20 years and more than triple by 2050 [1, 2]. As a neurodegenerative disease, dementia is reflected by cognitive impairments such as memory loss, disorientation, and degradation in language, motion, and other executive functions. This results in "a physical, psychological, social, and economic impact, not only on people with dementia, but also on their carers, families and society at large", stated by WHO [3, 4]. The substantial rise of the number of cases and the subsequent demand for care and facilities produces costs in both private and public sectors. The total worldwide cost of dementia is estimated to be US\$ 818 billion in 2015, with an increase of 35% from 2010. And it is predicted to reach \$2 trillion by 2030 [1].

Alzheimer's disease (AD) is always in the spotlight of dementia-related studies since it accounts for 60% to 80% of dementia cases [5]. This disease has a complex pathology that is yet thoroughly understood but is primarily marked by extracellular senile plaques formed by beta-amyloid and intracellular neurofibrillary tangles formed by tau protein [3]. Statistically, it displays some patterns of prevalence correlated to age, geography, and other habitual and socio-environmental backgrounds.

By comparing the prevalence and identifying the difference in social-environmental conditions among areas, scientists are able to discover the risk factors triggering AD and find the most effective measures to

prevent its occurrence. A number of social costs including the opportunity cost can be saved from care, hospitals, and research institutes if this disease is preventable or curable.

This research starts with a brief comparison of AD prevalence between China and the United States and points out the common pattern in epidemiology. Then, the pathophysiologic, socio-environmental, and other disease-causing factors are identified qualitatively, which provides hints on the prevention of Alzheimer's disease in the final part of the paper.

2 Methods

This study primarily relies on literature review and data analysis based on the literature. The author searched academic studies on PubMed and China National Knowledge Infrastructure (CNKI). "Alzheimer's disease" "dementia" "geographic" "prevalence" "epidemiology" "pathology/pathobiology" "China" and "the United States" as well as their corresponding Chinese key terms were applied in the search both collectively and respectively. The years of publications in the search were limited between 2005 and 2020.

The search results provided many studies including researches and reviews. This research mainly collected several nationwide studies of meta-analysis for the quantitative part, as well as studies and reviews about the pathophysiology and risk factors of Alzheimer's disease for the qualitative part. Meanwhile, this research also referred to several authoritative reports such as those from Alzheimer's disease International, WHO, and Alzheimer's Association. With the shirdummary of the global distribution of dementia and its world social and

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economic impacts, they provided an overall worldwide view of Alzheimer's dementia in these few decades, and helped further investigation specifically focused on the AD prevalence in China and the United States.

Related documents were traced from the bibliographies of selected researches, reviews, and reports. Since conclusions of the referenced studies have still been accepted and further investigated in recent years, the published years of the documents traced were not limited between 2005 and 2015, which differed from the searching step. From all literature collected, only data between 2013 and 2020 was used to illustrate the current epidemiology of Alzheimer's dementia.

Since it is impractical to examine the prevalence of Alzheimer's dementia and acquire first-hand data on a large scale, the quantitative comparison of AD prevalence between China and the United States is carried out by directly comparing the processed data from meta-analyses. These documents are authoritative because of their exclusion of unstandardized or incomplete data sets, and the unbiased horizontal process and analysis of the regionwide and nationwide statistics. In this study, only the prevalence, referred to as the number and proportion of cases in a population, is investigated instead of the incidence, referred to as the number of new cases per year, due to the lack of valid data.

Qualitative desk research is mainly the literature review. After abundant researches, reviews, and reports

about AD were gathered by the approach described above, the author comprehensively explored the pathology of every risky element of Alzheimer's disease. The author chose to pay more attention to the risk factors that have clear evidence of their effects on AD pathology, for there are many hypotheses. Finally, theories against AD occurrence is summarized according to his understanding based on desk research.

3 Prevalence

The prevalence of Alzheimer's dementia is summarized from several meta-analyses which demonstrate an average of all valid statistics from the studies in China and the United States.

