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.
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 near 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 ≥ 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 record-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,

| Authors (country)            | Study sample                                                                 | Diagnostic criteria | Prevalence          |
|-----------------------------|------------------------------------------------------------------------------|---------------------|---------------------|
| Samuelsson et al. (Sweden)  | Swedish Centenarian Study: n = 100, 82% women                                | DSM-III             | 27% (men 16%, women 30%) |
| Ravaglia et al. (Northern Italy) | Northern Italy Centenarian Study: n = 92, 59% women                      | DSM-IV             | 61.9% (men 50.0%, women 69.6%) |
| Gondo et al. (Tokyo, Japan) | Tokyo Centenarian Study: n = 304, 78.6% women                               | CDR ≥1             | 61.8% (men 41.5%, women 67.4%) |
| Andersen-Ranberg et al. (Denmark) | Longitudinal Study of Danish Centenarians: n = 207, 78.3% women       | ICD-10, CDR         | 50.7%               |
| Richmond et al. (Australia) | 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-ocurrence 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

| Authors (country)          | Study population and study periods                                                                 | Diagnostic criteria                      | Trends in prevalence |
|---------------------------|-----------------------------------------------------------------------------------------------------|------------------------------------------|----------------------|
| **North America**         |                                                                                                     |                                          |                      |
| Hall et al. (Indiana, US)  | Indianapolis-Ibadan Dementia Project, age ≥65, 1992 to 2001                                         | Dementia: ICD-10                         | Stable (African-Americans) |
| Kosteniuk et al. (Saskatchewan, Canada) | Age ≥45, 2005–2006 to 2012–2013, annual prevalence                                               | Dementia: Medical records (ICD-9, 10)    | Increased            |
| Langa et al. (US)         | US Health and Retirement Study, age ≥65, 2000 to 2012                                                | Dementia: validated self-report         | Decreased            |
| **Europe**                |                                                                                                     |                                          |                      |
| Lobo et al. (Zaragoza, Spain) | Zaragoza Study, age ≥65, 1988–1989 to 1994–1996                                                        | Dementia: DSM-IV                         | Overall stable; decreased in men |
| Ahmadi-Abhari et al. (England and Wales, UK) | English Longitudinal Study of Ageing, age ≥50, 2002 to 2013                                        | Dementia: DSM-IV                         | Decreased            |
| Skoog et al. (Gothenburg, Sweden) | Gothenburg 85-year-old study, age 85, 1986–1987 to 2008–2010                                        | Dementia: DSM-III-R                      | Decreased            |
| **Asia**                  |                                                                                                     |                                          |                      |
| Li et al. (Beijing, China) | Urban residents, age ≥60, 1986 to 1997, 2 waves                                                      | Dementia: ICD-10, DSM-IV                 | Increased            |
| Yu et al. (Hong Kong, China) | Systematic review, age ≥70, 1995–2006                                                               | Dementia: ICD-9, 10                      | Increased            |
| Chan et al. (Mainland China) | Systematic review, age ≥55, 1990 to 2010                                                           | Dementia and AD: various criteria        | Increased            |
| Kim et al. (Korea)        | Systematic review, age ≥60, 1990 to 2013                                                            | Dementia, AD: various criteria           | Increased slightly, especially AD |
| Ohara et al. (Hisayama, Japan) | 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.

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

| 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 (multietnics), 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) |
| Dobhammer 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: Algorithm-based diagnosis: stable | Clinical diagnosis: stable |
| 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 common risk 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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REFERENCES

[1] Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, Cedazo-Minguez A, Dubois B, Emilsson D, Feldman H, Fratiglioni L, Frisoni GB, Gauthier S, Georges J, Graff C, Iqbal K, Jessen F, Johansson G, Jonsson L, Kivipelto M, Knapp M, Mangialasche F, Melis R, Nordberg A, Rikkert MO, Qiu C, Sakmar TP, Scheltens P, Schneider LS, Sperling R, Tjernberg LO, Waldemar G, Wimo A, Zeiterberg H (2016) Defeating Alzheimer’s disease and other dementias: A priority for European science and society. Lancet Neurol 15, 455-532.

[2] Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP (2013) The global prevalence of dementia: A systematic review and metaanalysis. Alzheimers Dement 9, 63-75.e2.

