ARTERIAL STIFFNESS, FUNCTIONAL DECLINE AND MORTALITY RISK IN OLDER ADULTS

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A hallmark of vascular aging, central arterial stiffness is the primary determinant of hypertension in older adults and an important predictor of cardiovascular events and mortality. Few studies of older adults have evaluated the longitudinal association of arterial stiffness with cognitive and physical declines, two common consequences of vascular disease. We sought to characterize the relationships among aortic pulse wave velocity (PWV), a measure of central arterial stiffness, cognitive and physical declines and mortality risk among community-dwelling older adults participating in the Health, Aging and Body Composition (Health ABC) study. In an analysis of the Health ABC Cognitive Vitality Substudy, poorer performances in several cognitive domains were associated with accelerated gait speed decline, consistent with a shared cerebrovascular pathogenesis underlying cognitive and physical declines in aging. A second analysis of the substudy identified PWV as a predictor of longitudinal decline in psychomotor speed; this domain-specific association may reflect a vulnerability of the deep white matter to cerebral microvascular disease in the presence of aortic stiffness. In an analysis of the full Health ABC cohort, higher PWV was independently associated with slower gait at baseline and throughout the study period in participants with peripheral arterial disease (PAD), suggesting synergistic roles of arterial stiffness and PAD in mobility decline. Finally, in the full cohort rates of decline in the Modified Mini-Mental State Exam (3MS) and gait speed predicted mortality independent of each other, baseline performance and risk factors, demonstrating a prognostic value for

repeated assessments of both cognitive and physical performance in initially well-functioning older adults. The public health relevance of these findings is the potentially clinically important influence of central arterial stiffness to both cognitive and physical function, two central facets of successful aging.

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1.0 INTRODUCTION

Hypertension is increasingly recognized as a formidable public health threat to aging populations. More than 70% of US adults age 65 or older are hypertensive, defined as blood pressure of 140/90 mmHg or greater (McDonald, Hertz, Unger, & Lustik, 2009). Despite advances in awareness and treatment, prevalence is rising while control rates remain low (Hajjar & Kotchen, 2003). Uncontrolled blood pressure is a primary risk factor for heart disease and stroke, the first and third leading causes of death in the US. While these clinical risks were identified many years ago, cognitive and physical functional consequences of hypertension continue to emerge (Skoog & Gustafson, 2006) (Dahlof, 2007). Effective prevention and treatment of this potentially devastating condition are central to the promotion of successful aging.

Improved strategies to control blood pressure may develop from new understanding of the vascular alterations underlying hypertension in aging. Thickening and stiffening of the arterial walls are two well-described hallmarks of subclinical vascular disease in older adults (Lakatta, 1993); these risky features of arterial aging are both determinants and consequences of hypertension. Since the 1960s vascular imaging technology has provided valuable insight into these distinct, though often co-occurring structural changes. Noninvasive measurement of arterial stiffness has received growing attention in the investigation of arterial aging.

A measure of central arterial stiffness, aortic-pulse wave velocity (PWV) predicts mortality and morbidity independent of hypertension and other traditional vascular risk factors (Sutton-Tyrrell et al., 2005) (Matsuoka et al., 2005). During systole, ejection of the blood from the left ventricle produces a pressure wave that travels toward the periphery. PWV reflects the speed of the pressure wave along the arterial tree; higher values of PWV reflect greater aortic stiffness. Risk associated with elevated PWV has been attributed to two co-occurring mechanisms: 1) gradual loss of the cushioning capacity of the vasculature, associated with small-vessel injury of the target organs; and 2) early wave reflection from the periphery, accompanied by an increase in cardiac afterload (O'Rourke, 2007). These age-associated vascular changes increase risk of hypertension, heart attack, stroke, dementia and renal disease (Zieman, Melenovsky, & Kass, 2005).

Stiffening of the large arteries reflects a gradual dysregulation of the structural components of the vascular wall. Inflammatory and neuroendocrine changes in aging alter the balance of collagen and elastin, the primary scaffolding proteins which provide the structural integrity and elasticity of the vessel wall (Zieman et al., 2005). Because age is the primary risk factor for vascular stiffening, these structural alterations have been considered an indicator of vascular aging (O'Rourke, 2007) (Najjar, Scuteri, & Lakatta, 2005). In conflict with the assumption that vascular aging is unmodifiable, several traditional risk factors contribute to vascular stiffening independent of chronological age (Najjar et al., 2005). Hypertension, insulin resistance (Bhuiyan, Srinivasan, Chen, Paul, & Berenson, 2006) and excess salt intake (Zieman et al., 2005) may each accelerate the accumulation of collagen and degradation of elastin which contribute to arterial stiffening (O'Rourke, 2007). These findings highlight the potential to slow vascular stiffening through the control of modifiable risk factors.

In this review, we outline the epidemiology of hypertension in aging and the pathophysiology of underlying arterial stiffness. We then describe current methods of arterial stiffness measurement and review the relationships of arterial stiffness with both clinical and functional outcomes in aging. We consider the potential influences of missing data in observational studies of arterial stiffness and review methods of sensitivity analysis to account for nonrandom missingness. Finally, we discuss the public health implications of arterial stiffening and potential strategies to slow or reverse this risky process of arterial aging.

1.1 EPIDEMIOLOGY

The National Health and Nutrition Examination Survey (NHANES) 1999-2000 reported that 28.7% of US adults surveyed were hypertensive, defined as measured blood pressure of 140/90 or greater or reported use of antihypertensive medications (Hajjar & Kotchen, 2003). This finding represents a 3.7% increase in hypertension prevalence from 1988-1991, a trend which reflects the aging of the US population (Franklin, 2006a). In 1999-2000 prevalence increased with age (65% among those age 60 years or older), tended to be higher in women (30%), and was highest among non-Hispanic blacks (34%). Of those identified as hypertensive, 69% were aware of their condition, 58% were treated and hypertension was controlled in 31%. Control rates were significantly lower in those age 60 years or older, despite the higher rate of treatment in this age group (Hajjar & Kotchen, 2003). These data are consistent with the well-known difficulty in successfully treating isolated systolic hypertension, the predominant form of hypertension in older adults (Franklin, Jacobs, Wong, L'Italien, & Lapuerta, 2001).

1.2 PATHOPHYSIOLOGY

Vascular stiffening underlying hypertension in aging preferentially affects the large conduit arteries while sparing the peripheral vasculature. Hemodynamic forces in aging and hypertension, excess salt intake, and impaired glucose regulation each disrupt the balance of scaffolding proteins within the vascular wall. Arterial stiffening is often attributed to accumulation and cross-linking of collagen and fragmentation of elastin, two prominent structural components which provide the structural integrity and elasticity of the vessel wall (Zieman et al., 2005).

Multiple cellular and neuroendocrine mechanisms account for the dysregulation of collagen and elastin that characterizes arterial stiffening (Zieman et al., 2005). Catabolic matrix metalloproteases (MMPs) enzymatically degrade the extracellular matrix of the vessel wall, altering the composition of collagen and elastin in the intima and media layers. MMP activity is stimulated by inflammatory cells, oxidized LDL, reactive oxygen species, and a high flow state. Additionally, advanced glycation end products (AGEs), metabolic by-products that accumulate in aging and glucose intolerance (Brownlee, 1995), form irreversible cross-links between collagen molecules which contribute to arterial stiffening. AGEs may also influence endothelial dysfunction by inhibiting production of nitric oxide, a powerful vasodilator which regulates smooth muscle tone; resulting structural alterations may heighten the inflammatory response to vascular injury and promote atherosclerotic plaque formation (Zieman et al., 2005). Finally, angiotensin II contributes directly to vascular stiffening by stimulating collagen formation and matrix remodeling (Najjar et al., 2005) and reducing elastin synthesis; these mechanisms are amplified in hypertension and with high-sodium intake. Sodium further impairs nitric oxide

availability and stimulates production of reactive oxygen species, altering vascular tone and accelerating vascular stiffening (Zieman et al., 2005).

1.3 ARTERIAL STIFFNESS MEASUREMENT

The gold standard of arterial stiffness measurement, aortic pulse wave velocity (PWV) is a reliable and valid (Laurent & Boutouyrie, 2007), noninvasive measure that independently predicts cardiovascular events and mortality in older adults (Sutton-Tyrrell et al., 2005). The measure is more discriminant than pressure measured in the arm (brachial pressure) because PWV directly measures the central pressure that is exerted on the target organs, while brachial pressure is augmented by wave reflection from the periphery (Hirata, Kawakami, & O'Rourke, 2006). PWV measurement involves the simultaneous recording of pressure waves at two proximal and distal sites. The carotid and femoral arteries are common recording sites; these locations allow noninvasive measurement of pulse waveforms (Oliver & Webb, 2003). The PWV may be measured by pressure-sensitive transducers, Doppler ultrasound, or applanation tonometry, where the pressure within a micromanometer flattened next to an artery reflects the pressure within the artery. Each method records the time delay between the arrival of a specific part of the pulse wave, often the foot of the wave, at each recording site. The distance between the recording sites is measured over the body surface. PWV is calculated as the distance in m or cm divided by the time delay (m/s or cm/s). Higher values of PWV reflect greater vascular stiffness. A typical PWV value is 500 cm/s in a 20-year old and 1200 cm/s in an 80-year old, a six-fold difference over 60 years (Laurent et al., 2006; O'Rourke, 2007; O'Rourke, Staessen,

Vlachopoulos, Duprez, & Plante, 2002). In the Health, Aging and Body Composition (Heath ABC) Study, replicate testing of aortic PWV demonstrated high reproducibility between sonographers and between readers, as indicated by intraclass correlations >0.80 (Sutton-Tyrrell et al., 2005).

Several alternative methods are considered indirect measurements of arterial stiffness (Oliver & Webb, 2003). Ultrasound imaging of the carotid artery allows calculation of arterial distensibility by relating the change in vessel diameter to the distending pressure. The validity of this method is limited by the influence of pulse pressure amplification on the assumed pressure of the artery. Various methods of analyzing the arterial pulse waveform provide the augmentation index (AIx), the proportion of central pulse pressure that results from wave reflection. Although the AIx is primarily determined by arterial stiffness, the measure is also influenced by the elasticity and diameter of small arteries and arterioles (Oliver & Webb, 2003).

1.4 CLINICAL AND SUBCLINICAL CONSEQUENCES OF ARTERIAL STIFFNESS

1.4.1 Hypertension

In younger adults, narrowing of the arteries increases vascular resistance, which promotes co-occurring rises in systolic and diastolic blood pressure. By contrast, stiffening of the large conduit arteries in aging commonly manifests as isolated systolic hypertension, the predominant form of hypertension in older adults (Franklin, 2006b). This pattern of elevated systolic pressure and low or normal diastolic pressure reflects the altered wave mechanics as vessels stiffen with

advancing age. Arterial stiffening is accompanied by early reflection of the pulse wave from peripheral vessels, which reaches the origin of the aorta at systole rather than diastole (Schiffrin, 2004). This shifted timing increases cardiac afterload (the pressure that the left ventricle must generate in order to eject blood into the aorta) while failing to bolster coronary perfusion during diastole (O'Rourke, 2007). These mechanical alterations contribute to a widening of the pulse pressure and isolated systolic hypertension (Schiffrin, 2004).

Several studies have identified arterial stiffness as an important risk factor for hypertension in older adults. In the Baltimore Longitudinal Study of Aging (BLSA), elevated PWV predicted a longitudinal increase in SBP and incident hypertension over ten years (HR 1.10 per 100 cm/s increase in PWV, 95% CI 1.00 – 1.30) in normotensive or untreated hypertensive adults (Najjar et al., 2008). These relationships were not explained by demographics, BMI, smoking, heart rate, lipids, or fasting glucose. The Atherosclerosis Risk in Communities (ARIC) Study found a similar association of arterial stiffness with incident hypertension in normotensive men and women (Liao et al., 1999). Arterial stiffness was measured using B-mode ultrasound of the common carotid artery. Independent of vascular risk factors, lower arterial diameter change was associated with higher risk of incident hypertension over six years. This relationship is consistent with the association of lower aortic strain, or the percent change in aortic diameter from systole to diastole, with incident hypertension in a large cohort of normotensive older adults (Dernellis & Panaretou, 2005). These findings implicate elevated central arterial stiffness as an important determinant of hypertension in aging. In addition to traditional risk factors, arterial stiffness measurement may identify those at high risk for incident hypertension who may benefit from early intervention.

1.4.2 Cardiovascular Events and Mortality

Arterial stiffness is increasingly recognized as an independent predictor of cardiovascular events and mortality in older adults. In the Health, Aging and Body Composition (Health ABC) Study, higher PWV was significantly associated with higher risk of all-cause mortality (relative risk 1.5, 1.6 and 1.7 for PWV quartiles 2, 3, and 4 versus 1; $p = 0.019$), cardiovascular mortality (relative risk 2.1, 3.0, and 2.3 for PWV quartiles 2, 3, and 4 versus 1; $p = 0.004$), coronary heart disease (CHD) and stroke (Sutton-Tyrrell et al., 2005). These relationships remained after adjustment for demographics, systolic blood pressure, prevalent cardiovascular disease, and other risk factors. Additionally, the authors identified a potential threshold effect of PWV; elevated cardiovascular risk was limited to the three highest quartiles of PWV. These data suggest that low PWV may be a marker of successful vascular aging.

Earlier studies of arterial stiffness described similar cardiovascular risk in participants with hypertension or renal disease. In a cohort of 1980 hypertensive patients, each 500 cm/s increase in PWV was associated with a 2.14 times higher risk of all-cause and 2.35 times higher risk of cardiovascular mortality. These associations after adjustment for prevalent cardiovascular disease, age, and diabetes (Laurent et al., 2001). In 242 patients with end-stage renal disease, each 100 cm/s higher PWV was associated with a 14% increase in both all-cause and cardiovascular mortality after adjustment for vascular risk factors (Blacher et al., 2003). These findings highlight the potential value of arterial stiffness measurement in risk stratification for early intervention.

1.4.3 Target Organ Damage

Elevated arterial stiffness is closely associated with small vessel disease of the target organs (Mitchell, 2008). The brain and kidney, both passively perfused throughout the cardiac cycle, are particularly susceptible to vascular injury; stiffened vessels transmit, rather than cushion, damaging flow pulsations into the small vessels of these target organs (O'Rourke, 2007). Microvascular remodeling and impaired regulation of blood flow may result in small-vessel disease of the brain and kidney, which may contribute to decline in cognitive and renal function (Mitchell, 2008). Common clustering of microvascular brain abnormalities and chronic kidney disease suggest a shared vascular pathology underlying declines in cognitive and renal function (Thompson & Hakim, 2009).

The contribution of arterial stiffness to renal dysfunction has recently received growing attention. In patients with end stage renal disease, isolated systolic hypertension has been attributed to stiffness of the large arteries and resulting early wave reflections. Under these conditions, the diminished filtering function of the kidney requires continued increase of systolic pressure to maintain sodium balance. Subsequent arterial stiffening may then accelerate renal dysfunction via microvascular injury, establishing a dangerous bidirectional relationship between the two disease processes (Safar, London, & Plante, 2004).

Several studies have found inverse associations of arterial stiffness with renal function in older adults. In a cohort of 1290 adults with normal or low plasma creatinine (≤ 130 umol/L), higher PWV was associated with lower creatinine clearance independent of age, gender and blood pressure (Mourad et al., 2001). The Health ABC Study found that higher PWV was associated with higher cystatin C in 2,468 community-dwelling older adults after adjustment for

demographics and risk factors (Madero et al., 2009b). These findings suggest that small vessel alterations may contribute to kidney dysfunction in aging. Assessment of large arterial stiffness may serve to identify individuals at high risk for kidney disease.

Arterial stiffness has also been implicated in the development of small-vessel disease in the brain. This vascular pathology closely associated with hypertension (Longstreth et al., 1996) may manifest as white matter hyperintensities (WMH) or subcortical infarcts apparent on brain MRI. Commonly detected in older adults (Manolio et al., 1994), WMH are associated with cognitive decline, depression, disability, and incident stroke (Ovbiagele & Saver, 2006). In a recent study of 167 hypertensive patients, higher PWV was associated with greater volume of white matter hyperintensities and presence of lacunar infarcts (OR per SD higher PWV: 1.78; 95% CI: 1.06-2.99; $p < 0.05$) (Henskens et al., 2008). These relationships were independent of age, sex, brain volume, mean arterial pressure and heart rate. Higher PWV was further associated with the presence of periventricular hyperintensities independent of age and blood pressure in 132 community-dwelling older adults (Ohmine et al., 2008). These findings suggest that arterial stiffness may explain the relationship of hypertension with cerebral small-vessel disease; stiffened vessels may transmit highly pulsatile flow into the fragile vasculature deep within the brain (O'Rourke, 2007). The associated dysregulation of cerebral blood flow may play a prominent role in cognitive decline with advancing age (Iadecola, Park, & Capone, 2008).

1.5 ARTERIAL STIFFNESS AND COGNITIVE FUNCTION

Hypertension is an important risk factor for cognitive decline and dementia (Breteler, 2000; de la Torre, 2002). In both Alzheimer disease (AD) and vascular dementia (VaD), vascular risk factors may alter blood flow regulation in the cerebral small vessels. The resulting energy crisis and breakdown of the blood-brain barrier may manifest in neuronal cell injury or death, or acceleration of AD pathology (Iadecola et al., 2008). The contribution of arterial stiffness to these disease processes has received growing attention. Several studies have described independent, inverse associations of PWV with cognitive function in older adults (Table 1), suggesting that interventions to preserve cognitive function in aging should target both hypertension and underlying arterial stiffness.

Elevated PWV has been associated with lower cognitive function in several cross-sectional studies of older adults. In a cohort of 308 older adults with complaints of memory loss, carotid-femoral PWV was higher in participants with vascular dementia (VaD) or Alzheimer's disease (AD) relative to those without cognitive impairment (Hanon et al., 2005), and in participants with mild cognitive impairment (MCI) relative to those with normal cognitive function. Similarly, in a cohort of 203 community-dwelling older adults aged 85, PWV was higher in participants with impaired relative to normal cognitive function (Fukuhara et al., 2006). These relationships were not explained by traditional vascular risk factors.

One study further investigated the relationships of subclinical vascular disease with function in specific cognitive domains (Muller, Grobbee, Aleman, Bots, & van der Schouw, 2007). Carotid intima-media thickness (IMT), a marker of subclinical atherosclerosis, was evaluated by ultrasound of the left and right common carotid arteries. Arterial stiffness was

measured by carotid-femoral pulse wave velocity. In this community-dwelling cohort, higher IMT was associated with lower memory scores after adjustment for age and education. Associations of higher PWV with lower processing speed and executive function scores approached significance. The differential relationships of IMT and PWV with specific cognitive domains suggest that these measures may be sensitive to different stages of cognitive decline.

Few studies have investigated the association of arterial stiffness with cognitive decline, with mixed results. In 2,767 in the Rotterdam Study (mean age ± SD 72.0 ± 6.7 years), elevated PWV was cross-sectionally associated with poorer executive function cross-sectionally but not with cognitive decline over five years or risk of dementia over eight years (Poels et al., 2007). However, higher PWV was associated with greater cognitive decline in the Baltimore Longitudinal Study of Aging (BLSA) (Waldstein et al., 2008). In this community-based cohort, 582 participants (mean age ± SD 54.3 ± 17.1 years), received baseline assessment of PWV and cognitive testing on 1 to 6 occasions over 11 years. Higher PWV was associated with accelerated declines in verbal learning, memory, and global cognitive function but not executive function or processing speed after adjustment for vascular risk factors. These findings contrast with associations of white matter disease on brain MRI with decline in executive function and processing speed but not other cognitive domains (Jokinen et al., 2009; Prins et al., 2005). The inconsistent results of the Rotterdam Study and the BLSA may reflect important differences in the age distributions of the study populations, duration of follow-up, and selected cognitive assessments. Importantly, nonrandom withdrawal of less healthy participants is likely to underestimate the associations of arterial stiffness with cognitive decline in both cohorts. Sensitivity analyses that account for nonrandom dropout missingness may clarify the influence of bias in future studies of arterial stiffness and functional decline.

Finally, one study investigated the relationships of arterial stiffness, white matter disease, and cognitive function in hypertensive patients with complaints of memory loss (Kearney-Schwartz et al., 2009). Higher PWV was associated with greater risk of memory impairment in men but not women after adjustment for vascular risk factors; this sex-specific relationship may reflect the higher rate of memory impairment and greater burden of subclinical vascular disease in men in this population. Further, augmentation index (AI), a measure of vascular stiffness, but not PWV was associated with severity of white matter lesions on brain MRI, suggesting that cerebral small vessel disease may mediate the relationship of arterial stiffness with lower cognitive function. Longitudinal analyses are needed to clarify the contribution of arterial stiffness to progression of both small vessel disease and cognitive decline.

