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Acute phase response and plasma carotenoid concentrations in older women: Findings from the Nun Study

Maria G. Boosalis, David A. Snowdon, Christine L. Tully and Myron D. Gross

This cross-sectional study investigated whether the acute phase response was associated with suppressed circulating levels of antioxidants in a population of 85 Catholic sisters (nuns) who were 77 to 99 years old. Fasting blood was drawn to determine the presence of an acute phase response, as defined by an elevation in the serum concentration of C-reactive protein. Serum concentrations of albumin, thyroxine-binding prealbumin, zinc, copper, and fibrinogen were determined as were plasma concentrations of carotenoids and alpha tocopherol. Results showed that the presence of an acute phase response was associated with (1) an expected significant decrease in the serum concentrations of albumin [$p<0.001$] and thyroxine-binding prealbumin [$p<0.001$] and (2) an expected significant increase in copper [$p<0.001$] and fibrinogen [$p=0.003$] and (3) a significant decrease in the plasma concentrations of lycopene [$p=0.03$], alpha carotene [$p=0.02$], and beta carotene [$p=0.02$], as well as total carotenoids [$p=0.01$]. The acute phase response was associated with decreased plasma levels of the antioxidants lycopene, alpha carotene, and beta carotene. This decrease in circulating antioxidants may further compromise antioxidant status and increase oxidative stress and damage in elders.

Boosalis MG, Snowdon DA, Tully CT, Gross MD: Acute phase response and plasma carotenoid concentrations in older women: Findings from the Nun Study Nutrition 12:475-478, 1996.

Videotape dietary assessment: Validity, reliability, and comparison of results with 24-hour dietary recalls from elderly women in a retirement home

Judith E. Brown, Theresa M. Tharp, Elizabeth M. Dahlberg-Luby, David A. Snowdon, Sharon K. Ostwald, I. Marilyn Buzzard, S. Del Marie Rysavy and S. Mary Aloysius Wieser

The validity and reliability of a videotape method for quantifying food intake were tested, and results of the method were compared with results obtained from 24-hour dietary recalls. Participants were 37 elderly Catholic nuns (aged 81.8 ± 4.1 years) who were ambulatory and living in a retirement home. The videotape method of dietary assessment consisted of videotaping food trays of each participant for three meals during 1 day and the subsequent identification of food types and amounts from the videotapes. Estimates of food amounts obtained were used in the calculation of energy and nutrient intake. Correlation coefficients between values for energy and 14 nutrients obtained by direct measurement of food and estimates from the videotape method were high ($r=0.86$ to 1.0). Compared with measured food amounts, the videotape method underestimated food quantities by an average of 6%. The reliability test indicated that mean nutrient values obtained from the videotape method by two

research assistants differed by an average of 3.7% and were highly correlated (r=0.84 to 0.98). Comparison of the videotape method with 24-hour dietary recalls revealed differences between mean values that were greater than 10% for energy and 6 of the 14 nutrients and correlations that ranged from 0.09 to 0.82. These results suggest that use of 24-hour dietary recalls among the elderly may result in a high percentage of error.

Brown JE, Tharp TM, Dahlberg-Luby EM, Snowdon DA, Ostwald SK, Buzzard IM, Rysavy DM, Aloysius MA. Videotape dietary assessment: Validity, reliability, and comparison of results with 24-hour dietary recalls from elderly women in a retirement home Journal of the American Dietetic Association 90:1675-1679, 1990.

Artificial Neural Networks and Artificial Organisms Can Predict Alzheimer Pathology in Individual Patients Only on The Basis of Cognitive and Functional Status

Massimo Buscema, Enzo Grossi, David Snowdon, Piero Antuono,
Marco Intraligi, Guido Maurelli, Rita Savarè

Data from several studies have pointed out the existence of a strong correlation between Alzheimer's disease (AD) neuropathology and cognitive state. However, because of their highly complex and nonlinear relationship, it has been difficult to develop a predictive model for individual patient classification through traditional statistical approaches. When exposed to complex data sets, artificial neural networks (ANNs) can recognize patterns, learn the relationship of different variables, and address classification tasks. To predict the results of postmortem brain examinations, we applied ANNs to the Nun Study data set, a longitudinal epidemiological study, which includes annual cognitive and functional evaluation. One hundred seventeen subjects from the study participated in this analysis. We determined how demographic data and the cognitive and functional variables of each subject during the last year of her life could predict the presence of brain pathology expressed as Braak stages, neurofibrillary tangles (NFTs) and neuritic plaques (NPs) count in the neocortex and hippocampus, and brain atrophy. The result of this analysis was then compared with traditional statistical models. ANNs proved to be better predictors than Linear Discriminant Analysis in all experimentations (+ ~10% in overall accuracy), especially when assembled in Artificial Organisms (+ ~20% in overall accuracy). Demographic, cognitive, and clinical variables were better predictors of tangles count in the neocortex and in the hippocampus when compared to NPs count. These findings strengthen the hypothesis that neurofibrillary pathology may represent the major anatomic substrate of the cognitive impairment found in AD.

Buscema M, Grossi E, Snowdon D, Antuono P, Intraligi M, Maurelli G, Savarè R. Artificial Neural Networks and Artificial Organisms Can Predict Alzheimer Pathology in Individual Patients Only on The Basis of Cognitive and Functional Status Neuroinformatics 2(4):399-416, 2004.

Age, education and changes in the Mini-Mental State Exam scores of elderly women:

Findings from the Nun Study

Steven M. Butler, J. Wesson Ashford and David A. Snowdon

Objective: To describe the relationship of Mini-Mental State Exam (MMSE) scores and changes over time in MMSE scores to age and education in a population of elderly women.
Design: A prospective study of a defined population.
Setting: Various motherhouses and church-run health care facilities in the Eastern, Midwestern and Southern regions of the United States.
Participants: Catholic sisters (nuns) participating in the Nun Study, a study of aging and Alzheimer's Disease. The 678 participants were 75 to 102 years old (mean 83.3, standard deviation 5.5, median 82.3) at the time of the first functional assessment. Second assessments were obtained an average of 1.6 years later on 575 survivors.
Measurements: The outcome variables were MMSE scores at the first assessment (time-one), and MMSE scores at the second assessment (time-two). The independent variables were age at time-one, and education (bachelor's degree or no bachelor's degree).
Results: Time-one MMSE scores decreased with age at time-one. The decrease in MMSE scores with age was less in sisters with bachelor's degrees than in sisters without bachelor's degrees. The changes in MMSE scores had a "U-shaped" relationship with time-one score, where the greatest declines occurred in sisters with intermediate time-one scores. Stratified analysis by age, education, and time-one MMSE score was feasible only in sisters with time-one MMSE scores of 20 or above, due to the small numbers of sisters with time-one scores below 20. In sisters with time-one MMSE scores in the categories 20 to 23, 24 to 26, or 27 to 30, older ages at time-one were associated with greater decline in those with bachelor's degrees, but not in those without bachelor's degrees. Also, lower education was associated with greater decline in sisters aged 75 to 84 years at time-one, but this education effect disappeared or reversed in sisters who were 85 years of age or older at time-one.
Conclusions: Cognitive function as measured by the MMSE decreased with age at time-one, most steeply as a function of age in those without bachelor's degrees. Cognitive function declined over 1.6 years within individuals, and the extent of decline increased with age in the sisters with bachelor's degrees. The extent of decline varied with age and education in an interactive manner, which may have been due to a hardy survivor effect in lower educated sisters. It may be necessary to consider such interactions whenever changes in function are studied, particularly when analyses are stratified by the initial level of function.

Butler SM, Ashford JW, Snowdon DA: Age, education and changes in the Mini-Mental State Exam scores of elderly women: Findings from the Nun Study Journal of the American Geriatrics Society 44:675-681, 1996.

Trends in mortality in older women: Findings from the Nun Study

Steven M. Butler and David A. Snowdon

During this century, Catholic sisters have remained constant in many lifestyle characteristics such as smoking and reproduction (Catholic sisters are non-smoking and nulliparous). It is therefore of interest to compare trends in the health of elderly Catholic sisters to those in the general population. In this study, mortality rates at ages 50 to 84 years in a population of 2573 Catholic sisters were compared to those in the general population during the years 1965 to 1989. The Catholic sisters had a mortality advantage that increased dramatically over calendar-time, and from early to more recent birth-cohorts. This coincided with increases in smoking by U.S. women, while during the same time period the Catholic sisters had very low rates of mortality from smoking-related diseases. The Catholic sisters had high rates of mortality from cancers of the breast and reproductive organs, suggesting an effect of nulliparity manifested in older women.

Butler SM, Snowdon DA: Trends in mortality in older women: Findings from the Nun Study Journal of Gerontology: Social Sciences 51B(4):S201-S208, 1996.