Alone in China, the overall prevalence of Alzheimer's disease in 2007 was 0.40% (404 per 100,000) and that in 2014 was 0.60% (624 per 100,000), shown by a meta-analysis. The number of people with Alzheimer's disease in China has risen from approximately 1.93 million in 1990 to 5.69 million in 2010. Given that there were around 3.68 million dementia cases in 1990 and 9.19 million in 2010, the percentage of confirmed Alzheimer's disease in all types of dementia cases did not display an extensive change [6].

Figure 1. History and prediction of AD prevalence among 55-99 in China, displayed by age and by year [6-8]

Two charts, referred collectively as *Figure 1*, have been generated to illustrate the AD prevalence in China, one of which is sorted by age, the other one is sorted by year. These two figures adopt the history of AD prevalence above 55 years old in the last several decades as well as its expert prediction to 2030. The historical data has been collected in a consistent standard and analyzed cross-sectionally and longitudinally with the model in a systematic review [6]. The prediction of age-specific prevalence was derived from a regression model in another comprehensive review [7].

It is noticeable that the AD prevalence has increased in all age ranges during the past three decades, indicating a continuous growth of the risk, especially for the old population. According to the figures, the AD prevalence in age 55-59 raised from 0.14% to 0.23%, and that in 95-99 raised from 28.84% to 48.19% from 1990 to 2010. The prevalence in rural and urban areas also gave a difference, with 0.45% (452 per 100,000) and 0.40% (399 per 100,000), respectively. Evidence also illustrated that females generally have higher diagnosis risk than males, with the prevalence 0.59% (588 per 100,000) and 0.30% (301 per 100,000), respectively. Also, some studies did not find a significant difference between urban and rural residents in AD prevalence [6, 9, 10].

As for the United States, among the total population of 325 million, it was estimated that 3.65 million old people lived with preclinical or clinical AD in 2017, accounting for 1.12% of the population, of which 1.54 million of the 3.65 million cases live with late-stage clinical AD, accounting for 0.47% of the total population. 2.43 million Americans were estimated to suffer from cognitive impairment, mild or severe, mediated by Alzheimer's disease in 2017. Brookmeyer, Abdalla [11] predicted that the clinical AD cases would escalate to 9.30 million and the cases of cognitive impairment would grow to 5.07 million by 2060, while Matthews, Xu [12] had a more radical estimation that about 3.3% (13.9 million) Americans of a national population of 417 million will suffer from Alzheimer's dementia by 2060 with a 178% growth from 2014.

Figure 2. History and prediction of the number of adults >65 with Alzheimer's disease and related dementia in the United States, displayed (A) in all groups, (B) by sex, (C) by age, (D) and by race and ethnicity [12]

Evidence (*Figure 2*) also illustrated the relation between ethnicity and the AD prevalence in the United States. African Americans had the highest risk at 65 (14.7%), followed by Hispanics (12.9), non-Hispanics whites (11.3%), American Indians and Alaska Natives (10.5%), and Asians and Pacific Islanders (10.1%). This research did not utilize this set of data since China is predominated by one race, but this result provides hints that the genetic variation, including ethnicity, alters the AD prevalence.

Same as China, in the United States, a higher prevalence of Alzheimer's dementia was found in women than men in all races. According to *Figure 2*, as the average age continues raising and the aged population becomes larger, the growth of the number of cases above 85 years old will outpace that of the number of cases between 75 and 84 years old [5, 11, 12].

From all the data collected and analyzed above, little difference is observed between the prevalence in these two countries, meaning that compared to geographic or socio-environmental factors that alter between China and the United States, the pathologic or genetic factors influence more on the development of Alzheimer's disease.

