

Healthy Aging and Dementia: Findings from the Nun Study

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The Nun Study is a longitudinal study of 678 Catholic sisters 75 to 107 years of age who are members of the School Sisters of Notre Dame congregation. Data collected for this study include early and middle-life risk factors from the convent archives, annual cognitive and physical function evaluations during old age, and postmortem neuropathologic evaluations of the participants' brains. The case histories presented include a centenarian who was a model of healthy aging, a 92-year-old with dementia and clinically significant Alzheimer disease neuropathology and vascular lesions, a cognitively and physically intact centenarian with

almost no neuropathology, and an 85-year-old with well-preserved cognitive and physical function despite a genetic predisposition to Alzheimer disease and an abundance of Alzheimer disease lesions. These case histories provide examples of how healthy aging and dementia relate to the degree of pathology present in the brain and the level of resistance to the clinical expression of the neuropathology.

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The Nun Study is a longitudinal study of aging and Alzheimer disease in 678 Catholic sisters who are members of the School Sisters of Notre Dame congregation (1–11). The participants were 75 to 102 years of age at the beginning of the study in 1991, and the oldest member had survived to 107 years of age by 2002. There are three basic sources of data available about the participants. First, convent archives provide information about potential early and middle-life risk factors for Alzheimer disease and other disorders. Second, annual examinations document changes in the cognitive and physical function of each participant during old age. Third, because each sister agreed to brain donation at death, the structure and pathology of the brain can be related to early and middle-life risk factors and to late-life cognitive and physical function.

Although it may be difficult to generalize from this unique population, many factors that confound most epidemiologic studies have been eliminated or minimized because of the relative homogeneity of the sisters' environments and lifestyles. Overall, the Nun Study provides a unique longitudinal model of aging and disease.

Because of its inclusion of an entire population, the Nun Study consists of participants with widely differing cognitive and physical function, health and disease states, and longevity. For example, the study includes 75-year-old women who are so severely debilitated by dementing diseases that they can barely utter a word, 100-year-old women who are cognitively sharp and in outstanding physical condition, and participants with virtually every level of functional capacity between these extremes. Neuropathologically, the sisters exhibit a wide range of manifestations of dementing diseases—from participants with both severe Alzheimer disease pathology and vascular lesions to participants with almost no neuropathology present at autopsy. These wide ranges in function and health provide a unique opportunity to better understand the biological and social substrates of severe debility at one end of the continuum and vital, healthy aging at the other end.

SISTER MATTHIA: A MODEL OF HEALTHY AGING

Sister Matthia was born in 1894. She joined the religious congregation as a postulant in 1910 and eventually earned a bachelor's degree. She moved to the Mankato, Minnesota, convent in 1913, and after teaching elementary school in Wisconsin, Minnesota, and Washington for 62 years, she retired to the convent in 1971 when she was 77 years of age. In 1990, she became one of the first sisters to agree to participate in the Nun Study. Over the years, Sister Matthia became the "gold standard" for healthy aging in the Nun Study and became somewhat of a celebrity. At 103 years of age, *National Geographic* published a photograph of her long-fingered, heavily wrinkled hands knitting a pair of mittens. "I don't like that photo," she once remarked, "it makes me look old."

The photograph of Sister Matthia in **Figure 1** was taken when she was 104 years of age, 3 months before she died. She appeared happy and was still actively making use of her time by knitting mittens for the poor and teaching others how to knit. Happy, productive, and vivacious, Sister Matthia set a standard for what is possible in old age.

In an obituary that she wrote for herself in 1996, when she was 102 years of age, Sister Matthia wrote, "Now regarding my long living, it seems to be a special reward from God." Late in the afternoon of 14 December 1998, a few weeks shy of her 105th birthday, Sister Matthia asked a sister who was at her bedside to notify her relatives that she was dying. She then received communion and passed away 45 minutes later. She enjoyed more than 100 years of dementia-free life.

At the postmortem neuropathologic evaluation, her brain weighed 1170 grams and showed no gross abnormalities other than one tiny (0.2 × 0.1 cm) infarct in the left caudate nucleus. She had only mild atherosclerosis in the circle of Willis, the main arteries at the base of the brain (mild indicates atherosclerotic plaques in <25% of the vessel wall; moderate, 25% to 50%; and severe, >50% [3]). According to the Braak and Braak method of staging the severity (spread) of Alzheimer disease pathology in the brain, she was described as a stage 4, moderate spread of

Figure 1. Sister Matthia, a model of healthy aging in the Nun Study, at 104 years of age, 3 months before she died.



