Review Article

Challenges of Diagnosing Dementia in the Oldest Old Population

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People aged 90 and older are the fastest growing age group in most parts of the world. Since the prevalence of dementia has been shown to increase exponentially after the age of 65, there is an acceptance that the oldest old population has a high burden of dementia; however, there is a lack of consensus on how best to diagnose dementia in this population. This review summarizes the various approaches to diagnosing dementia and the prevalence and incidence rates of dementia that have been reported. We also summarize the literature on cognitive and functional performance and biomarkers for dementia and discuss the limitations to interpretation of these data. Finally, we make recommendations for both researchers and clinicians who intend to diagnose dementia in the oldest old population.

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The “oldest old” group, variously described as 80, 85, or 90 years and older, is the fastest growing age group in most parts of the world (1–3). Although the world population overall is predicted to increase by 34% between 2011 and 2050 to just more than 9 billion, the population of people aged 90 and older is predicted to increase by 558% to 86.5 million, that is, an increase of 291% in the more developed countries and 1065% in the less developed countries (4). This review will focus on the age group of 90 and older as representing the oldest old group as it is the fastest growing segment of the population (5). As their numbers grow, there is likely to be an increasing public health focus on the management of dementia in this age group.

Since the prevalence of dementia has been shown to increase exponentially after the age of 65, there is an acceptance that the oldest old population has a high burden of dementia. There is however a lack of consensus on how best to diagnose dementia in this population. Below, we have summarized the most common methods for diagnosing dementia and outlined challenges in implementing these criteria in the oldest old group. In particular, we focus on assessment of cognition and function, summarize the current literature, point out difficulties inherent in assessing cognition and function in the oldest old group, briefly review added benefits of biomarkers, summarize the literature on prevalence and incidence of mild cognitive impairment (MCI) and dementia in the oldest old population, and recommend how the field may be moved forward.

Diagnosis of Dementia

The criteria for the diagnosis of dementia have intrinsic difficulties when used with the oldest old population. The Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision defines dementia as characterized by multiple cognitive deficits including impairment in memory, which represent a decline from previous levels of functioning (6). There are several issues inherent with using this type of definition with the oldest old population. First, normative data, necessary to determine impairment in memory or any other cognitive domain, are not widely available for this age group. Second, in extreme old age, a decline from previous levels of cognition is often regarded as “normal”—that is, aging is considered to inevitably affect cognition (7), thereby making it difficult to distinguish it from cognitive decline from a pathological process assumed to underlie dementia. Third, sensory or physical limitations, fatigue, and medical comorbidities may affect cognitive performance, which may be difficult to account for or to avoid in this group (for an in-depth discussion of these issues, see [8]).
The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable Alzheimer’s disease (AD) include progressive worsening of memory and other cognitive functions and state that “Neuropsychological tests may provide additional information for the diagnosis of dementia. . . . A score falling in the lowest fifth percentile of an individual’s normal control group may be designated as ‘abnormal’” (p. 941, [9]), again reinforcing the need for normative, or at least control group, data. Although recent proposed diagnostic criteria exempt “inefficient retrieval strategies associated with normal ageing” (p. 738, [10]), the issue remains how to determine what is “normal” beyond the age of 90.

The concept of “normal” in this context is contentious. Statistically, if the vast majority of population aged more than 90 years have a significant cognitive or functional decline from previous levels, this decline would in fact be considered normal, and only those below the fifth percentile of decline (for example) would be classified as abnormal. This is the traditional method taken for normative data approaches to neuropsychological testing. Alternatively, normal could be considered to mean being relatively disease free and able to function independently, as would be true for a younger cohort. In that case, most oldest old population will meet criteria for abnormality. This is the approach taken for describing “impairment” in visual acuity, with no concession being given to age or disease. Further, when constructing standards of normal in the oldest old population and devising normative data sets, we need to question whether they should be a truly representative sample of the whole population or whether only disease-free participants’ data be included, so that aging and disease are not confounded (11). The latter approach creates a data set that represents a “statistically supernormal” group.

