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Preventing vascular effects on brain injury and cognition late in life: knowns and unknowns

Owen Carmichael

Neurology Department, University of California, Davis, Center For Neuroscience, 1544 Newton Court, Davis CA 95618-4859. USA

Owen Carmichael: ocarmichael@ucdavis.edu

Abstract

For some researchers, the relationship between prevalent cardiovascular risk factors and late-life cognitive decline is not worthy of further study. It is already known that effective treatment of vascular risk factors lowers risk of such major outcomes as stroke and heart attack, the argument goes; thus, any new information about the relationship between vascular risk factors and another major outcome - late-life cognitive decline-- is unlikely to have an impact on clinical practice. The purpose of this review is to probe the logic of this argument by focusing on what is known, and what is not known, about the relationship between vascular risk factors and late-life cognitive decline. The unknowns are substantial: in particular, there is relatively little evidence that current vascular risk factor treatment protocols are adequate to prevent late-life cognitive decline or the clinically silent brain injury that precedes it. In addition, there is relatively little understanding of which factors lead to differential vulnerability or resilience to the effects of vascular risk factors on silent brain injury. Differential effects of different classes of treatments are similarly unclear. Finally, there is limited understanding of the impact of clinically-silent neurodegenerative disease processes on cerebrovascular processes. Further study of the relationships among vascular risk factors, brain injury, and late-life cognitive decline could have a major impact on development of new vascular therapies and on clinical management of vascular risk factors, and there are promising avenues for future research in this direction.

2 Introduction

Vascular risk factors including hypertension (HTN), diabetes mellitus type II (DM) and hyperlipidemia (HYP) are highly prevalent among individuals older than 60 years of age (Crawford et al., 2010; Go et al., 2013; Kannel & Gordan, 1978; Wolf, D'Agostino, Belanger, & Kannel, 1991) and account for a high percentage of direct health expenditures in the United States. Besides being major risk factors for heart disease, stroke, and early mortality (Alexander et al., 2003; Chobanian et al., 2003), each of these risk factors is associated with decline in cognitive abilities late in life, including clinical dementia syndromes (S. DeBette et al., 2011; Joas et al., 2012; Kivipelto et al., 2001; Stewart et al., 2009; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005). Vascular risk factors are believed to increase risk of cognitive decline by promoting progressive, clinically silent brain injury

over the course of years or even decades (S. DeBette et al., 2011; D. S. Knopman et al., 2011; Korf, White, Scheltens, & Launer, 2004; Maillard et al., 2012; Tan et al., 2011). Such brain injury, manifested through lesions, tissue loss, and neural dysfunction on brain MRI, is among the most consistently replicated risk factors for late-life cognitive decline to date (Bombois et al., 2008; Carlson et al., 2008; L. H. Kuller et al., 2003; Lopez et al., 2003; O'Sullivan et al., 2004).

Because each one of these vascular risk factors is modifiable, these findings have led to the possibility that treatment of vascular risk factors might lessen the burden of late life brain injury, and in turn lower risk for future dementia (Gorelick et al., 2011). There is certainly much room for improvement in vascular risk factor treatment: for example, despite increasing public awareness, less than 7% of individuals with concurrent DM, HTN, and HYP achieve defined treatment goals (Schroeder et al., 2012). If it were actually true that sustained, effective treatment of vascular risk factors could reduce risk of late life cognitive decline, the potential effects are astounding: for example, in a population attributable risk analysis that makes assumptions about how many dementia cases are uniquely attributable to individual risk factor exposure, a 25% decrease in a handful of risk factors (predominantly vascular ones) is projected to prevent as many as half of dementia cases that will emerge moving forward (D. E. Barnes & Yaffe, 2011) (see also (Launer et al., 2010)).

However, the purpose of this review is to build the case that further clarification of the relationship between vascular risk factors and late-life cognitive decline is needed. The overarching point is that even if current treatment protocols are adequate to lower risk of heart attack, stroke, and early mortality, it is not known whether they are also adequate for lowering the burden of silent brain injury and the risk of late-life cognitive decline. This is true for a number of reasons: there is a lack of convincing clinical trial evidence; differential vulnerability or resilience to brain effects of vascular risk factor exposure is not well understood; and relationships between vascular risk factors and prevalent, clinically-silent neurodegenerative disease processes are not well understood. As a result, it is possible that many individuals who have effectively avoided heart attack and stroke by addressing their vascular risks may have done little more than set themselves up for cognitive decline later in life. In contrast, hypothetical vascular risk factor treatment protocols that avoid this “out of the frying pan, into the fire” scenario by reducing risk for cognitive decline as well as heart attack and stroke could benefit the growing population of elderly individuals, and potentially reduce the steadily increasing global burden of late-life cognitive decline.

The following sections will provide a review of what is currently known, and what is currently unknown, about the relationship between vascular risk factors and both silent brain injury and cognitive decline late in life. A set of ways to move forward is then presented for the field to better understand the ability of treatment protocols to reduce late life cognitive decline risk.

3 What is known

3.A Vascular risk factors increase risk for brain injury and cognitive decline

A growing number of studies suggest that middle-aged individuals exposed to vascular risk factors such as DM, HTN, and HYP go on to have elevated risk of dementia and cognitive decline in their elderly years (S. DeBette et al., 2011; Joas et al., 2012; Stewart et al., 2009; Swan et al., 1998; Whitmer et al., 2005), suggesting that cumulative exposure to vascular conditions, accumulated over possibly decades of life, may be a key driver of risk. These results are highly robust because they have been reproduced across a variety of study designs, nations of origins, and methodologies for assessment of both vascular risk and cognitive decline. This well-established link between vascular risk factors and late-life cognitive decline forms the starting point for investigation of vascular risk factor treatment as a preventive strategy against late-life cognitive decline.

Brain injury, as measured by in vivo brain MRI, is believed to be a key intermediary in the relationship between vascular risk factor exposure and late-life cognitive decline. The total volume of parenchymal tissue and CSF, as well as the volumes of brain tissue in specific compartments, from T1-weighted sequences, provide proxy measures of the accumulated burden of neuronal death, while the volume of white matter hyperintensities from T2-weighted sequences provide measures of accumulated protein-rich fluid hypothesized to be secondary to myelin breakdown, neuronal damage, or gliosis (F. Fazekas et al., 1998). Both T1-weighted and T2-weighted MRI are used to identify clinically-silent infarcts as another measure of brain injury that is vascular in origin (Vermeer, Longstreth, & Koudstaal, 2007). More recently, diffusion MRI has provided more sensitive and fine-grained measures of white matter injury (Le Bihan, 2003). Brain dysfunction that arises either as a manifestation of underlying neuronal injury or as a symptom of modified coupling between neural activity and vascular or metabolic processes can also be measured using neuroimaging. Cerebral hemodynamics—*i.e.*, localized cerebrovascular changes that are caused by proximal neuronal activity-- can be measured by dynamic MRI methods that are sensitive to blood oxygenation (such as blood oxygenation level dependent or BOLD functional MRI (Logothetis & Pfeuffer, 2004)) or blood flow (such as perfusion MRI with arterial spin labeling (Petersen, Zimine, Ho, & Golay, 2006)). Acquiring this data under varying neural stimuli or vascular conditions (such as carbon dioxide challenge) allows for proxy measurement of the hemodynamic response function, which can be used as an indicator of neurovascular coupling. In the absence of externally imposed neural and/or vascular conditions, BOLD functional MRI can also be used to measure functional connectivity—*i.e.*, synchrony of spontaneous blood oxygenation fluctuations between distinct brain regions (van den Heuvel & Hulshoff Pol, 2010). Low functional connectivity may be an indicator of disrupted synchrony of underlying neural activity, modified coupling of spontaneous neural activity to the vascular supply, or both. Brain glucose metabolism, including changes in local glucose metabolism due to changes in local neural stimuli, can be measured via positron emission tomography (PET) with the radiolabeled glucose tracer fluorodeoxyglucose (FDG). Numerous reports have suggested that all of the indicators of brain injury noted above become more prevalent late in the lifespan (Biswal et al., 2010; O. Carmichael & Lockhart, 2012; D'Esposito, Zarahn, Aguirre, & Rypma, 1999; S. DeBette &

Markus, 2010; DeCarli et al., 2005; Loessner et al., 1995; Parkes, Rashid, Chard, & Tofts, 2004; Raz et al., 2005; Vermeer et al., 2007).

Evidence has accumulated from several large epidemiological studies that individuals exposed to vascular risk factors, either in midlife or late in life, show a greater burden of brain injury that is *clinically silent*—that is, not accompanied by clinically evident cognitive deficits (Au et al., 2006; Carmelli et al., 1999; Das et al., 2008; Jeerakathil et al., 2004; Korf et al., 2004; Moran et al., 2013; Prabhakaran et al., 2008; Seshadri et al., 2004; Swan et al., 1998) (DeCarli et al., 1995; Hsu et al., 2012; Jeerakathil et al., 2004). While the majority of this evidence is focused on the relationship between vascular risk factors and white matter hyperintensities, there is increasing evidence that gray matter is affected by vascular risk as well (Brundel et al., 2010; Cardenas et al., 2012). In addition, several large studies have suggested that elderly individuals who are cognitively intact, yet manifest increased levels of clinically-silent brain injury on MRI, are at increased risk of clinically-relevant cognitive decline in the future (O. T. Carmichael et al., 2007; S. Debette & Markus, 2010). Large-scale autopsy studies complement this evidence by documenting: 1. clinically-silent brain injury in individuals who died cognitively intact (Morris & Price, 2001); and 2. greater burden of silent brain injury in individuals who had experienced greater exposure to vascular risk factors over the lifespan (D. S. Knopman & Roberts, 2010).

Taken together, this evidence strongly supports the notion that vascular risk factors contribute to increased dementia risk by elevating the burden of clinically silent brain injury that accumulates in the aging brain over the course of years or decades. But, it is important to note that the vast majority of such supporting evidence comes from observational trials in which trajectories of vascular risk factor exposure and treatment, as well as adherence to and efficacy of treatment, were not standardized or manipulated by the study. This makes it difficult to establish a causal relationship between vascular risk factor treatment and prevention of silent brain injury. As outlined in the next section, clinical trials of vascular risk factor treatments with brain MRI outcomes could provide stronger evidence to support this association, but such trials have been remarkably small in number.

