Gardner *et al. Alzheimer's Research & Therapy* 2013, **5**:27
http://alzres.com/content/5/4/27

alzheimer's research&therapy

REVIEW

Dementia in the oldest old: a multi-factorial and growing public health issue

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Abstract

The population of oldest old, or people aged 85 and older, is growing rapidly. A better understanding of dementia in this population is thus of increasing national and global importance. In this review, we describe the major epidemiological studies, prevalence, clinical presentation, neuropathological and imaging features, risk factors, and treatment of dementia in the oldest old. Prevalence estimates for dementia among those aged 85+ ranges from 18 to 38%. The most common clinical syndromes are Alzheimer's dementia, vascular dementia, and mixed dementia from multiple etiologies. The rate of progression appears to be slower than in the younger old. Single neuropathological entities such as Alzheimer's dementia and Lewy body pathology appear to have declining relevance to cognitive decline, while mixed pathology with Alzheimer's disease, vascular disease (especially cortical microinfarcts), and hippocampal sclerosis appear to have increasing relevance. Neuroimaging data are sparse. Risk factors for dementia in the oldest old include a low level of education, poor mid-life general health, low level of physical activity, depression, and delirium, whereas apolipoprotein E genotype, late-life hypertension, hyperlipidemia, and elevated peripheral inflammatory markers appear to have less relevance. Treatment approaches require further study, but the oldest old may be more prone to negative side effects compared with younger patients and targeted therapies may be less efficacious since single pathologies are less frequent. We also highlight the limitations and challenges of research in this area, including the difficulty of defining functional decline, a necessary component for a dementia diagnosis, the lack of normative neuropsychological data, and other shortcomings inherent in existing diagnostic criteria. In summary, our understanding of dementia in the oldest old has advanced dramatically in recent years, but more research is needed, particularly among varied racial, ethnic, and socioeconomic groups, and with respect to biomarkers such as neuroimaging, modifiable risk factors, and therapy.

Introduction

The oldest old, or people aged 85 and older, are the fastest growing segment of the population in the United States and many other high-income and middle-income countries across the globe [1] (Figure 1). According to the US Census Bureau, in 2010 there were nearly 5.5 million Americans aged 85 or older [2]. This number is expected to triple or quadruple over the next 40 to 50 years [3,4]. The increase in the oldest members of society is predicted to coincide with a dramatic decline in the potential support ratio, persons aged 20 to 64 per person aged 65 or older. For example, recent Bayesian probabilistic population projections for Brazil predict that the potential support ratio will drop from 8.4 in 2012 to 2.5 by 2050, and similar declines are expected in most countries worldwide [5]. Large population-based studies demonstrate an exponential increase in dementia incidence after the age of 65, doubling roughly every 5 years, such that more than 50% of centenarians may be expected to suffer from dementia [6]. The net effect globally will be to produce an expanding number of older people with dementia concurrent with a shrinking support ratio of potential caregivers. Furthermore, despite the fact that the oldest old represent the largest and fastest growing population with dementia [7], the majority of dementia research focuses on the younger old. An improved understanding of dementia in this oldest population is therefore of urgent national and global importance.

The use of the term 'oldest old' to refer to people aged 85 or older was originally suggested by Riley and Suzman

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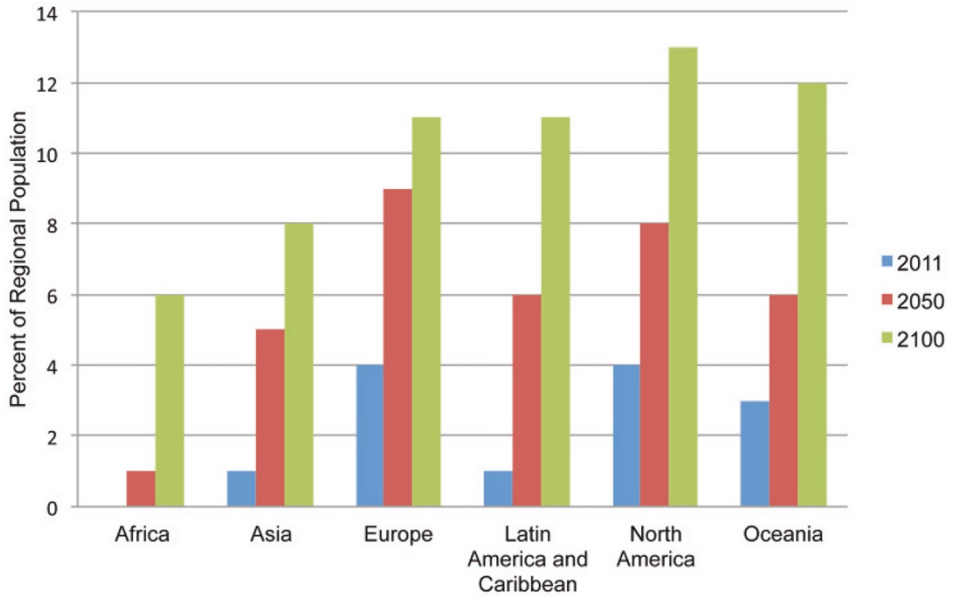