It can be argued that no matter which criteria are used, the essential elements of a dementia diagnosis is that the individual has suffered a decline in cognitive function to an extent that the person’s activities of daily living (ADLs) have been affected and they can no longer independently care for themselves. The first element warrants a careful assessment of cognitive status and a judgment that this indeed represents a decline from a previous level. The second element warrants an assessment of functional abilities whose loss can be attributed to the cognitive decline.

Assessment of Cognition in the Oldest Old Population

Cognitive assessment is core to dementia diagnosis, therefore, we have summarized the evidence for cognitive preservation or decline in the oldest old population here. Several studies have found continued decline of episodic memory through the tenth and eleventh decades of life using either longitudinal (12) or cross-sectional data (13). The strategies that the oldest old group use to remember may not change; however, as participants aged more than 90 in the Louisiana Healthy Aging Study used picture cues and organizational strategies as effectively as younger groups to support memory recall (14). Autobiographical memory is thought to be relatively preserved in older individuals (15–17), although we found only one published study that examined individuals aged more than 90. Fromholt and colleagues (18) found that centenarians recalled fewer and less detailed memories compared with 80-year-old participants using a free narrative method, when participants were asked to recall life events in an unstructured way within a time limit. This method is vulnerable to a number of confounds, such as language fluency and anxiety, which were not controlled for in this study.

Attentional resources or capacity are particularly susceptible to aging (19,20) and can have significant secondary effects on other cognitive domains. Along with memory, attention has been considered to be the most important neuropsychological function to discriminate older adults whose cognition may progressively deteriorate from those who will remain stable (21,22), and yet it is a relatively unexplored area in the oldest old population. Processing speed is also known to be particularly susceptible to the effects of aging (23) and is thought by some to be a major factor underlying age-related changes in cognition (24–26). Although several studies have investigated this in nonagenarians and centenarians, these used tests which require good fine motor control and vision, such as digit symbol substitution (27), and did not compare performance between people aged more than 90 and a younger group. Trail Making Test Part A has been variously categorized as a test of attention and processing speed, as well as visuospatial ability. Normative data have been published for this test, which show continuing decline with age, but the oldest old age groups have consisted of small samples ranging widely in age, such as “77–99” (28) or “≥85” (29). Aspects of language performance are thought to be relatively stable with age, in particular irregular word reading (30), but performance on animal fluency and naming was shown in a cross-sectional study to be poorer after age 90 (31).

Executive functions, such as planning and strategic problem solving for visuospatial tasks, were found to be largely preserved in Polish centenarians; however, verbal fluency and abstract thinking had deteriorated compared with a younger cohort, which the authors concluded was a sign of impaired right hemisphere function versus left (32).

In summary, there is evidence for the preservation of specific cognitive skills in the oldest old group, including memory strategies and aspects of language and executive function; there is also evidence for impairment in episodic memory, attention, processing speed, and aspects of language and executive function.

Longitudinal Assessment

Diagnosis of dementia most often depends on evidence of cognitive decline, so it makes sense that longitudinal
assessment would be useful. In young–old participants, a 15-fold acceleration in cognitive decline was found in the 6 years prior to a diagnosis of AD (33). Yet, few studies have examined rate of cognitive change in oldest old participants longitudinally, and no study has examined rate of decline in oldest old participants with respect to later dementia diagnosis. Hickman and colleagues (34) reported no differences in the rate of cognitive change over 4 years between their young–old (aged 65–74) and old–old (aged 84–93) dementia-free participants, and in fact concluded that neither group experienced a measurable decline in cognitive function over the 4 years. In contrast, Singer and colleagues (12) reported a more rapid rate of decline in their oldest old group (aged 78–100) compared with their young–old group (aged 70–77) over 6 years on a number of cognitive domains. Perceptual speed, memory, and verbal fluency all declined with age, with a marked acceleration of decline in perceptual speed in the oldest old participants. Knowledge (measured by tests of vocabulary) remained stable until 90 and then declined. Although not specifically examining cognitive decline over time, Fine and colleagues (35) used change in Mini-Mental State Examination (MMSE) scores from baseline to 20-year follow-up to exclude those participants with statistically significant cognitive decline from a normative sample of 85- to 95-year-olds.