[3] Fratiglioni L, Qiu C (2011) Prevention of cognitive decline in ageing: Dementia as the target, delayed onset as the goal. Lancet Neurol 10, 778-779.

[4] Corrada MM, Brookmeyer R, Paganini-Hill A, Berlau D, Kawas CH (2010) Dementia incidence continues to increase with age in the oldest old: The 90+ study. Ann Intern Med 67, 114-121.

[5] Lucca U, Tettamanti M, Logroscino G, Tiraboschi P, Landi C, Sacco L, Garri M, Ammesso S, Bertinotti C, Biotti A, Gargantini E, Piancara A, Nobili A, Pasina L, Franchi C, Djade CD, Riva E, Recchia A (2015) Prevalence of dementia in the oldest old: The Monzino 80-plus population based study. Alzheimers Dement 11, 258-70.e3.

[6] Wimo A, Guerchet M, Ali GC, Wu YT, Prina AM, Winblad B, Jonsson L, Liu Z, Prince M (2017) The worldwide costs of dementia 2015 and comparisons with 2010. Alzheimers Dement 13, 1-7.

[7] Robine JM, Cubaynes S. Worldwide demography of centenarians (2017) Mech Ageing Dev 165, 59-67.

[8] Arosio B, Ostan R, Mari D, Damanti S, Ronchetti F, Arcudi S, Scurti M, Franceschi C, Monti D (2017) Cognitive status in the oldest old and centenarians: A condition crucial for quality of life methodologically difficult to assess. Mech Ageing Dev 165, 185-194.

[9] Yang Z, Slavin MJ, Sachdev PS (2013) Dementia in the oldest old. Nat Rev Neurol 9, 382-393.

[10] Samuelsson SM, Alfredsson BB, Hagberg B, Samuelsson G, Nordbeck B, Brun A, Gustafson L, Risberg J (1997) The Swedish Centenarian Study: A multidisciplinary study of five consecutive cohorts at the age of 100. Int J Aging Hum Dev 45, 223-253.

[11] Ravaglia G, Forti P, De Ronchi D, Maioli F, Nesi B, Cucinotta D, Bernardi M, Cavalli G (1999) Prevalence and severity of dementia among northern Italian centenarians. Neurology 53, 416-418.

[12] Gondo Y, Hirose N, Arai Y, Inagaki H, Masui Y, Yamamura K, Shimizu K, Takayama M, Ebihara Y, Nakazawa S, Kitagawa K (2006) Functional status of centenarians in Tokyo, Japan: Developing better phenotypes of exceptional longevity. J Gerontol A Biol Sci Med Sci 61, 305-310.

[13] Andersen-Ranberg K, Vasegaard L, Jeune B (2001) Dementia is not inevitable: A population-based study of Danish centenarians. J Gerontol B Psychol Sci Soc Sci 56, P152-159.

[14] Richmond RL, Law J, Kay-Lambkin F (2011) Physical, mental, and cognitive function in a convenience sample of centenarians in Australia. J Am Geriatr Soc 59, 1080-1086.

[15] Sachdev PS, Levitan C, Crawford J, Sidhu M, Slavin M, Richmond R, Kochan N, Brodaty H, Wen W, Kang K, Mather KA (2011) The Sydney Centenarian Study: Methodology and profile of centenarians and near-centenarians. Int Psychogeriatr 25, 993-1005.

[16] Hazra NC, Dregan A, Jackson S, Gulliford MC (2015) Differences in health at age 100 according to sex: Population-based cohort study of centenarians using electronic health records. J Am Geriatr Soc 63, 1331-1337.

[17] Gao S, Hendrie HC, Hall KS, Hui S (1998) The relationships between age, sex, and the incidence of dementia and Alzheimer disease: A meta-analysis. Arch Gen Psychiatry 55, 809-815.

[18] Hall CB, Verghese J, Sliwinski M, Chen Z, Katz M, Derby C, Lipton RB (2005) Dementia incidence may increase more slowly after age 90: Results from the Bronx Aging Study. Neurology 65, 882-886.

[19] Miech RA, Breitner JC, Zandi PP, Khachaturian AS, other dementias: A priority for European science and soci- ety. Lancet Neurol 15, 455-532.

