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Review

Aging without Dementia is Achievable: Current Evidence from Epidemiological Research

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Abstract. Both the incidence and the prevalence of dementia increase exponentially with increasing age. This raises the question of whether dementia is an inevitable consequence of aging or whether aging without dementia is achievable. In this review article, we sought to summarize the current evidence from epidemiological and neuropathological studies that investigated this topic. Epidemiological studies have shown that dementia could be avoided even at extreme old ages (e.g., centenarians or supercentenarians). Furthermore, clinico-neuropathological studies found that nearly half of centenarians with dementia did not have sufficient brain pathology to explain their cognitive symptoms, while intermediate-to-high Alzheimer pathology was present in around one-third of very old people without dementia or cognitive impairment. This suggests that certain compensatory mechanisms (e.g., cognitive reserve or resilience) may play a role in helping people in extreme old ages escape dementia syndrome. Finally, evidence has been accumulating in recent years indicating that the incidence of dementia has declined in Europe and North America, which supports the view that the risk of dementia in late life is modifiable. Evidence has emerged that intervention strategies that promote general health, maintain vascular health, and increase cognitive reserve are likely to help preserve cognitive function till late life, thus achieving the goal of aging without dementia.

Keywords: Aging, Alzheimer's disease, centenarians, dementia, epidemiology, interventions

INTRODUCTION

Dementia is a clinical syndrome related to brain disorders characterized by the development of cognitive deficits that are severe enough to interfere with daily social and occupational functioning. Clinically, Alzheimer's disease (AD) is the most common type of dementia (∼50%–70%), followed by vascular dementia (∼20%–25%), although neuropathological and neuroimaging studies have revealed that the total burden of mixed brain vascular and neurodegenerative pathologies is the most common cause of dementia symptoms, especially among very old people [1]. There is currently neither a cure nor a disease-modifying therapy for AD or dementia. Advanced age or living longer is the strongest risk factor for dementia; after 65 years of age, both the prevalence and the incidence of dementia double approximately every 5–6 years until age 90, and ∼30% of people aged ≥85 years might be affected

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by dementia [1, 2]. In addition, ~80% of dementia cases occur in people aged ≥75 years [1, 3]. Furthermore, several studies have repeatedly shown that both the prevalence and the incidence of dementia steadily increase with age even in the extreme old ages (e.g., age ≥95 years) [4, 5]. This is a critical issue for public health and health policy development given the fact that the oldest old people (e.g., octogenarians, nonagenarians, and centenarians) are the fastest growing segment of the population, and that dementia has already posed a huge burden to our aging society. In 2015, dementia affected ~47 million people worldwide, with the annual global cost being US$818 billion [6].

In the past decades, the view that dementia is an inevitable consequence of aging has been challenged by findings from multidisciplinary research. In this narrative review article, we briefly summarize current evidence from epidemiological and neuropathological studies supporting the contrary: that aging without dementia is achievable.

