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Vascular Risk Factors: Imaging and Neuropathologic Correlates

David S. Knopman, MD[a,b] and **Rosebud Roberts, MBBCh**[b,c]

[a] Department of Neurology, Mayo Clinic

[b] Mayo Clinic Alzheimer's Disease Research Center

[c] Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic

Abstract

Cerebrovascular disease plays an important role in cognitive disorders in the elderly. Cerebrovascular disease and Alzheimer's disease interact on several levels, one important level being the overlap in risk factors. The major vascular risk factors such as diabetes and impaired glycemic control, hypertension, obesity and hyper- or dyslipidemia have been associated both with Alzheimer's disease and vascular dementia. The purpose of this review is to consider the context in which vascular dementia is diagnosed, place the pathophysiological consequences of cerebrovascular disease on cognition in the context of clinical and pathological Alzheimer's disease, and then to consider the evidence for the role of major vascular risk factors in late-life cognitive impairment, changes in brain imaging and neuropathological changes. Midlife diabetes mellitus, hypertension and obesity are established risk factors for clinically defined Alzheimer's disease as well as vascular dementia. The basis for these relationships could either be that the risk factors lead to microvascular brain disease, promote Alzheimer pathology or both. The associations of late-life onset diabetes mellitus, hypertension and obesity with cognitive impairment are either attenuated or reversed. The role of vascular risk factors in midlife should be the focus of public health efforts to reduce the burden of late-life cognitive impairment.

Keywords

Vascular Risk Factors; stroke; dementia; vascular dementia; cognitive impairment; diabetes; hypertension; obesity; hyperlipidemia

Introduction

Stroke and cerebrovascular disease play important roles in late-life cognitive decline, but their relationship to Alzheimer's Disease (AD), the most commonly diagnosed etiology of late-life cognitive impairment and dementia, has been enigmatic. Up until recently, the pathophysiologies of the two conditions have been regarded as distinct. However, "vascular" risk factors have also been shown to be associated with AD, further blurring the distinction between cerebrovascular and Alzheimer-type clinical diagnoses. The purpose of this review is to first consider the context in which cognitive impairment of vascular origin is diagnosed, place it in the context of clinical and pathological AD, and then to consider the evidence for the role of major vascular risk factors in late-life cognitive (after age 65 years) impairment.

Correspondence to: Dr. DS Knopman, Department of Neurology, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 USA, Telephone 507 538 1038, Fax 507 538 6012, knopman@mayo.edu.

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This is an area of growing interest because treatment of vascular risk factors, already important in their own right, would gain increased urgency for prevention of late-life cognitive impairment.

Terminology

In order to avoid confusion, some conventions for terminology should be clarified. Clinical diagnoses and pathological diagnoses must have unique designations because of the lack of perfect correspondence between the two. Hereafter, whenever we refer to Alzheimer's disease, we will specify whether we mean clinically diagnosed dementia due to AD (AD*c) or pathologically-defined AD (AD*p) based on the presence of neuritic plaques and neurofibrillary tangles in isocortex. The term "vascular dementia" (VaD) will refer to a clinical diagnosis of dementia in which CVD is presumed to be the etiology, whereas cerebrovascular pathology (CVP) refers to the pathologically observed processes of infarction and ischemia. The combination and possible interactions of CVP and AD*p are ultimately of the most interest. The label "Alzheimer's disease with cerebrovascular disease" [1] captures the overlap between the two, but doesn't do it in a very artful way. This review will focus on these two etiologies of cognitive impairment and their combination.

Cerebrovascular disease causes cognitive impairment

Stroke is one of the most common neurological diseases of advancing age. Strokes cause cognitive and motor impairments both acutely and persistently. Survivors of stroke have a far higher rate of incident dementia than age-matched peers [2–5]. A history of stroke at any point in the past is a risk factor for the development of cognitive impairment [6,7], MCI [8] and dementia [9,10]. MR imaging in population-based cohorts of elderly individuals has shown that 20% or more have clinically silent infarcts [11]. The burden of imaging-detectable cerebral infarction is even larger than clinically overt stroke [10]. Prospective observational studies show that numbers of lacunar infarcts are associated with risk for future cognitive impairment and dementia [12,13]. There is evidence that the burden of macrovascular [14] as well as microvascular pathology independently accounts for cognitive impairment [15–17], even after taking AD*p into account.

Despite this wealth of observation, CVP as a cause of cognitive impairment may still be under-appreciated for several reasons. It has been very difficult – both in life with imaging and at autopsy neuropathologically – to quantitate the burden of CVP. There is no validated scheme for assigning different grades to CVP burden though progress is being made [16,18,19] in developing pathological ratings that reflect increasing burden of CVP pathology. Not only is there the problem of properly accounting for the role of small but strategically placed infarcts versus the total burden of ischemic pathology, but quantitating microscopic evidence of infarction is prohibitively labor-intensive and therefore, most neuropathological examinations use only qualitative estimates of CVP. There is a nagging concern that current neuropathological methods may tend to undercount ischemic lesions. Analyses that attempt clinical-pathological correlations with CVP, AD*p and their overlap are inherently more complex and require larger numbers of subjects than ones that look at AD*p alone.

Where vascular disease fits in the Alzheimer pathological cascade

To talk about CVP and dementia, it is necessary to put AD*p in perspective. While the focus of this review is to highlight why AD*p cannot be considered in isolation from CVP, AD*p is nonetheless a major neuropathologic process in late-life dementia [18,20]. The loss of neurons, synapses, dendrites, axons in heteromodal association isocortices is the proximate cause of cognitive impairment from AD*p [18]. Neurodegeneration in AD*p is closely linked to the formation of neurofibrillary tangles (NFT) in neurons in heteromodal isocortex [21].

Modulators of the AD*p neurodegenerative cascade that could have either genetic or environmental bases affect the rate of accumulation of brain pathology or the time when the pathological changes express themselves clinically.

CVP could modulate the appearance of cognitive impairment in conjunction with AD*p by one of several mechanisms. If a certain volume of cortical or subcortical grey matter undergoes infarction, there will be a reduction in intact brain volume, loss of synapses and reduced connectivity between remaining neurons, and hence brain reserve. An increasing burden of CVP would either accelerate the appearance of cognitive impairment or increase its severity at a particular level of AD*p. There is substantial evidence that as the burden of CVP increases, the abundance of AD*p will be less, for a given severity of dementia [14,17,22–24]. The interaction of CVP and AD*p might account for the generally lower burden of AD*p for a given level of cognitive impairment after age 75–80 yrs [18]. There appears to be no interactive effect on dementia severity between the burden of cerebral infarcts and the amount of AD*p [19,25]. Conceivably, microscopic CVP could accelerate the neurodegenerative process in the AD*p cascade, but there is no direct evidence that such an interactive mechanistic pathway exists.

