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Epidemiology of Alzheimer's Disease

Weili Xu, Camilla Ferrari and Hui-Xin Wang

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1. Introduction

1.1. Global aging

The aging of populations has become a worldwide phenomenon [1]. In 1990, 26 nations had more than two million elderly citizens aged 65 years and older, and the projections indicate that an additional 34 countries will join the list by 2030. In 2000, the number of old people (65+ years) in the world was estimated to be 420 million and it was projected to be nearly one billion by 2030, with the proportion of old people increasing from 7 to 12%. The largest increase in absolute numbers of old people will occur in developing countries; it will almost triple from 249 million in 2000 to an estimated 690 million in 2030. The developing regions' sharing the worldwide aging population will increase from 59 to 71% [2]. Developed countries, which have already shown a dramatic increase in people over 65 years of age will experience a progressive aging of the elderly population. Underlying global population aging is a process known as the "demographic transition" in which mortality and then fertility decline [3]. Decreasing fertility and lengthening life expectancy have together reshaped the age structure of the population in most regions of the planet by shifting relative weight from younger to older groups.

Both developed and developing countries will face the challenge of coping with a high frequency of chronic conditions, such as dementia, which is a characteristic of aging societies. These conditions impair the ability of older persons to function optimally in the community and reduce well-being among affected individuals and their families. Further, these conditions are associated with significant health care costs that must be sustained by the society at large. Thus, the global trend in the phenomenon of population aging has a dramatic impact on public health, healthcare financing and delivery systems throughout the world [4]. Due to the aging of the population, dementia has become a major challenge to elderly care and public health.

1.2. Dementia and Alzheimer's disease

Dementia is defined as a clinical syndrome, and characterized by the development of multiple cognitive deficits that are severe enough to interfere with daily functioning, including social and professional functioning. The cognitive deficits include memory impairment and at least one of the other cognitive domains, such as aphasia, apraxia, agnosia or disturbances in executive functioning [5, 6]. Alzheimer's disease is the most common cause of dementia in the elderly, accounting for 60-70% of all demented cases [7]. Alzheimer's disease is strictly a neuropathological diagnosis determined by the presence of neurofibrillary tangles and senile plaques in the brain of patients with dementia. The disease frequently starts with memory impairment, but is invariably followed by a progressive global cognitive impairment [8]. Vascular dementia is the second most common cause of dementia in the elderly after Alzheimer's disease. Vascular dementia is defined as loss of cognitive function resulting from ischemic, hypoperfusive, or haemorrhagic brain lesions due to cerebrovascular disease or cardiovascular pathology. Diagnosis of vascular dementia requires cognitive impairment; vascular brain lesions, often predominantly subcortical, as demonstrated by brain imaging; a temporal link between stroke and dementia; and exclusion of other causes of dementia [9]. The combination of Alzheimer's disease and vascular dementia pathological changes in the brains of older people are extremely common, making mixed dementia probably the most common type of dementia [10].

Alzheimer's disease was first identified more than 100 years ago, but research into its symptoms, causes, risk factors and treatment has gained momentum only in the last 30 years. Although research has revealed a great deal about Alzheimer's, the precise physiologic changes that trigger the development of Alzheimer's disease largely remain unknown. The only exceptions are certain rare, inherited forms of the disease caused by known genetic mutations. Alzheimer's disease affects people in different ways, but the most common symptom pattern begins with gradually worsening ability to remember new information. This occurs because disruption of brain cell function usually begins in brain regions involved in forming new memories. As damage spreads, individuals experience other difficulties. The following are warning signs of Alzheimer's disease: memory loss that disrupts daily life; challenges in planning or solving problems; difficulty completing familiar tasks at home, at work or at leisure; confusion with time or place; trouble understanding visual images and spatial relationships; new problems with words in speaking or writing; misplacing things and losing the ability to retrace steps; decreased or poor judgment; withdrawal from work or social activities; and changes in mood and personality. As the disease progresses, the individual's cognitive and functional abilities decline. In advanced Alzheimer's disease, people need help with basic activities of daily living, such as bathing, dressing, eating and using the bathroom. Those in the final stages of the disease lose their ability to communicate, fail to recognize loved ones and become bed-bound and reliant on around-the-clock care. When an individual has difficulty moving because of Alzheimer's disease, they are more vulnerable to infections, including pneumonia (infection of the lungs).

2. Occurrence of Alzheimer's disease

The occurrence of a disease can be measured as proportion of people affected by the disease in a defined population at a specific time point (prevalence), or as number of new cases that occur during a specific time period in a population at risk for developing that disease (incidence). The prevalence reflects the public health burden of the disease, whereas the incidence indicates the risk of developing that disease. The prevalence is determined by both incidence and duration of the disease, and in certain circumstances, the prevalence may be estimated as $\text{incidence} \times \text{average disease duration}$.

2.1. Prevalence

Based on the available epidemiological data, a group of experts estimated that 24.3 million people have dementia today, with 4.6 million new cases of dementia every year (one new case every 7 seconds). The number of people affected will double every 20 years to 81.1 million by 2040 [11]. Similar estimates have been reported previously [12]. Most people with dementia live in developing countries. China and its western Pacific neighbours have the highest number of people with dementia (6 million), followed by the European Union (5.0 million), USA (2.9 million), and India (1.5 million). The rates of increase in the number of dementia cases are not uniform across the world; numbers in developed countries are forecasted to increase by 100% between 2001 and 2040, but to increase by more than 300% in India, China, and other south Asian and western Pacific countries [11]. About 70% of these cases were attributed to Alzheimer's disease [11, 13]. The pooled data of population-based studies in Europe suggests that the age-standardized prevalence in people 65+ years old was 6.4 % for dementia and 4.4 % for Alzheimer's disease [14]. In the US, a study of a national representative sample of people aged >70 years yielded a prevalence for Alzheimer's disease of 9.7 % [15].

