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CLINICALLY ASYMPTOMATIC VASCULAR BRAIN INJURY, A POTENT CAUSE OF COGNITIVE IMPAIRMENT AMONGST OLDER INDIVIDUALS

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Abstract

Cerebrovascular risk factors and stroke are highly prevalent with advancing age and stroke may be more common than Alzheimer's disease, particularly amongst older men. While stroke mortality continues to decline, the prevalence of individuals with various vascular risk factors continues to rise and many are undiagnosed or undertreated. Asymptomatic cerebrovascular brain injury that includes asymptomatic brain infarction, white matter hyperintensities and even accelerated brain atrophy is even more frequent than clinical stroke. Moreover, the impact of cerebrovascular risk factors on brain injury appears to begin in middle life and additively increases the likelihood of later life dementia. This review focuses on the use of neuroimaging and genetics to understand the impact of asymptomatic vascular risk factors on the trajectories of cognitive aging as well as incident cognitive impairment, stroke and mortality. Results of this review emphasize the need for early detection and treatment of vascular risk factors to improve the cognitive health of our rapidly aging population.

Keywords

Magnetic Resonanace Imaging; white matter hyperintensities; cerebrovascular disease; pathophysiology

INTRODUCTION

Growth in the number of individuals over 65 years of age in the world is unprecedented. For example, in Italy nearly 20% of the population is over age 65 [1]. In the United States, approximately 330 individuals per hour turn age 60 and as of 2010 as many as 45 million were 65 years of age or older [2], resulting in an expected near doubling of the population age 65 and older by 2030[1]. The percentage of individuals over age 65 is increasing even more rapidly in developing countries [1]. It is, therefore, timely to consider diseases of aging, such as cognitive impairment.

Complaints of cognitive impairment, particularly memory loss, are common to older individuals [3]. Cross-sectional epidemiological studies suggest linear age-related decline in memory performance, although remarkable differences in individual trajectories of decline exist [4]. These data have been used to suggest that the results of at least some of the studies of cognitive aging may be contaminated by the inclusion of individuals with incipient disease [4].

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While Alzheimer's disease (AD) is clearly the major cause for cognitive impairment amongst the elderly [5–7], current evidence suggests that an individual's lifetime risk for cerebrovascular disease (CVD) may be similar or even higher than AD [8] and these two diseases commonly occur in the same individual [9]. Although stroke is considered the clinical hallmark of CVD, it is important to recognize that the full spectrum of CVD includes clinically asymptomatic cerebral infarction, white matter hyperintensities (WMH) and even accelerated brain atrophy [10], that are common to advancing age amongst cognitively normal community dwelling individuals [11].

The potential impact of clinically asymptomatic cerebrovascular injury was first identified by Hachinksi and colleagues [12–18]. In this series of seminal articles, Hachinski's group described the presence of attenuated white matter signals seen on cerebral x-ray computed tomography which they called "leuko-araiosis" to indicate reduced x-ray absorption in cerebral white matter. First reports found significant associations between leuko-araiosis and vascular risk factors. In addition, the presence of leuko-araiosis was associated with cognitive impairment amongst older individuals with and without dementia. Finally, this group was the first to examine the pathologic consequences of this unique imaging finding [18]. Coincident to the discovery of leuko-araiosis, Awad and colleagues identified "incidental subcortical lesions" on MRI [19] (currently described as white matter hyperintensities; WMH) and noted that these lesions were significantly associated with advancing age and vascular disease. Pathologic study of these lesions also suggested a possible vascular etiology to which they ascribed to the state of "état criblé" [20].

These two series of seminal and seemingly independent, but coincident observations, heralded a new era in medical research relating to the risk and consequences of asymptomatic cerebrovascular brain injury as evaluated by various non-invasive neuroimaging methods. Subsequent studies focused on more fully describing the association between vascular risk factors and leukoaraiosis or WMH in mostly clinical samples [21–28]. Studies of essentially healthy and cognitively normal individuals, however, did not begin until sometime later.

