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Selected Findings from the Religious Orders Study and Rush Memory and Aging Project

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Abstract

The Religious Orders Study and the Rush Memory and Aging Project are both cohort studies of aging and dementia that include organ donation at death. Together, more than 2,700 persons have agreed to annual clinical evaluation and brain donation at death. A subset of participants also participated in a substudy that included ante-mortem imaging. We highlight recent findings that have been highly cited over the past five years. The findings fall into three general categories. The first relates to the neuropathology of probable Alzheimer's disease, mild cognitive impairment, and those without dementia or mild cognitive impairment. The second relates to risk factors for Alzheimer's disease and neuropathology. The third are clinical and imaging studies of mild cognitive impairment. The findings illustrate the range of insights that can be gained into cognitive aging by incorporating neuropathologic indices into well designed, prospective cohort studies.

Keywords

clinical-pathology; mild cognitive impairment; risk factors

INTRODUCTION

Alzheimer's disease (AD) is a large and growing public health problem for which prevention is the best long term strategy [1,2]. Disease prevention requires the identification of risk factors for the disease and subsequently the development of a means to intervene in the disease process thereby delaying disease onset. Because AD is most common in persons with advanced age, it rarely occurs in isolation. Rather, AD develops in the brains of persons with a variety of comorbid conditions that can also contribute to cognitive decline with a phenotype that is not easily distinguished from AD alone. This complicates the search for risk factors because, to the extent that the AD phenotype results from multiple comorbidities, risk factors for the clinical syndrome are not necessarily risk factors for the disease pathology [3].

The Religious Orders Study and the Rush Memory and Aging Project were designed to confront some of the challenges posed by the study of cognitive aging and AD. First, they are community based cohort studies of aging among persons without known dementia. The

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only inclusion criteria other than age is that persons understand the nature of the study and sign a consent for participation and an anatomical gift act for organ donation. Therefore, the study includes persons with a wide range of common age-related comorbidities. Second, the participants are 75 to 80 years old, on average, at study entry with an average age at death of about 87. Thus, they represent the common age at which AD is seen in the community. Third, studies of risk factors for AD that include organ donation offer a relatively unique opportunity to examine the relation of risk factors to both incident AD and to postmortem indices that underlie cognitive function. Finally, they are foundational studies which can also supply participants, data, and biospecimens to smaller more targeted projects such as neuroimaging studies.

This review highlights recent findings that have been highly cited over the past five years. The findings fall into three general categories: the neuropathology of probable AD, mild cognitive impairment (MCI), and those without dementia or MCI; the relation of risk factors for AD and neuropathology; and clinical and neuroimaging studies of MCI. The findings illustrate the range of insights that can be gained into cognitive aging by incorporating neuropathologic indices and neuroimaging into well designed, prospective cohort studies. These are just a sampling of the findings from more than 250 peer-reviewed publications generated by these data sets [4,5].

MATERIALS AND METHODS

Participants

Participants in the Religious Orders Study are older Catholic nuns, priests, or brothers from across the United States. Each person agrees to an annual detailed clinical evaluation and signs an Anatomical Gift Act donating his/her brain to Rush investigators at the time of death. Clinical evaluations started in 1994. To date, more than 1,150 persons have enrolled. The annual follow-up of survivors exceeds 95% and the autopsy rate exceeds 90% with more than 550 autopsies to date.

Participants in the Rush Memory and Aging Project are older lay persons from across northeastern Illinois. Each person agrees to an annual detailed clinical evaluation and signs an Anatomical Gift Act donating his/her brain, spinal cord, and selected nerves and muscles to Rush investigators at the time of death. Clinical evaluations started in 1997. To date, more than 1,550 persons have enrolled. The annual follow-up of survivors exceeds 90% and the autopsy rate exceeds 80% with more than 425 autopsies to date.

In 1997, selected participants from both studies were invited to take part in a targeted longitudinal neuroimaging project that included structural magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI). Both cohort studies and the imaging substudy were approved by the Institutional Review Board of Rush University Medical Center.