Clinical-pathological Correlations

Postmortem studies of patients dying with dementia that have compared clinical diagnoses with neuropathological findings have shown that the clinical diagnosis of VaD is very insensitive for predicting CVP [26–28], and furthermore, AD*c is often associated with some degree of CVP [17,29]. Problems with the diagnosis of VaD raise questions about the validity of the diagnosis, particularly when neuroimaging is not available. The clinical mis-recognition of CVP pathology in dementia patients has major implications for understanding the role vascular risk factors in the epidemiology of dementia. The presence of CVP in AD*c means that epidemiological studies that claim to study observations on risk factors for AD*c are actually targeting a dementing illness that includes some element of CVP. In other words, when an epidemiological study asserts that a risk factor is “associated with AD,” that really means “associations with a dementing illness that mostly includes persons with AD*p and some amount of CVP.” Conversely, factors reported to be associated with VaD may not be as specific for a dementing illness due only to CVP. An “association with VaD” means that the associations are with persons who have a higher burden of CVP but probably have coexistent AD*p. Therefore, in the absence of information about underlying pathology, investigations of risk factors using epidemiologic methods are limited in their inferences about the underlying dementia etiology.

Vascular Risk Factors (VRF)

A number of mid-life risk factors that have been traditionally viewed as causing vascular disease including the components of the metabolic syndrome –diabetes and impaired glycemic control, hypertension, hyper- or dyslipidemia and obesity – are associated with an increased incidence of cognitive impairment and dementia. This review focusses on individual vascular risk factors and their impact on structural changes on imaging and neuropathology.

Diabetes Mellitus

Diabetes mellitus (DM) is a common condition from middle age and beyond. By age 65 about 20% of the population carries a diagnosis of DM, mainly type 2 diabetes [30,31]. DM affects the kidney, heart, peripheral nerves and retina, in addition to the brain.

Alterations in midlife glycemic control and DM almost certainly have greater consequences for cognitive function than late-onset DM presumably because of the longer duration of

exposure, although a more metabolically aggressive disease might also occur at younger ages. A metaanalysis [32] observed that the magnitude of risks for dementia were generally higher when DM was diagnosed at midlife versus later life.

The evidence linking DM to late-life cognitive impairment includes its associations with cognitive decline in middle age [6,33–37], cognitive decline in later life, mild cognitive impairment [38,39], AD*c [40–48] and VaD [40,49–51]. In general, associations have been stronger for VaD than for AD*c. Not all studies show an association between dementia and DM [52], however, perhaps because of the age when DM was ascertained.

The nature of the cognitive deficits associated with DM provides some clues as to DM's brain targets. DM is associated with impairment of both amnestic and non-amnestic cognitive functions, but the association with non-amnestic dysfunction has been shown to be of greater magnitude [38,39]. Less amnestic and greater non-amnestic cognitive dysfunction would be more consistent with involvement of white matter pathways, basal ganglia or thalamus, which in turn are loci expected to undergo infarction as a result of CVP.

DM is associated with structural brain changes that can be detected on imaging [53–57]. In a metaanalysis, the major changes on imaging associated with DM were brain atrophy, lacunar infarcts and to a less extent, white matter hyperintensities [58]. In the Atherosclerosis Risk in Communities (ARIC) study that included persons in late middle age (50–73 yr), there was a 4 to 7% increased risk of ventricular enlargement for each 10mg/dL of fasting blood sugar elevation [53]. In the Cardiovascular Health Study (CHS), DM was associated with brain atrophy only in women. The CHS population was 65 and older [59]. Perhaps the less consistent associations in the CHS are a result of the older age of the subjects.

Neuropathological studies of diabetics also show an increased number of brain microinfarcts and lacunar infarcts compared to non-diabetics [60–63]. Several studies have shown that diabetics with dementia have a lower burden of β-amyloid pathology [60–62].

DM could cause also brain injury through non-CVP mechanisms. Hyperglycemia and impaired control of insulin homeostasis might have a direct effect on brain β-amyloidosis [64–67]. Insulin degrading enzyme (IDE), an enzyme that is involved in insulin trafficking, is also a key enzyme that degrades β-amyloid. With increases in peripheral insulin levels in midlife in type 2 diabetics, brain insulin levels could be raised [68]. Insulin might compete with β-amyloid for binding to IDE; thus, elevated insulin levels would lead to decreased β-amyloid clearance, and raised β-amyloid levels in the brain.

Because most patients with DM are treated with either oral hypoglycemic agents or insulin, it may be very difficult to determine whether treatments alter clinical-pathological correlations in DM. Severity of DM is more likely to be associated with the use of insulin, whereas hyperglycemia that doesn't exceed 125 mg/dL might not be treated with medication at all. Since more severe DM will almost always be treated with insulin, the unique contributions of DM severity and insulin use to structural and neuropathological changes may not be resolvable. With insulin use, the impact of DM severity versus episodes of hypoglycemia must also be considered in evaluating dementia risk.

Based on imaging and neuropathological evidence, microvascular disease is a very strong candidate mechanism to account for the impact of DM on late-life cognitive impairment. DM as a microvascular disease could influence the course of AD*p by *decreasing* the threshold at which AD*p produces clinical effects, even if DM itself had no direct impact on AD*p-mediated neurodegeneration. If this were the case, then for a given level of cognitive impairment, persons with diabetes should have *less* AD*p, which in fact has been observed [60,61]. An alternative hypothesis is that the metabolic or ischemic injury caused by DM

facilitates β-amyloid pathology, tau pathology or both. In this alternative model, DM would be associated with *more* AD*p. The evidence so far does not support this latter model.

Hypertension

Hypertension (HT) affects a majority of middle-aged and elderly populations [30]. While there are various ways to represent abnormal BP such as history of hypertension, systolic BP, diastolic BP, pulse pressure or mean arterial pressure, most of the data we will cite simply used either history of hypertension, systolic BP or diastolic BP. HT is a well-known major risk factor for ischemic heart disease, peripheral vascular disease, chronic kidney disease and CVP, via both ischemic and hemorrhagic mechanisms. HT in midlife is associated with later life cognitive impairment and dementia [69–71]. Associations are generally stronger for VaD than AD*c [72–77].

Interpretation of the effects of HT in later life is confounded by the rising prevalence of *hypo*tension in late-life. In late-life both HT and hypotension may cause brain injury. Orthostatic hypotension becomes common with advancing age, and hypotension is also deleterious to the brain [78–80]. Even among normotensives, there may be an admixture of borderline hypertensives and hypotensives, making it quite difficult to identify the deleterious effects of HT in the very elderly. Several studies have failed to show an association of HT with poor cognition when assessed in late-life [78,79,81–84].