NOT ALL VERY OLD PEOPLE DEVELOP DEMENTIA

Occurrence of dementia in centenarians

The exponential increases in both the incidence and the prevalence of dementia with increasing age until very advanced ages make the public assume that dementia is inevitable for individuals who are able to survive to 100 years and older. Although the oldest old adults are the fastest growing segment of the population, both the absolute number and proportion of centenarians remain relatively small in the population; in 2016, there were 0.5 million centenarians in the world, accounting for ~7.5% of people aged ≥65 years [7]. People living a century and beyond have neared the extreme limits of human life while escaping or delaying the major age-related diseases. Thus, these extraordinary individuals embody the best model to address the crucial question concerning whether cognitive decline still increases in extreme old age [8]. However, very few population-based studies have a sufficiently large sample size to provide reliable estimates of dementia prevalence among centenarians. Some reports, usually with very small samples (e.g., $n < 20$), indeed showed that all the examined centenarians appeared to be demented [9]. However, systematic reviews of studies with large samples of centenarians (e.g., $n \geq 100$) indicate that dementia prevalence varies between 45% and 70%, and that male centenarians are more likely to be cognitively intact than their female contemporaries [8–14] (Table 1). Notably, the large-scale Danish Centenarians Study ($n = 207$) showed that around one-third of centenarians were classified as having either no signs of dementia at all (25%) or probably no dementia (12%) [13]. The Sydney study of near-centenarians and centenarians ($n = 200$) showed that only 40% of participants (mean age, 97.4 years) were impaired on both global cognitive and physical functioning [15]. This suggests that even among centenarians a considerable proportion is able to escape dementia, or that the clinical expression of dementia syndrome has been markedly delayed until the very end of exceptionally long lives. In addition, a large-scale electronic health records-based study in the UK ($n =$ ~11,000 centenarians) found that dementia was recorded in only 11% of people who reached 100 years of age [16]. While dementia may be underdiagnosed in medical records,

Table 1
Prevalence of dementia among centenarians: a summary of major population-based studies

Authors (country)	Study sample	Diagnostic criteria	Prevalence
Samuelsson et al. (Sweden) [10]	Swedish Centenarian Study: $n = 100$, 82% Women	DSM-III	27% (men 16%, women 30%)
Ravaglia et al. (Northern Italy) [11]	Northern Italy Centenarian Study: $n = 92$, 59% women	DSM-IV	61.9% (men 50.0%, women 69.6%)
Gondo et al. (Tokyo, Japan) [12]	Tokyo Centenarian Study: $n = 304$, 78.6% women	CDR ≥1	61.8% (men 41.5%, women 67.4%)
Andersen-Ranberg et al. (Denmark) [13]	Longitudinal Study of Danish Centenarians: $n = 207$, 78.3% women	ICD-10, CDR	50.7%
Richmond et al. (Australia) [14]	A convenience sample of centenarians, $n = 188$, 80% women	MMSE score <21	20.1% (men 15.6%, women 21.2%)

CDR, Clinical Dementia Rating; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; MMSE, Mini-Mental State Examination.

results of this study may also suggest that centenarians as a selective group have a lower risk of certain age-related diseases such as dementia.

Data on the incidence of dementia among centenarians are sparse. The meta-analysis of population-based studies suggested that the pace of increasing incidence of AD and dementia with age slowed at advanced ages [17]. This was supported later by two population-based studies of octogenarians and even older adults, which suggested that the incidence of dementia continued to increase beyond age 90, but the rate of increase slowed or plateaued thereafter [18, 19]. These results suggest that the risk of dementia in the oldest old adults might not be related to the aging process itself.

Thus, current evidence from both prevalence and incidence studies of dementia appears to suggest that dementia is not an inevitable consequence of extreme old ages [15]. It is worth noting that studies of dementia in centenarians face methodological challenges such as small sample sizes, lack of representativeness of the population, high attrition rate, and difficulties in the cognitive assessment and accurate diagnosis of dementia [8, 20, 21].

Alzheimer pathologies in the brains of centenarians and older adults

Postmortem studies revealed that the brains of most centenarians exhibited extensive co-occurrence of multiple pathologies such as arteriolosclerosis, Alzheimer pathologies, hippocampal sclerosis, Lewy body pathology, and cerebral amyloid angiopathy, while Alzheimer pathology was not universal (∼60% with "moderate" neuritic amyloid plaque densities) [22, 23]. These findings are similar to those from octogenarians and nonagenarians [24]. Supercentenarians (age ≥110 years) are extremely rare in the world population (∼50 living supercentenarians in 2016, http://www.grg.org). Neuropathological data on four Japanese supercentenarians showed that the brain shapes and weights in the gross neuropathological findings were well preserved and that there was only mild frontal or temporal lobe atrophy in all cases [25]. Further, three cases showed an intermediate load of Alzheimer pathologies, and one was characterized as primary age-related tauopathy, but neither Lewy body pathology nor hippocampal sclerosis was observed. Finally, all four cases exhibited relatively mild cerebral atherosclerosis (e.g., brain infarcts) and arteriolosclerosis (e.g., small vessel diseases). Thus, neuropathological alterations associated with aging appeared to be relatively mild to moderate in the brains of centenarians and even supercentenarians. Population-based neuroimaging data (e.g., amyloid PET/CT images) also showed that exceptional aging without Alzheimer pathophysiology seemed possible in individuals with multiple protective factors over their lifespans [26]. This suggests that certain mechanisms may protect against the neuropathological evolution of brain aging.