[20] Brodaty H, Woolf C, Andersen S, Barzilai N, Brayne C, Cheung KS, Corrada MM, Crawford JD, Daly C, Gondo Y, Hagberg B, Hirose N, Holstege H, Kawas C, Kaye J, Kochan NA, Lau BH, Lucca U, Marcon G, Martin P, Poon LW, Richardson R, Robine JM, Skoog I, Slavin MJ, Szewieczek J, Tettamanti M, Viña J, Perls T, Sachdev PS (2016) ICC-dementia (International Centenarian Consor- tium - dementia): An international consortium to determine the prevalence and incidence of dementia in centenarians across diverse ethnic and sociocultural groups. BMC Neurol 16, 52.

[21] Slavin MJ, Brodaty H, Sachdev PS (2013) Challenges of diagnosing dementia in the oldest old population. J Gerontol A Biol Sci Med Sci 68, 1103-1111.

[22] Mizutani T, Shimada H (1992) Neuropathological back- ground of twenty-seven centenarian brains. J Neurol Sci 114-121.

[23] Mizutani T, Shimada H (1992) Neuropathological back- ground of twenty-seven centenarian brains. J Neurol Sci 114-121.

[24] Mizutani T, Shimada H (1992) Neuropathological back- ground of twenty-seven centenarian brains. J Neurol Sci 114-121.
[52] Zeng Y, Feng Q, Hesketh T, Christensen K, Vaupel JW (2017) Survival, disabilities in activities of daily living, and physical and cognitive functioning among the oldest-old in China: A cohort study. *Lancet* **389**, 1619-1629.

[53] Dodge HH, Buracchio TJ, Fisher GG, Kiyohara Y, Meguro K, Tanizaki Y, Kaye JA (2012) Trends in the prevalence of dementia in Japan. *Int J Alzheimers Dis* **2012**, 056354.

[54] Hebert LE, Bienias JL, Aggarwal NT, Wilson RS, Bennett DA, Shah RC, Evans DA (2010) Change in risk of Alzheimer disease over time. *Neurology* **75**, 786-791.

[55] Gao S, Oguniyi A, Hall KS, Baijewu O, Unverzagt FW, Lane KA, Murrell JR, Gureje O, Hake AM, Hendrie HC (2016) Dementia incidence declined in African-Americans but not in Yoruba. *Alzheimers Dement* **12**, 244-251.

[56] Satizabal CL, Beiser AS, Chourakis V, Chéné G, Dufouil C, Seshadri S (2016) Incidence of dementia over three decades in the Framingham Heart Study. *N Engl J Med* **374**, 523-532.

[57] Cer easuolo JO, Cipriano LE, Sposato LA, Kapral MK, Fang J, Gill SS, Hackam DG, Hachinski V (2017) Population-based stroke and dementia incidence trends: Age and sex variations. *Alzheimers Dementia* **13**, 1081-1088.

[58] Derby CA, Katz MJ, Lipton RB, Hall CB (2017) Trends in dementia incidence in a birth cohort analysis of the Einstein Aging Study. *JAMA Neurol* **74**, 1345-1351.

[59] Noble JM, Schupf N, Manly JJ, Andrews H, Tang MX, Mayeux R (2017) Secular trends in the incidence of dementia in a multi-ethnic community. *J Alzheimers Dis* **60**, 1065-1075.

[60] Schrijvers EM, Verhaaren BF, Koudstaal PJ, Hofman A, Noble JM, Schupf N, Manly JJ, Andrews H, Tang MX, Mayeux R (2017) Secular trends in the incidence of dementia in a multi-ethnic community. *J Alzheimers Dis* **60**, 1065-1075.

[61] Matthews FE, Verhaaren BF, Koudstaal PJ, Hofman A, Ikram MA, Breteler MM (2012) Is dementia incidence declining? Trends in dementia incidence since 1990 in the Rotterdam Study. *Neurology* **78**, 1456-1463.

[62] Dobhlammer G, Fink A, Zylla S, Willekens F (2015) Compression or expansion of dementia in Germany? An observational study of short-term trends in incidence and death rates of dementia between 2006/07 and 2009/10 based on German health insurance data. *Alzheimer's Res Ther* **7**, 66.

[63] Grasset L, Brayne C, Joly P, Jacquin-Gadda H, Péret K, Foubert-Samier A, Dartigues JF, Helmer C (2016) Trends in dementia incidence: Evolution over a 10-year period in France. *Alzheimers Dement* **12**, 272-280.