Different classes of antihypertensive medications have shown associations with lower rates of dementia in observational studies [85–87]. Similarly, clinical trials have demonstrated that treatment of persons with HT with several classes of antihypertensive medications reduces the incidence of dementia [88–91]. It is not clear which class or classes of antihypertensive provides the greatest protective effects for the brain. Duration of antihypertensive therapy also has an impact on associations of hypertension with dementia; especially in younger persons, those on antihypertensive therapies for longer periods of time had reduced rates of incident dementia [92]. Because therapy has an impact on blood pressure measurements themselves and also appears to impact cognitive function, naturalistic observations with either imaging or neuropathology are confounded by treatment.

In imaging studies involving both middle-aged and elderly persons, HT is more closely associated with white matter hyperintensities (WMH) than atrophy [53,54,93–99]. HT is the most consistent correlate of excess burden of WMH [97,99,100]. In the cross-sectional findings of the ARIC study, HT was not associated with increased ventricular volume, but there were strong associations with increasing burden of WMH [53]. In the longitudinal assessments of the ARIC cohort, systolic BP measured cumulatively over 14 years was strongly associated with progression of WMH. BP measurements from early years of follow-up showed stronger associations with WMH burden than later ones [101].

The effects of systolic versus diastolic BP on brain structure may differ. In elderly subjects (age 72 ± 7 yrs) from the Rotterdam Scan study, systolic blood pressure was not associated with brain atrophy. However, diastolic BP exhibited a J-shaped relationship to brain atrophy. Subjects with high and low diastolic BP had greater brain atrophy than subjects with diastolic BPs in the 65–74 mm Hg range. In addition, in a subset of subjects with BPs measured 20 years earlier, those with elevated diastolic BPs in midlife but who were not treated had greater brain atrophy than non-hypertensives. Subjects with elevated diastolic BP in midlife who were treated did not show any brain volume loss compared to non-hypertensives. Both elevated systolic and elevated diastolic BP were associated with WMH burden. The association between 20-year change in diastolic blood pressure and subcortical WMH was also J-shaped, indicating that both declines and elevations in BP over time were related to increasing burdens of WMH [102].

Several studies have found that midlife hypertension was associated with greater burdens of NFT and neuritic plaques in late life [103,104], but medication effects make interpretation complex. Neuropathological studies that have compared subjects with and without antihypertensive medications have shown that medicated patients had either less cognitive impairment or less AD pathology than the un-medicated hypertensive peers [104]. Persons receiving antihypertensive therapy had less AD*p than normotensives.

Despite the likelihood that the effects of HT on the brain are microvascular and are similar to that seen in other microvascular beds such as in the heart or kidney, the neuropathological evidence suggests that HT has direct effects on AD*p that are independent of infarction. These findings suggest that HT could alter β-amyloid or abnormal tau production or clearance. A final speculation is that of reverse causality: AD*p in brainstem structures [21] might promote HT.

Obesity

Rising levels of obesity across all age groups is a major public health issue. Obesity is usually defined by body mass index (BMI), but abdominal girth has been shown to have greater predictive ability for disease outcomes such as heart disease [105]. Obesity in midlife has been associated with later life cognitive impairment [106–108]. This association persists even when DM, HT and hyperlipidemia are included in the analytic models. The observation suggests that midlife obesity is associated with cognitive impairment in some ways that are unique from the other related risk factors. Similarly, obesity could promote microvascular disease by mechanisms that are distinct from DM and HT. Various circulating factors released by adipose tissue could play a role, perhaps by promoting inflammation. Increased fat mass, particularly visceral fat, elevates blood levels of inflammatory cytokines such as TNFα and IL6. Elevations of circulating levels of these factors could alter endothelial function, which in turn could lead to insulin resistance [109]. Leptin, a hormone released by adipose tissue, regulates lean body mass, complements insulin action in the peripheral circulation, decreases brain β secretase levels, and modulates β-amyloid turnover. In obesity, chronically elevated leptin levels result in leptin resistance and an inability to regulate weight. In the late-life, consistent with the decreased BMI that occurs prior to dementia, leptin levels decrease and are inversely associated with dementia [110]. Similarly, adiponectin, a complement related protein produced by adipose tissue, is a risk factor for coronary heart disease. The associations with dementia are yet to be determined.

Studies that have examined weight, body-mass index or other measures of adiposity in late-life have found either no association with dementia, or a protective effect [111–114]. Obesity may appear to be a protective factor for impaired cognitive function in late-life because of the competing effects of the associations of weight loss with illnesses such as cancer. Furthermore, some studies have shown that persons destined to develop dementia lose weight in the few years preceding the diagnosis. Persons with dementia are highly likely to be thinner than non-demented peers [111–114]. It is uncertain whether reverse causality could also be acting here, whereby subtle cognitive or behavioral changes that occurred prior to dementia altered dietary habits.

There were no significant associations between elevated BMI and structural brain changes in either ARIC [53] or an earlier analysis of the CHS [59] cohort. A more recent study of a smaller number of CHS participants (mean age = 77 yrs) observed reductions in grey matter volume in persons with high BMI (>30 kg/m^2), even after controlling for DM [115]. In younger persons there also is an association of obesity with reduced brain volume [116,117]. To our knowledge, there are no neuropathological studies that have assessed the role of midlife obesity on

neuropathology in late-life. Because late-life obesity appears to be protective for dementia, understanding the competing forces of midlife and late-life obesity may be very difficult.

Whether obesity plays an independent role in the genesis of dementia, AD*p or CVP, separate from DM and HT is not clear. Midlife obesity, to the extent that it promotes DM and HT, has adverse effects on the brain, regardless of whether these effects are direct or indirect.

Hyperlipidemia

The relationship between elevated lipid levels and dementia is uncertain, as many studies fail to show associations between elevated LDL cholesterol or triglycerides and dementia, cognitive impairment or abnormalities on brain imaging. A few studies have shown that midlife hypercholesterolemia was associated with later life MCI or dementia [77,118,119]. In contrast, the Framingham study failed to observe an association between midlife cholesterol levels and AD [120]. The ARIC study involving, mainly middle aged subjects, found that elevated LDL-C was not associated with cognitive impairment [6]. When lipid levels are measured in later life, the association is even more uncertain [121]. Elevated levels of total cholesterol were protective of dementia in late-life [122]. Low levels of cholesterol were associated with dementia [123,124], as well as a number of serious systemic diseases, in particular cancer and malnutrition, so that an admixture of persons with high and low cholesterol in epidemiological studies may obscure true associations between high cholesterol levels and dementia in late-life. Once again, processes that lower lipid levels and potential survival biases compete with hyperlipidemia and confound analyses.

