REVIEW

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What have we learned from cognition in the oldest-old

Claudia H. Kawas[a], *Nienke Legdeur*[b], *and María M. Corrada*[c]

Purpose of review
People over 90 are the fastest growing segment of the population with the highest rates of dementia. This review highlights recent findings that provide insight to our understanding of dementia and cognition at all ages.

Recent findings
Risk factors for Alzheimer's disease (AD) and dementia differ by age, with some factors, like the development of hypertension, actually becoming protective in the oldest-old. At least half of all dementia in this age group is due to non AD pathologies, including microinfarcts, hippocampal sclerosis and TDP-43. The number of pathologic changes found in the brain is related to both risk and severity of dementia, but many people in this age group appear to be 'resilient' to these pathologies. Resilience to Alzheimer pathology, in part, may be related to absence of other pathologies, and imaging and spinal fluid biomarkers for AD have limited utility in this age group.

Summary
Studies of dementia in the oldest-old are important for our understanding and eventual treatment or prevention of dementia at all ages.

Keywords
biomarkers, dementia, oldest-old, resilience, risk factors

INTRODUCTION

Until recently, studies of individuals who reached the tenth and eleventh decade of life have been relatively rare, in part because individuals reaching this age group were themselves quite rare. However, with the extension of life expectancy over the past century, individuals over age 90 are now the fastest growing segment of the population in the United States and most of the world. With the risk of dementia profoundly age-related, these individuals have the highest rates of dementia and portend an enormous public health burden in coming decades. While we tend to assume that dementia-related factors identified in younger elderly also apply to the oldest-old, current research suggests otherwise and provides some surprising observations that can contribute insight into dementia occurring at all ages.

In addition to investigations of cognitive loss, studies in very old individuals have also promoted the concepts of resilience and resistance. Resilience is most frequently defined as the presence of dementia-related pathological brain changes, most frequently Alzheimer disease (AD), in individuals who are cognitively normal. Paradoxically, this definition also serves to identify people who are presumably in the preclinical phase of their dementing illness [1]. The exceptionally high rate of this occurrence in people over 90, where approximately 40% of people without dementia have intermediate and high levels of AD, provides an ideal platform to investigate and understand these fundamental issues. We briefly summarize some of these issues and recent findings below.

[a]Department of Neurology and Department of Neurobiology & Behavior, University of California, Irvine, Irvine, California, USA, [b]Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC and Department of Internal Medicine, Spaarne Gasthuis, Haarlem, the Netherlands and [c]Department of Neurology and Department of Epidemiology, University of California, Irvine, Irvine, California, USA

Correspondence to Claudia H. Kawas, MD, Department of Neurology and Department of Neurobiology & Behavior, University of California, Irvine, 1121 Gillespie NRF, Irvine, California 92697, USA.
Tel: +949 824 2323; e-mail: ckawas@uci.edu

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KEY POINTS

- The oldest-old are the fastest growing segment of the population in most of the world and have the highest rates of dementia.
- Approximately half of all dementia in the oldest-old is related to non-AD pathologies, including microinfarcts, vascular disease, hippocampal sclerosis, and TDP-43 (LATE).
- Risk factors for dementia and AD in the oldest-old differ from younger elderly, and some established risk factors, such as hypertension, appear to be protective in this age group
- Imaging and spinal fluid biomarkers for AD have limited utility for predicting dementia in this age group, likely related to relatively short life expectancy and perhaps, 'resilience'.
- Potential resilience to dementia-related pathologies appears to be frequent in this age group, with 40% of individuals without dementia having AD or other pathologic changes associated with dementia.

TEXT OF REVIEW

The oldest-old are the fastest growing segment of the population throughout much of the world. Projections from the United Nations for the coming decades estimate that the number of people aged 90 and older will increase more than 5-fold from 21 million in 2020 to 113 million in 2060. In addition to Brazil and the United States, three of the top 5 countries expected to have the largest number of 90+ year-olds are in Asia, and by far the country with the largest number will be China, where the population of 90+ year-olds will grow from 2.8 million to a stunning 31 million (Fig. 1) [2]. Given that the oldest-old have the highest rates of cognitive impairment, functional disability, and comorbidities, the oldest-old present an immense public health and financial challenge for many parts of the world.