1.6 ARTERIAL STIFFNESS AND PHYSICAL FUNCTION

Estimated to affect 15% of adults aged 70 years or older (Selvin & Erlinger, 2004), obstructive peripheral arterial disease (PAD) is an important predictor of functional decline (McDermott et al., 2004), disability (Brach et al., 2008), and mortality (Newman et al., 1999). PAD is associated with elevated arterial stiffness as measured by aortic PWV (van Popele et al., 2001), consistent with the hypothesis that atherosclerosis may accelerate arterial stiffening (van Popele et al., 2001). In patients with PAD higher PWV is associated with lower functional capacity (Amoh-Tonto, Malik, Kondragunta, Ali, & Kullo, 2009), and reduction of PWV may improve walking performance (Ahimastos, Dart, Lawler, Blombery, & Kingwell, 2008). These findings may reflect impaired diastolic function in the presence of aortic stiffness. Elevated arterial

stiffness may further contribute to resistance vessel hypertrophy and increased vascular resistance (Intengan & Schiffrin, 2000; Park & Schiffrin, 2001), impeding blood flow to the peripheral microvasculature (Mitchell et al., 2005); however, few studies have evaluated the potential contribution of arterial stiffness to mobility decline in aging.

1.7 THE MICROVASCULAR FRONTAL-SUBCORTICAL SYNDROME OF AGING

Many studies have identified a close relationship between cognitive and physical performance in older adults, suggesting a shared pathogenesis of declines in both domains (Pugh & Lipsitz, 2002). Age-related dysfunction in cognition and motor control has been characterized as a microvascular frontal-subcortical syndrome of aging (Pugh & Lipsitz, 2002), in which cerebral small-vessel disease preferentially disrupts an extensive network of neural circuits that mediate executive cognitive function and movement. This common cerebrovascular pathology in older adults may manifest as white matter lesions or lacunar infarcts on brain MRI.

White matter disease in aging is generally attributed to cerebral ischemia associated with hypertension (Vermeer, Longstreth, & Koudstaal, 2007). Myelin loss represented by diffuse white matter lesions often occurs in the periventricular regions and may reflect transient periods of hypoperfusion; by contrast, focal lesions often represent completed lacunar infarcts due atherosclerotic obstruction of the small subcortical arterioles. Age, hypertension, and diabetes are well-established risk factors for white matter lesions (Launer, 2004).

Several mechanisms have been hypothesized to explain cerebrovascular alterations in aging and hypertension (Iadecola et al., 2008). Highly pulsatile flow through stiffened vessels

may accelerate the narrowing of the cerebral vasculature, impeding delivery of energy substrates and nutrients to active brain cells. The resulting state of chronic hypoperfusion may directly injure cerebral white matter or allow toxic metabolic byproducts to accumulate within the brain and blood vessels. Moreover, stiffening and thickening of the cerebral vasculature may contribute to endothelial dysfunction and subsequent breakdown of the blood-brain barrier; toxins, proteases, or other substances in the blood may then enter the brain interstitial space and injure surrounding neurons and glial cells. This mechanism may further accelerate the narrowing of the lumen and resulting ischemia (Wardlaw, Sandercock, Dennis, & Starr, 2003).

In well-functioning older adults, white matter lesions are associated with poorer executive function, information processing, and gait (Black, Gao, & Bilbao, 2009). These relationships are consistent with the diffuse anatomy of frontal-subcortical circuits which mediate these cognitive and motor processes; vascular insult to any region of these extended tracts may result in compromised function (Pugh & Lipsitz, 2002). Further, because much of the deep white matter lies within watershed zones located at the boundaries of large vessel perfusion territories, these regions are vulnerable to ischemic injury (Pugh & Lipsitz, 2002). Resulting white matter changes may contribute to co-occurring declines in cognitive and physical function with advancing age.

1.7.1 Relationships of cognitive and physical function in aging

Cross-sectional analyses have found associations of a variety of cognitive processes with gait speed and risk of falls (Ble et al., 2005; Holtzer et al., 2007; Rosano, Simonsick et al., 2005). Several studies of simultaneous cognitive and motor performance suggest that compromised

executive function and attention may be particularly important to explain gait slowing with age (Coppin et al., 2006; Holtzer, Verghese, Xue, & Lipton, 2006); these specific cognitive domains may influence mobility through the planning and execution of motor tasks and inhibition of competing demands from the environment.

Longitudinal studies of older adults have identified a seemingly reciprocal relationship between cognitive and physical function. In the Italian Longitudinal Study on Aging (ILSA), deficits in attention predicted decline in motor performance after three years (Inzitari, Baldereschi et al., 2007). Poorer global and executive function were also associated with accelerated gait speed decline over three years in Health ABC (Atkinson et al., 2007); conversely slower gait predicted decline in attention and psychomotor speed over five years (Inzitari, Newman et al., 2007). These findings are consistent with a shared pathogenesis underlying cognitive and mobility declines and further suggest that subtle executive and attention deficits may manifest in motor impairment, even before such deficits can be detected. It is unclear whether associations between cognitive and gait declines exist across multiple cognitive processes or are restricted to several specific domains. Longitudinal brain imaging studies of older adults may clarify the mechanisms underlying co-occurring declines in cognitive and physical performance, two central facets of successful aging.

1.7.2 Cognitive and physical declines as predictors of mortality

Both cognitive and physical performance measures are valuable prognostic tools in older adults (Guralnik et al., 2000; Spiers et al., 2005). In the Cardiovascular Health Study, lower scores on the Digit Symbol Substitution Test (DSST) and slower gait were each associated with higher risk

of incident disability and mortality over eight years (Rosano, Newman, Katz, Hirsch, & Kuller, 2008). Co-occurring cognitive and physical declines in this cohort may reflect a shared cerebrovascular pathogenesis or general physiological deterioration associated with inflammation or oxidative stress.

Few studies have evaluated whether changes in cognitive or physical function predict mortality independent of each other or baseline performance. Independent associations of declines in each domain with mortality may suggest a prognostic value for repeated cognitive and physical assessments. Further, if risk associated with functional declines is found attenuated in older adults who are initially high-functioning, these data may stress the importance of baseline performance as an indication of functional reserve (Newman et al., 2009; Stern, 2009).

1.8 ANALYSIS OF LONGITUDINAL DATA WITH CENSORING

Two recent studies evaluated the associations of elevated PWV with cognitive decline in community-dwelling older adults, with mixed results (Poels et al., 2007; Waldstein et al., 2008). These data are expected to underestimate this relationship in the population, because participants who experienced the greatest declines may have been unable complete the study. In general, a significant challenge to observational studies is nonrandom censoring, or dropout related to unobserved characteristics of study participants. This process may be especially problematic in studies of aging, where a healthy survivor effect is often an important source of bias.

Relationships between a risk factor and an outcome are often underestimated when less healthy participants are more likely to drop out of the study. For example, the Systolic

Hypertension in the Elderly Program (SHEP) identified a significant protective effect of antihypertensive therapy on cognitive function only after accounting for nonrandom censoring (Di Bari et al., 2001). Sensitivity analysis of longitudinal data with dropouts is useful in evaluating the robustness of parameter estimates and standard errors to missing data. Two commonly used methods of sensitivity analysis are multiple imputation (MI) and inverse probability weighted estimating equations (Mazumdar et al., 2007).

1.8.1 Multiple imputation

MI involves replacing missing data with multiple sets of plausible values, allowing each filled in dataset to be analyzed using standard methods. The results of these analyses are combined to calculate the mean of the multiple parameter estimates and a variance estimate that reflects both missing-data uncertainty and sample variation. MI may be performed using SAS Proc MI or MI ANALYZE. These procedures allow the analyst to select from several methods of imputation appropriate for different types of missing data patterns (Mazumdar et al., 2007).

When there is no missing data before a dropout (a monotone pattern), parametric regression methods or weighted estimation procedures may be used to impute missing data. The parametric regression method involves fitting a model for each variable with missing data using other available variables as covariates. The coefficients from this model are then applied to the available data to impute the missing outcomes. The weighted estimation method involves fitting a model for the probability of missingness given a set of observed covariates. This conditional probability, or propensity score, is calculated for all observations subject to dropout at a specified time (Rosenbaum & Rubin, 1984). Observations are then grouped by propensity score and

missing data are imputed using a Bayesian bootstrap imputation method within each group, where values are resampled with replacement from the observed data (Mazumdar et al., 2007).

A third, more complex method of imputation is preferred when the missing data pattern is unknown. The Markov Chain Monte Carlo (MCMC) method involves simulating random draws of missing data from a probability distribution via Markov chains, or sequences of random variables whose probabilities at a given time depend on the value at the previous time. The random draws generate multiple distributions of missing data, which are then used for inference (Schafer, 1997).

An important limitation of MI methods is the potential for misspecification of the model used for imputation. Additionally, most MI methods assume missing data are missing at random (MAR), where the probability of missingness does not depend on unobserved outcomes but may depend on observed covariates. If missing data are missing not at random (MNAR), where the probability of missingness is related to unobserved data values, a model must be specified for the dropout procedure in conjunction with one of the inferential procedures described above. The drop-out process may be modeled by selection models or pattern-mixture models, which differ in their treatment of the drop-out process and outcome process (Mazumdar et al., 2007).

1.8.2 Inverse probability weighted estimating equations

Generalized estimating equations (GEE) are often used to analyze longitudinal data when the pattern of correlation between repeated measurements is unknown (Zeger, Liang, & Albert, 1988). GEE provides unbiased estimates when data are missing completely at random (MCAR),

where the probability of missingness does not depend on observed or unobserved outcomes. When data are MAR, inverse probability weighted estimating equations may be used to adjust for the propensities for dropout (Fitzmaurice, Laird, & Ware, 2004). In this method, a model is fitted for the probability that a variable is observed, given a set of covariates. A weighting variable is then calculated as the inverse of the estimated probability for each individual; these weights may then be applied to GEE analyses of the outcome of interest. For example, if a participant has a ¼ probability of completing the study, data from this individual would contribute to the analysis once for herself and three times for those who did not complete the study (Fitzmaurice et al., 2004). An advantage of this approach is the flexibility in modeling the outcome. However, biased estimates may result if the model for the probability of completing the study is not correctly specified (Mazumdar et al., 2007).

1.9 INTERVENTIONS TO REDUCE ARTERIAL STIFFNESS

A variety of interventions have been shown to reduce arterial stiffness in adults (Boutouyrie, Laurent, & Briet, 2008). Lifestyle interventions with demonstrated success include exercise training, weight loss, salt restriction, and moderate alcohol consumption; pharmaceutical treatments include antihypertensive medications, treatments of congestive heart failure, statins, antidiabetic medications, hormone replacement therapy, and advanced-glycation end product (AGE) breakers. However, the reduction of arterial stiffness by these interventions may not be independent of blood pressure lowering. As the dangers of vascular stiffening are increasingly

recognized, there is growing interest in the potential of antihypertensive medications to slow or reverse this common process in aging vessels.

Antihypertensive medications that target the renin-angiotensin-aldosterone system (RAAS) have recently shown promise to combat arterial stiffening with age. In older adults, elevated RAAS activity, including increased circulation of the powerful vasoconstrictor angiotensin II, promotes arterial inflammation and fibrosis which contribute to vascular stiffening (Najjar et al., 2005). In a few studies, agents with RAAS involvement reduced arterial stiffness seemingly independent of blood pressure lowering (Mahmud & Feely, 2004). The angiotensin-converting enzyme (ACE) inhibitor ramipril increased arterial compliance and decreased PWV in patients with peripheral arterial disease; these effects were not explained by the extent of blood pressure reduction (Ahimastos, Natoli, Lawler, Blombery, & Kingwell, 2005). Similarly, several angiotensin II receptor blockers were found to reduce PWV independent of blood pressure lowering in hypertensive patients (Agata et al., 2004; Sasamura, Kitamura, Nakamura, Ryuzaki, & Saruta, 2006). These data suggest a potential for current antihypertensive medications to prevent or reverse vascular alterations associated with the RAAS. Further research is needed to evaluate the hypothesized causal link between specific agents, reduced vascular stiffening and disease risk independent of the effect of blood pressure lowering.

1.10 PUBLIC HEALTH IMPLICATIONS

Low rates of hypertension control in older adults (Hajjar & Kotchen, 2003) are consistent with the widely recognized difficulty in successfully treating isolated systolic hypertension (ISH), the predominant form of hypertension in aging (Franklin et al., 2001). Because arterial stiffness is the primary determinant of ISH (Franklin, 2006a), there is significant incentive to understand both the pathophysiology and consequences of this risky vascular alteration that progresses with age. Many studies have identified independent contributions of arterial stiffness to risk of cardiovascular events and mortality; several recent publications further implicate elevated arterial stiffness as a potential determinant of target organ damage and functional decline. While the clinical benefits of blood pressure control are well-established, more work is needed to evaluate the anticipated success of interventions that target both hypertension and underlying arterial stiffness.

1.11 SUMMARY

Aging populations have encountered an unprecedented burden of chronic disease and disability, highlighting glaring deficiencies in the prevention and control of hypertension. While clinical risks associated with hypertension are well-known, functional consequences of chronically elevated blood pressure are under recognized. Improved strategies to extend the healthy lifespan may depend on new understanding of the vascular alterations underlying hypertension in older adults. PWV, a measure of aortic stiffness, is a more discriminant measure of cardiovascular and

mortality risk than systolic pressure measured in the arm because PWV directly reflects the central pressure that is applied to the target organs. Several recent studies of older adults further implicate central arterial stiffness as an independent predictor of hypertension and cognitive decline.

Cerebral small-vessel disease, a common manifestation of ischemic injury in older adults, may in part explain the inverse association of arterial stiffness with cognitive function in older adults. Executive and motor functions may be particularly vulnerable to vascular damage secondary to arterial stiffness; co-occurring declines in these domains are hypothesized to reflect a shared cerebrovascular pathogenesis or general physiological deterioration. Although many studies have identified an inverse relationship of PWV with cognitive function cross-sectionally, an association of PWV with longitudinal cognitive decline has not been well-established. The few longitudinal studies that have investigated this relationship have been limited by nonrandom withdrawal of less healthy participants. This selection bias is a significant challenge in studies of older adults, often resulting in underestimated associations between a risk factor and outcome. Several analytic methods are recommended to evaluate the sensitivity of estimates to missing data in future studies of functional decline.

Finally, as central arterial stiffness continues to emerge as an important determinant of functional decline and mortality in older adults, there is growing interest in potential interventions to slow or reverse vascular alterations associated with aging. Hypertension, diabetes, and smoking each accelerate arterial stiffening independent of age; control of these modifiable risk factors are key strategies to promote successful aging. Recently, antihypertensive agents which target the renin-angiotensin-aldosterone system have shown promise to reduce or reverse arterial stiffness independent of blood pressure. Future work is

needed to clarify the contribution of these therapies to vascular health and disease risk independent of blood pressure lowering. Now faced with growing burdens of chronic disease and disability, aging populations must recognize the devastating consequences of hypertension and underlying arterial stiffness.

Table 1. Studies of pulse wave velocity and cognitive function or decline

Author	Study Design	Study Population	Cognitive Assessment	Results
Hanon et al. (Hanon et al., 2005) France 2005	Cross-sectional	308 older adults attending outpatient clinic reporting memory impairment; age 78+/-8 yrs; 64% women	MMSE	PWV higher in dementia and MCI relative to no cognitive impairment ($p<0.01$)
Scuteri et al. (Scuteri, Brancati, Gianni, Assisi, & Volpe, 2005) Italy 2005	Cross-sectional	84 older adults referred for memory deficit; age 78+/-5 yrs; 30 men, 40 women	MMSE	PWV inversely correlated with MMSE score ($r=-0.26$, $p<0.05$)
Fujiwara et al. (Fujiwara et al., 2005) Japan 2005	Cross-sectional	352 adults age 70 and older participating in comprehensive health examination in April 2003	MMSE	Poor cognitive function (MMSE < 24) associated with PWV middle tertile (OR=9.66, 95% CI = 1.15 - 80.93)
Fukuhara et al. (Fukuhara et al., 2006) Japan 2006	Cross-sectional	203 85-year old participants in health survey; 87 men, 116 women	MMSE	PWV significantly higher in impaired MMSE group compared to normal MMSE group ($p<0.05$)
Scuteri et al. (Scuteri et al., 2007) Italy 2007	Prospective	102 older adults reporting memory problems; age 79 +/6 years; 31 men, 71 women	MMSE	PWV predicted cognitive decline, explaining 15.2% of total variance ($p<0.001$)
Poels et al. (Poels et al., 2007) Netherlands 2007	Prospective	2767 adults age 55 and older participating in the Rotterdam Study	MMSE, Letter-Digit Substitution, Stroop Test, Word Fluency Test	Higher PWV associated with poorer performance on Stroop test (Beta [95% CI] = 1.13 [0.26 to 1.99] per SD higher PWV) but not cognitive decline or incident dementia
Muller et al. (Muller et al., 2007) Netherlands 2007	Cross-Sectional	400 community-dwelling men aged 40-80 years	MMSE, Rey test of auditory verbal learning, Doors test of visual memory, Digit Span, Trail Making Test, Digit Symbol Substitution	Subjects with subclinical or prevalent CVD had lower MMSE scores compared to subjects without CVD ($p=0.003$)

Table 1 continued.

Author	Study Design	Study Population	Cognitive Assessment	Results
Waldstein et al. (Waldstein et al., 2008) USA 2008	Prospective	582 adults participating in the Baltimore Longitudinal Study of Aging (BLSA); age 54 +/- 17 years; 44% men	MMSE, Blessed I-M-C cognitive screening test, Digits Forward and Backward, California Verbal Learning Test, Benton Visual Retention Test, Trail Making Test, Letter and Category Fluency, Boston Naming Test	Higher baseline PWV associated with greater decline in global cognitive function, learning, and memory, but not executive function or processing speed

2.0 EXECUTIVE FUNCTION, MEMORY AND GAIT SPEED DECLINE IN WELL-FUNCTIONING OLDER ADULTS

Manuscript in preparation

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2.1 ABSTRACT

Background: In community-dwelling older adults global cognitive function predicts gait speed decline. Whether specific cognitive deficits account for gait speed decline is unknown. ***Methods:*** Several cognitive domains were evaluated at baseline in 909 participants in the Health, Aging and Body Composition Study Cognitive Vitality Substudy (mean age 75.2 ± 2.8 years, 50.6% women, 48.4% black). Usual gait speed (m/s) over 20 m was assessed at baseline and over five-year follow-up. ***Results:*** Poorer performance in each cognitive domain was cross-sectionally associated with slower gait independent of demographic and health characteristics. In longitudinal analyses, each 1-SD poorer performance in global function, verbal memory and executive function was associated with 0.003-0.004 m/s greater gait speed decline per year (p=0.03-0.05) after adjustment for baseline gait speed, demographic and health characteristics. ***Conclusions:*** In this well-functioning cohort, several cognitive domains were associated with gait speed cross-sectionally and predicted longitudinal gait speed decline. These data are consistent with a shared pathology underlying cognitive and physical declines but do not suggest that specific cognitive deficits account for gait slowing in aging.

2.2 INTRODUCTION

Many studies have identified an independent relationship of cognitive and physical performance in older adults. While it is well-known that several cognitive processes are associated with

walking speed cross-sectionally (Ble et al., 2005; Holtzer et al., 2006; Rosano, Simonsick et al., 2005), there is reason to hypothesize that impairment of attention and executive function may in part explain gait slowing with age (Coppin et al., 2006; Melzer & Oddsson, 2004; van Iersel, Kessels, Bloem, Verbeek, & Olde Rikkert, 2008). Considered important for the planning and execution of movements, executive function and attention are mediated by frontal-subcortical circuits associated with mobility and balance (Blahak et al., 2009; Pugh & Lipsitz, 2002; Tekin & Cummings, 2002). This extensive neural network is vulnerable to ischemic changes within the deep white matter (Kuo & Lipsitz, 2004), suggesting that cerebrovascular alterations in aging (Iadecola, Park, & Capone, 2009) may contribute to declines in executive and motor functions (Pugh & Lipsitz, 2002; Roriz-Cruz et al., 2007).