Although hypercholesterolemia is a potent risk factor for cardiac disease, its impact on cerebrovascular disease has been inconsistent. In neither Northern Manhattan Study [125], ARIC [126] nor CHS [11] was there an association between HDL-C or LDL-C and either clinical strokes or infarctions on imaging. Why elevated cholesterol is not as strongly linked to cerebrovascular disease as it is to cardiovascular disease is a mystery that is beyond the scope of this essay.

Cholesterol or triglyceride level have not been associated with larger ventricular size or increased white matter hyperintensities in the ARIC cohort [53]. In the CHS cohort, high HDL and low LDL levels were associated with progression of WMH [98]. A few studies that investigated the relationship between lipid levels in late life and neuropathology have claimed associations between neuritic plaques and elevated HDL-C [127] or total cholesterol and LDL-C levels [128]. There are no studies of midlife lipid levels and neuropathology. Given the biphasic nature of the relationship between lipids and dementia, it may be midlife levels of HDL-C or LDL-C that are most relevant.

It is not clear at this point what specific role hyperlipidemia plays in the development of dementia, AD*p and CVP. Because of the multiple demonstrations of either neutral or protective effects of hyperlipidemia on cognition and brain structure, this risk factor does not offer many insights into the mechanisms of cognitive impairment.

VRF and socioeconomic status

Late-life dementia due to AD*p is strongly associated with educational attainment, occupation and socioeconomic status (SES) [129,130]. CVP and VRF are also moderately strongly associated with SES [131,132]. DM, HT, obesity, and heart disease itself are all more likely in persons of low educational attainment, the usual proxy for SES. Persons of lower SES are more likely to have a poor diet, to be overweight, to smoke, and to be sedentary, all of which contribute to higher burdens of VRF. Perhaps, VRFs are associated with cognitive impairment because they stand for an array of dysfunctional health behaviors that are more important than

the VRFs themselves. It seems likely that dysfunctional health behaviors in persons with lower education or lower SES promote DM, HT, and obesity. The description of the associations of low intelligence test scores in childhood with late-life VaD rather than AD*c [133] in a Scottish cohort suggests that the impact of low education and low SES on brain integrity might actually begin in childhood. It is possible that SES shares variance with brain reserve, and as a consequence different levels of brain reserve have an impact on the threshold for the appearance of dementia for a given level of AD*p or CVP.

Conclusions

VRFs, when present in midlife, exert a consistent deleterious effect on late-life cognition and dementia. For DM, HT and obesity parallel effects on subclinical infarction, cognition and brain structure support their distinct roles in the pathogenesis of late-life cognitive impairment. These disorders might either promote microvascular disease, AD*p or both. In contrast, while midlife hyperlipidemia may be associated with late-life cognitive impairment, hyperlipidemia does not seem to alter brain structure and is not clearly associated with an increased risk of stroke. The dissociation raises some doubts on how relevant hyperlipidemia is for cognitive impairment. In later life, the role of the VRFs is much more complex. For all four conditions when measured in late-life, their associations with cognitive impairment are either attenuated, neutral or reversed. The inverse of three of them – hypotension, low cholesterol and triglyceride levels and cachexia – are associated with serious systemic illnesses that worsen survival. The relationship of SES to VRF implies that the genesis of VRFs has its roots in childhood social class, education and culture.

The evidence from imaging studies suggests that treatment of VRFs in persons who already have late-life cognitive impairment may be too late to be curative, but there still could be lesser clinically important benefits. Treatment of VRFs in persons with both AD*c and VaD should be considered because of the etiological overlap of AD*p and CVP in both.

However, VRF can be treated in midlife, and that should be grounds for optimism. Public health initiatives to treat the VRFs in midlife are already well-justified on the grounds of preventing cardiovascular disease. Despite the cardiovascular imperatives, rates of effective treatment of DM, HT, obesity and hyperlipidemia are rather low [30,31]. Perhaps fear of cognitive impairment would spur more aggressive attempts to treat VRF in midlife.

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References

1. Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43:250–60. [PubMed: 8094895]
2. Henon H, Durieu I, Guerouaou D, Lebert F, Pasquier F, Leys D. Poststroke dementia: incidence and relationship to prestroke cognitive decline. Neurology 2001;57:1216–22. [PubMed: 11591838]
3. Kokmen E, Whisnant JP, O'Fallon WM, Chu CP, Beard CM. Dementia after ischemic stroke: a population-based study in Rochester, Minnesota (1960–1984). Neurology 1996;46:154–9. [PubMed: 8559366]
4. Pohjasvaara T, Mantyla R, Salonen O, Aronen HJ, Ylikoski R, Hietanen M, Kaste M, Erkinjuntti T. MRI correlates of dementia after first clinical ischemic stroke. J Neurol Sci 2000;181:111–7. [PubMed: 11099720]