Positive emotions in early life and longevity: Findings from the Nun Study

Deborah D. Danner, David A. Snowdon, and Wallace V. Friesen

Handwritten autobiographies from 180 Catholic nuns, composed when participants were a mean age of 22 years, were scored for emotional content and related to survival during ages 75 to 95. A strong inverse association was found between positive emotional content in these writings and risk of mortality in late life ($p < .001$). As the quartile ranking of positive emotion in early life increased, there was a stepwise decrease in risk of mortality resulting in a 2.5-fold difference between the lowest and highest quartiles. Positive emotional content in early-life autobiographies was strongly associated with longevity 6 decades later. Underlying mechanisms of balanced emotional states are discussed.

Danner D, Snowdon D, Friesen W: Positive emotions in early life and longevity: Findings from the Nun Study Journal of Personality and Social Psychology 80(5); 804-813, 2001.

An Automated Technique for Measuring Hippocampal Volumes from MR Imaging Studies

Karen M. Gosche, James A. Mortimer, Charles D. Smith, William R. Markesbery, and David A. Snowdon

Summary: We describe an automated volumetric measure of the hippocampus obtained with software called the Knowledge-Guided MRI Analysis Program (KGMAP). Postmortem MR images from 56 participants in the Nun Study were used to validate the measure. KGMAP-determined volumes strongly correlated with those obtained with manual tracings and neurofibrillary pathologic findings of Alzheimer disease in the hippocampus. KGMAP provides a rapid and accurate estimate of hippocampal volume that is suitable for use in clinical practice.

Gosche K, Mortimer J, Smith C, Markesbery W, Snowdon D: An automated technique for measuring hippocampal volumes from MR imaging studies. American Journal of Neuroradiology, 22:1686-1689, 2001.

Underrecognition of dementia by caregivers cuts across cultures

Lydia H. Greiner and David A. Snowdon

We investigated unrecognized dementia in 383 participants in the Nun Study, aged 75 to 102 years old (mean=88), who were under nursing supervision in assisted-living or skilled-nursing facilities. Participants have annual assessments of cognitive and physical function and neuropathological evaluations of their brains at death. Clinical criteria were used to identify those with dementia, and neuropathologic criteria were used to identify those with lesions sufficient to produce dementia. As part of the annual assessment, nurses were asked: "Based on your observations, do you think this sister has dementia?". Of the 179 participants who met the clinical criteria for dementia, nursing staff did not recognize dementia in 22% (95% confidence interval [95% CI],16-29). Results were similar in the 52 who later died and who met both clinical and neuropathologic criteria for dementia. Of the 204 participants who did not meet the clinical criteria for dementia, nursing staff labeled 16% (95% CI, 11-22) as having dementia. Results were similar in the 20 who later died and who did not meet either the clinical or neuropathologic criteria for dementia. Failure to accurately recognize dementia may present a substantial barrier to receiving appropriate health care.

Greiner LH, Snowdon DA: Underrecognition of dementia by caregivers cuts across cultures Journal of the American Medical Association (JAMA), 277(22):1757, 1997

The relationship of self-rated function and self-rated health to concurrent functionalability, functional decline, and mortality: Findings from the Nun Study

Philip A. Greiner, David A. Snowdon and Lydia H. Greiner

We investigated the relationship of self-rated function (i.e., the ability to take care of oneself) and self-rated health to concurrent functional ability, functional decline, and mortality in participants in the Nun Study, a longitudinal study of aging and Alzheimer's disease. A total of 629 of the 678 study participants self-rated their function and health and completed an initial functional assessment in 1991-93. Survivors completed a second assessment in 1993-94. Overall, self-rated function had a stronger relationship to functional ability at the first assessment and to functional decline between the first and second assessments than did self-rated health. Self-rated function also had a stronger relationship to mortality than did self-rated health. Self-rated function may be a better marker of global function than is self-rated health and may be a useful addition to clinical assessment and scientific investigation of the relationships among function, health, and disease.

Greiner PA, Snowdon DA, Greiner LH: The relationship of self-rated function and self-rated health to concurrent functional ability, functional decline, and mortality: Findings from the Nun Study Journal of Gerontology: Social Sciences 51B(5):S234-S241, 1996.

Self-rated fnction, slf-rated halth and pstmortem eidence of bain ifarcts: Findings from the Nun Study

Philip A. Greiner, David A. Snowdon, and Lydia H. Greiner

Objectives: Self-rated function is a new global measure. Previous findings suggest that self-rated function predicts future functional decline and is strongly associated with all-cause mortality. We hypothesized that the strength of the relationship of self-rated function to all-cause mortality was in part due to functional decline, such as would occur with brain infarcts.
Methods: Self-ratings of function and health (on a five-point scale ranging from excellent to poor) were assessed annually on 630 participants in the Nun Study. Mortality surveillance extended from October 31, 1991 to March 1, 1998, and, among those who died, neuropathological examination determined postmortem evidence of brain infarcts. Cox regression modeling with self-rated function and health as time-dependent covariates and stratification by assessment period were used in these analyses.
Results: Self-rated function and health ratings of good, fair, and poor were significantly associated with doubling of the risk of mortality, compared to ratings of very good and excellent. Self-rated function ratings of fair or poor were associated with a three-fold increase in the risk of mortality with brain infarcts, but self-rated function and health ratings of fair and poor were comparable in their association with all-cause mortality and mortality without brain infarcts.
Discussion: Self-rated function was significantly associated with mortality with brain infarcts, suggesting that brain infarcts may be experienced as functional loss, but not recognized or labeled as disease. Our results suggest that self-rated function and health should be explored simultaneously in future research.

Greiner PA, Snowdon DA, Greiner LG: Self-rated function, self-rated health and postmortem evidence of brain infarcts: Findings from the Nun Study. Journal of Gerontology: Social Sciences, 54B(3):S219-S222, 1999.

The loss of independence in activities of daily living: The role of low normal cognitive function in elderly nuns

Philip A. Greiner, David A. Snowdon and Frederick A. Schmitt

Objectives: We investigated the role of low normal cognitive function in the subsequent loss of independence in activities of daily living.
Methods: Of the 678 participants in The Nun Study who completed cognitive and physical function assessments in 1992-3, 575 were reassessed in 1993-4. Mini-Mental State Examination scores were divided into three categories (i.e., 0-23 as impaired; 24-27 as low normal; 28-30 as high normal) and related to the loss of independence in six activities of daily living.

Results: Participants with low normal cognitive function at first assessment had twice the risk of losing independence in three activities of daily living by second assessment as compared to those with high normal cognitive function. This relationship was largely due to a progression from low normal cognitive function at first assessment to impaired cognitive function at second assessment, and was associated with an elevated risk of losing independence in the six activities. Conclusions: Progression from low normal to impaired cognitive function was associated with loss of independence in activities of daily living. Thus, low normal cognitive function could be viewed as an early warning of impending cognitive impairment and loss of physical function.

Greiner PA, Snowdon DA, Schmitt, FA: The loss of independence in activities of daily living: The role of low normal cognitive function in elderly nuns American Journal of Public Health 86(1):62-66, 1996.

Plasma antioxidant concentrations in a population of elderly women: Findings from the Nun Study

Myron D. Gross and David A. Snowdon

Low plasma alpha-tocopherol and beta-carotene concentrations have been associated with an increased risk of numerous degenerative diseases, including cancer. Several characteristics that accompany aging, including changes in dietary habits and physiologic capacity, may place elderly populations at a high risk of low plasma antioxidant concentrations. Thus, the present study was undertaken to characterize plasma concentrations of alpha-tocopherol, beta-carotene and several other carotenoids in elderly subjects, to describe the relationship between age and plasma antioxidant concentrations in this population and to compare the concentrations of plasma antioxidants in middle-aged and elderly individuals. The study recruited 94 participants from the Nun Study, a longitudinal study of aging and Alzheimer disease. Women in this population were unique for their advanced age, 77-99 years old, and their comparability across age groups due to the absence of several potential confounders of plasma antioxidant concentrations. The population mean and standard deviation of several plasma carotenoids and alpha-tocopherol concentrations (g/dl) were as follows: lycopene, 15.0 +/- 10.0; beta-carotene, 30.0 +/- 19.7; alpha-carotene, 15.0 +/- 9.6; zeaxanthin plus lutein, 22.0 +/- 7.4; beta-cryptoxanthin, 14.0 +/- 8.6 and alpha-tocopherol, 980 +/- 310. Concentrations of all analytes, except lycopene, were similar to or higher than those reported for several middle-aged American populations. Lycopene concentrations were significantly lower in the population of sisters as compared with the middle-aged populations and tended to decrease across age groups within the population of sisters. Age appeared to be a relatively minor determinant of plasma alpha-tocopherol and the concentrations of carotenoids, other than lycopene, in this population. Importantly, the plasma concentrations of most carotenoids and alpha-tocopherol in this population of independent elderly women were apparently adequate on the basis of population comparisons. Further studies of this population may define determinants essential for the maintenance of antioxidant status in elderly populations.