Prevalence and incidence of dementia in the oldest-old

The incidence and prevalence of dementia increase exponentially with age beginning at age 65. We now know that this increase with age extends into ages

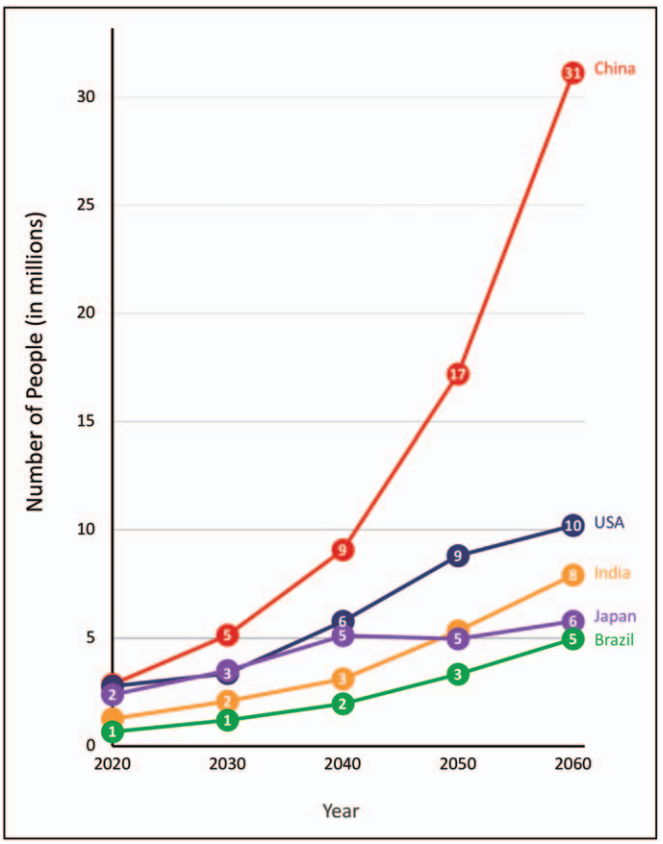

FIGURE 1. Projected oldest-old population (90+) from 2020 to 2060: top five countries. Created from information extracted from United Nations Department of Economics and Social Affairs Population Division. World Population Prospects 2019 [2].

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90 and above. Although some early studies suggested declines in dementia incidence at advanced ages, most recent studies, with larger sample sizes and more frequent visits, show a continued exponential rise with age reaching a staggering 40% per year among centenarians [3]. Prevalence of dementia is approximately 30% at ages 90–94 and reaches above 70% in centenarians. Women show higher prevalence of dementia than men primarily due to greater longevity in women. In terms of incidence, however, most large studies and meta-analyses do not show a difference between women and men [4▪].

Dementia and diversity in the oldest-old

Information about dementia prevalence and incidence comes almost exclusively from studies of White individuals in the US and Europe with very limited information from diverse populations. In one of the only incidence studies of the oldest-old to include ethnic minorities, the patterns of racial and ethnic disparities in dementia incidence seen in younger older adults persisted after the age of 90 [5▪▪]. In electronic medical records from an integrated healthcare system in Northern California, dementia incidence was lowest among Asians and Whites and highest among Latinos and Black individuals. The difference in incidence rates persisted after adjusting for sociodemographic and life course health conditions suggesting that differences may be due to other factors including early life adversity, vascular health, or underlying dementia associated neuropathologies [5▪▪].

There will be 9.5 million individuals aged 90 and older in the US by 2060 and more than one in every three individuals at this age will be from racial and ethnic minorities making studies of cognition and dementia in racially and ethnically diverse individuals crucial. The *Life After 90 Study* is a one-of-a-kind multiethnic cohort of individuals 90 and older established to help address the lack of knowledge in ethnically and racially diverse oldest-old individuals [6▪]. With more than 500 ethnically diverse participants 90 and older, the study has the potential to redefine our knowledge of cognition, dementia, and neuropathology in the oldest-old, provide new insights into early life risk and protective factors, and uncover etiological underpinnings of late-onset dementia and cognitive impairment in the oldest-old.

Factors contributing to dementia and cognition

Risk and protective factors for dementia and cognitive impairment have primarily been studied in younger elderly with the assumption that they are generalizable to the oldest-old. There is growing evidence that risk factors for dementia and cognitive impairment in the oldest-old differ from younger older individuals [7▪]. For example, the ε4 allele of the apolipoprotein E gene (APOEε4) represents the strongest susceptibility gene for dementia and AD at younger ages. However, its effect appears to lessen with age and in people who survive to very old age without dementia, the APOEε4 allele is no longer associated with an increased dementia risk [7▪,8]. Notably, several studies have reported that some midlife risk factors appear to become protective when developed in late life [9,10▪].

