

- 1 Mortimer, J. A. (2012). The Nun Study: risk factors for pathology and clinical-pathologic correlations. *Curr.Alzheimer Res.*, 9, 621-627.
Notes: The Nun Study was the first cohort study to enroll and follow a large, well-defined population that included demented and non-demented participants, all of whom agreed to donate their brains for research. The inclusion of systematic neuropathologic analysis in this study has resulted in a greater understanding of the role of Alzheimer and vascular pathology in the expression of memory deficits and dementia and has provided data showing that biomarkers for the pathology may be evident many decades earlier in adult life. Findings related to neuropathology in this study have included the following: (1) Although clinical outcomes were strongly correlated with Alzheimer neuropathology, about one-third of the participants fulfilling criteria for neuropathologic Alzheimer's disease (AD) were not demented at the time of death. (2) Brain infarcts by themselves had little effect on cognitive status, but played an important role in increasing the risk of dementia associated with Alzheimer pathology. (3) Hippocampal volume was strongly correlated with Braak neurofibrillary stage even in participants with normal cognitive function. (4) A linguistic characteristic of essays written in early adult life, idea density, had a strong association with not only clinical outcomes in late life, but the severity of Alzheimer neuropathology as well. (5) The effect of apolipoprotein E-e4 on dementia was mediated through Alzheimer, but not vascular pathology
- 2 Mortimer, J. A., Ding, D., Borenstein, A. R., DeCarli, C., Guo, Q., Wu, Y. et al. (2012). Changes in brain volume and cognition in a randomized trial of exercise and social interaction in a community-based sample of non-demented Chinese elders. *Journal of Alzheimers Disease*, 30, 757-766.
Notes: Physical exercise has been shown to increase brain volume and improve cognition in randomized trials of non-demented elderly. Although greater social engagement was found to reduce dementia risk in observational studies, randomized trials of social interventions have not been reported. A representative sample of 120 elderly from Shanghai, China was randomized to four groups (Tai Chi, Walking, Social Interaction, No Intervention) for 40 weeks. Two MRIs were obtained, one before the intervention period, the other after. A neuropsychological battery was administered at baseline, 20 weeks, and 40 weeks. Comparison of changes in brain volumes in intervention groups with the No Intervention group were assessed by t-tests. Time-intervention group interactions for neuropsychological measures were evaluated with repeated-measures mixed models. Compared to the No Intervention group, significant increases in brain volume were seen in the Tai Chi and Social Intervention groups ($p < 0.05$). Improvements also were observed in several neuropsychological measures in the Tai Chi group, including the Mattis Dementia Rating Scale score ($p = 0.004$), the Trailmaking Test A ($p = 0.002$) and B ($p = 0.0002$), the Auditory Verbal Learning Test ($p = 0.009$), and verbal fluency for animals ($p = 0.01$). The Social Interaction group showed improvement on some, but fewer neuropsychological indices. No differences were observed between the Walking and No Intervention groups. The findings differ from previous clinical trials in showing increases in brain volume and improvements in cognition with a largely non-aerobic exercise (Tai Chi). In addition, intellectual stimulation through social interaction was associated with increases in brain volume as well as with some cognitive improvements
- 3 Mortimer, J. A., Snowdon, D. A., & Markesbery, W. R. (2009). The effect of APOE-epsilon4 on dementia is mediated by Alzheimer neuropathology. *Alzheimer Disease and Associated Disorders*, 23, 152-157.
Notes: The degree to which the association of epsilon4 with dementia is mediated by AD lesions in comparison with vascular lesions is controversial. The present study was undertaken to determine the roles of Alzheimer disease (AD) and vascular pathology in mediating the effect of apolipoprotein E (APOE)-epsilon4 alleles on dementia. Clinicopathologic correlations were studied in 267 Catholic sisters participating in the Nun

Study. The extent to which AD and vascular pathologies mediated the effect of APOEepsilon4 on dementia was investigated using multiple logistic regression. Adjusted for age at death and education, possession of 1 or more epsilon4 alleles was an important risk factor for dementia (odds ratio=2.98; 95% confidence interval, 1.62-5.48). This association was lost (odds ratio=1.38; 95% confidence interval, 0.68-2.80) when an index of the severity of AD-related neuropathology was added to the model, but changed little when measures of the severity of vascular pathology were added. The findings suggest that the effect of epsilon4 on dementia is mediated by the severity of AD pathology. Although infarcts and atherosclerosis contribute to the occurrence of dementia, this contribution seems unrelated to APOE genotype