Figure 1. Projected increase in percentage of regional population comprised of people age 80+. Data derived from the United Nations, Department of Economic and Social Affairs, Population Division (2011) [84]. Data were not available for people aged 85+ or 90+.

in the mid-1980s in an effort to focus attention on this growing segment of the population [8,9]. It is important to note that the cutoff at age 85 is fairly arbitrary and largely serves to create consensus and uniformity between studies. As the population has continued to age since the term 'oldest old' was originally coined, there are those who may argue that the definition should be revised to include only those aged 90 and older.

In this review, we describe the major epidemiological studies, prevalence, clinical presentation, neuropathological and imaging features, risk factors, and treatment of dementia in the oldest old after highlighting the limitations and challenges of current medical research in this important area. This subject does not lend itself well to a systematic review given the evolving nature of this field. The information presented in this review was thus gathered via PubMed searches using a variety of search terms (including but not limited to 'oldest old', 'dementia', 'nonagenarian', and 'centenarian') and review of references from these publications. Throughout the text we will use the terms Alzheimer's dementia (AD) to refer to the clinical syndrome, while the phrase AD pathology will refer to the neuropathological entity. Lastly, while we acknowledge that many important epidemiological studies have included large numbers of oldest old subjects [10], for the purposes of this review we have chosen to focus on studies that have included only the oldest old or who have reported results of subgroup analyses of the oldest old. This decision was made in an effort to focus on what is known about this specific population without diluting the results with those from the younger old.

Challenges of diagnosing dementia in the oldest old

Numerous challenges are identified in diagnosing dementia among the oldest old (Table 1) and must be kept in mind whenever interpreting studies of dementia in this population. Many current research studies of the oldest old utilize the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [11] or revised 3rd edition [12] criteria for a diagnosis of dementia. Criteria from both of these Diagnostic and Statistical Manual of Mental Disorders versions require manifestation of impairment in memory and one or more other cognitive domains that is severe enough to produce significant functional decline. In the oldest old population, the growing number of noncognitive physical (sensory, musculoskeletal) and medical co-morbidities contribute to functional decline and may lead to overdiagnosis of significant functional decline. On the other hand, restricted cognitive demands on this population (who are generally no longer working and may have more limited household duties due to medical co-morbidities), societal perceptions about cognitive decline being a part of normal aging, or even the increased likelihood of cognitive impairment in the collateral informants of oldest old compared with younger old patients, could lead to underdiagnosis of decline.

Accurate neuropsychological assessment is challenging given the limited age-specific normative data in this population. Consensus criteria for cognitive impairment often require >1 or >1.5 standard deviations below norms [13]. While a few recent studies describe normative

Table 1. Challenges of diagnosing dementia in the oldest old

Challenges	Repercussions
Medical illness, sensory loss (vision/hearing), and physical impairments increasingly contribute to functional decline	Functional impairment is overestimated, leading to overdiagnosis of dementia
Retirement and restricted household responsibilities lead to reduced cognitive demands	Functional impairment is underestimated, leading to underdiagnosis of dementia
Cognitive decline may be considered part of normal aging	Functional impairment is underestimated, leading to underdiagnosis of dementia
Increased likelihood of cognitive impairment in collateral informants of the oldest old compared with the younger old	Functional impairment is underestimated, leading to underdiagnosis of dementia
Lack of normative neuropsychological data	Objective cognitive impairments are overestimated or underestimated, leading to misdiagnosis
Limitations of standard diagnostic criteria	More sensitive for some dementia subtypes, less sensitive for other types

neuropsychological data among the oldest old [14-17], more research is needed particularly among different socioeconomic and ethnic/racial groups. Normative values for a neuropsychological battery among Puerto Rican nonagenarians were recently published [18], which will be helpful for testing Spanish-speaking older people but may have limited applicability to subjects outside Puerto Rico.