The current research involving longitudinal cognitive assessment in oldest old participants has produced mixed findings, and no study has yet linked it to later dementia diagnosis. As it has proved useful in younger age groups as a predictor of dementia, it is a key area for future research in the oldest old group.

**Limitations of Data**

There are normative data available for individuals aged more than 90, though these studies have limitations. Although Anstey and colleagues (36) published data for individuals aged 90–95, sample sizes were very small—ranging from 3 to 10 in each of the three education bands. Comprehensive data from the 90+ study are presented for a wide range of tests, split into 90–91, 92–94, and 95+ year olds (31). Half of individuals within this normative sample were described as “cognitively impaired, not demented,” suggesting that some of them may have been in a predementia phase. Further, although many of the included tests are only accessible to neuropsychologists, normative data are presented for the MMSE and Modified Mini Mental State (3MS), stratified by age group but unfortunately not by education. Further, the age category of 95+ years is too wide a range to be useful when specifically examining performance in oldest old participants. Another study presented normative data on the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) battery for 85- to 89-year olds and 90 years and older, again a wide age group, and did not separately state the sample size of these groups (37). Selected normative data are presented for individuals aged 90–99 from the Mayo Older Adult Normative Studies (28,38–40), although again sample sizes are very small in the oldest old groups and wide age ranges are therefore reported. Fine and colleagues recently published normative data for several tests for 90- to 95-year-old women, stratified by education. This study included women who were followed for more than 20 years, which may represent a skewed sample (35). Normative data from the Georgia Centenarian Study were more recently published for several neuropsychological tests, separated by gender, race, residence, and education but not by age (41).

To summarize, it seems that although there is evidence for decline in memory and attention in the oldest old group, language and executive function may be somewhat preserved. Comprehensive normative data are lacking, and there is a paucity of data demonstrating cognitive change longitudinally in the oldest old group, particularly data examining dementia as an endpoint.

**Assessment of Function in the Oldest Old Group**

Level of functional independence is also core to the diagnosis of dementia. Several studies have examined functional status of people aged more than 90 through observation of levels of independence or administration of questionnaires of ADL and instrumental ADL, where either the participant or a close relative or friend is asked how well the individual performs self-care tasks, such as bathing and dressing, and domestic tasks, such as shopping and cooking. In the Danish 1905 cohort (assessed at age 100), 21% of female and 22% of male centenarians were able to perform five basic ADL independently (42). In Goteborg, Sweden, residents aged 95 years old, 48% of those not classified as demented, still required assistance in ADL (43).

Better cognitive status and higher instrumental ADL were found to predict survival without functional decline in the NonaSantfeliu study (44). One study that examined the direct relationship between cognitive abilities and functional status in centenarians found a significant correlation between the Clinical Dementia Rating (CDR) scale and Barthel Index ADL (45), however, using the CDR as a measure of cognition is questionable as it is very broad, and does incorporate functional measures. It would be useful to compare more specific tests of cognition to functional status to establish the validity and thereby the meaningfulness of these tests.

Using functional independence as one criterion (among others), various groups have found 12% of centenarians to be “autonomous” (46); 20% in “good health status” (47); 22% “functionally independent” (48); and 20% to be “exceptional” or “normal” (49). In the Danish 1905 cohort, 30%-40% of participants aged 92-100 were found to be independent (based on physical and cognitive assessment [50]).

Although functional impairment assessed for dementia diagnosis should be based on cognitive decline and not on physical limitations, this is often difficult to differentiate
(51), and not all studies have reported that assessment of function accounted for physical or sensory limitations. Furthermore, there is a lack of longitudinal data to demonstrate the normal trajectory of function.

There is therefore a wide range of findings when examining functional status in the oldest old group, probably due to the range of methodologies used. Functional status needs to be clearly operationalized in order to use it as a criterion for dementia diagnosis.