Clinical Evaluation

Each subject undergoes a structured detailed interview to document potential risk factors for AD, including a wide range of psychological and experiential risk factors such as self-perceived isolation (i.e., loneliness) and social network size [6,7]. A uniform structured clinical evaluation documents level of cognition and the presence of AD, MCI, and other causes of cognitive impairment each year, as previously described [8,9]. Neuropsychological indices of cognition were summarized as a global measure based on the average z-score of 19 tests in each study, using the mean and standard deviation from the baseline measure, and as separate summary measures of episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability as described [10,11]. A subset of 17 tests can be used in analyses that combine data from both cohorts [3]. All prescription and over the

counter medications were reviewed, recorded and entered into a database as described [12]. Follow-up evaluations were identical in all essential details.

Structural Neuroimaging

All structural MR images were acquired on a 1.5 Tesla General Electric Signa scanner with the manufacturer's three-dimensional (3D) Fourrier transform spoiled gradient recalled (SPGR) pulse sequence at the time of entry into a longitudinal study (baseline) and yearly thereafter. The acquisition parameters for the T1 weighted sequence and DTI have been previously described [13,14]. Regions of interest, e.g., hippocampus and entorhinal cortex, were outlined and volumes computed as previously described [13]. DTI is a technique that assesses microstructural changes in white matter. It combines MR diffusion-weighted pulse sequences with tensor mathematics to measure molecular diffusion in three dimensions. Commonly used DTI metrics include mean diffusivity, which can be used as a non-invasive proxy measure of the general integrity of tissue, and fractional anisotropy, which can be used to describe the parallel organization of white matter fibers [15].

Postmortem Examination

Brains of deceased subjects are removed, weighed, cut into 1 cm-thick coronal slabs and stored as previously described. Each brain is examined for the neuropathologic indices of common pathologies that contribute to cognitive impairment, including AD, cerebrovascular, and Lewy body pathology. The location, age, and volume of all macroscopic infarcts are recorded, and tissue was obtained for histological confirmation, in addition to the identification of microscopic infarctions, as previously described [16,17]. AD pathology is identified with modified Bielschowsky silver stain and summarized by modified CERAD criteria and NIA-Reagan criteria, as described [16]. Neuritic plaques, diffuse plaques, and neurofibrillary tangles are counted in five brain regions, standardized and averaged to yield a global measure of AD pathologic burden, as previously described [18]. Additionally, amyloid-β, labeled with a N-terminal directed monoclonal antibody is quantified for amyloid load, and neurofibrillary tangles, labeled with an antibody specific for phosphorylated tau, is quantified as the density of paired helical filament tau tangles, as previously described [19]. Lewy bodies, labeled with antibodies to α-synuclein, are recorded and Lewy body disease is designated as nigral, limbic, or neocortical, as described [20].

Analyses

The first set of analyses investigated the neuropathology of probable AD, MCI, and those without dementia or MCI. The second set related risk factors for AD and neuropathology. The third set included clinical and imaging studies of MCI. Cross-sectional associations of neuropathologic indices with level of cognition and clinical diagnoses are performed with linear and logistic regression models, adjusting for age, gender, and education. Associations of risk factors with clinical level of cognition and clinical diagnoses and neuropathologic indices may also include interaction terms for risk factors and neuropathologic indices to determine whether the risk factor modifies the relation neuropathology to cognition. Longitudinal associations of risk factors or clinical status such as MCI, or imaging variables, for incident AD employ Cox proportional hazards models. The relation of risk factors to cognitive decline is done with mixed effects models. Analyses are typically performed in SAS and models validated graphically and analytically.

RESULTS

Neuropathology of probable AD, MCI, and persons without dementia or MCI

We first showed that AD pathology and cerebral infarctions had an additive effect on the odds of dementia [21]. In fact, this effect was quite large for infarcts overall and for both cortical and subcortical infarctions. Interesting, in analyses examining level of cognition, both cortical and subcortical infarctions impacted several cognitive abilities, including episodic memory, the clinical hallmark of AD. We next added Lewy bodies to these analyses and showed that mixed pathologies were the most common cause of dementia in old age [21]. This was most commonly in the form of mixed AD pathology and cerebral infarctions, followed by AD pathology and Lewy bodies, and then all three. In a subsequent paper, we extended these findings to show that mixed pathology was also the most common cause of clinically diagnosed probable AD [16]. We also showed that mixed pathology was common in both amnestic and non-amnestic MCI, and that pathology was also common in persons without dementia or MCI. In the final paper in this series, we showed that AD pathology was associated with lower episodic memory performance among persons without dementia or MCI suggesting that subtle cognitive deficits associated with AD pathology occur prior to MCI [20].