Worldwide, the global prevalence of dementia was estimated to be 3.9 % in people aged 60+ years, with the regional prevalence being 1.6 % in Africa, 4.0 % in China and Western Pacific regions, 4.6 % in Latin America, 5.4 % in Western Europe, and 6.4 % in North America [11]. A meta-analysis including 18 studies from China during 1990-2010 showed prevalence of Alzheimer's disease of 1.9% [16]. More than 25 million people in the world are currently affected by dementia, most suffering from Alzheimer's disease, with around 5 million new cases occurring every year [11]. The number of people with dementia is anticipated to double every 20 years. Despite different inclusion criteria, several meta-analyses and nationwide surveys have yielded roughly similar age-specific prevalence of AD across regions (Figure 1) [17]. The age-specific prevalence of Alzheimer's disease almost doubles every 5 years after aged 65. Among developed nations, approximately 1 in 10 older people aged ≥ 65 is affected by some degree of dementia, whereas more than one third of very old people aged ≥ 85 years may have dementia-related symptoms and signs [18, 19]. There is a similar pattern of dementia subtypes across the world, with Alzheimer's disease and vascular dementia, the two most common forms of dementia, accounting for 50 % to 70 % and 15 % to 25 %, respectively, of all dementia cases.

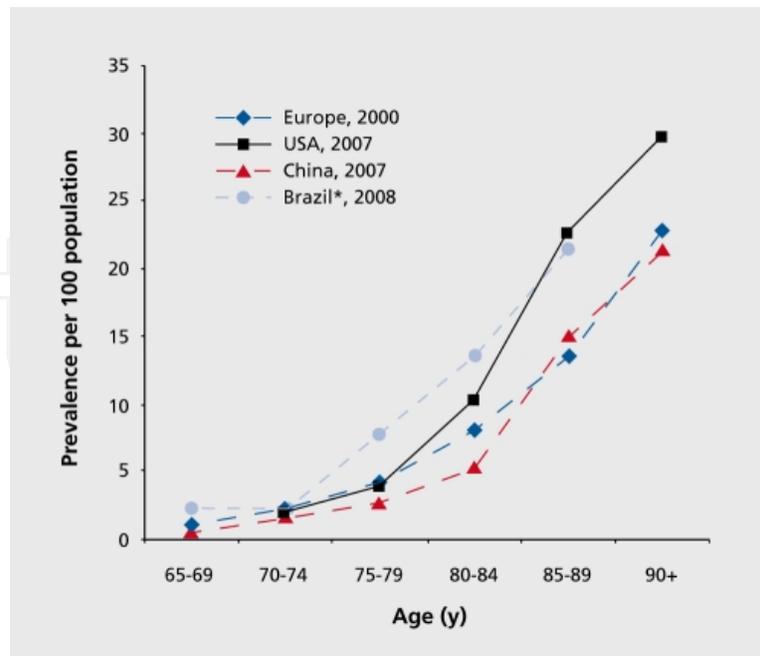


Figure 1. Age-specific prevalence of Alzheimer's disease (per 100 population) across continents and countries. *prevalence of all types of dementia [17].

Epidemiological research of dementia and AD in low- and middle-income countries has drawn much attention in recent years. A systematic review estimated that the overall prevalence of Alzheimer's disease in developing countries was 3.4 % (95 % CI, 1.6 % - 5.0 %) [20]. The prevalence of dementia (DSM-IV criteria) in people aged 65+ years in seven developing nations varied widely from less than 0.5 % to more than 6 %, which is substantially lower than in developed countries [21]. Indeed, the prevalence rates of dementia in India and rural Latin America were approximately a quarter of the rates in European countries. However, the prevalence of AD in persons 65+ years in urban areas of China was 3.5 %, and even higher (4.8 %) after post-hoc correction for negative screening errors [22], which is generally comparable with those from Western nations. Similar prevalence rates of dementia were also reported from the urban populations of Latin American nations such as Havana in Cuba (6.4 %) and São Paulo in Brazil (5.1 %) [20, 23, 24].

2.2. Incidence

The global annual incidence of dementia is around 7.5 per 1,000 persons [11]. The incidence rate of dementia increases exponentially with age, from approximately one per 1,000 person-year in people aged 60-64 years to more than 70 per 1,000 person-year in 90+ year-olds. The incidence rates of dementia across regions are quite similar in the younger-old (<75 years), but greater variations are seen among the older ages [25]. Slightly lower rates have been detected in the USA in comparison with Europe and Asia, and this is possibly due to differences in the study designs and the case ascertainment procedures. The pooled incidence rate of Alzheimer's disease among people 65+ years of age in Europe was 19.4 per 1000 person-year [26]. The pooled data from two large-scale community-based studies of people aged ≥ 65

years in the US Seattle and Baltimore areas yielded an incidence rate for Alzheimer's disease of 15.0 (male, 13.0; female, 16.9) per 1000 person-year [27, 28]. The incidence rate of Alzheimer's disease increases almost exponentially with increasing age until 85 years of age (Figure 2) [17]. A consistently exponential increase, with advancing age in Alzheimer incidence suggests that Alzheimer's disease is an inevitable consequence of aging, whereas a convergence to or a decline at certain age may suggest that very old people may have reduced vulnerability, owing perhaps to genetic or environmental factors. The Cache County Study further found that the incidence of AD increased with age, peaked, and then started to decline at extreme old ages for both men and women [29]. However, some meta-analyses and large-scale studies in Europe provided no evidence for the potential decline in the incidence of dementia and Alzheimer's disease among the oldest-old age groups [26, 30, 31]. The apparent decline suggested in some studies may be an artifact of poor response rate and survival effect in these very old age groups. Several studies from Europe observed a higher incidence rate of Alzheimer's disease among women than men, especially among the oldest-old age groups, whereas studies in North America found no significant gender difference [17].