Courtesy of Sandra Perry Raybourne.

the disease (stage 0 indicates the absence or only sparse appearance of neurofibrillary pathology; stages 1 and 2 indicate mild spread, present only in the entorhinal cortex; stages 3 and 4 indicate moderate spread, present in both the entorhinal cortex and hippocampus; and stages 5 and 6 indicate severe spread, present in the entorhinal cortex, hippocampus, and neocortex [12, 13]).

SISTER AGNES: A MIX OF NEUROPATHOLOGY

Sister Agnes was a “century baby,” born in 1900. She grew up on a midwestern farm, the last of 11 children, and abandoned her studies after the eighth grade to care for her invalid father and help her mother. In her spare time, she served at the local Catholic church, washing the altar lin-

ens, decorating the altar, and ringing the Angelus bell to call parishioners for prayer.

Her father died when she was 18 years of age, so she stayed home to help her mother until she became a Notre Dame sister at the relatively advanced age of 23 years. After professing her vows, Sister Agnes played the organ and taught music at churches and schools in Minnesota and North Dakota and spent summers attending high school classes at the Mankato, Minnesota, convent. She received her high school diploma at 28 years of age. After more than 50 years of service, she retired to the Mankato convent. Several years later, her developing disabilities forced her to move to the St. Joseph’s Health Care wing of the convent.

Like all participants in the Nun Study, Sister Agnes’s first annual examination was performed in the early 1990s. At that time, she was so cognitively and physically disabled that she could communicate only with an occasional smile and the expression of an isolated word or two. In late November, 10 days after her first examination in the Nun Study, a nurse observed that 92-year-old Sister Agnes was sleeping much of the time and “need[ed] to be coaxed to open her eyes.” On Christmas Eve, Sister Agnes became extremely congested, with loud rales emanating from her lungs each time she drew a breath. Before the year ended, a nurse filled the bottom of the last page in Sister Agnes’s chart: “Sister appeared comatose this evening.” Just as Mankato’s Angelus bell rang for evening prayers, the nurse noted, “Sister died peacefully 6 p.m. RIP.”

At the postmortem neuropathologic evaluation, her brain weighed 1090 grams and showed three small (lacunar) brain infarcts. One of the lacunar infarcts was located in the white matter of the parietal lobe of the neocortex, and the other two infarcts were in the deep regions of the brain’s white matter. In addition to these infarcts, Sister Agnes had a hemorrhagic stroke in the thalamus. She had a moderate degree of atherosclerosis in the main arteries at the base of the brain. The microscopic evaluation of her neocortex also indicated that she had sufficient numbers of lesions to meet our neuropathologic criteria for Alzheimer disease (abundant senile plaques and some neuritic plaques and neurofibrillary tangles).

Given the presence of clinically significant Alzheimer disease neuropathology and strokes, Sister Agnes’s dementia was classified as mixed dementia. Among participants in the Nun Study with dementia who have died and been neuropathologically evaluated, 33.9% had mixed dementia (both Alzheimer disease and stroke present), 43.2% had Alzheimer disease (essentially only Alzheimer disease pathology present), 2.5% had vascular dementia (strokes were the only apparent neuropathologic substrate for dementia), and 20.4% had other causes of dementia (such as Lewy bodies, meningioma, primary hydrocephalus, and contusions) (6).

SISTER MARCELLA: A LOW DEGREE OF NEUROPATHOLOGY

In May 1995, about a month after Sister Marcella turned 100 years old, she participated in her third annual Nun Study examination. Her performance was exceptional, even though she had earned only a high school diploma. On the Mini-Mental State Examination (14), a measure of global cognitive function, she scored 28 out of 30. On the delayed word recall (14), a test of short-term memory from a list of 10 words, she had a very high score of 8. On the tests of basic activities of daily living, such as walking, dressing, and feeding, she had the maximum score of 5. For the tests of instrumental activities of daily living, such as using the telephone and making change, she correctly performed all five tasks. She rated her ability to care for herself as “excellent.” In a short autobiography she composed during that examination, Sister Marcella wrote in fine penmanship about her childhood and how she got to school in the early 1900s: “Every day I walked about 3 miles with my two older brothers, rain or shine.”

In 1996, Sister Marcella died at 101 years of age. Her obituary states that she “had a delightful sense of humor and was blessed with a remarkable memory, which enabled her to tell wonderful stories.” When asked about her long life, she said, “God’s secret, not mine. I have lived an ordinary life. I have not done anything special.” Those who knew Sister Marcella saw her as anything but ordinary. Her life, cognitive abilities, and longevity were extraordinary.