The comparison of the prevalence has demonstrated several common characteristics. First, regardless of other factors, the AD prevalence of the entire population is increasing in both countries. Most studies also support this point regionally and internationally that the number of AD cases and the percentage of the diagnosed population both displayed growth in the near decades [1]. Second, it is not only that the higher the age, the higher the risk, but that the higher the age, the more substantial the growth of the risk. The probability of clinical AD for the same age rises across the years. The same pattern is also found in most other countries of the globe, creating huge worldwide stress on the care and treatment of Alzheimer's disease in China and around the world, according to the predicting model [13, 14]. Third, as socio-environmental factors, the level of education, career, and the rural and urban areas correlate with the prevalence of Alzheimer's dementia. Later in this study, the relation between these factors and Alzheimer's disease and how they affect the AD prevalence would be discussed.

4 Risk factors

The causes of Alzheimer's disease cannot be identified definitely, for its pathology is still currently in doubt. Whereas, as a "trillion-dollar question" described by Alzheimer's Disease International, crowds of scientists and institutes have put countless efforts on this area not only for financial benefits, but for the relief of burden on the families, medical systems, and the economies [4, 15]. Although the mechanism of this disease is not fully studied, scientists reached a level of consensus on the contributors to the AD progression, and there are also some new findings of the interactions between the brain neurons and other components of the body, for example, the immune system and gut microbiota, in the past few decades [16].

Furthermore, statistical studies suggested several non-genetic factors affecting the probability of the occurrence

of Alzheimer's disease. Unlike the gene coding, since the socio-environmental and habitual conditions can be altered artificially, the results of these studies are nowadays in the spotlight of the academic field, though people did not exactly see the approaches they influence the human brain.

Risk factors, including pathophysiologic and socio-environmental ones, shall all be taken into consideration in the investigation of the AD etiology, for Alzheimer's disease is prone to be driven by an interplay of genetic and environmental causes [2].

4.1 Pathophysiologic factors

It is comprehensively acknowledged that there are two proteins playing a heavy role in the pathology of Alzheimer's disease. One is called beta-amyloid (also A β or β -amyloid), which aggregates to form neurotic senile plaques in the intracellular space between neurons; the other is called tau protein (or tau), which accumulates into intercellular neurofibrillary tangles inside the neurons. When these two proteins turn into specific forms, they both fail to perform normal functions, form aggregates, and disrupt normal cell activity in the brain [15]. At the same time, there are also other genetic factors contributing to the progression of Alzheimer's disease in the, for example, inflammatory and cholesterol metabolic pathways [17].

4.1.1 Beta-amyloid

With the behavior non-consistent from the expectation, the enzymes generate altered forms of proteins, and the beta-amyloid is produced after a series of reactions [18]. Beta-amyloid was first identified in 1985 as the "plaque core" that occurs in Alzheimer's disease and Down syndrome [19].

It is produced by two proteases, beta-secretase enzyme (BACE1, beta-site APP-cleaving enzyme 1) and gamma-secretase enzyme, from beta-amyloid precursor protein (APP). The beta-secretase divides APP at N terminus into two segments, APP-beta and the C99 membrane-bound fragment [18, 20]. Then C99 is further processed by gamma-secretase on the membrane, producing C-terminal fragment (CTF) outside the membrane and beta-amyloid 48 (A β 48) inside the membrane. The gamma-secretase continues cleaving the remaining peptide of beta-amyloid repetitively until it is released from the enzyme-substrate complex [21, 22].

Evidence demonstrated that beta-amyloid is secreted predominantly inside endosomes in a neuron-modulated manner, and its overproduction at axons and dendrites reduces the number and plasticity of the spine or synapses locally [23, 24]. Following secretion, beta-amyloid peptides tend to produce higher-order oligomers and fibrils by the aggregation of beta-sheet conformations [25]. The formation of beta-amyloid oligomers involves the amyloid uptake in microglia which continues playing a role in further intracellular seeding process [26].

Genetic studies concluded that beta-amyloid aggregation is not the only factor of the progression of

Alzheimer's disease although it is necessary for the instigation of AD cascade. There are also other downstream factors having an interplay with beta-amyloid in the AD pathology, for the concentration of amyloid deposition has a weak correlation with the phase of Alzheimer's dementia and no current drug or therapy targeting amyloid pathology has been proved effective in clinical trials [27]. The amyloid cascade hypothesis in 1992 stated that beta-amyloid acts as an initiation activating tau aggregation, synaptic loss, and cognitive impairment [28]. Whereas, experiments provided evidence that beta-amyloid could lead to a degree of cognitive impairment independently though the current technology failed to detect the soluble beta-amyloid oligomers leaving a questionable correlation between the concentration of soluble oligomers and AD progression [3].

