

- 1 Scarmeas, N., Stern, Y., Mayeux, R., Manly, J. J., Schupf, N., & Luchsinger, J. A. (2009). Mediterranean diet and mild cognitive impairment. *Archives of Neurology*, 66, 216-225.  
Notes: BACKGROUND: Higher adherence to the Mediterranean diet (MeDi) may protect from Alzheimer disease (AD), but its association with mild cognitive impairment (MCI) has not been explored. OBJECTIVE: To investigate the association between the MeDi and MCI. DESIGN, SETTING, AND PATIENTS: In a multiethnic community study in New York, we used Cox proportional hazards to investigate the association between adherence to the MeDi (0-9 scale; higher scores indicate higher adherence) and (1) the incidence of MCI and (2) the progression from MCI to AD. All of the models were adjusted for cohort, age, sex, ethnicity, education, APOE genotype, caloric intake, body mass index, and duration between baseline dietary assessment and baseline diagnosis. MAIN OUTCOME MEASURES: Incidence of MCI and progression from MCI to AD. RESULTS: There were 1393 cognitively normal participants, 275 of whom developed MCI during a mean (SD) follow-up of 4.5 (2.7) years (range, 0.9-16.4 years). Compared with subjects in the lowest MeDi adherence tertile, subjects in the middle tertile had 17% less risk (hazard ratio [HR] = 0.83; 95% confidence interval [CI], 0.62-1.12; P = .24) of developing MCI and those in the highest tertile had 28% less risk (HR = 0.72; 95% CI, 0.52-1.00; P = .05) of developing MCI (trend HR = 0.85; 95% CI, 0.72-1.00; P for trend = .05). There were 482 subjects with MCI, 106 of whom developed AD during a mean (SD) follow-up of 4.3 (2.7) years (range, 1.0-13.8 years). Compared with subjects in the lowest MeDi adherence tertile, subjects in the middle tertile had 45% less risk (HR = 0.55; 95% CI, 0.34-0.90; P = .01) of developing AD and those in the highest tertile had 48% less risk (HR = 0.52; 95% CI, 0.30-0.91; P = .02) of developing AD (trend HR = 0.71; 95% CI, 0.53-0.95; P for trend = .02). CONCLUSIONS: Higher adherence to the MeDi is associated with a trend for reduced risk of developing MCI and with reduced risk of MCI conversion to AD  
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- 2 Scarmeas, N., Brandt, J., Blacker, D., Albert, M., Hadjigeorgiou, G., Dubois, B. et al. (2007). Disruptive behavior as a predictor in Alzheimer disease. *Archives of Neurology*, 64, 1755-1761.  
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BACKGROUND: Disruptive behavior is common in Alzheimer disease (AD). There are conflicting reports regarding its ability to predict cognitive decline, functional decline, institutionalization, and mortality. OBJECTIVE: To examine whether the presence of disruptive behavior has predictive value for important outcomes in AD. DESIGN: Using the Columbia University Scale for Psychopathology in Alzheimer Disease (administered every 6 months, for a total of 3438 visit-assessments and an average of 6.9 per patient), the presence of disruptive behavior (wandering, verbal outbursts, physical threats/violence, agitation/restlessness, and sundowning) was extracted and examined as a time-dependent predictor in Cox models. The models controlled for the recruitment cohort, recruitment center, informant status, sex, age, education, a comorbidity index, baseline cognitive and functional performance, and neuroleptic use. SETTING: Five university-based AD centers in the United States and Europe (Predictors Study). PARTICIPANTS: Four hundred ninety-seven patients with early-stage AD (mean Folstein Mini-Mental State Examination score, 20 of 30 at entry) who were recruited and who underwent semiannual follow-up for as long as 14 (mean, 4.4) years. MAIN OUTCOME MEASURES: Cognitive (Columbia Mini-Mental State Examination score, < or = 20 of 57 [approximate Folstein Mini-Mental State Examination score, < or = 10 of 30]) and functional (Blessed Dementia Rating Scale score, parts I and II, > or = 10) ratings, institutionalization equivalent index, and death. RESULTS: At least 1 disruptive behavioral symptom was noted in 48% of patients at baseline and in 83% at any evaluation. Their presence was associated with increased risks of cognitive decline (hazard ratio 1.45 [95% confidence interval (CI), 1.03-2.03]), functional decline (1.66 [95% CI, 1.17-2.36]), and