Given that mixed brain pathologies are common at the oldest old or extreme old ages and that ∼30% of centenarians show no symptoms of cognitive impairment or dementia, additional mechanisms such as cognitive reserve may help these people escape dementia symptoms [27]. Clinico-neuropathological studies support the role of cognitive reserve in centenarians. For instance, data from the Nun Study and the 100-Plus Study showed that some centenarians appeared to have no or minimal cognitive symptoms or dementia despite extensive neuropathologies in the brain [28, 29]. Reserve capacity can be built over a lifespan through high education, mentally complex jobs, leisure activities, and social engagement [30]. This suggests that dementia risk is potentially modifiable even in extreme old ages, which supports the view that dementia is not an inevitable consequence of aging.

TIME TRENDS IN OCCURRENCE OF DEMENTIA

In the last decade, there has been increasing interest in investigating secular trends in the incidence and the prevalence of dementia. A scenario concerning the past 3–4 decades has emerged from systematic reviews suggesting that the age-specific prevalence and incidence of dementia may have declined in Europe and North America but increased in Asian countries [1, 31].

Secular trends in prevalence of dementia

Despite differences in methodological aspects across studies, the primary evidence from systematic reviews of population-based studies generally shows a stable or decreasing prevalence of dementia in Europe and North America [32–48] (also [1] and [31] for detailed references) (Table 2). Repeated cross-sectional surveys in Spain suggested that the prevalence of dementia was stable in women but decreased in men from 1988 to 1994 [35]. In Sweden, population-based surveys showed that since the

Table 2
Key findings from major population-based studies on time trends in prevalence of dementia

Authors (country)	Study population and study periods	Diagnostic criteria	Trends in prevalence
North America			
Hall et al. (Indiana, US) [32]	Indianapolis-Ibadan Dementia Project, age ≥65, 1992 to 2001	Dementia: ICD-10	Stable (African-Americans)
Kosteniuk et al. (Saskatchewan, Canada) [33]	Age ≥45, 2005–2006 to 2012–2013, annual prevalence	Dementia: Medical records (ICD-9, 10)	Increased
Langa et al. (US) [34]	US Health and Retirement Study, age ≥65, 2000 to 2012	Dementia: validated self-report	Decreased
Europe			
Lobo et al. (Zaragoza, Spain) [35]	Zaragoza Study, age ≥65, 1988–1989 to 1994–1996	Dementia: DSM-IV	Overall stable; decreased in men
Qiu et al. (Stockholm, Sweden) [36]	Kungsholmen Projects, age ≥75, 1987–1989 to 2001–2004	Dementia: DSM-III-R	Stable
Wiberg et al. (Gothenburg, Sweden) [37]	Gothenburg Study, age 70, 1976–1977 to 2000–2001	Dementia: DSM-III-R	Stable
Matthews et al. (England, UK) [38]	CFAS, age ≥65, 1989–1994 to 2008–2011	Dementia: Geriatric Mental State Scale	Decreased
Wimo et al. (Nordanstig, Sweden) [39]	Nordanstig Projects, age ≥78, 1995–1998 to 2001–2003	Dementia: DSM-III-R	Decreased (north rural areas)
Doblhammer et al. (Germany) [40]	Health insurance claims database, age ≥65, 2007–2009	Dementia, ICD-10	Decreased, mainly in women
Pérès et al. (Bordeaux, France) [41]	PAQUID, age ≥65, 1988–1989 to 2007–2008	Dementia: Clinical: DSM-III-R	Clinical diagnosis: increased
		Algorithm	Algorithm-based diagnosis: decreased
Ahmadi-Abhari et al. (England and Wales, UK) [42]	English Longitudinal Study of Ageing, age ≥50, 2002 to 2013	Dementia: DSM-IV	Decreased
Skoog et al. (Gothenburg, Sweden) [43]	Gothenburg 85-year-old study, age 85, 1986–1987 to 2008–2010	Dementia: DSM-III-R	Decreased
Asia			
Li et al. (Beijing, China) [44]	Urban residents, age ≥60, 1986 to 1997, 2 waves	Dementia: ICD-10, DSM-IV	Increased
Yu et al. (Hong Kong, China) [45]	Systematic review, age ≥70, 1995–2006	Dementia: ICD-9, 10	Increased
Chan et al. (Mainland China) [46]	Systematic review, age ≥55, 1990 to 2010	Dementia and AD: various criteria	Increased
Kim et al. (Korea) [47]	Systematic review, age ≥60, 1990 to 2013	Dementia, AD: various criteria	Increased slightly, especially AD
Ohara et al. (Hisayama, Japan) [48]	Hisayama Study, age ≥65, from 1985, 1992, 1998 and 2005 to 2012	Dementia: DSM-III-R	Increased