**Biomarkers of Dementia in the Oldest Old Population**

More recently, the importance of biomarkers in making a dementia diagnosis has been highlighted (52,53). A range of neuropathologies accumulate with normal aging, including AD-type pathology, such as plaques and tangles, cerebral infarctions, and Lewy bodies (54). In the oldest old population in particular, significant amounts of neuropathology are found postmortem in both demented and nondemented individuals (55,56), there is less likely to be single pathology dementia, and the relationship between neuropathology and cognitive decline or dementia is less robust than in younger persons (56,57).

A number of biomarkers show promise for increasing the accuracy of antemortem diagnosis of AD and other dementias in younger age groups. Three categories of biomarker are the most validated for diagnosing AD: cerebrospinal fluid (amyloid β42, total tau, and phospho-tau), positron emission tomography (PET) imaging (amyloid tracer uptake, fluorodeoxyglucose), and structural MRI (medial temporal lobe atrophy [52,58]). Potential biomarkers related to other dementias include evidence of cerebrovascular disease on neuroimaging for vascular dementia and frontal or temporal atrophy on structural neuroimaging in frontotemporal dementia. These biomarkers have generally not yet been investigated in the oldest old population.

**Neuroimaging**

There is a linear decrease in grey matter volume with age (59). Greater atrophy of the hippocampus has been reported in MCI compared with normal aging on structural neuroimaging (60), and an increased rate of volume loss has been found in MCI compared with normal aging (61). Greater medial temporal lobe atrophy on postmortem MRI was associated with both clinically diagnosed dementia and pathologically confirmed AD in the oldest old group (aged more than 85), though it was not specific for AD (62). It is not yet established whether those in the oldest old group have atrophy rates consistent with normal aging or whether they start to look like pathological processes, such as MCI or AD. One longitudinal study of MRI in people aged 65-95 found constant rates of atrophy with age (63), however, the mean age of their oldest group was 87, with an average follow-up of 3 years.

The presence of white matter hyperintensities correlates with cerebrovascular risk factors and MRI infarction (64) and significantly increases the risk of MCI in the elderly people (65). Increasing severity of white matter hyperintensities is associated with cognitive impairment (66) independent of the effect of discrete cerebral infarction. White matter lesions are common in older adults, appearing in 94% of neuropathological samples in one community study (67). Previous studies have not assessed significant numbers of people aged more than 90. Piguet and colleagues (68) found that white matter hyperintensities were common in healthy older adults and were not related to cognitive functioning, however, the mean age of their cohort was 85.5 years.

Patients with AD show greater uptake of Pittsburgh Compound B (an amyloid tracer) on PET scans than controls (69), but we were unable to find published research examining these scans in the oldest old. Beeri and colleagues (70) used functional MRI during a recognition memory task in oldest old participants (aged more than 90) and compared their performance with participants in their seventies. They found that similar brain regions were activated in the oldest old group but to a lesser extent than the younger comparison group, in the context of relatively intact behavioral performance. This was interpreted as supportive of the cognitive reserve theory in these models of successful aging.

**Biomarkers in Cerebrospinal Fluid**

Low levels of amyloid β42 and elevated tau in cerebrospinal fluid have been associated with AD (71). The usefulness of measuring α-synuclein in cerebrospinal fluid for detecting Parkinson’s disease and dementia with Lewy bodies is questionable (72); however, it has been found to be useful to distinguish these dementias from AD (73). Again, we were unable to find research published on these biomarkers in the oldest old.

It seems therefore that while there is increasing interest in using biomarkers to support a diagnosis of dementia, how to interpret them in the oldest old remains unclear.

**Prevalence and Incidence of MCI and Dementia in the Oldest Old Population**

There is a range of dementia prevalence and incidence data reported in the oldest old literature. Studies of nonagenarians have reported that 12% have a diagnosis of MCI (74) and between 38% and 67% have a diagnosis of dementia (74–78).