Lastly, while the current DSM-IV criteria may be appropriate for identifying typical cases of AD, in which memory is affected early, they would be less accurate for vascular dementia, dementia with Lewy bodies (DLB), or mixed dementia in which memory may be relatively spared in the earlier disease stages. The DSM-IV criteria are currently undergoing revision and the revised version is expected to at least partially address this concern. Furthermore, the recently updated National Institute on Aging–Alzheimer's Association guidelines for the diagnosis of AD incorporate a broadened understanding of the different clinical presentations due to AD pathology.

Major epidemiological studies of the oldest old

Most study cohorts of the oldest old to date have either been small [19] or have been located in the United States or Europe, where predominantly white elders of high socioeconomic status were included. Most epidemiological data in this population were derived from four large cohort studies: the 90+ Study [6], the Leiden 85-Plus Study [20], the Vantaa 85+ Study [21], and the Women Cognitive Impairment Study of Exceptional Aging (WISE) [22], an ancillary study to the Study of Osteoporotic Fractures. The Kungsholmen Project [23,24], the Eurodem group [25], the Canadian Study of Health and Aging [26], and the Cache County Study on Memory, Health, and Aging [27] – while not dedicated exclusively to the study of the oldest old – all included very large cohorts of oldest old subjects, allowing contributions to our understanding of dementia in this demographic (Table 2). The Cache County Study was conducted within a unique population of men in Utah noted to have among the longest life expectancies in the United States, potentially limiting applicability to the broader US or global population. Dementia is a growing global health concern with most of the projected increases in prevalence over the next 40 years expected to occur in low and middle-income countries [28]. Studies completed among different racial, ethnic, and socioeconomic groups as well as across different continents are thus greatly needed.

Prevalence and incidence of dementia in the oldest old

Based on these eight large epidemiological studies, dementia prevalence ranges from 18 to 38% among those aged 85 and older, and from 28 to 44% among those aged 90 and older (Table 2). The Eurodem collaboration provided the first large prevalence study as they pooled multiple studies across Europe, and reported that dementia prevalence and incidence continue to increase dramatically with age, even beyond age 90 [29]. More recently, the 90+ Study confirmed that dementia prevalence and incidence continue to increase after age 90, but only for women [6,30]. The prevalence of dementia was found to double roughly every 5 years such that 27% of women aged 90 to 91 were diagnosed with dementia compared with 71% of women aged 98 to 99. Interestingly, the prevalence for men remained fairly stable, increasing only from 21% in the low-90s age group to 33% in men aged over 100. The overall prevalence of dementia for the entire cohort, which was mostly women, was 41%; the overall incidence of dementia was 18% and appeared to nearly double every 5 years after age 90. This disparity between dementia prevalence among oldest old women versus oldest old men is consistent with most prior prevalence studies [20,23,24,26,31-33]. This difference in prevalence is possibly due in part to women's different reproductive hormonal exposure, increased capacity for survival with any degree of cognitive or medical illness as compared with men [34], as well as lower levels of education among current oldest

Table 2. Prevalence of dementia according to major studies specifically examining the oldest old

Study	Age (years)	*n*	Population	Level of education	Baseline dementia prevalence
90+ Study [6]	90+	911	Survivors of Leisure World Cohort Study (77% female)	High (51% vocational school or college degree)	41% (45% of females; 28% of males)
Leiden 85-Plus Study [20]	85+	891	Inhabitants of Leiden, Sweden (72% female)	Not reported	23% (24% of females; 18% of males; 34% of 90+)
Vantaa 85+ Study [21]	85+	521	Inhabitants of Vantaa, Finland (79% female)	Low (mean 4.2 years)	38% (39% of females; 35% of males; 90+ data not available)
WISE [22]	85+	1,299	Ancillary study to Study of Osteoporotic Fractures (100% female)	High (85% high school or greater)	18% (28% of 90+)
Kungsholmen Project [23,24]	85+	987	Inhabitants of the Kungsholmen district, Stockholm, Sweden (68% female)	Low (63% of 90+ participants only elementary school)	32% (36% of females; 22% of males; 39% of 90+)
Cache County Study [27]	85+	719	Inhabitants of Cache County, Utah (66% female)	Medium (mean 12.1 years)	23% (24% of females; 20% of males; 38% of 90+)
Eurodem [25]	85+	1,623	Combined data from dementia prevalence studies conducted in 10 different European countries, including the Leiden 85-Plus Study (73% female)	Variable	24% (26% of females; 22% of males; 33% of 90+)
Canadian Study of Health and Aging [26]	85+	1,807	Inhabitants of Canada (72% female)	Medium (mean 9 years)	29% (31% of females; 23% of males; 44% of 90+)