5. Tatemichi TK, Desmond DW, Stern Y, Paik M, Sano M, Bagiella E. Cognitive impairment after stroke: frequency, patterns, and relationship to functional abilities. J Neurol Neurosurg Psychiatry 1994;57:202–7. [PubMed: 8126506]
6. Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, McGovern P, Folsom AR. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001;56:42–48. [PubMed: 11148234]
7. 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;29:388–98. [PubMed: 9472879]
8. Knopman DS, Roberts RO, Geda YE, Boeve BF, Pankratz VS, Cha RH, Tangalos EG, Ivnik RJ, Petersen RC. Association of prior stroke with cognitive function and cognitive impairment: A population-based study. Arch Neurol 2009;66:614–19. [PubMed: 19433661]
9. Reitz C, Luchsinger JA, Tang MX, Manly J, Mayeux R. Stroke and memory performance in elderly persons without dementia. Arch Neurol 2006;63:571–6. [PubMed: 16606771]
10. Kuller LH, Lopez OL, Jagust WJ, Becker JT, Dekosky ST, Lyketsos C, Kawas C, Breitner JC, Fitzpatrick A, Dulberg C. Determinants of vascular dementia in the Cardiovascular Health Cognition Study. Neurology 2005;64:1548–52. [PubMed: 15883315]
11. Longstreth WT Jr, Bernick C, Manolio TA, Bryan N, Jungreis CA, Price TR. Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. Arch Neurol 1998;55:1217–25. [PubMed: 9740116]
12. Longstreth WT Jr, Dulberg C, Manolio TA, Lewis MR, Beauchamp NJ Jr, O'Leary D, Carr J, Furberg CD. Incidence, manifestations, and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. Stroke 2002;33:2376–82. [PubMed: 12364724]
13. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348:1215–22. [PubMed: 12660385]
14. 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;64:168–76. [PubMed: 18496870]
15. Giannakopoulos P, Gold G, Kovari E, von Gunten A, Imhof A, Bouras C, Hof PR. Assessing the cognitive impact of Alzheimer disease pathology and vascular burden in the aging brain: the Geneva experience. Acta Neuropathol 2007;113:1–12. [PubMed: 17036244]
16. White L, Petrovitch H, Hardman J, Nelson J, Davis DG, Ross GW, Masaki K, Launer L, Markesbery WR. Cerebrovascular pathology and dementia in autopsied Honolulu-Asia Aging Study participants. Ann N Y Acad Sci 2002;977:9–23. [PubMed: 12480729]
17. Schneider JA, Boyle PA, Arvanitakis Z, Bienias JL, Bennett DA. Subcortical infarcts, Alzheimer's disease pathology, and memory function in older persons. Ann Neurol 2007;62:59–66. [PubMed: 17503514]
18. Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C. Age, neuropathology, and dementia. N Engl J Med 2009;360:2302–9. [PubMed: 19474427]
19. Chui HC, Zarow C, Mack WJ, Ellis WG, Zheng L, Jagust WJ, Mungas D, Reed BR, Kramer JH, Decarli CC, Weiner MW, Vinters HV. Cognitive impact of subcortical vascular and Alzheimer's disease pathology. Ann Neurol 2006;60:677–87. [PubMed: 17192928]
20. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007;69:2197–204. [PubMed: 17568013]
21. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol (Berl) 1991;82:239–59. [PubMed: 1759558]
22. Nagy Z, Esiri MM, Jobst KA, Morris JH, King EM, McDonald B, Joachim C, Litchfield S, Barnetson L, Smith AD. The effects of additional pathology on the cognitive deficit in Alzheimer disease. J Neuropathol Exp Neurol 1997;56:165–70. [PubMed: 9034370]

23. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA 1997;277:813–7. [PubMed: 9052711]
24. Heyman A, Fillenbaum GG, Welsh-Bohmer KA, Gearing M, Mirra SS, Mohs RC, Peterson BL, Pieper CF. Cerebral infarcts in patients with autopsy-proven Alzheimer's disease: CERAD, part XVIII. Consortium to Establish a Registry for Alzheimer's Disease. Neurology 1998;51:159–62. [PubMed: 9674796]
25. Schneider JA, Wilson RS, Bienias JL, Evans DA, Bennett DA. Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology. Neurology 2004;62:1148–55. [PubMed: 15079015]
26. Wetterling T, Kanitz RD, Borgis KJ. Comparison of different diagnostic criteria for vascular dementia (ADDTC, DSM-IV, ICD-10, NINDS-AIREN). Stroke 1996;27:30–6. [PubMed: 8553399]
27. Pohjasvaara T, Mantyla R, Ylikoski R, Kaste M, Erkinjuntti T. Comparison of different clinical criteria (DSM-III, ADDTC, ICD-10, NINDS-AIREN, DSM-IV) for the diagnosis of vascular dementia. Stroke 2000;31:2952–7. [PubMed: 11108755]
28. Gold G, Giannakopoulos P, Montes-Paixao C Jr, Herrmann FR, Mulligan R, Michel JP, Bouras C. Sensitivity and specificity of newly proposed clinical criteria for possible vascular dementia. Neurology 1997;49:690–4. [PubMed: 9305324]
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;62:406–13. [PubMed: 17879383]
30. Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. JAMA 2005;294:466–72. [PubMed: 16046653]
31. Molenaar EA, Hwang SJ, Vasan RS, Grobbee DE, Meigs JB, D'Agostino RB Sr, Levy D, Fox CS. Burden and rates of treatment and control of cardiovascular disease risk factors in obesity: the Framingham Heart Study. Diabetes Care 2008;31:1367–72. [PubMed: 18375414]
32. Kloppenborg RP, van den Berg E, Kappelle LJ, Biessels GJ. Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. Eur J Pharmacol 2008;585:97–108. [PubMed: 18395201]
33. Haan MN, Shemanski L, Jagust WJ, Manolio TA, Kuller L. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. JAMA 1999;282:40–6. [PubMed: 10404910]
34. Elias PK, Elias MF, D'Agostino RB, Cupples LA, Wilson PW, Silbershatz H, Wolf PA. NIDDM and blood pressure as risk factors for poor cognitive performance. The Framingham Study. Diabetes Care 1997;20:1388–95. [PubMed: 9283785]
35. Kalmijn S, Feskens EJ, Launer LJ, Stijnen T, Kromhout D. Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. Diabetologia 1995;38:1096–102. [PubMed: 8591825]
36. Yaffe K, Blackwell T, Kanaya AM, Davidowitz N, Barrett-Connor E, Krueger K. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. Neurology 2004;63:658–63. [PubMed: 15326238]
37. Saczynski JS, Jonsdottir MK, Garcia ME, Jonsson PV, Peila R, Eiriksdottir G, Olafsdottir E, Harris TB, Gudnason V, Launer LJ. Cognitive impairment: an increasingly important complication of type 2 diabetes: the age, gene/environment susceptibility--Reykjavik study. Am J Epidemiol 2008;168:1132–9. [PubMed: 18836152]
38. Roberts RO, Geda YE, Knopman DS, Christianson TJ, Pankratz VS, Boeve BF, Vella A, Rocca WA, Petersen RC. Association of duration and severity of diabetes mellitus with mild cognitive impairment. Arch Neurol 2008;65:1066–73. [PubMed: 18695056]
39. Luchsinger JA, Reitz C, Patel B, Tang MX, Manly JJ, Mayeux R. Relation of diabetes to mild cognitive impairment. Arch Neurol 2007;64:570–5. [PubMed: 17420320]
40. Ott A, Stolk RP, Hofman A, van Harskamp F, Grobbee DE, Breteler MM. Association of diabetes mellitus and dementia: the Rotterdam Study. Diabetologia 1996;39:1392–7. [PubMed: 8933010]
41. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology 1999;53:1937–42. [PubMed: 10599761]