AD, Alzheimer's disease; ICD, International Classification of Diseases; DSM, Diagnostic and Statistical Manual of Mental Disorders; CFAS, Cognitive Function and Ageing Studies.

1970s the prevalence of dementia had been relatively stable [36, 37] or decreasing [39, 43]. In the United Kingdom, a large-scale study of community residents suggested a cohort effect on the age-specific prevalence of dementia such that later-born cohorts had a lower likelihood of dementia than those born earlier in the twentieth century [38]. This was supported by a modelling study of the English Longitudinal Study of Aging, which demonstrated that in England and Wales, the age- and sex-standardized prevalence of dementia declined from 2002 to 2013 [42]. In France, the PAQUID Study suggested that the prevalence of dementia increased from 1988 to 2008 when dementia was diagnosed according to clinical criteria, but decreased when dementia was defined using an algorithm [41]. The Danish study also suggested that from 1998 to 2010 more people lived into advanced ages (e.g., nonagenarians) with better cognitive functioning [49]. In the United States, studies have shown either a relatively stable or declining age-adjusted prevalence of dementia and cognitive impairment in the past 3–4 decades [32, 34, 50]. In Canada, an increased age-standardized prevalence of dementia was reported, along with a decline in incidence, which suggests that the survival of patients with dementia may have improved over time [33].

By contrast, in the Asia-Pacific regions, systematic reviews showed that the prevalence of AD and

other dementias in mainland China had increased steadily from the 1990s to 2010 across all age groups of people aged 55+ years [46], although the secular trends might be partly due to certain methodological variations over time (e.g., diagnostic procedure, the defining criteria, and the study settings) [51]. In Hong Kong, China, systematic review revealed that the prevalence of clinical dementia among people aged 70+ years doubled from 1995 (4.5%) to 2006 (9.3%) [45]. While studies that explore the time trends of dementia prevalence in geographically defined populations in China are still lacking, there is evidence suggesting that the prevalence of global cognitive impairment increased from 1998 to 2008 among the oldest old people [52]. In Japan, the Hisayama Study suggested that the age-specific prevalence of dementia, and AD in particular, has markedly increased from the 1980s to the 2010s, driven largely by an increasing incidence and improved survival of people with AD [48]. The increasing prevalence of dementia in Japan was supported by a systematic review even when carefully taking the main methodological variations into consideration [53]. Finally, a systematic review suggested a slight increase in the prevalence of dementia in the past 20 years in Korea, characterized by an increase in AD prevalence but a decrease in the prevalence of vascular dementia [47].