4.1.2 Tau protein

With a high correlation between tau aggregation and AD development, previous studies proposed that tau is not only a biomarker, but a primary driver of neurodegeneration in Alzheimer's dementia [29]. Whereas, some newly published studies revised this idea by introducing tau accumulation without a cognitive decline in the medial temporal lobes. This protein is "subject to numerous post-translational modifications including phosphorylation" in neurons [3, 30]. In a healthy neuron, tau protein carries out a stabilizing function in the skeleton of axons composed of microtubules, while the defective hyperphosphorylated form of tau protein decreases its affinity with microtubules, thus detaches from the microtubules, moves to the soma of the neuron, and disrupts synaptic signaling in the cell soma. Tau is unfolded and highly soluble in the normal state, but it adopts a beta-sheet conformation containing many small insoluble forms in the vastly different paired helical filaments (PHFs), which are similar to beta-amyloid. As a result of tau disassembly and accumulation in the form of filaments, the neurofibrillary tangles marking the AD occurrence are formed [3, 31].

Unlike beta-amyloid, the aggregation of tau protein has a stronger correlation with the stage of cognitive degradation [27]. Tests on transgenic mouse models proved that the aggregated tau fibrils "self-propagate" in a prion-like manner along with the neuroanatomically connected networks, then the tau aggregates, neurofibrillary tangles, spread sequentially across synapses to remote cell populations in the brain [32-35]. The spread of misfolded tau proteins and its deposition could be used to predict the development of the AD symptoms [36]. In contrast, some investigations discovered primary age-related tauopathy (PART) that tau accumulates with the increase of age without showing cognitive decline [37]. Scientists seemed to find tau promotion along with cognitive impairment only if its aggregation spreads from the entorhinal cortex into the neocortex in the brain [38, 39].

4.1.3 Other genetic pathologic factors

Since gene codes for the protein synthesis and enzyme activity throughout the human body, about 70% of the risk of Alzheimer's disease comes from genetic factors [2]. Numerous SNPs (Single Nucleotide Polymorphism) in immune-related genes have been identified as risk factors for AD, and some of them (ApoE, Trem2, Cd33, Ms4a6d) may represent amyloid response genes. They act together to perform a complex interplay with the body and have effects on the AD development in ways.

From all the SNPs or coding variants, starting in the early 1990s, ApoE (apolipoprotein) is investigated the most in the academic field. It is a special protein that is recognized as the highest risk factor of late-onset Alzheimer's disease (LOAD). Corder, Saunders [40], a study on families with LOAD, found AD risk to increase from 20% to 90% and the mean age for the onset of dementia to decrease from 84 to 68 years old under an increasing number of defective ApoE gene. This 299 amino acid protein is controlled by the ApoE gene with 3 common polymorphisms, $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$, differed by single amino acid substitutions. ApoE $\epsilon 4$ isoform demonstrates a significant promotion effect on Alzheimer's disease, while ApoE $\epsilon 2$ seems to regulate AD progression.

With the expression in several organs of the body, especially in the liver and the brain, it is only supposed to serve as a lipid-binding protein which takes effect in the transport of lipids in lipoprotein; whereas, it appears to accelerate the progression of Alzheimer's dementia in numerous pathways [2, 40, 41]. Medical imaging provided evidence that the existence of ApoE $\epsilon 4$ makes amyloid deposition in the cerebral area more rapid and more significant. It inhibits the clearance of beta-amyloid, promotes "initial seeding" of fibrillar seeding deposition, and even directly binds to beta-amyloid in senile plaques. New theory proposed a competitive inhibition of ApoE to beta-amyloid receptors such as LDLR-related protein 1 (LRP1) on astrocytes. Thus, the promotion of beta-amyloid occurs by blocking the uptake of beta-amyloid, instead of direct binding to simple soluble beta-amyloid molecules, to achieve an abnormally high concentration of beta-amyloid [3, 42, 43]. The effect of ApoE on tauopathy is less certain. Dramatic tau-mediated neurodegeneration was observed in one experiment with ApoE $\epsilon 4$ [44], while the other experiment acquired similar observations with ApoE $\epsilon 2$ [45]. ApoE $\epsilon 4$ may also directly attack the neuronal networks in the way of inhibition of neurite outgrowth.