3.B Multiple pathways lead from vascular risk factors to brain injury

The observed association between vascular risk factor exposure and clinically silent brain injury naturally leads to the question regarding which biological mechanisms could lead from one to the other. To answer this question, investigators have sought to clarify the mechanisms by which vascular risk factors disrupt cerebrovascular function (i.e., the functioning of the blood vessels that supply brain tissue), with an understanding that damage to neuronal tissue is a likely consequence (Figure 1). At least three mechanisms have been proposed. First, elevated blood pressure is believed to promote *arterial stiffness*, i.e. lack of compliance of the central arteries. One result of increased arterial stiffness is transfer of cardiac flow pulsatility to the less compliant small blood vessels of the brain, resulting in increased mechanical stress on those vessels that eventually culminates in microhemorrhage (Henskens et al., 2008; Mitchell et al., 2011; O'Rourke & Safar, 2005; Ohmine et al., 2008; Tsao et al., 2013; Ziemann, Melenovsky, & Kass, 2005) (Kiechl & Willeit, 1999). Another result of increased arterial stiffness is enhancement of cardiac wave

reflection, i.e., a greater amount of oxygenated blood returning back up the descending aorta toward the heart rather than further down the vascular tree, resulting in less efficient oxygen transfer to smaller blood vessels including those in the brain. Second, elevated cholesterol promotes deposition of *atherosclerotic plaque*, leading to ischemic infarction and alterations to the fluid dynamics of blood flow through stenotic blood vessels supplying the brain (Amarenco et al., 1994; Manolio et al., 1999; Tell, Crouse, & Furberg, 1988). Third, chronic glucose intolerance is associated with *inflammation* of the endothelium that culminates in decreased efficiency of cerebral perfusion (Miranda, DeFronzo, Califf, & Guyton, 2005). These disparate mechanisms appear to interact with and reinforce each other; for example, inflammation may potentiate atherosclerotic plaque deposition by changing the adhesion properties of the vessel wall (Libby, Ridker, & Maseri, 2002), arterial stiffness may similarly predispose to plaque deposition (van Popele et al., 2001), and inflammation may exacerbate arterial stiffness (Schnabel et al., 2008). Mutual reinforcement of disparate mechanisms may mean that it is difficult to reverse any one of them individually once initiated. Altered cerebral perfusion, hemorrhage, and infarction contribute to a complex cascade of secondary injury processes including apoptosis, necrosis, oxidative stress, and excitotoxicity (Dirnagl, Iadecola, & Moskowitz, 1999; Madamanchi, Vendrov, & Runge; Snider, Gottron, & Choi, 1999), each of which promote neuronal injury.

Several in vivo neuroimaging studies support these hypothesized mechanisms (Bots et al., 1993; Dai et al., 2008; M. Muller et al., 2012; Poels et al., 2010; Vermeer et al., 2007). Individuals with greater exposure to vascular risk factors are at greater risk of clinically silent infarcts, identified on T1- and T2-weighted MRI (Das et al., 2008; Vermeer et al., 2007), as well as micro-hemorrhages visible on highly-sensitive T2*-weighted sequences such as susceptibility-weighted imaging (Cordonnier, Al-Shahi Salman, & Wardlaw, 2007; Goos et al., 2010; Poels et al., 2010). Deficits in cerebral perfusion, measured using perfusion MRI with arterial spin labeling, have been demonstrated in elderly individuals possessing vascular risk factors, especially hypertension (Dai et al., 2008; Ihab Hajjar, Zhao, Alsop, & Novak, 2010; M. Muller et al., 2012). Atherosclerosis of the blood vessels supplying the brain is most often measured at isolated locations, such as the carotid bifurcation, and is usually summarized in terms of univariate measures such as the carotid intima-media thickness based on ultrasound examination; however MRI sequences have the capability of providing more sensitive measures of plaque burden covering a greater extent of the vasculature. Using these techniques, a number of studies have suggested that elderly individuals with a greater burden of vascular risk factors have a greater risk of carotid atherosclerotic plaque (Ebrahim et al., 1999; O'Leary et al., 1992; Salonen & Salonen, 1991). Greater burden of systemic inflammation, measured through blood biomarkers, has been associated with silent infarcts, as well as greater burden of other indicators of silent brain injury (Fornage et al., 2008; Hoshi et al., 2005; Ishikawa et al., 2007; Jefferson et al., 2007; Miwa et al., 2011; van Dijk, 2005; Wright et al., 2009).

In turn, there is increasing evidence that cerebrovascular dysfunction is associated with clinically-silent brain injury (Pantoni & Garcia, 1997). Greater burden of carotid atherosclerosis has been associated with greater burden of white matter hyperintensities and greater brain atrophy both cross-sectionally and longitudinally (Kin et al., 2007; Manolio et

al., 1999; Majon Muller et al., 2011; Pico et al., 2002). Cerebral perfusion deficits, likewise, have been associated with both forms of silent brain injury in healthy elders (Appelman et al., 2008; van Es et al., 2010). Finally, autopsy findings of cerebrovascular pathology have been shown to be associated with greater burden of silent brain injury seen in corresponding pre-mortem brain MRI (Jagust et al., 2008).

Taken together, this evidence strongly supports the notion that vascular effects on clinically silent brain injury, and thus cognition, are determined by multiple biological processes. It follows that any attempt to prevent vascular effects on cognition would require a complex, multi-pronged intervention approach aimed at multiple biological targets, including targets that may be specific to the brain. Thus, it is not entirely clear that current protocols for treatment of vascular risk factors, which may or may not neutralize the biological processes implicated in the pathway from vascular processes to silent brain injury, are adequate to prevent silent brain injury.

3.C Cerebrovascular injury commonly co-occurs with other neurodegenerative diseases

As described above, any putative strategy for preventing the effects of vascular risk factors on late life cognition is complicated by the multiplicity of biological processes implicated in the pathway from vascular risk, to cerebrovascular dysfunction, to clinically silent brain injury and subsequent cognitive decline. An additional problem is that any putative treatment strategy must be sensitive to other neurobiological processes of aging that co-occur with the various vascular-related processes. A growing body of evidence from large-scale autopsy studies supports the notion that cerebrovascular dysfunction commonly co-occurs with, and likely interacts with, other neurobiological processes of aging. These studies suggest that among individuals who die clinically demented, a common autopsy finding is an admixture of cerebrovascular, Alzheimer, and Lewy body pathologies (Brayne et al., 2009; Schneider, Arvanitakis, Bang, & Bennett, 2007; L. White et al., 2005). Further studies suggest that each of the implicated pathologies may be clinically relevant to cognitive functioning; individuals with a certain level of a particular pathology at autopsy were more likely to have reduced cognitive functioning near the end of life when additional pathologies were also present at autopsy (Schneider, Boyle, Arvanitakis, Bienias, & Bennett, 2007).

In vivo studies of the co-occurrence of cerebrovascular injury and additional pathologies have been limited by the relative expense and technical requirements of measuring Alzheimer pathology in vivo using cerebrospinal fluid assays or positron emission tomography imaging. In addition, these studies have been limited by the relative lack of sensitive, robust, and circumspect measures of in vivo cerebrovascular injury burden. Small-scale studies of convenience samples disagree on the degree to which cerebral amyloid burden and white matter hyperintensity burden are correlated with each other (Grimmer et al., 2012; Hedden et al., 2012; Marchant et al., 2012). Other studies have observed that cerebral amyloid burden and white matter hyperintensity burden are independently associated with greater brain atrophy and hypometabolism (J. Barnes et al., 2013; Guzman et al., 2013; Haight et al., 2013), and additional studies support the view that the co-occurrence of amyloid and white matter hyperintensities is clinically relevant among those clinically

diagnosed with Alzheimer's disease (Provenzano et al., 2013). To the degree that white matter hyperintensities are a manifestation of cerebrovascular dysfunction, the *in vivo* data can be used to support the notion that cerebrovascular injury and Alzheimer's disease may have additive or multiplicative deleterious effects on the brain that hasten cognitive deterioration. While there is strong support for the view that white matter hyperintensities are primarily driven by cerebrovascular injury in the absence of Alzheimer pathology (F Fazekas et al., 1993; Pantoni & Garcia, 1997), there is a possibility Alzheimer's pathology itself could contribute to white matter hyperintensities (Chen et al., 2006; Gouw et al., 2011), thus complicating conclusions that can be drawn about the two distinct processes from these data.

There are plausible biological mechanisms through which cerebrovascular injury processes may facilitate or reinforce those of other neurobiological processes of aging, particularly Alzheimer's disease. For example, there is increasing evidence that the normal metabolism of cerebral amyloid involves clearance along perivascular spaces, and thus vascular compromise could hypothetically lead to amyloid accumulation in interstitial spaces (Preston, Steart, Wilkinson, Nicoll, & Weller, 2003) (Iliff et al., 2012). Failure of such vascular clearance mechanisms is one explanation for the common finding of cerebral amyloid angiopathy—amyloid accumulation within the cerebral blood vessels (Vinters & Gilbert, 1983). In turn, such vascular amyloidosis is believed to be its own cause of microhemorrhage (Gilbert & Vinters, 1983). Cholesterol metabolism and amyloid metabolism are also closely linked (Dietschy & Turley, 2001; Liu et al., 2007; Simons et al., 1998), although the precise effects of chronically elevated circulating cholesterol on this linkage are currently unclear (Höglund et al., 2004; Pappolla et al., 2003; Refolo et al., 2000). Amyloid itself, especially in its oligomeric form, appears to be pro-inflammatory, and thus has the potential to exacerbate the inflammatory effects of cerebrovascular processes (Salminen, Ojala, Kauppinen, Kaarniranta, & Suuronen, 2009; J. A. White, Manelli, Holmberg, Van Eldik, & LaDu, 2005). Taken together, this evidence suggests that even if effective treatment of vascular risk factors is able to halt the progression of cerebrovascular injury, this might have no major impact on downstream brain injury if additional processes such as cerebral amyloidosis have emerged and are able to continue to damage brain tissue on their own. This interaction between cerebrovascular injury and other aging processes casts further doubt on the notion that the putative treatment of vascular risk factors according to current treatment protocols has an easy-to-predict, straightforward effect on downstream brain injury and, eventually, late life cognitive decline.

4 What is not currently known

4.A It is not clear that effective vascular risk factor treatment prevents cognitive decline and clinically silent brain injury

Clinical trials examining the possibility that effective treatment of vascular risk factors may modify risk of clinically-relevant cognitive decline in the elderly have provided conflicting results (Novak & Hajjar, 2010). A Cochrane review did not find consistent high-level evidence that anti-hypertensives reduce risk of incident dementia or decline in cognitive test scores among elderly individuals (McGuinness, Todd, Passmore, & Bullock, 2009). Another

meta analysis suggested that successful blood pressure lowering may be associated with both improvement in, and diminishment of, cognitive abilities, depending on which cognitive measurements were used (Birns, Morris, Donaldson, & Kalra, 2006). To date, a very small number of clinical trials of vascular therapies have considered neuroimaging measures of silent brain injury as an outcome of interest. The largest such study (N=192) found that antihypertensive treatment significantly reduced the risk of progression of white matter hyperintensities among individuals with prevalent clinical stroke (Dufouil et al., 2005). Smaller pilot studies, each including roughly tens of individuals, have suggested that effective treatment with antihypertensive therapies may be associated with preservation of cerebrovascular functioning in the face of vascular challenge, as well as preservation of glucose metabolism (I. Hajjar et al., 2013; Imabayashi et al., 2011; Kimura et al., 2010; Matsumoto, Shimodozono, Miyata, & Kawahira, 2009). However it should be emphasized that to date, studies with brain injury outcomes have not been performed on a similar scale to those with cognitive indicators as the primary outcome (*i.e.*, with thousands of participants).

The lack of concurrence between trials is perhaps not surprising, as those conducted to date have been highly variable along a number of critical dimensions. Background characteristics of study participants have been particularly variable, with mean ages ranging from the 50s to the 80s, and target populations varying from those with isolated hypertension to those with prevalent clinical stroke. Treatment classes of interest have varied, as have individual treatments within classes. Treatment histories of participants have varied as well. Treatment protocols, especially the definition of successful blood pressure lowering and treatment modifications in the event of unsuccessful lowering, are another source of variability. In addition to these known differences among diverse trials, heterogeneity in study results may have been influenced by differences in latent characteristics of study participants that the trial failed to measure. In particular, most trials (outside of those performed in clinical stroke populations) did not attempt to sample participants based on their burden of pre-existing brain injury or neurodegenerative disease that was clinically silent. Thus, the results of these trials may have been confounded by pre-existing brain characteristics that pre-disposed participants to cognitive decline in spite of treatment.