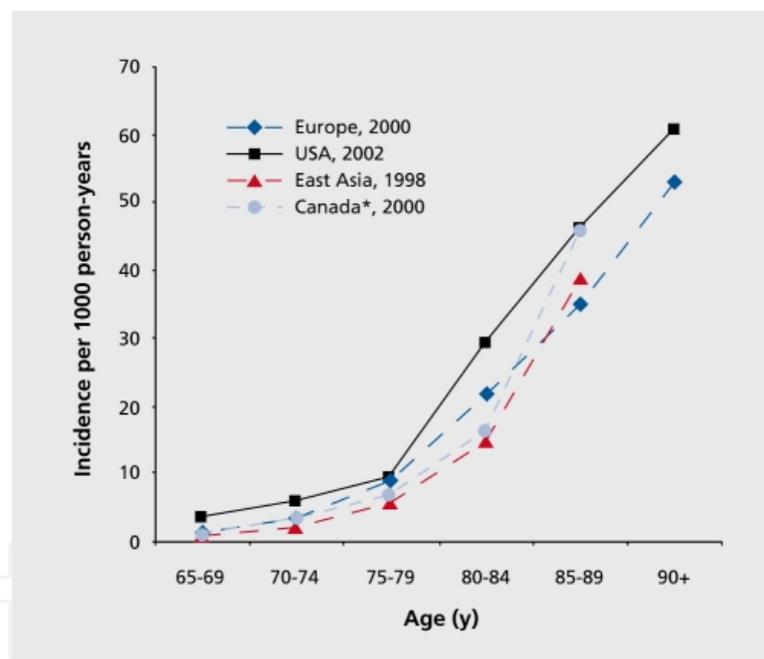


Figure 2. Age-specific incidence of Alzheimer's disease (per 1 000 person years) across continents and countries. *incidence of all types of dementia [17].

There appears to be some geographic variations in the incidence of Alzheimer's disease. The pooled data of eight European studies suggested a geographical dissociation across Europe, with higher incidence rates being found among the oldest-old people of north-western countries than among southern countries [26]. The incidence rates of Alzheimer's disease were reported to be slightly lower in North America than in Europe. Differences in methodology (e.g., differences in study design and procedure of case ascertainment), rather than real different regional distributions of the disease, may be partly responsible for the

geographic variations. The study using identical methods in UK found no evidence of variation in dementia incidence among five areas in England and Wales [30]. Studies have confirmed that AD incidence in developing countries is generally lower than in North America and Europe. For example, the incidence rate of AD among people aged 65+ years was 7.7 per 1 000 person-year in Brazil and 3.2 per 1 000 person-year in India [20, 32].

3. Prognosis and impact

Dementia is one of the leading causes of death in older people. However, death certificates grossly underreport its cause, even when multiple underlying causes of death are taken into account. The community-based follow-up studies could provide reliable data on mortality. In the Swedish Kungsholmen Project of people aged 75 years or over, the mortality rate of dementia was 2.4 per 100 person-year; 70% of incident dementia cases died within five years following the diagnosis. In three years, more than 50% of the dementia cases reached the severe stage. In the Kungsholmen Project, the proportion of severe dementia among prevalent cases increased from 19% at baseline to 48% after three years, and to 78% after seven years. This progression is due to both cognitive and functional decline [33]. Dementia is strongly associated with disability as it has been found to be the major determinant of developing dependence and functional decline over three years. Approximately half of the persons who developed functional dependence in a three year period can attribute to dementia [34]. In industrialised countries, mental disease and cognitive impairment are the most prevalent disorders among older adults living in nursing homes or other institutions. However, institutionalisation of demented patients varies depending on age structure, urban or rural residence, and other cultural aspects. In a 75+ year old population, 70% of incident dementia cases died in the five years following the diagnosis, accounting for a mortality rate specific for dementia of 2.4 per 100 person-years. Dementia triples the risk of death [35]. The demands of healthcare and social service of the huge and rapidly growing numbers of dementia patients have a major economic impact at the societal level [36]. The worldwide direct costs for dementia in 2003 were estimated at 156 billion USD in the main scenario of a worldwide prevalence of 27.7 million demented persons. It is obvious that due to these costs and the expected increase in the number of elderly people in developing countries, the dementing conditions will present a great challenge [37,38].

4. Risk and protective factors

Alzheimer's disease is multifactorial disorder that is determined by genetic and environmental factors as well as their interactions. Population-based prospective study is the major epidemiological approach to identifying influential factors for chronic multifactorial diseases such as dementia, in which the life-course approach should be taken into consideration. Age is the most powerful determinant of Alzheimer's disease, and gene mutations contribute to a small proportion of all cases. The strong association of Alzheimer's disease with in-

creasing age may partially reflect the cumulative effect of different risk and protective factors over the lifespan, including the effect of complex interactions of genetic susceptibility, psychosocial factors, biological factors, and environmental exposures experienced over the lifespan. Evidence from epidemiological, neuroimaging, and neuropathological research, supports the role of genetic, vascular, and psychosocial factors in the development of Alzheimer's disease, whereas evidence for the etiologic role of dietary or nutritional factors, occupational exposures, and inflammation is less clear [39].

4.1. Genetic factors

Mutations in amyloid precursor protein, presenilin-1, and presenilin-2 genes can cause early-onset familial Alzheimer's disease that account for no more than 5% of all cases. The majority of AD cases are sporadic, with considerable heterogeneity in their risk profiles and neuropathological features.

4.1.1. Apolipoprotein E $\epsilon 4$ (*APOE* $\epsilon 4$)

The *APOE* $\epsilon 4$ allele is the only established susceptibility gene for both early- and late-onset Alzheimer's disease, and is a susceptibility gene, being neither necessary nor sufficient for the development of Alzheimer's disease. *APOE* $\epsilon 4$ is one of three common forms ($\epsilon 2$, $\epsilon 3$ and $\epsilon 4$) of the *APOE* gene, which provides the blue print for a protein that carries cholesterol in the bloodstream. Everyone inherits one form of the *APOE* gene from each parent. Those who inherit one *APOE* $\epsilon 4$ gene have increased risk of developing Alzheimer's disease and of developing it at an earlier age than those who inherit the $\epsilon 2$ or $\epsilon 3$ forms of the *APOE* gene [40]. Those who inherit two *APOE*- $\epsilon 4$ genes have an even higher risk. Unlike inheriting a known genetic mutation for Alzheimer's disease, inheriting one or two copies of this form of the *APOE* gene does not guarantee that an individual will develop Alzheimer's disease. The risk effect of the *APOE* $\epsilon 4$ allele decreases with increasing age, and after age 75, 15–20% of Alzheimer's cases are attributable to *APOE* genotype [41]. Several other genes have been examined as possible candidates, but the reports are sporadic, and the results are inconsistent [42].