institutionalization (1.47 [95% CI, 1.10-1.97]). Sundowning was associated with faster cognitive decline, wandering with faster functional decline and institutionalization, and agitation/restlessness with faster cognitive and functional decline. There was no association between disruptive behavior and mortality (hazard ratio, 0.94 [95% CI, 0.71-1.25]).  
CONCLUSION: Disruptive behavior is very common in AD and predicts cognitive decline, functional decline, and institutionalization but not mortality

- 3 Scarmeas, N., Albert, S. M., Manly, J. J., & Stern, Y. (2006). Education and rates of cognitive decline in incident Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, 77, 308-316.  
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BACKGROUND: Some (but not all) epidemiological studies have noted faster rates of progression in high education patients with Alzheimer's disease (AD), which has been attributed to harbouring/tolerating a higher pathological burden at the time of clinical dementia for subjects with higher education. We wanted to assess the relationship between education and rates of decline in AD. METHODS: During the course of a community based multiethnic prospective cohort study of individuals aged > or = 65 years living in New York, 312 patients were diagnosed with incident AD and were followed overall for 5.6 (up to 13.3) years. The subjects received an average of 3.7 (up to 9) neuropsychological assessments consisting of 12 individual tests. With the aid of a normative sample, a standardised composite cognitive score as well as individual cognitive domain scores were calculated. Generalised estimating equation models were used to examine the association between education and rates of cognitive decline. RESULTS: Composite cognitive performance declined by 9% of a standard deviation per year. Rates of decline before and after AD incidence were similar. For each additional year of education there was 0.3% standard deviation lower composite cognitive performance for each year of follow up. The association between higher education and faster decline was noted primarily in the executive speed (0.6%) and memory (0.5%) cognitive domains and was present over and above age, gender, ethnicity, differential baseline cognitive performance, depression, and vascular comorbidity. CONCLUSIONS: We conclude that higher education AD patients experience faster cognitive decline
- 4 Scarmeas, N., Brandt, J., Albert, M., Hadjigeorgiou, G., Papadimitriou, A., Dubois, B. et al. (2005). Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Archives of Neurology*, 62, 1601-1608.  
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BACKGROUND: Delusions and hallucinations are common in Alzheimer disease (AD) and there are conflicting reports regarding their ability to predict cognitive decline, functional decline, and institutionalization. According to all previous literature, they are not associated with mortality. OBJECTIVE: To examine whether the presence of delusions or hallucinations has predictive value for important outcomes in AD. DESIGN, SETTING, AND PARTICIPANTS: A total of 456 patients with AD at early stages (mean Folstein Mini-Mental State Examination [MMSE] score of 21 of 30 at entry) were recruited and followed up semiannually for up to 14 years (mean, 4.5 years) in 5 university-based AD centers in the United States and Europe. Using the Columbia University Scale for Psychopathology in AD (administered every 6 months, for a total of 3266 visit-assessments, average of 7.2 per patient), the presence of delusions and hallucinations was extracted and examined as time-dependent predictors in Cox models. The models controlled for cohort effect, recruitment center, informant status, sex, age, education, a comorbidity index, baseline cognitive and baseline functional performance, behavioral symptoms, and use of neuroleptics and cholinesterase inhibitors. MAIN OUTCOME MEASURES: Cognitive (Columbia MMSE score of < or =20/57 [approximate Folstein MMSE score of < or =10/30]), functional (Blessed Dementia Rating Scale [parts I and II] score of > or =10), institutionalization equivalent index,

and death. RESULTS: During the full course of follow-up, 38% of patients reached the cognitive, 41% the functional, 54% the institutionalization, and 49% the mortality end point. Delusions were noted for 34% of patients at baseline and 70% at any evaluation. Their presence was associated with increased risk for cognitive (risk ratio [RR], 1.50; 95% confidence interval [CI], 1.07-2.08) and functional decline (RR, 1.41; 95% CI, 1.02-1.94). Hallucinations were present in 7% of patients at initial visit and in 33% at any visit. Their presence was associated with increased risk for cognitive decline (RR, 1.62; 95% CI, 1.06-2.47), functional decline (RR, 2.25; 95% CI, 1.54-2.27), institutionalization (RR, 1.60; 95% CI, 1.13-2.28), and death (RR, 1.49; 95% CI, 1.03-2.14). CONCLUSIONS: Delusions and hallucinations are very common in AD and predict cognitive and functional decline. Presence of hallucinations is also associated with institutionalization and mortality