Differential effects of ApoE isoforms are also displayed on the inflammatory responses. In fact, experiments have found a correlation between the immune system and beta-amyloid deposition. It promotes microglia clustering and microglia related intracellular endocytic beta-amyloid degradation, and the concentration of plaques varies along with the presence of ApoE-mediated microglia [3].

Since the genetic information is passed down the generations, although the vast majority of AD cases occur "on a sporadic basis", Alzheimer's disease does show a hereditary characteristic, supported by evidence. As a

result, this disease is often recognized as an inherited disease [46].

4.2 Socio-environmental and other factors

The results of many past statistical analyses agreed on several socio-environmental factors of the prevalence of Alzheimer's dementia although their interplay with the human brain is not comprehensively explained.

4.2.1 Age

Regardless the geography, age always shows the strongest correlation with the onset of Alzheimer's disease statistically, as shown above in *Figure 1* and *Figure 2 (C)* above. The probability of the onset of Alzheimer's disease is about to double every 5 years before 85 years old [46].

Given the evidence, age as a risk factor, is even more effective than the SNPs in the onset of Alzheimer's disease. It is proposed that as the age increases, the decrease of metabolism and body function weakens the immune system responsible for self-inspection and self-correction of the body, loses the ability to recover the neuron impairment, and causes further neurodegeneration in the brain [47].

4.2.2 Gender

As a biological concept, sex or gender refers to physical differences between men and women, with sex chromosomes XY or XX, morphological traits, and gonadal hormones modulating body characteristics at cell, organ, and system level [48, 49].

Nebel, Aggarwal [48] have noted that studies were inconsistent with the findings of AD prevalence regarding sex. A higher AD prevalence has been reported among women in Europe, while many more recent studies in the United States and around the world did not point out any difference in prevalence due to gender. From all literature collected in this research, about all literature in China before 2011 suggested a difference of prevalence [46, 50-52] in sex, while a portion of more recent meta-studies no longer mentioned or emphasized the effect of gender on AD progression even though most of them have noted a mild or significant statistical gender difference in epidemiology [6]. Anyway, only a few papers have looked into the gender difference in Alzheimer's disease, indicating limited comprehension of this factor and that the effects of sex on the brain still needs to be investigated [48].

Yang [52] has proposed several socio-environmental plausible reasons for the difference in the prevalence between the two genders. First, the aged population of women is larger than that of men, so longevity can be one reason that the case frequency of Alzheimer's dementia is higher in women. On average, women live longer than men, so they have a relatively higher lifetime risk at age 45 than men (20% vs 10%). As for the lifetime risk, Alzheimer's Association in 2017 defined it as "the probability that someone of a given age will develop a condition during his or her remaining life span". Second,

more women are less educated than men. In around 1990, a larger population of men has received higher education in China than that of women (13.8%, 3.6%, respectively), so was the literacy rate (88.8%, 50%, respectively). The level of education between the two genders has a significant difference among the old in China. Third, the change in the concentration of sex hormones in females may have effects on the probability of the onset of Alzheimer's disease. Fourth, there could be more social and psychological burden such as family, duties of care, and widowhood on aged women compared to men, putting stress on their mental state [48, 52].