Gross MD, Snowdon DA: Plasma antioxidant concentrations in a population of elderly women: Findings from the Nun Study Nutrition Research, 16(11/12):1881-1890, 1996.

Neuropathological findings processed by artificial neural networks (ANNs) can perfectly distinguish Alzheimer's patients from controls in the Nun Study

Enzo Grossi, Massimo P. Buscema, David Snowdon, Piero Antuono

Background: Many reports have described that there are fewer differences in AD brain neuropathologic lesions between AD patients and control subjects aged 80 years and older, as compared with the considerable differences between younger persons with AD and controls. In fact some investigators have suggested that since neurofibrillary tangles (NFT) can be identified in the brains of non-demented elderly subjects they should be considered as a consequence of the aging process. At present, there are no universally accepted neuropathological criteria which can mathematically differentiate AD from healthy brain in the oldest old.

The aim of this study is to discover the hidden and non-linear associations among AD pathognomonic brain lesions and the clinical diagnosis of AD in participants in the Nun Study through Artificial Neural Networks (ANNs) analysis

Methods: The analyses were based on 26 clinically- and pathologically-confirmed AD cases and 36 controls who had normal cognitive function. The inputs used for the analyses were just NFT and neuritic plaques counts in neocortex and hippocampus, for which, despite substantial differences in mean lesions counts between AD cases and controls, there was a substantial overlap in the range of lesion counts.

Results: By taking into account the above four neuropathological features, the overall predictive capability of ANNs in sorting out AD cases from normal controls reached 100%. The corresponding accuracy obtained with Linear Discriminant Analysis was 92.30%. These results were consistently obtained in ten independent experiments. The same experiments were carried out with ANNs on a subgroup of 13 non severe AD patients and on the same 36 controls. The results obtained in terms of prediction accuracy with ANNs were exactly the same.

Input relevance analysis confirmed the relative dominance of NFT in neocortex in discriminating between AD patients and controls and indicated the lesser importance played by NP in the hippocampus.

Conclusion: The results of this study suggest that: a) cortical NFT represent the key variable in AD neuropathology; b) the neuropathologic profile of AD subjects is complex, however, c) ANNs can analyze neuropathologic features and differentiate AD cases from controls.

BMC Neurology, 2007;7:15;doi:10.1186/1471-2377-7-15.

Temporomandibular joint dysfunction and selected health parameters in the elderly

Linda P. Harriman, David A. Snowdon, Louise B. Messer, Del Marie Rysavy,
Sharon K. Ostwald, Char-Huei Lai and Annelle H. Soberay

Little research has focused on temporomandibular joint dysfunction (TMJD) in the elderly. The present study describes relationships between TMJD and selected health parameters in a population of 75- to 94-year-old Roman catholic sisters (nuns). Mental, physical, and oral assessments made on 117 sisters identified 26 with TMJD. Among all sisters, TMJD was not associated with age, education, mental impairments, hand coordination, handgrip strength, mobility, or use of walking aids. In 75- to 84-year-old sisters, TMJD was positively associated with self-reported arthritis (p=0.12), edentulism (p=0.09), and the presence of complete dentures (p=0.05), and negatively associated with the number of teeth present (p=0.05), especially the posterior teeth. These associations were weaker in 85- to 94-year-old sisters. This study suggests that TMJD is associated with the presence of complete dentures and a low number of teeth, especially the posterior teeth.

Harriman LP, Snowdon DA, Messer LB, Rysavy DM, Ostwald SK, Lai C-H, Soberay AH. Temporomandibular joint dysfunction and selected health parameters in the elderly Oral Surgery, Oral Medicine, and Oral Pathology 70:406-413, 1990.

Language decline across the life span: Findings from the Nun Study

Susan Kemper, Lydia H. Greiner, Janet G. Marquis, Katherine Prenovost, and Tracy L. Mitzner

The present study examines language samples from the Nun Study. Measures of grammatical complexity and idea density were obtained from autobiographies written over a 60-year span. Participants who had met criteria for dementia were contrasted with those who did not. Grammatical complexity initially averaged 4.78 (on a 0-to-7 point scale) for participants who did not meet criteria for dementia and declined .04 units per year; grammatical complexity for participants who met criteria for dementia initially averaged 3.86 and declined .03 units per year. Idea density averaged 5.35 propositions per 10 words initially for participants who did not meet criteria for dementia and declined an average of .03 units per year, whereas idea density averaged 4.34 propositions per 10 words initially for participants who met criteria for dementia and declined .02 units per year. Adult experiences, in general, did not moderate these declines.

Kemper S, Greiner L, Marquis J, Prenovost K, Mitzner T. Languaage decline across the life span: Findings from the Nun Study Psychology and Aging 16(2):227-239, 2001.

Oral and written language in late adulthood: Findings from the Nun Study

Tracy L. Mitzner and Susan Kemper

As a part of the Nun Study, a longitudinal investigation of aging and Alzheimer's disease, oral and written autobiographies from 118 older women were analyzed to examine the relationship between spoken and written language. The written language samples were more complex than the oral samples, both conceptually and grammatically. The relationship between the linguistic measures and participant characteristics was also examined. The results suggest that the grammatical and conceptual characteristics of oral and written language are affected by participant differences in education, cognitive status, and physical function and that written language samples have greater power than oral language samples to differentiate between high and low ability older adults.

Mitzner TL, Kemper S: Oral and written language in late adulthood: Findings from the Nun Study Experimental Aging Research 2003;29(4):457-474.

Very early detection of Alzheimer neuropathology and the role of brain reserve in modifying its clinical expression

James A. Mortimer, Amy R. Borenstein, Karen M.Gosche, and David A. Snowdon

Numerous studies show that the pathology of Alzheimer's disease is present decades before a clinical diagnosis of dementia can be made. Given the likelihood that agents will become available that reliably delay onset and/or slow progression of Alzheimer's disease, it will be important to detect preclinical Alzheimer's disease as early as possible for maximal treatment effect. Detection of individuals by sensitive cognitive measures provides one way to identify people who are at high risk of developing clinical Alzheimer's disease. However, it is likely that those with considerable brain or cognitive reserve will be able to mask cognitive deficits until very close to the onset of the dementia, rendering such cognitive measures insensitive. Optimum biomarkers for Alzheimer's disease therefore need to target the severity of underlying brain pathology independently of brain reserve. Findings are presented showing the importance of higher education and larger brain size in masking the underlying disease pathology.

Journal of Geriatric Psychiatry and Neurology 2005; 18(4):218-223

Delayed recall, hippocampal volume and Alzheimer neuropathology: Findings from the Nun Study

Mortimer James, Gosche K, Riley K, Markesbery W and David A. Snowdon

Objective: To examine the associations of hippocampal volume and the severity of neurofibrillary lesions determined at autopsy with delayed verbal recall performance evaluated an average of 1 year prior to death.

Methods: Hippocampal volumes were computed using postmortem brain MRIs from the first 56 scanned participants of the Nun Study. Quantitative neuropathological studies included lesion counts, Braak staging and determination of whether neuropathological criteria for AD were met.

Multiple regression was used to assess the association of hippocampal volume and neuropathologic lesions with the number of words (out of 10) recalled on the CERAD Delayed Word Recall Test administered an average of 1 year prior to death.
Results: When entered separately, hippocampal volume, Braak stage, and the mean neurofibrillary tangle counts in the CA-1 region of the hippocampus and the subiculum were strongly associated with the number of words recalled after a delay, adjusting for age and education. When hippocampal volume was entered together with each neuropathologic index, only hippocampal volume retained a significant association with the delayed recall measure. The association between hippocampal volume and the number of words recalled was present in both demented and non-demented individuals as well as in those with and without substantial AD neurofibrillary pathology.
Conclusions: The findings suggest that hippocampal volume is strongly correlated with delayed recall performance and that the association of neurofibrillary tangles with delayed verbal recall may reflect associated hippocampal atrophy.

Mortimer J, Gosche K, Riley K, Markesbery W, Snowdon D: Delayed recall, hippocampal volume and Alzheimer neuropathology: Findings from the Nun Study Neurology 2004; 62:428-432.

Head Circumference, Education and Risk of Dementia: Findings from the Nun Study

James A. Mortimer, David A. Snowdon, and William R. Markesbery

To examine the prevalence of dementia associated with having a smaller brain, lower education or both of these characteristics, 294 Catholic sisters were assessed annually for dementia. Sixty participants died and their brains were evaluated to determine fulfillment of neuropathological criteria for Alzheimer's disease (AD). Lower education attainment and the interaction of smaller head circumference with lower education were associated with the presence of dementia, controlling for age and the presence of one or more apolipoprotein E-ε 4 alleles. By contrast, neither low educational attainment nor head circumference was significantly associated with fulfillment of neuropathological criteria for AD. Individuals having both low education and small head circumference were 4 times as likely to be demented as the rest of the sample. The findings suggest that higher education and larger head size, alone or in combination, may reduce the risk of expressing dementia in late life.