Risk factors for AD and neuropathology

A series of four papers examined the association of potential risk factors with clinical and postmortem indices. Interesting, the results of these associations differed markedly from one another illustrating the complexity of the AD phenotype. First, because mixed pathology is the most common cause of probable AD, it is possible that risk factors for comorbidities, e.g., cerebral infarction, could masquerade as a risk factor for AD. We had previously shown that diabetes is related to AD risk and rate of cognitive decline [22]. We subsequently examined the relation of diabetes to measures of pathology and found associations with cerebral infarctions but not with measures of AD pathology [23].

Studies have shown that several aspects of the social environment are related to AD risk [24]. We did not find a direct effect of social network size on cognition or on AD pathology [7]. However, we found a strong interaction such that AD pathology had less of a deleterious effect on cognition among persons with a larger social network size relative to those with a smaller social network size. A related factor is loneliness, or self perceived social isolation. Loneliness was related to risk of AD and to rate of cognitive decline [6]. Interestingly, it was not directly related to any pathology nor did it interact with any pathology suggesting that loneliness works through yet to be identified mechanisms.

The final paper in this group examined the relation of statin use to incident AD, cognitive decline, and neuropathologic indices [25]. We failed to find an association between statin use and risk of AD or cognitive decline. However, we did find that statin users were less likely to have amyloid. However, there was no relation between statin use and level of amyloid in analyses restricted to those with amyloid. Thus, the interpretation of the finding is unclear.

Clinical and neuroimaging studies of MCI

We first showed that MCI was associated with risk of AD and rate of cognitive decline in the Memory and Aging Project consistent with prior reports in the Religious Orders Study [8,26,27].

In a prior study, we found that both baseline entorhinal cortex volume and its slope of decline were independent predictors of incident AD among persons with MCI, but baseline

hippocampal size and its slope of decline were not, after controlling for entorhinal volume suggesting that the extent of entorhinal involvement in the disease process is a stronger predictor than hippocampal involvement [13].

White matter changes can disrupt or degrade information flow from one region of the brain to another and contribute to cognitive changes during the progression of AD. DTI can detect, *in vivo*, the directionality of molecular diffusion and estimate the microstructural integrity of white matter tracts. We reported regional reductions in fractional anisotropy in multiple posterior regions in both participants with MCI and mild AD [14]. There was substantial overlap in the pattern of locations suggesting that white matter changes are present in persons with MCI.

Finally, we found a reduction in the volume of the parahippocampal white matter region that includes the perforant pathway in people with MCI compared to healthy control subjects and that hippocampal and parahippocampal white matter volume were significant predictors of episodic memory performance. [28]. These data suggest that disruption of parahippocampal white matter fibers contributes to memory decline in older individuals by partially disconnecting the hippocampus from multi-modal sensory information relayed from the entorhinal cortex via the perforant pathway.

DISCUSSION

The Religious Orders Study and the Rush Memory and Aging Project are both cohort studies of incident AD and other common chronic conditions of aging that include organ donation at death. Together, they enrolled more than 2,700 persons, have high follow-up rates with large numbers of persons with incident AD, and large numbers of persons coming to autopsy with high autopsy rates. The studies permit the linking of neurobiologic indices to clinical data collected proximate to death, and to linking risk factor data to clinical and neurobiological outcomes in the same persons. Together the studies can provide unique insights into the neurobiologic pathways linking risk factors to clinical disease.