Outside of clinical trials, several large observational studies support the notion that individuals with a history of successful vascular risk factor treatment possess lower levels of silent brain injury (Godin, Tzourio, Maillard, Mazoyer, & Dufouil, 2011; Ihab Hajjar, Brown, Mack, & Chui, 2012; Lewis H Kuller et al., 2010; Valeo, 2013). In particular, two of these studies found an association between use of specific classes of antihypertensive treatment—beta blockers and angiotensive receptor blockers—and lower burden of neuropathology at autopsy. The other studies found that individuals who effectively lowered blood pressure showed a lower burden of, or slower progression of, white matter hyperintensities on MRI. These studies were not prospectively designed to sample individuals based on trajectories of vascular risk factor exposure and treatment however, and they were not designed to manipulate vascular risk factors to determine the effect of this manipulation on the brain. While these studies provide valuable hints that effective treatment of vascular risk factors may potentially ameliorate brain injury burden, this notion

has not been strongly demonstrated in any large-scale, prospective, randomized controlled trial to date.

4.B It is not known whether there is a critical treatment window for prevention of vascular effects on the brain and cognition

Many of the aforementioned clinical trials focused on individuals who were elderly and relatively likely to experience cognitive decline over a fairly brief follow-up interval (McGuinness et al., 2009). However, accumulating evidence suggests that vascular effects on silent brain injury may commence in mid-life, possibly as early as the fourth decade of life (Maillard et al., 2012), even among individuals whose vascular injury burden is so mild that they do not meet criteria for recognized clinical conditions such as hypertension. The effects of vascular conditions on silent brain injury appear to accumulate steadily between early midlife years and elderly years, until elderly individuals possessing decades of exposure to vascular risks have a substantial burden of silent brain injury and an elevated risk of consequent cognitive decline (S. DeBette et al., 2011; Havlik et al., 2002; D. Knopman et al., 2001; Korf et al., 2004; Swan et al., 1998). For this reason there is a growing belief that the clinical trials in elderly populations may simply have been “too little, too late”—attempting to arrest the effects of vascular processes on the brain long after those processes have wrought the major damage leading to cognitive decline.

An obvious consequence of the “too little, too late” problem is that clinical trials of vascular risk factor therapies as preventive agents for late-life cognitive decline should be performed earlier. But the key unanswered question is when, exactly. In other words, there may be a *critical treatment window*, i.e. a period of the lifespan during which emerging vascular injury processes must be controlled to prevent eventual consequences for the brain and cognition. If treatment in 75-year-olds is too little, too late, it is unclear whether treatment in 65-year-olds, or 55-year-olds, is any different. Another possibility is that the key determinant of the brain benefits of treatment is not chronological age per se, but duration of exposure to vascular risks. The emergence and trajectory of vascular risk factors such as hypertension is highly variable across the population, with blood pressure rising to elevated levels at variable points in the lifespan. It could be that to prevent effects on the brain, it is critical to aggressively treat vascular risks soon after they emerge, regardless of when in the lifespan they emerge. If such a critical treatment window were established, it could have tremendous implications for the surveillance of vascular risk factors and protocols for treatment initiation: for example, if vascular effects on silent brain injury are evident even among 30-year-olds as suggested above, and it is critical to arrest these effects in the 30s, careful surveillance of vascular measures and aggressive pursuit of treatment may be warranted even in this young age group, contrary to current practice. Whether such critical treatment windows exist, and what their parameters are, is currently unknown due to a lack of studies relating vascular risk factor treatment to brain outcomes across a wide range of ages¹.

¹Note that a similar “too little, too late” problem is widely agreed to be a critical failure in most clinical trials of treatments for Alzheimer's disease, and that a major focus of current research is testing promising treatments earlier in the trajectory.

4.C It is not known whether achieving current treatment targets is adequate to prevent silent brain injury

Clinical trials with cardiovascular disease outcomes (Vasan et al., 2001) have carefully considered how obtained levels of blood pressure, cholesterol, blood glucose, and other relevant parameters of vascular risk relate to relevant outcomes. The cumulative result of these trials is a set of *treatment targets*: optimal ranges of these parameters that should be sought in order to minimize risks of cardiovascular outcomes. Treatment protocols then index success of treatment against the ability to move vascular parameters into the target range. There does not appear to have been any such attempt to identify treatment targets for prevention of silent brain injury or cognitive decline, or at least to determine whether currently accepted treatment targets for cardiovascular outcomes should be considered optimal targets for prevention of silent brain injury or cognitive decline. One possibility is that while current treatment targets may be adequate for lowering risk of heart attack, stroke, or other major outcomes, they may be less than adequate for lowering risk of silent brain injury and cognitive decline. For example, while attainment of a systolic blood pressure of 130 may be considered adequate for cardiovascular outcomes, perhaps going even lower (for example, to 110) may be required to lower risk of silent brain injury. One reason this possibility may have merit is that there may be a continuous relationship between healthier values of vascular parameters and lesser burden of silent brain injury, across a very broad range of vascular parameter values, even to values considered quite low in terms of current treatment targets (Maillard et al., 2012). In other words, there is not a strong base of evidence for a lower bound for the vascular parameter beyond which further lowering would incur no benefit in terms of brain injury prevention. This suggests that lowering vascular parameters even lower than current treatment targets could have benefits for brain injury and cognitive outcomes. Establishing treatment targets for reduction of risk of brain injury and cognitive decline could clearly have major implications for clinical practice, but due to a lack of clinical trials measuring brain injury outcomes in individuals who achieved varying levels of vascular parameters through treatment, such targets are currently unknown.

4.D It is not known whether some individuals are especially vulnerable to vascular effects on the brain, and if so whether they should be treated differently

As described above, many prior studies suggested that greater levels of vascular risk factor burden are associated with greater levels of silent brain injury burden. However, a more precise summary of findings from these studies is that while there is a general population-level trend in this direction, there is evidence of a great deal of inter-individual heterogeneity, such that some individuals appear to be *differentially vulnerable*—i.e., possessing a high level of silent brain injury relative to their low burden of vascular risk—and some individuals appear to be *differentially resilient*—i.e., possessing a low level of silent brain injury relative to their high burden of vascular risk. While numerous biological factors could be hypothesized to explain this inter-individual variability, data on this phenomenon is scarce. For example, a number of genetic factors that increase risk of dementia are implicated in the same general biological pathways that lead from vascular risk factors to brain injury; one prominent example is apolipoprotein E, a cholesterol transport protein that is by far the most widely replicated genetic risk factor for Alzheimer's disease

(Roses, 1996; Yip et al., 2005). Similarly, several other genes implicated in pro-inflammatory pathways also increase risk of AD, potentially by exacerbating the effects of vascular-driven systemic inflammatory processes on the brain (McGeer & McGeer, 2001). The presence of genetically-driven vascular brain injury diseases such as CADASIL (Ruchoux & Maurage, 1997), along with the emergence of genetic risk factors for cerebral infarction (Chou et al., 2013; Stéphanie Debette et al., 2010), further supports the notion of differential vulnerability to vascular-driven brain injury arising from background factors. However, the concept that the effects of vascular risk factors on silent brain injury could be influenced by differential vulnerability does not appear to have been explored in depth ².

The concept of differential vulnerability to disease, identified by background factors such as family history of disease, ethnic background, or genetic markers; or by presence of concomitant risk factors, is a guiding concept governing surveillance for a variety of chronic diseases, and it increasingly influences personal health recommendations for those deemed differentially vulnerable. Thus, it should be clear that identification of individuals differentially vulnerable to the effects of vascular risk factors on the brain could have a major impact on clinical management of vascular risks, with those individuals followed especially closely and treatment pursued the most aggressively. However, such at-risk groups have not been identified, due to a lack of studies that measure the level of vulnerability—*i.e.* measure the level of brain injury indexed against the level of vascular risk factor burden—and relate this vulnerability to predictors such as family history or genetic markers. In addition, as mentioned above, the functioning of the cerebral vasculature is generally under-studied in the relationship between vascular risk factors and silent brain injury. Further study with measurement of vascular risk, the cerebral vasculature, and brain tissue is needed to clarify whether vulnerable individuals feel an especially severe impact of vascular risk factors on the cerebral vasculature itself, or whether relatively mild damage to cerebrovascular functioning culminates in especially severe damage to brain tissue, or whether both of these are true.

4.E It is not known if different treatments have different protective effects on the brain

Prior studies supporting an association between effective treatment of vascular risk factors and lower burden of brain injury and cognitive decline were not designed to answer the question of whether differing treatments provide differing benefits to the brain. There have only been a limited number of reports related to this question. One preliminary report suggested an association between antihypertensive treatment use and lesser burden of neuropathology on autopsy, but only within one class of medication (beta blockers) (L. White et al., 2013). There is a larger group of studies suggesting that angiotensin receptor blockers have specific neuroprotective effects (Ihab Hajjar et al., 2012; Thöne-Reineke et al., 2004; Wilms, Rosenstiel, Unger, Deuschl, & Lucius, 2005). These reports largely arose from observational studies that were not designed to sample participants according to treatment regimen, nor control for duration of treatment exposure or adherence to treatment.

²While differential vulnerability of brain tissue to vascular processes does not appear to be a major research focus currently, differential vulnerability of cognitive functioning to brain injury is. Cognitive resilience to such brain injury is referred to as “cognitive reserve.” Differential vulnerability of brain tissue to cerebral amyloidosis (*i.e.*, differential “amyloid toxicity”) is under study as well.

Nonetheless, they raise the possibility that effects on the brain could enter the already complex calculus about risk and benefit of differing treatments.

It should be clear that an understanding of neuroprotective effects of specific classes of vascular risk factor treatments could have a major impact on clinical management of these conditions. But a lack of studies designed to compare brain and cognitive outcomes between treatment categories has prevented such an understanding from developing.

4.F How time courses of vascular brain injury relate to time courses of neurodegenerative brain injury is not well understood

As stated above, there is a growing body of evidence that in individuals clinically diagnosed with dementia, cerebrovascular injury commonly co-occurs with neurodegenerative pathology, especially that associated with Alzheimer's disease. But the strongest evidence comes from large autopsy studies, along with in vivo studies that are for the most part cross-sectional and small. This means that the time course of cerebrovascular injury accrual, and how it relates to the time courses of neurodegenerative pathology accrual and consequent development of silent brain injury, is poorly understood. Better understanding the relative time courses of these two processes could have major implications for the viability of vascular risk factor treatment as a preventive strategy against silent brain injury and consequent cognitive decline. For example, evidence that cerebrovascular injury tends to build up prior to Alzheimer's disease pathology would suggest that preventing cerebrovascular injury through vascular risk factor treatment could potentially forestall cognitive decline by forestalling accrual of silent brain injury, even if such brain injury is destined to eventually accumulate due to the effects of Alzheimer's disease processes. Current epidemiological evidence tends to support this scenario, as vascular risk factors and their brain effects become detectable earlier in the lifespan than Alzheimer's disease pathology does (Berenson et al., 1998; Maillard et al., 2012). Nonetheless, evidence that it is more typical for cerebrovascular injury to accumulate secondary to Alzheimer's pathology may suggest that in individuals with Alzheimer's pathology, efforts to treat vascular risk factors could be futile for prevention of cerebrovascular injury. In addition, better understanding the relative time courses of these two processes could clarify various additional aspects of treatment strategies: for example, it could clarify whether various aspects of the time course of vascular risk factor exposure (such as the time of onset and fluctuations in the level of severity over time) place one in a higher-risk category for accumulation of Alzheimer's pathology, or whether the critical period for applying a hypothetical Alzheimer preventive agent is earlier or later in individuals exposed to vascular risk factors. Longitudinal studies that chart the relative time courses of these two processes are needed to clarify these issues.