Mortimer J, Snowdon D, Markesbery W: Head Circumference, Education and Risk of Dementia: Findings from the Nun Study Journal of Clinical and Experimental Neuropsychology 2002; 25(5):671-679.

Manual dexterity as a correlate of dependency in the elderly

Sharon K. Ostwald, David A. Snowdon, S. Del Marie Rysavy, Nora L. Keenan, and Robert L. Kane

Physical and mental correlates of dependent living were determined in 128 Catholic sisters (nuns), aged 75-94 years, who had similar social support systems and lifestyles. The primary a priori hypothesis was that poor manual dexterity would correlate strongly with living in the nursing home. Stepwise discriminant analysis indicated that manual dexterity explained 51% of the variance in the sisters' residential living site (ie, nursing home, retirement home, or living in community). The discriminant analysis equation using manual dexterity predicted living site correctly for 63% of the sisters in the nursing home with a specificity of 99%, a positive predictive value of 96% and a negative predictive value of 84%. The addition of age and mental status to the equation improved the prediction only slightly.

Ostwald SK, Snowdon DA, Rysavy DM, Keenan NL, Kane RL: Manual dexterity as a correlate of dependency in the elderly Journal of the American Geriatrics Society7:963-969, 1989.

The Use of Convent Archival Records in Medical Research: The School Sisters of Notre Dame Archives and the Nun Study

Gari-Anne Patzwald and Sister Carol Marie Wildt

The School Sisters of Notre Dame (SSND) archives program is a cooperative system for the arrangement and preservation of the records of the SSND provinces in North America, including records of individual sisters. Archival records include autobiographies, school and college transcripts, employment histories, and family socioeconomic data. The Nun Study, a longitudinal study of Alzheimer’s disease and aging in 678 SSND sisters, compares data extracted from these records with data on late-life cognitive and physical function and postmortem brain neuropathology to explore early life factors that may affect late-life cognitive function and longevity.

Patzwald GA, Wildt CM: The Use of Convent Archival Records in Medical Research: The School Sisters of Notre Dame Archives and the Nun Study American Archivist, 67(1):86-106, 2004.

The challenges and successes of aging: Findings from the Nun Study

Kathryn P.Riley and David A. Snowdon

The Nun Study is a longitudinal study of aging and Alzheimer's disease conducted in a population of Catholic sisters (nuns) aged 75 to 102 when the study began in 1991. All participants agreed to annual medical examinations and functional assessments, as well as to brain donation at death. A major purpose of the Nun Study is to identify predictors and correlates of the clinical symptoms and neuropathologic signs of Alzheimer's disease and other dementias. Other key themes include change and stability in functional abilities, factors related to mortality and survival, and successful aging as defined by cognitive, functional, and neuropathologic indicators. The multidisciplinary team working with the Nun Study includes researchers from a diverse set of scientific and academic fields of study. These researchers bring a variety of

perspectives to bear upon their examinations of the data collected in the study. This chapter will present a brief overview of the Nun Study, focusing on a synthesis of its major findings.

Riley KP, Snowdon DA: The challenges and successes of aging: Findings from the Nun Study In: Advances in Medical Psychotherapy & Psychodiagnosis Volume 10 1999-2000, Lichtenberg P, Christensen BK, Barth JT, Anchor KN, editors, pp.1-12, Kendall/Hunt Publishing Company: Dubuque IA, 1999.

Early life linguistic ability, late life cognitive function, and neuropathology: Findings from the Nun Study

Kathryn P. Riley, David A. Snowdon, Mark F. Desrosiers, and William R. Markesbery

The relationships between early life variables, cognitive function, and neuropathology were examined in participants in the Nun Study who were between the ages of 75 and 95. Our early life variable was idea density, which is a measure of linguistic ability, derived from autobiographies written at a mean age of 22 years. Six discrete categories of cognitive function, including mild cognitive impairments, were evaluated, using the CERAD battery of cognitive tests. Neuropathologic data included Braak staging, neurofibrillary tangle and senile plaque counts, brain weight, degree of cerebral atrophy, severity of atherosclerosis, and the presence of brain infarcts. Early-life idea density was significantly related to the categories of late-life cognitive function, including mild cognitive impairments: low idea density was associated with greater impairment. Low idea density also was significantly associated with lower brain weight, higher degree of cerebral atrophy, more severe neurofibrillary pathology, and the likelihood of meeting neuropathologic criteria for Alzheimer's disease.

Riley KP, Snowdon DA, Desrosiers MF, Markesbery WR: Early life linguistic ability, late life cognitive function, and neuropathology: Findings from the Nun Study Neurobiology of Aging, 26(3):341-347, 2005

Cognitive function and apolipoprotein-E in the very old: findings from the Nun Study

Kathryn P. Riley, David A. Snowdon, Ann M. Saunders, Allen D. Roses, James A. Mortimer and Nuwan Nanayakkara

Objectives: The ε4 allele of apolipoprotein E (APOE) has been associated with Alzheimer=s disease and with milder forms of cognitive impairment. We investigated the possibility that the absence of the ε4 allele may predict the maintenance of high cognitive function among very old individuals.
Methods: Our data are from the Nun Study, a longitudinal study of aging and Alzheimer=s disease in 678 Catholic sisters. All sisters participate in annual functional exams which include the CERAD battery of cognitive tests. High cognitive function was defined as intact scores on five of the CERAD tests. A total of 241 participants aged 75 to 98 met this criterion at the first exam.

Results: Findings showed that 62% of the 241 participants maintained intact scores on the five CERAD tests throughout their participation in the study. Life table analyses indicated that those without the APOE ε4 allele spent more time with intact cognitive function than those with the ε4 allele ($p = .007$). Cox regression analyses indicated those without the ε4 allele had half the risk of losing their intact status during the study when compared to those with the ε4 allele ($p < .01$). Discussion: Our findings suggest that the APOE ε4 allele may be included among the variables that predict high cognitive function in the cognitively intact very old. While the presence or absence of the ε4 allele is known to be related to the risk of dementia, it also appears to be related to maintaining high levels of cognitive function in old age.

Riley KP, Snowdon DA, Saunders AM, Roses AD, Mortimer JA, Nanayakkara N: Cognitive function and apolipoprotein-E in the very old: findings from the Nun Study Journal of Gerontology: Social Sciences, 55B(2):S69-S75, 2000.

Estimating intensity functions on multi-state Markov models with application to the NUN Study.

JC Salazar, SL Tyas, MF Desrosiers, DA Snowdon, KP Riley, MS Mendiondo, RJ Kryscio

We consider a multi-state Markov process with two competing absorbing states (dementia and death) and several transitory non-demented states. Transitions among states are determined by intensity functions which account for the effect of covariates. The likelihood function is derived and inference for estimating the effects of the covariates on transitions is determined when the process can be view as a Markov chain and when the likelihood function can be factored as the product of several functions: one for the transitions among non-absorbing states and the others for transitions from transient to absorbing states. Inference for more general cases such as when the progression of the disease is assumed to follow a Markov-process will be discussed. These approaches are illustrated using a longitudinal study on aging and Alzheimer's disease conducted in a population of 678 catholic sisters (NUN Study) aged 75 to 102 when the study began in 1991.

JC Salazar, SL Tyas, DA Snowdon, MF Desrosiers, KP Riley, MS Mendiondo, and RJ Kryscio. Estimating intensity functions on multi-state Markov models with application to the Nun Study. Proceedings of the Joint Statistical Meeting, San Francisco 2003. Biometrics section, 3616-3623..

Dental amalgam and cognitive function in older women: Findings from the Nun Study

Stanley R. Saxe, David A. Snowdon, Merle W. Wekstein, Robert G. Henry, Sara Jean Donegan , and David R. Wekstein

The number and surface area of occlusal dental amalgams were determined in a group of 129 Catholic sisters who were 75 to 102 years of age. Findings from this study of women with

relatively homogeneous adult lifestyles and environments suggest that existing amalgams are not associated with lower performance on eight different tests of cognitive function.

Saxe SR, Snowdon DA, Wekstein MW, Henry RG, Grant FT, Donegan SJ, Wekstein DR: Dental amalgam and cognitive function in older women: Findings from the Nun Study Journal of the American Dental Association 126:1495-1501, 1995.