In the Health, Aging and Body Composition (Health ABC) study, poorer global and executive function were associated with accelerated gait speed decline over three years (Atkinson et al., 2007); conversely, gait speed at baseline predicted decline in attention and psychomotor speed over five years (Inzitari, Newman et al., 2007). These findings are consistent with a shared etiology of cognitive and physical decline (Pugh & Lipsitz, 2002) and further suggest that executive and psychomotor deficits may manifest in gait slowing (Soumare, Tavernier, Alperovitch, Tzourio, & Elbaz, 2009), even before such deficits can be detected (Inzitari, Newman et al., 2007). It is unclear whether an association of cognitive function with gait decline exists across multiple cognitive processes or is restricted to a few specific domains.

We evaluated the relationship of cognitive function with usual gait speed at baseline and over five years in the Health ABC Cognitive Vitality Substudy, in which participants completed a detailed assessment of memory and other specific domains not evaluated in the full Health ABC cohort. Cross-sectional associations of cognitive and gait performance in this analysis

would support a shared pathology underlying cognitive and physical declines in aging. Further, associations of specific cognitive domains with gait speed decline would suggest that deficits in these domains may in part account for gait slowing in older adults.

2.3 METHODS

2.3.1 Population

From 1997 to 1998 the Health ABC study enrolled 3,075 Medicare-eligible well-functioning men and women aged 70-79 from Pittsburgh, Pa. and Memphis, Tn., USA. The population was 52% women and 42% black with a mean age of 73.6 years. Participants were recruited from Medicare-eligible adults with contact information provided by the Centers for Medicare & Medicaid Services (formerly the Health Care Financing Administration) on a random sample of white and all black beneficiaries in pre-designed zip code areas surrounding the study centers. Other household members aged 70-79 were also eligible for recruitment. Exclusion criteria included reported difficulty walking one quarter of a mile, climbing 10 steps without resting, or performing basic activities of daily living or need for a walking aid.

In Year 3 of Health ABC, the Cognitive Vitality Substudy was initiated. Participants represent approximately the top 20% of performers on an endurance walk test (Simonsick, Montgomery, Newman, Bauer, & Harris, 2001) in Year 2 from each of eight groups defined by sex, race, and study site (Memphis or Pittsburgh) and an equal number drawn at random from the remaining members of each group yielding 951 black and white women and men aged 72-81

years who received additional cognitive testing. Substudy participants were slightly younger (75.5 years versus 75.7 years) and more likely to be white (65% versus 55%) compared to the Health ABC participants who were not part of the substudy. Exclusion criteria included self-reported difficulty seeing large print or grasping a pen. The Institutional Review Boards of the University of Pittsburgh, Pa., and University of Tennessee at Memphis approved the study, and written, informed consent was obtained from each volunteer. Of the 951 participants in the substudy, 920 completed cognitive and gait speed testing at Year 3. Of these participants, we excluded those with either lower extremity revascularization (n=8) or angioplasty (n=3), leaving 909 participants for cross-sectional analyses (mean age 75.2 ± 2.8 years, 50.6% women, 48.4% black). Longitudinal analyses included 865 participants who also had at least one gait speed measurement over the subsequent five-year period (mean age 75.2 ± 2.8 years, 50.5% women, 47.5% black).

2.3.2 Cognitive Tests

Cognitive function was assessed at baseline of the substudy (Year 3). The Modified Mini-Mental Status Exam (3MS) (Teng & Chui, 1987) is a comprehensive evaluation of global cognitive function, including orientation, attention, calculation, language and short-term memory. Scores can range from 0 to 100 points, with lower scores indicating poorer performance. The Buschke Selective Reminding Test (SRT) (Buschke & Fuld, 1974) is a multiple-trial list-learning task used to measure verbal learning and memory. In this task, the examiner presents a list of 12 written words and reads each word aloud. The participant is then asked to recall the words presented. For the next trial, the examiner repeats the words the

participant failed to recall and then asks the participant to provide the full list of 12 words. This procedure is repeated five times. Long-term storage is scored as the number of words recalled at least twice in a row that were also recalled in Trial 6. The 15-item Executive Interview (EXIT 15) was developed for the Health ABC study and constitutes a shortened version of the 25-item Executive Interview (Royall, Mahurin, & Gray, 1992). The test assesses several executive control functions such as inhibition of automatic responses, word and design fluency, and sequencing, and is scored from 0 to 30, with lower scores indicating better performance. The Boxes and Digit Copying (BDC) tests are timed tests of attention and psychomotor speed (Salthouse, 1996). The participant is asked to complete as many boxes and copy as many digits as possible within 30 seconds for each test. Psychomotor speed is scored as the sum of total boxes and digits completed (rho = 0.77). Finally, the Pattern and Letter Comparison (PLC) tests are timed tests of attention and perceptual speed (Salthouse, 1996). The participant is asked to determine whether pairs of patterns and letters are the same or different within 30 seconds for each test. Perceptual speed is scored as the sum of correct pattern and letter comparisons (rho=0.64).

2.3.3 Gait Speed

Gait speed was measured as the time needed to walk a 20-meter straight course at usual pace. Timing began at the first footfall over the starting line and ended with the first footfall over the finishing line. This analysis includes up to five measurements of gait speed collected Years 3-6 and Year 8 in Health ABC.

2.3.4 Covariates

We considered as covariates variables that were identified in the literature as potential confounders of the relationship between cognitive function and gait speed, or were associated with both cognitive function and gait speed in this cohort with a p-value <0.15. Selected covariates included demographic variables (age, race, sex, education and clinic site), vascular risk factors (body mass index (BMI), smoking, and physical activity), depressive symptoms and chronic conditions (prevalent coronary heart disease, cerebrovascular disease, hypertension, diabetes mellitus, and peripheral arterial disease). Presence of chronic conditions was determined from participant reports at the baseline visit. Depressive symptoms were assessed using the Centers for Epidemiologic Studies of Depression 10-item scale (CESD-10) (Andresen, Malmgren, Carter, & Patrick, 1994). BMI was calculated as measured weight in kilograms divided by measured height in meters squared. Walking frequency and duration was determined from responses to questions which distinguished walking for exercise and other types of walking from a standardized, interviewer-administered physical activity battery (Brach, Simonsick, Kritchevsky, Yaffe, & Newman, 2004). Participants walking a total of <30 minutes per week were defined as sedentary. Finally, ankle-arm index was calculated as the ratio of the systolic blood pressure obtained in the ankle to the systolic blood pressure of the right arm. Measures were performed twice and the results were averaged; the lower average value between the two legs was used to define an individual's ankle-arm index. Peripheral arterial disease was then defined as ankle-arm index less than or equal to 0.9, according to traditional diagnostic criteria (Yao, Hobbs, & Irvine, 1969).

2.3.5 Statistical Analysis

Differences in baseline characteristics across quartiles of gait speed and cognitive function were tested with Chi-square tests for categorical variables and analysis of variance or Kruskal-Wallis tests for continuous variables. Associations between cognitive domains were evaluated using Pearson correlations adjusted for demographics. Linear regression was used to test the cross-sectional association between cognitive function as the independent variable and gait speed as the dependent variable adjusting for demographics, risk factors, depressive symptoms and chronic conditions. Cognitive scores were standardized to allow direct comparison of regression coefficients. Multivariable models were built using a backward procedure (p out=0.5) after entering in cognitive test score and demographics. Low values of the variance inflation factor (<2) excluded the risk of multicollinearity.

Because patterns of specific cognitive deficits differ in normal aging and dementia (Buckner, 2004), we tested interactions between each cognitive test and cognitive status, categorized as normal cognitive function vs. cognitive impairment or decline. For these analyses, cognitive impairment was defined as a 3MS score less than 80 at Year 3, and cognitive decline as a decrease in 3MS score of 5 or more points from Year 1 to Year 3.

Linear mixed-effects models were used to evaluate associations of cognitive performance with the rate of gait speed decline over five years. A simple model for each cognitive domain included a random intercept for each subject, a random slope for time, baseline gait speed and demographics as fixed effects, and interaction terms for baseline cognitive score and covariates with time. Full models were built using a backward procedure (p out = 0.05) to additionally adjust for vascular risk factors and chronic conditions and the interactions of each covariate with

time. No structure was imposed on the covariance matrix of the random effects. Analyses were performed in Stata 10 (STATA, Houston, TX).

Finally, we used random-effects pattern mixture models (Hedeker & Gibbons, 1997) to evaluate the influence of missing gait speed data at final follow-up (n=303; 33.3%) in the analysis of gait speed decline. This method involves stratifying participants by their missing data pattern, then evaluating the influence of each missing data pattern on the outcome of interest. The results of the pattern-mixture model may then be averaged over the missing data patterns to obtain overall estimates that are corrected for missing data patterns. We performed these analyses using adapted code (Hedeker & Gibbons, 1997) in SAS 9 (SAS Institute, Inc., Cary, NC).

2.4 RESULTS

Mean age of the cohort was 75.2 years (SD 2.8); 49.4% were men and 48.4% black (Table 2). Mean gait speed at baseline was 1.20 (SD 0.22) m/s. Participants in lower quartiles of gait speed were more likely to be female, black, sedentary, and have less education, higher BMI, chronic conditions and poorer performance on all cognitive tests (Tables 2 and 3). Cognitive domains showed low to moderate correlation with each other after adjustment for demographics (Table 4).

In separate linear regression models of each cognitive test, poorer performance in each test (SD) was significantly associated with slower gait speed after adjustment for demographics, risk factors and chronic conditions (Table 5). Interaction terms for each cognitive test and

cognitive status were nonsignificant. In analyses excluding participants with cognitive impairment or decline, associations were similar to those observed in the whole sample.

In separate mixed models of each cognitive domain and gait speed decline, each interaction term for cognitive test score and time represents the calculated contribution of cognitive score to the rate of gait speed decline per year (Table 6). Each 1-SD poorer performance in global function, verbal memory and executive function was associated with 0.003-0.004 m/s greater gait speed decline per year (p=0.03-0.05) after adjustment for baseline gait speed, demographic and health characteristics. Psychomotor and perceptual speed performances were not significantly associated with rate of gait speed decline in simple or full models.

Pattern-mixture models of gait speed decline indicated that participants who did not complete gait speed testing at final follow-up had significantly slower gait and faster gait speed decline relative to completers. However, interactions of cognitive test score with time did not vary among completers and non-completers. Overall estimates for these interaction terms were similar to estimates from mixed models.

2.5 DISCUSSION

In this community-dwelling cohort, poorer performances in several cognitive domains were associated with slower gait speed cross-sectionally and predicted gait speed decline over five years. These results are consistent with a shared pathology underlying cognitive and physical

declines but do not suggest that specific cognitive deficits account for gait speed decline in aging.

Previous analyses in Health ABC found relationships of poorer psychomotor speed and executive function with slower gait or accelerated gait speed decline (Atkinson et al., 2007; Rosano, Simonsick et al., 2005), providing support to the hypothesis that compromised attention and executive function may be particularly important to explain gait slowing with age. However, in this analysis of participants who completed additional, detailed cognitive assessments, we identified similar associations with gait speed decline across global function, memory and executive function, suggesting that relationships between cognitive and physical function in aging are not restricted to specific cognitive domains.

Considered evidence of cerebral small vessel injury related to hypertension (Longstreth et al., 1996; Ovbiagele & Saver, 2006), hyperintensities of white matter tracts seen on brain MRI preferentially influence frontal-subcortical circuits that mediate executive and motor functions (Prins et al., 2005; Pugh & Lipsitz, 2002), although multiple cognitive domains, including memory, may be affected (de Groot et al., 2000). White matter hyperintensities predict gait speed decline (Rosano, Kuller et al., 2005), physical disability (Sachdev, Wen, Christensen, & Jorm, 2005) and functional limitation (Rosano, Kuller et al., 2005), suggesting underlying microvascular abnormalities may explain associations of several cognitive domains with gait speed decline. Although brain imaging data were not available to test this hypothesis in this cohort, we identified BMI, physical activity, cerebrovascular disease, diabetes, hypertension and peripheral arterial disease as important covariates in cross-sectional analyses of each cognitive test and gait speed, consistent with a shared vascular contribution to age-associated cognitive and physical declines.

Similar to our findings, poorer global and executive function in the full Health ABC cohort (Atkinson et al., 2007) and verbal fluency, involving memory, executive and processing speed components, in the Three-City Study (Soumare et al., 2009) were associated with accelerated gait speed decline. Although we did not identify an association of psychomotor or perceptual speed with rate of gait speed decline, in the Three-City Study poorer performance on the Trail Making Test part A (TMT-A) (Reitan, 1958), a test of psychomotor speed, was associated with greater gait speed decline after seven years. The inconsistent findings may reflect the exceptional functional status of substudy participants or sensitivity of the TMT-A to subtle psychomotor deficits. Additionally, this analysis may be limited by nonrandom withdrawal of substudy participants with chronic conditions, in that persons experiencing the greatest declines in gait speed may have been unable to continue study participation. However, pattern-mixture models of gait speed decline did not suggest that estimated contributions of cognitive function to gait speed decline are sensitive to missing data.

Additional limitations should be considered. First, some components of the cognitive tests required motor skills (e.g. drawing and copying figures), possibly obscuring the distinction between cognitive and physical function. Second, the potential influence of executive function on mobility may best be evaluated under challenging conditions that represent unpredictable environments in daily life [4]. In additional cross-sectional analyses of cognitive performance and gait speed at fast pace, the association of executive function with this task condition was substantially strengthened, possibly reflecting a higher demand of attention in the fast relative to usual pace walk (Fitzpatrick et al., 2007).

Finally, strengths of our study include the large community-dwelling population, assessment of memory and other specific cognitive domains, ability to account for several

potential confounders, and repeated assessments of gait speed, a reliable and valid measure of physical function that predicts functional limitation (Cesari et al., 2005; Guralnik et al., 2000) in older adults.

2.6 CONCLUSION

Several specific cognitive domains were associated with gait speed cross-sectionally and predicted gait speed decline in this well-functioning cohort. These findings are consistent with a shared etiology of cognitive and physical declines but do not suggest that deficits in specific cognitive domains account for gait slowing in aging. More work is needed to evaluate the potential role of vascular disease in dysfunction of both systems; MRI studies of cerebral small-vessel disease may clarify the mechanisms underlying co-occurring declines in cognitive and physical performance. Further understanding of these pathways may provide targeted strategies to preserve function in both central facets of successful aging.

Table 2. Characteristics of the cohort by quartiles (range in parentheses) of baseline gait speed (m/s)

	Mean ± SD, Median (IQR) or %					
	Overall (0.47-1.93)	**Q1 (<1.05)**	**Q2 (1.05-1.21)**	**Q3 (1.21-1.36)**	**Q4 (≥1.36)**	**p**
	n = 909	**n = 228**	**n = 229**	**n=226**	**n=226**	
Age, years	75.2 ± 2.8	75.8 ± 2.9	75.1 ± 2.8	75.2 ± 2.7	74.7 ± 2.5	<0.001
Male %	49.4	36.4	49.8	51.8	59.7	<0.001
Black %	48.4	73.3	59.4	38.1	22.6	<0.001
Education ≥ 12 yr %	78.4	65.2	72.4	86.2	89.8	<0.001
BMI, kg/m^2	26.9 ± 4.6	28.5 ± 5.7	26.8 ± 4.3	26.6 ± 4.2	25.6 ± 3.3	<0.001
Current or former smoker %	52.2	47.8	53.7	51.8	55.6	0.391
Sedentary %	68.2	83.7	71.5	62.5	54.7	<0.001
Coronary heart disease %	17.1	20.0	16.1	16.9	15.5	0.594
Cerebrovascular disease %	6.2	9.8	7.1	4.4	3.6	0.026
Diabetes %	19.5	31.3	21.8	12.4	12.4	<0.001
Hypertension %	59.4	78.5	60.7	53.1	45.1	<0.001
CES-D 10	3 (5)	4 (5)	3 (5)	3 (4)	3 (4)	<0.001*
Ankle arm index < 0.9 %	13.9	26.0	15.3	7.1	7.1	<0.001

P-values are from Chi-square tests of proportions for categorical variables and analysis of variance for comparison of mean values of continuous variables, unless otherwise noted.
*Kruskal-Wallis test of equal medians
CES-D 10 = Centers for Epidemiologic Studies of Depression 10-item scale

Table 3. Cognitive performance by quartiles (range in parentheses) of baseline gait speed (m/s)

	Mean ± SD or Median (IQR)					
	Overall (0.47-1.93)	**Q1 (<1.05)**	**Q2 (1.05-1.21)**	**Q3 (1.21-1.36)**	**Q4 (≥1.36)**	**p**
	n = 909	**n = 228**	**n = 229**	**n=226**	**n=226**	
Global function	90.2 ± 7.9	89 (12)	90 (10)	94 (9)	95 (6)	<0.001*
Verbal memory	6.6 ± 3.0	5.6 ± 3.0	6.3 ± 2.8	7.0 ± 2.9	7.5 ± 2.9	<0.001
Executive function	6.3 ± 4.2	8 (6)	6 (5)	5 (6)	4 (5)	<0.001*
Psychomotor speed	76.5 ± 20.6	66.0 ± 19.1	72.0 ± 20.0	79.6 ± 18.9	88.6 ± 16.9	<0.001
Perceptual speed	15.6 ± 5.4	13.3 ± 5.3	14.5 ± 5.2	16.4 ± 5.2	18.2 ± 4.6	<0.001

P-values are from analysis of variance for comparison of mean values of continuous variables, unless otherwise noted.
*Kruskal-Wallis test of equal medians

Table 4. Partial correlation coefficients[*] between cognitive domains at baseline

	Global function	Verbal memory	Executive function	Psychomotor speed	Perceptual speed
Global function	---	0.44	0.54	0.31	0.36
Verbal memory	0.44	---	0.27	0.21	0.26
Executive function	0.54	0.27	---	0.32	0.39
Psychomotor speed	0.31	0.21	0.32	---	0.58
Perceptual speed	0.36	0.26	0.39	0.58	---

p<0.001 for all
*adjusted for age, sex, race, education and clinic site

Table 5. Coefficients with SE in parentheses from multivariable linear regression models of baseline gait speed (m/s)

Cognitive Measure (SD)	Model 1		Model 2		Model 3	
	Beta (SE)	p	Beta (SE)	p	Beta (SE)	p
Global function (7.9)	0.032 (0.008)	<0.001	0.037 (0.008)	<0.001	0.031 (0.008)	<0.001
Verbal memory (3.0)	0.027 (0.007)	<0.001	0.026 (0.007)	<0.001	0.021 (0.007)	0.002
Executive function (4.2)	0.030 (0.008)	<0.001	0.032 (0.008)	<0.001	0.021 (0.008)	0.007
Psychomotor speed (20.6)	0.056 (0.008)	<0.001	0.056 (0.007)	<0.001	0.048 (0.007)	<0.001
Perceptual speed (5.4)	0.036 (0.008)	<0.001	0.038 (0.007)	<0.001	0.029 (0.007)	<0.001

Model 1 adjusted for age, sex, race, education and clinic site
Model 2 additionally adjusted for body mass index, smoking status, and physical activity
Model 3 additionally adjusted for depressive symptoms, coronary heart disease, cerebrovascular disease, diabetes mellitus, hypertension, and peripheral arterial disease

Table 6. Calculated contribution of a 1-SD lower cognitive performance to decline in gait speed (m/s) per year

Cognitive Measure (SD)	Model 1		Model 2		Model 3	
	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p
Global function (7.6)	0.003 (0.002)	0.04	0.003 (0.002)	0.03	0.003 (0.002)	0.03
Verbal memory (3.0)	0.004 (0.001)	0.01	0.004 (0.001)	0.03	0.004 (0.001)	0.03
Executive function (4.0)	0.003 (0.001)	0.04	0.003 (0.001)	0.04	0.003 (0.001)	0.05
Psychomotor speed (20.4)	0.002 (0.002)	0.29	0.002 (0.002)	0.27	0.002 (0.002)	0.32
Perceptual speed (5.3)	0.001 (0.001)	0.57	0.001 (0.001)	0.55	0.001 (0.001)	0.60

Model 1 adjusted for age, sex, race, education, clinic site, baseline gait speed, and interaction of each covariate with time
Model 2 additionally adjusted for body mass index, smoking status, physical activity, and interaction of each covariate with time
Model 3 additionally adjusted for depressive symptoms, coronary heart disease, cerebrovascular disease, diabetes mellitus, hypertension, peripheral arterial disease, and interaction of each covariate with time

3.0 ARTERIAL STIFFNESS AND COGNITIVE DECLINE IN WELL-FUNCTIONING OLDER ADULTS

Manuscript in preparation

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3.1 ABSTRACT

Objective: To evaluate associations of central arterial stiffness with cognitive function and decline in several specific cognitive domains in an older community-based population. ***Design:*** Observational cohort study. ***Setting:*** Five hundred fifty-two participants in the Health, Aging and Body Composition (Health ABC) study Cognitive Vitality Substudy (mean age ± SD 73.1 ± 2.7 years, 48% men, 42% black). ***Measurements:*** Pulse wave velocity (PWV) (cm/s), a measure of aortic stiffness, was assessed at baseline via Doppler-recorded carotid and femoral pulse waveforms. Multiple cognitive domains were evaluated over six years. ***Results:*** After adjustment for demographics, vascular risk factors and chronic conditions, each 1-SD higher PWV (389 cm/s) was associated with poorer cognitive function: -0.11 SD for global function (SE = 0.04, $p < 0.01$); -0.09 SD for psychomotor speed (SE = 0.04, $p = 0.03$), and -0.12 SD for perceptual speed (SE = 0.04, $p < 0.01$). Higher PWV was also associated with greater decline in psychomotor speed, defined as >1 SD more than the mean change (OR 1.42 (95% CI 1.06, 1.90)) but not with verbal memory or longitudinal decline in global function, verbal memory or perceptual speed. Results were consistent with mixed models of decline in each cognitive test. ***Conclusions:*** Central arterial stiffness may contribute to cognitive decline independent of hypertension and other vascular risk factors. Frontal and subcortical regions that mediate psychomotor speed may be particularly vulnerable to cerebrovascular injury in the presence of arterial stiffness.