4.2.3 Brain activity

There is a consensus among researchers that the level of education and literacy has a relation to the probability of AD onset. Unlike China, fewer studies indicated the difference in prevalence due to sex in the United States. It could be because in the United States, after the first university accepted women in 1833, there were more than 30% of universities and colleges accepting women in 1880 and about 71% in 1990. There were 3.26 million registered females in 1970 and the number of women who received higher education has exceeded that of men. The increase in women's literacy rate and advance in their level of education in these two centuries might be the reason why there is no significant difference in AD case frequency [53].

The probability of AD development is affected by the type of career, frequency of communication, the participation of activities, and length of sleep, all of which reflect the brain activity of a person. Early life experience like the growing conditions of a person also correlates with AD prevalence. One hypothesis is that the educated population has a higher socioeconomic status offering high nutrition, better health care, etc., resulting in a low risk of diabetes other chronic diseases [5].

4.2.4 Rural and urban areas

Almost all epidemiological studies found a higher prevalence in rural areas than in urban areas. One reason would be that the urbanization makes the youngsters to the towns, cities, and metropolises, and the aged population in rural areas tends to become more dominant in both China and the United States [54]. More investigations are still required to explain this pattern further.

5 Prevention and therapy

As a non-reversible disease with few effective treatments, Alzheimer's disease has been regarded as unpredictable, unobservable, and unpreventable. Until the late 20th century when MRI and other scanning technologies were introduced, it could be now observed and diagnosed before the autopsy. Recently, a preclinical phase of Alzheimer's disease is identified in the brain with protein accumulation prior to clinical symptoms [55]. The cellular phase hypothesis proposes that the CNS tolerates early cerebral amyloid and tau pathology which is slow and gradual, and

the early protein accumulation only serves as a risk factor for clinical AD. The clinical disease occurs whilst cellular homeostasis fails, represented by the impaired clearance of aggregates, increased cellular stress, and intercellular neurotic and immune malfunction [56]. With the imaging technology enabling the scanning of protein aggregates, the early signal of AD onset helps the patients enhance brain activity in the way of thinking, working, and communicating to delay clinical AD and makes the families support the patients.

Over the last few decades, as the understanding of the pathophysiological changes in the onset of Alzheimer's disease advanced, more targeted medicines were developed to interfere with one or more than one pathologies of the disease. Most of them are inhibitors of a particular enzyme for the determent of product formation or the remaining of a substrate. For example, the cholinesterase inhibitors target the cholinesterase which decreases the synaptic level of acetylcholine and causes a general cholinergic deficit. Many medical studies focused on the therapeutics directed by the discoveries of beta-amyloid and tau pathology, and their effects have yet been determined or proved unsuccessful. The author suggests that combination therapy might be the future direction of medicine researches of Alzheimer's disease [3].

6 Discussion

Under the efforts of researchers worldwide, the criteria for diagnosis of Alzheimer's disease became standardized in recent years, making comparison studies more meaningful. Whereas, we still expect more multiregional and multinational researches which might involve the cooperation among research institutes and health authorities to provide a more thorough set of data for broader and more reliable cross-sectional analysis.

The comparison between the statistics of Alzheimer's disease in China and the United States is meaningful because of the variations in lifestyle, geography, and the economic stage and development. If consistent patterns are found in both countries, this disease is more likely to be dependent on common genetic factors given the thorough difference of the social-environmental conditions, vice versa. A global trend can also be projected from these two countries.

Prospective studies are still needed for future discoveries in genetic pathobiology involving, for example, sex hormones, and non-genetic habitual and socio-environmental pathobiology such as diet, smoking, and region. Although age and gender are regarded as non-genetic factors in this research, they might be, to some extent, controlled by the gene coding in numerous unknown approaches such as hormonal pathways. It takes years for scientists to study Alzheimer's disease, but we believe it would be worthwhile and meaningful.

7 Conclusion

There is no significant statistical difference between AD prevalence in China and the United States. Beta-amyloid aggregation is regarded as the initiation of Alzheimer's

disease, while tau deposition occurs along with the cognitive decline at most time. Age and SNPs correlate with AD onset the most, and the brain activity, indicated by the level of education, etc. also plays a role.

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