A small sample of centenarians was reported to have an MCI prevalence of 15.2% (79). Widely divergent prevalence rates of dementia in centenarians are reported—from lows of 27% (although this rose to 42% once dropouts were accounted for; [80]) to highs of 76% (81) and 85% (albeit in a very small sample; [76]).
One study combining nonagenarians and centenarians found prevalence rates of 5.9% for cognitive impairment no dementia, 17.6% for age-associated memory impairment, and 32.4% for MCI (82), highlighting the importance of the classification system used for “predementia syndromes.” The same group reported differing dementia prevalence rates according to the classification system: 47.1% for Diagnostic and Statistical Manual of Mental Disorders, third edition, revised; 41.2% for Diagnostic and Statistical Manual of Mental Disorders, fourth edition; and 29.4% for International Classification of Diseases-Tenth Revision (83).

The much lower rate of MCI than dementia in these studies of the oldest old participants is counterintuitive and warrants analysis, as this contrast with studies that include the young—old in which the prevalence of MCI is reported to be higher than that of dementia (84). This may be a real effect, in that more oldest old individuals have multiple cognitive deficits plus significant functional impairment and so meet the criteria for dementia diagnosis more readily. This may reflect shortcomings in the current diagnostic schemata as outlined earlier. For example, the lack of sufficient normative data for cognitive tests in this age group may result in more oldest old participants being classified as having deficits in multiple cognitive domains due to the investigators comparing performance with normative data for younger adults, or their own impression based on experience based mainly on younger participants. Further, as the critical difference between multiple-domain MCI and dementia is significant functional impairment, dementia may be overdiagnosed due to the aforementioned difficulties of assessing function in the oldest old group.

The incidence of MCI and dementia has not been well investigated in those aged more than 90 years. There is some evidence that the usual rapid decline of cognitive performance just prior to death slows down in extreme old age (85), however, only simple tests of cognition were used in this study. A more comprehensive cognitive assessment of centenarians, which included longitudinal follow-up found decline in all tests except for inductive reasoning, but unfortunately they did not compare the results with a younger cohort (86). Incidence of undifferentiated dementia in 90- to 94-year olds was 10.8%, and in 95+ it was 15.7% in the Medical Research Council Ageing in Liverpool Project—Health Aspects study (87). A large study of those aged 90 and older found that prevalence of dementia doubles every 5 years for women (consistent with younger age groups; [88]) but not for men (75). These authors also reported dementia incidence of 18.2% per year in all those aged 90 and older, with a peak of 40.7% per year in centenarians alone (89). These figures were consistent for men and women, indicating that previously observed gender inequality may have been due to shorter survival in men. Recently, this same group reported a fourfold increase in dementia incidence in participants aged 90+ with amnestic MCI (31.4% per year) compared with cognitively normal individuals (8.4% per year), similar to that found in younger participants (90).

Despite predictions by some that all individuals who reach the extremes of old age would have some cognitive problem (91,92), between 21% and 54% of centenarians have been reported to be cognitively intact (45,93–97), and stable over time (85).

The inconsistencies in reported prevalence and incidence rates across studies may be due to how the diagnostic criteria were operationalized, the classification system used, or the sampling method (98). Many groups do not state details about their dementia diagnosis, simply including a standard statement that the diagnosis was made according to DSM or NINCDS-ADRDA or ICD criteria. This is unsatisfactory as operationalizing these criteria in the oldest old group is very difficult. Additionally, most studies present data collapsed across gender and age groups, both of which have been shown to affect dementia prevalence (75).

Further, many studies have simply used a global cognition or staging measure such as the MMSE (99), CDR scale (100), or Global Deterioration Scale (101) to determine cognitive impairment and/or clinical status, which presents a number of problems. First, the MMSE does not assess all cognitive domains, most notably missing executive function and psychomotor speed. Second, variable cutoffs for normal cognition have been used in studies of the oldest old group, including 24 and above (102), 23 and above (50), or 21 and above (49). Two studies have however provided more comprehensive normative data—the 90+ study presented thresholds for dementia on the MMSE (103), and the Georgia Centenarian Study presented percentile tables, stratified by age and education (104).

The CDR requires subjective decisions that are not clearly operationalized (ie, examiners are instructed to “score only as decline from previous usual level due to cognitive loss, not impairment due to other factors”; [105]). There has also been debate over using the CDR or Global Deterioration Scale to determine clinical status, especially whether a CDR of 0.5 does in fact represent MCI or a combination of MCI and early dementia (106).