My own work began in 1992 with the publication of a novel method for the measurement of brain volume and WMH from MRI [29]. After an initial report of age-related differences in brain structure amongst optimally healthy older individuals [30], we examined the impact of hypertension on brain structure [31]. Even within this select group of patients with well-controlled hypertension, we identified significant reductions in brain volume and expansion of cerebral ventricles. A number of individuals had extensive WMH, but the finding of brain atrophy associated with hypertension remained even when subjects with extensive WMH were removed from the analysis. The observation that WMH were common to older individuals with hypertension led to a follow-up study of 51 very healthy older individuals free of chronic medical illnesses and not taking any prescription medications [32]. We hypothesized that if vascular disease caused WMH, these individuals would have very little WMH. Using quantitative analysis of WMH volume, however, we identified a bimodal distribution, with 10% of subjects with extensive WMH burden. Further evaluation of this cohort found that systolic blood pressure (SBP), even within the range of normal, was associated with increased WMH when adjusting for age. In addition, WMH volume was significantly and negatively associated with cognitive performance after adjusting for age and education. Individuals with extensive WMH (greater than the 95% confidence interval for age) also had significantly higher SBP and significantly lower frontal glucose metabolism. The finding that systolic blood pressure, even when in the normal range for age, was a significant independent predictor of WMH volume suggests that the effect of systolic blood pressure may operate along a continuum. A later publication from the ARIC study using qualitative WMH measures confirmed this finding [33, 34]. Our findings also

confirmed previous observations suggesting that WMH must be extensive to have an impact on brain structure and function [35]. These results suggested that vascular risk factors, even within the normal range, may impact brain structure and function among older individuals, possibly increasing risk for late life dementia.

It was evident from these early studies that clinically silent CVD was ubiquitous to older individuals, but the impact on brain function was somewhat subtle, particularly for individuals who were otherwise healthy. In response to this observation, I refocused my research activities to the study of larger subject cohorts that included individuals with varying degrees of medical health. With this focus, I sought collaborations with established, longitudinal programs in order to increase the size of the study populations and broaden health inclusion, as well as to acquire middle-life health risk data that would allow me to assess life course effects of CVD on brain structure and cognition. The rationale for this approach was two-fold. First, the prevalence of vascular risk factors, particularly hypertension has a prevalence of nearly 10% amongst individuals 20–34 years of age [36], is generally unrecognized in this age group, similarly undertreated [37] and increases in prevalence steadily with advancing age. This results in an increased prevalence of individuals surviving to advanced age with multiple systemic vascular injuries. Second, the impact of vascular risk factors may be greatest when sustained over decades. This hypothesis may be extremely relevant given the reduction in vascular mortality over the last decade [37] resulting in an increasing prevalence of individuals living to more advanced age with comorbid vascular disease burdens (Figure 1).

I was fortunate to begin this work with Dr. Dorit Carmelli, principal investigator of the NHLBI Twin Study. Together, Dr. Carmelli and I developed a research program that focused on MRI measures of CVD-associated brain injury [38–43]. Using a method developed by Lenore Launer [44], we identified patterns of blood pressure regulation identified in middle-life (Figure 2) and investigated the impact of these patterns on later-life brain structure and function. Two observations were apparent from these analyses. First, the impact of blood pressure pattern was most strong for systolic blood pressure [38]. Second, there was a nearly linear association between blood pressure pattern and MRI measures of brain injury as well as the prevalence of associated systemic vascular diseases such as coronary artery disease, peripheral vascular disease and stroke. Longitudinal analyses confirmed initial findings [43]. Finally, there were significant associations between blood pressure patterns and impairments in cognitive function including clinically significant memory impairment such as mild cognitive impairment (MCI) that were equal in magnitude to the effect of apolipoprotein E4 genotype [45]. These results confirmed my initial hypothesis that vascular risk factors result in untoward effects that impact brain structure and function. These findings, however, extended current observations to include clinically relevant cognitive impairment (confirmed by a later community based study [46, 47]) suggesting that more aggressive treatment of vascular risk factors may result in reduced risk for later-life cognitive impairment. Moreover, these results pointed to an important facet of hypertension care: the pattern of early life SBP appeared to be sustained in this cohort, despite 78% of those with high BP receiving treatment [38].

