Is Dementia Inevitable?

Does the incidence of dementia steadily increase as we grow older? Or is there a decrease or plateau in risk? To answer these questions, this article reviews the epidemiology of dementia in extremely old age and examines the distribution of specific causes of dementia. Important risk factors for and possible mechanisms of dementia also are discussed.

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Many diseases are either age-related or aging-related. An age-related disease is a disease that typically occurs around a specific age (*e.g.*, Hodgkin's disease, rheumatoid arthritis). An aging-related disease is a disease that typically occurs with increasing age, and often is considered to be caused, at least in part, by degeneration of and/or "wear and tear" on the body's cells and tissues (*e.g.*, osteoarthritis, atherosclerosis). Aging-related diseases are diseases that many of us can expect to develop, if we live long enough. Into which category does dementia—specifically Alzheimer's disease (AD)—fall?

The prevalence and incidence of AD increase exponentially with age, and some studies have reported a prevalence of dementia close to 100% in people around 100 years of age (centenarians).[1] Most of these types of epidemiologic studies, however, have included very few people older than 90 years of age.

This review will briefly discuss studies that have evaluated the eldest of the elderly population, and also will review explanations for some of the conflicting findings.

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Epidemiology of Dementia in Late Life

Early epidemiologic studies of dementia included very few subjects older than 95 years of age. For example, the EURODEM-prevalence-research-group analyses, which included close to 16,000 subjects, had only 69 subjects older than 95 years of age.[2] An early systematic review did not attempt to draw conclusions about the extremely elderly, because of their under-representation in the 47 studies reviewed.[3]

Several large, recent epidemiologic studies have reported the prevalence of dementia in their eldest participants:

- ***The Kungsholmen study.***[4] Investigators from this study found a 30% prevalence of dementia in men and a 50% prevalence of dementia in women ≥ 95 years of age, with another 12% of subjects having questionable dementia.
- ***Canadian Study of Health and Aging (CSHA).***[5] This study reported a 59% prevalence of dementia in those aged 95 years and older, with 86% of those aged 100 years and older having dementia.
- ***The Kame project.***[6] This study evaluated Japanese-Americans in Washington State and found a steady increase in the prevalence of dementia with increasing age, with over 70% of men and women aged 95 years and older having dementia.
- ***The MRC-ALPHA project.***[7,8] This study took place in Liverpool, England and found only a 47% prevalence of dementia in centenarians.
- ***Ritchie and Kildea.***[9] This 1995 meta-analysis concentrated on the extremely elderly and analyzed data from 1,388 subjects aged 90-94 years and 317 subjects aged 95-99 years. The prevalence of dementia did not increase exponentially compared to younger ages; rather, the rate of increase in dementia prevalence was found to fall in the age range 80-84 years; around the age of 95 years, prevalence was seen to level off. The prevalence of dementia at age 95-99 years was 44.8%.

Unfortunately these cross-sectional studies are plagued with biases. Sample sizes often are very small and non-response rates are very high. For example, the Kungsholmen study had a 40% non-response rate in the ≥ 95-year age group. And in the CSHA study, the

extremely elderly were almost all nursing-home residents. Subjects with dementia are more likely to refuse participation in such studies,[10,11] and since dementia increases mortality,[12-14] cross-sectional studies may underestimate the true burden of disease, through both non-response bias and selective mortality.

A more useful approach may be to conduct studies specifically aimed at the extremely elderly. This may decrease the non-response bias and improve the appropriateness of any cognitive examinations used.

A number of centenarian studies have investigated cognition in detail. Table 1 summarizes the results of population-based centenarian studies.[15-23] The prevalence of dementia in these studies is most often between 30% to 60%, with women generally having a higher prevalence than men. When causes of dementia are reported, AD emerges as the most common, with over 75% of cases in Italy, Finland and Japan having that diagnosis.[16-18] The exception is Denmark, where 50% of dementia cases are classified under vascular dementia.[22] Many of the studies also include a cognitive impairment—not dementia—category; 20% to 30% of cases are classified under this diagnosis.

Some centenarian studies include neuropathologic examinations. A small series of studies evaluating cognitively normal Japanese centenarians found that 92% had incurred at least one infarct, but few had any changes associated with AD, such as plaques or tangles.[24] Furthermore, a small French study found no relationship between the density of senile plaques and the degree of cognitive impairment.[25]

Table 1

Population-based Centenarian Studies

Place	Complete Examinations	Non-response Rate	Prevalence
Leiden[15]	34	—	41%
Finland[16]	185	32%	36% male/17% female
Japan[17]	47	6%	70%
Italy[18]	92	60%	70% male/50% female
Netherlands[19]	15	12%	87% male/100% female
Sweden[20]	100	39%	30% male/16% female
Tokyo[20]	218	67%	71% male/43% female
Denmark[21,22]	207	19%	51%
New England[23]	34	21%	64%

Several studies suggest that the extent of neuropathologic changes and degree of cognitive impairment are poorly correlated in the extremely elderly.[26,27] In the New England Centenarian Study,[28,29] infarcts were common, but few patients met neuropathologic criteria for AD (even among those with a clinical diagnosis of AD). Several patients had no cognitive impairment, despite extensive neuropathologic abnormalities, and conversely, several patients with significant cognitive impairment had no identified neuropathologic abnormality.

