Published in final edited form as:

J Alzheimers Dis. 2013 ; 33(0 1): S427–S438. doi:10.3233/JAD-2012-129015.

Patterns of Compensation and Vulnerability in Normal Subjects at Risk of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most frequent form of dementia in elderly individuals and its incidence and prevalence increases with age. This risk of AD is increased in the presence of genetic and demographic factors including apolipoprotein E 4 allele, lower education, and family history of AD. There are medical risk modifiers including systemic hypertension, diabetes mellitus, cardiovascular disease, and cerebrovascular disease that *increase* the vulnerability for AD. By contrast, there are lifestyle risk modifiers that *reduce* the effects of AD risk factors include diet and physical and cognitive activity. Our research has consistently shown that it is the interactions among these risk factors with the pathobiological cascade of AD that determine the likelihood of a clinical expression of AD—either as dementia or mild cognitive impairment. However, the association between “vulnerability” and “protective” factors varies with age, since the effects of these factors on the risk for AD may differ in younger (age < 80) versus older (age > 80) individuals. The understanding of the dynamic of these factors at different age periods will be essential for the implementation of primary prevention treatments for AD.

Keywords

Alzheimer's disease; cardiovascular disease; cerebrovascular disease; mild cognitive impairment

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia in the elderly, and age is the most important risk factor. The prevalence of AD increases exponentially between the ages of 65 and 85, approaching 50% in the oldest old (>85 years old) [1, 2]. After 90 years of age, the incidence of AD increases dramatically with older age, from 12.7%/year in the 90–94 age group, to 21.2%/year in the 95–99 age group, and to 40.7%/year in those >100 years old [3].

This risk of AD is increased in the presence of genetic and demographic factors including apolipoprotein E (APOE) 4 allele, age, female gender, lower education, and family history of AD [1, 4, 5]. Medical risk modifiers include systemic hypertension (HTN), diabetes mellitus (DM), cardiovascular disease, and cerebrovascular disease (CVD) [6-11]. Lifestyle risk modifiers that *reduce* the effects of AD risk factors include physical and cognitive activity, and diet [12-14]. Our research over the past 10 years has consistently shown that it is the interactions among these risk factors with the pathobiological cascade of AD determine the likelihood of a clinical expression of AD—either as dementia or mild cognitive impairment (MCI).

AGING AND DEMENTIA

There are two critical assumptions that must be understood in the study of risk factors for AD. First, it has become increasingly apparent that the AD pathology is present several years before the development of the clinical symptomatology [15]. This distinction is critical because there are few, if any, unambiguous genetic, metabolic, or vascular factors that alter the risk to express the pathology. However, there is an ever-increasing set of variables that alter the risk to express the dementia. The core of our research has been to examine how those variables modify the risk for the clinical syndrome either by increasing or decreasing vulnerability. The second assumption is that if we accept the position that age itself is less important as a risk modifier then the various medical factors that change as a consequence of age [16]. For example, in our analysis of 924 cognitively normal individuals participating in the Cardiovascular Health Study-Cognition Study (CHS-CS), we found the commonly observed correlation between performance on the digit symbol substitution task (DSST) and chronological age ($r = -0.32, p < 0.001$) [17]. However following a series of regression analyses, we found that DSST performance was uniquely predicted by brain volumes in the hippocampus and frontal cortex. The structural integrity of these two brain regions was predicted not only by the presence of the APOE4 allele, but also by the presence of white matter lesions (WMLs), an indicator of the presence of small vessel disease. Age did not have a direct effect on DSST performance; it acted only by increasing the risk for WMLs and independently decreasing the volume of the hippocampus. Thus, one of our goals in our research program has been to try to “minimize” the effects of age by being able to more fully decompose its effects into the component parts (e.g., vascular disease, metabolic syndromes, etc.).

VULNERABILITY FACTORS

Aging

Older age has a global impact on brain structure [18], but the effects are not homogenous [19]; some areas are more vulnerable than others [20]. Atrophy in the prefrontal, frontal, and calcarine cortices [19, 21, 22] and hippocampal/parahippocampal regions [23-25] is common with increasing age. However, the cross-sectional studies of age effects are limited because we do not know antecedent information and, most important, we do not know what happened after the scan; it is possible that within a short period of time they progressed to dementia (e.g., [26]) and, consequently, we may attribute to age effects those that are actually due to neurodegeneration.

We took advantage of the longitudinal CHS-CS data by examining the magnetic resonance imaging (MRI) scans of 169 cognitively normal subjects who remained cognitively normal 5 years after the scan, and 33 AD patients [27]. We found that with older age, there were lower gray matter (GM) volumes in sensorimotor and heteromodal association areas in frontal, temporal, occipital, and parietal lobes, as well as in the cerebellum. While age was associated with atrophy in the posterior hippocampus, thalamus, and middle cingulate gyrus,

AD was associated with atrophy in the anterior hippocampal/parahippocampal regions and also in the precuneus. Normal aging and AD strongly overlapped in the hippocampus, specifically in the entorhinal cortex, and Cornu Ammonis. Age and AD are independently “connected” with GM atrophy but overlap substantially in the hippocampus, including entorhinal cortex.

The size of the hippocampus decreases 0.86% per decade, increasing to 1.85%/decade after age 70 [28]. However, the rate of atrophy was associated not only with baseline brain parenchymal fraction, but also hemoglobin A1c and severity of the WMLs [29], which themselves are more common with advancing age. The Atherosclerosis Risk in Communities study showed that DM, HTN, history of stroke, and the presence of the *APOE4* allele contributed to cognitive decline in late middle age subjects followed during 14 years [30]. Studies that examined ventricular expansion over time noted that this process is faster in subjects who will develop MCI [31], although Carmichael and colleagues, using the CHS-CS database, found that the rate of expansion can be accelerated by DM and HTN in normal individuals [32]. Taken together these observations, it seems that vascular risk factors play a role in the point of inflection of the slope that leads to cognitive deficits during the aging process.

Vascular disease

The relationship between vascular disease and AD pathology has not been clearly established, although ischemic vascular lesions may modulate AD clinical manifestation by expressing clinical dementia with fewer AD pathological changes [33, 34]. Cerebral infarctions increased the odds of clinical dementia in persons with AD pathology [35, 36] and arteriosclerosis in the Circle of Willis was more severe in AD patients than in non-demented subjects [37]. By contrast, other studies have reported no association between AD and brain infarcts [38, 39]. These pathological studies provide important insights into the relationship between AD and CVD but they are cross-sectional, do not provide a temporal relationship between the two pathologies, and they only address severe CVD (i.e., infarcts). Nevertheless, they have suggested that the critical vascular disease influence on AD pathology occurs in early stages of the clinical syndrome, but not in more advance stages [35].

Although the prevalence of dementia continues to increase with age, pathological studies found that AD pathology can be seen in a high proportion of autopsied cognitively-normal subjects after age 80 + [40-42] suggesting that some individuals have sufficient “brain reserve” to tolerate this pathology. On the other hand, it has been found that the association between neo-cortical neuritic plaques and dementia in subjects age 95+ was attenuated [41], which was due primarily to increased pathology in the cognitively normal subjects, and the density of AD pathology is reduced in subjects age 90+ compared to those age 80 or younger [40]. A recent study showed that the primary cause of dementia in subjects age 90 + was still AD pathology [43]. These findings suggest that the threshold to express dementia is not the same in all individuals, some can manifest the symptoms with less pathology than others, and the border zone between normalcy and dementia is very “narrow” in subjects 90+.

WMLs, as a manifestation of a subclinical CVD (see below), have been reported as risk factors for MCI [44] and AD [6]. WMLs are associated with hippocampal and amygdala volumes [45, 46]. WMLs correlate with age, HTN and DM, urinary incontinence, and loss of strength in lower limbs [47-51]. Sub-clinical systemic vascular disease has also been shown to increase the risk for dementia. Markers of peripheral atherosclerosis [52] and measures of pulse pressure and pulse wave velocity, as markers of arterial stiffness, have been associated with cognitive impairment [53]. We have shown that incident AD was

associated with prevalent peripheral artery disease (i.e., ankle-arm index), and with cardiovascular disease, defined as internal carotid artery wall thickness (in mm) [52]. These findings indicated that subjects with vascular disease other than stroke and MRI-infarcts had higher risk of AD than did those without vascular disease.