5 Ways forward

The previous section presented the case that numerous aspects of the relationship between vascular risk factor treatment and silent brain injury and cognitive decline are poorly understood, and a better understanding could have major implications for efforts to prevent and treat vascular risk factors in a clinical setting. In this section, the most promising avenues for enhancing the state of scientific knowledge in this area are presented.

5.A Conduct more clinical trials of vascular risk factor treatments with cerebrovascular function and silent brain injury as primary outcomes of interest

Possibly the greatest impediment to understanding the viability of vascular approaches to cognitive decline prevention is a lack of clinical trials that measure what happens to the cerebral vasculature and brain tissue in groups of individuals whose prior exposures to cardiovascular risk factors and treatments are matched to the greatest degree possible, and whose key difference is exposure to a novel treatment agent. If a hypothetical treatment is beneficial for cardiovascular endpoints and if the cerebral vasculature and brain tissue are better maintained in those on treatment, this would be the strongest evidence to date for the vascular hypothesis. Clinical trials of this nature seem to be the only way to rigorously assess more detailed aspects of the relationship between vascular risk factor treatment and the brain, such as dose-response relationships and optimal treatment. The major difference between conventional clinical trials and these proposed ones is the longitudinal assessment of brain outcome measures using MRI; collecting and using such data in a large-scale clinical trial setting is feasible in middle aged and elderly individuals as shown by large-scale studies such as ADNI.

5.B Develop and validate sensitive measures of systemic vascular injury and cerebrovascular injury

As described above, multiple biological pathways could lead from vascular risk factors to cerebrovascular dysfunction, silent brain injury, and consequent cognitive decline, but it is not clear how specifically vascular risk factor treatments impact each of these pathways, and it is not clear whether arresting individual pathways is adequate to prevent consequent cerebrovascular dysfunction. Clinical trials of vascular risk factor treatments with brain and cognitive outcomes would thus be enhanced by measuring sensitive and robust markers of these pathways to determine which pathways, in which individuals, are engaged by the proposed treatment. For treatments that fail to enhance brain outcomes, such biomarkers would help to determine whether the treatment failed to modify the systemic processes that impinge upon the brain, or whether engaging those pathways was inadequate to prevent cerebrovascular dysfunction. A result of these biomarkers could be the development of relationships between the systemic vascular biomarkers and cerebrovascular dysfunction markers, to give a better sense of what target levels of systemic markers must be achieved to meaningfully benefit the cerebral vasculature. In the long term, such biomarkers could motivate biologically-driven combination therapies that, taken together, engage all of the multiple pathways that must be modified to preserve the cerebral vasculature and thus protect brain tissue. Promising brain-relevant vascular biomarkers are described in the remainder of this section.

Arterial stiffness is now commonly assessed indirectly, by measuring pulse wave velocity—the speed with which blood ejected from the heart travels through various levels of the vascular tree (Hansen et al., 2006). The basic intuition behind pulse wave velocity is that compliant blood vessels are able to expand, increasing their volume to accommodate a bolus of newly-arriving blood from the heart; the newly arriving blood is thus more able to reside in the expanded vessel and travel through it more slowly. In contrast, less-compliant vessels cannot expand and thus have no choice but to immediately send the newly arriving blood

down the vessel at a high speed. Non-invasive, tonometric devices are now available that measure the blood pressure waveform at multiple arteries (for example, at the carotid and femoral arteries) and quantify the difference in arrival times of the pulse wave between the two (i.e., the “carotid-femoral pulse wave velocity”) as a proxy measure of the velocity of the pulse wave through the central arteries. Measurements of this type are relatively straightforward to acquire and are easily tolerated by patients. However, there is some debate over which pair of arteries provides valid proxy measures of the pulse wave velocity in which parts of the vasculature (Tanaka et al., 2009), and the correlation between the proxy measures and the true speed of the pulse wave down any individual vessel is not perfect (Yamashina et al., 2002). MRI techniques, meanwhile, are able to directly measure the velocity of the pulse wave as it flows through specific arteries whose caliber is large enough to surpass the inherent spatial resolution limits of MRI. Figure 2 shows an example of MRI measurement of pulse wave velocity in the descending aorta. MRI and ultrasound are also capable of directly measuring variations in the diameter of large blood vessels over the course of the cardiac cycle; together with concurrent measurement of blood pressure or flow in the vessel, these measurements provide direct measurement of vessel compliance that is the primary physiological parameter of interest in arterial stiffness (Lehmann, Parker, Hopkins, Taylor, & Gosling, 1993). However, compliance measurements are complicated by the fact that vessel diameter changes may be quite small relative to the spatial resolution of MRI or ultrasound. In summary, while sophisticated measures of arterial stiffening are still under development, emerging clinical trials are now able to collect validated biomarkers through tonometric devices or imaging modalities.

Numerous markers of systemic inflammatory processes have been developed and are commonly deployed in research and clinical practice. Traditional, indirect measures of systemic inflammation include C-reactive protein and homocysteine, while more modern markers include the suite of inflammatory cytokines (e.g., IL-1, IL-6, TNF-alpha) (Dinarello, 1996) and vascular adhesion molecules (e.g., VCAM, ICAM, P-selectin, E-selectin) (Gearing & Newman, 1993). While these measures can be collected from cerebrospinal fluid, the assessment of neuroinflammation, in particular the spatial distribution of inflammatory activity throughout the brain, has remained an elusive target. Development of positron emission tomography ligands that specifically target inflammatory activity has been ongoing for many years, with PK11195 emerging as the first viable compound. Due to its limited specificity, a number of replacements for PK11195 have emerged (Chauveau, Boutin, Van Camp, Dollé, & Tavitian, 2008), many of which bind selectively to translocator protein 18 kDa (TSPO), which is upregulated in activated microglia (previously, TSPO had been referred to as the peripheral benzodiazepine receptor or PBR) (Ching et al., 2012). There is currently no consensus on which of the several TSPO binding compounds is the most specific and easy to deploy. In addition, complications to TSPO as a neuroinflammation target have arisen, including inter-individual variability in the binding affinity of TSPO ligands driven by genetic variability in the TSPO gene (Owen et al., 2012). However, as TSPO ligands and other neuroinflammation PET agents come on line, incorporating them into clinical trials of vascular risk factor treatments targeting inflammatory processes would be essential to understanding benefits these treatments have for the brain.

Quantitative measures of atherosclerotic plaque burden from ultrasound or MRI are also prominent due to their relevance to stroke, but more fine-grained measures of stenosis and blood flow within the blood vessels supplying the brain could provide deeper insight into the effects of atherosclerotic plaque on cerebrovascular function. Typically, ultrasound examination provides summary measures of stenosis and flow at isolated sites deemed differentially vulnerable to plaque deposition, such as the carotid bifurcation (Touboul et al., 2006). Atherosclerosis-oriented MRI methods, similarly, can provide a characterization of plaque composition at a small number of carotid artery cross-sections (Yuan & Kerwin, 2004). However, MRI angiography techniques are now capable of providing high-resolution characterization of the structure of arteries throughout the brain, thus enabling a brain-wide view of the capability of the cerebral vasculature to deliver blood to all brain tissue. An example angiogram, and data showing vessel structural differences between young and elderly individuals, are shown in Figure 3. Such characterization of arterial structure could allow modeling at an individual level of what parts of the brain are differentially vulnerable to injury due to inadequate vascularization. While methods for isolating the structure of the cerebral vasculature from imagery have been presented (for example, (Flasque, Desvignes, Constans, & Revenu, 2001)), it is unclear what summary measures should be extracted from such a structural description to best characterize vulnerability to cerebrovascular dysfunction. Identifying the best summary measures, and clarifying the utility of whole-brain arterial structure in studies of cerebrovascular injury, is a promising avenue for future research.

5.C Develop better ways to measure duration and severity of vascular injury processes over years or decades

There is a key knowledge gap in how the time course of exposure and severity of vascular risk factors relates to the time course of brain injury accrual. Some evidence suggests that the duration of exposure is a crucial variable. For example, silent brain injury among the elderly appears to be more strongly determined by the presence of vascular risk factors at midlife rather than concurrently (Ninomiya et al., 2011); if midlife exposure is a valid proxy measure of duration of exposure, this suggests that duration of exposure is a stronger determinant of effects on the brain. If both duration and severity of exposure are key factors promoting silent brain injury, clinical trials of treatments to prevent silent brain injury should ideally recruit participants that are well characterized and homogeneous in terms of both of these variables; otherwise, those with greater duration of more severe vascular risk factor exposure could be predisposed to poorer brain outcomes regardless of their current vascular risk factor status. Several epidemiological studies have been able to gather such long-term exposure data by measuring vascular parameters every several years in roughly thousands of research participants over the course of years to decades (Guo et al., 2009; Stewart et al., 2009; Wills et al., 2011; Wills et al., 2012). However, traditionally such long-term exposure data has been limited to a relatively small pool of epidemiological cohorts, and the vascular measurements have been temporally sparse enough that they risk failing to provide an adequately fine-grained characterization of vascular risk factor trajectory. In addition, these epidemiological studies had limited ability to provide a fine-grained characterization of treatment trajectories, including initiation, adherence, and changes or cessation. Luckily, the ability to capture fine-grained trajectories of vascular risk factor

surveillance, exposure, and treatment have emerged within the past decade, with the development of electronic medical record (EMR) databases that record each and every clinical assessment, lab result, and pharmacy interaction occurring longitudinally in tens to hundreds of thousands of health system enrollees. A few health care systems that were early adopters of EMR and invested heavily in the medical informatics technology required to characterize long time courses of exposure are now positioned to recruit participants for research studies based on decade-long trajectory information (two examples are the Veterans Affairs system (Siegel, Lopez, & Meier, 2007) and Kaiser Permanente (Adams, Uratsu, Dyer, & et al., 2013)). However, there are still a number of technical hurdles to such studies. First, automated extraction of such trajectory information from individual EMR databases remains a difficult task due to the complexity and heterogeneity of represented clinical interaction data. While much of the relevant data is in a standardized, easy to manipulate format, some critical data remain in freely-typed notes that are prohibitively time consuming to parse manually and difficult to extract information from automatically. Large-scale, multi-site studies have been stymied by a lack of data standardization across disparate EMR systems.

Finally, while modeling of individual longitudinal trajectory data is already a major research problem in biostatistics (see for example (Harvey, Laurel, & Mungas, 2003)), fine-grained EMR data poses additional analytic problems due to the presence of multiple, correlated, high-dimensional trajectories (of vascular parameters, clinical interactions, and treatment behaviors) per individual. Addressing these technical challenges will provide a major opportunity to design studies that better characterize vascular effects on the brain in the context of lifetime exposures.