However, not all $\epsilon 4$ -carriers develop dementia. Studies have demonstrated that high education, active leisure activities, or maintaining vascular health seems to reduce the risk of dementia related to *APOE* $\epsilon 4$ [40, 41]. The $\epsilon 4$ -carriers with these characteristics appear to have similar dementia-free survival time to non $\epsilon 4$ -carriers. Further, the obese related *FTO* gene may interact with *APOE* $\epsilon 4$ to increase the risk of Alzheimer's disease [44].

4.1.2. Family history

Individuals who have a parent, brother or sister with Alzheimer's are more likely to develop the disease than those who do not have a first-degree relative with Alzheimer's [45-47]. Those who have more than one first-degree relative with Alzheimer's disease are at even higher risk of developing the disease [48]. When diseases run in families, heredity (genetics), shared environmental and /or lifestyle factors or both may play a role.

4.2. Biological risk factors

Increasing age is a well-established risk factor for Alzheimer's disease. The incidence of Alzheimer's disease almost doubles with every 5 years of age [49, 50]. Female sex is often associated with an increased risk of AD, especially at the oldest-old age [25]. Men seem to be at greater risk for vascular dementia than women [51].

4.3. Vascular disorders and risk factors

A number of vascular risk factors and disorders have been linked to Alzheimer's disease, but some factors may have a differential association with the risk of Alzheimer's disease depending on the age when the exposure is assessed.

4.3.1. Blood pressure

Several studies have consistently reported an association between midlife high blood pressure and increased risk of dementia and Alzheimer's disease [52, 53]. Hypertension has been linked to neurodegenerative markers in the brain, suggesting that long-term high blood pressure may play a causal role in the neurodegenerative process itself or by causing brain atrophy. In very old people, the deleterious effect of high blood pressure is less evident, whereas low blood pressure seems to be predictive of dementia and Alzheimer's disease. As dementia has a long latent period, low blood pressure may be a sign of impending illness [54], which was confirmed by the longitudinal data from the Kungsholmen Project, suggesting the involvement of late life low blood pressure and cerebral hypo-perfusion in the development of dementia and Alzheimer's disease [55]. All these findings suggest that the relation of blood pressure to dementia may be age-dependent [25].

Recent follow-up studies have suggested that the protective effect of antihypertensive therapy on dementia and AD may depend on the duration of treatment and the age when people take the medications; the more evident efficacy was seen among young-old people (i.e., <75 years) and those with long-term treatment [56, 57]. Evidence from clinical trials of antihypertensive therapy and dementia is summarized in the section on intervention trials towards primary prevention. Antihypertensive treatment may protect against dementia and AD by postponing atherosclerotic process, reducing the number of cerebrovascular lesions, and improving cerebral perfusion [52]. It has also been suggested that some antihypertensive agents (e.g., calcium-channel antagonists) may have neuroprotective effects. The recent neuropathological study found substantially less Alzheimer neuropathological changes (i.e., neuritic plaque and neurofibrillary tangle densities) in the medicated hypertension group than non-hypertensive group, which may reflect a salutary effect of antihypertensive therapy against Alzheimer's disease-associated neuropathology [57].

4.3.2. Cardiovascular disease

A healthy heart helps ensure that enough blood is pumped through blood vessels to the brain. The follow-up data of the Cardiovascular Health Study showed that cardiovascular disease was associated with an increased risk of Alzheimer's disease, especially in people

with peripheral arterial disease [58], suggesting that extensive peripheral atherosclerosis is a risk factor for Alzheimer's disease. Other cardiovascular diseases, such as heart failure and atrial fibrillation, have been independently related to increased risk of dementia. In the Kungsholmen Project, heart failure was associated with a more than 80% increased risk of dementia and Alzheimer's disease [59].

4.3.3. *Cerebrovascular disease*

Cerebrovascular changes such as haemorrhagic infarcts, small and large ischemic cortical infarcts, vasculopathy, and white matter changes all increase the risk of dementia [13]. Systematic reviews of population-based studies reveal an approximately two- to four-fold increased risk of incident dementia associated with clinical stroke (post-stroke dementia). Multiple cerebral infarcts, recurrent and strategic strokes are main risk factors for post-stroke dementia. Silent stroke and white matter lesions detected on neuroimaging are associated with increased risk of dementia and cognitive decline. Spontaneous cerebral emboli were related to both AD and VaD. Some studies reported an association of stroke with Alzheimer's disease and cognitive decline [60]. Cerebral vascular lesions may interact with neurodegenerative lesions to produce a dementia syndrome in individuals not having sufficient neurodegenerative damages to express dementia [25]. Neuropathological studies suggested that cerebrovascular lesions, atherosclerosis, and neurodegenerative changes in the brain often coexist, and may be coincident processes converging to cause additive damage to the aging brain and to promote clinical expression of the dementia syndrome [61].

4.3.4. *Diabetes mellitus*

A potential link between diabetes and cognitive impairment was first reported more than 80 years ago. The association of diabetes with these cognitive changes is now well established [62]. There is substantial evidence suggesting that type 2 diabetes is associated with cognitive impairment involving both memory and executive function [63-65]. Several large longitudinal population-based studies have also shown that the rate of cognitive decline is accelerated in elderly people with type 2 diabetes [66]. An increased risk of not only vascular dementia but also neurodegenerative type dementia among persons with diabetes has been reported in several longitudinal studies [67-70], and the risk effect was confirmed by a systematic review [71]. Midlife diabetes or a longer duration of diabetes may play a crucial role in dementia and Alzheimer's disease [68, 72]. Overall, diabetes leads to a 20-70% greater decline in cognitive performance, and a 60% higher risk of dementia [73]. In addition, borderline or prediabetes or impaired glucose tolerance, is also linked to an increased risk of dementia and Alzheimer's disease in very old people [74].