HTN is very common in old individuals, and the fact that subjects with HTN have a diminished cerebrovascular dilative response to physiological stimuli has served as the basis for the studies of the effects of the regional cerebral blood flow (rCBF) responses on cognitive stimulation [54-57]. Several studies have found a pattern of decreased MRI volume and altered metabolism/perfusion in middle-aged and elderly subjects with HTN [45, 55, 58-60], as well as cognitive deficits [56, 61]. A longitudinal study conducted in 14 highly selected hypertense, cognitively normal subjects (mean age: 60), with biannual H₂¹⁵O-PET scans, showed decreased rCBF overtime in the middle and inferior prefrontal cortex, anterior cingulate gyrus, and occipital-temporal cortex [60]. A recent study showed an association between HTN and amyloid deposition, especially in *APOE4* allele carriers [62].

Perfusion MRI studies conducted by the CHS-CS in cognitively healthy individuals showed that there was diminished rCBF in heteromodal association areas usually affected in AD in hypertensives compared to normotensives [63]. These findings were consistent with previous observations in untreated, relatively young (mean age 61), and cognitively normal subjects with HTN [55, 61], who had reduced rCBF and less cortical grey matter in the hippocampus, anterior cingulate gyrus, and middle temporal and parietal lobes. Mid-life HTN is associated with hippocampal volume after age 65 [64], and low cerebral blood flow, as measured with transcranial Doppler, and is associated with the development of dementia [65]. We have reported a relationship between dementia and prevalent and incident stroke, MRI-identified infarcts, and the severity of WMLs in CHS [66].

HTN and small vessel ischemic disease increase the risk for AD; how they affect brain structure in cognitively-normal subjects is not clear. Increased aortic stiffness, even in subjects without overt HTN, was associated with lower memory scores, MRI silent infarcts, and WMLs in non-demented subjects [67]. Such insights are important in understanding how these factors raise brain vulnerability for neurodegeneration. We found that severity of WMLs inversely correlated with GM volumes, especially in the frontal cortex [17], and that age-related atrophy was observed in the hippocampus and posterior cingulate gyrus. Regression analyses revealed links among age, HTN, WMLs, *APOE4* allele, GM, and digit symbol substitution scores. Both advancing age and HTN predicted WMLs, which is itself associated with GM atrophy. These data demonstrated that small vessel disease, as indicated by WMLs, is associated with GM tissue loss that results in decreases in cognitive function in cognitively normal subjects. This observation showed that multiple factors have to be taken into account to interpret the effects of WMLs on brain function and in normal individuals.

There is an association between DM, abnormal glucose metabolism, and incident dementia [10, 11, 68-73], especially when DM is uncontrolled [74], and in *APOE4* allele carriers [75]. The CHS-CS found that DM was associated with atrophy in the frontal, temporal, and subcortical regions, while insulinemia was associated with atrophy of the frontal lobes, hippocampus, and corpus callosum [76]. However, these associations were attenuated when we controlled for body mass index (BMI).

Renovascular disease and markers of inflammation

The CHS has found that MRI-infarcts and WMLs were predictors of incident dementia [6], and that elevated CRP and IL-6 (as markers of low grade inflammation) were associated with myocardial infarction, WML, and death [77-79]. This indicated that inflammatory

markers were present in individuals with cardiovascular and cerebrovascular diseases, suggesting that their relationships with AD pathology could be related to underlying vascular disease. CRP and IL-6 levels have been found associated with silent infarcts in the brain [80, 81], and it has been suggested that inflammatory markers (CRP) were involved in the pathogenesis of small vessel disease, in particular the development of WMLs [82, 83]. Furthermore, several studies conducted in non-selected populations found that CRP was associated with WMLs, which subsequently led to executive function deficits [83, 84].

There are not many studies that have examined the relationship between brain volumes with inflammatory markers in normal or demented subjects. A study conducted by the Framingham Heart Study on 1926 participants age 35–85 (mean 60) found that markers of inflammation were associated with MRI total brain volume, even after excluding participants with incident cardiovascular disease [85]. This study confirmed that inflammatory markers are associated with greater brain atrophy than expected for age. However, it did not examine the specific brain regions affected by these markers, and there is no knowledge about selective brain vulnerability to inflammatory markers in elderly subjects (age > 75).

Cystatin C is considered a marker of glomerular excretion function [86, 87], and it has been associated with the presence of peripheral vascular disease [88], cardiovascular disease [89], stroke [90], subclinical brain infarction [91], markers of inflammation [92], and death [93, 94]. The CHS has also found a correlation between plasma amyloid- β ($A\beta$)₁₋₄₀ and $A\beta$ ₁₋₄₂ levels and cystatin C levels in normal subjects [95], which it may explain the relationship between reduced insulin clearance and plasma $A\beta$ levels in AD patients [96], and the modulation of plasma $A\beta$ levels by drugs (e.g., non-steroidal anti-inflammatory drugs) that affect glomerular function in normal subjects [97]. However, the relationship between cystatin C and AD is not well established. Some studies found that low cystatin C levels predicted AD [98], and they speculated that this was secondary to an increased deposition in the brain parenchyma, as part of a physiological process of neuroprotection [99]. By contrast, other studies have found no association [100] or increased levels of cystatin C in the cerebrospinal fluid of AD patients [101]. The current state of the research suggests that cystatin C is a marker of renovascular disease, which it should be increased in individuals with vascular disease in general.

These studies have shown sub-clinical vascular disease is a widespread phenomenon that affects kidney and cardiovascular function, and brain structure. Therefore, it is expected that measures of cardiovascular disease, cystatin-C levels, and markers of inflammation will be higher in normal subjects who will convert to MCI/AD.

Cholesterol metabolism

Epidemiological studies have shown that total cholesterol levels in mid-life were associated with dementia in old age [102], and the association was attenuated with statin use [103]. However, these findings have not been replicated in other studies [104, 105]. Similarly, the relationship between cholesterol and AD in the elderly was not consistent; some studies found that low [106] or high [107] cholesterol levels were associated with AD in elderly subjects. It is possible that the discrepancy was related to the age of the cohorts and to timing in the use of lipid-lowering therapy, although a trial of pravastatin in subjects at risk for cardiovascular disease found no difference between the placebo and treatment arms in cognitive function after 3-year follow-up [108].

Although the relationship between AD and systemic cholesterol could be explained by increased CVD [37], it is important to know that the central nervous system (CNS) cholesterol is produced in the brain, and lipid metabolism is essential for neuronal

functioning. Therefore, markers of CNS metabolites (e.g., 24S-hydroxycholesterol) that are formed only in the brain and that can cross the brain blood barrier could be better markers of brain cholesterol metabolism than those of peripheral etiology [109]. Finally, the role of the APOE as a lipid transporter and in lipid delivery for growth and repair of axons after an injury underscores the importance of the relationship between lipids and AD [110]. Subjects carrying the *APOE4* allele, a risk factor for AD [111], have low levels of APOE and consequently decreased cholesterol transportation from neuronal bodies to axons with the subsequent reduction of axonal extension and sprouting [110]. The relationship between cholesterol metabolism and neurodegeneration is not well-understood, and it is possible that systemic and CNS cholesterol-associated factors converge to create a vulnerability state for AD.

Neuroimaging in normal subjects at risk for MCI and AD

PET, SPECT, and MRI have demonstrated abnormal cerebral structure and metabolism in the mesial temporal lobes and other heteromodal association cortices in MCI subjects who progressed to AD [112-124], and in normal subjects at risk for AD [125-127], especially those who are homozygous for *APOE4* allele with family history of dementia.