We found that mixed pathology is the most common cause of dementia and probable AD in old age. Several other studies have reported similar findings for dementia [29–31]. However, we are not aware of other studies examining this association in large numbers of persons with clinically diagnosed probable AD, and both amnestic and non-amnestic MCI. The finding that mixed pathology is the most common cause of probable AD in old age has important implications. First, it suggests that reducing the burden of co-morbidities will reduce the occurrence of clinically diagnosed AD. This is important is increasing evidence from several studies, including data from these cohorts, suggests that conditions other than AD pathology play an increasingly important role in dementia among the oldest old who represent the most rapidly growing segment of the population [32–36]. One of these studies suggested that synaptic proteins may be an important marker of cognition in the oldest old and we found a similar association across the full spectrum of old age [35,37]. Second, it suggests that risk factors for comorbidities may mimic risk factors for the clinical AD phenotype. In other words, to the extent that the terms AD dementia and MCI due to AD refer to the cognitive and functional consequences of cortical amyloid deposition and tangle formation, as in the recent NIA-Alzheimer's Association criteria, some risk factors for clinically diagnosed AD will actually be risk factors for comorbid conditions rather than risk factors for amyloid or tangles [38–40]. We illustrate this situation with data on the relation of diabetes to clinically diagnosed AD but not to pathological AD. Others have examined the association of diabetes with AD with mixed results with some studies finding associations with infarcts and one showing an association with less AD pathology [41–44].

We examined the relation of three other risk factors to AD pathology and cognition each with different results from one other and different from diabetes findings. We found that the association of loneliness with clinical AD was independent of AD pathology. Other studies have also reported relationships between loneliness and cognition [45,46]. The basis of the association is not known. Interestingly, loneliness has been associated with all cause mortality and in particular with mortality from cardiovascular disease [47]. It has also been associated with inflammatory markers [48]. Thus, it is possible that the association of loneliness with cognition is mediated in part by cerebrovascular disease. Although we did not find such an association, we may have been under-powered and require a larger sample size to detect the association.

In contrast to findings with self-perceived social isolation, we found that social network size modified the relation of AD pathology to cognition. Social networks have been associated with a range of adverse health outcomes including mortality, disability, and dementia [49–52]. Social networks have also been related to risk of stroke as well as inflammatory markers [53,54]. So, like loneliness, it is possible that social networks mediate their effect on cognition through cerebrovascular disease. However, this would not account for its interesting effect modification on AD pathology suggesting that other mechanisms will need to be investigated.

We failed to find an association between statin use and risk of AD or rate of cognitive decline. By contrast, we found that statin users were less likely to have amyloid. At least one other study examined the relation of statin use and AD pathology and found that statin users had less tangle pathology but not less neuritic plaque pathology [55]. The paper did not directly assess amyloid burden, though the findings appear to differ. The reason for the discrepancy is unclear. However, one must interpret findings regarding medication use from observational studies with caution due to possible indication bias.

The final set of findings relate to MCI. Clinically, persons with MCI in these studies progressed to AD as has been reported in many other studies [8,56–59].

The neuroimaging studies demonstrate that MRI can provide sensitive markers of risk of AD. In addition to gray matter changes that take place early in the disease process, especially in medial temporal lobe regions, alterations in white matter can be detected in posterior regions of the brain even in MCI. The volumetric and microstructural white matter changes seen in the parahippocampal white matter in the region of the perforant pathway contribute to episodic memory deficits seen in MCI. White matter volume change may reflect not only loss of afferent and efferent fibers in the region of the parahippocampal gyrus, but may also be due to partial demylenation or degradation in the integrity of remaining fibers, an area of investigation that can be addressed with DTI. In fact, recent DTI findings suggest that remaining parahippocampal white matter fibers are not normal in MCI and mild AD thus further contributing to the degradation of incoming multi-modal sensory information [50,61]. These findings have been confirmed and extended by the work of many other groups [62–68].