Study of twins also allowed us to examine potential genetic influences on brain structure. In this seminal work, we found that structural brain measures such as intracranial, brain and WMH volumes were highly heritable [48–52]. The notion that genetic influences might extend to later-life was an unexpected finding suggesting that a substantial proportion of brain aging may be under genetic control. We also hypothesized that these influences could be modified through environmental interactions or other complex genetic traits. Evidence for this hypothesis comes from two additional studies. First, Carmelli et al., found that differences in brain injury among monozygotic twins were significantly associated with

differences in vascular risk factor prevalence [39]. Second, longitudinal studies of heritability estimates of brain volume strongly suggest a significant environmental influence [53]. These initial findings indicated that there exist strong genetic influences on brain aging which may place certain individuals at higher risk for poor cognitive aging. The fact that these genetic influences may be modified by environmental influences and other associated and possibly treated complex traits also suggests that the increased genetic vulnerability to brain aging may be ameliorated by preventive therapy [45]. The ability to extend the findings from the NHLBI Twins Study to the general population, however, was limited by the fact that the NHLBI subjects were Caucasian, male, veterans and twins.

In order to expand the relevance of my research, I joined with Dr. Philip Wolf to study the participants of the Framingham Heart Study (FHS), a community based population study which would assure that further results of my work would have relevance to the general population. The FHS satisfied four important needs of my evolving research program: the population is considered generally representative; it included both men and women; it had considerable longitudinal data; and it included both parent and offspring members (and now the third generation) enabling further study of the genetics of brain structure. Through serial studies, we were able to confirm that CVD risk factors lead to accelerating brain aging and cognitive impairment in the general population [11, 54–64]. Moreover, we extended current understanding of vascular influences on brain structure and function, by identifying that noticeable untoward influences begin at 55 years of age [55, 56] (Figure 3). This subsequent finding underscores the potent influence of vascular risk factors on cognitive aging that likely begin at least a decade before similar influences due to Alzheimer's disease [5, 65]. The clinical relevance of vascular risk factors on brain structure and function were further supported by the finding of longitudinal influences [64] and significant associations with clinically relevant outcomes such as MCI, dementia, stroke and even death [66].

Results from the FHS confirmed that the untoward effects of vascular risk factors on brain structure and function were true for both men and women, but also led to the novel observation that the impact of vascular risks on brain structure and function may begin earlier than expected. The FHS studies and those of the NHLBI Twins consistently show elevated blood pressure as the leading cause of brain atrophy, increased WMH volume, silent brain infarction and cognitive impairment. Recognizing that vascular risk factors are prevalent and often detectable at a relatively young age, these results may have substantial public health ramifications relating to the time and extent of risk factor treatment.

Both the NHLBI and FHS studies examined predominately Caucasian individuals. My ability to collaborate productively with the FHS encouraged other collaborations with epidemiologically based studies such as the Northern Manhattan Stroke Study (NOMAS), the Washington Heights Innwood Columbia Aging Projects (WHICAP) and the Chicago Healthy Aging Projects (CHAP) which included mixed racial and ethnic populations. Research with these groups confirmed the prominent role of cerebrovascular disease on cognition [67–84] seemingly independent of race or ethnicity [77, 85] suggesting that racial and ethnic differences in prevalent and potentially treatable vascular risk factors [86] may explain similar differences in prevalent dementia [87].

My experience with epidemiological research helped me to further refine questions regarding the impact of CVD on brain structure and function, allowing for more targeted research focusing on specific causal pathways that epidemiological studies cannot answer. For example, we developed new methods to examine the spatial extent of WMH in order to further analyze how regional variations in WMH may impact brain structure and function. Using this method, we found that increasing extent of WMH was associated with expansion around the ventricular system [88] and that WMH affected frontal lobe metabolism