- 5 Scarmeas, N. & Stern, Y. (2005). fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease. *Neurology*, 65, 1514-1515.
- 6 Scarmeas, N., Zarahn, E., Anderson, K. E., Honig, L. S., Park, A., Hilton, J. et al. (2004). Cognitive reserve-mediated modulation of positron emission tomographic activations during memory tasks in Alzheimer disease. *Archives of Neurology*, 61, 73-78.  
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BACKGROUND: Cognitive reserve (CR) is the ability of an individual to cope with advancing brain pathological abnormalities so that he or she remains free of symptoms. Epidemiological data and evidence from positron emission tomography suggest that it may be mediated through education or IQ. OBJECTIVE: To investigate CR-mediated differential brain activation in Alzheimer disease (AD) subjects compared with healthy elderly persons. PARTICIPANTS: Using radioactive water positron emission tomography, we scanned 12 AD patients and 17 healthy elderly persons while performing a serial recognition memory task for nonverbalizable shapes under 2 conditions: low demand, in which one shape was presented in each study trial, and titrated demand, in which the study list length was adjusted so that each subject recognized shapes at approximately 75% accuracy. Positron emission tomographic scan acquisition included the encoding and recognition phases. A CR factor score that summarized years of education, National Adult Reading Test estimated IQ, and Wechsler Adult Intelligence Scale-Revised vocabulary subtest score (explaining 71% of the total variance) was used as an index of CR. Voxel-wise, multiple regression analyses were performed with the "activation" difference (titrated demand-low demand) as the dependent variables and the CR factor score as the independent one. Brain regions where regression slopes differed between the 2 groups were identified. RESULTS: The slopes were significantly more positive for the AD patients in the left precentral gyrus and in the left hippocampus and significantly more negative in the right fusiform, right middle occipital, left superior occipital, and left middle temporal gyri. CONCLUSION: Brain regions where systematic relationships (slopes) between subjects' education-IQ and brain activation differ as a function of disease status may mediate the differential ability to cope with (ie, delay or modify) clinical manifestations of AD
- 7 Scarmeas, N., Zarahn, E., Anderson, K. E., Habeck, C. G., Hilton, J., Flynn, J. et al. (2003). Association of life activities with cerebral blood flow in Alzheimer disease: implications for the cognitive reserve hypothesis. *Archives of Neurology*, 60, 359-365.  
BACKGROUND: Regional cerebral blood flow (CBF), a good indirect index of cerebral pathologic changes in Alzheimer disease (AD), is more severely reduced in patients with higher educational attainment and IQ when controlling for clinical severity. This has been interpreted as suggesting that cognitive reserve allows these patients to cope better with the pathologic changes in AD. OBJECTIVE: To evaluate whether premorbid engagement in various activities may also provide cognitive reserve. DESIGN: We evaluated intellectual, social, and physical activities in 9 patients with early AD and 16 healthy elderly controls who underwent brain H(2)(15)O positron emission tomography. In voxelwise multiple regression

analyses that controlled for age and clinical severity, we investigated the association between education, estimated premorbid IQ, and activities, and CBF. RESULTS: In accordance with previous findings, we replicated an inverse association between education and CBF and IQ and CBF in patients with AD. In addition, there was a negative correlation between previous reported activity score and CBF in patients with AD. When both education and IQ were added as covariates in the same model, a higher activity score was still associated with more prominent CBF deficits. No significant associations were detected in the controls. CONCLUSIONS: At any given level of clinical disease severity, there is a greater degree of brain pathologic involvement in patients with AD who have more engagement in activities, even when education and IQ are taken into account. This may suggest that interindividual differences in lifestyle may affect cognitive reserve by partially mediating the relationship between brain damage and the clinical manifestation of AD