Cardiovascular diseases in midlife, which are commonly associated with increased risk of cognitive impairment and dementia in later life, also seem to have weaker or no associations later in life. A recent investigation that included more than 400,000 individuals aged ≥65 years from a primary care database studied the risk of hypertension, diabetes mellitus, dyslipidemia, stroke, myocardial infarction, heart failure, and atrial fibrillation for all-cause dementia [11▪▪]. The results indicated that the risk for dementia decreased with increasing age for all vascular disorders and was no longer significant in individuals aged ≥90 years (Fig. 2). Another study, with more than 2,000 cognitively healthy individuals aged ≥ 55 years, investigated the age dependency of genetic and cardiovascular risk factors, depressive symptoms, inflammation markers and lifestyle risk factors for cognitive decline [12]. In general, there was a trend towards a decreasing adverse effect of various risk factors on cognitive decline with increasing age. A similar change with age has been observed in studies of BMI [10▪], cholesterol [13], and triglycerides levels [14▪] with some of these risk factors appearing protective in late life.

Several hypotheses have been proposed to explain the age-dependent relationship of risk factors to cognition. These hypotheses can be divided in risk factor-specific explanations and explanations that are generalizable to all risk factors. With regard to hypertension, it has been hypothesized that with increasing age a higher blood pressure is necessary to ensure adequate cerebral blood flow [15]. Reverse causality, in which neurodegeneration leads to a decrease in blood pressure, may also play a role. However, as the age-dependency of risk factors is not specific for hypertension, generalizable explanations might be likely. First, selective survival may lead to a selection of oldest-old individuals who are less susceptible to the negative consequences of risk factors. Second, the higher prevalence of risk factors in the oldest-old may dilute the distinction between individuals with and without a risk factor. Third,

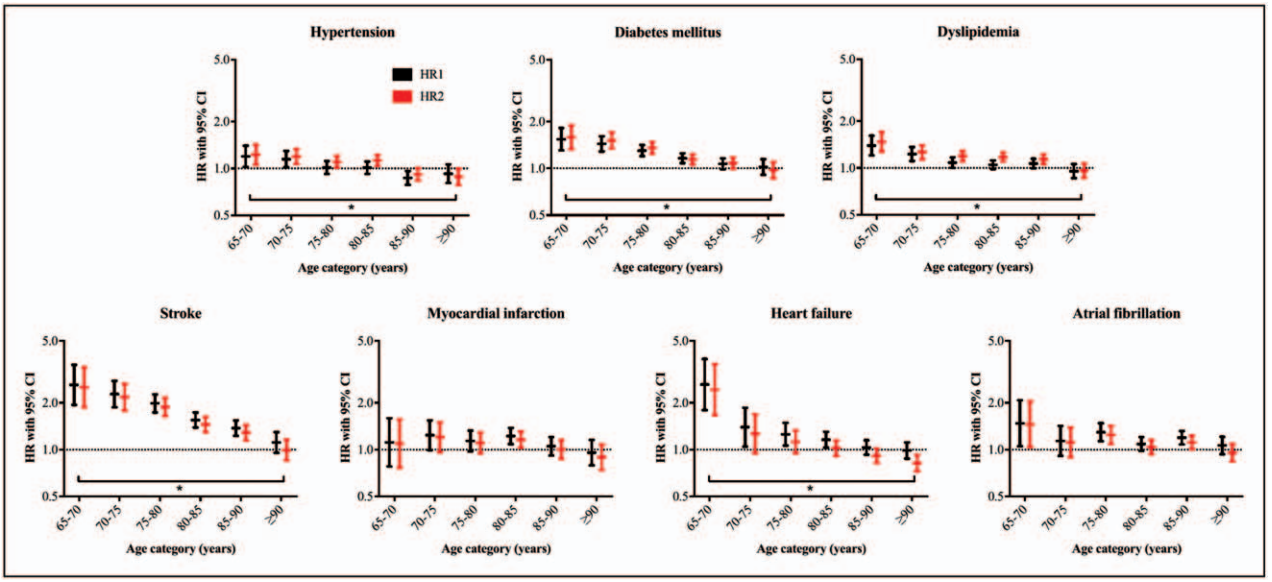

FIGURE 2. Risk of incident dementia in the presence of a risk factor per 5-year age group. For individuals ≥ 90 no upper age limit was used. Hazard Ratio 1 (HR1) determined with Cox regression analyses adjusted for age at study entry and sex; Hazard Ratio 2 (HR2) determined with competing risk analyses adjusted for age at study entry and sex; the HR on the y-axis is graphed on a log scale. CI, confidence interval; *HRs changed significantly ($P < 0.0071$) between age groups as determined with trend analysis including the interaction of age group with risk factor. Figure previously published in [11▪▪].

neuropathological studies indicate that in the oldest-old pathologies other than AD contribute to dementia risk such as TAR DNA-binding protein 43 kDa (TDP-43) and hippocampal sclerosis (HS). These pathologies may relate to different risk factors, attenuating the effect of risk factors for AD on dementia risk in the oldest-old. Last, studies focusing on older individuals need to consider potential biases that are more likely to occur in an aging population. For example, competing risk by mortality (which describes the potentially lower chance in individuals with a vascular disorder to develop dementia as they may die faster than individuals without a vascular disorder) and the selection towards healthier individuals during follow-up. Nevertheless, despite these concerns, evidence is mounting that what is normal or what should be recommended for optimal cognition in the oldest-old may be very different from younger elderly in many of the risk factors [14▪,16].