3.2 INTRODUCTION

Vascular risk factors are important predictors of cognitive decline and dementia (Breteler, 2000; de la Torre, 2002). Independent of traditional risk factors, arterial stiffness is associated with cerebral microvascular disease (Henskens et al., 2008; Kearney-Schwartz et al., 2009; Ohmine et al., 2008) commonly detected on brain MRI in older adults as hyperintensities of white matter tracts (Manolio et al., 1994). This relationship has been attributed to the exposure of fragile cerebral small vessels to damaging central pulse pressures that are transmitted, rather than cushioned, by stiffened vessels (Mitchell, 2008; O'Rourke & Safar, 2005). Small-vessel disease in the brain preferentially affects frontal-subcortical regions that mediate executive and motor functions (Buckner, 2004; Pugh & Lipsitz, 2002), suggesting that arterial stiffness may contribute to decline in these specific cognitive domains.

Several studies have found elevated pulse wave velocity (PWV), a measure of central arterial stiffness, cross-sectionally associated with poorer cognitive function in older adults (Elias et al., 2009; Fujiwara et al., 2005; Fukuhara et al., 2006; Scuteri et al., 2005; Triantafyllidi et al., 2009). Associations of PWV with cognitive decline over time are less consistent. Elevated PWV did not predict decline in either global cognitive function, verbal fluency, executive function or processing speed in the Rotterdam study (mean age 72 years) (Poels et al., 2007); however, in an analysis of the Baltimore Longitudinal Study of Aging (BLSA) (mean age 54 years) (Waldstein et al., 2008) higher PWV was associated with accelerated decline in learning and memory. Findings from BLSA may reflect a contribution of arterial stiffness and associated central pressures to cognitive decline in mid to late life.

To clarify the association of central arterial stiffness with cognitive decline in aging, we evaluated the relationships of PWV with global cognitive function and performance in several cognitive tasks over six years in the Health, Aging and Body Composition (Health ABC) Cognitive Vitality Substudy. This study extends on previous work by characterizing associations of PWV with longitudinal cognitive decline among older adults who were initially free of functional limitation.

3.3 METHODS

3.3.1 Population

From 1997 to 1998 the Health ABC study enrolled 3,075 Medicare-eligible well-functioning men and women aged 70-79 from Pittsburgh, Pa. and Memphis, Tn., USA. The population was 52% women and 42% black with a mean age of 73.6 years. Participants were recruited from Medicare-eligible adults with contact information provided by the Centers for Medicare & Medicaid Services (formerly the Health Care Financing Administration) on a random sample of white and all black beneficiaries in pre-designed zip code areas surrounding the study centers. Other household members aged 70-79 were also eligible for recruitment. Exclusion criteria included reported difficulty walking one quarter of a mile, climbing 10 steps without resting, or performing basic activities of daily living or need for a walking aid.

In Year 3 of Health ABC, the Cognitive Vitality Substudy was initiated. Participants were selected from the top 20% of performers on an endurance walk test (Simonsick et al., 2001)

in Year 2 from each of eight groups defined by sex, race, and study site (Memphis or Pittsburgh). An equal number were then drawn at random from the remaining members of each group yielding 951 black and white women and men aged 71-82 years who received additional cognitive testing. Substudy participants were slightly younger (75.5 years versus 75.7 years), more likely to be female (54% versus 50%) and white (65% versus 55%) and have <12 years education (30% versus 23%) compared to the Health ABC participants who were not part of the substudy. Substudy exclusion criteria included self-reported difficulty seeing large print or grasping a pen. The Institutional Review Boards of the University of Pittsburgh, Pa., and University of Tennessee at Memphis approved the study, and written, informed consent was obtained from each volunteer. Of the 951 participants in the substudy, 727 had valid PWV data at baseline and cognitive data at Year 3. Of the 727 participants, we excluded those with evidence of cognitive impairment at Year 3 (Teng-modified Mini-Mental Status Exam (3MS) score less than 80; N = 75) or decline prior to Year 3 (decrease in 3MS score of 5 or more points; N = 100), leaving 552 participants for analysis (mean age 73.1 ± 2.7 years, 48% men, 42% black).

3.3.2 Pulse wave velocity

Aortic PWV was measured noninvasively via simultaneous Doppler-recorded carotid and femoral pulse waveforms (model 810A, 9.0- to 10-MHz probes, Parks Medical Electronics, Inc). A minimum of ten beats were recorded for each simultaneous recording site. Three separate runs were recorded for each participant, and all usable runs were averaged to calculate the final PWV measure. The distance between the carotid and femoral recording sites was measured above the

surface of the body with a tape measure. The time delay between the feet of the pressure waves at each site was divided by the associated distance to calculate PWV in cm/s. Replicate measures of PWV in 14 subjects revealed intraclass correlations of 0.88 between sonographers and 0.84 between readers (Sutton-Tyrrell et al., 2005).

3.3.3 Cognitive Tests

Cognitive function was assessed at Years 3, 5, 7, and 9. The Modified Mini-Mental Status Exam (3MS) (Teng & Chui, 1987) is a comprehensive evaluation of global cognitive function, including orientation, attention, calculation, language and short-term memory. Scores can range from 0 to 100 points, with lower scores indicating poorer performance. The Buschke Selective Reminding Test (SRT) (Buschke & Fuld, 1974) is a multiple-trial list-learning task used to measure verbal learning and memory. In this task, the examiner presents a list of 12 written words and reads each word aloud. The participant is then asked to recall the words presented. For the next trial, the examiner repeats the words the participant failed to recall and then asks the participant to provide the full list of 12 words. This procedure is repeated five times. Delayed recall is scored as the number of words recalled 20-30 minutes after the sixth trial. The Boxes and Digit Copying (BDC) tests are timed tests of psychomotor speed (Salthouse, 1996). The participant is asked to complete as many boxes and copy as many digits as possible within 30 seconds for each test. Psychomotor speed is scored as the sum of total boxes and digits completed (rho = 0.77). Finally, the Pattern and Letter Comparison (PLC) tests are timed tests of perceptual speed (Salthouse, 1996). The participant is asked to determine whether pairs of

patterns and letters are the same or different within 30 seconds for each test. Perceptual speed is scored as the sum of correct pattern and letter comparisons (rho = 0.64).

3.3.4 Covariates

We considered as covariates variables that were identified in the literature as potential confounders of the relationship between arterial stiffness and cognitive function, or were associated with both baseline PWV and Year 3 3MS score in this cohort at a significance level of 0.15. Selected covariates included demographic variables (age, race, sex, education (years of school, ≤12 years versus >12 years) and clinic site), risk factors (body mass index (BMI), history of smoking, physical activity, total cholesterol, resting heart rate, mean arterial pressure and depressive symptoms), and comorbid conditions (prevalent hypertension, coronary heart disease, cerebrovascular disease and diabetes mellitus). All covariates were obtained from the baseline visit with the exception of depressive symptoms, which were evaluated at Year 3. BMI was calculated as measured weight in kilograms divided by measured height in meters squared. Physical activity was assessed by questionnaire and used to calculate the kilocalories expended for all forms of walking and exercise, stair climbing and vigorous activity in the previous week; participants with at least 1,000 kcal expended were defined as active. Total cholesterol was determined from fasting blood samples collected at the baseline clinic visit. Systolic and diastolic blood pressures were each measured twice and averaged; mean arterial pressure was calculated as diastolic pressure + 1/3 (systolic pressure – diastolic pressure). Depressive symptoms were assessed using the Centers for Epidemiologic Studies of Depression 10-item scale (CES-D) (Andresen et al., 1994). Presence of hypertension and other conditions at baseline

was determined from participant reports of diagnosis and use of specific medications or procedures.

3.3.5 Statistical Analysis

Differences in baseline characteristics across tertiles of PWV and 3MS score were tested with Chi-squared tests for categorical variables and analysis of variance or Kruskal-Wallis tests for continuous variables. Separate linear regression models were used to evaluate the association between PWV as the independent variable and performance on each cognitive test as the dependent variable. In these models, scores for each cognitive test were standardized to allow for direct comparison of regression coefficients. Logistic regression was used to test the association of PWV with cognitive decline, defined as 5 points or more decline on the 3MS (Andrew & Rockwood, 2008), and >1 SD more than the mean change on the SRT, BDC and PLC from Year 3 to Year 9. Multivariate linear and logistic regression models were built using a backward procedure (p out = 0.05) to adjust for vascular risk factors and comorbid conditions after entering in PWV and demographics.

Because the relationship of hypertension with cognitive decline may differ in normal aging and preclinical dementia, we repeated logistic regression models of cognitive decline after including in the sample participants with evidence of cognitive or impairment or decline at Year 3 (n=175). These analyses tested interactions of PWV and cognitive status, categorized as normal cognitive function versus cognitive impairment or decline.

Finally, mixed models were used to confirm the associations of PWV with decline in each cognitive test. The models included as outcomes all cognitive data available throughout the

study period, improving statistical power and reducing potential bias due to nonrandom censoring, relative to logistic regression models. To account for an apparent learning effect in the verbal memory test from Year 3 to Year 5, models of decline in this test were restricted to Years 5, 7, and 9. Simple models of decline in each cognitive test included a random intercept for subject, a random slope with time, and clinic site, PWV and the interaction of PWV with time as fixed effects. A second model additionally adjusted for demographics and the interactions of each covariate with time. Full models were built using a backward procedure (p out = 0.05) to additionally adjust for vascular risk factors and comorbidities and the interactions of each covariate with time. No structure was imposed on the covariance matrix of the random effects. Continuous covariates were centered to reduce multicollinearity and simplify interpretation of model coefficients. Analyses were performed in SAS (version 9.1; SAS Institute, Inc., Cary, NC) and Stata 10 (STATA, Houston, TX).

3.4 RESULTS

Mean age (SD) of this cohort at baseline was 73.1 (2.7) years; 48% were men and 42% black. Mean (SD) PWV was 886 (389) cm/s. Participants with higher PWV were more likely to be black, hypertensive, less active, and have higher BMI, heart rate, and mean arterial pressure (Table 7). In linear regression models adjusted for demographics, higher PWV at baseline was significantly associated with poorer performance on tests of global cognitive function, psychomotor speed and perceptual speed but not verbal memory. Further adjustment for risk

factors and comorbidities in the backward procedure did not substantially change the coefficients for PWV in full models of each cognitive test (Table 8).

Of the 552 participants in the sample, 406 completed cognitive testing at Year 9 and were included in logistic regression models of cognitive decline (mean age 73.0 ± 2.7 years, 47% men, 42% black). Cognitive decline >1 SD from the mean change related to a decline of ≥ 3 points on the SRT (n = 49); ≥ 20 on the BDC (n = 49); and ≥ 5 on the PLC (n = 68). 64 participants declined ≥ 5 points on the 3MS. Fully adjusted, with each SD higher PWV the odds ratio increased by a factor of 1.42 for risk of decline in psychomotor speed (Table 9). The association of PWV with psychomotor speed decline was attenuated (OR 1.10, 95% CI 0.82, 1.47) after inclusion of participants with evidence of cognitive impairment or decline at Year 3; however, interactions of PWV with cognitive status were nonsignificant. PWV was not associated with risk of decline in global cognitive function, verbal memory, or perceptual speed in logistic regression models adjusted for demographics.

Results of mixed models of cognitive decline in the full sample were consistent with results of logistic regression models (Table 10). Fully adjusted, the calculated contribution of each SD higher PWV to psychomotor speed decline was modest though statistically significant: 0.298 points per year (95% CI 0.099, 0.498). PWV was not associated with decline in global cognitive function, verbal memory, or perceptual speed in mixed models adjusted for demographics.

3.5 DISCUSSION

In this cohort of community-dwelling older adults, higher PWV was associated with poorer performance on tests of global cognitive function, psychomotor speed and perceptual speed and with decline in psychomotor speed after six years. PWV was not associated with verbal memory or decline in global function, verbal memory or perceptual speed. These data suggest that frontal-subcortical regions that mediate psychomotor speed may be particularly sensitive to central arterial stiffness.

This study further investigates the recently identified inverse relationship of arterial stiffness with global cognitive function in older adults (Fujiwara et al., 2005; Fukuhara et al., 2006; Scuteri et al., 2005). The domain-specific associations in this cohort are consistent with a mediating role of cerebral small-vessel disease (Triantafyllidi et al., 2009), a common manifestation of ischemic injury that preferentially affects executive function and processing speed while sparing verbal memory (Jokinen et al., 2009; Prins et al., 2005). Executive function and processing may be particularly vulnerable to vascular injury (Buckner, 2004; Pugh & Lipsitz, 2002) because much of the deep white matter is perfused by arterioles with few interconnections available to preserve blood supply in the presence of ischemic injury (Pantoni, 2002).

Although several studies of older adults have identified inverse associations between arterial stiffness and cognitive function cross-sectionally, few have evaluated the relationship of arterial stiffness with cognitive decline. PWV did not predict cognitive decline in one recent study of community-dwelling older adults (Poels et al., 2007). In another cohort, elevated PWV was associated with accelerated decline on tests of language and memory but not executive

function or psychomotor speed (Waldstein et al., 2008). This pattern contrasts with our finding that elevated PWV predicted decline in psychomotor speed but not other cognitive domains. Inconsistent associations across studies may in part reflect important differences in selected cognitive assessments; for example, memory tasks that are more demanding of executive control and attention may be more sensitive to cerebrovascular changes in aging (Buckner, 2004). Further, in previous studies the contribution of arterial stiffness to cognitive decline in normal aging may have been partially obscured by the inclusion of participants with preclinical dementia.

Several pathways have been hypothesized to link arterial stiffness with cerebral microvascular disease and cognitive function (Iadecola et al., 2009). First, the loss of cushioning capacity of the stiffened aorta allows damaging central pulse pressures to be transmitted into the fragile small vessels of target organs (Mitchell, 2008; O'Rourke & Safar, 2005). Highly pulsatile flow may accelerate the narrowing of the cerebral vasculature, impeding delivery of energy substrates and nutrients to active brain cells. The resulting state of chronic hypoperfusion may directly injure cerebral white matter or allow toxic metabolic byproducts to accumulate within the brain and blood vessels (Iadecola et al., 2009). Moreover, stiffening and thickening of the cerebral vasculature may contribute to endothelial dysfunction and associated breakdown of the blood-brain barrier. Toxins, proteases, or other substances in the blood may then enter the brain interstitial space and injure surrounding neurons and glial cells (Wardlaw et al., 2003).

Important limitations of this study should be considered. Our analyses do not account for unmeasured progression of subclinical vascular disease from PWV assessment at baseline to cognitive assessment at Year 3. Additionally, the estimated associations of PWV with cognitive decline may be sensitive to nonrandom withdrawal of participants who experienced the greatest

functional declines throughout the study period. As expected, participants who completed final follow-up (n=406) were slightly younger at baseline (73.0 years versus 73.5 years) and less likely to have cerebrovascular disease (4% versus 8%) and hypertension (47% versus 58%) relative to noncompleters (n=146). These limitations are expected to underestimate the associations of PWV with cognitive function and cognitive decline in the population. Strengths of this study include the large community-dwelling population, assessment of function in specific cognitive domains, ability to account for important confounders, and a reliable and valid measure of arterial stiffness that predicts morbidity and mortality in older adults (Sutton-Tyrrell et al., 2005).

In this initially well-functioning cohort, central arterial stiffness was inversely associated with performance in several cognitive tasks and predicted longitudinal decline in psychomotor speed independent of hypertension and other vascular risk factors. Longitudinal brain imaging studies of older adults may clarify the spatial distribution of cerebrovascular injury in relationship to vascular stiffening. Further work is needed evaluate whether reduction of central arterial stiffness and associated central pressures may reduce risk of cognitive decline beyond that expected by brachial blood pressure lowering. As the cognitive consequences of arterial stiffening continue to emerge, strategies to combat this risky process of arterial aging should emphasize the long-term control of modifiable vascular risk factors.