[64] van Bussel EF, Richard E, Arts DL, Nooyens AC, Coloma PM, de Waal MW, van den Akker M, Biermans MC, Nielen MM, van Boven K, Smeets H, Matthews FE, Brayne C, Busschers WB, van Gool WA, Moll van Charante EP (2017) Dementia incidence trend over 1992-2014 in the Netherlands: Analysis of primary care data. *PloS Med* **14**, e1002235.

[65] Langa KM, Larson EB, Karlswish JH, Cutler DM, Kabeto MU, Kim SY, Rosen AB (2008) Trends in the prevalence and mortality of cognitive impairment in the United States: Is there evidence of a compression of cognitive morbidity? *Alzheimers Dement* **4**, 134-144.

[66] Jagger C, Matthews FE, Wohland P, Fouweather T, Steph an BC, Robinson L, Arthur A, Brayne C (2016) A comparison of health expectancies over two decades in England: Results of the Cognitive Function and Ageing Study I and II. *Lancet* **387**, 779-786.

[67] Crimmins EM, Saito Y, Kim JK (2016) Change in cognitively healthy and cognitively impaired life expectancy in the United States: 2000-2010. *SSM Popul Health* **2**, 793-797.

[68] Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, Wang X, Yu S, Jiang Y, Naghavi M, Vos T, Wang H, Lopez AD, Murray CJ (2013) Rapid health transition in China, 1990-2010: Findings from the Global Burden of Disease Study 2010. *Lancet* **381**, 1987-2015.

[69] Qiu C (2012) Preventing Alzheimer’s disease by targeting vascular risk factors: Hope and gap. *J Alzheimers Dis* **32**, 721-731.

[70] Gorelick PB, Furie KL, Iadecola C, Smith EE, Waddy SP, Lloyd-Jones DM, Bae HJ, Bauman MA, Dichgans M, Duncan PW, Girgus M, Howard VJ, Lazar RM, Seshadri S, Testai FD, van Gaal S, Yaffe K, Wasik H, Zerna C (2017) Defining optimal brain health in adults: A presidential advisory from the American Heart Association/American Stroke Association. *Stroke* **48**, e284-e303.

[71] Qiu C, Fratiglioni L (2015) A major role for cardiovascular burden in age-related cognitive decline. *Nat Rev Cardiol* **12**, 267-277.

[72] Pase MP, Satizabal CL, Seshadri S (2017) Role of improved vascular health in the declining incidence of dementia. *Stroke* **48**, 2013-2020.

[73] Qiu C (2011) Epidemiological findings of vascular risk factors in Alzheimer’s disease: Implications for therapeutic and preventive intervention. *Expert Rev Neurother* **11**, 1593-1607.

[74] Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Attila C, Antikainen R, Bäckman L, Hänninen J, Tula A, Latikainen T, Lindström J, Mangialasche F, Pajunen T, Sajala S, Peltonen M, Rauramaa R, Stigsdotter-Neely A, Strandberg T, Tuomilehto J, Soininen H, Kivipelto M (2015) A 2 year multimodal intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomized controlled trial. *Lancet* **385**, 2255-2263.

[75] Moll van Charante EP, Richard E, Eurlings LS, van Dalen JW, Ligthart SA, van Bussel EF, Hoevenaar-Blom MP, Vermeulen M, van Gool WA (2016) Effectiveness of a 6-year multimodal vascular care intervention to prevent dementia (preDIVA): A cluster-randomised controlled trial. *Lancet* **388**, 797-805.

[76] Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, Bories L, Cui NN, Dantoine T, Martigues JF, Desclaux F, Gabelle A, Gasnier Y, Pesce A, Sudres K, Touchon J, Robert P, Rouaud O, Legrand P, Payoux P, Caubre JP, Weiner M, Carrié I, Ousset PJ, Vellas B (2017) Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multimodal intervention on cognitive function in elderly adults with memory complaints (MAPT): A randomised, placebo-controlled trial. *Lancet Neurol* **16**, 377-389.

[77] Yates LA, Ziser S, Specter A, Orrell M (2016) Cognitive leisure activities and future risk of cognitive impairment and dementia: Systematic review and meta-analysis. *Int Psychogeriatr* **28**, 1791-1806.