Major publications from which prevalence data were derived are cited for each study. WISE, Women Cognitive Impairment Study of Exceptional Aging.

old women, a factor that is associated with higher rates of dementia [22,30].

WISE focused on oldest old women and assessed dementia and mild cognitive impairment (MCI). They reported that the prevalence of significant cognitive impairment is 41% among women aged 85 and over. Of these, 18% were diagnosed with dementia (28% of women aged 90 and over), while 23% were diagnosed with MCI [22]. The dementia prevalence was somewhat lower than most prior studies, including the 90+ Study. Since MCI was not specifically assessed in prior studies, it is possible that some MCI cases were inaccurately categorized as dementia.

The 90+ Study and WISE were both comprised predominantly of white subjects with high socioeconomic status. There is a small body of literature examining dementia prevalence in different ethnic/racial groups within the United States. The North Manhattan Aging Project, for example, included a small cohort of 85+ year olds and found that dementia prevalence was higher in Latinos (63%) and African-Americans (59%) compared with non-Latino whites (30%) [35]. Rural populations are difficult to access, are understudied, and may be at increased risk for cognitive decline as demonstrated by a small study of elders living in rural Oregon aged 97+ that found near-universal cognitive impairment (61% with dementia; 29% with MCI) [36]. These dramatic disparities require further study in larger populations and, if confirmed, should stimulate research to better understand underlying risk factors or biological differences.

The variability in prevalence rates reported by different studies may thus be indicative of differences between populations, differences in study design and diagnostic criteria, or even shifting prevalence rates over time. A recent Swedish study assessed dementia prevalence among the oldest old in two separate population-based assessments 5 years apart, each including >400 subjects with equivalent age and gender distributions. The prevalence of dementia in the earlier study was 27% versus 37% in the later study, in which subjects were taking significantly more β-blockers and anti-lipid agents [37]. These findings suggest that prevalence of dementia among oldest old may gradually increase over time either because patients with dementia are living longer or because increased medical interventions are inadvertently contributing to cognitive dysfunction in this vulnerable population.

Clinical presentation of dementia in the oldest old

There is some debate in the literature regarding clinical subtypes of dementia in the oldest old, which may be, in part, due to methodological differences among studies. The most common subtypes of dementia identified in the 90+ Study, the Canadian Study of Health and Aging, and

a large European meta-analysis were AD and vascular dementia [26,30,38]. The most common subtypes in WISE, however, were AD and mixed dementia (defined as evidence of multiple etiologies), the latter of which was not assessed in most prior studies. There is little known about behavioral changes that may accompany cognitive decline in the oldest old, aside from the development of depression as discussed below in the risk factor section.

There is some evidence that dementia, particularly AD, has a slower rate of progression (according to neuropsychiatric measures and cerebrospinal fluid and imaging biomarkers) in the oldest old compared with the younger old [39]. Progression of functional decline and dependency, however, may be more rapid [40]. These findings could have major implications for treatment trials because any therapeutic drug effect, as measured by cognitive testing or other disease-specific biomarkers, could be much smaller than in a younger old population.

Neuropathology and neuroimaging of dementia in the oldest old

Alzheimer's dementia pathology and Lewy body pathology become less clinically relevant with age

There is mounting evidence that the underlying neuropathological basis of dementia among the oldest old is quite different from that of younger old patients. Two large autopsy series have reported decreasing density of AD pathology and decreasing association between AD pathology and dementia with advancing age [41,42]. Interestingly, cortical cerebral atrophy remained strongly associated with dementia despite advancing age [41]. Subsequently, an analysis of a large autopsy dataset from the National Alzheimer's Coordinating Center database noted that, while there was a continued association between AD pathology and clinical dementia even in the oldest old, this relationship declined with age, specifically for neurofibrillary tangle pathology [43]. Others have reported a continued association between AD pathology and dementia in the oldest old [44,45], but the strength of the association is generally less than that reported in the younger old [46]. These findings suggest that there is something other than or in addition to AD pathology that is driving cerebral atrophy, and resultant dementia, in the oldest old.