While perfusion studies showed that an association between temporal, parietal, and posterior cingulate regions and subsequent conversion to AD in normal subjects, structural volumetric studies showed that hippocampal, amygdala, and the ventral striatum volumes were predictors of AD [26, 128, 129]. The CHS-CS examined the MRI volumetric characteristics of the normal subjects who progressed to AD during a 4.5 years follow-up using modulated voxel-based morphometry found that the ventral striatum and hippocampal volumes were associated with incident AD [26]. This finding is particularly important since amyloid ligand studies have found amyloid deposition in the ventral striatum and frontal lobes in patients with early AD [130, 131] and in cognitively-normal subjects [132]. In another study, we found that hippocampal volume and MRI-infarcts were independent predictors of conversion to dementia in normal subjects [128]. These data showed that both the ventral striatum (which includes the basal forebrain) and hippocampal volumes were associated with conversion to AD; and the conversion was faster in those subjects who had greater basal forebrain atrophy. Therefore, the perfusion and volumetric studies indicated that there is a widespread compromise of cortical and subcortical structures in normal subjects destined to develop AD.

COMPENSATORY MECHANISMS

One important aspect of the transition from normalcy to dementia is that in spite of the presence of progressive neuronal loss and atrophy, these subjects are able maintain a certain level of functional capacity. For example, PET studies that used activation paradigms [133, 134] have found that subjects with mild/moderate AD have a greater activation than normals in the brain regions usually involved in memory tasks, as well as in others (frontal lobes) that only activate with increasing task difficulty. This compensation response occurs without necessarily resulting in improved cognitive function. Similarly, fMRI studies have found that MCI subjects have a greater activation of the hippocampus compared to normal controls and AD subjects in memory tasks [135]. Studies that used attentional/executive tasks found increased activation in the parietal lobes, with decreased activation in the prefrontal cortex, and anterior cingulate gyrus [136].

We have extensively examined the effect of physical activity and obesity on brain volume in cognitively normal individuals in the CHS-CS [13, 137-140]. Because there is a closed association between educational level and physical activity in elderly subjects, we examined whether educational level or physical activity (based on leisure-time energy expenditure)

was associated with brain tissue expansion in cognitively normal subjects in CHS-CS [139]. After controlling for age, gender, and physical activity, higher educational levels were associated with ~2–3% greater tissue volumes, on average, in the temporal lobe GM. When controlling for age, gender, and education, greater physical activity was associated with ~2–2.5% greater average tissue volumes in the white matter of the *corona radiata* extending into the parietal-occipital junction. However, the effects of education and exercise on brain structure were attenuated when including BMI in the statistical model. This study showed a dynamic role of vulnerability (obesity) and protective (physical activity) factors on the aging brain, although BMI may be the dominant explanatory factor mediating the observed relationship among education, physical activity, and brain structure; there is an negative association between education level and obesity [139].

We have also conducted longitudinal studies to examine the effect of physical activity and brain volume in the CHS-CS. Erikson and colleagues examined whether physical activity (measured in 1991–92) was associated with greater GM volume (MRI in 1998–99) after a 9-year follow-up, and whether a threshold could be identified for the amount of walking (measured in blocks walked per week) necessary to spare GM volume, and whether GM volume associated with physical activity would be associated with a reduced risk for cognitive impairment (MCI/dementia) 13 years later (after 2002–03) in cognitively normal subjects [13]. After controlling for WMLs, MRI-identified infarcts, and other variables (including BMI), greater physical activity predicted greater volumes of frontal, occipital, entorhinal, and hippocampal regions 9 years later. Walking 72 blocks per week was necessary to detect increased GM volume, and greater GM volume associated with physical activity reduced the risk for MCI/dementia 2-fold between 1998–99 and 2002–03. Therefore, in this longitudinal model, physical activity had a long-term effect, as it was associated with greater GM volume, which is in turn associated with a reduced risk of cognitive impairment. These studies have shown the positive effects of physical activity on the brain, although vascular factors can attenuate these effects.

Perfusion MRI studies have also shown that early AD patients can also have areas of increased rCBF (inferior frontal and anterior temporal cortices) compared to controls [141, 142]. The CHS-CS found that there were decreases and increases in rCBF in specific brain regions in early AD and MCI (e.g., anterior cingulate gyrus, ventral striatum, hippocampus) [142]. A study with perfusion-weighted MRI showed increased rCBF in the medial temporal region, amygdala, and anterior cingulate gyrus in a subgroup of MCI subjects [143]. In addition, this latter study found a tendency to increased rCBF in the frontobasal region when both groups (AD/MCI) were examined together. This is particularly important in view of studies conducted in Pittsburgh where we examined the relationship between amyloid ligand of A β deposition with cerebral metabolism in amyloid-positive control subjects and patients with MCI or AD [144]. Glucose metabolism in parietal and precuneus cortices of AD patients was negatively correlated with Pittsburgh Compound-B (PiB) retention. By contrast, in MCI patients with A β deposition, there was a lack of negative correlations between A β and metabolism, but there were frequent positive correlations. This suggested that, at the MCI stage of the disease, A β deposition was independent of brain metabolism in specific brain areas, which was similar to the pMRI studies conducted in CHS-CS.

The hypothesis that educational level, through the development of increased synaptic formation, is a plausible explanation for the “protective” effect in cognitively-normal subjects. However, there are other critical factors that are associated with education and incident AD. For example systemic vascular disease is highly prevalent in the elderly and the treatment and care of this condition is closely associated with education level [145–147]. Indeed, pathological studies have found an association between vascular disease and education level, but not with AD pathology [148], although this was not confirmed by others

[149]. Subjects with low education level may seek diagnosis and treatment after those with high education level, and they may not be able to receive the proper treatments. Therefore, the role of the educational factor in the clinical manifestation of AD may not be related to the years of education, but to treatment and diagnosis of vascular disease. Finally, we have shown that cerebral ventricular volumes progressed faster in elderly subjects with HTN and DM than in those without these conditions [32, 150].

SUMMARY

The studies conducted at the CHS-CS as well as those described in the literature suggested that vascular disease creates a vulnerability state to AD pathology and modulates its clinical presentation. Our studies have been oriented to examine whether vascular disease can accelerate the transition from normal to abnormal cognition, either MCI or AD, by attenuating the effect of physiological compensatory mechanisms. In addition, we are examining the relationship between vascular disease and amyloid deposition using PiB. The understanding of this process will determine when and how the cerebral vascular process could be treated, and how this process influence future primary prevention therapies for AD.

Acknowledgments

This manuscript was supported, in part, by grants AG20098, AG15928, and AG05133 from the National Institute on Aging.

REFERENCES

1. Fitzpatrick AL, Kuller LH, Ives D, Lopez OL, Jagust W, Breitner J, Jones B, Lyketsos C, Dulberg C. Incidence and prevalence of dementia in the cardiovascular health study. *J Am Geriatr Soc*. 2004; 52:195–204. [PubMed: 14728627]
2. Evans DA, Funkenstein HH, Albert MS. Prevalence of Alzheimer's disease in a community population of older persons: Higher than previously reported. *JAMA*. 1989; 262:2551–2556. [PubMed: 2810583]
3. Corrada MM, Brookmeyer R, Paganini-Hill A, Berlau D, Kawas CH. Dementia incidence continues to increase with age in the oldest old: The 90+ study. *Ann Neurol*. 2010; 67:114–121. [PubMed: 20186856]
4. Tang M, Maestre G, Tsai W, Liu X, Feng L, Chung W, Chun M, Schofield P, Stern Y, Tycko B, Mayeux R. Relative risk of Alzheimer disease and age-at-onset distributions, based on APOE genotypes among elderly African Americans, Caucasians, and Hispanics in New York City. *Am J Hum Genet*. 1996; 58:574–584. [PubMed: 8644717]
5. Launer LJ, Andersen K, Dewey ME, Letenneur L, Amaducci LA, Brayne C, Copeland JRM, Dartigues JF, Kragh-Sorensen P, Lobo A, Martinez-Lage JM, Stijnen T, Hofman A. Rates and risk factors for dementia and Alzheimer's disease: Results from EURODEM pooled analyses. *Neurology*. 1999; 52:78–84. [PubMed: 9921852]
6. Kuller LH, Lopez OL, Newman A, Beauchamp NJ, Burke G, Dulberg C, Fitzpatrick A, Fried L, Haan MN. Risk factors for dementia in the cardiovascular health cognition study. *Neuroepidemiology*. 2003; 22:13–22. [PubMed: 12566949]
7. Irie F, Fitzpatrick A, Lopez OL, Kuller LH, Peila R, Newman A, Launer L. Type 2 diabetes, genetic susceptibility, and the incidence of dementia in the cardiovascular health study. *Cardiovascular Health Study Paper Proposal*. 2005:A210.
8. Luchsinger JA, Tang M-X, Stern Y, Shea S, Mayeux R. Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. *Am J Epidemiol*. 2001; 154:635–641. [PubMed: 11581097]
9. Skoog I, Lernfeldt B, Landahl S. 15-year longitudinal study of blood pressure and dementia. *Lancet*. 1996; 347:1141–1145. [PubMed: 8609748]