independent of location [89]. This led to further studies that found differences in anatomical localization of WMH between normal aging, MCI and dementia [90] where rostral-caudal extension of WMH was associated with increasing degrees of cognitive impairment. This finding differed from the previously described periventricular location of WMH associated with vascular risk factors suggesting that vascular and degenerative processes may interact to cause white matter injury [90]. With further studies we also observed that there exists a subset of individuals with significant memory loss related to vascular brain injury [91], that MRI measures and vascular risk factors differ amongst subtypes of MCI [92] and that the WMH also affect cognitive trajectories measured over one to two years follow-up [93, 94]. By adding newer methods of diffusion tensor imaging (DTI), we further characterized differences in white matter integrity as they related to vascular and degenerative pathologies [95, 96] and found that anterior white matter injury was mediated by vascular risk factors, but posterior white matter injury was more strongly associated with degeneration. We have recently extended our observations on the biology of WMH formation by identifying a “penumbra” of at risk tissue surrounding WMH [97]. By combining DTI and FLAIR imaging, we found that white matter integrity declined in areas close to WMH suggesting that WMH are the extreme expression of more general injury in the vascular watershed region of the cerebral white matter. This new observation may be important to monitoring at risk brain tissue that may respond to clinical treatment.

More recently, I started a small program of cognitive neuroscience research in collaboration with Neuroscience and Psychology graduate students. In our first study, we used functional MRI to show that the extent of functional activation of dorsal lateral prefrontal cortex during working memory tasks in a group of older normal individuals was significantly and inversely associated with the extent of WMH volume [98]. These data suggested that WMH lead to functional disconnection of central executive processes necessary for working memory by injury to cerebral white matter tracks. These findings are consistent with my previous hypothesis [45] and some of my earlier work showing that WMH reduce frontal metabolism [32]. More recent work has focused further on other cognitive systems affected by WMH [99]. In this study we found that high WMH volumes in older individuals lead to impairments in cognitive control, reduced activation of dorsal lateral cortex and loss of correlations between dorsal lateral cortex and frontal and parietal targets. In addition, WMH were also associated with lack of suppression of the dorsal node of the default mode network, suggesting, like Alzheimer’s disease that there is an inverse relationship between suppression of the default mode during activation and performance [100]. These results suggest that at least some of the symptoms common to aging evidenced as subtle frontal lobe dysfunction [101] may result, in part, to the presence of asymptomatic vascular brain injury.

With increasing emphasis on genome wide association studies and evidence that brain and WMH volumes are heritable, I also collaborated with family based genetic association from the FHS [102], the Multi-institutional Research in Alzheimer Genetic Epidemiology (MIRAGE) study and community based studies as part of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. In these studies, we confirmed the heritability of WMH [103] and showed that heritability was high throughout most of the adult life span. We also performed linkage analysis [104] and found significant linkage with a locus on chromosome 4. Additional studies with MIRAGE identified pleotropic effects of the SORL1 gene using MRI as an endophenotype [105] that suggested two separate biological pathways (one through amyloid precursor metabolism and the other through lipid metabolism) by which SORL1 may lead to increased risk for late life dementia. New work with the CHARGE consortium has identified risk alleles for both WMH and asymptomatic MRI infarction [106, 107], but further work will be necessary to fully characterize the biology of these findings.

In summary, my focus on the impact of CVD on cognition has resulted in a number of important observations related to advancing age and cognitive impairment. First and foremost, MRI evidence of CVD-associated brain injury is common and likely begins in midlife. The symptoms of vascular brain injury are often subtle, but may falsely contribute to our current notion of cognitive weaknesses associated with advancing age. Importantly, however, vascular brain injury is clearly a substantial risk factor for clinically significant cognitive impairment such as MCI and dementia as well as increased mortality. While considerable evidence also suggests that vascular brain injury may be under genetic influence, vascular risk factors are treatable and have been associated with reduced likelihood of expressed dementia in preliminary studies [108]. Despite increased awareness of the impact on vascular disease and health individuals are often unaware of their vascular risk factor status, particularly at younger ages [37]. As an example, the United States is currently witnessing an obesity epidemic [109] and studies show that obesity is associated with multiple vascular disease and significantly increased risk for late-life dementia [110]. I strongly believe that clinically silent CVD results from poorly controlled risk factors and leads to late-life cognitive impairment. Aggressive public health policies which advocate healthy life-styles and the early treatment of hypertension and other vascular risk factors, therefore, will likely result in improved later-life cognitive health, substantially alleviating what is likely to become a huge public health burden [111].