Similar findings have been reported for Lewy body pathology. A large autopsy series reported an age-related decline in the prevalence of pathological diagnoses of DLB, less severe Lewy body pathology among cases that met pathological criteria for DLB, a shift in Lewy body distribution from diffuse neocortical localization in the younger old to brainstem restricted localization, and no association between either AD or Lewy body pathology and cognitive impairment in the oldest old. In this study, none of the oldest old patients with dementia and brainstem restricted Lewy body pathology met the pathological criteria for AD, suggesting that an additional pathological process may have been responsible for their dementia [47]. The National Alzheimer's Coordinating Center dataset study also reported a decreasing association between Lewy body pathology and dementia with age [43]. These findings hint at the possibility that the pathological phenotype of DLB in the oldest old is different from that in the younger old, and suggest that dementia in the oldest old is probably a result of mixed pathology rather than a single neuropathological entity.

Other recent work has investigated additional neuropathological contributors to dementia in the oldest old. Cerebrovascular pathology appears to correlate well with cognition across all ages, even among the oldest old [48]. With age, mixed pathology with AD and vascular disease has been reported to increase while pure AD or pure Lewy body pathology decreases [49]. A careful study assessing different types of vascular pathology in the oldest old found that cortical microinfarcts correlate best with cognitive impairment rather than diffuse white matter disease, periventricular disease, or even thalamic and basal ganglia lacunes [45]. Others report that as the prevalence of AD pathology begins to decline in extreme old age (95+), the prevalence of TAR DNA protein 43 (TDP-43)-associated hippocampal sclerosis begins to dramatically increase, an association that is not seen in younger patients with hippocampal sclerosis [50]. The etiology of this TDP-43-associated hippocampal sclerosis of aging is currently poorly understood and requires further research.

Overall, there is mounting evidence that with advancing age there are increasing burdens of often co-morbid AD, vascular, and Lewy body pathology [51]. A recent large autopsy series demonstrated that AD plus vascular disease appears to be the most common type of mixed pathology in the oldest old. Furthermore, co-existing pathologies appear to increase risk for dementia, with proportionally greater numbers of oldest old patients with mixed pathology demonstrating dementia compared with the oldest old with single pathologies [52].

Imaging

There is limited literature on imaging findings in the oldest old. A postmortem radiological–pathological study from the Vantaa 85+ Study demonstrated that frontal lobe white matter lesions on magnetic resonance imaging were more common in brains that had concomitant AD pathology, and demonstrated that medial temporal lobe atrophy was not specific for AD pathology in the oldest old [53,54]. A computed tomography study of 236 subjects aged 85 and older found higher rates of white matter hypodensities in demented compared with nondemented subjects [55]. Furthermore, the severity of

white matter lesion burden correlated with increasing risk for dementia. A small florbetapir F18 positron emission tomography study of 13 nondemented older people from the 90+ Study reported that greater amyloid load was associated with worse cognitive performance and faster cognitive decline [56]. The authors argue that the discrepancy with neuropathological findings arises from the high number of nondemented oldest old with substantial burden of amyloid pathology and suggest that these older people may be in the early preclinical stages of dementia. These imaging findings further support the idea that dementia in the oldest old has important contributions from multiple pathologies occurring simultaneously, but more imaging research is needed in this understudied population.

Risk factors for dementia in the oldest old

Studying dementia risk factors in the oldest old is limited by major confounders of survival effect and cohort effect. Survival effect may lead the same factors that increase risk of dementia and mortality in the younger old to no longer appear as risk factors for dementia in the oldest old, since those who survive despite these risk factors may somehow be resilient to them. Cohort effects may cause certain risk factors to become more or less relevant across time and place, due to, for example, increasing rates of mid-life obesity in the United States or declining rates of gender disparity in level of education. With these confounders in mind, we summarize findings from the growing, but still incomplete, body of literature regarding dementia risk factors in this population (Table 3).