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References

1. Sloane PD, Zimmerman S, Suchindran C, Reed P, Wang L, Boustani M, Sudha S. The public health impact of Alzheimer's disease, 2000–2050: potential implication of treatment advances. Annu Rev Public Health. 2002; 23:213–231. [PubMed: 11910061]
2. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement. 2007; 3:186–191. [PubMed: 19595937]
3. Bennett DA, De Jager PL, Leurgans SE, Schneider JA. Neuropathologic intermediate phenotypes enhance association to Alzheimer susceptibility alleles. Neurology. 2009; 72:1495–1503. [PubMed: 19398704]
4. Bennett DA, Schneider JA, Buchman AS, Barnes LL, Wilson RS. Overview and findings from the Rush Memory and Aging Project. Curr Alzheimer Res. 2012 in press (no doi #).
5. Bennett DA, Schneider JA, Arvanitakis Z, Wilson RS. Overview and findings from the Religious Orders Study. Curr Alzheimer Res. 2012 in press (no doi #).
6. Wilson RS, Krueger KR, Arnold SE, Schneider JA, Kelly JF, Barnes LL, Tang Y, Bennett DA. Loneliness and risk of Alzheimer's disease. Archives of General Psychiatry. 2007; 64:234–240. [PubMed: 17283291]
7. Bennett DA, Schneider JA, Arnold SE, Tang Y, Wilson RS. The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. The Lancet Neurology. 2006; 5:406–412.
8. Bennett DA, Wilson RS, Schneider JA, Evans DA, Beckett LA, Aggarwal NT, Barnes LL, Fox JH, Bach J. Natural history of mild cognitive impairment in older persons. Neurology. 2002; 59:198–205. [PubMed: 12136057]
9. Bennett DA, Schneider JA, Aggarwal NT, Arvanitakis Z, Shah RC, Kelly JF, Fox JH, Cochran EJ, Arends D, Treinkman AD, Wilson RS. Prediction rules guiding the clinical diagnosis of Alzheimer's disease in two community-based cohort compared to standard practice in a clinic-based cohort study. Neuroepidemiology. 2006; 27:169–176. [PubMed: 17035694]
10. Wilson RS, Beckett LA, Barnes LL, Schneider JA, Bach J, Evans DA, Bennett DA. Individual differences in rates of change in cognitive abilities of older persons. Psychology and Aging. 2002; 17:179–193. [PubMed: 12061405]
11. Wilson RS, Barnes LL, Kreuger KR, Hoganson G, Bienias JL, Bennett DA. Early and late life cognitive activity and cognitive systems in old age. Journal of the International Neuropsychological Society. 2005; 11:400–407. [PubMed: 16209420]
12. Shah RC, Wilson RS, Bienias JL, Arvanitakis Z, Evans DA, Bennett DA. Blood pressure and lower limb function in older persons. Journal of Gerontology: Medical Sciences. 2006; 61:839–843.
13. Stoub TR, Bulgakova M, Leurgans S, Bennett DA, Fleischman D, Turner DA, deToledo-Morrell L. MRI predictors of risk of Alzheimer's disease: A longitudinal study. Neurology. 2005; 64:1520–1524. [PubMed: 15883311]
14. Medina D, deToledo-Morrell L, Urresta F, Gabrieli JD, Moseley M, Fleischman D, Bennett DA, Leurgans S, Turner DA, Stebbins GT. White matter changes in mild cognitive impairment and AD. Neurobiol Aging. 2006; 27:663–672. [PubMed: 16005548]
15. Moseley M. Diffusion tensor imaging and aging – a review. NMR in Biomedicine. 2002; 15:553–560. [PubMed: 12489101]
16. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. Neuropathology of probable AD and amnestic and non-amnestic MCI. Ann Neurol. 2009; 66:200–208. [PubMed: 19743450]
17. Arvanitakis Z, Leurgans SE, Barnes LL, Bennett DA, Schneider JA. Microinfarct pathology, dementia, and cognitive systems. Stroke. 2011; 42:722–727. [PubMed: 21212395]
18. Bennett DA, Wilson RS, Schneider JA, Evans DA, Aggarwal NT, Arnold SE, Cochran EJ, Berry-Kravis E, Bienias JL. Apolipoprotein E4 allele, Alzheimer's disease pathology, and the clinical expression of Alzheimer's disease. Neurology. 2003; 60:246–252. [PubMed: 12552039]
19. Bennett DA, Schneider JA, Wilson RS, Bienias JL, Arnold SE. Neurofibrillary tangles mediate the association of amyloid load and with clinical Alzheimer's disease and level of cognitive function. Arch Neurol. 2004; 61:378–384. [PubMed: 15023815]