Table 7. Baseline characteristics of the cohort by tertiles of PWV (cm/s)

Characteristic	(329-2823)	(329-673)	(673-925)	(925-2823)	p
Age, yrs	73.1 ± 2.7	73.0 ± 2.5	73.1 ± 2.8	73.3 ± 2.7	0.28
Male %	47.5	42.9	48.9	50.5	0.31
Black %	42.2	35.3	44.6	46.7	0.06
Education >12 yrs %	54.0	63.4	47.8	51.1	0.01
BMI, kg/m^2	27.0 ± 4.6	26.0 ± 4.0	27.6 ± 4.3	27.0 ± 4.6	<0.01
Mean arterial blood pressure, mmHg	94.1 ± 12.3	90.2 ± 10.9	95.2 ± 11.8	96.9 ± 13.1	<0.01
Cholesterol, mg/dl	202.7 ± 38.0	202.4 ± 33.8	205.1 ± 40.1	200.6 ± 39.8	0.53
Heart rate, bpm	62.7 ± 10.6	61.0 ± 10.2	63.5 ± 11.2	63.7 ± 10.2	0.03
Current or former smoker %	51.1	47.3	56.0	50.0	0.23
Physical activity >1000 kcal/wk %	45.1	51.6	45.7	38.0	0.03
Hypertension %	50.0	33.7	52.8	63.6	<0.01
Coronary heart disease %	14.8	12.6	15.4	16.4	0.58
Cerebrovascular disease %	5.3	2.7	6.0	7.1	0.15
Diabetes mellitus %	13.3	10.4	14.2	15.2	0.36
CES-D 10	4.2 ± 3.8	4.2 ± 3.7	4.1 ± 3.8	4.3 ± 4.0	0.95
Global cognitive function (3MS)	93.5 ± 4.9	94.4 ± 4.2	93.7 ± 5.1	92.3 ± 5.3	<0.01
Verbal memory (SRT)	6.6 ± 3.0	6.7 ± 3.0	6.7 ± 3.0	6.3 ± 2.9	0.23
Psychomotor speed (BDC)	80.9 ± 18.6	86.4 ± 17.3	79.6 ± 19.7	76.7 ± 17.5	<0.01
Perceptual speed (PLC)	16.7 ± 5.0	18.2 ± 4.6	16.2 ± 5.0	15.8 ± 5.0	<0.01

CES-D 10 = Center for Epidemiologic Studies Depression Scale; 3MS = Modified Mini-Mental Status Exam; SRT = Buschke Selective Reminding Test; BDC = Boxes and Digit Copying Tests; PLC = Pattern and Letter Comparison Tests
P-values are from Chi-square tests of proportions for categorical variables and analysis of variance for comparison of mean values of continuous variables

Table 8. Multivariable regression adjusted associations of 1-SD (389 cm/s) higher baseline PWV with lower Year 3 cognitive scores

Cognitive Measure (SD)	Model 1 PWV Beta (95% CI)		Model 2 PWV Beta (95% CI)		Model 3 PWV Beta (95% CI)	
	Cognitive Measure SDs*	Cognitive Measure Original Units†	Cognitive Measure SDs*	Cognitive Measure Original Units†	Cognitive Measure SDs*	Cognitive Measure Original Units†
Global function (4.9)	-0.17 (-0.25, -0.09)	-0.82 (-1.24, -0.40)	-0.11 (-0.19, -0.03)	-0.53 (-0.89, -0.17)	-0.11 (-0.19, -0.03)	-0.55 (-0.91, -0.19)
Verbal memory (3.0)	-0.09 (-0.17, -0.01)	-0.26 (-0.52, 0.00)	-0.06 (-0.14, 0.02)	-0.17 (-0.41, 0.07)	-0.07 (-0.15, 0.01)	-0.20 (-0.44, 0.04)
Psychomotor speed (18.6)	-0.18 (-0.26, -0.10)	-3.40 (-4.96, -1.84)	-0.11 (-0.19, -0.03)	-2.13 (-3.53, -0.73)	-0.09 (-0.17, -0.01)	-1.59 (-3.03, -0.15)
Perceptual speed (5.0)	-0.18 (-0.26, -0.10)	-0.90 (-1.32, -0.48)	-0.12 (-0.20, -0.04)	-0.61 (-0.97, -0.25)	-0.12 (-0.20, -0.04)	-0.60 (-0.98, -0.22)

Model 1 unadjusted
Model 2 adjusted for age, sex, race, education and clinic site
Model 3 additionally adjusted for body mass index, mean arterial pressure, cholesterol, heart rate, smoking status, physical activity, depressive symptoms, prevalent hypertension, coronary heart disease, cerebrovascular disease, and diabetes mellitus

* Beta= Δ SD's of Cognitive Measure per SD of PWV
† Beta= Δ Cognitive Measure (original units) per SD of PWV

Table 9. Risk of decline* in cognitive performance after six years, per SD (387 cm/s) higher baseline PWV

Cognitive Measure	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)
Global function	1.33 (1.05, 1.68)	1.24 (0.96, 1.60)	1.22 (0.90, 1.67)
Verbal memory	1.01 (0.75, 1.35)	0.98 (0.71, 1.36)	1.05 (0.74, 1.50)
Psychomotor speed	1.32 (1.02, 1.71)	1.32 (1.01, 1.72)	1.42 (1.06, 1.90)
Perceptual speed	0.99 (0.76, 1.29)	0.96 (0.73, 1.26)	0.97 (0.72, 1.31)

Model 1 unadjusted
Model 2 adjusted for age, sex, race, education and clinic site
Model 3 additionally adjusted for body mass index, mean arterial pressure, cholesterol, heart rate, smoking status, physical activity, depressive symptoms, prevalent hypertension, coronary heart disease, cerebrovacular disease and diabetes mellitus

*Decline ≥ 5 points in global function; ≥ 3 points in verbal memory; ≥ 20 points in psychomotor speed; ≥ 20 points in psychomotor speed; ≥ 5 points in perceptual speed

Table 10. Calculated contribution of 1-SD (389 cm/s) higher baseline PWV to cognitive decline (points per year)

Cognitive Measure	Model 1 Estimate (95% CI)	Model 2 Estimate (95% CI)	Model 3 Estimate (95% CI)
Global function	0.110 (0.017, 0.204)	0.085 (-0.008, 0.178)	0.081 (-0.012, 0.173)
Verbal memory	0.012 (-0.047, 0.070)	0.021 (-0.038, 0.080)	0.019 (-0.039, 0.078)
Psychomotor speed	0.272 (0.072, 0.471)	0.292 (0.094, 0.491)	0.298 (0.099, 0.498)
Perceptual speed	0.018 (-0.040, 0.075)	0.022 (-0.036, 0.080)	0.019 (-0.039, 0.077)

Model 1 adjusted for clinic site
Model 2 additionally adjusted for age, sex, race, education, and interaction of each covariate with time
Model 3 additionally adjusted for body mass index, mean arterial pressure, cholesterol, heart rate, smoking status, physical activity, depressive symptoms, prevalent hypertension, coronary heart disease, cerebrovacular disease, diabetes mellitus, and interaction of each covariate with time

4.0 ARTERIAL STIFFNESS AND GAIT SPEED DECLINE IN OLDER ADULTS WITH AND WITHOUT PERIPHERAL ARTERIAL DISEASE

Manuscript in preparation

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4.1 ABSTRACT

Central arterial stiffness is increasingly recognized as an important predictor of cardiovascular events and mortality in older adults; however, few studies have evaluated the association of arterial stiffness with mobility decline, a common consequence of vascular disease. We analyzed the association of pulse wave velocity (PWV), a measure of aortic stiffness, with longitudinal gait speed over seven years in 2,172 participants in the Health, Aging and Body Composition (Health ABC) Study (mean age ± SD 73.6 ± 2.9 years, 48% men, 39% black). In mixed-effects models adjusted for demographics, each SD higher PWV was associated with 0.014 (SE 0.004) m/s slower gait at baseline and throughout the study period in the full cohort ($p<0.001$). This relationship was explained by hypertension and other vascular risk factors. However, in participants with peripheral arterial disease (PAD) (n = 261; 12.7%), each SD higher PWV was independently associated with a 0.030 (SE 0.010) m/s slower gait speed at baseline and throughout the study period ($p<0.01$). These findings suggest that aortic stiffness may be especially detrimental to mobility in older adults with already compromised arterial function.

4.2 INTRODUCTION

The primary determinant of systolic hypertension in older adults, central arterial stiffness predicts cardiovascular events and mortality independent of systolic blood pressure and other vascular risk factors (Sutton-Tyrrell et al., 2005). Clinical consequences of arterial stiffness have

been attributed to early wave reflection from the periphery and loss of cushioning capacity of the aorta (O'Rourke, 2007); these risky processes of arterial aging increase cardiac afterload, reduce diastolic filling and promote small-vessel injury of the brain and kidney (Mottram et al., 2005; O'Rourke, 2007; O'Rourke & Safar, 2005; Safar & Lacolley, 2007). Aortic stiffness may further contribute to resistance vessel hypertrophy and increased vascular resistance (Intengan & Schiffrin, 2000; Park & Schiffrin, 2001), impeding blood flow to the peripheral microvasculature (Mitchell et al., 2005). However, the relationship of aortic stiffness with mobility decline, a common consequence of vascular disease, has not been well-characterized in older adults.

Among patients with obstructive peripheral arterial disease (PAD), reductions in aortic stiffness by an angiotensin-converting enzyme (ACE) inhibitor were recently found associated with improved walking endurance beyond the extent expected by blood pressure lowering (Ahimastos et al., 2008), suggesting that aortic stiffness may contribute to compromised leg perfusion or diastolic function in PAD. To evaluate whether aortic stiffness may also in part explain mobility decline in initially well-functioning older adults, we analyzed the association of PWV with longitudinal gait speed in the Health, Aging, and Body Composition Study and evaluated its role in participants with PAD. Independent associations of PWV with gait speed in this cohort may reflect physical functional consequences of impaired diastolic function or microvascular perfusion in the presence of aortic stiffness (Ahimastos et al., 2008).

4.3 METHODS

4.3.1 The Health ABC Study and Participants

From 1997 to 1998 the Health ABC study enrolled 3,075 Medicare-eligible nondisabled men and women aged 70-79 from Pittsburgh, Pa. and Memphis, Tn., USA. The population was 52% women and 42% black with a mean age of 73.6 years. Participants were recruited from Medicare-eligible adults with contact information provided by the Centers for Medicare & Medicaid Services (formerly the Health Care Financing Administration) on a random sample of white and all black beneficiaries in pre-designed zip code areas surrounding the study centers. Other household members aged 70-79 were also eligible for recruitment. Exclusion criteria included reported difficulty walking one quarter of a mile, climbing 10 steps without resting, or performing basic activities of daily living or need for a walking aid. The Institutional Review Boards of the University of Pittsburgh, Pa. as well as the University of Tennessee at Memphis approved the study and written, informed consent was obtained from each volunteer. PWV data were missing for 354 participants due to an equipment problem and an additional 233 participants who had unusable waveforms. Of the remaining 2,488 participants, 2,172 had valid gait speed data at baseline and were included in the analysis (mean age ± SD 73.6 ± 2.9 years, 48% men, 39% black).

4.3.2 Pulse wave velocity

Aortic PWV was measured noninvasively via simultaneous Doppler-recorded carotid and femoral pulse waveforms (model 810A, 9.0- to 10-MHz probes, Parks Medical Electronics, Inc). A minimum of ten beats were recorded for each simultaneous recording site. Three separate runs were recorded for each participant, and all usable runs were averaged to calculate the final PWV measure. The distance between the carotid and femoral recording sites was measured above the surface of the body with a tape measure. The time delay between the feet of the pressure waves at each site was divided by the associated distance to calculate PWV in cm/s. Replicate measures of PWV in 14 subjects revealed intraclass correlations of 0.88 between sonographers and 0.84 between readers (Sutton-Tyrrell et al., 2005).

4.3.3 Peripheral arterial disease

Ankle-arm index (AAI) was calculated as the ratio of the systolic blood pressure obtained in the ankle to the systolic blood pressure of the right arm. Measures were performed twice and the results averaged; the lower average value between the two legs was used to define an individual's AAI. Peripheral arterial disease (PAD) was defined as an AAI less than 0.9, according to traditional diagnostic criteria (Yao et al., 1969).

4.3.4 Gait speed

Usual gait speed was assessed over a 20-meter straight course at baseline and annually through Year 8, except Year 7. Participants were instructed to walk at their usual pace from the starting point to the end of the course. Timing began at the first footfall over the starting line and ended with the first footfall over the finishing line.

4.3.5 Covariates

We considered as potential confounders variables that were identified in the literature as confounders of the relationship between vascular disease and physical function, or were associated with arterial stiffness and gait speed in this cohort at a significance level of 0.15. Selected covariates included smoking status, body-mass index (BMI), physical activity, resting heart rate, systolic blood pressure, total cholesterol, prevalent coronary heart disease, diabetes and hypertension. Presence of chronic conditions was determined from participant reports from the baseline visit and confirmed by use of specific medications or procedures (Madero et al., 2009a). BMI was calculated as measured weight in kilograms divided by measured height in meters squared. Physical activity was assessed by questionnaire and used to calculate the kilocalories expended for all forms of walking and exercise, stair climbing and vigorous activity in the previous week; participants with at least 1,000 kcal expended were defined as active. Systolic blood pressure was measured twice and the results averaged. Total cholesterol was determined from fasting blood samples collected at the baseline clinic visit.

Because aortic stiffness is associated with both overt and subclinical cerebrovascular disease (Henskens et al., 2008; Sutton-Tyrrell et al., 2005), we also evaluated whether an association of PWV with gait speed may be explained by prevalent cerebrovascular disease or performance on the Digit Symbol Substitution Test (DSST), a test of attention and psychomotor speed (*Wechsler Adult Intelligence Scale F Revised*, 1981) that is sensitive to cerebral small-vessel disease (O'Sullivan, Morris, & Markus, 2005) and predicts incident stroke in older adults (Elkins, Knopman, Yaffe, & Johnston, 2005).

4.3.6 Statistical Analysis

Differences in baseline characteristics across quartiles of PWV and gait speed were evaluated using Chi-square tests for categorical variables and Kruskal-Wallis tests or analysis of variance for continuous variables. Mixed-effects models were used to evaluate the association of PWV with longitudinal gait speed over seven years. In these models, coefficients for fixed effect variables represent the association of the variable with gait speed (m/s) at baseline and throughout the study period; interactions of fixed effect variables with time represent the contribution of the variable to the rate of gait speed decline (m/s) per year. Simple models included a random intercept for subject, a random slope with time, clinic site and PWV as fixed effects, and the interaction of PWV with time. A second model additionally adjusted for demographics (age, sex, and race) and the interaction of each covariate with time. A backward procedure (p-out = 0.05) was used to build a full model additionally adjusted for vascular risk factors and chronic conditions, the interaction of each covariate with time and the interaction of PWV with PAD. Analyses were then repeated in subgroups stratified by PAD and additionally

adjusted for prevalent cerebrovascular disease, DSST score, and AAI. Finally, to evaluate the sensitivity of estimates to missing data, we repeated the analysis of the full sample after limiting followup to four years. No structure was imposed on the covariance matrix of the random effects. Continuous covariates were centered to simplify interpretation of model coefficients and to reduce multicollinearity. Analyses were performed in Stata 10 (STATA, Houston, TX).

4.4 RESULTS

Mean age (SD) of the cohort was 73.6 (2.9) years; 48% were men and 39% were black (Table 11). Participants in higher PWV quartiles were older, more likely to be male, black, less active, and have higher BMI, systolic blood pressure, resting heart rate, a history of smoking, and prevalent diabetes and hypertension (Table 11). Higher PWV quartiles were also associated with PAD, lower DSST score and slower baseline gait speed (Table 12).

In mixed models adjusted for demographics, each SD higher PWV was associated with a 0.014 m/s slower gait speed at baseline and throughout the study period, represented by the significant main effect of PWV ($p<0.01$) (Table 13). The effect was attenuated after additional adjustment for vascular risk factors and chronic conditions (Model 3); the covariates BMI, systolic blood pressure, heart rate, diabetes and hypertension were particularly important to explain the association of PWV with gait speed. No significant interaction was identified for PWV with time, indicating no significant contribution of PWV to the longitudinal decrease in gait speed.

Although the interaction of PWV with PAD was not statistically significant, in analyses restricted to participants with PAD (n = 261; 12.7%), each SD higher PWV was associated with a 0.030 (SE 0.010) m/s slower gait speed at baseline and through the study period after adjustment for demographics, risk factors and chronic conditions ($p<0.01$) (Table 14). This effect did not substantially change after additional adjustment for prevalent cerebrovascular disease, DSST score, or AAI. As in the full cohort, the interaction of PWV with time was nonsignificant.

In the full cohort, significant interactions with time were identified for the covariates age, sex, race, hypertension and cerebrovascular disease in a full model of gait speed decline. Calculated contributions to annual gait speed decline, represented by interaction terms for each covariate with time, were modest although statistically significant: -0.0008 m/s per year older age at baseline; -0.006 m/s each for male sex and white race; -0.003 m/s for prevalent hypertension; and -0.007 m/s for cerebrovascular disease ($p<0.01$ for all).

Finally, 1673 (77%) of participants completed gait speed testing at Year 5 and 1219 (56%) at Year 8. In analyses restricted to followup through Year 5, estimates for PWV and the interaction of PWV with time did not substantially change, suggesting reported estimates are not sensitive to missing observations.

4.5 DISCUSSION

Although PWV was not independently associated with gait speed in this initially well-functioning cohort, among those with evidence of PAD, higher PWV was associated with slower

gait independent of hypertension and other vascular risk factors. These data suggest that aortic stiffness may be especially detrimental to mobility in older adults with already compromised arterial function.

Cardiovascular consequences of arterial stiffening may be explained by gradual loss of the cushioning capacity of the aorta and early wave reflection from the periphery, resulting in small-vessel injury of target organs and reduced diastolic filling (O'Rourke, 2007; O'Rourke & Safar, 2005; Safar & Lacolley, 2007). Current findings are consistent with those of a recent publication that found arterial stiffness independently associated with impaired functional capacity in patients evaluated for peripheral arterial disease (PAD) (Ahimastos et al., 2008), and further suggest a clinically important synergistic relationship of aortic stiffness and PAD. In a recent randomized trial among PAD patients, reduction of PWV by an ACE inhibitor was associated with improved performance on a treadmill walk test, consistent with the hypothesis that arterial stiffness may in part mediate the relationship of PAD with functional impairment by contributing to resistance vessel hypertrophy and increased vascular resistance. These data suggest a potential to improve peripheral perfusion and walking distance through the reduction of arterial stiffness in individuals with PAD (Ahimastos et al., 2008).

Although we did not identify an association of PWV with rate of gait speed decline, this analysis may be limited by the initially high mobility status of the sample, in which no participants reported difficulty walking and only 7% had gait speed below 1.0 m/s, a clinically relevant cutpoint found predictive of lower extremity limitation and hospitalization (Cesari et al., 2005). It is also possible that arterial stiffness may have contributed to gait decline prior to our observation, resulting in the slower gait observed throughout the study period in participants with PAD who also had elevated PWV. These data are consistent with an influence of the oscillatory

component of blood pressure, or pulse pressure, on the structure and function of the peripheral vasculature in PAD (Amoh-Tonto et al., 2009). With widening of the pulse pressure, primarily determined by altered wave reflections with aortic stiffness, lower diastolic pressure may be inadequate to overcome increased peripheral vascular resistance associated with both obstructive atherosclerosis and arterial stiffness (Amoh-Tonto et al., 2009). Resulting insufficient leg perfusion during muscle contraction may account for slower walking speed even in the absence of intermittent claudication. Because the association of aortic stiffness with slower gait in PAD was not explained by AAI, these data may suggest a value for PWV in identifying individuals with PAD who are at highest risk of functional decline.

The independent association of hypertension with accelerated gait decline in the full cohort is consistent with previous data (Hajjar, Lackland, Cupples, & Lipsitz, 2007) including a contribution of cerebral microvascular disease to functional decline in aging (Rosano, Kuller et al., 2005; Silbert, Nelson, Howieson, Moore, & Kaye, 2008; Starr et al., 2003). Considered evidence of cerebral small vessel injury (Black et al., 2009), hyperintensities of white matter tracts on brain MRI are closely associated with elevated systolic blood pressure (Longstreth et al., 1996) and predict gait speed decline and incident physical impairment in older adults (Rosano, Kuller et al., 2005). The relationship of hypertension with functional decline may be further mediated by chronic inflammation (Brinkley et al., 2009; Cesari et al., 2004; Kritchevsky, Cesari, & Pahor, 2005), oxidative stress (Semba et al., 2007), alterations in the renin-angiotensin aldosterone system (Carter, Onder, Kritchevsky, & Pahor, 2005), or deficits in executive cognitive function (Royall, Palmer, Chiodo, & Polk, 2004). Our findings do not suggest that the contribution of hypertension to gait speed decline is explained by underlying arterial stiffness.

Strengths of this study include the large, community-based population, ability to account for several potential confounders, and repeated assessment of gait speed, a reliable, valid measure of physical function that predicts incident disability in older adults (Guralnik et al., 2000). The analysis may be limited by nonrandom withdrawal of participants with chronic conditions, in that participants experiencing the greatest declines in gait speed may have been unable to continue study participation. However, analyses restricted to four years of followup did not suggest that estimated associations are sensitive to missing observations. Finally, gait speed and other lower-extremity performance measures may not capture subtle functional changes in healthier older adults; rather, extended walking tests (Newman et al., 2006; Simonsick et al., 2001) may be more sensitive to diastolic dysfunction associated with aortic stiffness.

In summary, arterial stiffness was inversely related to gait speed in participants with PAD, but was not independently associated with gait speed or the rate of gait speed decline in the full cohort. The association of hypertension with accelerated gait speed decline in this cohort reinforces the value of blood pressure control in maintaining function in aging. Current evidence implicates arterial stiffness as a potential target of interventions to improve peripheral perfusion and walking performance in PAD. More work is needed to evaluate whether reduction of aortic stiffness may reduce risk of functional decline and disability in PAD independent of blood pressure lowering.