10. Matsuzaki T, Sasaki K, Tanizaki Y, Hata J, Fujimi K, Matsui Y, Sekita A, Suzuki SO, Kanba S, Kiyohara Y, Iwaki T. Insulin resistance is associated with the pathology of Alzheimer disease: The Hisayama study. *Neurology*. 2010; 75:764–770. [PubMed: 20739649]
11. Ohara T, Doi Y, Ninomiya T, Hirakawa Y, Hata J, Iwaki T, Kanba S, Kiyohara Y. Glucose tolerance status and risk of dementia in the community. The Hisayama Study. *Neurology*. 2011; 77:1126–1134. [PubMed: 21931106]
12. Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, Ambrose AF, Sliwinski M, Herman B. Leisure activities and the risk of dementia in the elderly. *New Engl J Med*. 2003; 348:2508–2516. [PubMed: 12815136]
13. Erickson KI, Raji CA, Lopez OL, Becker JT, Rosano C, Newman AB, Gach HM, Thompson PM, Ho AJ, Kuller LH. Physical activity predicts gray matter volume in late adulthood: The Cardiovascular Health Study. *Neurology*. 2010; 75:1415–1422. [PubMed: 20944075]
14. Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. *Ann Neurol*. 2006; 59:912–921. [PubMed: 16622828]
15. Rowe CC, Ellis KA, Rimajova M, Bourgeat P, Pike KE, Jones G, Fripp J, Tochon-Danguy H, Morandau L, O'Keefe G, Price R, Raniga P, Robins P, Acosta O, Lenzo N, Szoek C, Salvado O, Head R, Martins R, Masters CL, Ames D, Villemagne VL. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiol Aging*. 2010; 31:1275–1283. [PubMed: 20472326]
16. Rabbit P, Abson V. Do older people know how good they are? *Br J Psychol*. 1991; 82:137–151. [PubMed: 1873649]
17. Raji CA, Lopez OL, Kuller LH, Carmichael OT, Longstreth WT Jr, Gach HM, Boardman J, Bernick CB, Thompson PM, Becker JT. White matter lesions and brain gray matter volume in cognitively normal elders. *Neurobiol Aging*. 2012; 33:834.e7–e16. [PubMed: 21943959]
18. Sigurdsson S, Aspelund T, Forsberg L, Fredriksson J, Kjartansson O, Oskarsdottir B, Jonsson PV, Eiriksdottir G, Harris TB, Zijdenbos A, van Buchem MA, Launer LJ, Gudnason V. Brain tissue volumes in the general population of the elderly The AGES-Reykjavik Study. *Neuroimage*. 2012; 59:3862–3870. [PubMed: 22119006]
19. Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RS, Busa E, Morris JC, Dale AM, Fischl B. Thinning of the cerebral cortex in aging. *Cereb Cortex*. 2004; 14:721–730. [PubMed: 15054051]
20. Raz N, Rodrigue KM. Differential aging of the brain patterns: Cognitive correlates and modifiers. *Neurosci Behav Rev*. 2006; 30:730–748.
21. Salat DH, Kaye JA, Janowsky JS. Prefrontal gray and white matter volumes in healthy aging and Alzheimer disease. *Arch Neurol*. 1999; 56:338–344. [PubMed: 10190825]
22. Salat DH, Kaye JA, Janowsky JS. Selective preservation and degeneration within the prefrontal cortex in aging and Alzheimer disease. *Arch Neurol*. 2000; 58:1403–1408. [PubMed: 11559311]
23. Tisserand DJ, van Boxtel MP, Pruessner JC, Hofman P, Evans AC, Jolles J. A voxel-based morphometric study to determine individual differences in gray matter density associated with age and cognitive change over time. *Cereb Cortex*. 2004; 14:966–973. [PubMed: 15115735]
24. Tisserand DJ, Visser PJ, van Boxtel MP, Jolles J. The relation between global and limbic brain volumes on MRI and cognitive performance in healthy individuals across the age range. *Neurobiol Aging*. 2000; 21:569–576. [PubMed: 10924774]
25. Zimmerman ME, Brickman AM, Paul RH, Grieve SM, Tate DF, Gunstad J, Cohen RA, Aloia MS, Williams LM, Clark CR, Whitford TJ, Gordon E. The relationship between frontal gray matter volume and cognition varies across the healthy adult lifespan. *Am J Geriatr Psychiatry*. 2006; 14:823–833. [PubMed: 17001022]
26. Hall AM, Moore RY, Lopez OL, Kuller LH, Becker JT. Basal forebrain atrophy is a presymptomatic marker for Alzheimer's disease. *Alzheimers Dement*. 2008; 4:271–279. [PubMed: 18631978]
27. Raji CA, Lopez OL, Kuller LH, Carmichael OT, Becker JT. Age, Alzheimer disease, and brain structure. *Neurology*. 2009; 73:1899–1905. [PubMed: 19846828]
28. Raz N, Rodrigue KM, Head D, Kennedy KM, Acker JD. Differential aging of the medial temporal lobe: A study of a five-year change. *Neurology*. 2004; 62:433–438. [PubMed: 14872026]

29. Enzinger C, Fazekas F, Matthews PM, Ropele S, Schmidt H, Smith S, Schmidt R. Risk factors for progression of brain atrophy in aging: Six-year follow-up of normal subjects. *Neurology*. 2005; 64:1704–1711. [PubMed: 15911795]
30. Knopman DS, Mosley TH, Catellier DJ, Sharrett AR. Cardiovascular risk factors and cerebral atrophy in a middle-aged cohort. *Neurology*. 2005; 65:876–881. [PubMed: 16186527]
31. Carlson NE, Moore MM, Dame A, Howieson D, Silbert LC, Quinn JF, Kaye JA. Trajectories of brain loss in aging and the development of cognitive impairment. *Neurology*. 2008; 70:828–833. [PubMed: 18046010]
32. Carmichael OT, Kuller LH, Lopez OL, Thompson PM, Dutton RA, Lu A, Lee SE, Lee JY, Aizenstein HJ, Meltzer CC, Liu Y, Toga AW, Becker JT. Acceleration of cerebral ventricular expansion in the Cardiovascular Health Study. *Neurobiol Aging*. 2007; 28:1316–1321. [PubMed: 16875759]
33. Snowdon DA, Grainer LH, Mortimer JA, Riley KP, Grainer PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease: The nun study. *JAMA*. 1997; 277:813–817. [PubMed: 9052711]
34. Petrovitch H, Ross GW, Steinborn SC, Abbott RD, Markesbury 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]
35. Esiri MM, Nagy Z, Smith MZ, Barnettson L, Smith AD. Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. *Lancet*. 1999; 354:919–920. [PubMed: 10489957]
36. Schneider JA, Wilson RS, Cochran EJ, Bienias JL, Arnold SE, Evans DA, Bennett DA. Relation of cerebral infarctions to dementia and cognitive function in older persons. *Neurology*. 2003; 60:1082–1088. [PubMed: 12682310]
37. Roher AE, Esh C, Kokjohn TA, Kalback W, Luehrs DC, Seward JD, Sue LI, Beach TG. Circle of Willis Atherosclerosis is a risk factor for sporadic Alzheimer's disease. *Arterioscler Thromb Vasc Biol*. 2003; 23:2055–2062. [PubMed: 14512367]
38. Launer LJ, Petrovitch H, Ross GW, Markesbery W, White LR. AD brain pathology: Vascular origins? Results from the HAAS autopsy study. *Neurobiol Aging*. 2008; 29:1587–1590. [PubMed: 17466414]
39. Schneider JA, Wilson RS, Bienias JL, Evans DA, Bennett DA. Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology. *Neurology*. 2004; 62:1148–1155. [PubMed: 15079015]
40. 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]
41. 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]
42. 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 studies. *Neurology*. 2006; 66:1837–1844. [PubMed: 16801647]
43. Robinson JL, Geser F, Corrada MM, Berlau DJ, Arnold SE, Lee VM, Kawas CH, Trojanowski JQ. Neocortical and hippocampal amyloid-beta and tau measures associate with dementia in the oldest-old. *Brain*. 2011; 134:3705–3712.
44. Lopez OL, Jagust WJ, Dulberg C, Becker JT, DeKosky ST, Fitzpatrick A, Breitner J, Lyketsos CG, Jones B, Kawas C, Carlson M, Kuller LH. Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: Part 2. *Arch Neurol*. 2003; 60:1394–1399. [PubMed: 14568809]
45. den Heijer T, Launer LJ, van Dijk EJ, Vermeer SE, Hofman A, Koudstaal PJ, Breteler MMB. Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology*. 2005; 64:263–267. [PubMed: 15668423]
46. van der Flier WM, Middelkoop AM, Weverling-Rijnsburger AWE, Admiraal-Behloul F, Spilt A, Bollen ELEM, Westendorp RGJ, van Buchem MA. Interaction of medial temporal lobe atrophy and white matter hyperintensities in AD. *Neurology*. 2004; 62:1862–1864. [PubMed: 15159496]