Cognitive reserve and level of education

Similar to studies of the younger old, both the 90+ Study and WISE have confirmed an association between lower level of education and increased risk of dementia in the oldest old [6,22]. This finding highlights the importance of cognitive reserve, even in the most advanced ages. A lingering unanswered question remains of whether continued learning into advanced age is similarly protective.

Mid-life medical illness

A compelling analysis from the Honolulu Asia Aging Study of Japanese-American men found an association between mid-life general health and the likelihood of disability-free and cognitive-impairment-free survival until age 85. Healthy survival was significantly associated with higher grip strength, leaner body habitus, absence of hyperglycemia, hypertriglyceridemia, or hypertension, avoidance of excessive alcohol intake or smoking, and higher level of education in mid-life [57]. This study was methodologically strong since it examined these men in mid-life and then re-examined them again in late life.

Late-life cardiovascular risk factors

Diabetes

In the Vantaa 85+ Study, a history of diabetes was associated with more extensive vascular pathology at autopsy and a doubled dementia incidence during life [58]. In WISE, however, diabetes was not a risk factor for dementia – an unexpected finding that was attributed to increased mortality among patients with diabetes and cognitive impairment [59]. Overall, these data indicate that diabetes may increase the risk of dementia among the oldest old, specifically by increasing the burden of vascular, rather than AD, pathology, and they highlight the importance of controlling diabetes earlier in life before vascular injury has been sustained.

Hypertension

The Kungsholmen Project reported that systolic blood pressure <130 mmHg or >180 mmHg may increase risk of cognitive decline in people aged 75 and older [60]. More recently, both the Leiden 85-Plus and Vantaa 85+ study groups have examined this question among the oldest old. The Leiden 85-Plus group reported that higher blood pressure at age 85 was associated with less functional and cognitive decline over time, particularly among subjects with more physical disability, defined as disability in activities of daily living. This finding was independent of cardiovascular risk factors or even heart failure [61]. The authors speculate that the oldest old with physical disability may require higher blood pressure to maintain adequate cerebral perfusion to prevent cognitive decline. The Vantaa 85+ group reported increased mortality among the oldest old with lower blood pressure [21] but no significant relationship between baseline blood pressure and incident dementia [62]. These studies raise the question of whether relative hypotension in the oldest old is a direct consequence of the pathophysiology of dementia and other medical co-morbidities or actually a risk factor for dementia. Thus, while midlife hypertension appears to be a risk factor for development of later-life dementia, more research is needed to pinpoint the ideal blood pressure range for the oldest old population.

Dyslipidemia

A higher total cholesterol level has been associated with improved memory function [63] and increased longevity [64] in the oldest old. Lower high-density lipoprotein cholesterol, however, has been associated with increased risk of dementia in the oldest old, independent of prior history of cardiovascular disease or stroke [65]. Thus, while it seems that controlling dyslipidemia in middle-life is quite important for the prevention of stroke and probably also dementia in later life, it is unclear whether there is a role for continued lipid control in very advanced

Table 3. Risk factors for dementia in the oldest old

Associated with increased dementia risk	No clear association with dementia risk	Equivocal, more research needed
Low level of education	APOE E4 allele	Late-life dyslipidemia
Poor mid-life health[a]	APOE E2 allele	Late-life diabetes
Low level of physical activity		Late-life elevations in C-reactive protein or other inflammatory markers
Delirium		Late-life hypertension
Depression		

APOE, apolipoprotein E. [a]Low grip-strength, overweight/obesity, hypertriglyceridemia, hyperglycemia, hypertension, excessive alcohol intake, smoking.

age or whether aggressive lipid control could actually be detrimental. Further research in this area is needed.

Late-life medical illness

The above discussion of late-life cardiovascular risk factors raises the question of whether optimizing general health at or after the age of 85 has any measurable effect on dementia risk. A small observational study from the Oregon Brain Aging Study prospectively followed 100 optimally healthy subjects aged 85+ for an average of 5.6 years [66]. Over the study period, 23 subjects developed AD. Overall, the lifetime risk of AD was similar to the general population, but the age of onset was dramatically later (mean age of onset for AD was 100). This study suggests that while being in optimal general medical health at age 85+ does not guarantee against development of AD, it may delay the onset, which could have significant public health implications.