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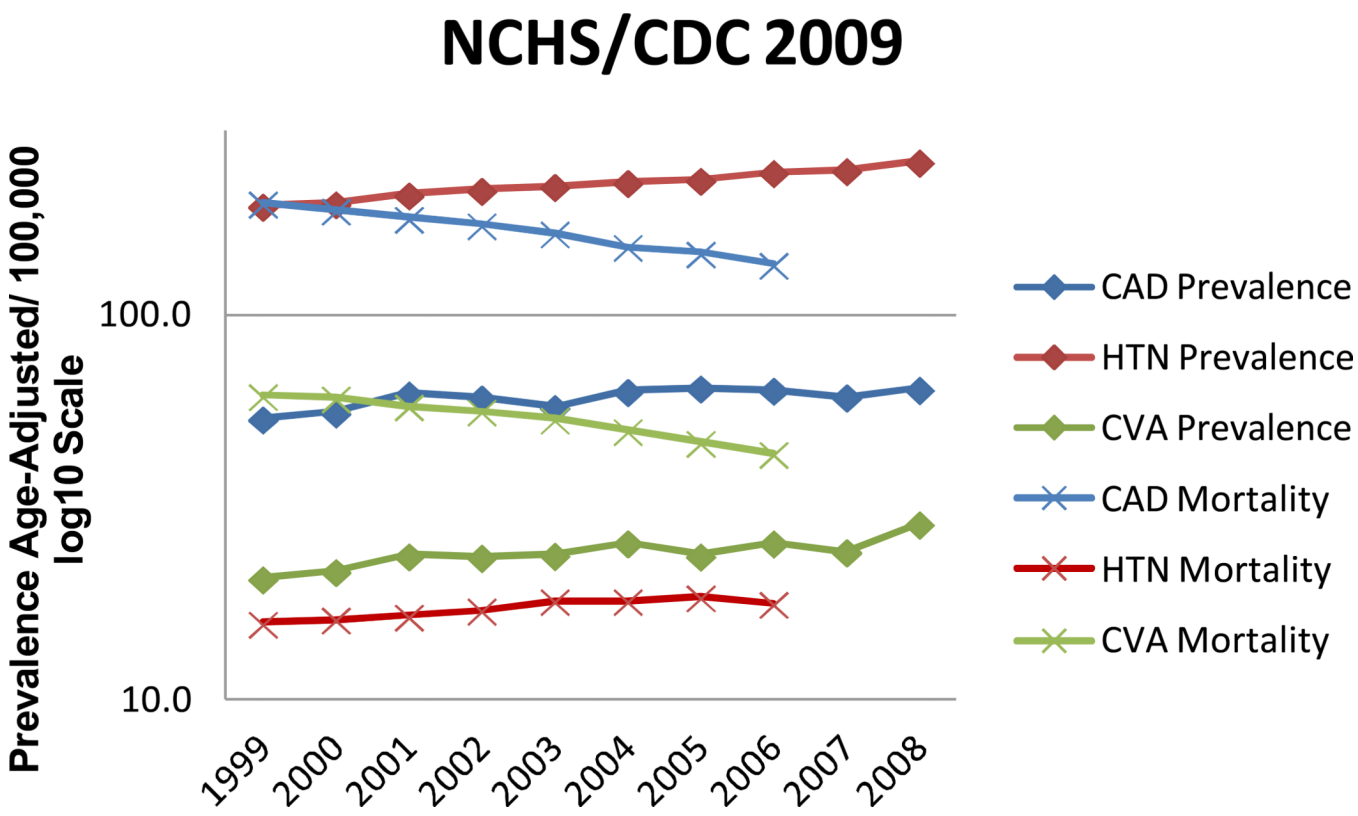

Figure 1.
Center for Disease Control, National Health Statistics 2009 prevalence figures for trends in cardiovascular disease and mortality for the decade beginning in 1999. Note that mortality declined steadily while prevalence has remained or increased slightly over this decade of observation.