47. Liao D, Cooper L, Cai J, Tolle JF, Bryan NR, Hutchinson RG, Tyroler HA. Presence and severity of cerebral white matter lesions and hypertension, its treatment, and its control: The ARIC Study. Arteriosclerosis Risk in Communities Study. *Stroke*. 1996; 27:2262–2270. [PubMed: 8969791]
48. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Leukoaraiosis in stroke patients: The Copenhagen Stroke Study. *Stroke*. 1995; 26:588–592. [PubMed: 7709402]
49. Inzitari DI, Diaz F, Fox A, Hachinski VC, Steingart A, Lau C, Donald A, Wade J, Mulic H, Merskey H. Vascular risk factors and leuko-araiosis. *Arch Neurol*. 1987; 44:42–47. [PubMed: 3800721]
50. Chamorro A, Pujol J, Saiz A, Vila N, Vilanova JC, Alday M, Blanc R. Periventricular white matter lucencies in patients with lacunar stroke. *Arch Neurol*. 1997; 54:1284–1288. [PubMed: 9341575]
51. Longstreth WT, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, Enright PL, O'Leary D, Fried L. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. *Stroke*. 1996; 27:1274–1282. [PubMed: 8711786]
52. Newman AB, Fitzpatrick AL, Lopez O, Jackson S, Lyketsos C, Jagust W, Ives D, Dekosky ST, Kuller LH. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. *J Am Geriatr Soc*. 2005; 53:1101–1107. [PubMed: 16108925]
53. Waldstein SR, Rice SC, Thayer JF. Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore Longitudinal Study of Aging. *Hypertension*. 2008; 51:99–104. [PubMed: 18025297]
54. Jennings JR, Muldoon MF, Ryan CM, Mintun MA, Meltzer C, Townsend D, Sutton-Tyrel K, Shapiro AP, Manuck SB. Cerebral blood flow in hypertensive patients: An initial report of reduced and compensatory blood flow responses during performance of two cognitive tasks. *Hypertension*. 1998; 31:1216–1222. [PubMed: 9622132]
55. Jennings JR, Muldoon MF, Ryan C, Price JC, Greer P, Sutton-Tyrell K, van der Veen FM, Meltzer CC. Reduced cerebral blood flow response and compensation among patients with untreated hypertension. *Neurology*. 2005; 64:1358–1365. [PubMed: 15851723]
56. Gianaros PJ, Derbyshire SW, May JC, Siegle GJ, Gamalo MA, Jennings JR. Anterior cingulate activity correlates with blood pressure during stress. *Psychophysiology*. 2005; 42:627–636. [PubMed: 16364058]
57. Jennings JR, Muldoon MF, Price J, Christie IC, Meltzer CC. Cerebrovascular support for cognitive processing in hypertensive patients is altered by blood pressure treatment. *Hypertension*. 2008; 52:65–71. [PubMed: 18519845]
58. Fujishima S, Imaizumi T, Abe I, Takeshita A, Fujishima M. Effects of intra-arterial infusion of insulin on forearm vasoreactivity in hypertensive humans. *Hypertens Res*. 1995; 18:327–333.
59. Mentis MJ, Salerno J, Horwitz B, Grady CL, Schapiro MB, Murphy DC, Rapoport SI. Reduction of functional neuronal connectivity in long-term treated hypertension. *Stroke*. 1994; 25:601–607. [PubMed: 8128513]
60. Beason-Held LL, Moghekar A, Zonderman AB, Kraut MA, Resnick SM. Longitudinal changes in cerebral blood flow in the older hypertensive brain. *Stroke*. 2007; 39:1766–1773. [PubMed: 17510458]
61. Gianaros PJ, Greer PJ, Ryan CM, Jennings JR. Higher blood pressure predicts lower regional grey matter volume: Consequences on short-term information processing. *Neuroimage*. 2006; 31:754–765. [PubMed: 16488626]
62. Langbaum JB, Chen K, Launer LJ, Fleisher AS, Lee W, Liu X, Protas HD, Reeder SA, Bandy D, Yu M, Caselli RJ, Reiman EM. Blood pressure is associated with higher brain amyloid burden and lower glucose metabolism in healthy late middle-age persons. *Neurobiol Aging*. 2012; 33:827.e11–e19. [PubMed: 21821316]
63. Dai W, Lopez OL, Carmichael OT, Becker JT, Kuller LH, Gach HM. Abnormal regional cerebral blood flow in cognitively normal elderly subjects with hypertension. *Stroke*. 2008; 39:349–354. [PubMed: 18174483]
64. Korf ESC, White LR, Scheltens P, Launer LJ. Midlife blood pressure and the risk of hippocampal atrophy: The Honolulu Asia aging study. *Hypertension*. 2004; 44:29–34. [PubMed: 15159381]