On the postmortem evaluation, her brain weighed 1280 grams and showed almost no signs of any gross or microscopic abnormalities. The main arteries at the base of her brain showed only the slightest hint of atherosclerosis. She was described as a Braak and Braak stage 0, indicating the absence of neurofibrillary pathology. Overall, she had a remarkably clean, large brain.

SISTER BERNADETTE: RESISTANCE TO THE CLINICAL EXPRESSION OF NEUROPATHOLOGY

Sister Bernadette had earned a master’s degree and taught elementary school for 21 years and high school for another 7 years. She died of a massive heart attack in the mid-1990s at the age of 85 years. Her pathologic report indicated that her brain weighed 1020 grams, at the border of normal. A gross examination of her brain indicated the presence of infarcts, which might have occurred at the time of the fatal heart attack. She had only mild atherosclerosis in the main arteries at the base of the brain.

The microscopic analysis of her brain tissue, however, left little doubt that Alzheimer disease had spread extensively. Neurofibrillary tangles cluttered her hippocampus and neocortex up to the frontal lobe. Her neocortex had an abundance of senile plaques. On the Braak and Braak scale, she had the maximum score of 6, indicating the greatest spread of Alzheimer disease pathology. This was consistent with the presence of two copies of the apolipoprotein E $\epsilon 4$

allele, a relatively prevalent and well-recognized genetic marker for Alzheimer disease.

Her performance on the annual cognitive tests at ages 81, 83, and 84 years, however, showed a remarkably different picture. She scored very high on each examination, showing no mental deterioration. In a particularly impressive videotaped exchange recorded at her last examination, Sister Bernadette—without looking at a clock or a watch—stated the time within 4 minutes of the actual time.

Sister Bernadette represents an extreme example: Despite a genetic predisposition to Alzheimer disease and an abundance of Alzheimer disease lesions in her neocortex, the function of that brain region seemed to be remarkably preserved. This is consistent with findings from a postmortem magnetic resonance imaging scan that showed that, despite being in the 90th percentile for neurofibrillary tangles in her neocortex, she scored in the 90th percentile for the volume of gray matter in her brain, the main material of the neocortex. It was as if her neocortex were resistant to Alzheimer-related neurodegeneration.

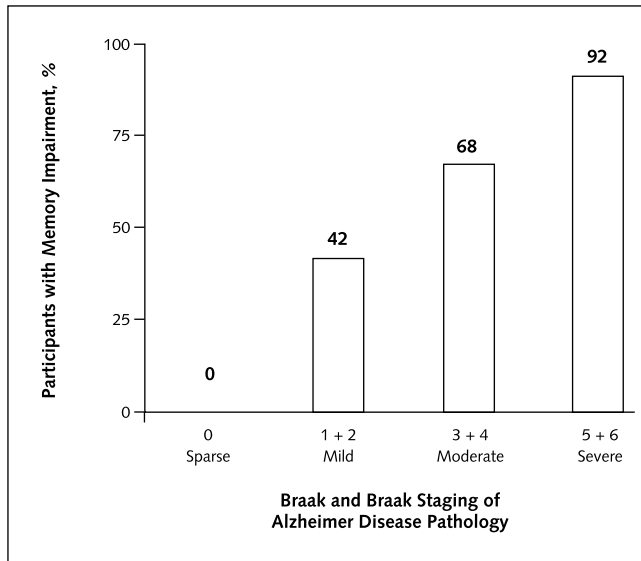
DISCUSSION

These case histories exemplify the broad range in cognitive and physical function and neuropathologic conditions present in the sisters participating in the Nun Study. Whether or not a participant exhibits symptoms of dementia or maintains a state of healthy aging depends, in part, on two main factors. First is the degree of pathology present in the brain. Second is the degree of resistance to the clinical expression of the neuropathology, since some participants have substantial neuropathology but few, if any, symptoms.

The clinical consequences of neuropathologic lesions depend, in part, on their location, type, and amount. The most important factor may be the location of the lesions because some regions of the brain are more integral than others to cognitive, social, and physical functioning. For example, in the Nun Study, small brain infarcts seem to be more important in triggering the symptoms of dementia than large infarcts, possibly because the small infarcts are more likely to occur in the white matter (wiring and networking) of the brain (3). Stroke-free participants in the Nun Study also seem to tolerate more Alzheimer disease lesions in their brain before exhibiting the symptoms of dementia (3). This suggests that the absence of other comorbid conditions may help buffer individuals from expressing the symptoms that are expected from existing neuropathology. Some conditions besides stroke, such as brain trauma, depression, and metabolic abnormalities, also may overwhelm the Alzheimer brain and trigger the clinical onset of symptoms.