Secular trends in incidence of dementia

While the time trends in the prevalence of dementia over time are determined by trends in the incidence of dementia and the duration of the disease, the secular trends in the incidence of dementia could indicate whether the risk of late-life dementia is modifiable. Several community-based studies in Europe (e.g., the Netherlands, France, Germany, and the UK) have shown that the incidence of dementia has been declining in the past 2–4 decades [33, 42, 44, 48, 50, 54–64] (Table 3). For instance, the Rotterdam Study reported a 25% decrease, though statistically marginal, in the incidence of all-cause dementia between 1990 and 2000 in people aged 55+ years [60]. Using an algorithmic diagnostic approach, the UK Cognitive Function and Aging Study showed a 20% decline in dementia incidence from 1989–1994 to 2008–2011, but only in men [62]. Similarly, the modelling study using data from the English Longitudinal Study of Ageing suggested a declining age-specific incidence of dementia that corresponded to 20% reduced dementia incidence over 20 years [42]. The French study showed that dementia incidence decreased when using an algorithmic approach to define dementia but was stable when clinical criteria were used [63]. In North America, the Framingham Heart Study showed a 20% decrease in dementia incidence from the late 1970s to the early 2010s [56]. Similarly, several additional population-based studies from the US and Canada also showed a declining incidence of dementia and AD in older adults from the 1990s through the 2010s [33, 55–59]. Although some studies in the US and the Netherlands showed a relatively stable incidence of dementia [50, 54, 64], no study from Europe or North America has reported an increasing trend in dementia incidence in older adults [42]. On the contrary, the study in an urban area of Beijing, China, and the well-defined Hisayama Study in Japan showed evidence of the incidence of dementia increasing since the 1980s [44, 48].

Possible explanation of different time trends in dementia occurrence

Given that the late-life occurrence of dementia is affected by numerous factors over a lifespan, it is not surprising that secular trends of dementia vary within and among countries. Evidence suggests that the decreasing incidence of dementia in Europe and North America might be partly attributable to higher education and better control of cardiovascular risk factors in successive cohorts [56, 59]. First, the increase in early-life educational attainment might contribute to cognitive reserve and better cognition later in life via a positive effect on brain development and mental stimulation over the life course (e.g., cognitively demanding jobs and leisure activities). Further, adopting a brain-healthy lifestyle (e.g., no smoking and regular exercise), better control of major vascular risk factors (e.g., hypertension, diabetes, and dyslipidemia), and better access to health care interventions may help maintain vascular health and reduce the overall burden of cerebrovascular and neurodegenerative pathologies, thus delaying the onset of dementia [42, 60]. Finally, societal evolution in Western societies in the past century such as improvements in living conditions and social welfare may have led to enhanced general health, thus contributing to the delayed onset of dementia [31]. Taken together, the declining incidence of dementia in recent decades may partly reflect a successful compression of cognitive morbidity in aging, as suggested in several studies [65–67].

Table 3
Key findings from major population-based studies on time trends in incidence of dementia