65. Ruitenberg A, den Heijer T, Bakker SLM, van Swieten JC, Koudstaal PJ, Hoffman A, Breteler MMB. Cerebral hypoperfusion and clinical onset of dementia: The Rotterdam study. *Ann Neurol*. 2005; 57:780–794.
66. Kuller LH, Shemanski L, Manolio T, Haan M, Fried L, Bryan N, Burke GL, Tracy R, Bhadelia R. Relationship between ApoE, MRI findings, and cognitive function in the cardiovascular health study. *Stroke*. 1998; 29:388–398. [PubMed: 9472879]
67. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ. Arterial stiffness, pressure and flow pulsatility and brain structure and function: The Age, Gene/Environment Susceptibility–Reykjavik study. *Brain*. 2011; 134:3398–3407. [PubMed: 22075523]
68. Leibson CL, Rocca WA, Hanson VA, Cha R, Kokmen E, O’Brien PC, Palumbo PJ. Risk of dementia among persons with diabetes mellitus: A population-based cohort study. *Am J Epidemiol*. 1997; 145:301–308. [PubMed: 9054233]
69. Kuusisto J, Koivisto K, Mykkanen L, Helkala EL, Vanhanen M, Hanninen T, Kervinen K, Kesaniemi YA, Riekkinen PJ, Laakso M. Association between features of the insulin resistance syndrome and Alzheimer’s disease independently of apolipoprotein E4 phenotype: Cross sectional population based study. *BMJ*. 1997; 315:1045–1049. [PubMed: 9366728]
70. Luchsinger JA, Tang MX, Stern Y, Shea S, Mayeux R. Diabetes mellitus and risk of Alzheimer’s disease and dementia with stroke in a multiethnic cohort. *Am J Epidemiol*. 2001; 154:635–641. [PubMed: 11581097]
71. Luchsinger JA, Tang MX, Shea S, Mayeux R. Hyper-insulinemia and risk of Alzheimer disease. *Neurology*. 2004; 63:1187–1192. [PubMed: 15477536]
72. Xu WL, Qiu CX, Wahlin A, Winblad B, Fratiglioni L. Diabetes mellitus and risk of dementia in the Kungsholmen project. A 6-year follow-up study. *Neurology*. 2004; 63:1181–1186. [PubMed: 15477535]
73. Peila R, Rodriguea BL, White LR, Launer LJ. Fasting insulin and incident dementia in an elderly population of Japanese-American men. *Neurology*. 2004; 63:228–233. [PubMed: 15277613]
74. Xu WL, von Strauss E, Qiu CX, Winblad B, Fratiglioni L. Uncontrolled diabetes increases the risk of Alzheimer’s disease: A population-based cohort study. *Diabetologia*. 2009; 52:1031–1039. [PubMed: 19280172]
75. Irie F, Fitzpatrick AL, Lopez OL, Kuller LH, Peila R, Newman AB, Launer LJ. Enhanced risk for Alzheimer disease in persons with type 2 diabetes and APOE epsilon4: The Cardiovascular Health Study Cognition Study. *Arch Neurol*. 2008; 65:89–93. [PubMed: 18195144]
76. Ho AJ, Raji CA, Becker JT, Lopez OL, Kuller LH, Hua X, Lee S, Hibar D, Dinov ID, Stein JL, Jack CR Jr, Weiner MW, Toga AW, Thompson PM. Obesity is linked with lower brain volume in 700 AD and MCI patients. *Neurobiol Aging*. 2010; 31:1326–1339. [PubMed: 20570405]
77. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. *Am J Epidemiol*. 1996; 144:537–547. [PubMed: 8797513]
78. Tracy RP, Lemaitre RN, Psaty BM, Ives DG, Evans RW. Relationship of c-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. *Arterioscler Thromb Vasc Biol*. 1997; 17:1121–1127. [PubMed: 9194763]
79. Fornage M, Chiang YA, O’Meara ES, Psaty BM, Reiner AP, Siscovick DS, Tracy RP, Longstreth WT Jr. Biomarkers of Inflammation and MRI-Defined Small Vessel Disease of the Brain: The Cardiovascular Health Study. *Stroke*. 2008; 39:1952–1959. [PubMed: 18436879]
80. Hoshi T, Kitagawa K, Yamagami H, Furukado S, Hougaka H, Hori M. Relations of serum high-sensitivity C-reactive protein and interleukin-6 levels with silent brain infarction. *Stroke*. 2005; 36:768–772. [PubMed: 15746456]
81. Yoshida M, Higashi K, Kobayashi E, Saeki N, Wakui K, Kusaka T, Takizawa H, Kashiwado K, Suzuki N, Fukuda K, Nakamura T, Watanabe S, Tada K, Machi Y, Mizoi M, Toida T, Kanzaki T, Tomitori H, Kashiwagi K, Igarashi K. Correlation between images of silent brain infarction, carotid atherosclerosis and white matter hyperintensity, and plasma levels of acrolein, IL-6 and CRP. *Atherosclerosis*. 2010; 211:475–479. [PubMed: 20417516]

82. van Dijk EJ, Prins ND, Vermeer SE, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MM. C-reactive protein and cerebral small-vessel disease: The Rotterdam Scan Study. *Circulation*. 2005; 112:900–905. [PubMed: 16061741]
83. Wersching H, Duning T, Lohmann H, Mohammadi S, Stehling C, Fobker M, Conty M, Minnerup J, Ringelstein EB, Berger KL, Deppe M, Knecht S. Serum C-reactive protein is linked to cerebral microstructural integrity and cognitive function. *Neurology*. 2010; 74:1022–1029. [PubMed: 20350977]
84. Gunstad J, Bausserman L, Paul RH, Tate DF, Hoth K, Poppas A, Jefferson AL, Cohen RA. C-reactive protein, but not homocysteine, is related to cognitive dysfunction in older adults with cardiovascular disease. *J Clin Neurosci*. 2006; 13:540–546. [PubMed: 16723232]
85. Jefferson AL, Massaro JM, Wolf PA, Seshadri S, Au R, Vasani RS, Larson MG, Meigs JB, Keaney JF Jr, Lipinska I, Kathiresan S, Benjamin EJ, DeCarli C. Inflammatory biomarkers are associated with total brain volume: The Framingham Heart Study. *Neurology*. 2007; 68:1032–1038. [PubMed: 17389308]
86. Christensson AG, Grubb AO, Nilsson JA, Norrgren K, Sterner G, Sundkvist G. Serum cystatin C advantageous compared with serum creatinine in the detection of mild but not severe diabetic nephropathy. *J Intern Med*. 2004; 256:510–518. [PubMed: 15554952]
87. Odden MC, Tager IB, Gansevoort RT, Bakker SJ, Katz R, Fried LF, Newman AB, Canada RB, Harris T, Sarnak MJ, Siscovick D, Shlipak MG. Age and cystatin C in healthy adults: A collaborative study. *Nephrol Dial Transplant*. 2010; 25:463–469. [PubMed: 19749145]
88. Madero M, Wassel CL, Peralta CA, Najjar SS, Sutton-Tyrrell K, Fried L, Canada R, Newman A, Shlipak MG, Sarnak MJ. Cystatin C associates with arterial stiffness in older adults. *J Am Soc Nephrol*. 2009; 20:1086–1093. [PubMed: 19357259]
89. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman A, Siscovick DS, Stehman-Breen C. Cystatin C and the risk of death and cardiovascular events among elderly persons. *NEngl J Med*. 2005; 352:2049–2060.
90. Aguilar MI, O'Meara ES, Seliger S, Longstreth WT Jr, Hart RG, Pergola PE, Shlipak MG, Katz R, Sarnak MJ, Rifkin DE. Albuminuria and the risk of incident stroke and stroke types in older adults. *Neurology*. 2010; 75:1343–1350. [PubMed: 20810996]
91. Seliger SL, Longstreth WT Jr, Katz R, Manolio T, Fried LF, Shlipak M, Stehman-Breen CO, Newman A, Sarnak M, Gillen DL, Bleyer A, Siscovick DS. Cystatin C and subclinical brain infarction. *J Am Soc Nephrol*. 2005; 16:3721–3727. [PubMed: 16236809]
92. Shlipak MG, Katz R, Cushman M, Sarnak MJ, Stehman-Breen C, Psaty BM, Siscovick D, Tracy RP, Newman A, Fried L. Cystatin-C and inflammatory markers in the ambulatory elderly. *Am J Med*. 2005; 118:1416. [PubMed: 16378798]
93. Zethelius B, Berglund L, Sundstrom J, Ingelsson E, Basu S, Larsson A, Venge P, Arnlov J. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med*. 2008; 358:2107–2116. [PubMed: 18480203]
94. Rifkin DE, Shlipak MG, Katz R, Fried LF, Siscovick D, Chonchol M, Newman AB, Sarnak MJ. Rapid kidney function decline and mortality risk in older adults. *Arch Intern Med*. 2008; 168:2212–2218. [PubMed: 19001197]
95. Lopez OL, Kuller LH, Mehta PD, Becker JT, Gach HM, Sweet RA, Chang YF, Tracy R, DeKosky ST. Plasma amyloid levels and the risk of AD in normal subjects in the Cardiovascular Health Study. *Neurology*. 2008; 70:1664–1671. [PubMed: 18401021]
96. Kulstad JJ, Green PS, Cook DG, Watson GS, Reger MA, Baker LD, Plymate SR, Asthana S, Rhoads K, Mehta PD, Craft S. Differential modulation of plasma Beta-amyloid by insulin in patients with Alzheimer disease. *Neurology*. 2006; 66:1506–1510. [PubMed: 16717209]
97. Blasko I, Kemmler G, Krampla W, Jungwirth S, Wichart I, Jellinger KA, Tragl KH, Fischer P. Plasma amyloid Beta-protein 42 in non-demented persons aged 75 years: Effects of concomitant medication and medial temporal lobe atrophy. *Neurobiol Aging*. 2005; 26:1135–1143. [PubMed: 15917096]
98. Sundelof J, Arnlov J, Ingelsson E, Sundstrom J, Basu S, Zethelius B, Larsson A, Irizarry MC, Giedraitis V, Ronnema E, Degerman-Gunnarsson M, Hyman BT, Basun H, Kilander L, Lannfelt