Alzheimer's disease, dental amalgam and mercury

Stanley R. Saxe, Merle W. Wekstein, Richard J. Kryscio, Robert G. Henry, Charles R. Cornett, David A. Snowdon, Ford T. Grant, Frederick A. Schmitt, Sara Jean Donegan, David R. Wekstein, William D. Ehmann, William R. Markesbery

Background: Mercury is a neurotoxin and it has been speculated that it may play a role in the pathogenesis of Alzheimer's disease. Dental amalgams (silver fillings) release low-levels of mercury vapor and are a potential source of mercury for a large segment of the adult population.
Methods: Mercury levels in multiple brain areas at autopsy and dental amalgam status and history were determined in Alzheimer's disease subjects and prospectively evaluated normal control subjects. Participants were from central Kentucky and from the Nun Study at a covent in Elm Grove, Wisconsin. Dental amalgam assessments were carried out during life in the majority of subjects and in some subjects at the time of autopsy. Three dental indices of amalgam were determined, Event (placement, repair or removal of amalgam), Location and Time In Mouth in addition to the number and surface area of occlusal amalgams. Mercury levels were determined in multiple brain regions. Full neuropathological evaluation was performed to confirm the normal status or the presence of Alzheimer's disease. Sixty-eight AD patients and 33 control subjects were autopsied.
Results: No significant association of Alzheimer's disease with the number, surface area or past history of dental amalgams was found. No statistically significant differences in brain mercury level between Alzheimer's disease and control subjects were found.
Conclusions: Mercury in dental amalgam restorations does not appear to be a neurotoxic factor in the pathogenesis of Alzheimer's disease. Brain mercury levels are not associated with dental amalgam, either existing amalgams or past dental amalgam experience..

Saxe SR, Wekstein MW, Kryscio RJ, Henry RG, Cornett CR, Snowdon DA, Grant FT, Schmitt FA, Donegan SJ, Wekstein DR, Ehmann WD, Markesbery WR: Alzheimer's disease, dental amalgam and mercury Journal of the American Dental Association, 130: 191-199, 1999.

Periventricular white matter hyperintensities on MRI: Correlation with neuropathologic findings

Charles D. Smith, David Snowdon and William R. Markesbery

Periventricular white matter hyperintensities on postmortem magnetic resonance imaging (MRI) and myelin-stained frontal and parietal histologic sections were evaluated independently in 12 cases. There was a strong relationship between the extent of white matter hyperintensities on MRI and the extent of gross and microscopic changes seen in the white matter of myelin-stained sections, particularly in the frontal lobe. In this material, the extent of myelin rarefaction correlated with an 0-8 point white matter hyperintensity scale rating on MRI in the same brains.

Smith CS, Snowdon DA, Markesbery WR: Periventricular white matter hyperintensities on MRI: correlation with neuropathologic findings Journal of Neuroimaging, 10:13-16, 2000.

White matter volumes and periventricular white matter hyperintensities in aging and dementia

Charles D. Smith, David Snowdon , Hao Wang and William R. Markesbery

Objective: To determine the relationship between MRI periventricular white matter hyperintensities, cerebral white matter volumes, neuropathologic findings and cognitive status in aged individuals.
Background: The significance of periventricular white matter hyperintensities seen on MR images in aged individuals remains controversial. The Nun Study is a longitudinal cohort aging study in which all 678 initially enrolled participants agreed to autopsy neuropathologic examination.
Methods: We used magnetic resonance imaging to measure white matter volumes of the cerebral hemispheres in 52 formalin-fixed brains for correlation with white matter and neocortical pathology, post mortem magnetic resonance imaging observations, and cognitive measures.
Results: Reduced white matter volume is associated with dementia, but periventricular white matter hyperintensities were not related to white matter volume, stroke, or dementia.
Conclusions: Our results do not support the hypothesis that periventricular hyperintensities seen on magnetic resonance images have deleterious consequences in these aged individuals.

Smith CS, Snowdon DA, Wang H, Markesbery WR: White matter volumes and periventricular white matter hyperintensities in aging and dementia Neurology, 54(4):838-842, 2000.

Healthy aging and dementia: Findings from the Nun Study

David A. Snowdon

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.

Snowdon D: Healthy aging and dementia: Findings from the Nun Study Annals of Internal Medicine 2003; 139 (5 Part 2):450-454

Aging and Alzheimer's disease: Lessons from the Nun Study

David A. Snowdon

Sister Mary, the gold standard for the Nun Study, was a remarkable woman who had high cognitive test scores before her death at 101 years of age. What is more remarkable is that she maintained this high status despite having abundant neurofibrillary tangles and senile plaques, the classic lesions of Alzheimer's disease. Findings from Sister Mary and all 678 participants in the Nun Study may provide unique clues about the etiology of aging and Alzheimer's disease, exemplify what is possible in old age, and show how the clinical expression of some diseases may be averted.

Snowdon DA: Aging and Alzheimer's disease: Lessons from the Nun Study The Gerontologist, 37(2):150-156, 1997.

Making mammography a habit

David A. Snowdon, Nelly Gonzalez, Barbara M. O'Leary, and Sharon K. Ostwald

Approximately 50% of the 114,000 Roman Catholic sisters (nuns) in the United States are 65 years of age or older and virtually 100% are nulliparous. Since old age and lack of reproduction are major risk factors for breast cancer, Catholic sisters have an especially high risk of developing breast cancer. Based on the above considerations, in 1986, we investigated the frequency of routine (screening) mammography in 155 members of the Mankato (MN) Province of the School Sisters of Notre Dame who were 75 years of age and older. We concluded that the proportion of elderly Catholic sisters who have an annual mammographic examination, as recommended by the American Cancer Society, is less than 20%. This percentage appears to be unacceptably low in a population with such a high risk of breast cancer. Given that early detection of breast cancer can improve survival and is cost-effective, annual mammographic examinations should be made a habit among Catholic sisters.

Snowdon DA, Gonzalez N, O'Leary BM, Ostwald SK: Making mammography a habit Journal of the American Medical Association 262:207, 1989.

Linguistic ability in early life and longevity: Findings from the Nun Study

David A. Snowdon PhD, Lydia H. Greiner BSN, Susan J. Kemper PhD,
Nuwan Nanayakkara PhD and James A. Mortimer

Findings from the Nun Study indicate that low linguistic ability in early life has a strong relationship to poor cognitive function and dementia in late life, and the number of Alzheimer's disease lesions in the brain. In the present analyses, we investigated the relationship between linguistic ability in early life and all cause mortality in late life in a subset of 180 participants in the Nun Study. Two measures of linguistic ability in early life, idea (proposition) density and grammatical complexity, were derived from autobiographies written by the participants when they were 18 to 32 years old. An average of 58 years later, when these participants were 75 to 93 years old, all cause mortality rates were determined. Of the two linguistic measures, idea density in early life had the strongest and most consistent relationship to the rate of all cause mortality in late life: A one-unit decrease in idea density in early life (i.e., one idea expressed per ten words in a sentence) was associated with a 49 percent increase in the mortality rate (95% CI=17-89; p-value=0.001). This finding did not appear to be due to confounding by birth year, education attained at the time when the autobiography was written, or age during the mortality surveillance period. Standard life table analyses indicated that the median age at death for 75-year-olds was 81.7 years for those with low idea density in early life and 88.5 years for those with high idea density in early life. Low linguistic ability in early life may reflect suboptimal cognitive and neurological development which may increase susceptibility to aging-related declines and disease processes, resulting in a higher mortality rate late in life. Overall, low linguistic ability and its correlates in early life may place potent limits on the longevity of individuals.

Snowdon DA, Greiner LH, Kemper SJ, Nanayakkara N, Mortimer JA: Linguistic ability in early life and longevity: Findings from the Nun Study In: The Paradoxes of Longevity, Robine J-M, Forette B, Franceschi C, Allard M, editors, pp. 103-113, Springer-Verlag: Berlin, 1999.

Linguistic ability in early life and the neuropathology of Alzheimer's disease and cerebrovascular disease: Findings from the Nun Study

David A. Snowdon, Lydia H. Greiner, William R. Markesbery

Findings from the Nun Study indicate that low linguistic ability in early life has a strong association with dementia and premature death in late life. In the present study, we investigated the relationship of linguistic ability in early life to the neuropathology of Alzheimer's disease and cerebrovascular disease. The analyses were done on a subset of 74 participants in the Nun Study for whom we had handwritten autobiographies completed some time between the ages of 19 and 37 (mean=23). An average of 62 years after writing the autobiographies, when the participants were 78 to 97 years old, they died and their brains were removed for our

neuropathologic studies. Linguistic ability in early life was measured by the idea (proposition) density of the autobiographies, i.e., a standard measure of the content of ideas in text samples. Idea density scores from early life had strong inverse correlations with the severity of Alzheimer's disease pathology in the neocortex: Correlations between idea density scores and neurofibrillary tangle counts were -0.59 for the frontal lobe, -0.48 for the temporal lobe, and -0.49 for the parietal lobe (all p-values < 0.0001). Idea density scores were unrelated to the severity of atherosclerosis of the major arteries at the base of the brain and to the presence of lacunar and large brain infarcts. Low linguistic ability in early life may reflect suboptimal neurological and cognitive development which might increase susceptibility to the development of Alzheimer's disease pathology in late life.