Other older adults may have abundant senile plaques and neurofibrillary tangles of Alzheimer disease but show little, if any, neurodegeneration of the brain. For example, findings from our study suggest that the degree of atrophy of the neocortex is inversely correlated with the serum level

Figure 2. The relationship between the Braak and Braak staging of the degree or spread of Alzheimer disease neurofibrillary pathology and the prevalence of impairments in short-term memory (delayed word recall) at the last examination before death.



of the vitamin folic acid (8). Since Alzheimer disease is a brain-wasting disease, it is biologically reasonable to assume that specific nutritional deficits, possibly folic acid and other vitamins, might accelerate the disease's neurodegenerative capacities.

Given nearly the same location, type, and amount of neuropathologic lesions, participants in our study show an incredible range of clinical manifestations, from no symptoms to severe symptoms. **Figure 2** shows the relationship between the Braak and Braak staging of the degree or spread of Alzheimer disease neurofibrillary pathology and the prevalence of impairments in short-term memory (delayed word recall) at the last examination before death. These analyses focused exclusively on the clinical manifestations of the entire range of Alzheimer disease neurofibrillary pathology exhibited in our study population. All 130 sisters in this analysis were, therefore, free of neuropathologic conditions other than Alzheimer disease, such as stroke (11).

A substantial proportion of participants in the mild (Braak and Braak stages 1 and 2) to moderate (Braak and Braak stages 3 and 4) stages of Alzheimer disease pathology showed no symptoms of memory impairment (**Figure 2**). Whether through reduced neurodegeneration, increased brain reserve, or some other defense or adaptive mechanism, a sizeable percentage of participants with the same degree of Alzheimer disease pathology resist the clinical expression of symptoms. Even 8% of participants with the most severe spread of Alzheimer disease pathology (Braak and Braak stages 5 and 6) did not show any symptoms of memory impairments.

It would be useful to better understand the biological and perhaps environmental and social reasons that some people tolerate moderate to severe neuropathology and exhibit few, if any, symptoms. The degree of resistance to the clinical manifestation of neuropathology probably relates to events and processes occurring throughout life. The degree of resistance may relate to the amount of brain tissue and synapses developed in early life, the degree of brain damage from head trauma and strokes in middle and later years of life, and the nutritional deficits in middle and later years of life that make brain tissue more vulnerable to neurodegeneration. Even social factors, such as cognitive training interventions, during old age may improve cognitive function (15).

Over the years, scientists have struggled to define and investigate cognitive reserve—the capacity of the brain to resist the expression of symptoms in the face of existing neuropathology. This area of investigation is still in its infancy. However, in a recent critical review of the literature, Stern (16) presented a potentially useful theoretical framework in which to view cognitive reserve. This theoretical model divides reserve into two components—passive and active. To some extent, the passive model of reserve incorporates the biological processes and capacities that people bring to old age that may give them additional biological buffers (for example, brain size and synapse count) against the clinical expression of pathology. The passive component of reserve can be viewed as the degree of development of normal brain function and performance.

Such biological reserve may have been formed during fetal, childhood, and adolescent development through such avenues as genetic expression, nutrition, social support, education, and intellectual stimulation. Nonetheless, throughout young adulthood and middle age, biological reserve must be maintained and protected through environmental, lifestyle, and preventive medical care. These include a prudent diet, exercise, prevention of head trauma, and the early treatment of disorders, such as diabetes and hypertension, that might ultimately lead to neurodegeneration and the reduction of brain reserve.

In the second, active, component of Stern's conceptual model, cognitive reserve is viewed as a measure of the brain's ability to adapt to or compensate for the presence of pathology. That is, in the presence of pathology, the brain activates regions and networks of the brain that are normally not activated. Stern described one of his own studies that used positron emission tomography to compare differences in blood flow to specific brain regions in patients with Alzheimer disease and healthy controls (16). In response to a memory (verbal recognition) task, healthy controls used a network of brain regions that included the left anterior cingulate, anterior insula, and left basal ganglia. Only 3 of the patients with Alzheimer disease activated this network in a similar manner, while the other 11 patients activated a different network that included the left poste-

rior temporal cortex, calcarine cortex, posterior cingulate, and vermis. With the recent development of brain imaging methods to assess the degree of spread of Alzheimer disease lesions, in the future it will be easier to determine precisely the severity of Alzheimer disease pathology, the type of compensation and adaptation of the brain, and the resulting expression of dementia symptoms.