20. Bennett DA, Schneider JA, Arvanitakis Z, Kelly JF, Aggarwal NT, Shah RC, Wilson RS. Neuropathology of older persons without cognitive impairment from two community-based clinical-pathologic studies. Neurology. 2006; 66:1837–1844. [PubMed: 16801647]
21. Schneider JA, Boyle PA, Arvanitakis Z, Bienias JL, Bennett DA. Subcortical cerebral infarcts, episodic memory, and AD pathology in older persons. Annals of Neurology. 2007; 62:59–66. [PubMed: 17503514]
22. Arvanitakis Z, Bienias JL, Wilson RS, Evans DA, Bennett DA. Diabetes and risk of Alzheimer's disease and decline in cognitive function. Archives of Neurology. 2004; 61:661–666. [PubMed: 15148141]
23. Arvanitakis Z, Schneider JA, Wilson RS, Li Y, Arnold SE, Wang Z, Bennett DA. Diabetes mellitus is related to cerebral infarction but not Alzheimer's disease pathology in older persons. Neurology. 2006; 67:1960–1965. [PubMed: 17159101]
24. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol. 2004; 3:343–353. [PubMed: 15157849]
25. Arvanitakis Z, Schneider JA, Wilson RS, Bienias JL, Kelly JF, Evans DA, Bennett DA. Statins, incident AD change in cognitive function, and neuropathology. Neurology. 2008; 70:1795–1802. [PubMed: 18199831]
26. Boyle PA, Wilson RS, Aggarwal NT, Tang Y, Bennett DA. Risk of Alzheimer's disease and rate of cognitive decline among persons with mild cognitive impairment. Neurology. 2006; 67:441–445. [PubMed: 16894105]
27. Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Bennett DA. Mild cognitive impairment in different functional domains and incident Alzheimer's disease. Journal of Neurology, Neurosurgery, & Psychiatry. 2005; 76:1479–1484.
28. Stoub TR, deToledo-Morrell L, Stebbins GT, Leurgans S, Bennett DA, Shah RC. Hippocampal disconnection contributes to the memory dysfunction in individuals at risk of Alzheimer's disease. Proceedings of the National Academy of Sciences. 2006; 103:10041–10045.
29. Sonnen JA, Larson EB, Crane PK, Haneuse S, Li G, Schellenberg GD, Craft S, Leverenz JB, Montine TJ. Pathological correlates of dementia in a longitudinal, population-based sample of aging. Ann Neurol. 2007; 62:406–413. [PubMed: 17879383]
30. Troncoso JC, Zonderman AB, Resnick SM, Crain B, Pletnikova O, O'Brien RJ. Effect of infarcts on dementia in the Baltimore longitudinal study of aging. Ann Neurol. 2008; 64:168–176. [PubMed: 18496870]
31. Petrovitch H, Ross GW, Steinhorn SC, Abbott RD, Markesbery W, Davis D, Nelson J, Hardman J, Masaki K, Vogt MR, Launer L, White LR. AD lesions and infarcts in demented and non-demented Japanese-American men. Ann Neurol. 2005; 57:98–103. [PubMed: 15562458]
32. Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C. Age, neuropathology, and dementia. N Engl J Med. 2009; 360:2302–2309. [PubMed: 19474427]
33. Haroutunian V, Schnaider-Beeri M, Schmeidler J, Wysocki M, Purohit DP, Perl DP, Libow LS, Lesser GT, Maroukian M, Grossman HT. Role of the neuropathology of Alzheimer disease in dementia in the oldest-old. Arch Neurol. 2008; 65:1211–1217. [PubMed: 18779425]
34. Dolan D, Troncoso J, Resnick SM, Crain BJ, Zonderman AB, O'Brien RJ. Age, Alzheimer's disease and dementia in the Baltimore Longitudinal Study of Ageing. Brain. 2010; 133:2225–2231. [PubMed: 20647264]
35. Head E, Corrada MM, Kahle-Wrobleski K, Kim RC, Sarsoza F, Goodus M, Kawas CH. Synaptic proteins, neuropathology and cognitive status in the oldest-old. Neurobiol Aging. 2009; 30:1125–1134. [PubMed: 18006193]
36. James BD, Bennett DA, Boyle PA, Leurgans S, Schneider JA. Dementia in the old versus oldest old: the role of Alzheimer's and mixed pathologies. Journal of the American Medical Association. In press.
37. Honer WG, Barr AM, Sawada K, Thornton AE, Morris MC, Leurgans SE, Schneider JA, Bennett DA. Cognitive reserve, presynaptic proteins and dementia in the elderly. Translational Psychiatry. In press.
38. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC,

Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7:263–269. [PubMed: 21514250]

39. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7:270–279. [PubMed: 21514249]
40. Sperling RS, Aisen P, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer Association Workgroup. Alzheimer's & Dementia. 2011; 7:280–292.
41. Ahtiluoto S, Polvikoski T, Peltonen M, Solomon A, Tuomilehto J, Winblad B, Sulkava R, Kivipelto M. Diabetes, Alzheimer disease, and vascular dementia: a population-based neuropathologic study. Neurology. 2010; 75:1195–1202. [PubMed: 20739645]
42. Peila R, Rodriguez BL, Launer LJ. Honolulu-Asia Aging Study. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. Diabetes. 2002; 51:1256–1262. [PubMed: 11916953]
43. Sonnen JA, Larson EB, Brickell K, Crane PK, Woltjer R, Montine TJ, Craft S. Different patterns of cerebral injury in dementia with or without diabetes. Arch Neurol. 2009; 66:315–322. [PubMed: 19139294]
44. Beeri MS, Silverman JM, Davis KL, Marin D, Grossman HZ, Schmeidler J, Purohit DP, Perl DP, Davidson M, Mohs RC, Haroutunian V. Type 2 diabetes is negatively associated with Alzheimer's disease neuropathology. J Gerontol A Biol Sci Med Sci. 2005; 60:471–475. [PubMed: 15933386]
45. O'Luanaigh C, O'Connell H, Chin AV, Hamilton F, Coen R, Walsh C, Walsh JB, Caokley D, Cunningham C, Lawlor BA. Loneliness and cognition in older people: The Dublin Healthy Ageing study. Aging Ment Health. 2011 [Epub].
46. Cacioppo JT, Hawkley LC. Perceived social isolation and cognition. Trends Cogn Sci. 2009; 13:447–454. [PubMed: 19726219]
47. O'Luanaigh C, Lawlor BA. Loneliness and the health of older people. Int J Geriatr Psychiatry. 2008; 23:1213–1221. [PubMed: 18537197]
48. O'Luanaigh C, O'Connell H, Chin AV, Hamilton F, Coen R, Walsh C, Walsh JB, Coakley D, Molloy A, Scott J, Cunningham CJ, Lawlor BA. Loneliness and vascular biomarkers: the Dublin Healthy Ageing Study. Int J Geriatr Psychiatry. 2012; 27:83–88. [PubMed: 21370279]
49. Stoykova R, Matharan F, Dartigues JF, Amieva H. Impact of social network on cognitive performances and age-related cognitive decline across a 20-year follow-up. Int Psychogeriatr. 2011 Epub].
50. Amieva H, Stoykova R, Matharan F, Helmer C, Antonucci TC, Dartigues JF. What aspects of social network are protective for dementia? Not the quantity but the quality of social interactions is protective up to 15 years later. Psychosom Med. 2010; 72:905–911. 2010. [PubMed: 20807876]
51. Crooks VC, Lubben J, Petitti DB, Little D, Chiu V. Social network, cognitive function, and dementia incidence among elderly women. Am J Public Health. 2008; 98:1221–1227. [PubMed: 18511731]
52. Giles LC, Glonek GF, Luszcz MA, Andrews GR. Effect of social networks on 10 year survival in very old Australians: the Australian longitudinal study of aging. J Epidemiol Community Health. 2005; 59:574–579. [PubMed: 15965141]
53. Rutledge T, Linke SE, Olson MB, Francis J, Johnson BD, Bittner V, York K, McClure C, Kelsey SF, Reis SE, Cornell CE, Vaccarino V, Sheps DS, Shaw LJ, Krantz DS, Parashar S, Merz CN. Social networks and incident stroke among women with suspected myocardial ischemia. Psychosom Med. 2008; 70:282–287. [PubMed: 18378868]