Snowdon D, Greiner L, Markesbery W: Linguistic ability in early life and the neuropathology of Alzheimer's disease and cerebrovascular disease: Findings from the Nun Study In: Vascular factors in Alzheimer's disease, Volume 903, Kalaria RN, Ince P, eds., pp. 34-38, New York: New York Academy of Scicences, 2000.

Brain infarction and the clinical expression of Alzheimer disease: The Nun Study

David A. Snowdon, Lydia H. Greiner, James A. Mortimer,
Kathryn P. Riley, Philip A. Greiner and William R. Markesbery

Objective: To determine the relationship of brain infarction to the clinical expression of Alzheimer's disease (AD).
Design: Cognitive function and the prevalence of dementia were determined for participants in the Nun Study who later died. At autopsy, lacunar and larger brain infarcts were identified, and senile plaques and neurofibrillary tangles in the neocortex were quantitated. Participants with abundant senile plaques and some neurofibrillary tangles in the neocortex were classified as having met the neuropathologic criteria for AD.
Setting: Convents in the Midwestern, Eastern, and Southern United States.
Participants: A total of 102 college-educated women aged 76 to 100 years.
Main Outcome Measures: Cognitive function assessed by standard tests, and dementia and AD assessed by clinical and neuropathologic criteria.
Results. Among 61 participants who met the neuropathologic criteria for AD, those with brain infarcts had poorer cognitive function and a higher prevalence of dementia than those without infarcts. Participants with lacunar infarcts in the basal ganglia, thalamus, or deep white matter had an especially high prevalence of dementia, compared to those without infarcts (the odds ratio [OR] for dementia was 20.7, 95% confidence internal [95%CI]=1.5-288.0). Fewer neuropathologic lesions of AD appeared to result in dementia in those with lacunar infarcts in the basal ganglia, thalamus, or deep white matter, than in those without infarcts. In contrast, among 41 participants who did not meet the neuropathologic criteria for AD, brain infarcts were only weakly associated with poor cognitive function and dementia. Among all 102 participants, atherosclerosis of the circle of Willis was strongly associated with lacunar and large brain infarcts.
Conclusion. These findings suggest that cerebrovascular disease may play an important role in determining the presence and severity of the clinical symptoms of AD.

Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR: Brain infarction and the clinical expression of Alzheimer disease: The Nun Study Journal of the American Medical Association (JAMA), 277(10):813-817, 1997.

Brain infarction and the clinical expression of Alzheimer disease

David A. Snowdon, Lydia H. Greiner, Kathryn P. Riley, William R. Markesbery, Philip A. Greiner, and James A. Mortimer

In Reply to Editor:

The analyses of Drs. Mirra and Gearing indicate that brain infarcts are not associated with NFTs in the neocortex. Our analyses also indicated that brain infarcts were not associated with the number of NFTs, senile plaques, or neuritic plaques in the neocortex, suggesting that AD lesions and brain infarcts were likely to have occurred independently of each other.

While AD and brain infarction may represent separate disease processes, their combination may nonetheless increase the likelihood that dementia will occur. Among the participants in our study who met our neuropathologic criteria for AD (i.e., abundant senile plaques and some NFTs in the neocortex), those with 1 or 2 lacunar infarcts in the basal ganglia, thalamus, or deep white matter had an especially high prevalence of dementia, compared with those without brain infarcts. The prevalence of dementia was 93% for those with such subcortical lacunar infarcts and 57% in those without infarcts. Because of the vital connections between the neocortex and the basal ganglia, thalamus, and deep white matter, infarcts in these subcortical regions may be particularly disabling if the neocortex has already been damaged by AD. Mirra and Gearing did not specify the size or location of the infarcts in their study, making it difficult to compare our findings with theirs.

As Mirra and Gearing noted, our findings also indicated that fewer AD lesions may be required to produce dementia if subcortical lacunar infarcts are present. As shown in Figure 2, at a mean of 1.9 or more NFTs in the neocortex, 100% of participants with subcortical lacunar infarcts were demented, compared with 64% (95% confidence interval, 45%-83%) of those without infarcts. In contrast, it took a mean of 15.7 or more NFTs in the neocortex to produce dementia in 100% of those without infarcts.

These findings reflect the traditional way of testing dose responses -- i.e., examining the percentage of individuals affected at any given dose. In this case, dose is represented by the number of Alzheimer lesions, and response is represented by the percentage of individuals who are demented. Because Mirra and Gearing used data from an autopsy series of demented individuals, they could not look at the percentage demented at any given lesion count.

We agree with Dr. Roman that lacunar infarcts may only be part of the story. While we have not yet investigated the extent of periventricular white matter lesions, atherosclerosis of the major blood vessels of the brain was associated with lacunar brain infarcts in our study. Thus, small-vessel disease and ischemic damage to the brain (short of an infarct) also may be involved in the clinical expression of AD.

Overall, our findings and those cited by Roman suggest that cerebrovascular disease may play an important role in determining the presence and severity of the symptoms of AD.

Snowdon DA, Greiner LH, Riley KP, Markesbery WR, Greiner PA, Mortimer JA: Brain infarction and the clinical expression of Alzheimer disease Journal of the American Medical Association (JAMA), 278(2):113, 1997.

Linguistic ability in early life and Alzheimer's disease in late life

David Snowdon, Lydia Greiner, David Wekstein, Deborah Danner, William Markesbery, Susan Kemper and James Mortimer

In Reply to Editor:
Massey and Miranda raise issues that we considered when investigating the relationship between writing style demonstrated in autobiographies written at an average age of 22 years, and cognitive function and Alzheimer's disease assessed an average of 58 years later. We found a strong relationship between low idea (proposition) density in autobiographies written in early life and poor cognitive function and Alzheimer's disease in late life.
In agreement with Massie, the correlation with idea density was 0.26 (P=0.01) for the density of positive-emotion words, and 0.19 (P=0.07) for the density of negative- emotion words. However, the correlation with cognitive function, as measured by the Mini-Mental State Exam score in late life, was 0.66 (P=0.0001) for idea density; 0.19 (P=0.07) for the density of positive-emotion words; 0.19 (P=0.07) of negative-emotion words. While emotion may play an important role in the generation of ideas expressed, these correlations indicate that emotional content does not explain the relationship between idea density and cognitive function.
Before involving a linguist in our research, we (D.A.S. and L.H.G.) believed that those with poor cognitive function in late life wrote autobiographies that were less emotional or sensuous. We have often described sisters with low late life cognitive function as "listers" i.e., they had a high concentration of dates, numbers, and proper nouns in their autobiographies from early life. We also have described their writing style as monotone, and the writing style of other sisters with high cognitive function in late life as high fidelity.
In agreement with Miranda, sentences that were low in idea density were in general less complex and easier to understand. However, it should not be inferred that sisters with low idea density had poor linguistic ability. There was nothing wrong with their sentences, they just lacked a complexity of interrelated ideas. Overall, a reading of the autobiographies of sisters who did and did not develop Alzheimer's disease reveals stark contrasts in their abilities to express ideas in early life. This difference in written expression may be more a reflection of fundamental differences in their cognitive abilities during early life, than their linguistic proficiency.

Snowdon DA, Greiner LH, Wekstein DR, Danner D, Markesbery WR, Kemper SJ, Mortimer JA: Linguistic ability in early life and Alzheimer disease in late life Journal of the American Medical Association, 275(24):1879, 1996.

Antioxidants and reduced functional capacity in the elderly: Findings from the Nun Study

David A. Snowdon PhD, Myron D. Gross PhD, and Steven M. Butler PhD

Background: This study investigated the relationship of plasma antioxidants to reduced functional capacity in the elderly. A hallmark of reduced functional capacity in the elderly is dependence in self-care (i.e., requiring assistance with bathing, walking, dressing, standing, toileting, and feeding).
Methods: This relationship was assessed in a cross-sectional study of 88 Catholic sisters (nuns). These 77 to 98 year old women lived in the same building, ate food prepared in the same kitchen, and had all nursing services provided by the same staff. In 1993, ability to perform self-care was assessed and blood was drawn to determine plasma carotenoids (lycopene, beta carotene, alpha carotene, zeaxanthin and lutein combined, and beta cryptoxanthin) and alpha tocopherol.
Results: Dependence in self-care had a strong negative association with lycopene, but was not clearly related to other carotenoids or alpha tocopherol. Results from age-adjusted least squares regression indicated that a 30 ug/dl decrease in lycopene was associated with 2.4 additional dependencies in self-care (95% confidence interval = 1.5, 3.3; $p<0.001$). Lycopene's relationship to dependence was modified by plasma LDL-cholesterol, the predominant carrier of lycopene in the blood. Women with low lycopene and low LDL-cholesterol had 3.6 dependencies (95% confidence interval = 3.1, 4.2; $p<0.001$), compared to 1.0 dependency (95% confidence interval = 0.3,1.8) in those with high lycopene and low LDL-cholesterol.
Conclusions: This is the first study to report an association between lycopene and functional status. This finding needs to be replicated in other human and animal studies before the association is accepted as real.