We will probably have to wait many more years for the development of drugs, vaccines, and other biotechnologies that can safely stop or slow the spread in the brain of neurodegenerative diseases such as Alzheimer disease. In the meantime, uncovering more information about resistance to the clinical manifestations of existing neuropathologic lesions is a potentially effective means of allowing more people to experience healthy aging. It is also worthwhile to continue to explore how some individuals survive more than 100 years with excellent cognitive, social, and physical function without developing any neuropathologic conditions. Overall, a two-pronged approach, reducing neuropathologic lesions while increasing the brain's resistance to the expression of symptoms, is potentially a powerful method of extending the years of healthy aging.

What is the future of the Nun Study? The study of 678 sisters began in 1991, and by the end of 2003 we expect to have completed over 400 neuropathologic evaluations and have approximately 150 survivors, ranging in age from 87 years to older than 100 years of age. We are now turning this well-documented cohort study into a permanent archival source of unique and valuable research material for use by other scientists. The information and variables contained in the Nun Study Archive will grow over the years and decades as more pathologists stain brain tissue for other anatomic and pathologic markers, geneticists screen for hundreds of other genes, and neuropsychologists and biometricians continue to characterize our annual functional examinations into more robust profiles of healthy aging and symptom expression. The School Sisters of Notre Dame have much more to teach us, as reflected by the words of one of our participants: "The Nun Study allows me to keep teaching, even after I die."

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References

1. Snowdon DA, Kemper SJ, Mortimer JA, Greiner LH, Wekstein DR, Markesbery WR. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the Nun Study. *JAMA*. 1996;275:528-32. [PMID: 8606473]
2. Butler SM, Snowdon DA. Trends in mortality in older women: findings from the Nun Study. *J Gerontol B Psychol Sci Soc Sci*. 1996;51:S201-8. [PMID: 8673649]
3. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. *The Nun Study*. *JAMA*. 1997;277:813-7. [PMID: 9052711]
4. Snowdon DA. Aging and Alzheimer's disease: lessons from the Nun Study. *Gerontologist*. 1997;37:150-6. [PMID: 9127971]
5. Snowdon DA, Greiner LH, Kemper SJ, Nanayakkara N, Mortimer JA. Linguistic ability in early life and longevity: findings from the Nun Study. In: Robine J-M, Forette B, Francheschi C, Allard M, eds. *The Paradoxes of Longevity*. Berlin: Springer-Verlag; 1999:103-13.
6. Snowdon DA, Markesbery WR. The prevalence of neuropathologically confirmed vascular dementia: findings from the Nun Study. In: Korczyn AD, ed. *First International Congress on Vascular Dementia*. Bologna, Italy: Monduzzi Editore; 1999:19-24.
7. Snowdon DA, Greiner LH, Markesbery WR. Linguistic ability in early life and the neuropathology of Alzheimer's disease and cerebrovascular disease. Findings from the Nun Study. *Ann N Y Acad Sci*. 2000;903:34-8. [PMID: 10818486]
8. Snowdon DA, Greiner LH, Markesbery WR. Linguistic ability in early life and the neuropathology of Alzheimer's disease and cerebrovascular disease. Findings from the Nun Study. *Ann N Y Acad Sci*. 2000;903:34-8. [PMID: 10818486]
9. Danner DD, Snowdon DA, Friesen WV. Positive emotions in early life and longevity: findings from the Nun Study. *J Pers Soc Psychol*. 2001;80:804-13. [PMID: 11374751]
10. Snowdon D. *Aging with Grace: What the Nun Study Teaches Us about Leading Longer, Healthier, and More Meaningful Lives*. New York: Bantam; 2001.
11. Riley KP, Snowdon DA, Markesbery WR. Alzheimer's neurofibrillary pathology and the spectrum of cognitive function: findings from the Nun Study. *Ann Neurol*. 2002;51:567-77. [PMID: 12112102]
12. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol (Berl)*. 1991;82:239-59. [PMID: 1759558]
13. Ohm TG, Müller H, Braak H, Bohl J. Close-meshed prevalence rates of different stages as a tool to uncover the rate of Alzheimer's disease-related neurofibrillary changes. *Neuroscience*. 1995;64:209-17. [PMID: 7708206]
14. Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*. 1989;39:1159-65. [PMID: 2771064]
15. Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA*. 2002;288:2271-81. [PMID: 12425704]
16. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc*. 2002;8:448-60. [PMID: 11939702]