For a long time, many clinicians assumed that as an aging-related disease, Alzheimer disease (AD) was inevitable at extreme old age. In reaction in part to some earlier prevalence studies contending the same, John Morris1 contended otherwise. First, Morris pointed out a number of common mistakes that likely lead to the supposition of inevitability. Then, he went on to describe longitudinal comprehensive neuropsychological testing results correlated with quantitative postmortem studies that indicated there can be a dissociation between AD and aging and that there are people who remain cognitively intact and without neuropathological evidence well into their nineties. Morris warned that we should keep the following in mind when undertaking epidemiological study of AD: (1) cross-sectional studies in which 1 age cohort is compared against another are highly prone to confounding, for instance by years of education and other environmental exposures; (2) cross-sectional studies are less reliable in establishing a neurocognitive diagnosis, particularly at the early stages of disease; (3) multiple and reliable cognitive tests are required to test different cognitive function domains in order to achieve acceptable sensitivity for early impairment; (4) rather than subscribing to the ageist generalization that a person is doing well given their extreme age, we should rely on sensitive and specific diagnostic criteria no matter what the age; and (5) longitudinal study is far superior to cross-sectional study for achieving reliable levels of sensitivity and specificity. In my own experience as a geriatrics fellow, having 2 centenarian patients who appeared to be completely cognitively intact was my first tipoff that at least some extremely old individuals must have a resistance to AD.

Using data from the University of Amsterdam’s 100-plus Study, Beker and colleagues2 held fast (from the Dutch word houd vast) to John Morris’ rules in their longitudinal study of 340 self-reported cognitively intact centenarians. Annual and comprehensive cognitive function testing was performed with a range for the sample of 0 to 4 years, and key potential confounders were accounted for with appropriate statistical methods. Forty-four of these participants went on to neuropathological study.

There are at least 2 interesting and important findings from this work. During a mean (SD) 1.6 (0.8) years of follow-up, no decline in cognitive function was observed except for a minor decrement in memory. This suggests that, among this sample of centenarians, the incidence of dementia was low and implies resilience or resistance to AD and related dementias, despite the facts that they have the most potent risk factor in the general population, extreme old age,3 and that brain amyloid-β and tau deposition generally increase with age.4 Indeed, in 44 autopsies there were numerous instances of good cognitive function in the presence of substantial neuropathology, which is consistent with the presence of functional reserve or resilience.

While a mean follow-up of 1.6 years might at first blush seem short, for a segment of the population where annual mortality is approximately 30%, this is a relatively long time and an important positive feature of the work. An autopsy rate of approximately 10% reflects what is generally possible with a sample like this. An enrollment rate of 32.3% (330 out of 1023 approached) is actually quite good for a centenarian study given that many centenarians are quite frail and in their last year of life. Enrollees in centenarian studies are often substantially better off than centenarians in general because of a healthy volunteer bias, and this study is no exception. However, this is acceptable because the authors explicitly state that they studied a population of cognitively healthy

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centenarians. As extreme outliers, these centenarians are likely an informative cohort for discovering behavioral, environmental, and/or biological mechanisms of resistance and resilience to AD and related dementias.\(^5\)

It is difficult enough to recruit and enroll 330 centenarians, but to then have neuropathological findings from 44 study participants who had timely neuropsychological assessments makes for a truly unique study. It is also notable that the neuropsychological assessments in the 100-plus Study were comprehensive, which is not the case for other studies of extremely old study participants that may rely only on a Mini-Mental Status Examination. Cognitive and brain resilience are defined respectively by level of cognitive function and brain tissue structural integrity in spite of a high degree of AD pathological burden. Rather than being resilient, individuals who live to age 100 years or more who do not have AD neuropathologic changes are considered resistant to AD. By integrating neuropsychological assessments and neuropathological studies, subsets of centenarian cognitive superagers and offspring who are either resistant or resilient to AD neuropathologic changes can be identified.

Various studies support the hypothesis that, rather than enjoying a relative absence of neurodegenerative causative factors, centenarians benefit from protective mechanisms.\(^6\) Studies have demonstrated that there is an increasingly strong genetic influence with age beyond approximately 95 years on the variation in age of survival, and the extremeness of these spectacular cases belies an increased power over younger cognitive superager samples to discover biological mechanisms that afford cognitive resilience and, in some cases, even resistance to neurodegenerative processes and diseases.\(^7\) Thus, there is significant promise that the 100-plus Study and others that emulate it truly have the potential of discovering the how and why these very special people so markedly delay or even escape AD and other dementias.

**REFERENCES:**