Table 11. Baseline characteristics of the cohort by quartiles (range in parentheses) of PWV (cm/s)

	Mean ± SD or %					
	Total (312-2998) n=2172	Q1 (312-636) n=543	Q2 (636-800) n=545	Q3 (801-1046) n=541	Q4 (1047-2998) n=543	p-value
Age, years	73.6 ± 2.9	73.3 ± 2.8	73.5 ± 2.8	73.9 ± 2.9	73.9 ± 2.8	<0.01
Men	48.1	44.9	44.2	50.1	53.2	<0.01
Black	38.5	33.5	37.3	39.9	43.5	<0.01
BMI, kg/m ^{2}	27.3 ± 4.7	26.1 ± 4.4	27.4 ± 4.5	28.1 ± 4.8	27.4 ± 4.8	<0.01
Systolic blood pressure, mmHg	135.5 ± 19.3	129.8 ± 19.3	133.9 ± 18.6	137.5 ± 19.0	140.6 ± 19.5	<0.01
Heart rate, bpm	64.5 ± 10.6	62.0 ± 9.9	64.4 ± 9.9	65.4 ± 10.5	66.4 ± 11.5	<0.01
Cholesterol, mg/dL	203.7 ± 37.8	203 ± 35.0	204.7 ± 36.3	204.5 ± 40.8	202.7 ± 38.9	0.74
Current or former smoker	55.4	49.5	54.1	59.7	58.2	<0.01
Physical activity > 1000 kcal/wk	32.9	37.6	33.0	31.1	29.8	0.04
Coronary heart disease	18.4	15.9	17.2	21.3	19.3	0.11
Diabetes	14.0	8.3	12.0	17.0	19.6	<0.01
Hypertension	49.0	36.9	46.6	52.2	60.5	<0.01

Table 12. Baseline characteristics of the cohort by quartiles (range in parentheses) of PWV (cm/s)

	Mean ± SD or %					
	Total (312-2998) n=2172	Q1 (312-636) n=543	Q2 (636-800) n=545	Q3 (801-1046) n=541	Q4 (1047-2998) n=543	p-value
Gait speed, m/s	1.34 ± 0.25	1.38 ± 0.25	1.35 ± 0.25	1.31 ± 0.26	1.32 ± 0.24	<0.01
DSST score	36.5 ± 14.5	39.2 ± 15.1	37.6 ± 14.1	34.7 ± 14.3	34.7 ± 13.8	<0.01
Cerebrovascular disease, %	7.4	6.9	6.3	6.9	9.3	0.25
AAI < 0.9, %	12.7	8.1	10.3	14.3	18.2	<0.01

DSST = Digit Symbol Substitution Test

Table 13. Coefficients and standard errors (value in parenthese s) estimated by mixed models of PWV as a predictor of longitudinal gait speed (m/s) in the full cohort (n = 2172)

	Model 1	Model 2	Model 3
PWV (SD)	-0.019 (0.004)*	-0.014 (0.004)*	-0.005 (0.004)
Time (yrs)	-0.041 (0.001)**	-0.039 (0.001)**	-0.038 (0.001)*
PWV*Time	-0.001 (0.001)	-0.001 (0.001)	0.000 (0.001)

* p<0.05, ** p<0.01

Model 1 adjusted for site
Model 2 additionally adjusted for age, sex, race, and interaction of each covariate with time
Model 3 additionally adjusted for BMI, systolic blood pressure, heart rate, total cholesterol, smoking, physical activity, coronary heart disease, diabetes, hypertension, and interaction of each covariate with time

Table 14. Coefficients and standard errors (values in parentheses) estimated by mixed models of PWV as a predictor of longitudinal gait speed (m/s) in participants with PAD (AAI < 0.9; n = 261)

	Model 1	Model 2	Model 3
PWV (SD)	-0.033 (0.011)**	-0.032 (0.010)**	-0.030 (0.010)**
Time (yrs)	-0.044 (0.002)**	-0.046 (0.004)**	-0.046 (0.004)**
PWV*Time	0.001 (0.002)	0.001 (0.002)	0.001 (0.002)

* p<0.05, ** p<0.01

Model 1 adjusted for site
Model 2 additionally adjusted for age, sex, race, and interaction of each covariate with time
Model 3 additionally adjusted for BMI, systolic blood pressure, heart rate, total cholesterol, smoking, physical activity, coronary heart disease, diabetes, hypertension, and interaction of each covariate with time

5.0 RATES OF COGNITIVE AND PHYSICAL DECLINES PREDICT MORTALITY IN OLDER ADULTS

Manuscript in preparation

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5.1 ABSTRACT

Background/Aims: Both cognitive and physical performance declines are important prognostic factors for mortality in community-dwelling older adults. Few studies have evaluated whether rates of decline in each domain predict mortality independent of each other or baseline performance. ***Methods:*** Global cognitive function (Modified Mini-Mental State Examination [3MS]) and usual gait speed (m/s) over 20 meters were assessed at baseline (1997/98) and after four years (2001/02) in the Health, Aging, and Body Composition (Health ABC) Study. Total and cardiovascular mortality were ascertained following the 2001/02 visit in 2,345 participants who had valid 3MS or gait speed data from 1997/98 and 2001/02 (mean age ± SD 73.5 ± 2.8 yrs; 47% men; 38% black). ***Results:*** 521 deaths, including 189 (36.3%) cardiovascular deaths, occurred by the end of follow-up (median of 5.4 years). In a multivariate Cox proportional hazards model predicting total mortality, greater rates of decline in 3MS score and gait speed over four years were independently associated with greater risk: HR (95%CI) 1.18 (1.04, 1.35) per SD decrease in 3MS score; 1.59 (1.39, 1.81) per SD decrease in gait speed after adjustment for baseline 3MS score and gait speed, demographic and health characteristics. Concurrent 3MS and gait speed declines were more specifically related to cardiovascular mortality: HR (95%CI) 4.46 (2.36, 8.41) relative to no decline in either test. ***Conclusion:*** In this initially well-functioning cohort, rates of decline in 3MS score and gait speed, independent of each other, baseline performance and traditional risk factors, were associated with greater risk of total and cardiovascular mortality. These data suggest a prognostic value for followup assessments of both cognitive and physical performance in community-dwelling older adults.

5.2 INTRODUCTION

Both cognitive and physical performance measures provide valuable prognostic information in older adults living in the community (Guralnik et al., 2000; Spiers et al., 2005). In the Cardiovascular Health Study, the combination of lower scores on the Digit Symbol Substitution Test (DSST) and slower gait was found to improve prediction of disability and mortality, beyond either of these tests alone (Rosano et al., 2008). Co-occurrence of poor cognitive and physical performance in this cohort may reflect a shared cerebrovascular pathogenesis or general physiological deterioration associated with increased disability and mortality risk.

Although clinical risks associated with either cognitive or physical declines are well-described (Perera, Studenski, Chandler, & Guralnik, 2005; Schupf et al., 2005; van Gelder, Tijhuis, Kalmijn, Giampaoli, & Kromhout, 2007), few studies have evaluated risks associated with changes in cognitive and physical function in combination or in relation to previous performance. Importantly, independent risks associated with rates of decline in each domain would suggest a prognostic value for followup measures of both cognitive and physical performance. Moreover, if mortality risks associated with rates of functional decline is found attenuated in individuals with high baseline performance, these data may stress the importance of baseline performance as an indication of functional reserve (Newman et al., 2009; Stern, 2009).

To clarify the predictive value of changes in both cognitive and physical performance in aging, we compared the associations of rates of decline in Modified Mini-Mental State Examination (3MS) score and gait speed with all-cause and cardiovascular mortality risk in the Health, Aging, and Body Composition (Health ABC) Study. We then evaluated whether

mortality risks associated with accelerated cognitive and physical declines are attenuated among participants who were initially high-functioning.

5.3 METHODS

5.3.1 The Health ABC Study and Participants

From 1997 to 1998 the Health ABC Study enrolled 3,075 Medicare-eligible nondisabled men and women aged 70-79 from Pittsburgh, Pa. and Memphis, Tenn., USA. The population was 52% women and 58% white with a mean age of 73.6 years. Participants were recruited from Medicare-eligible adults with contact information provided by the Centers for Medicare & Medicaid Services (formerly the Health Care Financing Administration) on a random sample of white and all black beneficiaries in pre-designed zip code areas surrounding the study centers. Other household members aged 70-79 were also eligible for recruitment. Exclusion criteria were difficulty in either walking without an assistive device, walking one quarter of a mile or climbing 10 steps without resting. Participants were contacted every six months, alternating in-person examinations and telephone interviews. Both Institutional Review Boards of the University of Pittsburgh, Pa. as well as the University of Tennessee at Memphis approved the study and written, informed consent was obtained from each volunteer. Of the 3,075 participants enrolled in Health ABC, 2,345 had valid 3MS or gait speed data from the 1997/98 and 2001/02 visits and were included in the current analysis (mean age ± SD 73.5 ± 2.8 yrs; 47% men; 38% black).

5.3.2 Functional measures

Cognitive and physical function were assessed at the 1997/98 and 2001/02 visits using the Modified Modified Mini-Mental Status Exam (3MS) (Teng & Chui, 1987) and usual gait speed. The 3MS is a commonly used evaluation of global cognitive function, including orientation, attention, calculation, language and short-term memory. Scores can range from 0 to 100 points, with lower scores indicating poorer performance. Gait speed, a reliable and valid measure of physical function (Guralnik et al., 2000), was measured as the time needed to walk a 20-meter straight course at usual pace. Timing began at the first footfall over the starting line and ended with the first footfall over the finishing line.

5.3.3 Mortality Outcomes

Total mortality outcomes were ascertained from the 2001/2002 visit through November 27 2007. Cardiovascular mortality outcomes were ascertained from the 2001/2002 visit through December 31 2006 (Memphis) or June 30 2007 (Pittsburgh), when adjudication was complete for each site. A central committee adjudicated immediate and underlying causes of death by review of hospital records, death certificates, informant interviews and autopsy data. Cardiovascular mortality was defined as atherosclerotic cardiovascular disease (definite fatal myocardial infarction, or definite or possible fatal coronary heart disease), stroke, atherosclerotic disease other than coronary or cerebrovascular, and other cardiovascular disease.

5.3.4 Covariates

Health characteristics that are associated with mortality and were considered potential confounders included smoking status, body-mass index (BMI), physical activity, depressive symptoms, prevalent coronary heart disease, diabetes, hypertension and peripheral arterial disease as ascertained from the 1999/00 or 2001/02 clinic visit. Presence of chronic conditions was determined from participant reports and confirmed by use of specific mediations or procedures (Madero et al., 2009a). BMI was calculated as measured weight in kilograms divided by measured height in meters squared. Walking frequency and duration was determined from responses to question which distinguished walking for exercise and other types of walking from a standardized, interviewer-administered physical activity battery (Brach et al., 2004). Participants walking a total of <30 minutes per week were defined as sedentary. Depressive symptoms were assessed using the Centers for Epidemiologic Studies of Depression 10-item scale (CESD-10) (Andresen et al., 1994). Ankle-arm index was calculated as the ratio of the systolic blood pressure obtained in the ankle to the systolic blood pressure of the right arm. Measures were performed twice and the results were averaged; the lower average value between the two legs was used to define an individual's ankle-arm index. Peripheral arterial disease was defined as ankle-arm index less than or equal to 0.9, according to traditional diagnostic criteria (Yao et al., 1969).

To evaluate whether subclinical or undiagnosed conditions may in part explain associations of rates of performance decline with mortality, we further considered as covariates systolic blood pressure, total cholesterol and fasting glucose evaluated at the 1999/00 or 2000/01

visit. Systolic blood pressure was measured twice and the results averaged. Cholesterol and glucose levels were measured after an overnight fast.

5.3.5 Statistical analysis

Chi-square tests and unpaired t-tests were used to test differences in characteristics by survival status. Kaplan-Meier plots and log-rank tests were used to compare survival curves across categories of decline in 3MS and gait speed from 1997/98 – 2001/02, where 3MS decline was defined as change of 5 points or more and gait speed decline as 0.4 m/s (average change of 0.1 m/s per year) or more, according to traditional criteria (Andrew & Rockwood, 2008; Perera et al., 2005). Crude incidence rates were calculated per 1,000 person years. Cox proportional hazards models were used to estimate hazard ratios (HRs) for changes in each test as predictors of total and cardiovascular mortality. The proportional hazards assumption was verified for all independent variables using log-log plots and Grambsch and Therneau tests. Simple models of 3MS change or gait speed change as predictors of mortality adjusted for baseline 3MS score or gait speed, age, sex, race, education and clinic site. A second model included both change measures in a single model. Full models additionally adjusted for potential confounders (BMI, physical activity, depressive symptoms, smoking, coronary heart disease, cerebrovascular disease, hypertension, diabetes, peripheral arterial disease) and indicators of subclinical or undiagnosed conditions (systolic blood pressure, total cholesterol and fasting glucose). Analyses were repeated for non-cardiovascuar deaths to determine whether cardiovascular deaths may account for associations of rates of functional decline with total mortality.

To evaluate whether mortality risks associated with rates of performance decline were attenuated in participants who were initially high-functioning, we tested interactions of 3MS score and gait speed change with baseline performance in each measure and stratified analyses at the median baseline performance (93 for 3MS; 1.34 m/s for gait speed). To determine whether accelerated declines in each measure may synergistically increase mortality risk, we then tested the interaction of 3MS score change with gait speed change and analyzed mortality risks associated with concurrent declines in 3MS and gait speed as defined in Kaplan-Meier plots. Receiver operator characteristic (ROC) curves (Cook, 2008) were used to compare predictive values of alternative cutpoints for declines in 3MS score (≥4 or ≥6 point change) and gait speed (≥0.3 or ≥ 0.5 m/s change).

Finally, we adjusted each full model for performance at followup (2001/02) rather than baseline (1997/98) to determine whether effects of changes in 3MS and gait speed may be explained by the most recent performance (DeFries, Avendano, & Glymour, 2009). Analyses were performed in Stata 10 (STATA, Houston, TX).

5.4 RESULTS

Mean age ± SD of the 2,345 participants was 73.5 ± 2.8 years; 47% were men and 38% black. 521 deaths (45.4/1,000 p-y), including 189 cardiovascular deaths (17.5/1,000 p-y), occurred by the end of follow-up (median of 5.4 years) from the 2001/02 visit. Survivors had higher 3MS scores (91.5 ± 7.1 vs 89.0 ± 9.0 points) and faster gait speed (1.37 ± 0.25 vs 1.30 ± 0.25 m/s) at baseline, and declined less in each test after four years: -0.27 ± 5.8 vs -2.31 ± 8.5 points for 3MS

change; -0.24 ± 0.20 vs -0.29 ± 0.21 m/s for gait speed change ($p<0.001$ for all) (Table 15). Figures 1 and 2 show survival curves for each outcome by categories of decline in 3MS score and gait speed. Total and cardiovascular mortality rates were highest for participants with evidence of both cognitive and physical declines, and lowest for those with no evidence of decline in either domain.

In separate Cox proportional hazards models of change in each test as predictors of total mortality, greater rates of decline in 3MS score and gait speed were associated with higher risk after adjustment for baseline performance and demographics: HR (95%CI) 1.28 (1.19, 1.38) per SD decrease in 3MS score; 1.56 (1.39, 1.75) per 0.1 m/s decrease in gait speed. Inclusion of both change measures in a single model only slightly attenuated hazard ratios for decline in each test (Table 16). HRs were moderately strengthened or attenuated after further adjustment for risk factors and chronic conditions but changed minimally after additional adjustment for indicators of subclinical or undiagnosed disease.

In a fully adjusted model of cardiovascular mortality, changes in 3MS score and gait speed change remained independently associated with mortality risk and HRs for 3MS score change were substantially strengthened (Table 17). In a final model of non-cardiovascular mortality, only gait speed change remained associated with mortality risk: HR (95%CI) 1.02 (0.86, 1.21) for 3MS score change: 1.66 (1.41, 1.97) for gait speed change. After adjustment for performance at followup (2001/02) rather than baseline (1997/98), mortality risks associated with changes in 3MS score and gait speed were no longer significant.

Mortality risk associated with 3MS decline (5 points or more) was higher among the subgroup of participants with higher baseline 3MS score: fully adjusted HR (95% CI) 1.71 (1.21, 2.42) vs. 1.28 (0.92, 1.78) for participants with scores above vs. below the median of 93. By

contrast, risk associated with gait speed decline (0.4 m/s or more) was higher among participants with slower baseline gait speed: fully adjusted HR (95% CI) 1.60 (1.16, 2.20) vs. 2.02 (1.30, 3.12) for participants with gait speed above vs. below the median of 1.34 m/s. However, interactions of change in each test with baseline performance were nonsignificant, preventing a stronger conclusion that mortality risks associated with functional declines may vary by baseline functional status.

Although the interaction of 3MS score change with gait speed change was nonsignificant, concurrent declines in 3MS score and gait speed were associated with higher mortality risks relative to decline in neither or one test, independent of baseline performance, demographic and health characteristics (Tables 18-19). HRs for concurrent declines remained significant after adjustment for 3MS score and gait speed at followup (2001/02) rather than baseline (1997/98).

Finally, ROC curves showed similar predictive values for alternative cutpoints for 3MS and gait speed declines, while HRs gradually increased with worsening decline in each test. These data do not suggest a threshold effect of performance declines in risk prediction.

5.5 DISCUSSION

In this cohort of initially well-functioning older adults, rates of decline in 3MS score and gait speed over four years predicted subsequent mortality independent of each other, demographic and health characteristics. Co-occurring declines in cognitive and physical function were more predictive of mortality relative to declines in either domain alone. These data suggest that

repeated assessments of cognitive and physical performance, alone and in combination, may be important prognostic factors in older adults living in the community.

Cognitive and physical performance measures are widely recognized as valuable predictors of adverse outcomes in well-functioning older adults. In several cohorts, poorer scores on the 3MS or abbreviated version, the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), were found associated with greater risk of incident stroke (DeFries et al., 2009), disability (Lee, Kim, Lee, Han, & Kim, 2005), and mortality (Lavery, Dodge, Snitz, & Ganguli, 2009) in the absence of dementia. In nondisabled populations, slower gait at usual pace predicted incident disability (Guralnik et al., 2000), hospitalization (Cesari et al., 2005), and mortality (Abellan van Kan et al., 2009; Cesari et al., 2005). Shared risk factors for cognitive and physical impairments include smoking (Atkinson et al., 2005), hypertension and cardiovascular disease (Newman et al., 2009), suggesting an important potential to prevent or delay functional decline in late life.

In the Cardiovascular Health Study (CHS), DSST score and gait speed were recently found to improve prediction of disability and mortality beyond either test alone (Rosano et al., 2008). Risks associated with rates of cognitive and physical decline in combination and in relation to baseline performance have not previously been evaluated. Our finding that accelerated declines in 3MS score and gait speed, independent of each other, baseline performance and other risk factors, predicted total and cardiovascular mortality suggest a value for both followup assessments in risk stratification. In fact, concurrent cognitive and physical declines more strongly predicted mortality risk relative to declines in neither or only one measure, suggesting a combined effect of declines in both domains. This risky pattern of functional decline may indicate an ongoing process of physiological deterioration associated

with chronic inflammation or oxidative stress, two proposed determinants of biological aging (Simm et al., 2008) and functional decline (Penninx et al., 2004; Semba et al., 2007; Tracy, 2003). Alternatively, the more specific association of co-occurring declines with cardiovascular mortality in this cohort may reflect a shared cerebrovascuar pathogenesis (Rosano, Aizenstein, Studenski, & Newman, 2007) believed to preferentially influence executive and motor functions (Pugh & Lipsitz, 2002).

Our finding that mortality risks associated with rates of cognitive and physical decline were independent of baseline performance suggests that these risks are not explained by low functional reserve. In fact, risks associated with accelerated functional declines in this cohort were not restricted to participants with lower baseline performance, suggesting a prognostic value for followup measures in older adults of various levels of function. Importantly, elevated mortality risks associated with concurrent cognitive and physical declines were also independent of followup performance, indicating that risk prediction may be improved by knowledge of previous performance even when current performance measures are available.

Our study has several limitations. In initially high-functioning participants, subtle cognitive and physical declines may have been obscured by ceiling effects of the 3MS and gait speed tests. Measures of brain integrity were not available to evaluate the hypothesis that focal changes in executive function-related networks may account in part for co-occurring cognitive and physical declines. Also, because participants who experienced the greatest functional declines may have been unable to complete the followup visit, our results may not generalize to less healthy participants. Strengths of this study include the large community-dwelling population, long followup, ability to account for several important confounders, and availability of two reliable and valid performance measures to evaluate longitudinal functional decline.

In this cohort of initially well-functioning older adults, rates of cognitive and physical performance decline predicted total and cardiovascular mortality, independent of each other, baseline performance, and traditional risk factors. Concurrent cognitive and physical declines were associated with greater mortality risk relative to decline in either domain, suggesting a value for followup assessments of both cognitive and physical performance in identifying individuals at highest risk of adverse outcomes. Further understanding of the contributions of oxidative stress, chronic inflammation, and cerebrovascular alterations to cognitive and physical declines in aging may guide preventative strategies to extend the healthy lifespan.