Even the centenarian studies have significant non-response and cannot account for any mortality bias. Additionally, surveys of particular age groups, at particular points in time, are vulnerable to cohort effects, where the findings may be due to something common to that cohort of subjects, rather than reflecting some biological property of aging. Longitudinal studies can overcome some of these weaknesses by accounting for mortality and, perhaps, comparing multiple cohorts. Unfortunately, even longitudinal studies are vulnerable to non-response, as drop-outs from these studies are more likely to be cognitively impaired.[30]

The longitudinal studies that have reported results in extremely old age generally show a decline in incidence of dementia for men, with the decline in women, if present, occurring later.[31-37] However, several studies have shown no decline in incidence.[7,38-40] When examining subtypes, most studies showed a decrease in the incidence of AD, particularly in men, even when the incidence of all dementias continued to increase.[32,33,36,37,39,40]

The investigators from the Cache County study[37] performed a particularly thorough analysis. This study included a largely Mormon and rural population with AD and other forms of dementia. The investigators found a decrease in the incidence of all dementias in men and women in the oldest age group

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(≥ 93 years). Careful examination suggested that this decline was not a methodologic artifact. Possible explanations for the results include: unusual aspects of the population; heterogeneity, such that an "early-" onset group disappears, leaving an impervious group; or the interaction of vascular and dementia risk factors (*i.e.*, those at highest risk die younger).

Apolipoprotein E and Dementia in Late Life

The presence of an apolipoprotein E (ApoE) epsilon 4 allele may increase one's risk of AD, however its effect in late life is controversial. Several centenarian studies have demonstrated no increased risk of AD with an ApoE epsilon 4 allele,[16,17,41] but results from other studies conflict.[42] Studies also have shown that the epsilon 4 allele may not impair cognition in very old people who are not demented,[42,43] but again, results from other studies suggest otherwise.[44] Interesting results from a Finnish study[45] found that ApoE status did not correlate with clinical dementia, but did correlate with neuropathologic AD (*i.e.*, 42% of participants carrying the epsilon 4 allele, who were not demented, had neuropathologic AD). Investigators also have found that, although the epsilon 4 allele predicts early onset of dementia, there is a peak after which both the incidence and prevalence of dementia decrease, even in the presence of the epsilon 4 allele.[46,47] Investigators from the Adult Changes in Thought study found similar results.[40]

Is There a Primary Dementia of Aging?

Terry and Katzman[48] argue that there is a primary dementia of aging. They believe that with ongoing neuronal and, most importantly, synaptic losses, we all will develop dementia. Their hypothesis suggests that humans gain synapses in early life (a process accelerated by education) and then, after adolescence, inexorably lose synapses. Any negative effects of these synapse losses are not seen until a critical threshold is reached—a threshold that is far past most people's expected life span. People with less education and/or neuronal loss due to other factors (*e.g.*, alcohol abuse, head injury, hypertension) may exhibit this primary dementia of aging at a younger age.

Although this is an interesting hypothesis, there is little hard evidence to support it at this time. However, sophisticated magnetic-resonance-imaging (MRI) studies suggest that "connectivity" is lower in older, healthy subjects compared to younger, healthy subjects.[49] Terry and Katzman's hypothesis certainly is one method to explain the apparent "disconnection" between neuropathologic changes and cognition in extremely late life.

Conclusions

This review, in effect, raises more questions than answers:

1) Is the decline in incidence of AD in men a true finding, or is it due to the frequency of coexisting stroke and the difficulty operationalizing standard criteria in the extremely elderly?
2) How can the disconnection between neuropathologic findings and dementia be explained?
3) How appropriate are neuropsychologic examinations in these subjects, who often have severe vision and hearing impairment, and functional impairment unrelated to their cognition?
4) Does the effect of ApoE truly disappear?
5) Are cholinesterase inhibitors safe and effective in the extremely elderly—an age group which is typically excluded from clinical trials?
6) Can lifestyle changes and chronic-disease management prevent dementia even in extremely old age?

Despite the need for further investigations to answer these questions, the results of this review are hopeful in the sense that there is definitely a substantial minority of centenarians who remain cognitively intact. Therefore, there is one final question we can answer:

Is dementia inevitable? No.

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