Although the importance of some risk factors for dementia appears to decline with increasing age, other risk factors have drawn attention in the oldest-old. Lower physical strength and performance, less participation in cognitive stimulating activities, and lower kidney function have been associated with cognitive impairment in the oldest-old [17▪,18▪,19]. Although it is difficult to disentangle cause and effect in these relationships, preserving physical health seems to be of utmost importance to preserve cognitive health in the oldest-old [20].

Multiple pathologies in dementia

Although it is now appreciated that the majority of individuals with dementia have two or more dementia-related pathological findings at autopsy, research has tended to focus on AD, overlooking many of the concomitant pathologies. Non-AD pathologies including microvascular disease (microinfarcts, atherosclerosis, arteriosclerosis), HS, and TDP-43 are related to cognitive performance independently of AD and account for at least half of the attributable risk of dementia in the oldest-old [21,22▪▪]. Moreover, the number of pathologies is highly associated with dementia severity as well as risk [23,24▪]. Unlike AD, these pathologies continue to increase in prevalence with age (Fig. 3) [25▪▪] and their high prevalence in the oldest-old makes them an optimal group for investigations of these lesions. At present, these processes cannot be diagnosed without an autopsy, nor do we understand factors related to their presence and expression. For example, microinfarcts, a presumed form of vascular disease, are not related to traditional vascular risk factors in the oldest-old [26]. In HS, the clinical profile suggest that HS dementia is associated with cognitive deficits similar to AD but often progress more slowly [27▪]. Pathologies, such as HS, TDP-43 and AD frequently co-occur but are each known to cause dementia even when not accompanied by the other pathologies [28]. Our understanding of these pathologic contributions to dementia is modest and represents an area with potentially great public health impact.

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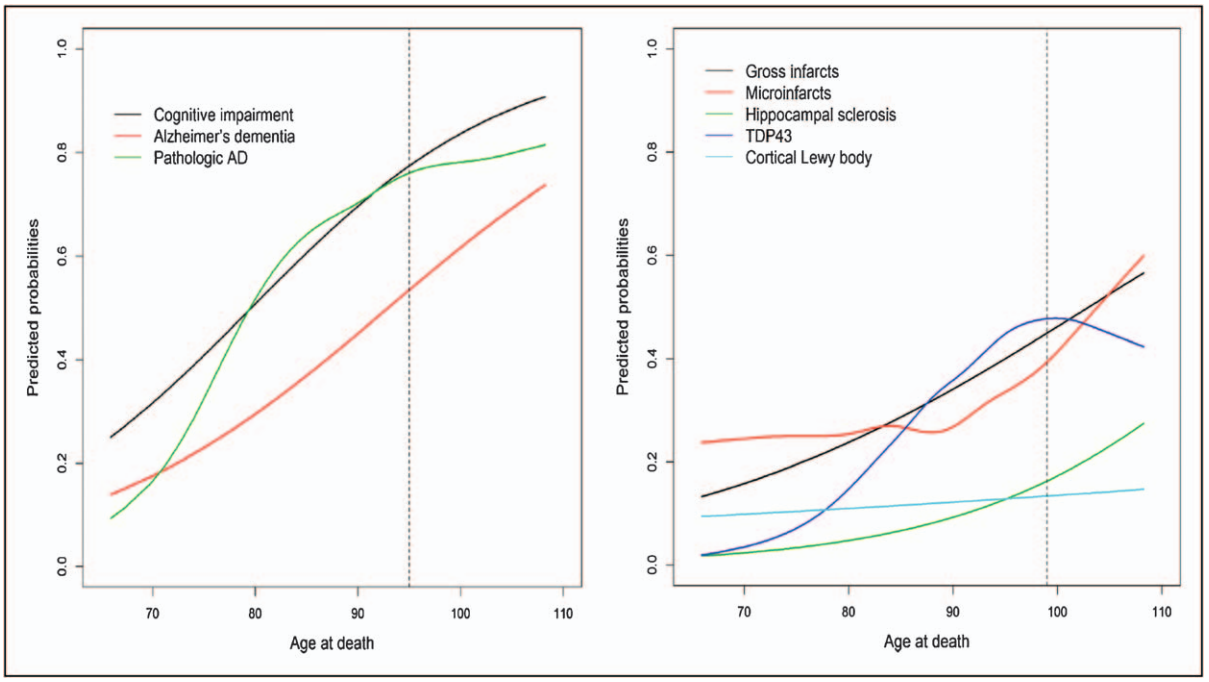

FIGURE 3. Estimated probability of Alzheimer's dementia, cognitive impairment, and various neuropathologies according to age. Panel A) Alzheimer dementia, cognitive impairment, and AD neuropathology. Panel B) non-AD neuropathologies. Data are from separate models. Figures previously published in [25▪▪].