- L. Serum cystatin C and the risk of Alzheimer disease in elderly men. *Neurology*. 2008; 71:1072–1079. [PubMed: 18824671]
99. Tizon B, Ribe EM, Mi W, Troy CM, Levy E. Cystatin C protects neuronal cells from amyloid-beta-induced toxicity. *J Alzheimers Dis*. 2010; 19:885–894. [PubMed: 20157244]
 100. Mares J, Kanovsky P, Herzig R, Stejskal D, Vavrouskova J, Hlustik P, Vranova H, Burval S, Zapletalova J, Pidrman V, Obereigner R, Suchy A, Vesely J, Podivinsky J, Urbanek K. The assessment of beta amyloid, tau protein and cystatin C in the cerebrospinal fluid: Laboratory markers of neurodegenerative diseases. *Neurol Sci*. 2009; 30:1–7. [PubMed: 19153649]
 101. Sundelof J, Sundstrom J, Hansson O, Eriksdotter-Jonhagen M, Giedraitis V, Larsson A, Degerman-Gunnarsson M, Ingelsson M, Minthon L, Blennow K, Kilander L, Basun H, Lannfelt L. Cystatin C levels are positively correlated with both Abeta42 and tau levels in cerebrospinal fluid in persons with Alzheimer's disease, mild cognitive impairment, and healthy controls. *J Alzheimers Dis*. 2010; 21:471–478. [PubMed: 20555147]
 102. Solomon A, Kareholt I, Ngandu T, Winblad B, Nissinen A, Tuomilehto J, Soininen H, Kivipelto M. Serum cholesterol changes after midlife and late-life cognition twenty-one-year follow-up study. *Neurology*. 2007; 68:351–356.
 103. Solomon A, Sippola R, Soininen H, Wolozin B, Tuomilehto J, Laatikainen T, Kivipelto M. Lipid-lowering treatment is related to decreased risk of dementia: A population-based study (FINRISK). *Neurodegener Dis*. 2010; 7:180–182. [PubMed: 20224281]
 104. Mielke MM, Zandi PP, Shao H, Waern M, Ostling S, Guo X, Bjorkelund C, Lissner L, Skoog I, Gustafson DR. The 32-year relationship between cholesterol and dementia from midlife to late life. *Neurology*. 2010; 75:1888–1895. [PubMed: 21068429]
 105. Rea TD, Breitner JC, Psaty BM, Fitzpatrick AL, Lopez OL, Newman AB, Hazzard WR, Zandi PP, Burke JL, Lyketsos CG, Bernick C, Kuller LH. Statins and the risk of incident dementia: The Cardiovascular Health Study. *Arch Neurol*. 2005; 62:1047–1051. [PubMed: 16009757]
 106. Reitz C, Tang MX, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. Association of higher levels of high-density lipoprotein cholesterol in elderly individuals and lower risk of late-onset Alzheimer disease. *Arch Neurol*. 2010; 67:1491–1497. [PubMed: 21149810]
 107. Mielke MM, Zandi PP, Sjogren M, Gustafson D, Ostling S, Steen B, Skoog I. High total cholesterol levels in late life associated with a reduced risk of dementia. *Neurology*. 2005; 64:1689–1695. [PubMed: 15911792]
 108. Trompet S, van Vliet P, de Craen AJ, Jolles J, Buckley BM, Murphy MB, Ford I, Macfarlane PW, Sattar N, Packard CJ, Stott DJ, Shepherd J, Bollen EL, Blauw GJ, Jukema JW, Westendorp RG. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. *J Neurol*. 2010; 257:85–90. [PubMed: 19653027]
 109. Hughes TM, Kuller LH, Lopez OL, Becker JT, Evans RW, Sutton-Tyrrell K, Rosano C. Markers of cholesterol metabolism in the brain show stronger associations with cerebrovascular disease than Alzheimer's disease. *J Alzheimers Dis*. 2012; 30:53–61. [PubMed: 22377780]
 110. Vance JE, Campenot RB, Vance DE. The synthesis and transport of lipids for axonal growth and nerve regeneration. *Biochim Biophys Acta*. 2000; 1486:84–96. [PubMed: 10856715]
 111. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD. High avidity binding to beta-amyloid and increase frequency of type 4 allele in late-onset familial Alzheimer's disease. *Proc Natl Acad Sci U S A*. 1993; 90:1977–1981. [PubMed: 8446617]
 112. Berent S, Giordani B, Foster N, Minoshima S, Lajiness-O'Neil R, Koeppe R, Kuhl DE. Neuropsychological function and cerebral glucose utilization in isolated memory impairment and Alzheimer's disease. *J Psychiatr Res*. 1999; 33:7–16. [PubMed: 10094234]
 113. De Santi S, de Leon MJ, Rusinek H, Convit A, Tarshish CY, Roche A, Tsui WH, Kandil E, Boppana M, Daisley K, Wang GJ, Schlyer D, Fowler J. Hippocampal formation, glucose metabolism, and volume losses in MCI and AD. *Neurobiol Aging*. 2001; 22:529–539. [PubMed: 11445252]
 114. Jagust WJ, Eberling JL, Wu CC, Finkbeiner A, Mungas D, Haan MN. Brain function and cognition in a community sample of elderly Latinos. *Neurology*. 2002; 59:378–383. [PubMed: 12177371]

115. Chetelat G, Desgranges B, de la Sayette V, Viader F, Eustache F, Baron J-C. Mild cognitive impairment. Can FDG-PET predict who is to rapidly convert to Alzheimer's disease? *Neurology*. 2003; 60:1374–1377. [PubMed: 12707450]
116. Drzezga A, Lautenschlager N, Siebner H, Riemenschneider M, Willoch F, Minoshima S, Schwaiger M, Kurz A. Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: A PET follow-up study. *Eur J Nucl Med Mol Imaging*. 2003; 30:1104–1113. [PubMed: 12764551]
117. Nestor PJ, Fryer TD, Smielewski P, Hodges JR. Limbic hypometabolism in Alzheimer's disease and mild cognitive impairment. *Ann Neurol*. 2003; 54:343–351. [PubMed: 12953266]
118. de Leon MJ, Golomb J, George AE, Convit A, Tarshish CY, McRae T, DeSanti S, Smith G, Ferris SH, Noz M, Rusinek H. The radiologic prediction of Alzheimer disease: The atrophic hippocampal formation. *AJNR*. 1993; 14:897–906. [PubMed: 8352162]
119. Soininen HS, Partanen K, Pitkanen A, Vainio P, Hanninen T, Hallikainen M, Koivisto K, Reikkinen PJ. Volumetric MRI analysis of the amygdala and the hippocampus in subjects with age-associated memory impairment: Correlation to visual and verbal memory. *Neurology*. 1994; 44:1660–1668. [PubMed: 7936293]
120. Du AT, Schuff N, Amend D, Laakso MP, Hsu YY, Jagust WJ, Yaffe K, Framer JH, Reed B, Norman D, Chui HC, Weiner MW. Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2001; 71:441–447. [PubMed: 11561025]
121. Jack CR, Petersen RC, Xu YC, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, Waring SC, Tangalos EG, Kokmen E. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology*. 1999; 52:1397–1403. [PubMed: 10227624]
122. Visser PJ, Scheltens P, Verhey FRJ, Schmand B, Launer LJ, Jolles J, Jonker C. Medial temporal lobe atrophy and memory dysfunction as predictors for dementia in subjects with mild cognitive impairment. *J Neurol*. 1999; 246:477–485. [PubMed: 10431775]
123. Pennanen C, Kivipelto M, Tuomainen S, Hartikainen P, Hanninen T, Laakso MP, Hallikainen V, Vanhanen M, Nissinen A, Helkala E-L, Vainio P, Vanninen R, Partanen K, Soininen H. Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. *Neurobiol Aging*. 2004; 25:303–310. [PubMed: 15123335]
124. Becker JT, Davis SA, Hayaski KM, Meltzer CC, Thompson PM, Lopez OL, Toga AW. Three-dimensional patterns of hippocampal atrophy in mild cognitive impairment. *Arch Neurol*. 2006; 63:97–101. [PubMed: 16401741]
125. Reiman EM, Caselli RJ, Yun LS, Chen K, Bandy D, Minoshima S, Thibodeau SN, Osborne D. Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *N Engl J Med*. 1996; 334:752–758. [PubMed: 8592548]
126. Caselli RJ, Chen K, Lee W, Alexander GE, Reiman EM. Correlating cerebral hypometabolism with future memory decline in subsequent converters to amnesic pre-mild cognitive impairment. *Arch Neurol*. 2008; 65:1231–1236. [PubMed: 18779428]
127. Small GW, LaRue A, Komo S, Kaplan A, Mandelkern MA. Predictors of cognitive change in middle-aged and older adults with memory loss. *Am J Psychiatry*. 1995; 152:1757–1764. [PubMed: 8526242]
128. Rosano R, Aizenstein HJ, Wu M, Newman A, Becker JT, Lopez OL, Kuller LH. Focal atrophy and cerebrovascular disease increase dementia risk among cognitively normal older adults. *J Neuroimaging*. 2007; 17:148–155. [PubMed: 17441836]
129. den Heijer T, Geerlings MJ, Hoebeek FE, Hofman A, Koudstaal PJ, Bereteler MB. Use of hippocampal and amygdalar volumes on magnetic resonance imaging to predict dementia in cognitively intact elderly people. *Arch Gen Psychiatry*. 2006; 63:57–62. [PubMed: 16389197]
130. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, Savitcheva MB, Huang I, Estrada GS. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol*. 2004; 55:306–319. [PubMed: 14991808]
131. Ikonomic MD, Klunk WE, Abrahamson EE, Mathis CA, Price JC, Tsopoulos ND, Lopresti BJ, Ziolko S, Bi W, Paljug WR, Debnath ML, Hope CE, Isanski BA, Hamilton RL, DeKosky ST.