A further consideration is the skewness of the samples in the studies of the oldest old group. Even those studies that have attempted to collect data from the entire population of oldest old in a region have a significant rate of nonparticipation, probably representing the most impaired individuals.

A Critique of Dementia Diagnosis in the Oldest Old Group And Some Recommendations

The traditional interpretation of the diagnostic criteria for dementia involves first establishing cognitive impairment in multiple domains; documenting that these impairments represent decline; and then establishing, usually through informant questionnaire, decline in everyday functioning.
More recently, there is interest in using biomarkers to support the diagnosis. Cognitive impairment is usually documented by comparison with normative data for the age group, classifying the bottom second to fifth percentile as impaired. This would however conflict with the literature for the oldest old group as summarized earlier, which suggests that well above the bottom second to fifth percentile are classified with cognitive impairment. Further, the vast majority of oldest old are classified with lowered levels of everyday functioning, yet many are still classified as not demented. Finally, there is a paucity of data on dementia biomarkers in the oldest old group. It is therefore obvious that most investigators depart from this strict definition of dementia in the oldest old group.

The purpose of the dementia diagnosis needs to be considered and may guide our approach. If we consider that dementia is a concept, which essentially means that persons have cognitive impairment, which impacts on their ability to cope with everyday function, is it more appropriate to compare their cognitive test scores to people who are functioning well in everyday life; for example, a normal younger cohort (an approach taken by the Georgia Centenarian Study, in comparing their centenarian and octogenarian cohorts [104,107])? The crucial point is whether the impairment in cognition precludes independent function. This is perhaps a more pragmatic approach to dementia diagnosis, where the focus would then be on whether the individual can function independently or requires services.

An alternative approach is to measure rate of decline in cognition or function on the basis that some decline is normal with age, but a more rapid rate of decline is indicative of impending dementia as demonstrated dramatically in younger groups (33). There are currently only a few studies that present longitudinal data for cognitive or functional change in the oldest old group and none that examines dementia diagnosis in light of the rate of change. It would be useful if comprehensive normative data for cognitive change in the oldest old group were available and linked to clinical outcome so that we know what trajectory may be indicative of dementia. Ideally, serial assessments will be conducted in order to document rate of decline, however in practice, previous levels of functioning may have to be estimated using retrospective report from an informant.

Given that the various diagnostic criteria have not been operationalized, a minimum requirement for publishing research studies should be a detailed explanation of how diagnoses were made. It is not sufficient to state that “dementia was diagnosed using NINCDS-ADRDA criteria.” How was each criterion assessed? For example, were normative data used to determine cognitive impairment? Which data and what cutoff was used? How were missing data (due to sensory or physical impairments) handled?

Clinically, the purpose of a dementia diagnosis needs to be considered. In the absence of disease-modifying treatment, the main advantage of diagnosis in the oldest old group would be to plan services and project future planning requirements. These are mainly dependent on functional needs, which can be assessed independent of diagnosis.

Looking forward to the possibility of disease-modifying drugs, diagnosis will be more important and clinicians need to be aware of the issues involved in working with the oldest old and trained in detecting dementia in this group.

Our recommendations are as follows:

- Researchers should provide more details of their diagnostic methods when reporting dementia or MCI in the oldest old population.
- More comprehensive normative data are required, including longitudinal rates of change and investigation of a range of dementia biomarkers.
- Publication of normative data must be accompanied by an explanation of how missing data due to sensory and physical impairments were handled.
- Clinicians should consider the purpose of a dementia diagnosis in someone aged more than 90.
- Clinicians should consider the rate of decline as this will affect the individual’s future needs.

**Conclusion**

As the population of centenarians and near-centenarians is increasingly exponentially throughout the world, and rates of dementia in this group are high, a concerted effort is needed to standardize the assessment and diagnosis of dementia in this age group. From the available information, it is unclear whether the same biomarkers and clinical and neuropathological criteria can be applied to oldest old populations as in younger populations. Satisfactory answers to these questions may provide insights into factors that determine healthy brain aging to the extreme end of life and help push back dementia.

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