Authors (country)	Study population and study periods	Diagnostic criteria	Trends in incidence
North America			
Rocca et al. (Minnesota, US) [50]	Minnesota, age ≥70, 1975–1994	Dementia: ICD codes (similar to DSM-II-R)	Stable
Hebert et al. (Chicago, US) [54]	Chicago Health and Aging Project, age ≥65, 1993–2008	AD: NINCDS-ADRDA criteria	Stable
Gao et al. (Indiana, US) [55]	Indianapolis-Ibadan Dementia Project, age ≥70, 1992 to 2001	Dementia: DSM-III-R; AD: NINCDS-ADRDA	African-Americans: decreased
Satizabal et al. (Boston, US) [56]	FHS, age ≥60, 1977–1983 to 2003–2008, 4 time periods	Dementia: DSM-IV; AD: NINCDS-ADRDA	Decreased
Cerasuolo et al. (Ontario, Canada) [57]	Age ≥65, 2002 to 2013, annual incidence	Dementia: Medical records (ICD-9, 10)	Stable in age 65–79; decreased in age ≥80
Derby et al. (New York, US) [58]	Einstein Aging Study, age ≥70, 1993–2015, annual incidence	Dementia: DSM-IV	Decreased
Kosteniuk et al. (Saskatchewan, Canada) [33]	Age ≥45, 2005–2006 to 2012–2013, annual incidence	Dementia: Medical records (ICD-9, 10)	Decreased
Noble et al. (New York, US) [59]	WHICAP (multiethnics), age ≥65, 1992–1994 to 1999–2001	Dementia: DSM-IV	Decreased
Europe			
Schrijvers et al. (The Netherlands) [60]	Rotterdam Study, age ≥60, 1990 to 2000	Dementia: DSM-III-R	Decreased ($p = 0.06$)
Doblhammer et al. (Germany) [61]	Health insurance database, age ≥65, 2006–2007 to 2009–2010	Dementia, ICD-10	10% decrease
Matthews et al. (England, UK) [62]	CFAS, age ≥65, 1991–1995 to 2008–2013	Dementia: Similar to DSM-III-R	Decreased
Grasset et al. (Bordeaux, France) [63]	PAQUID and 3-City Studies, age ≥65, 1988–1989 to 1999–2000	Dementia: Clinical: DSM-III-R; Algorithmic	Clinical diagnosis: stable Algorithm-based diagnosis: decline
van Bussel et al. (The Netherlands) [64]	Age ≥60, 1992 to 2014, annual incidence	Dementia: Primary care records	Stable
Ahmadi-Abhari et al. (England and Wales, UK) [42]	English Longitudinal Study of Ageing, age ≥50, 2002 to 2013	Dementia: DSM-IV	Decreased
Asia			
Li et al. (Beijing, China) [44]	Urban residents, age ≥60, 1986–1989 to 1997–1999	Dementia: ICD-10, DSM-IV	Increased
Ohara et al. (Hisayama, Japan) [48]	Hisayama Study, age ≥65, 1988–1998 to 2002–2012	Dementia: DSM-III-R; AD: NINCDS-ADRDA	Increased

AD, Alzheimer's disease; ICD, International Classification of Diseases; NINCDS-ADRDA, National Institute of Neurological Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; DSM, Diagnostic and Statistical Manual of Mental Disorders; WHICAP, Washington Heights-Inwood Columbia Aging Project; FHS, Framingham Heart Study; CFAS, Cognitive Function and Ageing Studies.

More research is needed to understand time trends in the incidence of dementia in China. However, the upward trend in the prevalence of dementia from the 1990s to 2010 is consistent with the increasing epidemic of stroke, ischemic heart disease, and related lifestyle and metabolic risk factors (e.g., physical inactivity, obesity, and diabetes) over similar periods, together with a rapidly aging population [68]. In Japan, the increasing incidence of dementia may be associated with a decrease in the competing risk of premature death, along with the increasing epidemic of an unhealthy diet, physical inactivity, and diabetes [48]. Clarifying major modifiable factors that contribute to changes in dementia incidence in different regions will help develop effective intervention strategies and health policies.

INTERVENTIONS TO DELAY THE ONSET OF DEMENTIA

Current evidence supports the view that the risk of dementia appears to be modifiable through multimodal interventions, especially at critical time windows over a life course [69]. Intervention measures include promoting healthy lifestyles (e.g., no smoking, physical activity, and a balanced diet), reducing the cardiovascular risk burden (e.g., optimal

control of hypertension, diabetes, and high cholesterol), and increasing cognitive reserve (e.g., education, social engagement, and mental activities).