- Post-mortem correlates of *in vivo* PiBPET amyloid imaging in a typical case of Alzheimer's disease. *Brain*. 2008; 131(Pt 6):1630–1645. [PubMed: 18339640]
132. Aizenstein HJ, Nebes RD, Saxton JA, Price J, Mathis CA, Tsopelas ND, Ziolk S, James JA, Snitz B, Houck PR, Bi W, Cohen AD, Lopresti BJ, DeKosky ST, Halligan EM, Klunk WE. Frequent amyloid deposition without significant cognitive impairment among the elderly. *Arch Neurol*. 2008; 65:1509–1517. [PubMed: 19001171]
 133. Becker JT, Mintun MA, Aleva K, Wiseman MB, Nichols T, DeKosky ST. Compensatory reallocation of brain resources supporting verbal episodic memory in Alzheimer's disease. *Neurology*. 1996; 46:692–700. [PubMed: 8618669]
 134. Herberster AN, Mintun MA, Nebes RD, Becker JT. Regional cerebral blood flow during word and nonword reading. *Hum Brain Mapp*. 1997; 5:84–92. [PubMed: 10096413]
 135. Dickerson BC, Salat DH, Greve DN, Chua EF, Rand-Giovanette E, Rentz DM, Bertram L, Mullin K, Tanzi RE, Blacker D, Albert MS, Sperling RA. Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology*. 2005; 65:405–411.
 136. Rosano C, Aizenstein HJ, Cochran J, Saxton J, Newman AB, Kuller LH, Lopez OL. Event-related fMRI investigation of executive control in very old individuals with mild cognitive impairment. *Biol Psychiatry*. 2005; 57:761–767. [PubMed: 15820233]
 137. Rosano C, Brach J, Studenski S, Longstreth WT Jr, Newman AB. Gait variability is associated with subclinical brain vascular abnormalities in high-functioning older adults. *Neuroepidemiology*. 2007; 29:193–200. [PubMed: 18043004]
 138. Rosano C, Aizenstein H, Cochran J, Saxton J, DeKosky S, Newman AB, Kuller LH, Lopez OL, Carter CS. Functional neuroimaging indicators of successful executive control in the oldest old. *NeuroImage*. 2005; 28:881–889. [PubMed: 16226041]
 139. Ho AJ, Raji CA, Becker JT, Lopez OL, Kuller LH, Hua X, Dinov ID, Stein JL, Rosano C, Toga AW, Thompson PM. The effects of physical activity, education, and body mass index on the aging brain. *Hum Brain Mapp*. 2011; 32:1371–1382. [PubMed: 20715081]
 140. Raji CA, Ho AJ, Parikshak NN, Becker JT, Lopez OL, Kuller LH, Hua X, Leow AD, Toga AW, Thompson PM. Brain structure and obesity. *Hum Brain Mapp*. 2010; 31:353–364. [PubMed: 19662657]
 141. Alsop DC, Casement M, de Bazelaire C, Fong T, Press DZ. Hippocampal hyperperfusion in Alzheimer's disease. *Neuroimage*. 2008; 42:1267–1274. [PubMed: 18602481]
 142. Dai W, Lopez OL, Carmichael OT, Becker JT, Kuller L, Gach HM. Mild Cognitive Impairment and Alzheimer disease: Patterns of altered cerebral blood flow at MR Imaging. *Radiology*. 2009; 250:856–866. [PubMed: 19164119]
 143. Luckhaus C, FluB MO, Wittsack H-J, Grass-Kapanake B, Janner M, Khalili-Amiri R, Friedrich W, Supprian T, Graebel W, Modder U, Cohnen M. Detection of changed regional cerebral blood flow in mild cognitive impairment and early Alzheimer's dementia by perfusion-weighted magnetic resonance imaging. *NeuroImage*. 2008; 40:495–503. [PubMed: 18207425]
 144. Cohen AD, Price JC, Weissfeld LA, James J, Rosario BL, Bi W, Nebes RD, Saxton JA, Snitz BE, Aizenstein HA, Wolk DA, Dekosky ST, Mathis CA, Klunk WE. Basal cerebral metabolism may modulate the cognitive effects of Abeta in mild cognitive impairment: An example of brain reserve. *J Neurosci*. 2009; 29:14770–14778. [PubMed: 19940172]
 145. Cutler JA, Sorlie PD, Wolz M, Thom T, Fields LE, Roccella EJ. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988–1994 and 1999–2004. *Hypertension*. 2008; 52:818–827. [PubMed: 18852389]
 146. Meisinger C, Doring A, Heier M. Blood pressure and risk of type 2 diabetes mellitus in men and women from the general population: The Monitoring Trends and Determinants on Cardiovascular Diseases/Cooperative Health Research in the Region of Augsburg Cohort Study. *J Hypertens*. 2008; 26:1809–1815. [PubMed: 18698216]
 147. Steinvil A, Shirom A, Melamed S, Toker S, Justo D, Saar N, Shapira I, Berliner S, Rogowski O. Relation of educational level to inflammation-sensitive biomarker level. *Am J Cardiol*. 2008; 102:1034–1039. [PubMed: 18929705]
 148. Del Ser T, Hachinski V, Merskey H, Munoz DG. An autopsy-verified study of the effect of education on degenerative dementia. *Brain*. 1999; 122(Pt 12):2309–2319. [PubMed: 10581224]

149. Bennett DA, Schneider JA, Wilson RS, Bienias JL, Arnold SE. Education modifies the association of amyloid but not tangles with cognitive function. *Neurology*. 2005; 65:953–955. [PubMed: 16186546]
150. Carmichael OT, Kuller LH, Lopez OL, Thompson PM, Dutton RA, Lee SE, Lee JY, Aizenstein HA, Meltzer CC, Liu Y, Toga A, Becker JT. Ventricular volume and dementia progression in the Cardiovascular Health Study. *Neurobiol Aging*. 2007; 28:389–397. [PubMed: 16504345]