4.3.5. *Overweight and obesity*

Similar to hypertension, recent studies suggested a lifespan-dependent relation of obesity with dementia [75, 76]. A higher body mass index (BMI) at middle age was related to an increased risk of dementia in late life [77, 78]. A greater decline in BMI approximately 10 years prior to dementia onset was detected, which is in line with the other studies suggesting an

association of accelerated BMI decline with Alzheimer's disease [79, 80]. Low BMI in late life and weight loss may be related to high risk of dementia and Alzheimer's disease [81], but low BMI and weight loss can be interpreted as markers of preclinical Alzheimer's disease, especially when measured less than 10 years prior to clinical diagnosis [25]. In line with these findings, several follow-up studies of older people suggested that accelerated decline in BMI was associated with future development of Alzheimer's disease [79, 82, 83]. Low BMI in late life was related to a higher risk for Alzheimer's disease over a subsequent 5- to 6-year period [81]. Thus, late-life low BMI and weight loss can be interpreted as markers for preclinical Alzheimer's disease, particularly when measured just a few years prior to clinical diagnosis of the disease [17].

4.3.6. *Hyperlipidaemia*

An association of elevated cholesterol at middle life with increased risk of late-life Alzheimer's disease was reported in some studies [53]. Controversial findings have also been reported on the relation of cholesterol in late life to dementia risk. Some cohort studies found no association or even an inverse association of total cholesterol with dementia risk [84]. A study showed a decline in total cholesterol at least 15 years before dementia onset [85]. Recently, a bidirectional cholesterol-cognition relationship has been reported. High midlife cholesterol was associated with poorer late-life cognition, but decreasing cholesterol after midlife may reflect poorer cognitive status [86].

4.3.7. *The metabolic syndrome*

Instead of exploring the effect of its subcomponents, several studies have assessed the relationship between metabolic syndrome as a whole and the risk of Alzheimer's disease or cognitive decline. A clustering of interrelated metabolic risk factors such as diabetes, obesity, hypertension and dyslipidaemia has received increasing attention in the past few years. Several components of the metabolic syndrome have been individually related to cognitive outcomes. A prospective study found that the metabolic syndrome contributed to cognitive decline [87]. But this finding was not confirmed in a population of the oldest old. The concept of the metabolic syndrome may be less valid in this age group [88]. Finally, two studies showed that metabolic syndrome was associated with an increased risk of Alzheimer's disease [89, 90].

4.3.8. *Alcohol consumption*

Excessive alcohol intake can cause alcoholic dementia and may increase the risk of vascular dementia. Heavier alcohol intake at middle age was associated with increased risk of late-life dementia [91]. By contrast, increasing evidence suggests that light to moderate alcohol consumption may be associated with a reduced risk of dementia and cognitive decline [92], a similar effect as observed for cardiovascular disease [25]. In a meta-analysis of 15 prospective studies on the effect of alcohol on dementia risk, light to moderate alcohol consumption was associated with a reduction in the risk of Alzheimer's disease and dementia [93]. However, the role of moderate alcohol consumption in dementia still remains controversial be-

cause the inverse association may be due to information bias, the confounding of healthy lifestyles and high socioeconomic status, different approaches in assessments of alcohol consumption, or outcome misclassification.

4.3.9. *Cigarette smoking*

The relationship between smoking and cognitive decline remains uncertain. Case-control studies have largely suggested that smoking lowers the risk of Alzheimer's disease [13]. Some prospective studies have found an increased risk of Alzheimer's disease associated with smoking [94]. A meta-analysis that examined the association between smoking and Alzheimer's disease while accounting for tobacco-industry affiliation found that the combined results of 18 cross-sectional studies without industry affiliations yielded no association [95]. Analysis of 14 cohort studies without tobacco-industry affiliations yielded a significant increase in the risk of Alzheimer's disease [13]. In the Kungsholmen Project, smoking affected survival in Alzheimer's disease cases more than in non-demented subjects, and the protective effect of smoking on the Alzheimer's disease was no longer present when incident Alzheimer's cases were studied [7] suggesting that previously reported association of cigarette smoking with low prevalence of dementia was probably due to survival bias.

4.3.10. *Diet and nutrients*

Diets high in fish, fruits and vegetables are high in anti-oxidants and polyunsaturated fatty acids (PUFAs). In some observational studies, high or supplementary intake of vitamins C, E, B6, B12, and folate has been related to a decreased risk of Alzheimer's disease [96, 97]. Indeed, low levels of B12 and folate were found to be related to an increased risk of Alzheimer's disease in a study from the Kungsholmen Project [98]. Investigations on the effect of dietary PUFAs on the risk of cognitive dysfunction proved inconclusive. Several studies showed that the consumption of PUFAs led to reduction in the risk of Alzheimer's disease and dementia, mild cognitive impairment [99]. Population-based studies suggested that moderate to high intake of unsaturated fats at midlife is protective, whereas a moderate intake of saturated fats may increase the risk of dementia and Alzheimer's disease [100, 101], especially among *APOE* ϵ 4 carriers [102, 103]. Fatty acids may affect dementia through various mechanisms such as atherosclerosis and inflammation. Adherence to 'Mediterranean diet' (higher intake of fish, fruits, and vegetables rich in antioxidants) was associated with a reduced risk of Alzheimer's disease independent of vascular pathways [104].

4.4. **Psychosocial factors**

Psychological factors include social economic status, education attainment in early life, and work complexity in adult-life and leisure activities. Evidence from epidemiological research has been accumulating that some psychosocial factors and healthy lifestyle may postpone the onset of dementia, possibly by enhancing cognitive reserve.