Limbic-predominant age-associated TDP-43 encephalopathy (LATE)

First recognized as the disease protein in amyotrophic lateral sclerosis (ALS) and many cases of frontotemporal lobar degeneration (FTLD-TDP), phosphorylated TDP-43 was subsequently identified in the brains of many people with dementia and HS over age 80 [28]. Despite frequent co-occurrence with AD at this advanced age, autopsy studies in the oldest-old have identified many individuals with dementia who have HS or limbic-predominant TDP-43 without the presence of AD pathology. In 2019, a consensus working group proposed a sampling and staging system for routine autopsy diagnosis to characterize the anatomical distribution of TDP-43 proteinopathy in these individuals [29▪▪]. Dubbed Limbic-predominant Age-associated TDP-43 Encephalopathy (LATE), the progressive amnestic syndrome associated with this pathology is most frequently diagnosed during life as Alzheimer dementia even when AD pathology is not present. In autopsy studies, LATE accounts for at least 20% of dementia in the oldest-old [29▪▪]. Currently, we are not able to effectively diagnose this disorder during life, but TDP-43 biomarker development is an active area of research [30,31▪,32] and would greatly facilitate research in this understudied disorder. Pathologically, TDP-43 has been shown to be associated with atherosclerosis and Lewy bodies, despite the latter being relatively infrequent in this age group [33▪▪]. It is likely that phosphorylated TDP-43 and other, as yet unidentified, pathologic processes account for the 30–50% of dementia of unknown origin that has been noted in the oldest-old [22▪▪,34].

Biomarkers in the oldest-old

Most studies about the utility of biomarkers for dementia in the oldest-old have been in relation to imaging biomarkers. A recent review of neuroimaging findings in the oldest-old (Woodworth D, Scambray K, Corrada MM, Kawas CH, Sajjadi AS, manuscript under review) noted a lack of imaging studies in this age group. In general, studies found greater global, medial temporal, or hippocampal atrophy to be related to dementia risk [35], cognitive performance [18▪,36▪▪,37▪▪] and faster rates of cognitive decline [37▪▪,38▪]. High burden of white matter lesions was also a common finding and was associated with worse baseline scores and faster decline in measures of global cognition [18▪,37▪▪]. Amyloid burden assessed through PET, is usually high in the oldest-old and associated with dementia risk [35], worse cognitive performance [18▪,38▪], and faster cognitive decline [38▪,39]. However, many oldest-old can maintain normal cognition in the presence of a high amyloid burden [35,40].

The utility of biomarkers to estimate risk of dementia due to AD, changes with age and in the oldest-old is low compared to younger elderly, mostly due to a lower life expectancy. A study estimating the risk of AD dementia noted that in 90+ year olds with normal cognition, the lifetime-risk is <10% if either amyloid positivity or neurodegeneration were present and <20% when both were present [41]. The risk was significantly higher and reached 47% in the oldest-old only if mild cognitive impairment was also present (Fig. 4). This finding suggests that due to lower life expectancy, using biomarkers to predict dementia in the oldest-old may have limited utility [42▪] and is helpful only if cognitive impairment is already present.

Resistance and resilience

Although the presence of cerebral amyloid is strongly age-related, the prevalence of amyloid deposits levels off in advanced age, and approximately 20% of individuals over age 90 do not have significant amyloid in their brain at autopsy (CERAD stage 0) [43]. Absence of amyloid at younger ages does not preclude the eventual deposition later in life but at very advanced ages, it raises the possibility that these individuals may be resistant to the deposition of amyloid. Although we do not yet know factors related to absence of amyloid, these studies can provide important clues for understanding AD dementia, which is defined by evidence of amyloid. It is interesting to note that, unlike amyloid, low levels of tau are virtually always present in 90+ year olds (Braak stages I & II) [23,44▪], even in the absence of amyloid deposition.