Table 15. Characteristics (mean ± SD or %) of the population

	Survived N = 1770	Total mortality N = 521	CVD mortality N = 189
Age, years	77.3 ± 2.8	78.1 ± 2.9***	78.2 ± 3.0***
Male	44.8	55.9***	52.4*
Black	35.5	44.7***	47.1**
Education > 12 years	46.7	38.0***	40.6
Baseline 3MS score	91.5 ± 7.1	89.0 ± 9.0***	89.3 ± 8.2***
3MS score Δ	-0.27 ± 5.8	-2.31 ± 8.5***	-3.38 ± 9.2***
Baseline gait speed, m/s	1.37 ± 0.25	1.30 ± 0.25***	1.29 ± 0.24***
Gait speed Δ, m/s	-0.24 ± 0.20	-0.29 ± 0.21***	-0.29 ± 0.19*
BMI (kg/m^2)	27.4 ± 4.8	26.5 ± 5.1	26.5 ± 4.8**
Sedentary	50.6	55.6*	58.8*
CES_D10	4.8 ± 4.2	5.6 ± 4.6***	5.4 ± 4.8**
History of smoking	52.3	62.5***	61.4*
Coronary heart disease	22.6	30.8***	43.1***
Cerebrovascular disease	7.4	12.2***	15.5***
Hypertension	66.3	72.0*	77.3**
Diabetes	20.2	26.1*	31.2***
AAI < 0.9	13.1	26.4***	32.1
Systolic blood pressure (mmHg)	135.1 ± 20.2	137.1 ± 24.1	136.4 ± 25.4
Total cholesterol (mg/dL)	192.7 ± 36.4	187.7 ± 38.5**	187.2 ± 40.1
Fasting glucose (mg/dL)	100.6 ± 24.8	106.7 ± 37.9***	103.4 ± 31.6***

Characteristics evaluated in 2000/01 or 2001/02 unless otherwise noted.
Δ = change from 1997/98 to 2001/02
*p<0.05, **p<0.01, ***p<0.001 for t-test or chi-square test for comparisons by survival

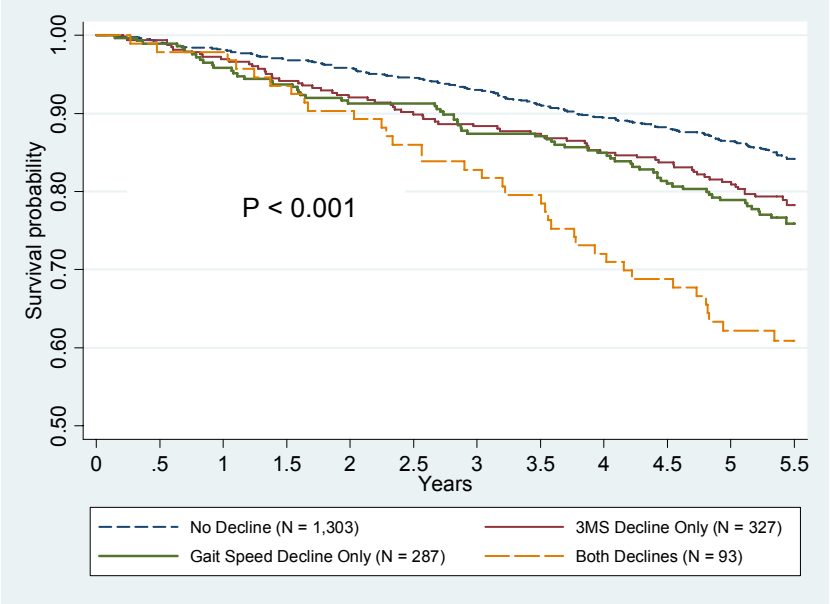

Figure 1. Kaplan-Meier plot of total mortality by 3MS and gait speed decline*

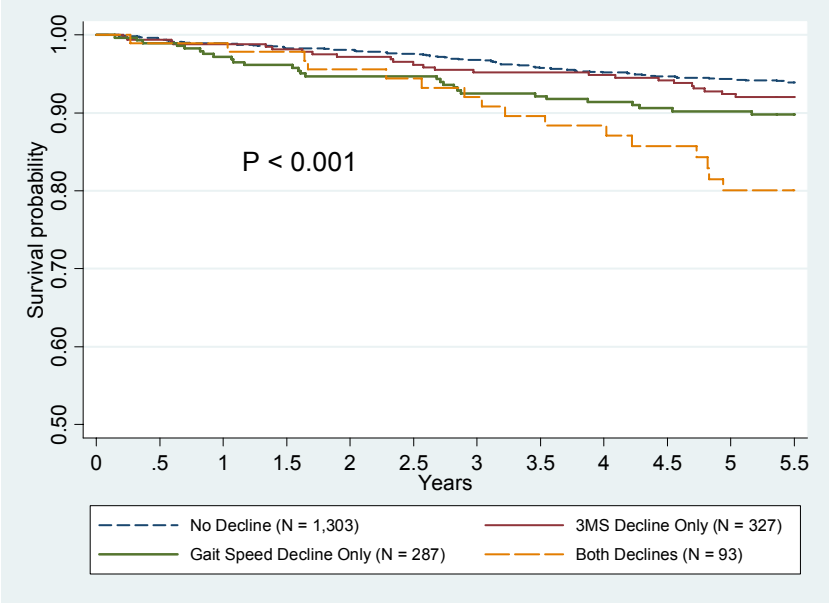

Figure 2. Kaplan-Meier plot of cardiovascular mortality by 3MS and gait speed decline*

*3MS decline defined as change ≥ 5 points and gait speed decline as change ≥ 0.4 m/s from 1997/98 to 2001/02

Table 16. Associations of change in 3MS and gait speed with total mortality risk

Predictor	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
3MS change, per SD (6.5 pts) decrease	1.28 (1.19, 1.38)	1.23 (1.12, 1.36)	1.18 (1.04, 1.35)
Gait speed change, per SD (0.20 m/s) decrease	---	1.50 (1.34, 1.68)	1.59 (1.39, 1.81)

Model 1: baseline 3MS, 3MS change, age, sex, race, education, clinic site
Model 2: Model 1 + baseline gait speed and gait speed change
Model 3: Model 2 + BMI, physical activity, depressive symptoms, smoking, coronary heart disease, cerebrovascular disease, hypertension, diabetes and peripheral arterial disease

Table 17. Associations of change in 3MS and gait speed with cardiovascular mortality risk

Predictor	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
3MS change, per SD (6.5 pts) decrease	1.38 (1.25, 1.53)	1.34 (1.16, 1.55)	1.49 (1.22, 1.84)
Gait speed change, per SD (0.20 m/s) decrease	---	1.51 (1.24, 1.83)	1.47 (1.18, 1.84)

Model 1: baseline 3MS, 3MS change, age, sex, race, education, clinic site
Model 2: Model 1 + baseline gait speed and gait speed change
Model 3: Model 2 + BMI, physical activity, depressive symptoms, smoking, coronary heart disease, cerebrovascular disease, hypertension, diabetes and peripheral arterial disease

Table 18. Associations of 3MS and gait speed decline* with total mortality risk

Decline Category	Events	Events per 1,000 Person-Years	Model 1 HR (95% CI)	Model 2 HR (95% CI)
No Decline (N = 1,303)	225	34.1	1.00	1.00
3MS Decline Only (N = 327)	70	44.0	1.37 (1.04, 1.81)	1.22 (0.89, 1.69)
Gait Speed Decline Only (N = 287)	72	52.3	1.67 (1.25, 2.24)	1.72 (1.26, 2.36)
Both Declines (N = 93)	72	93.3	2.51 (1.73, 3.63)	2.77 (1.82, 4.21)

Model 1 adjusted for age, sex, race, education, clinic site, baseline 3MS and baseline gait speed
Model 2 additionally adjusted for BMI, physical activity, depressive symptoms, smoking, coronary heart disease, cerebrovascular disease, hypertension, diabetes and peripheral arterial disease

Table 19. Associations of 3MS and gait speed decline* with cardiovascular mortality risk

Decline Category	Events	Events per 1,000 Person-Years	Model 1 HR (95% CI)	Model 2 HR (95% CI)
No Decline (N = 1,303)	75	11.4	1.00	1.00
3MS Decline Only (N = 327)	24	15.1	1.47 (0.93, 2.32)	1.52 (0.92, 2.52)
Gait Speed Decline Only (N = 287)	28	20.3	1.83 (1.11, 3.01)	1.79 (1.06, 3.03)
Both Declines (N = 93)	16	38.3	3.64 (2.03, 6.57)	4.46 (2.36, 8.41)

Model 1 adjusted for age, sex, race, education, clinic site, baseline 3MS and baseline gait speed
Model 2 additionally adjusted for BMI, physical activity, depressive symptoms, smoking, coronary heart disease, cerebrovascular disease, hypertension, diabetes and peripheral arterial disease

*3MS decline defined as change $\geq$ 5 points and gait speed decline as change $\geq$ 0.4 m/s from 1997/98 to 2001/02

6.0 DISCUSSION

6.1 SUMMARY OF FINDINGS

In this community-dwelling cohort, greater central arterial stiffness, a hallmark of vascular aging, was associated with poorer performance in several cognitive domains and predicted longitudinal decline in psychomotor speed independent of hypertension and other vascular risk factors. These findings are consistent with a vulnerability of the deep white matter to cerebrovascular injury, as stiffened vessels transmit damaging flow pulsations into the fragile cerebral microvasculature.

Also independent of vascular risk factors, elevated arterial stiffness was associated with slower gait speed in participants with peripheral arterial disease (PAD), suggesting vascular stiffening may be especially detrimental to mobility in older adults with already compromised arterial function. With widening of the pulse pressure, primarily determined by aortic stiffening, lower diastolic pressure and increased vascular resistance may contribute to insufficient leg perfusion in peripheral arterial disease. Because the association of PWV with gait speed in PAD

was not explained by ankle-arm index or other risk factors, these data suggest a potential value for PWV in identifying older adults with PAD who are at highest risk of mobility impairment.

In the Health ABC Cognitive Vitality Substudy, poorer verbal memory, global and executive function were each associated with slower gait cross-sectionally and predicted longitudinal gait speed decline. Hypertension, peripheral arterial disease and other vascular risk factors partially explained the relationship of cognitive performance with gait speed in this sample. These findings are consistent with a shared cerebrovascular pathogenesis underlying cognitive and mobility declines, but do not suggest that specific cognitive deficits account for gait slowing in aging.

Finally, in the full Health ABC cohort, greater rates of decline in 3MS score and gait speed predicted total and cardiovascular mortality independent of each other, baseline performance and traditional risk factors. These data suggest a prognostic value for follow-up assessments of both cognitive and physical function in nondisabled older adults. The particularly risky pattern of concurrent declines in cognitive and physical function may reflect a shared cerebrovascular pathogenesis or general degradation of physiologic reserve.

6.2 PUBLIC HEALTH SIGNIFICANCE

Challenged by growing burdens of chronic disease and disability, aging populations must recognize hypertension as a crucial target of strategies to extend the healthy lifespan. Improved efforts to combat hypertension may develop from new understanding of both the pathogenesis and consequences of central arterial stiffness, a hallmark of vascular aging. Several recent

publications have identified a potential contribution of arterial stiffness to cognitive decline independent of hypertension and other vascular risk factors; these findings have been attributed to the transmission of damaging central pressures to the fragile cerebral microvasculature. Other studies have demonstrated associations of deficits in executive function and attention with accelerated gait speed decline, consistent with a shared, hypothesized cerebrovascular pathogenesis underlying cognitive and motor impairments in aging. These data suggest an important potential to prevent or delay disability through the control of modifiable vascular risk factors.

Taken together, findings from the Health ABC study implicate central arterial stiffness as a determinant both cognitive and physical functional declines, two valuable prognostic factors in older adults in the community. Current evidence supports a direct relationship between blood pressure levels, cardiovascular and mortality risks; however, rising prevalence and persistently low control rates highlight deficiencies in current approaches to combat hypertension. More work is needed to determine whether reduction of central arterial stiffness may reduce risk of functional decline beyond the extent expected by blood pressure lowering. Promising results of several observational studies suggest that angiotensin-converting enzyme (ACE) inhibitors may improve mobility and reduce risk of cognitive decline beyond hypertension control; these findings may reflect important roles of this specific class of agents in directly altering the structure of arterial walls, leading to reductions in large arterial stiffness and improvements in microvascular perfusion. Randomized, controlled trials are warranted to confirm this hypothesized advantage of ACE inhibitors over other classes of antihypertensive drugs in preventing or delaying functional decline, a looming threat to aging populations.

BIBLIOGRAPHY

Abellan van Kan, G., Rolland, Y., Andrieu, S., Bauer, J., Beauchet, O., Bonnefoy, M., et al. (2009). Gait Speed at Usual Pace as a Predictor of Adverse Outcomes in Community-Dwelling Older People An International Academy on Nutrition and Aging (IANA) Task Force. *J Nutr Health Aging, 13*(10), 881-889.

Agata, J., Nagahara, D., Kinoshita, S., Takagawa, Y., Moniwa, N., Yoshida, D., et al. (2004). Angiotensin II receptor blocker prevents increased arterial stiffness in patients with essential hypertension. *Circ J, 68*(12), 1194-1198.

Ahimastos, A. A., Dart, A. M., Lawler, A., Blombery, P. A., & Kingwell, B. A. (2008). Reduced arterial stiffness may contribute to angiotensin-converting enzyme inhibitor induced improvements in walking time in peripheral arterial disease patients. *J Hypertens, 26*(5), 1037-1042.

Ahimastos, A. A., Natoli, A. K., Lawler, A., Blombery, P. A., & Kingwell, B. A. (2005). Ramipril reduces large-artery stiffness in peripheral arterial disease and promotes elastogenic remodeling in cell culture. *Hypertension, 45*(6), 1194-1199.

Amoh-Tonto, C. A., Malik, A. R., Kondragunta, V., Ali, Z., & Kullo, I. J. (2009). Brachial-ankle pulse wave velocity is associated with walking distance in patients referred for peripheral arterial disease evaluation. *Atherosclerosis*.

Andresen, E. M., Malmgren, J. A., Carter, W. B., & Patrick, D. L. (1994). Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *Am J Prev Med, 10*(2), 77-84.

Andrew, M. K., & Rockwood, K. (2008). A five-point change in Modified Mini-Mental State Examination was clinically meaningful in community-dwelling elderly people. *J Clin Epidemiol, 61*(8), 827-831.

Atkinson, H. H., Cesari, M., Kritchevsky, S. B., Penninx, B. W., Fried, L. P., Guralnik, J. M., et al. (2005). Predictors of combined cognitive and physical decline. *J Am Geriatr Soc, 53*(7), 1197-1202.

Atkinson, H. H., Rosano, C., Simonsick, E. M., Williamson, J. D., Davis, C., Ambrosius, W. T., et al. (2007). Cognitive function, gait speed decline, and comorbidities: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci, 62*(8), 844-850.

Bhuiyan, A. R., Srinivasan, S. R., Chen, W., Paul, T. K., & Berenson, G. S. (2006). Correlates of vascular structure and function measures in asymptomatic young adults: the Bogalusa Heart Study. *Atherosclerosis, 189*(1), 1-7.

Blacher, J., Safar, M. E., Guerin, A. P., Pannier, B., Marchais, S. J., & London, G. M. (2003). Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney Int, 63*(5), 1852-1860.

Black, S., Gao, F., & Bilbao, J. (2009). Understanding white matter disease: imaging-pathological correlations in vascular cognitive impairment. *Stroke, 40*(3 Suppl), S48-52.

Blahak, C., Baezner, H., Pantoni, L., Poggesi, A., Chabriat, H., Erkinjuntti, T., et al. (2009). Deep frontal and periventricular age related white matter changes but not basal ganglia and infratentorial hyperintensities are associated with falls: cross sectional results from the LADIS study. *J Neurol Neurosurg Psychiatry, 80*(6), 608-613.

Ble, A., Volpato, S., Zuliani, G., Guralnik, J. M., Bandinelli, S., Lauretani, F., et al. (2005). Executive function correlates with walking speed in older persons: the InCHIANTI study. *J Am Geriatr Soc, 53*(3), 410-415.

Boutouyrie, P., Laurent, S., & Briet, M. (2008). Importance of arterial stiffness as cardiovascular risk factor for future development of new type of drugs. *Fundam Clin Pharmacol, 22*(3), 241-246.

Brach, J. S., Simonsick, E. M., Kritchevsky, S., Yaffe, K., & Newman, A. B. (2004). The association between physical function and lifestyle activity and exercise in the health, aging and body composition study. *J Am Geriatr Soc, 52*(4), 502-509.

Brach, J. S., Solomon, C., Naydeck, B. L., Sutton-Tyrrell, K., Enright, P. L., Jenny, N. S., et al. (2008). Incident physical disability in people with lower extremity peripheral arterial disease: the role of cardiovascular disease. *J Am Geriatr Soc, 56*(6), 1037-1044.

Breteler, M. M. (2000). Vascular risk factors for Alzheimer's disease: an epidemiologic perspective. *Neurobiol Aging, 21*(2), 153-160.

Brinkley, T. E., Leng, X., Miller, M. E., Kitzman, D. W., Pahor, M., Berry, M. J., et al. (2009). Chronic inflammation is associated with low physical function in older adults across multiple comorbidities. *J Gerontol A Biol Sci Med Sci, 64*(4), 455-461.

Brownlee, M. (1995). Advanced protein glycosylation in diabetes and aging. *Annu Rev Med, 46*, 223-234.

Buckner, R. L. (2004). Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron, 44*(1), 195-208.

Buschke, H., & Fuld, P. A. (1974). Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology, 24*(11), 1019-1025.

Carter, C. S., Onder, G., Kritchevsky, S. B., & Pahor, M. (2005). Angiotensin-converting enzyme inhibition intervention in elderly persons: effects on body composition and physical performance. *J Gerontol A Biol Sci Med Sci, 60*(11), 1437-1446.

Cesari, M., Kritchevsky, S. B., Penninx, B. W., Nicklas, B. J., Simonsick, E. M., Newman, A. B., et al. (2005). Prognostic value of usual gait speed in well-functioning older people--results from the Health, Aging and Body Composition Study. *J Am Geriatr Soc, 53*(10), 1675-1680.

Cesari, M., Penninx, B. W., Pahor, M., Lauretani, F., Corsi, A. M., Rhys Williams, G., et al. (2004). Inflammatory markers and physical performance in older persons: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci, 59*(3), 242-248.

Cook, N. R. (2008). Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. *Clin Chem, 54*(1), 17-23.

Coppin, A. K., Shumway-Cook, A., Saczynski, J. S., Patel, K. V., Ble, A., Ferrucci, L., et al. (2006). Association of executive function and performance of dual-task physical tests among older adults: analyses from the InChianti study. *Age Ageing, 35*(6), 619-624.

Dahlof, B. (2007). Prevention of stroke in patients with hypertension. *Am J Cardiol, 100*(3A), 17J-24J.

de Groot, J. C., de Leeuw, F. E., Oudkerk, M., van Gijn, J., Hofman, A., Jolles, J., et al. (2000). Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. *Ann Neurol, 47*(2), 145-151.

de la Torre, J. C. (2002). Alzheimer disease as a vascular disorder: nosological evidence. *Stroke, 33*(4), 1152-1162.

DeFries, T., Avendano, M., & Glymour, M. M. (2009). Level and change in cognitive test scores predict risk of first stroke. *J Am Geriatr Soc, 57*(3), 499-505.

Dernellis, J., & Panaretou, M. (2005). Aortic stiffness is an independent predictor of progression to hypertension in nonhypertensive subjects. *Hypertension, 45*(3), 426-431.

Di Bari, M., Pahor, M., Franse, L. V., Shorr, R. I., Wan, J. Y., Ferrucci, L., et al. (2001). Dementia and disability outcomes in large hypertension trials: lessons learned from the systolic hypertension in the elderly program (SHEP) trial. *Am J Epidemiol, 153*(1), 72-78.

Elias, M. F., Robbins, M. A., Budge, M. M., Abhayaratna, W. P., Dore, G. A., & Elias, P. K. (2009). Arterial pulse wave velocity and cognition with advancing age. *Hypertension, 53*(4), 668-673.

Elkins, J. S., Knopman, D. S., Yaffe, K., & Johnston, S. C. (2005). Cognitive function predicts first-time stroke and heart disease. *Neurology, 64*(10), 1750-1755.

Fitzmaurice, G. M., Laird, N. M., & Ware, J. H. (2004). *Applied Longitudinal Analysis*. Hoboken, NJ: John Wiley & Sons, Inc.

Fitzpatrick, A. L., Buchanan, C. K., Nahin, R. L., Dekosky, S. T., Atkinson, H. H., Carlson, M. C., et al. (2007). Associations of gait speed and other measures of physical function with cognition in a healthy cohort of elderly persons. *J Gerontol A Biol Sci Med Sci, 62*(11), 1244-1251.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res, 12*(3), 189-198.

Franklin, S. S. (2006a). Hypertension in older people: part 1. *J Clin Hypertens (Greenwich), 8*(6), 444-449.