Even within EMR databases, measurement of vascular parameters over time requires interaction with patients in a clinical setting. This is especially problematic given the earlier contention that vascular injury processes, and vascular effects on the brain, may commence early in the lifespan, among nominally healthy young individuals that are otherwise asymptomatic and unlikely to believe that frequent, routine clinical evaluations confer much benefit to them (Berenson et al., 1998; Maillard et al., 2012). In addition, recent research suggests that office measurement of certain vascular parameters, especially blood pressure, provides an inadequate characterization of vascular status (Sega et al., 2005; Verdecchia et al., 1994). Wearable electronic health monitors that have emerged in recent years have the potential to provide surveillance of systemic vascular processes around the clock in an unobtrusive manner. Various devices are able to provide chronic measurement of blood pressure, pulse rate, blood glucose, and even the electrophysiology of the heart. Time courses of data from these devices can then be transmitted from devices to cell phones and onward to health care providers who can incorporate this fine-grained longitudinal vascular characterization into EMR. The comfort and convenience of these devices, as well as the threat of electronic theft of such highly sensitive personal health data, are ongoing concerns. Nonetheless, continued development of wearable health devices could provide vastly superior characterization of time courses of vascular risk duration and severity at a granularity never seen before, and this information could be used to better control clinical trials for the vascular history of participants.

6 Conclusion

While there is ample evidence that individuals possessing a history of vascular risk factor exposure have poorer outcomes late in life with respect to clinically-silent brain injury and clinically relevant cognitive decline, there is a relatively little convincing evidence that current protocols for vascular risk factor treatment are adequate to prevent these outcomes. Identifying vascular risk factor treatment protocols that optimally reduce risk of late-life silent brain injury and cognitive decline will require investigating critical treatment windows, interactions between vascular and other biological processes of aging, differential vulnerability to silent brain injury, and optimal targets for vascular parameters. Clinical trials of vascular treatments with brain injury outcomes are desperately needed to investigate these questions. Sensitive and robust biomarkers of the cerebral and central vasculature, and better characterization of time courses of vascular risk factor exposure are needed to clarify what insights should be derived from these trials. It is expected that longitudinal biomedical imaging, data mining of electronic medical records, and chronic ecological monitoring devices will play a critical role in this characterization effort.

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References

- Adams A, Uratsu C, Dyer W, et al. Health system factors and antihypertensive adherence in a racially and ethnically diverse cohort of new users. *JAMA Internal Medicine*. 2013; 173(1):54–61. [PubMed: 23229831]
- Alexander CM, Landsman PB, Teutsch SM, Haffner SM. Third National, H., Nutrition Examination, S., & National Cholesterol Education, P. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes*. 2003; 52(5):1210–1214. [PubMed: 12716754]
- Amarenco P, Cohen A, Tzourio C, Bertrand B, Hommel M, Besson G, et al. Boussier MG. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. *N Engl J Med*. 1994; 331(22):1474–1479.10.1056/NEJM199412013312202 [PubMed: 7969297]
- Appelman AP, van der GY, Vincken KL, Tiehuis AM, Witkamp TD, Mali WP, Geerlings MI. Total cerebral blood flow, white matter lesions and brain atrophy: the SMART-MR study. *J Cereb Blood Flow Metab*. 2008; 28(3):633–639. [PubMed: 17912270]
- Au R, Massaro JM, Wolf PA, Young ME, Beiser A, Seshadri S, et al. DeCarli C. Association of white matter hyperintensity volume with decreased cognitive functioning: the Framingham Heart Study. *Arch Neurol*. 2006; 63(2):246–250. [PubMed: 16476813]
- Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol*. 2011; 10(9):819–828.10.1016/S1474-4422(11)70072-2 [PubMed: 21775213]
- Barnes J, Carmichael OT, Leung KK, Schwarz C, Ridgway GR, Bartlett JW, et al. Biessels GJ. Vascular and Alzheimer's disease markers independently predict brain atrophy rate in Alzheimer's Disease Neuroimaging Initiative controls. *Neurobiology of Aging*. 2013
- Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. *New England Journal of Medicine*. 1998; 338(23):1650–1656. [PubMed: 9614255]
- Birns J, Morris R, Donaldson N, Kalra L. The effects of blood pressure reduction on cognitive function: a review of effects based on pooled data from clinical trials. *Journal of hypertension*. 2006; 24(10):1907–1914. [PubMed: 16957545]

- Biswal BB, Mennes M, Zuo XN, Gohel S, Kelly C, Smith SM, et al. Milham MP. Toward discovery science of human brain function. *Proc Natl Acad Sci U S A*. 2010; 107(10):4734–4739.10.1073/pnas.0911855107 [PubMed: 20176931]
- Bombois S, Dobbie S, Bruandet A, Delbeuck X, Delmaire C, Leys D, Pasquier F. Vascular subcortical hyperintensities predict conversion to vascular and mixed dementia in MCI patients. *Stroke*. 2008; 39(7):2046–2051. [PubMed: 18436882]
- Bots ML, Breteler MMB, Hofman A, Grobbee DE, van Swieten JC, van Gijn J, de Jong PTVM. Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. *The Lancet*. 1993; 341(8855):1232–1237.
- Brayne C, Richardson K, Matthews FE, Fleming J, Hunter S, Xuereb JH, et al. the Cambridge City over-75s Cohort study neuropathology, c. Neuropathological Correlates of Dementia in Over-80-Year-Old Brain Donors from the Population-Based Cambridge City over-75s Cohort (CC75C) Study. *Journal of Alzheimer's Disease*. 2009; 18(3):645–658.
- Brundel M, van den Heuvel M, de Bresser J, Kappelle LJ, Biessels GJ. Utrecht Diabetic Encephalopathy Study, G. Cerebral cortical thickness in patients with type 2 diabetes. *J Neurol Sci*. 2010; 299(1-2):126–130.10.1016/j.jns.2010.08.048 [PubMed: 20869085]
- Cardenas VA, Reed B, Chao LL, Chui H, Sanossian N, Decarli CC, et al. Weiner MW. Associations Among Vascular Risk Factors, Carotid Atherosclerosis, and Cortical Volume and Thickness in Older Adults. *Stroke*. 2012;10.1161/STROKEAHA.112.659722
- 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(11):828–833. [PubMed: 18046010]
- Carmelli D, Swan GE, Reed T, Wolf PA, Miller BL, DeCarli C. Midlife cardiovascular risk factors and brain morphology in identical older male twins. *Neurology*. 1999; 52(6):1119. [PubMed: 10214731]
- Carmichael O, Lockhart S. The role of diffusion tensor imaging in the study of cognitive aging. *Curr Top Behav Neurosci*. 2012; 11:289–320.10.1007/7854_2011_176 [PubMed: 22081443]
- Carmichael OT, Kuller LH, Lopez OL, Thompson PM, Dutton RA, Lu A, et al. Becker JT. Ventricular volume and dementia progression in the Cardiovascular Health Study. *Neurobiol Aging*. 2007; 28(3):389–397. [PubMed: 16504345]
- Chauveau F, Boutin H, Van Camp N, Dollé F, Tavittian B. Nuclear imaging of neuroinflammation: a comprehensive review of [11C] PK11195 challengers. *European journal of nuclear medicine and molecular imaging*. 2008; 35(12):2304–2319. [PubMed: 18828015]
- Chen Y, Gurol M, Rosand J, Viswanathan A, Rakich S, Groover T, et al. Smith E. Progression of white matter lesions and hemorrhages in cerebral amyloid angiopathy. *Neurology*. 2006; 67(1):83–87. [PubMed: 16832082]
- Ching ASC, Kuhnast B, Damont A, Roeda D, Tavittian B, Dollé F. Current paradigm of the 18-kDa translocator protein (TSPO) as a molecular target for PET imaging in neuroinflammation and neurodegenerative diseases. *Insights into imaging*. 2012; 3(1):111–119. [PubMed: 22696004]
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003; 289(19):2560–2572. doi: 10.1001/jama.289.19.2560 289.19.2560 [pii]. [PubMed: 12748199]
- Chou SY, Shulman J, Keenan B, Secor E, Buchman A, Schneider J, et al. De Jager P. Genetic susceptibility for ischemic infarction and arteriolosclerosis based on neuropathologic evaluations. *Cerebrovascular Diseases*. 2013; 36(3):181–188. [PubMed: 24135527]
- Cordonnier C, Al-Shahi Salman R, Wardlaw J. Spontaneous brain microbleeds: systematic review, subgroup analyses and standards for study design and reporting. *Brain*. 2007; 130(8):1988–2003. [PubMed: 17322562]
- Crawford AG, Cote C, Couto J, Daskiran M, Gunnarsson C, Haas K, et al. Schuette R. Prevalence of obesity, type II diabetes mellitus, hyperlipidemia, and hypertension in the United States: findings from the GE Centricity Electronic Medical Record database. *Popul Health Manag*. 2010; 13(3): 151–161.10.1089/pop.2009.0039 [PubMed: 20521902]

- D'Esposito M, Zarahn E, Aguirre GK, Rypma B. The effect of normal aging on the coupling of neural activity to the bold hemodynamic response. *Neuroimage*. 1999; 10(1):6–14. [PubMed: 10385577]
- 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(2):349–354. [PubMed: 18174483]
- Das RR, Seshadri S, Beiser AS, Kelly-Hayes M, Au R, Himali JJ, et al. Wolf PA. Prevalence and correlates of silent cerebral infarcts in the Framingham offspring study. *Stroke*. 2008; 39(11):2929–2935. [PubMed: 18583555]
- DeBette S, Bis JC, Fornage M, Schmidt H, Ikram MA, Sigurdsson S, et al. van der Lugt A. Genome-Wide Association Studies of MRI-Defined Brain Infarcts Meta-Analysis From the CHARGE Consortium. *Stroke*. 2010; 41(2):210–217. [PubMed: 20044523]
- DeBette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ*. 2010; 341:c3666. [PubMed: 20660506]
- DeBette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C, et al. DeCarli C. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology*. 2011; 77(5):461–468. [PubMed: 21810696]
- DeCarli C, Massaro J, Harvey D, Hald J, Tullberg M, Au R, et al. Wolf PA. Measures of brain morphology and infarction in the framingham heart study: establishing what is normal. *Neurobiol Aging*. 2005; 26(4):491–510. [PubMed: 15653178]
- DeCarli C, Murphy DG, Tranh M, Grady CL, Haxby JV, Gillette JA, 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(11):2077–2084. [PubMed: 7501162]
- Dietschy JM, Turley SD. Cholesterol metabolism in the brain. *Current opinion in lipidology*. 2001; 12(2):105–112. [PubMed: 11264981]
- Dinarello C. Role of pro-and anti-inflammatory cytokines during inflammation: experimental and clinical findings. *Journal of biological regulators and homeostatic agents*. 1996; 11(3):91–103. [PubMed: 9498158]
- Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. *Trends in Neurosciences*. 1999; 22(9):391–397. [PubMed: 10441299]
- Dufouil C, Chalmers J, Coskun O, Besançon Vr, Bousser MG, Guillon P, et al. Investigators, f. t. P. M. S. Effects of Blood Pressure Lowering on Cerebral White Matter Hyperintensities in Patients With Stroke. *Circulation*. 2005; 112(11):1644–1650.10.1161/circulationaha.104.501163 [PubMed: 16145004]
- Ebrahim S, Papacosta O, Whincup P, Wannamethee G, Walker M, Nicolaides AN, et al. Rumley A. Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women the British Regional Heart Study. *Stroke*. 1999; 30(4):841–850. [PubMed: 10187889]
- Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, et al. Lechner H. Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology*. 1993; 43(9):1683–1683. [PubMed: 8414012]
- Fazekas F, Schmidt R, Kleinert R, Kapeller P, Roob G, Flooh E. The spectrum of age-associated brain abnormalities: their measurement and histopathological correlates. *J Neural Transm Suppl*. 1998; 53:31–39. [PubMed: 9700644]
- Flasque N, Desvignes M, Constans JM, Revenu M. Acquisition, segmentation and tracking of the cerebral vascular tree on 3D magnetic resonance angiography images. *Medical Image Analysis*. 2001; 5(3):173–183. [PubMed: 11524224]
- Fornage M, Chiang YA, O'Meara ES, Psaty BM, Reiner AP, Siscovick DS, et al. Longstreth WT. Biomarkers of Inflammation and MRI-Defined Small Vessel Disease of the Brain: The Cardiovascular Health Study. *Stroke*. 2008; 39(7):1952–1959.10.1161/strokeaha.107.508135 [PubMed: 18436879]
- Gearing AJ, Newman W. Circulating adhesion molecules in disease. *Immunology today*. 1993; 14(10):506–512. [PubMed: 7506035]