4.4.1. Social economic status

A number of studies have found that higher socioeconomic status (SES) is associated with a reduced risk of developing Alzheimer's disease [105-107]. In most of these studies, SES was assessed based on occupational attainment, current income to reflect socioeconomic level in adulthood, or educational attainment. Findings from a prospective study, however, suggested that early life socioeconomic status assessed at the household or community level was related to level of cognition in late life but not to rate of cognitive decline or risk of Alzheimer's disease [47].

4.4.2. High education

Numerous longitudinal studies have consistently shown that a higher educational achievement in early life is associated with a decreased incidence of dementia, and of Alzheimer's disease in particular. Low dementia prevalence among highly educated persons has been reported by numerous surveys. Educational attainment and lifespan mental activity associated with childhood education may reduce the risk of dementia [25]. The cognitive reserve hypothesis has been proposed to interpret this association such that education could enhance neural and cognitive reserve that may provide compensatory mechanisms to cope with degenerative pathological changes in the brain, and therefore delay onset of the dementia syndrome [17]. Alternatively, educational achievement may be a surrogate or an indicator of intelligent quotient, early life living environments, and occupational toxic exposure experienced over adulthood [108].

4.4.3. Physical activity

Basic science and observational evidence on humans strongly supports the hypothesis that increased physical activity prevents the onset of dementia. Regular exercise, even low-intensity activity such as walking, has been associated with reduced risk of dementia and cognitive decline [109-111]. In the Kungsholmen Project, the component of physical activity presenting in various leisure activities, rather than sports and any specific physical exercise, was related to a decreased dementia risk [110]. A strong protective effect of regular physical activity in middle age against the development of dementia and Alzheimer's disease in late life was reported, especially for persons with the *APOE* ϵ 4 allele [112]. As it may take years to achieve high levels of physical fitness, brief periods of exercise training may not have substantial benefits on cognitive processes, but could still be detectable in the subsets of cognitive domains that are more sensitive to the age related decrements. Physical activity is important not only in promoting general and vascular health, but also in promoting brain plasticity, and it may also affect several gene transcripts and neurotropic factors that are relevant for the maintenance of cognitive functions. There is now increasing amounts of trial evidence to support this hypothesis in terms of cognitive benefits in healthy older adults as well as in people at risk for dementia. However, to date there are no RCTs confirm that increased physical activity prevents dementia.

4.4.4. *Mentally stimulating activity*

Various types of mentally demanding activities have been examined in relation to dementia and AD, including knitting, gardening, dancing, playing board games and musical instruments, reading, social and cultural activities, and watching specific television programs, which often showed a protective effect [113]. Due to the cultural and individual differences in choosing specific activities, some researchers summarize mentally stimulating activities into a composite score, which showed that a cognitive activity score involving participation in seven common activities with information processing as a central component was associated with a reduced risk of AD, even after controlling for APOE ϵ 4 allele, medical conditions, and depressive symptoms [114, 115]. The Swedish Twin Study showed that greater complexity of work, and particularly complex work with people, may reduce the risk of Alzheimer's disease [116]. The Canadian Study of Health and Aging found that high complexity of work appeared to be associated with a reduced risk of dementia, but mostly for vascular dementia [117]. In supporting of these findings, the recent neuroimaging study suggested that a high level of complex mental activity across the lifespan was correlated with a reduced rate of hippocampal atrophy [118].

4.4.5. *Social network and social engagement*

A poor social network or social disengagement in late life was associated with an elevated risk of dementia. Evidence from longitudinal observational studies suggests that a poor social network or social disengagement is associated with cognitive decline and dementia [119, 120]. The risk for dementia and AD was also increased in older people with increasing social isolation and less frequent and unsatisfactory contacts with relatives and friends. Furthermore, low social engagement in late life and a decline in social engagement from middle age to late life were associated with a doubly increased risk of developing dementia and AD in late life. Rich social networks and high social engagement imply better social support, leading to better access to resources and material goods [123]. Rich and large social networks also provide affective and intellectual stimulation that could influence cognitive function and different health outcomes through behavioural, psychological, and physiological pathways [122]. Finally, a recent study suggested that low neuroticism in combination with high extraversion was the personality trait associated with the lowest dementia risk, and among socially isolated individuals even low neuroticism alone seemed to decrease the risk of dementia [121].

4.4.6. *Depression*

Recent evidence suggests a strong relationship between depression and Alzheimer's disease. A lifetime history of major depression has been considered as a risk factor for later development of Alzheimer's disease [124, 125]. The presence of depressive symptoms can affect the conversion of mild cognitive impairment to Alzheimer's disease. Neuronal plaques and neurofibrillary tangles, the two major hallmarks of Alzheimer's disease brain, are more pronounced in the brains of Alzheimer's disease patients with comorbid depression as compared with Alzheimer's disease patients without depression. On the other hand, neuro-

degenerative phenomena have been observed in different brain regions of patients with a history of depression. Recent evidence suggests that molecular mechanisms and cascades that underlie the pathogenesis of major depression, such as chronic inflammation and hyper-activation of hypothalamic–pituitary–adrenal (HPA) axis, are also involved in the pathogenesis of Alzheimer's disease [125]. A recent study has shown that depression increased the risk of dementia among patients with diabetes [126].

4.5. Other factors

4.5.1. Inflammation

Inflammation is known to be involved in the atherosclerotic process. Thus, serum inflammatory makers may be associated with dementia. Some cohort studies found such an association, and C-reactive protein may be the most promising in predicting dementia risk [127]. In addition, long-term use of non-steroidal anti-inflammatory drugs was suggested to be associated with a lower risk of AD [25].

4.5.2. Hormone replacement therapy

Hormone replacement therapy in postmenopausal women has been frequently reported to be associated with a lower risk of AD. An association between hormone replacement therapy and a reduced risk of dementia and Alzheimer's disease among postmenopausal women had been frequently reported in numerous observational studies until 2004 when, instead of a protective effect, a significantly increased risk of dementia associated with estrogenic therapy was found in the Women's Health Study [128].