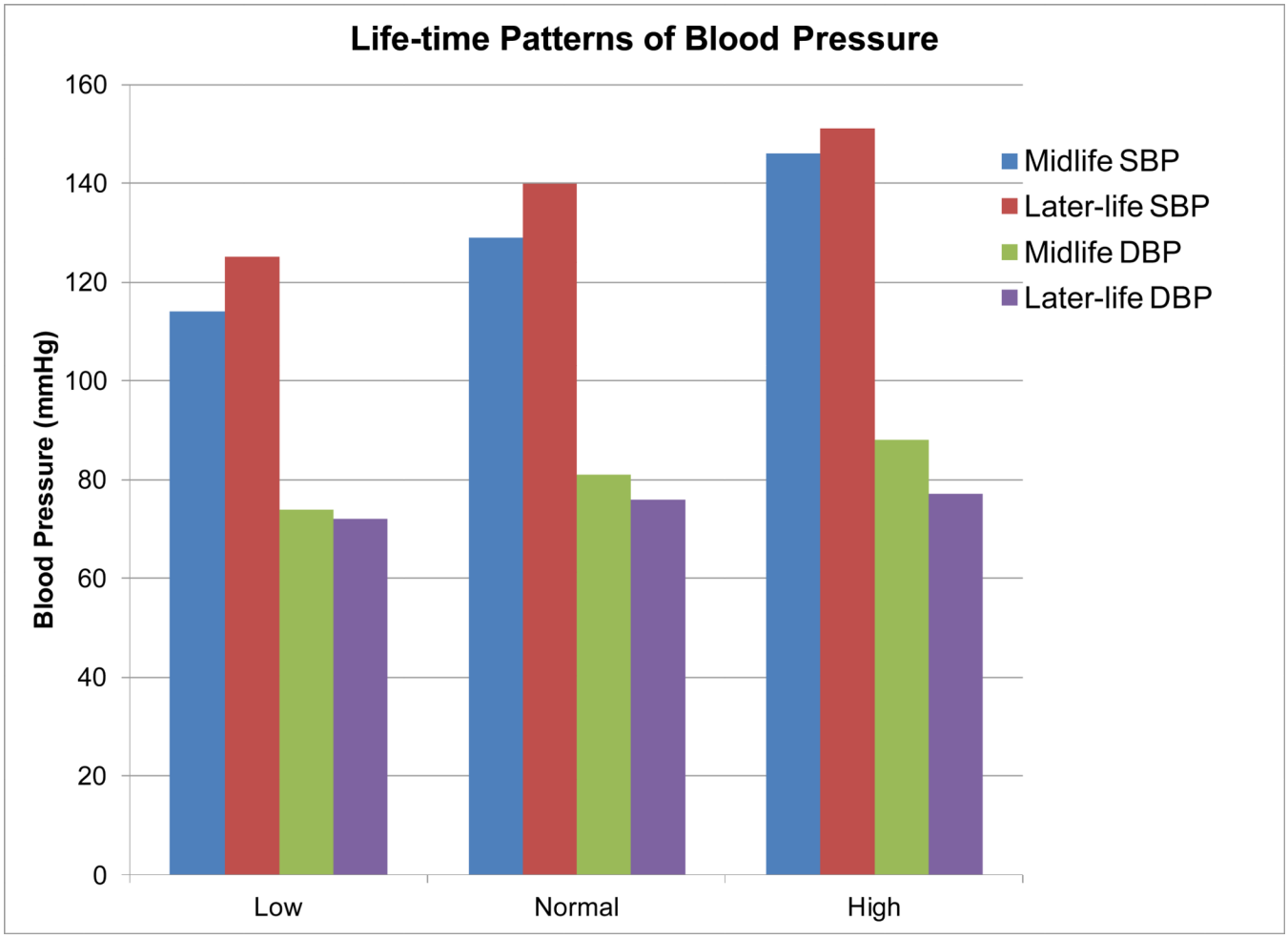

Figure 2.
Life-time pattern of systolic and diastolic blood pressures for three categories determined in middle life. Note that 78% of individuals in the high blood pressure category received treatment.