- Gilbert J, Vinters H. Cerebral amyloid angiopathy: incidence and complications in the aging brain. I. Cerebral hemorrhage. *Stroke*. 1983; 14(6):915–923. [PubMed: 6658995]
- Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Stroke Statistics, S. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation*. 2013; 127(1):e6–e245.10.1161/CIR.0b013e31828124ad [PubMed: 23239837]
- Godin O, Tzourio C, Maillard P, Mazoyer B, Dufouil C. Antihypertensive Treatment and Change in Blood Pressure Are Associated With the Progression of White Matter Lesion VolumesClinical Perspective The Three-City (3C)–Dijon Magnetic Resonance Imaging Study. *Circulation*. 2011; 123(3):266–273. [PubMed: 21220733]
- Goos JD, Henneman WJ, Sluimer JD, Vrenken H, Sluimer IC, Barkhof F, et al. van der Flier WM. Incidence of cerebral microbleeds: a longitudinal study in a memory clinic population. *Neurology*. 2010; 74(24):1954–1960. doi:10.1212/WNL.0b013e3181e396ea [doi]. [PubMed: 20548041]
- Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Seshadri S. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2011; 42(9):2672–2713. doi:STR.0b013e3182299496 [pii] 10.1161/STR.0b013e3182299496. [PubMed: 21778438]
- Gouw AA, Seewann A, van der Flier WM, Barkhof F, Rozemuller AM, Scheltens P, Geurts JJ. Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations. *Journal of Neurology, Neurosurgery & Psychiatry*. 2011; 82(2):126–135.
- Grimmer T, Faust M, Auer F, Alexopoulos P, Förstl H, Henriksen G, et al. Drzezga A. White matter hyperintensities predict amyloid increase in Alzheimer's disease. *Neurobiology of Aging*. 2012; 33(12):2766–2773. [PubMed: 22410648]
- Guo X, Pantoni L, Simoni M, Bengtsson C, Björkelund C, Lissner L, et al. Skoog I. Blood Pressure Components and Changes in Relation to White Matter Lesions. *Hypertension*. 2009; 54(1):57–62.10.1161/hypertensionaha.109.129700 [PubMed: 19487586]
- Guzman VA, Carmichael OT, Schwarz C, Tosto G, Zimmerman ME, et al. Brickman AM. White matter hyperintensities and amyloid are independently associated with entorhinal cortex volume among individuals with mild cognitive impairment. *Alzheimer's & Dementia*. 2013
- Haight T, Carmichael O, Landau S, Schwarz C, DeCarli C, et al. Jagust W. Dissociable effects of Alzheimer's Disease and white matter hyperintensities on brain metabolism. *Archives of neurology*. 2013 In Press.
- Hajjar I, Brown L, Mack WJ, Chui H. Impact of Angiotensin Receptor Blockers on Alzheimer Disease Neuropathology in a Large Brain Autopsy SeriesARB Impact on AD Neuropathology. *Archives of neurology*. 2012; 69(12):1632–1638. [PubMed: 22964777]
- Hajjar I, Hart M, Chen YL, Mack W, Novak V, H CC, Lipsitz L. Antihypertensive therapy and cerebral hemodynamics in executive mild cognitive impairment: results of a pilot randomized clinical trial. *J Am Geriatr Soc*. 2013; 61(2):194–201.10.1111/jgs.12100 [PubMed: 23350899]
- Hajjar I, Zhao P, Alsop D, Novak V. Hypertension and cerebral vasoreactivity a continuous arterial spin labeling magnetic resonance imaging study. *Hypertension*. 2010; 56(5):859–864. [PubMed: 20876450]
- Hansen TW, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation*. 2006; 113(5):664–670. [PubMed: 16461839]
- Harvey D, Laurel B, Mungas D. Multivariate modeling of two associated cognitive outcomes in a longitudinal study. *Journal of Alzheimer's Disease*. 2003; 5(5):357–365.
- Havlik RJ, Foley DJ, Sayer B, Masaki K, White L, Launer LJ. Variability in Midlife Systolic Blood Pressure Is Related to Late-Life Brain White Matter Lesions. *Stroke*. 2002; 33(1):26–30.10.1161/hs0102.101890 [PubMed: 11779884]
- Hedden T, Mormino EC, Amariglio RE, Younger AP, Schultz AP, Becker JA, et al. Rentz DM. Cognitive profile of amyloid burden and white matter hyperintensities in cognitively normal older adults. *The Journal of Neuroscience*. 2012; 32(46):16233–16242. [PubMed: 23152607]
- Henskens LH, Kroon AA, van Oostenbrugge RJ, Gronenschild EH, Fuss-Lejeune MM, Hofman PA, et al. de Leeuw PW. Increased aortic pulse wave velocity is associated with silent cerebral small-

- vessel disease in hypertensive patients. *Hypertension*. 2008; 52(6):1120–1126. [PubMed: 18852384]
- Höglund K, Wiklund O, Vanderstichele H, Eikenberg O, Vanmechelen E, Blennow K. Plasma levels of β -amyloid (1-40), β -amyloid (1-42), and total β -amyloid remain unaffected in adult patients with hypercholesterolemia after treatment with statins. *Archives of neurology*. 2004; 61(3):333–337. [PubMed: 15023808]
- Hoshi T, Kitagawa K, Yamagami H, Furukado S, Hougaku H, Hori M. Relations of serum high-sensitivity C-reactive protein and interleukin-6 levels with silent brain infarction. *Stroke*. 2005; 36(4):768–772. [PubMed: 15746456]
- Hsu JL, Chen YL, Leu JG, Jaw FS, Lee CH, Tsai YF, et al. Leemans A. Microstructural white matter abnormalities in type 2 diabetes mellitus: a diffusion tensor imaging study. *Neuroimage*. 2012; 59(2):1098–1105.10.1016/j.neuroimage.2011.09.041 [PubMed: 21967726]
- Illiff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. Goldman SA. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β . *Science translational medicine*. 2012; 4(147):147ra111–147ra111.
- Imabayashi E, Matsuda H, Yoshimaru K, Kuji I, Seto A, Shimano Y, et al. Araki N. Pilot data on telmisartan short-term effects on glucose metabolism in the olfactory tract in Alzheimer's disease. *Brain and behavior*. 2011; 1(2):63–69. [PubMed: 22399085]
- Ishikawa J, Tamura Y, Hoshida S, Eguchi K, Ishikawa S, Shimada K, Kario K. Low-grade inflammation is a risk factor for clinical stroke events in addition to silent cerebral infarcts in Japanese older hypertensives the Jichi Medical School ABPM Study, wave 1. *Stroke*. 2007; 38(3):911–917. [PubMed: 17272770]
- Jagust WJ, Zheng L, Harvey DJ, Mack WJ, Vinters HV, Weiner MW, et al. Chui HC. Neuropathological basis of magnetic resonance images in aging and dementia. *Ann Neurol*. 2008; 63(1):72–80. doi:10.1002/ana.21296 [doi]. [PubMed: 18157909]
- Jeerakathil T, Wolf PA, Beiser A, Massaro J, Seshadri S, D'Agostino RB, DeCarli C. Stroke risk profile predicts white matter hyperintensity volume: the Framingham Study. *Stroke*. 2004; 35(8):1857–1861. [PubMed: 15218158]
- Jefferson A, Massaro J, Wolf P, Seshadri S, Au R, Vasan R, et al. Lipinska I. Inflammatory biomarkers are associated with total brain volume The Framingham Heart Study. *Neurology*. 2007; 68(13):1032–1038. [PubMed: 17389308]
- Joas E, Bäckman K, Gustafson D, Östling S, Waern M, Guo X, Skoog I. Blood pressure trajectories from midlife to late life in relation to dementia in women followed for 37 years. *Hypertension*. 2012; 59(4):796–801. [PubMed: 22331381]
- Kannel WB, Gordan T. Evaluation of cardiovascular risk in the elderly: the Framingham study. *Bull N Y Acad Med*. 1978; 54(6):573–591. [PubMed: 274986]
- Kiechl S, Willeit J. The natural course of atherosclerosis. Part II: vascular remodeling. Bruneck Study Group. *Arterioscler Thromb Vasc Biol*. 1999; 19(6):1491–1498. [PubMed: 10364080]
- Kimura Y, Kitagawa K, Oku N, Kajimoto K, Kato H, Tanaka M, et al. Hatazawa J. Blood pressure lowering with valsartan is associated with maintenance of cerebral blood flow and cerebral perfusion reserve in hypertensive patients with cerebral small vessel disease. *Journal of Stroke and Cerebrovascular Diseases*. 2010; 19(2):85–91. [PubMed: 20189083]
- Kin T, Yamano S, Sakurai R, Kajitani M, Okahashi Y, Nishiura N, et al. Ueno S. Carotid atherosclerosis is associated with brain atrophy in Japanese elders. *Gerontology*. 2007; 53(1):1–6. doi:10.1159/000095385 [doi]. [PubMed: 16940733]
- Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, et al. Nissinen A. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ*. 2001; 322(7300):1447–1451. [PubMed: 11408299]
- Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, et al. Atherosclerosis Risk in Communities Study, I. Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology*. 2001; 56(1):42–48. [PubMed: 11148234]
- Knopman DS, Penman AD, Catellier DJ, Coker LH, Shibata DK, Sharrett AR, Mosley TH Jr. Vascular risk factors and longitudinal changes on brain MRI: the ARIC study. *Neurology*. 2011; 76(22):1879–1885. [PubMed: 21543737]