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- 4 Mortimer, J. A., Snowden, D. A., & Markesbery, W. R. (2008). Small head circumference is associated with less education in persons at risk for Alzheimer disease in later life. *Alzheimer Disease and Associated Disorders*, 22, 249-254.
Notes: Studies suggest that individuals who are at increased risk for Alzheimer disease (AD) in late life differ on measures of cognition, linguistic performance, and brain metabolism in earlier adult life compared with those with lower risk of this illness. The present study was undertaken to determine whether smaller head circumference (HC), a predictor of AD in late life, could influence educational attainment earlier in life, specifically among individuals at increased risk for AD. Data from the Nun Study, a longitudinal clinicopathologic study of dementia, were analyzed using logistic regression to assess the association between HC and attainment of less than a bachelor's degree. Modification of this association was studied by comparing those with and without evidence of increased AD risk, including possession of apolipoprotein E (APOE)-epsilon 4 alleles, occurrence of dementia before death, and satisfaction of AD neuropathologic criteria at autopsy. Small HC was associated with lower educational attainment in those carrying an APOE-epsilon 4 allele [odds ratio (OR)=6.27, 1.21 to 32.48], those who became demented (OR=3.23, 1.27 to 8.21), and those who fulfilled AD neuropathologic criteria (OR=5.03, 1.29 to 19.66), but not in those without these characteristics. These findings suggest that small HC limits educational attainment only among individuals who have greater risk of AD owing to their APOE genotype or who are destined to develop this illness later in life
- 5 Mortimer, J. A. & Petersen, R. C. (2008). Detection of prodromal Alzheimer's disease. *Annals of Neurology*, 64, 479-480.
- 6 Mortimer, J. A. & Borenstein, A. R. (2006). Tools of the epidemiologist. *Alzheimer Disease and Associated Disorders*, 20, S35-S41.
Notes: This review provides a summary of epidemiologic tools to facilitate understanding of the design and analysis of studies of Alzheimer disease (AD) and related disorders. Proportions, ratios, rates, prevalence, incidence, study designs, bias, confounding, effect modification, odds and risk ratios, statistical power, and confidence intervals are defined and discussed. Descriptive epidemiology is concerned with describing the distribution of disease by person, place, and time. It is useful for hypothesis generation, but not generally for hypothesis testing. Observational analytic epidemiology focuses on identifying putative causes for an illness. Although its primary mission is hypothesis testing, it can lead to new hypotheses as well. Finally, experimental analytic epidemiology or clinical trials can provide rigorous tests of presumed causal associations. The strengths and limitations of various designs as they apply to determining causal associations in studies of AD and dementia are reviewed. Over the past 60 years, the epidemiologic study of dementia has evolved from basic descriptive studies of prevalence and incidence to case-control and cohort studies and finally to the first clinical trials to prevent AD
- 7 Mortimer, J. A., Borenstein, A. R., Gosche, K. M., & Snowden, D. A. (2005). Very early detection of Alzheimer neuropathology and the role of brain reserve in modifying its clinical

expression. *Journal of Geriatric Psychiatry and Neurology*, 18, 218-223.

Notes: 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

- 8 Mortimer, J. A., Gosche, K. M., Riley, K. P., Markesbery, W. R., & Snowdon, D. A. (2004). Delayed recall, hippocampal volume and Alzheimer neuropathology: findings from the Nun Study. *Neurology*, 62, 428-432.
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 MRI from the first 56 scanned participants of the Nun Study. Quantitative neuropathologic studies included lesion counts, Braak staging, and determination of whether neuropathologic criteria for Alzheimer disease (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 Consortium to Establish a Registry for Alzheimer's Disease 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 nondemented individuals as well as in those with and without substantial AD neurofibrillary pathology. CONCLUSIONS: The association of neurofibrillary tangles with delayed verbal recall may reflect associated hippocampal atrophy
- 9 Mortimer, J. A., Snowdon, D. A., & Markesbery, W. R. (2003). Head circumference, education and risk of dementia: findings from the Nun Study. *Journal of Clinical and Experimental Neuropsychology*, 25, 671-679.
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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 educational 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-epsilon 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 four 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
- 10 Mortimer, J. A. (1997). Brain reserve and the clinical expression of Alzheimer's disease. *Geriatrics*, 52 Suppl 2.

Notes: Institute on Aging, University of South Florida, Tampa, USA Prospective clinicopathologic studies show that a large proportion of older, nondemented individuals have sufficient numbers of plaques and tangles to meet neuropathologic criteria for Alzheimer's disease (AD). One explanation for this finding is that these individuals had greater brain reserve, which buffered clinical expression of the disease. Three types of brain reserve are discussed: (1) the number of neurons and/or the density of their interconnections in youth, (2) the collection of cognitive strategies for solving problems and taking neuropsychological tests, and (3) the amount of functional brain tissue remaining at any age. Evidence is presented showing that brain reserve reduces clinical expression of AD and can be altered through several means, including early-life nutrition, prevention of cerebrovascular disease and intellectual stimulation

11 Mortimer, J. A. (1994). What are the risk factors for dementia? In F.A.Huppert, C. Brayne, & D. W. O'Connor (Eds.), *Dementia and normal aging* (pp. 208-229). Cambridge: Cambridge University Press.

12 Mortimer, J. A., French, L. R., Hutton, J. T., & Schuman, L. M. (1985). Head injury as a risk factor for Alzheimer's disease. *Neurology*, *35*, 264-267.

Notes: A case-control study was performed in which the frequency of prior head injury was assessed in 78 patients with dementia of the Alzheimer type (DAT) and 124 control subjects matched for age, sex, and race. A history of head injury with loss of consciousness was reported in 25.6% of patients and 5.3% and 14.6% of hospital and neighborhood controls, respectively. Matched-pair analysis of patients and hospital controls yielded an odds ratio of 4.50, which was significant (p less than 0.01). The ranges of times of occurrence of head injuries were similar in patients and controls, spanning several decades. The findings suggest a possible etiologic role for head injury in DAT