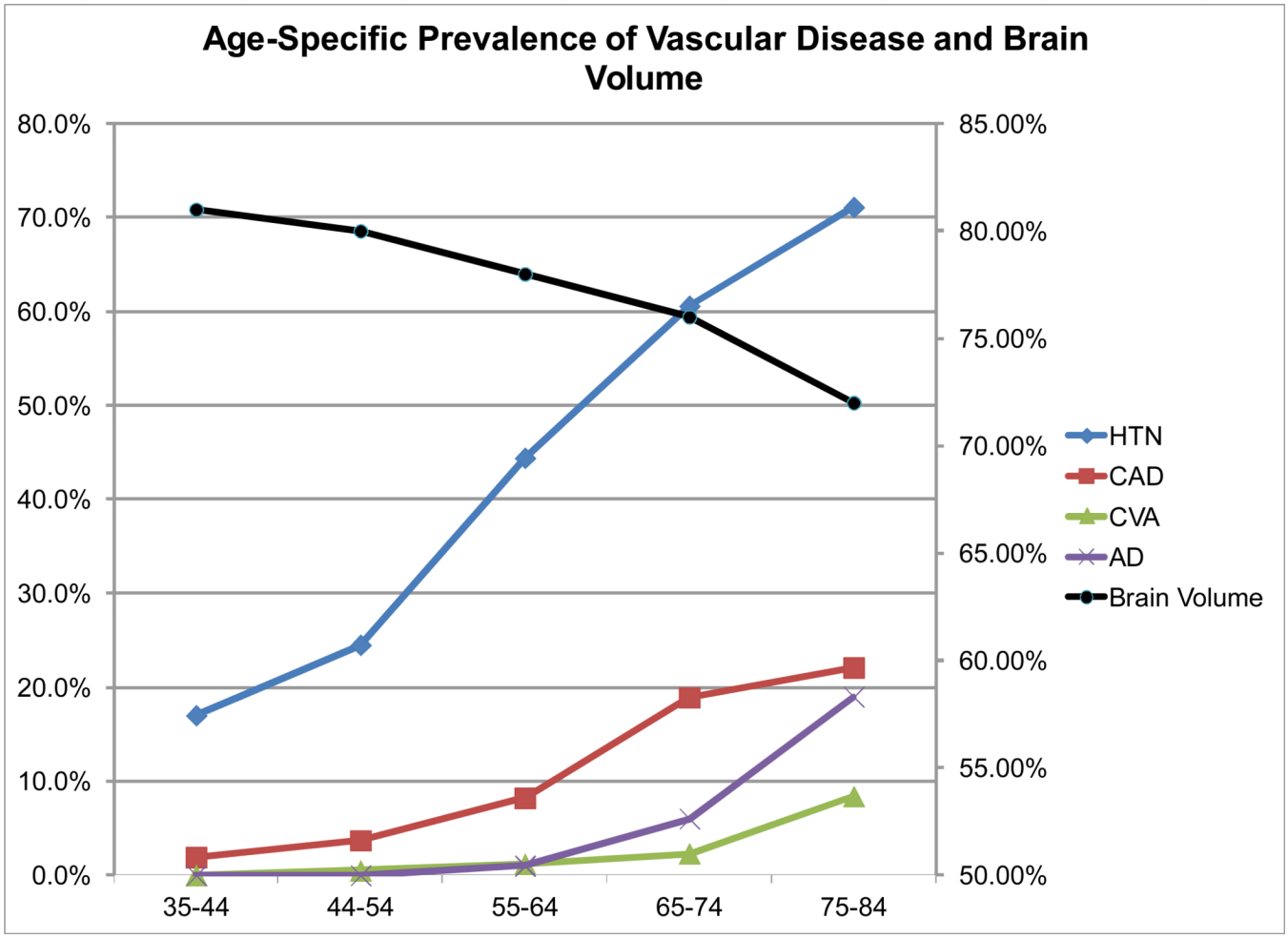

Figure 3.
Age-specific prevalence of vascular disease and brain volumes from the offspring cohort of the Framingham Heart Study (modified after DeCarli et al. [11]).