Physical activity

Studies of younger older people have demonstrated that physical activity throughout the lifespan as well as physical activity in late-life is associated with reduced risk of dementia [67,68]. There is mounting evidence that physical activity may remain important for modifying dementia risk even for the oldest old. An analysis from the Oregon Brain Aging Study prospectively followed 66 initially healthy men and women aged 85+, demonstrating that women who self-reported at least 4 hours of exercise per week had an 88% reduced risk of cognitive decline compared with women who reported exercising less than 4 hours per week. In men, a similar but insignificant association was found, probably due to the smaller sample size (27 men versus 39 women) [69]. These findings warrant further study and intervention trials in the oldest old population.

Depression

Depression is common among older adults and has been associated with increased risk of cognitive decline [70,71]. Until recently, little was known about the relationship of depression to dementia among the oldest old. WISE found that 65% of women with depressive symptoms at baseline developed dementia over a 5-year follow-up compared with only 37% of those without significant depressive symptoms [72]. These findings raise the question of whether depression is the earliest sign of cognitive decline or an actual risk factor for dementia. Research on subjects of various ages has demonstrated that a history of repeated episodes of major depression correlates with smaller hippocampal volumes [73], suggesting a possible causal relationship but not ruling out the possibility of a shared underlying disease process.

Delirium

Neurologists have long suspected that delirium may be a marker of preclinical dementia. This association was rigorously evaluated by the Vantaa 85+ investigators, where a history of delirium increased the incident dementia odds ratio more than eightfold, was associated with more severe dementia, increased mortality among those already demented, and was associated with faster decline in cognitive scores across the entire cohort. These findings support the idea that dementia is a risk factor for delirium and *vice versa*. Among the 288 members of their cohort that underwent autopsy, staging of classical neuropathological entities such as AD, vascular, and α-synuclein pathology was associated with dementia in subjects without a history of delirium, but was not associated with dementia in subjects with a history of delirium [74]. This neuropathological finding, while underpowered, raises the question of whether patients with delirium have been exposed to certain environmental or iatrogenic factors that play a significant role in development and progression of dementia and whether delirium may not only be a marker of but a contributor to cognitive decline. These are questions that require further research.

Apolipoprotein E genotype

The prevalence of apolipoprotein E (APOE) ε4 alleles drops significantly with age (50% lower in octogenarians compared with middle-aged adults) while the prevalence of APOE ε2 alleles may remain static or increase slightly with age [75]. These age-related shifts in APOE genotype

prevalence are interesting in light of recent literature regarding APOE genotype and dementia risk in the oldest old. The Vantaa 85+ Study reported no increased incidence of dementia among oldest old APOE ε4 allele carriers compared with noncarriers. Among the oldest old already found to have dementia at the baseline assessment, however, the rate of progression was faster among APOE ε4 carriers [76]. Interestingly, WISE reported no evidence of a protective effect from the APOE ε2 allele with respect to lowering the risk of dementia in the oldest old, an association that has been reported previously for younger old. These results are similar to those reported in the 90+ Study [77]. These findings may reflect a survival effect or may suggest that once an older person reaches a very advanced age in a dementia-free state, then both the protective and deleterious effects of the APOE genotype may be outweighed by other more powerful genetic or environmental factors. In conclusion, the role of APOE ε4 and APOE ε2 alleles may have declining relevance among dementia-free oldest old, thus arguing against the concept that the high-risk APOE ε4 allele may be fully penetrant if one lives long enough.

Peripheral inflammation

Many large epidemiological studies have reported an association between higher levels of serum inflammatory markers and increased risk of cognitive decline among older adults. The role of inflammation among the oldest old remains unclear. For example, while the 90+ Study reported increased all-cause dementia prevalence and mortality among the oldest old with higher levels of C-reactive protein, particularly among women, elevated C-reactive protein levels did not increase the incidence of all-cause dementia [78,79]. Similarly, the Vantaa 85+ Study reported only a weak association between cognitive decline and inflammatory markers among nondemented oldest old enrollees [80]. Others have reported a lower risk of dementia in relatives of oldest old cognitively intact subjects with elevated C-reactive protein, suggesting a possible genetic predisposition for successful aging in these subjects [81]. A rigorous autopsy analysis of brain gene and protein expression in demented and nondemented older adults reported that immune response genes are downregulated in nondemented younger old subjects, but are actually upregulated in nondemented oldest old subjects. Thus, increased immune activation in the brain may actually be protective against cognitive impairment in the oldest old [82]. An important question raised by this line of research is whether the finding is due to survival effect.