- 8 Scarmeas, N. & Stern, Y. (2003). Cognitive reserve and lifestyle. *Journal of Clinical and Experimental Neuropsychology*, 25, 625-633.  
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The concept of cognitive reserve (CR) suggests that innate intelligence or aspects of life experience like educational or occupational attainments may supply reserve, in the form of a set of skills or repertoires that allows some people to cope with progressing Alzheimer's disease (AD) pathology better than others. There is epidemiological evidence that lifestyle characterized by engagement in leisure activities of intellectual and social nature is associated with slower cognitive decline in healthy elderly and may reduce the risk of incident dementia. There is also evidence from functional imaging studies that subjects engaging in such leisure activities can clinically tolerate more AD pathology. It is possible that aspects of life experience like engagement in leisure activities may result in functionally more efficient cognitive networks and therefore provide a CR that delays the onset of clinical manifestations of dementia
- 9 Scarmeas, N., Zarahn, E., Anderson, K. E., Hilton, J., Flynn, J., Van Heertum, R. L. et al. (2003). Cognitive reserve modulates functional brain responses during memory tasks: a PET study in healthy young and elderly subjects. *NeuroImage*, 19, 1215-1227.  
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Cognitive reserve (CR) is the ability of an individual to cope with advancing brain pathology so that he remains free of symptomatology. Epidemiological evidence and in vivo neurometabolic data suggest that CR may be mediated through education or IQ. The goal of this study was to investigate CR-mediated differential brain activation in 17 healthy young adults and 19 healthy elders. Using nonquantitative H(2)(15)O PET scanning, we assessed relative regional cerebral blood flow while subjects performed a serial recognition memory task under two conditions: nonmemory control (NMC), in which one shape was presented in each study trial; and titrated demand (TD), in which study list length was adjusted so that each subject recognized shapes at approximately 75% accuracy. A factor score that summarized years of education and scores on two IQ indices was used as an index of CR. Voxel-wise, multiple regression analyses were performed with TD minus NMC difference PET counts as the dependent variable and the CR variable as the independent variable of interest. We identified brain regions where regression slopes were different from zero in each separate group, and also those where regression slopes differed between the two age groups. The slopes were significantly more positive in the young in the right inferior temporal gyrus, right postcentral gyrus, and cingulate, while the elderly had a significantly more positive slope in left cuneus. Brain regions where systematic relationships between CR and brain activation differ as a function of aging are loci where compensation for aging has occurred. They may mediate differential ability to cope with brain changes in aging

- 10 Scarmeas, N., Levy, G., Tang, M. X., Manly, J., & Stern, Y. (2001). Influence of leisure activity on the incidence of Alzheimer's disease. *Neurology*, 57, 2236-2242.
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- OBJECTIVE: To determine whether leisure activities modify the risk for incident dementia.
- BACKGROUND: Although high educational and occupational attainments have been associated with reduced risk of incident dementia, the relation between leisure activities and dementia risk has not been adequately investigated. METHODS: A total of 1,772 nondemented individuals aged 65 years or older, living in northern Manhattan, New York, were identified and followed longitudinally in a community-based cohort incidence study. Subjects' leisure activities at baseline were assessed, annual examinations with the same standardized neurologic and neuropsychological measures were performed for up to 7 years (mean 2.9 years), and incident dementia was assessed as the main outcome measure. Cox proportional hazards models, adjusting for age, ethnic group, education, and occupation, were used to estimate the relative risk (RR) of incident dementia associated with high leisure activities. RESULTS: Of the 1,772 subjects, 207 became demented. The risk of dementia was decreased in subjects with high leisure activities (RR, 0.62; 95% CI 0.46 to 0.83). The association of high leisure with decreased RR of incident dementia was present even when baseline cognitive performance, health limitations interfering with desired leisure activities, cerebrovascular disease, and depression were considered. CONCLUSIONS: The data suggest that engagement in leisure activities may reduce the risk of incident dementia, possibly by providing a reserve that delays the onset of clinical manifestations of the disease