- Knopman DS, Roberts R. Vascular risk factors: imaging and neuropathologic correlates. *J Alzheimers Dis.* 2010; 20(3):699–709.10.3233/JAD-2010-091555 [PubMed: 20182020]
- Korf ESC, White LR, Scheltens P, Launer LJ. Midlife Blood Pressure and the Risk of Hippocampal Atrophy. *Hypertension.* 2004; 44(1):29–34.10.1161/01.HYP.0000132475.32317.bb [PubMed: 15159381]
- Kuller LH, Lopez OL, Newman A, Beauchamp NJ, Burke G, Dulberg C, et al. Haan MN. Risk factors for dementia in the cardiovascular health cognition study. *Neuroepidemiology.* 2003; 22(1):13–22. doi:10.1159/000067109 [doi] 67109 [pii]. [PubMed: 12566949]
- Kuller LH, Margolis KL, Gaussoin SA, Bryan NR, Kerwin D, Limacher M, et al. Robinson JG. Relationship of hypertension, blood pressure, and blood pressure control with white matter abnormalities in the Women's Health Initiative Memory Study (WHIMS)—MRI trial. *The Journal of Clinical Hypertension.* 2010; 12(3):203–212. [PubMed: 20433539]
- Launer LJ, Hughes T, Yu B, Masaki K, Petrovitch H, Ross GW, et al. White LR. Lowering midlife levels of systolic blood pressure as a public health strategy to reduce late-life dementia: perspective from the Honolulu Heart Program/Honolulu Asia Aging Study. *Hypertension.* 2010; 55(6):1352–1359. doi:10.1161/HYPERTENSIONAHA.109.147389 [doi]. [PubMed: 20404223]
- Le Bihan D. Looking into the functional architecture of the brain with diffusion MRI. *Nat Rev Neurosci.* 2003; 4(6):469–480.10.1038/nrn1119 [PubMed: 12778119]
- Lehmann E, Parker J, Hopkins K, Taylor M, Gosling R. Validation and reproducibility of pressure-corrected aortic distensibility measurements using pulse-wave-velocity Doppler ultrasound. *Journal of biomedical engineering.* 1993; 15(3):221–228. [PubMed: 8320981]
- Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation.* 2002; 105(9):1135–1143. [PubMed: 11877368]
- Liu Q, Zerbiniatti CV, Zhang J, Hoe HS, Wang B, Cole SL, et al. Bu G. Amyloid precursor protein regulates brain apolipoprotein E and cholesterol metabolism through lipoprotein receptor LRP1. *Neuron.* 2007; 56(1):66–78. [PubMed: 17920016]
- Loessner A, Alavi A, Lewandrowski KU, Mozley D, Souder E, Gur RE. Regional cerebral function determined by FDG-PET in healthy volunteers: normal patterns and changes with age. *J Nucl Med.* 1995; 36(7):1141–1149. [PubMed: 7790936]
- Logothetis NK, Pfeuffer J. On the nature of the BOLD fMRI contrast mechanism. *Magn Reson Imaging.* 2004; 22(10):1517–1531.10.1016/j.mri.2004.10.018 [PubMed: 15707801]
- Lopez OL, Jagust WJ, Dulberg C, Becker JT, DeKosky ST, Fitzpatrick A, et al. Kuller LH. Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 2. *Arch Neurol.* 2003; 60(10):1394–1399. [PubMed: 14568809]
- Madamanchi NR, Vendrov A, et al. Runge MS. Oxidative Stress and Vascular Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 25(1):29–38.10.1161/01.atv.0000150649.39934.13
- Maillard P, Seshadri S, Beiser A, Himali J, Au R, Fletcher E, et al. DeCarli C. Effects of Systolic Blood Pressure on White Matter Integrity in Young Adults: from the Framingham Heart Study. *The Lancet Neurology.* 2012 In Press.
- Manolio TA, Burke GL, O'Leary DH, Evans G, Beauchamp N, Knepper L, Ward B. Relationships of cerebral MRI findings to ultrasonographic carotid atherosclerosis in older adults : the Cardiovascular Health Study. CHS Collaborative Research Group. *Arterioscler Thromb Vasc Biol.* 1999; 19(2):356–365. [PubMed: 9974419]
- Marchant NL, Reed BR, DeCarli CS, Madison CM, Weiner MW, Chui HC, Jagust WJ. Cerebrovascular disease, beta-amyloid, and cognition in aging. *Neurobiology of Aging.* 2012; 33(5):1006. e1025, 1006. e1036. [PubMed: 22048124]
- Matsumoto S, Shimodozono M, Miyata R, Kawahira K. Effect of the angiotensin II type 1 receptor antagonist olmesartan on cerebral hemodynamics and rehabilitation outcomes in hypertensive post-stroke patients. *Brain Injury.* 2009; 23(13-14):1065–1072. [PubMed: 19891533]
- McGeer PL, McGeer EG. Polymorphisms in inflammatory genes and the risk of Alzheimer disease. *Archives of neurology.* 2001; 58(11):1790–1792. [PubMed: 11708985]
- McGuinness B, Todd S, Passmore P, et al. Bullock R. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *Cochrane*

- Database Syst Rev. 2009; (4):CD004034. doi:10.1002/14651858.CD004034.pub3 [doi]. [PubMed: 19821318]
- Miranda PJ, DeFronzo RA, Califf RM, et al. Guyton JR. Metabolic syndrome: definition, pathophysiology, and mechanisms. *Am Heart J*. 2005; 149(1):33–45. doi:10.1016/j.ahj.2004.07.013 [doi]. [PubMed: 15660032]
- Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson Ó, et al. Gudnason V. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility–Reykjavik Study. *Brain*. 2011; 134(11):3398–3407. [PubMed: 22075523]
- Miwa K, Tanaka M, Okazaki S, Furukado S, Sakaguchi M, Kitagawa K. Relations of blood inflammatory marker levels with cerebral microbleeds. *Stroke*. 2011; 42(11):3202–3206. [PubMed: 21868735]
- Moran C, Phan TG, Chen J, Blizzard L, Beare R, Venn A, et al. Srikanth V. Brain Atrophy in Type 2 Diabetes: Regional distribution and influence on cognition. *Diabetes Care*. 2013;10.2337/dc13-0143
- Morris JC, Price AL. Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. *J Mol Neurosci*. 2001; 17(2):101–118. [PubMed: 11816784]
- Muller M, van der Graaf Y, Algra A, Hendrikse J, Mali WP, Geerlings MI. Carotid atherosclerosis and progression of brain atrophy: The SMART-MR Study. *Annals of Neurology*. 2011; 70(2):237–244. doi:10.1002/ana.22392 [PubMed: 21674583]
- Muller M, van der Graaf Y, Visseren FL, Mali WP, Geerlings MI. for the, S. S..G. Hypertension and longitudinal changes in cerebral blood flow: The SMART-MR study. *Ann Neurol*. 2012 doi: 10.1002/ana.23554 [doi].
- Ninomiya T, Ohara T, Hirakawa Y, Yoshida D, Doi Y, Hata J, et al. Kiyohara Y. Midlife and Late-Life Blood Pressure and Dementia in Japanese Elderly The Hisayama Study. *Hypertension*. 2011; 58(1):22–28. [PubMed: 21555680]
- Novak V, Hajjar I. The relationship between blood pressure and cognitive function. *Nat Rev Cardiol*. 2010; 7(12):686–698. doi:10.1038/nrcardio.2010.161 [PubMed: 20978471]
- O'Leary D, Polak J, Kronmal R, Kittner S, Bond M, Wolfson S Jr, et al. Savage P. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. The CHS Collaborative Research Group. *Stroke*. 1992; 23(12):1752–1760. [PubMed: 1448826]
- O'Sullivan M, Morris RG, Huckstep B, Jones DK, Williams SCR, Markus HS. Diffusion tensor MRI correlates with executive dysfunction in patients with ischaemic leukoaraiosis. *J Neurol Neurosurg Psychiatr*. 2004; 75(3):441–447. [PubMed: 14966162]
- O'Rourke MF, Safar ME. Relationship Between Aortic Stiffening and Microvascular Disease in Brain and Kidney Cause and Logic of Therapy. *Hypertension*. 2005; 46(1):200–204. [PubMed: 15911742]
- Ohmine T, Miwa Y, Yao H, Yuzuriha T, Takashima Y, Uchino A, et al. Sasaguri T. Association between arterial stiffness and cerebral white matter lesions in community-dwelling elderly subjects. *Hypertension Research*. 2008; 31(1):75–81. [PubMed: 18360021]
- Owen DR, Yeo AJ, Gunn RN, Song K, Wadsworth G, Lewis A, et al. Parker CA. An 18-kDa translocator protein (TSPO) polymorphism explains differences in binding affinity of the PET radioligand PBR28. *Journal of Cerebral Blood Flow & Metabolism*. 2012; 32(1):1–5. [PubMed: 22008728]
- Pantoni L, Garcia JH. Pathogenesis of Leukoaraiosis : A Review. *Stroke*. 1997; 28(3):652–659. doi:10.1161/01.str.28.3.652 [PubMed: 9056627]
- Pappolla M, Bryant-Thomas T, Herbert D, Pacheco J, Garcia MF, Manjon M, et al. Zambon D. Mild hypercholesterolemia is an early risk factor for the development of Alzheimer amyloid pathology. *Neurology*. 2003; 61(2):199–205. [PubMed: 12874399]
- Parkes LM, Rashid W, Chard DT, Tofts PS. Normal cerebral perfusion measurements using arterial spin labeling: reproducibility, stability, and age and gender effects. *Magn Reson Med*. 2004; 51(4):736–743. doi:10.1002/mrm.20023 [PubMed: 15065246]