42. Luchsinger JA, Tang MX, Shea S, Mayeux R. Hyperinsulinemia and risk of Alzheimer disease. Neurology 2004;63:1187–92. [PubMed: 15477536]
43. 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;154:635–41. [PubMed: 11581097]
44. Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. Arch Neurol 2004;61:661–6. [PubMed: 15148141]
45. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. Diabetes 2002;51:1256–62. [PubMed: 11916953]
46. Peila R, Rodriguez BL, White LR, Launer LJ. Fasting insulin and incident dementia in an elderly population of Japanese-American men. Neurology 2004;63:228–33. [PubMed: 15277613]
47. 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;63:1181–6. [PubMed: 15477535]
48. Schnaider Beeri M, Goldbourt U, Silverman JM, Noy S, Schmeidler J, Ravona-Springer R, Sverdlick A, Davidson M. Diabetes mellitus in midlife and the risk of dementia three decades later. Neurology 2004;63:1902–7. [PubMed: 15557509]
49. Curb JD, Rodriguez BL, Abbott RD, Petrovitch H, Ross GW, Masaki KH, Foley D, Blanchette PL, Harris T, Chen R, White LR. Longitudinal association of vascular and Alzheimer's dementias, diabetes, and glucose tolerance. Neurology 1999;52:971–5. [PubMed: 10102414]
50. 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;145:301–8. [PubMed: 9054233]
51. MacKnight C, Rockwood K, Awalt E, McDowell I. Diabetes mellitus and the risk of dementia, Alzheimer's disease and vascular cognitive impairment in the Canadian Study of Health and Aging. Dement Geriatr Cogn Disord 2002;14:77–83. [PubMed: 12145454]
52. Akomolafe A, Beiser A, Meigs JB, Au R, Green RC, Farrer LA, Wolf PA, Seshadri S. Diabetes mellitus and risk of developing Alzheimer disease: results from the Framingham study. Arch Neurol 2006;63:1551–5. [PubMed: 17101823]
53. Knopman DS, Mosley TH, Catellier DJ, Sharrett AR. Cardiovascular risk factors and cerebral atrophy in a middle-aged cohort. Neurology 2005;65:876–81. [PubMed: 16186527]
54. Knopman DS, Mosley TH Jr, Bailey KR, Jack CR Jr, Schwartz GL, Turner ST. Associations of microalbuminuria with brain atrophy and white matter hyperintensities in hypertensive sibships. J Neurol Sci 2008;271:53–60. [PubMed: 18442832]
55. 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;64:1704–11. [PubMed: 15911795]
56. Schmidt R, Launer LJ, Nilsson LG, Pajak A, Sans S, Berger K, Breteler MM, De Ridder M, Dufouil C, Fuhrer R, Giampaoli S, Hofman A. Magnetic Resonance Imaging of the Brain in Diabetes: The Cardiovascular Determinants of Dementia (CASCADE) Study. Diabetes 2004;53:687–692. [PubMed: 14988253]
57. den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, Hofman A, Breteler MM. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. Diabetologia 2003;46:1604–10. [PubMed: 14595538]
58. van Harten B, de Leeuw FE, Weinstein HC, Scheltens P, Biessels GJ. Brain imaging in patients with diabetes: a systematic review. Diabetes Care 2006;29:2539–48. [PubMed: 17065699]
59. Longstreth WT Jr, Arnold AM, Manolio TA, Burke GL, Bryan N, Jungreis CA, O'Leary D, Enright PL, Fried L. Clinical correlates of ventricular and sulcal size on cranial magnetic resonance imaging of 3,301 elderly people. The Cardiovascular Health Study. Collaborative Research Group. Neuroepidemiology 2000;19:30–42. [PubMed: 10654286]
60. 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;66:315–22. [PubMed: 19139294]

61. 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;60:471–5. [PubMed: 15933386]
62. Arvanitakis Z, Schneider JA, Wilson RS, Li Y, Arnold SE, Wang Z, Bennett DA. Diabetes is related to cerebral infarction but not to AD pathology in older persons. Neurology 2006;67:1960–5. [PubMed: 17159101]
63. Korf ES, White LR, Scheltens P, Launer LJ. Brain aging in very old men with type 2 diabetes: the Honolulu-Asia Aging Study. Diabetes Care 2006;29:2268–74. [PubMed: 17003305]
64. Craft S. Insulin resistance syndrome and Alzheimer's disease: age- and obesity-related effects on memory, amyloid, and inflammation. Neurobiol Aging 2005;26(Suppl 1):65–9. [PubMed: 16266773]
65. Craft S, Peskind E, Schwartz MW, Schellenberg GD, Raskind M, Porte D Jr. Cerebrospinal fluid and plasma insulin levels in Alzheimer's disease: relationship to severity of dementia and apolipoprotein E genotype. Neurology 1998;50:164–8. [PubMed: 9443474]
66. Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol 2004;3:169–78. [PubMed: 14980532]
67. Ronnemaa E, Zethelius B, Sundelof J, Sundstrom J, Degerman-Gunnarsson M, Berne C, Lannfelt L, Kilander L. Impaired insulin secretion increases the risk of Alzheimer disease. Neurology 2008;71:1065–71. [PubMed: 18401020]
68. Watson GS, Peskind ER, Asthana S, Purganan K, Wait C, Chapman D, Schwartz MW, Plymate S, Craft S. Insulin increases CSF Abeta42 levels in normal older adults. Neurology 2003;60:1899–1903. [PubMed: 12821730]
69. Elias MF, Wolf PA, D'Agostino RB, Cobb J, White LR. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. Am J Epidemiol 1993;138:353–64. [PubMed: 8213741]
70. Carmelli D, Swan GE, Reed T, Miller B, Wolf PA, Jarvik GP, Schellenberg GD. Midlife cardiovascular risk factors, ApoE, and cognitive decline in elderly male twins. Neurology 1998;50:1580–5. [PubMed: 9633697]
71. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. JAMA 1995;274:1846–51. [PubMed: 7500533]
72. Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. Neurology 2005;65:545–51. [PubMed: 16116114]
73. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 2005;64:277–81. [PubMed: 15668425]
74. Hebert R, Lindsay J, Verreault R, Rockwood K, Hill G, Dubois MF. Vascular dementia : incidence and risk factors in the Canadian study of health and aging. Stroke 2000;31:1487–93. [PubMed: 10884442]
75. Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, Persson G, Oden A, Svanborg A. 15-year longitudinal study of blood pressure and dementia. Lancet 1996;347:1141–5. [PubMed: 8609748]
76. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kareholt I, Winblad B, Helkala EL, Tuomilehto J, Soininen H, Nissinen A. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol 2005;62:1556–60. [PubMed: 16216938]
77. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ 2001;322:1447–51. [PubMed: 11408299]
78. Guo Z, Viitanen M, Winblad B, Fratiglioni L. Low blood pressure and incidence of dementia in a very old sample: dependent on initial cognition. J Am Geriatr Soc 1999;47:723–6. [PubMed: 10366174]
79. Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ. Low blood pressure and the risk of dementia in very old individuals. Neurology 2003;61:1667–72. [PubMed: 14694027]