A growing body of research has been focused on so-called 'resilience' [45▪▪] where individuals with normal cognition have significant dementia-related neuropathologic changes in their brains, particularly AD [43,44▪]. Until recently, we were not able to identify these individuals until autopsy, if indeed an autopsy occurred. However, recent advances in imaging, spinal fluid and blood biomarkers have paved the way for identifying individuals with AD pathology while still alive, greatly enhancing our ability to study them. Biomarker development for most of the other pathologies associated with dementia is underway but at less advanced stages. These biomarkers will be crucial for our understanding of resilience because increasing evidence from

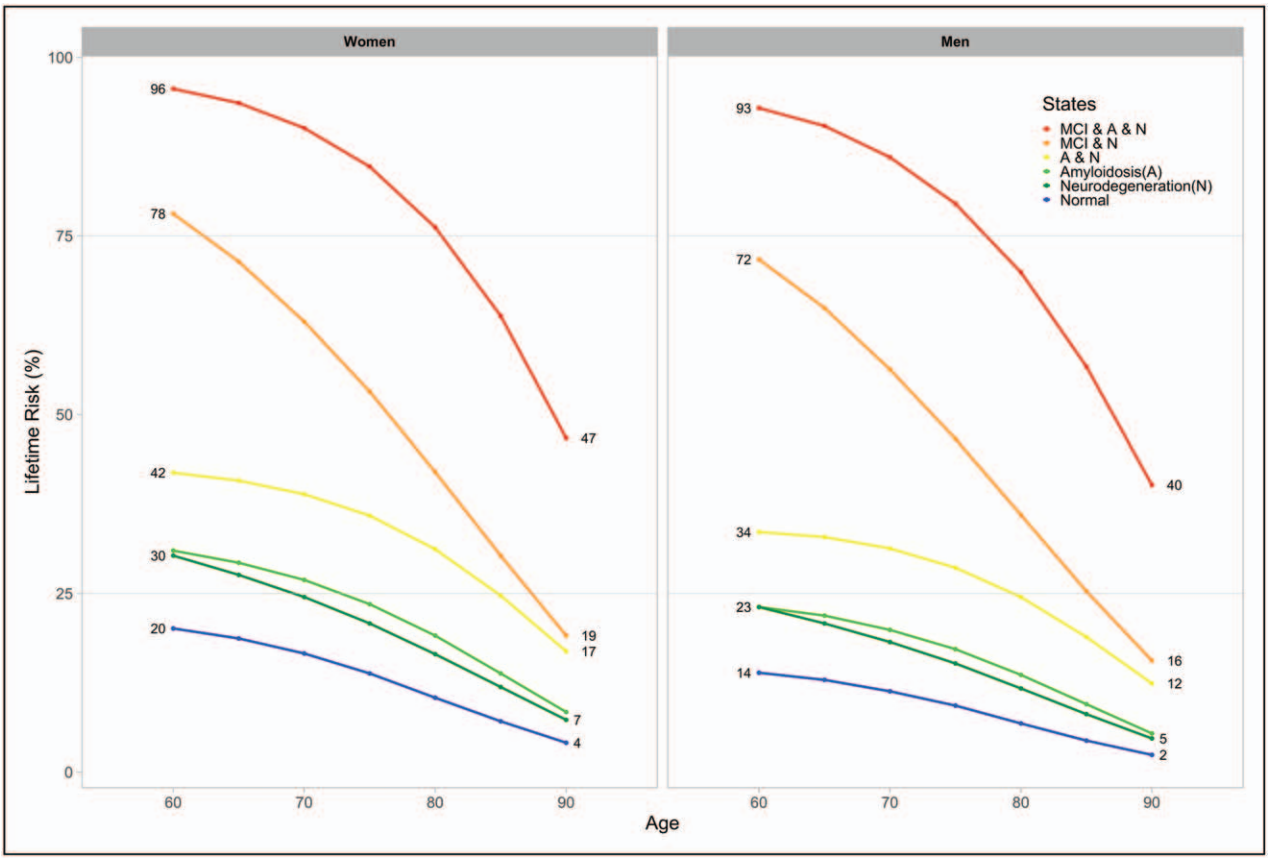

FIGURE 4. Lifetime risk of Alzheimer's dementia for women and men based on screening for amyloidosis, neurodegeneration, and mild cognitive impairment (MCI). Created from data published in [41].

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autopsy studies in the oldest-old suggests that resilience to AD may in large part reflect the absence of other, non-AD pathologies including cerebrovascular disease, HS and TDP-43 [43,44▪].

CONCLUSION

The oldest-old are the fastest growing segment of the population in most of the world and have the highest risk of dementia. Clinical and neuropathological investigations of cognition in these individuals have revealed surprising findings and given new insights into the expression of dementia in aging. Factors generally associated with dementia risk are not always relevant to this age group (e.g., APOEε4) and in some cases may even be protective against the development of dementia (e.g., hypertension developing after age 85). At least half of dementia in this age group is attributable to causes other than AD which deserve more intensive study. Conversely, some individuals in this age group with AD or other neuropathologies appear to be resilient to the effects of these pathologies. Investigations in the oldest-old provide an important platform for investigating cognitive loss and dementia, as well as resistance and resilience, and will inform our understanding of dementia at all ages.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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This meta-analysis combines data from seven large cohort studies in Europe and the US and found incidence rates similar between men and women at all ages up to age 89. It also observed a decline in incidence of dementia of about 13% per decade over the past 25 years.