Health promotion

Healthy aging in general is critical for healthy brain aging. Dementia and cardiovascular disease share commonrisk factors such as long-term hypertension, diabetes, an unbalanced diet, and obesity. Thus, health promotion initiatives for healthy brain aging and dementia risk reduction should be incorporated with those for cardiovascular health. The modifiable lifestyle and medical risk factors of dementia can be targeted for health promotion or primordial prevention [70]. In addition, a brain-healthy lifestyle can build brain and cognitive reserves, which helps to maintain cognitive functioning until the very end of life. Indeed, health promotion programs targeting the risk reduction of dementia have been developed in several countries (e.g., Australia, the US, Canada, France, and the UK) and by professional organizations (e.g., WHO, Alzheimer's Disease International, and Age UK).

Reduction of cardiovascular risk burden

Increasing evidence suggests that vascular mechanisms play a pivotal role in cognitive decline and dementia and that a clinical expression of the dementia syndrome involves complex interactions of convergent cerebrovascular and neurodegenerative processes in old people [71, 72]. Indeed, traditional cardiovascular risk factors such as midlife hypertension, diabetes, and high cholesterol, especially when occurring concurrently, confer a substantial risk for dementia and AD. This suggests that interventions targeting multiple major vascular risk factors may represent a promising approach to reducing dementia risk and delaying its onset. However, there remains a gap between the major findings of observational studies and randomized controlled trials, such that observational studies often show a reduced risk of dementia associated with the use of cardiovascular medications (e.g., antihypertensive drugs and statins), whereas randomized controlled clinical trials that targeted individual vascular risk factors such as hypertension, high cholesterol, or hyperglycemia have generally yielded negative results [69, 73]. Recently, multidomain intervention studies of unhealthy lifestyles, vascular risk factors, diet, and cognitive training have also shown mixed results [74–76]. Hopefully, the ongoing effort may provide additional evidence, which can help to form evidence-based recommendations for multimodal intervention against cognitive decline and dementia (e.g., World Wide FINGERS, http://wwfingers.com/).

Increasing brain and cognitive reserve

Cognitive reserve has been proposed as explaining (1) the link of higher education and more frequent participation in social and intellectual activities with resistance to cognitive decline, and (2) the discrepancy between the extent of Alzheimer pathology and the severity of cognitive symptoms [27]. Early-life greater educational achievement is the major driving factor for cognitive reserve. In addition, numerous prospective studies have reported that people who frequently engage in mentally stimulating activities (e.g., learning, reading, or playing games) from young adulthood through midlife and old age are less likely to develop dementia [77]. Finally, occupational complexity, social networks, and social engagement (e.g., frequent contacts with friends and relatives, attending clubs and church, and going to movies) also contribute to cognitive reserve and reduce the risk of cognitive impairment and dementia. Thus, enhancing cognitive capacity through increased educational attainment in early life and lifelong cognitive and social activities represents an alternative strategy to mitigate cognitive decline and postpone the onset of clinical dementia [30].

CONCLUSION

Epidemiological data show that dementia could be avoided even at extreme old ages (e.g., among centenarians or supercentenarians). This implies that people are able to reach very advanced ages without experiencing severe mental deterioration. Further, clinico-neuropathological studies of centenarians and even older people found that nearly half of those with dementia did not have sufficient brain neuropathology to explain their cognitive symptoms, while intermediate-to-high Alzheimer pathologies were present in around one-third of very old people without dementia or cognitive impairment. This suggests that certain compensatory mechanisms (e.g., cognitive reserve or cognitive resilience) may play a part in helping people escape the dementia syndrome in extreme old age. Finally, recent evidence of a declining incidence of dementia in Europe and

North America suggests that the risk of late-life dementia is modifiable. This supports the potential that intervention strategies that aim to promote general health, maintain vascular health, and increase cognitive reserve may indeed help achieve a life without dementia.

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