80. Ruitenberg A, Skoog I, Ott A, Aevarsson O, Witteman JC, Lernfelt B, van Harskamp F, Hofman A, Breteler MM. Blood pressure and risk of dementia: results from the Rotterdam study and the Gothenburg H-70 Study. Dement Geriatr Cogn Disord 2001;12:33–9. [PubMed: 11125239]
81. Johnson KC, Margolis KL, Espeland MA, Colenda CC, Fillit H, Manson JE, Masaki KH, Mouton CP, Prineas R, Robinson JG, Wassertheil-Smoller S. A prospective study of the effect of hypertension and baseline blood pressure on cognitive decline and dementia in postmenopausal women: the Women's Health Initiative Memory Study. J Am Geriatr Soc 2008;56:1449–58. [PubMed: 18637980]
82. Posner HB, Tang MX, Luchsinger J, Lantigua R, Stern Y, Mayeux R. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. Neurology 2002;58:1175–81. [PubMed: 11971083]
83. Obisesan TO, Obisesan OA, Martins S, Alamgir L, Bond V, Maxwell C, Gillum RF. High blood pressure, hypertension, and high pulse pressure are associated with poorer cognitive function in persons aged 60 and older: the Third National Health and Nutrition Examination Survey. J Am Geriatr Soc 2008;56:501–9. [PubMed: 18179496]
84. Morris MC, Scherr PA, Hebert LE, Glynn RJ, Bennett DA, Evans DA. Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study. Arch Neurol 2001;58:1640–6. [PubMed: 11594923]
85. in't Veld BA, Ruitenberg A, Hofman A, Stricker BH, Breteler MM. Antihypertensive drugs and incidence of dementia: the Rotterdam Study. Neurobiol Aging 2001;22:407–12. [PubMed: 11378246]
86. Guo Z, Fratiglioni L, Zhu L, Fastbom J, Winblad B, Viitanen M. Occurrence and progression of dementia in a community population aged 75 years and older: relationship of antihypertensive medication use. Arch Neurol 1999;56:991–6. [PubMed: 10448805]
87. Khachaturian AS, Zandi PP, Lyketsos CG, Hayden KM, Skoog I, Norton MC, Tschanz JT, Mayer LS, Welsh-Bohmer KA, Breitner JC. Antihypertensive medication use and incident Alzheimer disease: the Cache County Study. Arch Neurol 2006;63:686–92. [PubMed: 16533956]
88. Hanon O, Forette F. Treatment of hypertension and prevention of dementia. Alzheimer's & Dementia: Journal of the Alzheimer's Association 2005;1:30–7.
89. Forette F, Seux ML, Staessen JA, Thijs L, Birkenhager WH, Babarskiene MR, Babeanu S, Bossini A, Gil-Extremera B, Girerd X, Laks T, Lilov E, Moisseyev V, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Fagard R. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998;352:1347–51. [PubMed: 9802273]
90. Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, Chalmers J. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med 2003;163:1069–75. [PubMed: 12742805]
91. Bosch J, Yusuf S, Pogue J, Sleight P, Lonn E, Rangoonwala B, Davies R, Ostergren J, Probstfield J. Use of ramipril in preventing stroke: double blind randomised trial. BMJ 2002;324:699–702. [PubMed: 11909785]
92. Haag MDM, Hofman A, Koudstaal PJ, Breteler MM, Stricker BH. Duration of antihypertensive drug use and risk of dementia, a prospective cohort study. Neurology 2009;72:1727–34. [PubMed: 19228584]
93. Veldink JH, Scheltens P, Jonker C, Launer LJ. Progression of cerebral white matter hyperintensities on MRI is related to diastolic blood pressure. Neurology 1998;51:319–20. [PubMed: 9674838]
94. DeCarli C, Murphy DG, Tranh M, Grady CL, Haxby JV, Gillette JA, Salerno JA, Gonzales-Aviles A, Horwitz B, Rapoport SI, et al. The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults. Neurology 1995;45:2077–84. [PubMed: 7501162]
95. Swan GE, DeCarli C, Miller BL, Reed T, Wolf PA, Jack LM, Carmelli D. Association of midlife blood pressure to late-life cognitive decline and brain morphology. Neurology 1998;51:986–93. [PubMed: 9781518]
96. Dufouil C, de Kersaint-Gilly A, Besancon V, Levy C, Auffray E, Brunnereau L, Alperovitch A, Tzourio C. Longitudinal study of blood pressure and white matter hyperintensities: The EVA MRI Cohort. Neurology 2001;56:921–6. [PubMed: 11294930]

97. van Dijk EJ, Breteler MM, Schmidt R, Berger K, Nilsson LG, Oudkerk M, Pajak A, Sans S, de Ridder M, Dufouil C, Fuhrer R, Giampaoli S, Launer LJ, Hofman A. The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study. Hypertension 2004;44:625–30. [PubMed: 15466662]

98. Longstreth WT Jr, Arnold AM, Beauchamp NJ Jr, Manolio TA, Lefkowitz D, Jungreis C, Hirsch CH, O'Leary DH, Furberg CD. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. Stroke 2005;36:56–61. [PubMed: 15569873]

99. Liao D, Cooper L, Cai J, Toole J, Bryan N, Burke G, Shahar E, Nieto J, Mosley T, Heiss G. The prevalence and severity of white matter lesions, their relationship with age, ethnicity, gender, and cardiovascular disease risk factors: the ARIC Study. Neuroepidemiology 1997;16:149–62. [PubMed: 9159770]

100. Longstreth WT Jr, 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. The Cardiovascular Health Study. Stroke 1996;27:1274–82. [PubMed: 8711786]

101. Gottesman RF, Coresh J, Catellier DJ, Sharrett AR, Rose KM, Coker LH, Shibata DK, Knopman DS, Jack CR, Mosley TH. Blood pressure and white matter disease progression in a biethnic cohort: the Atherosclerosis Risk in Communities (ARIC) Study. Stroke 2010;41:3–8. [PubMed: 19926835]

102. de Leeuw FE, de Groot JC, Oudkerk M, Witteman JC, Hofman A, van Gijn J, Breteler MM. A follow-up study of blood pressure and cerebral white matter lesions. Ann Neurol 1999;46:827–33. [PubMed: 10589534]

103. Petrovitch H, White LR, Izmirilian G, Ross GW, Havlik RJ, Markesbery W, Nelson J, Davis DG, Hardman J, Foley DJ, Launer LJ. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia aging Study. Neurobiol Aging 2000;21:57–62. [PubMed: 10794849]