54. Loucks EB, Sullivan LM, D'Agostino RB Sr, Larson MG, Berkman LF, Benjamin EJ. Social networks and inflammatory markers in the Framingham Heart Study. J Bio soc Sci. 2006; 38:835–842.
55. Li G, Larson EB, Sonnen JA, Shofer JB, Petrie EC, Schantz A, Peskind ER, Raskind MA, Breitner JC, Montine TJ. Statin therapy is associated with reduced neuropathologic changes of Alzheimer disease. Neurology. 2007; 69:878–885. [PubMed: 17724290]
56. Manly JJ, Tang MX, Schupf N, Stern Y, Vonsattel JP, Mayeux R. Frequency and course of mild cognitive impairment in a multiethnic community. Ann Neurol. 2008; 63:494–506. [PubMed: 18300306]
57. Jicha GA, Parisi JE, Dickson DW, Johnson K, Cha R, Ivnik RJ, Tangalos EG, Boeve BF, Knopman DS, Braak H, Petersen RC. Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. Arch Neurol. 2006; 63:674–681. [PubMed: 16682537]
58. Fischer P, Jungwirth S, Zehetmayer S, Weissgram S, Hoenigschnabl S, Gelpi E, Krampla W, Tragl KH. Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. Neurology. 2007; 68:288–291. [PubMed: 17242334]
59. Storandt M, Grant EA, Miller JP, Morris JC. Longitudinal course and neuropathologic outcomes in original vs revised MCI and in pre-MCI. Neurology. 2006; 67:467–473. [PubMed: 16894109]
60. Rogalski EJ, Murphy CM, deToledo-Morrell L, Shah RC, Moseley ME, Bammer R, Stebbins GT. Changes in parahippocampal white matter integrity in amnestic mild cognitive impairment: A diffusion tensor imaging study. Behav Neurol. 2009; 21:51–61. [PubMed: 19847045]
61. Wang C, Stebbins GT, Medina DA, Shah RC, Bammer R, Moseley ME, deToledo-Morrell L. Atrophy and dysfunction of the parahippocampal white matter in mild Alzheimer's disease. Neurobiol Aging. 2012; 33:43–52. [PubMed: 20359781]
62. Scola E, Bozzali M, Agosta F, Magnani G, Franceschi M, Sormani MP, Cercignani M, Pagani E, Falautano M, Filippi M, Falini A. A diffusion tensor MRI study of patients with MCI and AD with a 2-year clinical follow-up. J Neurol Neurosurg Psychiatry. 2010; 81:798–805. [PubMed: 20392973]
63. Devanand DP, Pradhaban G, Liu X, Khandji A, De Santi S, Segal S, Rusinek H, Pelton GH, Honig LS, Mayeux R, Stern Y, Tabert MH, de Leon MJ. Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease. Neurology. 2007; 68:828–836. [PubMed: 17353470]
64. Ewers M, Walsh C, Trojanowski JQ, Shaw LM, Petersen RC, Jack CR Jr, Feldman HH, Bokde AL, Alexander GE, Scheltens P, Vellas B, Dubois B, Weiner M, Hampel H. Prediction of conversion from mild cognitive impairment to Alzheimer's disease dementia based upon biomarkers and neuropsychological test performance. Neurobiol Aging. 2010 Epub].
65. Risacher SL, Shen L, West JD, Kim S, McDonald BC, Beckett LA, Harvey DJ, Jack CR Jr, Weiner MW, Saykin AJ. Longitudinal MRI atrophy biomarkers: relationship to conversion in the ADNI cohort. Neurobiol Aging. 2010; 31:1401–1418. [PubMed: 20620664]
66. Fleisher AS, Sun S, Taylor C, Ward CP, Gamst AC, Petersen RC, Jack CR Jr, Aisen PS, Thal LJ. Volumetric MRI vs clinical predictors of Alzheimer disease in mild cognitive impairment. Neurology. 2008; 70:191–199. [PubMed: 18195264]
67. Chua TC, Wen W, Slavin MJ, Sachdev PS. Diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease: a review. Curr Opin Neurol. 2008; 21:83–92. [PubMed: 18180656]
68. Reitz C, Brickman AM, Brown TR, Manly J, DeCarli C, Small SA, Mayeux R. Linking hippocampal structure and function to memory performance in an aging population. Arch Neurol. 2009; 66:1385–1392. [PubMed: 19901171]