5. ▪▪ Gilsanz P, Corrada MM, Kawas CH, *et al.* Incidence of dementia after age 90 in a multiracial cohort. Alzheimers Dement 2019; 15:497–505.

This study estimates for the first time the incidence of dementia in a diverse sample of oldest-old individuals. Incident dementia diagnoses were obtained from an integrated healthcare system for more than 2000 individuals aged 90 and older. The study found that patterns of racial/ethnic disparities in dementia seen in younger older adults continue after the age of 90 years.

6. ▪ Corrada MM, Gilsanz P, DeCarli C, *et al.* Introducing Life After 90, an Ethnically Diverse Cohort of Oldest-Old Individuals. Alzheimers Dement 2019; 15(7S_Part_9):P495–P496.

This is one of the first reports from a unique epidemiological cohort of oldest-old individuals recruited from an integrated healthcare system in Northern California where most of the participants are ethnic minorities. The study found potential disparities in the way racial/ethnic groups report their depressive symptoms but not their cognitive abilities.

7. ▪ Hall A, Pekkala T, Polvikoski T, *et al.* Prediction models for dementia and neuropathology in the oldest old: the Vantaa 85+ cohort study. Alzheimers Res Ther 2019; 11:11.

This investigation from the Vantaa 85+ cohort study using multifactorial models noticed that predictors of dementia in the oldest-old differed from those of younger elderly highlighting that the risk profile for dementia in the oldest-old is multifactorial and more complex than in younger elderly.

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This study found that in individuals 85 and older higher BMI was associated with better performance in tests of executive function and language but noted the opposite association in younger elderly. The authors attribute this reversal in the association with age to the 'protected survivor model', a small subpopulation with characteristics that protect them from both mortality and cognitive decline even in the presence of risk factors.

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In this longitudinal prospective study of Chinese individuals 80 and older, a higher concentration of serum triglycerides was associated with slower decline in cognition and other outcomes common at very advanced age. The authors argue that 'the lower the better' for triglycerides does not apply to the oldest-old.

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In this study of 193 individuals 90 and older from The 90+ Study, lower kidney function as measured by higher cystatin C levels, were associated with greater impairment in various cognitive tests. The study also showed higher cystatin C levels being associated with infratentorial cerebral microbleeds. The findings suggest that maintaining kidney health may be important to maintaining cognitive function at very advanced age and suggest a possible mechanism of uremic pathways of brain vascular injury.

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This cross-sectional study of extensively phenotyped individuals, identified a broad range of factors associated with cognitive impairment in the oldest-old. Physical-performance and grip strength were noted as particularly important in relation to cognitive function thus identifying potential intervention targets.

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This study of more than 1,100 participants from the Religious Orders Study and the Rush Memory and Aging Project, found that AD dementia can be attributed in large part to AD neuropathology. It also noted, however, that multiple other neuropathologies, such as infarcts, Lewy bodies, HS, TDP-43, cerebral amyloid angiopathy, atherosclerosis, and arteriosclerosis also contribute. Furthermore, the study estimated that about one-third of dementia could not be attributed to these neuropathologic changes suggesting that other diseases may be important.

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This large clinicopathological study in Brazil, found that the frequency of most neuropathologies and the odds of having multiple neuropathologies was higher in the very old compared to younger elderly. This study is important as clinicopathological studies from low- or middle-income countries (LMIC), where 54% of very old people live, are rare.

25. Farfel JM, Yu L, Boyle PA, *et al.* Alzheimer's disease frequency peaks in the ■■ tenth decade and is lower afterwards. Acta Neuropathol Commun 2019; 7:104.

In this study of more than 1,400 autopsied individuals, although the probability of AD dementia and cognitive impairment continued to increase with age, the probability of AD neuropathology peaked around age 95 and plateaued after. Conversely, the frequency of other non-AD neuropathologies (gross infarcts, microinfarcts, hippocampal sclerosis, and TDP-43) increased dramatically with age after age 95 making them an important target for interventions in the oldest-old.

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This article proposed new terminology and uniform pathologic assessment for the autopsy evaluation and staging of TDP43 in association with dementia. The importance of LATE as a contributing factor in neurodegeneration and late life dementia is outlined, as are the needs for specific LATE biomarker development and TDP-43 focused drug discovery.

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31. Makkinejad N, Schneider JA, Yu J, *et al.* Associations of amygdala volume ■ and shape with transactive response DNA-binding protein 43 (TDP-43) pathology in a community cohort of older adults. Neurobiol Aging 2019; 77:104–111.