Treatment of dementia in the oldest old

To date, no drug trials have been targeted specifically at dementia in the oldest old. As mentioned above, the slower rate of progression among the oldest old with dementia may present a challenge to the design of clinical trials, as more subjects may be needed to observe an effect. Furthermore, the increasing prevalence of mixed pathologies among the oldest old renders targeted disease-modifying agents less appealing in this population.

Another important consideration in this population is the possibility that side effects may differ from those observed in the younger old. For example, one study recently reported on the safety and tolerability of donepezil at 10 mg versus 23 mg dose in a large cohort of older patients with dementia, including 116 patients aged 85 to 90 years [83]. They reported higher rates of diarrhea and urinary tract infections with increasing age regardless of dose. They also found higher rates of fatigue, somnolence, and urinary incontinence with increasing age only in the 23 mg dose group. These findings raise concern that the 23 mg dose of donepezil may be relatively contraindicated in the oldest old.

There are thus few data on which to base recommendations for alterations in the pharmacologic management of dementia in the oldest old. The geriatrician's mantra of 'start low and go slow' may be wisely employed in this population, which may be more prone to adverse side effects that their younger old counterparts.

Future directions and recommendations

As the global population of the oldest old continues to increase, the number of oldest old living with dementia in the United States could increase from 1 to 2 million in 2010 to more than 8 million by 2050 or 2060. Research into the prevalence, clinical presentation, neuropathology, and risk factors of dementia in the oldest old has advanced considerably in recent years, but further research is greatly needed. Improved diagnostic criteria and neuropsychological norms are needed to ensure accurate diagnosis in this population. Our understanding of the prevalence of dementia among the oldest old of different socioeconomic, ethnic, and racial backgrounds is lacking. Small studies hint at dramatic disparities between dementia prevalence among Caucasians, Hispanics, African Americans, and rural populations in the United States; a finding that may ultimately render estimates from the major epidemiological studies profoundly inaccurate. The growing evidence for the importance of mixed pathology with Alzheimer's, vascular, and Lewy body pathology as well as TDP-43-mediated hippocampal sclerosis and the possibility of additional undiscovered neuropathologies accounting for cognitive decline among the oldest old requires further study and makes targeted disease-modifying therapies less appealing in this population. The possibility of slower rates of progression of dementia among the oldest old

may make it more difficult to adequately power therapeutic trials. The role of many traditional risk factors for dementia, such as cardiovascular risk factors and inflammation, remain unclear in extreme old age, but may have important relevance for the delivery of primary care to these patients.

In conclusion, based on the current evidence, a focus on establishing and maintaining a healthy active lifestyle from mid-life onwards appears to be of utmost importance with respect to staving off dementia in old age. Once a patient reaches old age, aggressive treatment of cardiovascular risk factors should perhaps be approached with caution. In the event that dementia develops at the age of 85+, the utility of targeted therapy should be carefully weighed against potential side effects and the likelihood of mixed underlying pathology.

Abbreviations

AD, Alzheimer's dementia; APOE, apolipoprotein E; DLB, dementia with Lewy bodies; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; MCI, mild cognitive impairment; TDP-43, TAR DNA protein 43; WISE, Women Cognitive Impairment Study of Exceptional Aging.

Competing interests

RCG and VV have nothing to disclose. KY has served on data safety monitoring boards for Takeda Pharmaceuticals, Inc. and the National Institutes of Health (National Institute of Mental Health and National Institute on Aging trials), and has received research support from the National Institutes of Health (National Institute on Aging, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Mental Health), the Department of Defense, the American Health Assistance Foundation, the Anonymous Foundation, and the Alzheimer's Association.

Acknowledgements

Research reported in this publication was supported by the National Institute on Aging of the National Institutes of Health under Award Number T32AG023481 (RCG), K24AG031155 (KY), and R01AG05401 (KY). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This research was also supported by the Alzheimer's Association, grant IIRG-08-88872 (KY).

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Published: 1 July 2013

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doi:10.1186/alzrt181
Cite this article as: Gardner RC, *et al.*: Dementia in the oldest old: a multi-factorial and growing public health issue. *Alzheimer's Research & Therapy* 2013, **5:**27.