4.5.3. Occupational exposures

Manual work involving goods production has been associated with an increased risk of AD and dementia. Occupation and occupational exposures (e.g., electromagnetic fields and heavy metals) may play a role in dementia and Alzheimer's disease [129, 130]. Data from the Kungsholmen Project showed that manual work involving goods production was associated with an increased risk of dementia and Alzheimer's disease [130], and specifically a risk effect was detected with electromagnetic exposure [129]. Occupational exposure to extremely-low-frequency electromagnetic fields (ELF-EMF) has been related to an increased risk of dementia and AD in a number of follow-up studies [129, 131]. The meta-analysis of epidemiological evidence suggests an association between occupational exposure to ELF-EMF and AD [132].

4.5.4. Head trauma and traumatic brain injury

For many years, head trauma has been suggested as a possible risk factor for Alzheimer's disease, and it has been extensively investigated in several studies, but this possible association still remains controversial. Moderate head injuries are associated with twice the risk of developing Alzheimer's compared with no head injuries, and severe head injuries are asso-

ciated with 4.5 times the risk [133, 134]. Moderate head injury is defined as a head injury resulting in loss of consciousness or post-traumatic amnesia lasting more than 30 minutes; if either of these lasts more than 24 hours, the injury is considered severe. These increased risks have not been shown for individuals experiencing mild head injury or any number of common mishaps, such as bumping one's head while exiting a car. Groups that experienced repeated head injuries, such as boxers, football players and combat veterans, may be at increased risk of dementia, late-life cognitive impairment and evidence of tau tangles (a hallmark of Alzheimer's) at autopsy [135-138]. Additional research is needed to better understand the association between brain injury and increased risk of Alzheimer's disease.

5. Summary of evidence from systematic review

Meta-analyses and systematic reviews have provided robust evidence that cognitive reserve (a concept combining the benefits of education, occupation, and mental activities) [139], physical activity and exercise [140, 141], midlife obesity [142], alcohol intake [93], and smoking [142] are the most important modifiable risk factors for Alzheimer's disease. There is insufficient overall evidence from epidemiological studies to support any association between dietary or supplementary antioxidant or B vitamins and altered risk of incident dementia [143, 144]. Data from several independent time points from a large Swedish epidemiological study suggest that better social networks and social activities might be associated with reduced incidence of Alzheimer's disease [119], but this has not been examined systematically in other large epidemiological cohorts [61].

Many treatable medical conditions have also been associated with an increased risk of Alzheimer's disease, including stroke [145], diabetes [146], midlife hypertension [52], and midlife hypercholesterolemia [147, 148]. Blood pressure and cholesterol both seem to be reduced in late life and in the prodromal to Alzheimer's disease; thus, the difference between midlife and late life is an important distinction. There is probably an important relation between some of these conditions and the lifestyle factors mentioned previously, and interventions to promote healthy living will probably reduce the incidence of diabetes and stroke as well as having other, more direct, effects on dementia. There is limited evidence about the potential effect of management of diabetes or stroke on the risk of subsequent dementia, more intervention trials on this topic are needed (Table 1) [61,149].

Less than two decades have passed since the first incidence data for Alzheimer's disease and other dementias were reported, during which there have been many achievements in the understanding of risk and protective factors of Alzheimer's disease. Accumulated evidence from epidemiological research strongly supports a role for lifestyle and cardiovascular risk factors in the pathogenesis and development of dementia. However, none of these factors has been proven to have a causal relation specifically with Alzheimer's disease. Indeed, this topic is further complicated by the fact that the traditional diagnosis of dementia subtypes has been challenged by population-based neuropathological and neuroimaging studies. Research has shown a range of dementia-associated brain abnormalities from pure vascular le-

sions at one end to pure Alzheimer's pathologies at the other, with most dementia cases being attributable to both vascular disease and neurodegeneration.

Factors	Systematic review	Results
Overweight and obesity	Meta-analysis of ten studies. Sixteen articles on 15 prospective studies with 3.2–36 years follow-up	Overweight: Dementia RR 1.26 (95% CI 1.10–1.44); Alzheimer's disease 1.35 (95% CI 1.19–1.54) Obesity: Dementia RR 1.64 (95% CI 1.34–2.00); Alzheimer's disease RR 2.04 (95% CI 1.59–2.62)
Smoking	Meta-analysis of four prospective studies with 2–25 years follow-up in over 17 000 people. In the four studies the dementia ORs were 3.17 (95% CI 1.37–7.35), 1.42 (1.07–1.89), 1.60 (1.00–2.57), and 1.63 (1.00–2.67)	Dementia RR 2.2 (95% CI 1.3–3.6)
Physical activity	13 prospective studies focusing on Alzheimer's disease, dementia, or both, with at least 150 000 participants	Dementia RR 0.72 (95% CI 0.60–0.86); Alzheimer's disease 0.55 (95% CI 0.36–0.84)
Cognitive reserve (intelligence, occupation, and education)	22 prospective studies with at least 29 000 participants followed up for a median of 7.1 years	Dementia OR 0.54 (95% CI 0.49–0.59)
Alcohol	15 longitudinal studies with 2–8 years follow-up and at least 14 000 participants	Dementia RR 0.74 (95% CI 0.61–0.91); Alzheimer's disease 0.72 (0.61–0.86)
Medical conditions		
Midlife hypertension	At least 15 years follow-up in most studies, with at least 16 000 participants	Four of five longitudinal studies focusing on midlife hypertension suggested that it is a significant risk factor for incident dementia (RR 1.24–2.8 in different studies) The biggest differences were reported in studies using 160/95 mm Hg as the threshold for hypertension
Stroke	16 studies with at least 25 000 participants, mainly included patients aged 65 years and over	12 of 16 studies showed significant association between stroke and incident dementia, with overall doubling of incidence
Diabetes	15 prospective cohort studies	Dementia RR 1.47 (95% CI 1.25–1.73); Alzheimer's disease RR 1.39 (95% CI 1.16–1.66)