This investigation from the Rush Memory and Aging Project and Religious Orders Study identified, through ex-vivo MRI, a spatial pattern of the amygdala that distinguishes TDP-43 pathology from hippocampal sclerosis and Alzheimer's pathology. This investigation is significant as it identifies potential biomarkers that could identify TDP43 pathology via neuroimaging.

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This study in individuals with cognitive impairment and pathological AD, found the presence of HS and TDP-43 was related to longer duration of symptoms, suggesting they are part of the late stages of AD pathology. They also noted Lewy bodies to be a common co-pathology in people with HS or TDP-43.

34. Crystal HA, Dickson D, Davies P, *et al.* The relative frequency of 'dementia of unknown etiology' increases with age and is nearly 50% in nonagenarians. Arch Neurol 2000; 57:713–719.

35. Lopez OL, Becker JT, Chang Y, *et al.* Amyloid deposition and brain structure as long-term predictors of MCI, dementia, and mortality. Neurology 2018; 90:e1920–e1928.

36. Eguchi Y, Noda Y, Nakajima S, *et al.* Subiculum volumes associated with ■■ memory function in the oldest-old individuals aged 95 years and older. Geriatr Gerontol Int 2019; 19:347–351.

In this investigation from the Arakawa 95+ study, better memory scores were associated with larger volumes of the subiculum. This is the first study to examine hippocampal subfields in relation to memory function in the oldest-old.

37. Legdeur N, Visser PJ, Woodworth DC, *et al.* White Matter Hyperintensities ■■ and Hippocampal Atrophy in Relation to Cognition: The 90+ Study. J Am Geriatr Soc 2019; 67:1827–1834.

In this investigation of 141 individuals aged 90 and older from The 90+ Study, higher levels of white matter hyperintensities and hippocampal atrophy were both independently related to worse cognitive scores at baseline and to faster rates of cognitive decline in tests of global cognition. Hippocampal atrophy was also associated with faster decline in memory tests. These results suggest a potential focus of research aimed at maintaining cognition or slowing down decline in the oldest-old.

38. Pelkmans W, Legdeur N, ten Kate M, *et al.* Amyloid-β, cortical thickness, and ■ subsequent cognitive decline in cognitively normal oldest-old. Ann Clin Transl Neurol 2021; Jan 9. doi: 10.1002/acn3.51273.

In this study, oldest-old individuals with Aβ positivity showed faster cognitive decline than those without Aβ positivity. Furthermore, cortical thickness predicted cognitive decline similarly in oldest-old individuals regardless of Aβ burden.

39. Zhao Y, Tudorascu DL, Lopez OL, *et al.* Amyloid beta Deposition and Suspected Non-Alzheimer Pathophysiology and Cognitive Decline Patterns for 12 Years in Oldest Old Participants Without Dementia. JAMA Neurol 2018; 75:88–96.

40. Mathis CA, Kuller LH, Klunk WE, *et al.* In vivo assessment of amyloid-beta deposition in nondemented very elderly subjects. Ann Neurol 2013; 73:751–761.

41. Brookmeyer R, Abdalla N. Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease. Alzheimers Dement 2018; 14:981–988.

42. Lilamand M, Cognat E, Goutagny S, *et al.* Biomarkers of Alzheimer's disease ■ in older and oldest old patients. Geriatr Psychol Neuropsychiatr Vieil 2019; 17:65–72.

This study examines issues related to the difficulty of interpreting AD biomarkers in the oldest-old. The study discusses the importance of patient-centered approaches and cautions about the use of biomarkers in asymptomatic individuals.

43. Robinson JL, Corrada MM, Kovacs GG, *et al.* Non-Alzheimer's contributions to dementia and cognitive resilience in The 90+ Study. Acta Neuropathol 2018; 136:377–388.

44. Tanprasertsuk J, Johnson EJ, Johnson MA, *et al.* Clinico-Neuropathological ■ Findings in the Oldest Old from the Georgia Centenarian Study. J Alzheimers Dis 2019; 70:35–49.

In this study of 49 centenarians, AD-neuropathology, HS, cerebral amyloid angiopathy, and TDP-43 were all associated with severe dementia and poor performance in cognitive tests. In addition, a wide range of AD neuropathological changes were observed in individuals with dementia as well as without dementia, noting that is possible to maintain normal cognition in the presence of AD neuropathology.

45. Montine TJ, Cholerton BA, Corrada MM, *et al.* Concepts for brain aging: resis- ■■ tance, resilience, reserve, and compensation. Alzheimers Res Ther 2019; 11:22.

This commentary proposes operational definitions of the concepts of resistance, resilience, and reserve, widely used concepts for which consensus definitions do not yet exist. This operationalization allows for focused studies to identify predictors and correlates of these concepts.

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