104. Hoffman LB, Schmeidler J, Lesser GT, Beeri MS, Purohit DP, Grossman HT, Haroutunian V. Less Alzheimer disease neuropathology in medicated hypertensive than nonhypertensive persons. Neurology 2009;72:1720–6. [PubMed: 19228583]

105. Kannel WB, Cupples LA, Ramaswami R, Stokes J 3rd, Kreger BE, Higgins M. Regional obesity and risk of cardiovascular disease; the Framingham Study. J Clin Epidemiol 1991;44:183–90. [PubMed: 1995775]

106. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. Neurology 2008;71:1057–64. [PubMed: 18367704]

107. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ 2005;330:1360–4. [PubMed: 15863436]

108. Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I. An 18-year follow-up of overweight and risk of Alzheimer disease. Arch Intern Med 2003;163:1524–8. [PubMed: 12860573]

109. Meigs JB, Hu FB, Rifai N, Manson JE. Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. JAMA 2004;291:1978–86. [PubMed: 15113816]

110. Tezapsidis N, Johnston JM, Smith MA, Ashford JW, Casadesus G, Robakis NK, Wolozin B, Perry G, Zhu X, Greco SJ, Sarkar S. Leptin: a novel therapeutic strategy for Alzheimer's disease. J Alzheimers Dis 2009;16:731–40. [PubMed: 19387109]

111. Knopman DS, Edland SD, Cha RH, Petersen RC, Rocca WA. Incident dementia in women is preceded by weight loss by at least a decade. Neurology 2007;69:739–46. [PubMed: 17709705]

112. Buchman AS, Wilson RS, Bienias JL, Shah RC, Evans DA, Bennett DA. Change in body mass index and risk of incident Alzheimer disease. Neurology 2005;65:892–7. [PubMed: 16186530]

113. Stewart R, Masaki K, Xue QL, Peila R, Petrovitch H, White LR, Launer LJ. A 32-year prospective study of change in body weight and incident dementia: the honolulu-Asia aging study. Arch Neurol 2005;62:55–60. [PubMed: 15642850]

114. Nourhashemi F, Deschamps V, Larrieu S, Letenneur L, Dartigues JF, Barberger-Gateau P. Body mass index and incidence of dementia: the PAQUID study. Neurology 2003;60:117–9. [PubMed: 12525731]
115. 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. 2009 epub ahead of print.
116. Taki Y, Kinomura S, Sato K, Inoue K, Goto R, Okada K, Uchida S, Kawashima R, Fukuda H. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. Obesity (Silver Spring) 2008;16:119–24. [PubMed: 18223623]
117. Pannacciulli N, Del Parigi A, Chen K, Le DS, Reiman EM, Tataranni PA. Brain abnormalities in human obesity: a voxel-based morphometric study. Neuroimage 2006;31:1419–25. [PubMed: 16545583]
118. Kivipelto M, Helkala EL, Hanninen T, Laakso MP, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. Neurology 2001;56:1683–9. [PubMed: 11425934]
119. Dufouil C, Richard F, Fievet N, Dartigues JF, Ritchie K, Tzourio C, Amouyel P, Alperovitch A. APOE genotype, cholesterol level, lipid-lowering treatment, and dementia: The Three-City Study. Neurology 2005;64:1531–8. [PubMed: 15883313]
120. Tan ZS, Seshadri S, Beiser A, Wilson PW, Kiel DP, Tocco M, D'Agostino RB, Wolf PA. Plasma total cholesterol level as a risk factor for Alzheimer disease: the Framingham Study. Arch Intern Med 2003;163:1053–7. [PubMed: 12742802]
121. Li G, Shofer JB, Kukull WA, Peskind ER, Tsuang DW, Breitner JC, McCormick W, Bowen JD, Teri L, Schellenberg GD, Larson EB. Serum cholesterol and risk of Alzheimer disease: a community-based cohort study. Neurology 2005;65:1045–50. [PubMed: 16217057]
122. 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;64:1689–95. [PubMed: 15911792]
123. 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;68:751–6. [PubMed: 17339582]
124. Romas SN, Tang MX, Berglund L, Mayeux R. APOE genotype, plasma lipids, lipoproteins, and AD in community elderly. Neurology 1999;53:517–21. [PubMed: 10449113]
125. Willey JZ, Xu Q, Boden-Albala B, Paik MC, Moon YP, Sacco RL, Elkind MS. Lipid profile components and risk of ischemic stroke: the Northern Manhattan Study (NOMAS). Arch Neurol 2009;66:1400–6. [PubMed: 19901173]
126. Chambless LE, Shahar E, Sharrett AR, Heiss G, Wijnberg L, Paton CC, Sorlie P, Toole JF. Association of transient ischemic attack/stroke symptoms assessed by standardized questionnaire and algorithm with cerebrovascular risk factors and carotid artery wall thickness. The ARIC Study, 1987–1989. Am J Epidemiol 1996;144:857–66. [PubMed: 8890664]
127. Launer LJ, White LR, Petrovitch H, Ross GW, Curb JD. Cholesterol and neuropathologic markers of AD: a population-based autopsy study. Neurology 2001;57:1447–52. [PubMed: 11673587]
128. Lesser GT, Haroutunian V, Purohit DP, Schnaider Beeri M, Schmeidler J, Honkanen L, Neufeld R, Libow LS. Serum lipids are related to Alzheimer's pathology in nursing home residents. Dement Geriatr Cogn Disord 2009;27:42–9. [PubMed: 19129700]
129. Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. JAMA 1994;271:1004–10. [PubMed: 8139057]
130. Evans DA, Hebert LE, Beckett LA, Scherr PA, Albert MS, Chown MJ, Pilgrim DM, Taylor JO. Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons. Arch Neurol 1997;54:1399–405. [PubMed: 9362989]
131. Avendano M, Kawachi I, Van Lenthe F, Boshuizen HC, Mackenbach JP, Van den Bos GA, Fay ME, Berkman LF. Socioeconomic status and stroke incidence in the US elderly: the role of risk factors in the EPESE study. Stroke 2006;37:1368–73. [PubMed: 16690902]

132. Kanjilal S, Gregg EW, Cheng YJ, Zhang P, Nelson DE, Mensah G, Beckles GL. Socioeconomic status and trends in disparities in 4 major risk factors for cardiovascular disease among US adults, 1971–2002. Arch Intern Med 2006;166:2348–55. [PubMed: 17130388]

133. McGurn B, Deary IJ, Starr JM. Childhood cognitive ability and risk of late-onset Alzheimer and vascular dementia. Neurology 2008;71:1051–6. [PubMed: 18579804]