Factors	Systematic review	Results
Midlife hypercholesterolemia	18 studies, but only five assessed high cholesterol specifically in midlife. All five midlife studies had over 15 years follow-up and a total of over 15 000 participants	Four of five longitudinal studies in midlife suggested a significant positive association between high total cholesterol and incident dementia. For overall difference the RR was 1.4–3.1
Intervention studies		
Hypertension	12 091 participants between the three trials (SHEP, SYST-EUR, and SCOPE) with mean follow-up of 3.3 years. Only SYST-EUR reported significant benefit	OR 0.89 (95% CI 0.69–1.16) for incident dementia
Statins for prevention of dementia	26 340 participants between the two trials (PROSPER and HPS), with follow-up of 3.2 and 5 years. Cognition was measured with different instruments at different timepoints	Neither of the two trials reported significant benefit of statin therapy
Vitamins B12 or folic acid	Four trials in older people without existing cognitive impairment	Three trials showed no benefit. One trial (the only that selected participants based on increased homocysteine) reported benefit with respect to global function

RR=relative risk. OR=odds ratio. SHEP=Systolic Hypertension in the Elderly Program. SYST-EUR=Systolic Hypertension in Europe. SCOPE=Study on Cognition and Prognosis in the Elderly. PROSPER=PROspective Study of Pravastatin in the Elderly at Risk. HPS=Heart Protection Study.

Table 1. Meta-analyses or systematic reviews of risk factors for dementia and Alzheimer's disease [61,149]

Population studies have identified many factors that could be important in reducing the risk of dementia, including factors that identify people at risk for dementia (vascular risk factors, depressive symptoms) and factors that may reduce the risk of dementia (cognitive, physical, and social activity, a diet rich in antioxidants and polyunsaturated fatty acids, vascular risk factor control). While early interventional studies have been less conclusive, future trials should continue to examine the effect of risk factor modification on cognitive outcomes. In particular, interventions that combine a number of factors, such as healthy nutrition along with cognitive, social, and physical activity, should be investigated. In the most optimistic view, dementia could be delayed or even prevented by these interventions. At worst, people will improve their overall health, especially their cardiovascular health, and enjoy a more cognitively and socially engaging life.

5.1. Intervention strategies against Alzheimer's disease

Despite the specific challenges posed by neurological disorders, such as Alzheimer's disease and other dementias, interventions need to be implemented to verify findings from the

many population-based observational studies, which suggest that preventive and therapeutic interventions have great potential [150].

5.1.1. Vascular factors and related disorders

Most vascular risk factors and related disorders are modifiable or treatable that can serve as targets in the development of primary preventative strategies against dementia. For example, antihypertensive therapy has been shown to reduce the risk of dementia in observational studies, and this finding was partly confirmed by clinical trials. Furthermore, studies have confirmed that obesity and diabetes can be prevented by changing dietary habits and lifestyles, and that health education may help quit smoking. Finally, preventing recurrent cerebrovascular disease and maintaining sufficient cerebral blood perfusion seems to be critical for postponing expression of the dementia syndrome in older people. Thus, controlling high blood pressure and obesity, especially from middle age, and preventing diabetes and recurrent stroke could be the primary preventive measures against late-life dementia.

5.1.2. Intervention towards psychosocial factors and lifestyles

High educational achievements in early life can provide cognitive reserve that benefits the whole life in terms of cognitive health and delaying the onset of late-life dementia. Extensive social networks and active engagements in intellectually stimulating activities such as reading, doing crosswords, and playing board games may significantly lower the risk of dementia by providing cognitive reserve or by reducing psychosocial stress. It is likely that mentally and socially integrated lifestyles could postpone the onset of dementia [119]. Regular physical exercise may reduce the risk of the dementias resulting from cerebral atherosclerosis. Leisure activities with all three components of physical, mental, and social activities may have the most beneficial effect on dementia prevention. Many of the risk factors for dementia, such as hypertension, diabetes, and obesity, may be modified by diet. In addition, a diet high in antioxidants may reduce inflammation, which is associated with the risk of dementia. Thus, it is reasonable to suggest that the risk of dementia itself could be modified by diet. The treatment of depression also seems to improve cognitive function in people who are depressed. Taking together, the most promising strategy for the primary prevention of dementia may be to encourage people implementing multiple preventative measures throughout the life course, including high educational attainment in childhood and early adulthood, an active control of vascular factors (e.g., smoking) and disorders (e.g., hypertension and diabetes) in adulthood, and maintenance of mentally, physically, and socially active lifestyles during middle age and later in life.

6. Conclusions

Alzheimer's disease is a major cause of functional dependence, institutionalisation, and mortality among elderly people. Population-based studies have made a great contribution to our knowledge of Alzheimer's disease. Although many aspects of Alzheimer's disease are

still unclear, we are now able to make more accurate diagnoses than before, and the pattern of dementia distribution has been sufficiently described to guide the planning of medical and social services. Epidemiological studies have shown that vascular risk factors in middle age and later in life significantly contribute to the development and progression of the dementia syndrome, whereas extensive social network and active engagement in social, physical, and mental activities may delay the onset of the dementing disorders. Hence, one of the promising strategies to deal with the tremendous challenge from the epidemic of dementia is to implement appropriate intervention measures from a life-course perspective. Achieving high education in early life and engaging mentally stimulating activity over adulthood to enhance cognitive reserve, and maintaining vascular health by adopting healthy lifestyles and optimally controlling vascular diseases to reduce the burden of vascular lesions in the brain. These preventive measures will enable people to maintain cognitive ability in late life, even though they may have developed a high load of Alzheimer pathologies in their brain.

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Author details

Weili Xu^{1,2*}, Camilla Ferrari^{2,3} and Hui-Xin Wang²

*Address all correspondence to: weili.xu@ki.se

1 Department of Epidemiology, Tianjin Medical University, Tianjin, P.R., China

2 Aging Research Center, Karolinska Institutet-Stockholm University, Stockholm, Sweden

3 Department of Neurological and Psychiatric Sciences, University of Florence, Italy

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