Snowdon DA, Gross MD, Butler SM: Antioxidants and reduced functional capacity in the elderly: Findings from the Nun Study Journal of Gerontology: Medical Sciences 51A(1):M10-M16, 1996.

Linguistic ability in early life and cognitive function and Alzheimer's disease in late life: Findings from the Nun Study

David A. Snowdon, Susan J. Kemper, James A. Mortimer, Lydia H. Greiner,
David R. Wekstein, and William R. Markesbery

Objective: To determine if linguistic ability in early life is associated with cognitive function and Alzheimer's disease in late life.
Design: Two measures of linguistic ability in early life, idea density and grammatical complexity, were derived from autobiographies written at a mean age of 22 years. Approximately 58 years later, the women who wrote these autobiographies participated in an assessment of cognitive function, and those who subsequently died were evaluated neuropathologically.
Setting: Convents in the United States participating in the Nun Study; primarily convents in the Milwaukee, Wis, area.
Participants: Cognitive function was investigated in 93 participants who were aged 75 to 95 years at the time of their assessments, and Alzheimer's disease was investigated in the 14 participants who died at 79 to 96 years of age.
Main Outcome Measures: Seven neuropsychological tests and neuropathologically confirmed Alzheimer's disease.

Results: Low idea density and low grammatical complexity in autobiographies written in early life were associated with low cognitive test scores in late life. Low idea density in early life had stronger and more consistent associations with poor cognitive function than did low grammatical complexity. Among the 14 sisters who died, neuropathologically confirmed Alzheimer's disease was present in all of those with low idea density in early life and in none of those with high idea density.
Conclusions: Low linguistic ability in early life was a strong predictor of poor cognitive function and Alzheimer's disease in late life.

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 Journal of the American Medical Association (JAMA), 275(7):528-532, 1996.

The prevalence of neuropathologically confirmed vascular dementia: Findings from the Nun Study

David A. Snowdon and William R. Markesbery

The Nun Study is a longitudinal study of aging and Alzheimer’s disease in 678 Catholic sisters who agreed to annual examinations and brain donation at death. By the end of 1997, 262 participants had died and brains were collected and neuropathologic examinations completed on 241 (92 %). These 241 women were 76 to 103 years of age at death (mean=89). Prior to death, 118 (49 %) of the 241 women fulfilled our clinical criteria for dementia and only 3 of them had neuropathologic confirmation of vascular dementia. That is, the 3 cases had vascular pathology that was judged by a neuropathologist to be sufficient to produce dementia and they had no other significant pathology that could have produced the dementia, such as Alzheimer’s disease. Overall, vascular dementia appears to be an uncommon cause of dementia in this population.
1st International Congress on Vascular Dementia 1999;10:19-24

Snowdon DA, Markesbery WR: The prevalence of neuropathologically confirmed vascular dementia: findings from the Nun Study In: 1st International Congress on Vascular Dementia, Korczyn AD, ed., pp. 19-24, Monduzzi Editore: Bologna Italy, 1999.

Education, survival, and independence in elderly Catholic sisters, 1936-1988

David A. Snowdon, Sharon K. Ostwald, Robert L. Kane

Mortality among 306 Roman Catholic sisters (nuns) from Mankato, Minnesota, was assessed during the period 1936-1988; daily use of nursing services by survivors was determined in 1986; and the ability of survivors to eat, dress, and perform other self-care activities was evaluated in 1987. The median age at death was 89.4 years for sisters with educational attainment of a bachelor's degree or higher, 82.2 years for sisters with some high school or college education,

and 82.0 years for sisters with only a grade school education. Odds ratios were calculated for "survival and independence" (i.e., sisters survived to 1986 (ages 75-94 years) and did not use daily nursing services at that time). These odds ratios were 2.67 (95% confidence interval (CI) 1.16-6.16) for sisters with a bachelor's degree or higher, 1.00 for the reference group with some high school or college, and 0.94 (95% CI 0.32-2.73) for sisters with only grade school. Sisters with a bachelor's degree or higher were also more likely than others to survive to old age while maintaining their ability to perform self-care activities. These findings suggest that college graduates lived longer and maintained their ability to care for themselves longer than other persons.

Snowdon DA, Ostwald SK, Kane RL: Education, survival, and independence in elderly Catholic sisters American Journal of Epidemiology 130:999-1012, 1989.

Years of life with good and poor mental and physical function in the elderly

David A. Snowdon, Sharon K. Ostwald, Robert L. Kane, and Nora L. Keenan

A population of Roman Catholic sisters (nuns) were divided into a high education group (i.e. at least a Bachelor's degree) and a low education group (i.e. less than a Bachelor's degree). Prevalence data on 132, 75-94 year old, sisters indicated that the high-educated had better mobility and hand coordination, stronger handgrip, better distant and near visual acuity, and fewer mental impairments than the low-educated group. Life table analyses on 154 sisters indicated that the high-educated lived an average of 3.28 years longer after age 75 than the low-educated. Years of life with relatively good and poor mental and physical function after age 75 were estimated by a mathematical model that used mortality and prevalence data. According to the model, high-educated sisters lived an average of 3.57 years longer with good function and 0.29 of a year less with poor function than low-educated sisters.

Snowdon DA, Ostwald SK, Kane RL, Keenan NL: Years of life with good and poor mental and physical function in the elderly Journal of Clinical Epidemiology 42:1055-1066, 1989.

Serum folate and the severity of atrophy of the neocortex in Alzheimer disease: Findings from the Nun Study

David A. Snowdon, Christine L. Tully, Charles D. Smith, Kathryn P. Riley, and William R. Markesbery

Background: Previous studies suggest that low levels of folate in the blood are related to poor cognitive function, dementia, and Alzheimer’s disease-related neurodegeneration of the brain.
Objective: To determine whether serum folate is inversely associated with the severity of atrophy of the neocortex.
Design: Nutrients, lipoproteins, and nutritional markers were measured in the blood of 30 participants in the Nun Study from one convent who later died when they were 78 to 101 years

old (mean=91). At autopsy, several neuropathologic indicators of Alzheimer's disease were determined, including an assessment by a neuropathologist of the degree of atrophy of three lobes of the neocortex (i.e., frontal, temporal, and parietal), and the number of neocortical Alzheimer's disease lesions (i.e., senile plaques and neurofibrillary tangles).
Results: The correlation between serum folate and the severity of atrophy of the neocortex was -0.40 (P = 0.03). Among a subset of 15 participants with significant numbers of Alzheimer's disease lesions in the neocortex, the correlation between folate and atrophy was -0.80 (P = 0.0006). Atrophy may be specific to low folate, since none of the 18 other nutrients, lipoproteins, or nutritional markers measured in the blood had statistically significant negative correlations with atrophy.
Conclusions: Among elderly Catholic sisters who lived in one convent, ate out of the same kitchen, and were highly comparable on a wide range of environmental and lifestyle factors, low serum folate was strongly associated with atrophy of the cerebral cortex. Definitive evidence for this relationship awaits the findings of other studies.

Snowdon DA, Tully CL, Smith CD, Riley KP, Markesbery WR: Serum folate and the severity of atrophy of the neocortex in Alzheimer disease American Journal of Clinical Nutrition, 71(4):993-998, 2000.

Tooth loss, dementia and neuropathology in the Nun Study

Pamela Sparks Stein, Mark Desrosiers, Sara Jean Donegan, SSND,
Juan F. Yepes, and Richard J. Kryscio

Background. Numerous studies have linked dementia to the subsequent deterioration of oral health. Few investigators, however, have examined oral disease as a potential risk factor in the development of dementia. The authors conducted a study to investigate a potential association between a history of oral disease and the development of dementia.

Methods. Longitudinal dental records supplemented data collected from 10 annual cognitive assessments of 144 Milwaukee participants in the Nun Study, a longitudinal study of aging and Alzheimer disease, who were 75 to 98 years old. Neuropathologic findings at autopsy were available for 118 participants who died.

Results. A low number of teeth increased the risk of higher prevalence and incidence of dementia.

Conclusion. Participants with the fewest teeth had the highest risk of prevalence and incidence of dementia.

Clinical Implications. Edentulism or very few (one to nine) teeth may be predictors of dementia late in life.