- Petersen ET, Zimine I, Ho YC, Golay X. Non-invasive measurement of perfusion: a critical review of arterial spin labelling techniques. *Br J Radiol.* 2006; 79(944):688–701.10.1259/bjr/67705974 [PubMed: 16861326]
- Pico F, Dufouil C, Levy C, Besancon V, de Kersaint-Gilly A, Bonithon-Kopp C, et al. Alperovitch A. Longitudinal study of carotid atherosclerosis and white matter hyperintensities: the EVA-MRI cohort. *Cerebrovasc Dis.* 2002; 14(2):109–115. doi:ced14109 [pii]. [PubMed: 12187015]
- Poels MM, Vernooij MW, Ikram MA, Hofman A, Krestin GP, van der Lugt A, Breteler MM. Prevalence and risk factors of cerebral microbleeds: an update of the Rotterdam scan study. *Stroke.* 2010; 41(10 Suppl):S103–106. [PubMed: 20876479]
- Prabhakaran S, Wright CB, Yoshita M, Delapaz R, Brown T, DeCarli C, Sacco RL. Prevalence and determinants of subclinical brain infarction: the Northern Manhattan Study. *Neurology.* 2008; 70(6):425–430. doi:01.wnl.0000277521.66947.e5 [pii] 10.1212/01.wnl.0000277521.66947.e5. [PubMed: 17898325]
- Preston SD, Steart PV, Wilkinson A, Nicoll JA, et al. Weller RO. Capillary and arterial cerebral amyloid angiopathy in Alzheimer's disease: defining the perivascular route for the elimination of amyloid beta from the human brain. *Neuropathol Appl Neurobiol.* 2003; 29(2):106–117. doi:424 [pii]. [PubMed: 12662319]
- Provenzano FA, Muraskin J, Tosto G, Narkhede A, Wasserman BT, Griffith EY, et al. Brickman AM. White matter hyperintensities and cerebral amyloidosis: necessary and sufficient for clinical expression of Alzheimer disease? *JAMA neurology.* 2013; 70(4):455–461. [PubMed: 23420027]
- Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, et al. Acker JD. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb Cortex.* 2005; 15(11):1676–1689. [PubMed: 15703252]
- Refolo LM, Pappolla MA, Malester B, LaFrancois J, Bryant-Thomas T, Wang R, et al. Duff K. Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. *Neurobiology of disease.* 2000; 7(4):321–331. [PubMed: 10964604]
- Roses M, Allen D. Apolipoprotein E alleles as risk factors in Alzheimer's disease. *Annual review of medicine.* 1996; 47(1):387–400.
- Ruchoux MM, Muraige CA. CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Journal of Neuropathology & Experimental Neurology.* 1997; 56(9):947–964. [PubMed: 9291937]
- Salminen A, Ojala J, Kauppinen A, Kaarniranta K, Suuronen T. Inflammation in Alzheimer's disease: amyloid- β oligomers trigger innate immunity defence via pattern recognition receptors. *Progress in neurobiology.* 2009; 87(3):181–194. [PubMed: 19388207]
- Salonen R, Salonen JT. Determinants of carotid intima-media thickness: a population-based ultrasonography study in Eastern Finnish men. *Journal of internal medicine.* 1991; 229(3):225–231. [PubMed: 2007840]
- Schnabel R, Larson MG, Dupuis J, Lunetta KL, Lipinska I, Meigs JB, et al. Newton-Cheh C. Relations of inflammatory biomarkers and common genetic variants with arterial stiffness and wave reflection. *Hypertension.* 2008; 51(6):1651–1657. [PubMed: 18426996]
- Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology.* 2007; 69(24):2197–2204. [PubMed: 17568013]
- 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(1):59–66. [PubMed: 17503514]
- Schroeder EB, Hanratty R, Beaty BL, Bayliss EA, Havranek EP, Steiner JF. Simultaneous control of diabetes mellitus, hypertension, and hyperlipidemia in 2 health systems. *Circ Cardiovasc Qual Outcomes.* 2012; 5(5):645–653.10.1161/CIRCOUTCOMES.111.963553 [PubMed: 22851534]
- Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) Study. *Circulation.* 2005; 111(14):1777–1783. [PubMed: 15809377]

- Seshadri S, Wolf PA, Beiser A, Elias MF, Au R, Kase CS, et al. DeCarli C. Stroke risk profile, brain volume, and cognitive function: the Framingham Offspring Study. *Neurology*. 2004; 63(9):1591–1599. doi:63/9/1591 [pii]. [PubMed: 15534241]
- Siegel D, Lopez J, Meier J. Antihypertensive medication adherence in the Department of Veterans Affairs. *The American journal of medicine*. 2007; 120(1):26–32. [PubMed: 17208076]
- Simons M, Keller P, De Strooper B, Beyreuther K, Dotti CG, Simons K. Cholesterol depletion inhibits the generation of β -amyloid in hippocampal neurons. *Proceedings of the National Academy of Sciences*. 1998; 95(11):6460–6464.
- Snider BJ, Gottron FJ, Choi DW. Apoptosis and Necrosis in Cerebrovascular Disease. *Annals of the New York Academy of Sciences*. 1999; 893(1):243–253.10.1111/j.1749-6632.1999.tb07829.x [PubMed: 10672241]
- Stewart R, Xue QL, Masaki K, Petrovitch H, Ross GW, White LR, et al. Launer LJ. Change in blood pressure and incident dementia: a 32-year prospective study. *Hypertension*. 2009; 54(2):233–240. doi:10.1161/HYPERTENSIONAHA.109.128744 [doi]. [PubMed: 19564551]
- 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(4):986–993. [PubMed: 9781518]
- Tan ZS, Beiser AS, Fox CS, Au R, Himali JJ, Debette S, et al. Seshadri S. Association of metabolic dysregulation with volumetric brain magnetic resonance imaging and cognitive markers of subclinical brain aging in middle-aged adults: the Framingham Offspring Study. *Diabetes Care*. 2011; 34(8):1766–1770. doi:10.2337/dc11-0308 [doi]. [PubMed: 21680719]
- Tanaka H, Munakata M, Kawano Y, Ohishi M, Shoji T, Sugawara J, et al. Sawayama T. Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. *Journal of hypertension*. 2009; 27(10):2022–2027. [PubMed: 19550355]
- Tell GS, Crouse JR, Furberg CD. Relation between blood lipids, lipoproteins, and cerebrovascular atherosclerosis. A review. *Stroke*. 1988; 19(4):423–430. [PubMed: 3284015]
- Thöne-Reineke C, Zimmermann M, Neumann C, Krikov M, Li J, Gerova N, Unger T. Are angiotensin receptor blockers neuroprotective? *Current hypertension reports*. 2004; 6(4):257–266. [PubMed: 15257859]
- Touboul PJ, Hennerici M, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Fatar M. Mannheim carotid intima-media thickness consensus (2004– 2006). *Cerebrovascular Diseases*. 2006; 23(1): 75–80. [PubMed: 17108679]
- Tsao CW, Seshadri S, Beiser AS, Westwood AJ, DeCarli C, Au R, et al. Mitchell GF. Relations of Arterial Stiffness and Endothelial Function to Brain Aging in the Community. *Neurology*. 2013 In Press.
- Valeo T. NEWS FROM THE AAN ANNUAL MEETING: Autopsied Brains Show Seniors on Beta Blockers Had Fewer Signs of Dementia. *Neurology Today*. 2013; 13(5):1–6.
- van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: A review on resting-state fMRI functional connectivity. *European Neuropsychopharmacology*. 2010; 20(8):519–534. [PubMed: 20471808]
- van Dijk EJ. C-Reactive Protein and Cerebral Small-Vessel Disease: The Rotterdam Scan Study. *Circulation*. 2005; 112(6):900–905.10.1161/circulationaha.104.506337 [PubMed: 16061741]
- van Es AC, van der Grond J, ten Dam VH, de Craen AJ, Blauw GJ, Westendorp RG, et al. Group, P. S. Associations between total cerebral blood flow and age related changes of the brain. *PLoS One*. 2010; 5(3):e9825. doi:10.1371/journal.pone.0009825 [doi]. [PubMed: 20352115]
- van Popele NM, Grobbee DE, Bots ML, Asmar R, Topouchian J, Reneman RS, et al. Witteman JC. Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke*. 2001; 32(2):454–460. [PubMed: 11157182]
- Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med*. 2001; 345(18):1291–1297.10.1056/NEJMoa003417 [PubMed: 11794147]
- Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, et al. Santucci A. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension*. 1994; 24(6):793–801. [PubMed: 7995639]

- Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol.* 2007; 6(7):611–619. [PubMed: 17582361]
- Vinters H, Gilbert J. Cerebral amyloid angiopathy: incidence and complications in the aging brain. II. The distribution of amyloid vascular changes. *Stroke.* 1983; 14(6):924–928. [PubMed: 6658996]
- White JA, Manelli AM, Holmberg KH, Van Eldik LJ, LaDu MJ. Differential effects of oligomeric and fibrillar amyloid- β 1–42 on astrocyte-mediated inflammation. *Neurobiology of disease.* 2005; 18(3):459–465. [PubMed: 15755672]
- White, L.; Gelber, R.; Launer, L.; Zarow, C.; Sonnen, J.; Uyehara-Lock, J.; et al. Petrovitch, H. Beta Blocker Treatment of Hypertensive Older Persons Ameliorates the Brain Lesions of Dementia Measured at Autopsy: The Honolulu-Asia Aging Study; Paper presented at the American Academy of Neurology Annual Meeting; San Diego. 2013.
- White L, Small BJ, Petrovitch H, Ross GW, Masaki K, Abbott RD, et al. Markesbery W. Recent Clinical-Pathologic Research on the Causes of Dementia in Late Life: Update From the Honolulu-Asia Aging Study. *Journal of Geriatric Psychiatry and Neurology.* 2005; 18(4):224–227.10.1177/0891988705281872 [PubMed: 16306244]
- Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology.* 2005; 64(2):277–281.10.1212/01.wnl.0000149519.47454.f2 [PubMed: 15668425]
- Wills AK, Lawlor DA, Matthews FE, Sayer AA, Bakra E, Ben-Shlomo Y, et al. Kivimaki M. Life course trajectories of systolic blood pressure using longitudinal data from eight UK cohorts. *PLoS medicine.* 2011; 8(6):e1000440. [PubMed: 21695075]
- Wills AK, Lawlor DA, Muniz-Terrera G, Matthews F, Cooper R, Ghosh AK, et al. Hardy R. Population heterogeneity in trajectories of midlife blood pressure. *Epidemiology (Cambridge, Mass).* 2012; 23(2):203.
- Wilms H, Rosenstiel P, Unger T, Deuschl G, Lucius R. Neuroprotection with Angiotensin Receptor Antagonists. *American journal of cardiovascular drugs.* 2005; 5(4):245–253. [PubMed: 15984907]
- Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke.* 1991; 22(3):312–318. [PubMed: 2003301]
- Wright CB, Moon Y, Paik MC, Brown TR, Rabbani L, Yoshita M, et al. Elkind MS. Inflammatory biomarkers of vascular risk as correlates of leukoariorosis. *Stroke.* 2009; 40(11):3466–3471. [PubMed: 19696417]
- Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, et al. Yamamoto Y. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertension Research.* 2002; 25(3):359–364. [PubMed: 12135313]
- Yip A, McKee A, Green R, Wells J, Young H, Cupples L, Farrer L. APOE, vascular pathology, and the AD brain. *Neurology.* 2005; 65(2):259–265. [PubMed: 16043796]
- Yuan C, et al. Kerwin WS. MRI of atherosclerosis. *J Magn Reson Imaging.* 2004; 19(6):710–719. doi: 10.1002/jmri.20070 [doi]. [PubMed: 15170778]
- Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 2005; 25(5):932–943.

Figure 1.

Conceptual model in which vascular injury processes lead to preclinical cerebrovascular injury, which in turn contributes to brain injury and subsequent cognitive decline.

Figure 2.

Left: Phase-contrast MRI provides time series of 3D blood velocity vectors in the aortic arch and descending aorta, and analytic software measures instantaneous blood flow rate at a set of user-defined analysis planes (numbered). **Center:** Pulse wave velocity is estimated by dividing the distance between analysis planes by the time interval (Δt) between systolic upstroke curves at those planes. **Right:** Pulse wave velocities of 4 subjects are within the expected range of values and show an expected general trend of increase with age.

Figure 3.

Fine grained MRI measurement of internal carotid artery (ICA) radii. **Top left:** The ICA is clearly visible on a 3D time-of-flight MR angiography. **Top middle:** 3D modeling of the vessel allows identification of a vessel center line and calculation of vessel radius at each point along the vessel. **Top right:** Plot of local radius of the ICA as a function of position along the ICA center line reveals intra- and inter-individual variability in ICA radius in a typical young and elderly participant. **Lower left:** The ratio of minimum to maximum vessel radius along the ICA was significantly smaller ($p < .001$, bottom left) among a group of 10 elderly individuals compared to a group of 10 young adults. **Lower middle:** Lesser values of this ratio, a summary measure of stenosis, was associated with lesser gray matter volume in the older subjects ($p = .02$, bottom right).