Weight change and physical function in elderly women: Findings from the Nun Study

Christine L. Tully nd David A. Snowdon

Objective: Investigate the association between change in weight and decline in physical function in elderly women.
Design: Longitudinal study of a defined population of Catholic sisters (nuns) whose weight and function were assessed twice, an average of 584 days apart.
Setting: Unique life communities (convents) located throughout the United States.
Participants: 475 Catholic sisters who were 75 to 99 years old (mean, M=82.1; standard deviation, SD=4.8) and were independent in at least one Activity of Daily Living at the first assessment of weight and function.
Interventions: None.
Measurements: At each assessment, weight, Activities of Daily Living, and cognitive function were evaluated as part of the Nun Study, a longitudinal study of aging and Alzheimer's disease. Annual percent weight change was calculated using weights from the two assessments and the days that elapsed between assessments.
Results: Mean weight at first assessment was 140 pounds (range 78 to 232, SD=27). The mean annual percent weight change was 0.1% (range 22% loss to 16% gain, SD=3.8). Age- and initial weight-adjusted findings indicated that those with an annual percent weight loss of 3% or greater had 2.7 to 3.9 times the risk of becoming dependent in each Activity of Daily Living, compared to those with no weight change. The elevated risk persisted in those who were mentally intact or independent in eating.
Conclusions: Monitoring of weight may be an easy and inexpensive method of identifying older individuals at increased risk of disability.

Tully CL, Snowdon DA: Weight change and physical function in older women: Findings from the Nun Study Journal of the American Geriatrics Society 43:1394-1397, 1995.

Serum zinc and plasma lipoproteins in elderly women: Findings from the Nun Study

Christine L. Tully, David A. Snowdon, and John D. Belcher

Supplementation with zinc has been associated with changes in lipoprotein levels in prior studies. The purpose of this study was to define further the relationship between serum zinc and plasma total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides. This study was conducted in a homogeneous population of elderly women who were not taking zinc supplements. Fasting blood samples were drawn from 87 women who were 77 to 99 years old. Serum zinc concentrations were significantly positively correlated with total cholesterol (r=0.37, p=<0.01) and with LDL-cholesterol (r=0.41. p=<0.001). In 77 to 84 year old women (N=47), a normal serum zinc level (70 to 150 µg/dl) was associated with a 27 mg/dl higher mean LDL-cholesterol (p=0.06) compared to low serum zinc (<70 µg/dl). In 85 to 99 year old women (N=40), a normal serum zinc was associated with a 49 mg/dl higher mean LDL-cholesterol (p=0.002) compared to low serum zinc. These associations were not materially affected by the potential confounding effects of weight, weight change over 8 years,

triceps skinfold, or serum C-reactive protein. Overall, serum zinc concentration had a strong positive association with plasma LDL-cholesterol and, to a lesser extent, with total plasma cholesterol in this population of elderly women. The association between serum zinc and plasma cholesterol may be due to a third factor, such as red meat consumption which is a significant source of zinc and saturated fat. Alternatively, zinc may play a role in cholesterol metabolism.

Tully CL, Snowdon DA, Belcher JD: Serum zinc and plasma lipoproteins in elderly women: Findings from the Nun Study Journal of Trace Elements in Experimental Medicine 8(4):201-209, 1995-1996.

Serum zinc, senile plaques, and neurofibrillary tangles: Findings from the Nun Study

Christine L. Tully, David A. Snowdon, and William R. Markesbery

Zinc appears to have a role in binding amyloid precursor protein in vitro. It is not known whether zinc plays a role in senile plaque formation in vivo in humans. Serum zinc concentrations were available from 12 sisters who died in the Nun Study, a longitudinal study of aging and Alzheimer's disease. Fasting serum zinc concentrations, determined approximately one year before death, had moderate to strong negative correlations with senile plaque counts in seven brain regions. In all brain regions combined, the age-adjusted negative correlations with serum zinc were statistically significant for total senile plaques and diffuse plaques, and suggestive for neuritic plaques. Thus serum zinc in the normal range may be associated with low senile plaque counts in elders.
NeuroReport 1995;6:2105-2108

Tully CL, Snowdon DA, Markesbery WR. Serum zinc, senile plaques, and neurofibrillary tangles: Findings from the Nun Study NeuroReport 6:2105-2108, 1995.

Transitions to Mild Cognitive Impairments, Dementia, and Death: Findings from the Nun Study

Suzanne L. Tyas, Juan Carlos Salazar, David A. Snowdon, Mark F. Desrosiers, Kathryn P. Riley, Marta S. Mendiondo, and Richard J. Kryscio

The potential of early interventions for dementia has increased interest in cognitive impairments less severe than dementia. However, predictors of the trajectory from intact cognition to dementia have not yet been clearly identified. The purpose of this study was to determine whether known risk factors for dementia increased the risk of mild cognitive impairments or progression from mild cognitive impairments to dementia. A polytomous logistic regression model was used, with parameters governing transitions within transient states (intact cognition, mild cognitive impairments, global impairment) estimated separately from parameters governing the transition from transient to absorbing state (dementia or death). Analyses were based on seven annual examinations (1991–2002) of 470 Nun Study participants aged 75 years at baseline and living in the United States. Odds of developing dementia increased with age primarily for

those with low educational levels. In these women, presence of an apolipoprotein E gene *E4 allele increased the odds more than fourfold by age 95 years. Age, education, and the apolipoprotein E gene were all significantly associated with mild cognitive impairments. Only age, however, was associated with progression to dementia. Thus, risk factors for dementia may operate primarily by predisposing individuals to develop mild cognitive impairments; subsequent progression to dementia then depends on only time and competing mortality.

Tyas S, Salazar J, Snowdon D, Desrosiers M, Riley K, Mendiondo M, Kryscio R: Transitions to mild cognitive impairments, dementia, and death: Findings from the Nun Study American Journal of Epidemiology, 165(11):1231-1238, 2007.

Healthy ageing in the Nun Study: Definition and neuropathologic correlates

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Background: although the concept of healthy ageing has stimulated considerable interest, no generally accepted definition has been developed nor has its biological basis been determined.

Objective: to develop a definition of healthy ageing and investigate its association with longevity and neuropathology.

Methods: analyses were based on cognitive, physical, and post-mortem assessments from 1991 to 1998 in the Nun Study, a longitudinal study of ageing in participants 75+ years at baseline. We defined three mutually exclusive levels of healthy ageing (excellent, very good, and good) based on measures of global cognitive function, short-term memory, basic and instrumental activities of daily living, and self-rated function. Mortality analyses were based on 636 participants; neuropathologic analyses were restricted to 221 who had died and were autopsied.

Results: only 11% of those meeting criteria for the excellent level of healthy ageing at baseline subsequently died, compared with 24% for the very good, 39% for the good, and 60% for the remaining participants. Survival curves showed significantly greater longevity with higher levels of healthy ageing. The risk of not attaining healthy ageing, adjusted for age, increased two-fold in participants with brain infarcts alone, six-fold in those with Alzheimer neuropathology alone, and more than thirteen-fold in those with both brain infarcts and Alzheimer neuropathology.

Conclusions: the biological validity of our definition of healthy ageing is supported by its strong association with mortality and longevity. Avoiding Alzheimer and stroke neuropathology is critical to the maintenance of healthy ageing, and the presence of both pathologies dramatically decreases the likelihood of healthy ageing.

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Progression of regional neuropathology in Alzheimer disease and normal elderly: Findings from the Nun Study

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Although diffuse plaques in the neocortex may represent an early stage in the evolution of neuritic plaques, plaques in the striatum and cerebellum retain their predominantly diffuse nature in Alzheimer disease (AD), regardless of disease duration. We had the opportunity to explore the progression of these regional features by using autopsy brain specimens from 15 cognitively normal and five AD subjects, all Catholic sisters enrolled in the Nun Study, a longitudinal study on aging and AD. Neuropathologic changes were assessed in the temporal cortex, striatum, and cerebellum without knowledge of clinical status. We found diffuse plaques in the striatum in six (40%) and cerebellar plaques in none of the brains from the non-demented subjects. Striatal plaques were present in all five and cerebellar plaques in four of the five AD cases. In the 20 cases overall, the presence of striatal plaques generally paralleled the occurrence of neuritic plaques in neocortex and correlated with lower scores on several neuropsychologic tests assessing memory. Our findings suggest that striatal diffuse plaques occur relatively early in the progression of AD pathology and coincide with neocortical pathology and cognitive changes. Thus, it is unlikely that temporal factors alone account for regional differences in progression of AD neuropathology.

Wolf DS, Gearing M, Snowdon DA, Mori H, Markesbery WR, Mirra S: Progression of regional neuropathology in Alzheimer disease and normal elderly: findings from the Nun Study Alzheimer Disease and Associated Disorders, 13(4):226-231, 1999.