Franklin, S. S. (2006b). Hypertension in older people: part 2. *J Clin Hypertens (Greenwich), 8*(7), 521-525.

Franklin, S. S., Jacobs, M. J., Wong, N. D., L'Italien, G. J., & Lapuerta, P. (2001). Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. *Hypertension, 37*(3), 869-874.

Fujiwara, Y., Chaves, P. H., Takahashi, R., Amano, H., Yoshida, H., Kumagai, S., et al. (2005). Arterial pulse wave velocity as a marker of poor cognitive function in an elderly community-dwelling population. *J Gerontol A Biol Sci Med Sci, 60*(5), 607-612.

Fukuhara, M., Matsumura, K., Ansai, T., Takata, Y., Sonoki, K., Akifusa, S., et al. (2006). Prediction of cognitive function by arterial stiffness in the very elderly. *Circ J, 70*(6), 756-761.

Guralnik, J. M., Ferrucci, L., Pieper, C. F., Leveille, S. G., Markides, K. S., Ostir, G. V., et al. (2000). Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci, 55*(4), M221-231.

Hajjar, I., & Kotchen, T. A. (2003). Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. *JAMA, 290*(2), 199-206.

Hajjar, I., Lackland, D. T., Cupples, L. A., & Lipsitz, L. A. (2007). Association between concurrent and remote blood pressure and disability in older adults. *Hypertension, 50*(6), 1026-1032.

Hanon, O., Haulon, S., Lenoir, H., Seux, M. L., Rigaud, A. S., Safar, M., et al. (2005). Relationship between arterial stiffness and cognitive function in elderly subjects with complaints of memory loss. *Stroke, 36*(10), 2193-2197.

Hedeker, D., & Gibbons, R. D. (1997). Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychological Methods, 2*, 64-78.

Henskens, L. H., Kroon, A. A., van Oostenbrugge, R. J., Gronenschild, E. H., Fuss-Lejeune, M. M., Hofman, P. A., et al. (2008). Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. *Hypertension, 52*(6), 1120-1126.

Hirata, K., Kawakami, M., & O'Rourke, M. F. (2006). Pulse wave analysis and pulse wave velocity: a review of blood pressure interpretation 100 years after Korotkov. *Circ J, 70*(10), 1231-1239.

Holtzer, R., Friedman, R., Lipton, R. B., Katz, M., Xue, X., & Verghese, J. (2007). The relationship between specific cognitive functions and falls in aging. *Neuropsychology, 21*(5), 540-548.

Holtzer, R., Verghese, J., Xue, X., & Lipton, R. B. (2006). Cognitive processes related to gait velocity: results from the Einstein Aging Study. *Neuropsychology, 20*(2), 215-223.

Iadecola, C., Park, L., & Capone, C. (2008). Threats to the Mind. Aging, Amyloid, and Hypertension. *Stroke*.

Iadecola, C., Park, L., & Capone, C. (2009). Threats to the mind: aging, amyloid, and hypertension. *Stroke, 40*(3 Suppl), S40-44.

Intengan, H. D., & Schiffrin, E. L. (2000). Structure and mechanical properties of resistance arteries in hypertension: role of adhesion molecules and extracellular matrix determinants. *Hypertension, 36*(3), 312-318.

Inzitari, M., Baldereschi, M., Di Carlo, A., Di Bari, M., Marchionni, N., Scafato, E., et al. (2007). Impaired attention predicts motor performance decline in older community-dwellers with normal baseline mobility: results from the Italian Longitudinal Study on Aging (ILSA). *J Gerontol A Biol Sci Med Sci, 62*(8), 837-843.

Inzitari, M., Newman, A. B., Yaffe, K., Boudreau, R., de Rekeneire, N., Shorr, R., et al. (2007). Gait Speed Predicts Decline in Attention and Psychomotor Speed in Older Adults: The Health Aging and Body Composition Study. *Neuroepidemiology, 29*(3-4), 156-162.

Jokinen, H., Kalska, H., Ylikoski, R., Madureira, S., Verdelho, A., van der Flier, W. M., et al. (2009). Longitudinal Cognitive Decline in Subcortical Ischemic Vascular Disease - The LADIS Study. *Cerebrovasc Dis, 27*(4), 384-391.

Kearney-Schwartz, A., Rossignol, P., Bracard, S., Felblinger, J., Fay, R., Boivin, J. M., et al. (2009). Vascular structure and function is correlated to cognitive performance and white matter hyperintensities in older hypertensive patients with subjective memory complaints. *Stroke, 40*(4), 1229-1236.

Kritchevsky, S. B., Cesari, M., & Pahor, M. (2005). Inflammatory markers and cardiovascular health in older adults. *Cardiovasc Res, 66*(2), 265-275.

Kuo, H. K., & Lipsitz, L. A. (2004). Cerebral white matter changes and geriatric syndromes: is there a link? *J Gerontol A Biol Sci Med Sci, 59*(8), 818-826.

Lakatta, E. G. (1993). Cardiovascular regulatory mechanisms in advanced age. *Physiol Rev, 73*(2), 413-467.

Launer, L. J. (2004). Epidemiology of white matter lesions. *Top Magn Reson Imaging, 15*(6), 365-367.

Laurent, S., & Boutouyrie, P. (2007). Arterial stiffness: a new surrogate end point for cardiovascular disease? *J Nephrol, 20 Suppl 12*, S45-50.

Laurent, S., Boutouyrie, P., Asmar, R., Gautier, I., Laloux, B., Guize, L., et al. (2001). Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension, 37*(5), 1236-1241.

Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., et al. (2006). Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J, 27*(21), 2588-2605.

Lavery, L. L., Dodge, H. H., Snitz, B., & Ganguli, M. (2009). Cognitive decline and mortality in a community-based cohort: the Monongahela Valley Independent Elders Survey. *J Am Geriatr Soc, 57*(1), 94-100.

Lee, Y., Kim, J. H., Lee, K. J., Han, G., & Kim, J. L. (2005). Association of cognitive status with functional limitation and disability in older adults. *Aging Clin Exp Res, 17*(1), 20-28.

Liao, D., Arnett, D. K., Tyroler, H. A., Riley, W. A., Chambless, L. E., Szklo, M., et al. (1999). Arterial stiffness and the development of hypertension. The ARIC study. *Hypertension, 34*(2), 201-206.

Longstreth, W. T., Jr., Manolio, T. A., Arnold, A., Burke, G. L., Bryan, N., Jungreis, C. A., et al. (1996). Clinical correlates of white matter findings on cranial magnetic resonance

imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke, 27*(8), 1274-1282.

Madero, M., Wassel, C. L., Peralta, C. A., Najjar, S. S., Sutton-Tyrrell, K., Fried, L., et al. (2009a). Cystatin C associates with arterial stiffness in older adults. *J Am Soc Nephrol, 20*(5), 1086-1093.

Madero, M., Wassel, C. L., Peralta, C. A., Najjar, S. S., Sutton-Tyrrell, K., Fried, L., et al. (2009b). Cystatin C Associates with Arterial Stiffness in Older Adults. *J Am Soc Nephrol*.

Mahmud, A., & Feely, J. (2004). Arterial stiffness and the renin-angiotensin-aldosterone system. *J Renin Angiotensin Aldosterone Syst, 5*(3), 102-108.

Manolio, T. A., Kronmal, R. A., Burke, G. L., Poirier, V., O'Leary, D. H., Gardin, J. M., et al. (1994). Magnetic resonance abnormalities and cardiovascular disease in older adults. The Cardiovascular Health Study. *Stroke, 25*(2), 318-327.

Matsuoka, O., Otsuka, K., Murakami, S., Hotta, N., Yamanaka, G., Kubo, Y., et al. (2005). Arterial stiffness independently predicts cardiovascular events in an elderly community -- Longitudinal Investigation for the Longevity and Aging in Hokkaido County (LILAC) study. *Biomed Pharmacother, 59 Suppl 1*, S40-44.

Mazumdar, S., Tang, G., Houck, P. R., Dew, M. A., Begley, A. E., Scott, J., et al. (2007). Statistical analysis of longitudinal psychiatric data with dropouts. *J Psychiatr Res, 41*(12), 1032-1041.

McDermott, M. M., Liu, K., Greenland, P., Guralnik, J. M., Criqui, M. H., Chan, C., et al. (2004). Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA, 292*(4), 453-461.

McDonald, M., Hertz, R. P., Unger, A. N., & Lustik, M. B. (2009). Prevalence, awareness, and management of hypertension, dyslipidemia, and diabetes among United States adults aged 65 and older. *J Gerontol A Biol Sci Med Sci, 64*(2), 256-263.

Melzer, I., & Oddsson, L. I. (2004). The effect of a cognitive task on voluntary step execution in healthy elderly and young individuals. *J Am Geriatr Soc, 52*(8), 1255-1262.

Mitchell, G. F. (2008). Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. *J Appl Physiol, 105*(5), 1652-1660.

Mitchell, G. F., Vita, J. A., Larson, M. G., Parise, H., Keyes, M. J., Warner, E., et al. (2005). Cross-sectional relations of peripheral microvascular function, cardiovascular disease risk

factors, and aortic stiffness: the Framingham Heart Study. *Circulation, 112*(24), 3722-3728.

Mottram, P. M., Haluska, B. A., Leano, R., Carlier, S., Case, C., & Marwick, T. H. (2005). Relation of arterial stiffness to diastolic dysfunction in hypertensive heart disease. *Heart, 91*(12), 1551-1556.

Mourad, J. J., Pannier, B., Blacher, J., Rudnichi, A., Benetos, A., London, G. M., et al. (2001). Creatinine clearance, pulse wave velocity, carotid compliance and essential hypertension. *Kidney Int, 59*(5), 1834-1841.

Muller, M., Grobbee, D. E., Aleman, A., Bots, M., & van der Schouw, Y. T. (2007). Cardiovascular disease and cognitive performance in middle-aged and elderly men. *Atherosclerosis, 190*(1), 143-149.

Najjar, S. S., Scuteri, A., & Lakatta, E. G. (2005). Arterial aging: is it an immutable cardiovascular risk factor? *Hypertension, 46*(3), 454-462.

Najjar, S. S., Scuteri, A., Shetty, V., Wright, J. G., Muller, D. C., Fleg, J. L., et al. (2008). Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. *J Am Coll Cardiol, 51*(14), 1377-1383.

Newman, A. B., Arnold, A. M., Sachs, M. C., Ives, D. G., Cushman, M., Strotmeyer, E. S., et al. (2009). Long-term function in an older cohort--the cardiovascular health study all stars study. *J Am Geriatr Soc, 57*(3), 432-440.

Newman, A. B., Shemanski, L., Manolio, T. A., Cushman, M., Mittelmark, M., Polak, J. F., et al. (1999). Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. *Arterioscler Thromb Vasc Biol, 19*(3), 538-545.

Newman, A. B., Simonsick, E. M., Naydeck, B. L., Boudreau, R. M., Kritchevsky, S. B., Nevitt, M. C., et al. (2006). Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. *JAMA, 295*(17), 2018-2026.

O'Rourke, M. F. (2007). Arterial aging: pathophysiological principles. *Vasc Med, 12*(4), 329-341.

O'Rourke, M. F., & Safar, M. E. (2005). Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertension, 46*(1), 200-204.

O'Rourke, M. F., Staessen, J. A., Vlachopoulos, C., Duprez, D., & Plante, G. E. (2002). Clinical applications of arterial stiffness; definitions and reference values. *Am J Hypertens, 15*(5), 426-444.

O'Sullivan, M., Morris, R. G., & Markus, H. S. (2005). Brief cognitive assessment for patients with cerebral small vessel disease. *J Neurol Neurosurg Psychiatry, 76*(8), 1140-1145.

Ohmine, T., Miwa, Y., Yao, H., Yuzuriha, T., Takashima, Y., Uchino, A., et al. (2008). Association between arterial stiffness and cerebral white matter lesions in community-dwelling elderly subjects. *Hypertens Res, 31*(1), 75-81.

Oliver, J. J., & Webb, D. J. (2003). Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. *Arterioscler Thromb Vasc Biol, 23*(4), 554-566.

Ovbiagele, B., & Saver, J. L. (2006). Cerebral white matter hyperintensities on MRI: Current concepts and therapeutic implications. *Cerebrovasc Dis, 22*(2-3), 83-90.

Pantoni, L. (2002). Pathophysiology of age-related cerebral white matter changes. *Cerebrovasc Dis, 13 Suppl 2*, 7-10.

Park, J. B., & Schiffrin, E. L. (2001). Small artery remodeling is the most prevalent (earliest?) form of target organ damage in mild essential hypertension. *J Hypertens, 19*(5), 921-930.

Penninx, B. W., Kritchevsky, S. B., Newman, A. B., Nicklas, B. J., Simonsick, E. M., Rubin, S., et al. (2004). Inflammatory markers and incident mobility limitation in the elderly. *J Am Geriatr Soc, 52*(7), 1105-1113.

Perera, S., Studenski, S., Chandler, J. M., & Guralnik, J. M. (2005). Magnitude and patterns of decline in health and function in 1 year affect subsequent 5-year survival. *J Gerontol A Biol Sci Med Sci, 60*(7), 894-900.

Poels, M. M., van Oijen, M., Mattace-Raso, F. U., Hofman, A., Koudstaal, P. J., Witteman, J. C., et al. (2007). Arterial stiffness, cognitive decline, and risk of dementia: the Rotterdam study. *Stroke, 38*(3), 888-892.

Prins, N. D., van Dijk, E. J., den Heijer, T., Vermeer, S. E., Jolles, J., Koudstaal, P. J., et al. (2005). Cerebral small-vessel disease and decline in information processing speed, executive function and memory. *Brain, 128*(Pt 9), 2034-2041.

Pugh, K. G., & Lipsitz, L. A. (2002). The microvascular frontal-subcortical syndrome of aging. *Neurobiol Aging, 23*(3), 421-431.

Reitan, R. M. (1958). Validity of the trail making test as an indicator of organic brain damage. *Perceptual Motor Skills, 8*, 271-276.

Roriz-Cruz, M., Rosset, I., Wada, T., Sakagami, T., Ishine, M., De Sa Roriz-Filho, J., et al. (2007). Cognitive impairment and frontal-subcortical geriatric syndrome are associated with metabolic syndrome in a stroke-free population. *Neurobiol Aging, 28*(11), 1723-1736.

Rosano, C., Aizenstein, H. J., Studenski, S., & Newman, A. B. (2007). A regions-of-interest volumetric analysis of mobility limitations in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci, 62*(9), 1048-1055.

Rosano, C., Kuller, L. H., Chung, H., Arnold, A. M., Longstreth, W. T., Jr., & Newman, A. B. (2005). Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. *J Am Geriatr Soc, 53*(4), 649-654.

Rosano, C., Newman, A. B., Katz, R., Hirsch, C. H., & Kuller, L. H. (2008). Association between lower digit symbol substitution test score and slower gait and greater risk of mortality and of developing incident disability in well-functioning older adults. *J Am Geriatr Soc, 56*(9), 1618-1625.

Rosano, C., Simonsick, E. M., Harris, T. B., Kritchevsky, S. B., Brach, J., Visser, M., et al. (2005). Association between physical and cognitive function in healthy elderly: the health, aging and body composition study. *Neuroepidemiology, 24*(1-2), 8-14.

Rosenbaum, P. R., & Rubin, D. B. (1984). Reducing bias in observational studies using subclassification on the propensity score. *Journal of American Statistical Association, 79*, 516-524.

Royall, D. R., Mahurin, R. K., & Gray, K. F. (1992). Bedside assessment of executive cognitive impairment: the executive interview. *J Am Geriatr Soc, 40*(12), 1221-1226.

Royall, D. R., Palmer, R., Chiodo, L. K., & Polk, M. J. (2004). Declining executive control in normal aging predicts change in functional status: the Freedom House Study. *J Am Geriatr Soc, 52*(3), 346-352.

Sachdev, P. S., Wen, W., Christensen, H., & Jorm, A. F. (2005). White matter hyperintensities are related to physical disability and poor motor function. *J Neurol Neurosurg Psychiatry, 76*(3), 362-367.

Safar, M. E., & Lacolley, P. (2007). Disturbance of macro- and microcirculation: relations with pulse pressure and cardiac organ damage. *Am J Physiol Heart Circ Physiol, 293*(1), H1-7.

Safar, M. E., London, G. M., & Plante, G. E. (2004). Arterial stiffness and kidney function. *Hypertension, 43*(2), 163-168.

Salthouse, T. A. (1996). General and specific speed mediation of adult age differences in memory. *J Gerontol B Psychol Sci Soc Sci, 51*(1), P30-42.

Sasamura, H., Kitamura, Y., Nakamura, M., Ryuzaki, M., & Saruta, T. (2006). Effects of the angiotensin receptor blocker candesartan on arterial stiffness and markers of extracellular matrix metabolism in patients with essential hypertension. *Clin Exp Hypertens, 28*(5), 511-520.

Schafer, J. L. (1997). *Analysis of incomplete multivariate data*. London: Chapman & Hall.

Schiffrin, E. L. (2004). Vascular stiffening and arterial compliance. Implications for systolic blood pressure. *Am J Hypertens, 17*(12 Pt 2), 39S-48S.

Schupf, N., Tang, M. X., Albert, S. M., Costa, R., Andrews, H., Lee, J. H., et al. (2005). Decline in cognitive and functional skills increases mortality risk in nondemented elderly. *Neurology, 65*(8), 1218-1226.

Scuteri, A., Brancati, A. M., Gianni, W., Assisi, A., & Volpe, M. (2005). Arterial stiffness is an independent risk factor for cognitive impairment in the elderly: a pilot study. *J Hypertens, 23*(6), 1211-1216.

Scuteri, A., Tesauro, M., Appolloni, S., Preziosi, F., Brancati, A. M., & Volpe, M. (2007). Arterial stiffness as an independent predictor of longitudinal changes in cognitive function in the older individual. *J Hypertens, 25*(5), 1035-1040.

Selvin, E., & Erlinger, T. P. (2004). Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation, 110*(6), 738-743.

Semba, R. D., Ferrucci, L., Sun, K., Walston, J., Varadhan, R., Guralnik, J. M., et al. (2007). Oxidative stress and severe walking disability among older women. *Am J Med, 120*(12), 1084-1089.

Silbert, L. C., Nelson, C., Howieson, D. B., Moore, M. M., & Kaye, J. A. (2008). Impact of white matter hyperintensity volume progression on rate of cognitive and motor decline. *Neurology, 71*(2), 108-113.

Simm, A., Nass, N., Bartling, B., Hofmann, B., Silber, R. E., & Navarrete Santos, A. (2008). Potential biomarkers of ageing. *Biol Chem, 389*(3), 257-265.

Simonsick, E. M., Montgomery, P. S., Newman, A. B., Bauer, D. C., & Harris, T. (2001). Measuring fitness in healthy older adults: the Health ABC Long Distance Corridor Walk. *J Am Geriatr Soc, 49*(11), 1544-1548.

Skoog, I., & Gustafson, D. (2006). Update on hypertension and Alzheimer's disease. *Neurol Res, 28*(6), 605-611.

Soumare, A., Tavernier, B., Alperovitch, A., Tzourio, C., & Elbaz, A. (2009). A cross-sectional and longitudinal study of the relationship between walking speed and cognitive function in community-dwelling elderly people. *J Gerontol A Biol Sci Med Sci, 64*(10), 1058-1065.

Spiers, N. A., Matthews, R. J., Jagger, C., Matthews, F. E., Boult, C., Robinson, T. G., et al. (2005). Diseases and impairments as risk factors for onset of disability in the older population in England and Wales: findings from the Medical Research Council Cognitive Function and Ageing Study. *J Gerontol A Biol Sci Med Sci, 60*(2), 248-254.

Starr, J. M., Leaper, S. A., Murray, A. D., Lemmon, H. A., Staff, R. T., Deary, I. J., et al. (2003). Brain white matter lesions detected by magnetic resonance [correction of resosnance] imaging are associated with balance and gait speed. *J Neurol Neurosurg Psychiatry, 74*(1), 94-98.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*(10), 2015-2028.

Sutton-Tyrrell, K., Najjar, S. S., Boudreau, R. M., Venkitachalam, L., Kupelian, V., Simonsick, E. M., et al. (2005). Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation, 111*(25), 3384-3390.

Tekin, S., & Cummings, J. L. (2002). Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. *J Psychosom Res, 53*(2), 647-654.

Teng, E. L., & Chui, H. C. (1987). The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry, 48*(8), 314-318.

Thompson, C. S., & Hakim, A. M. (2009). Living beyond our physiological means: small vessel disease of the brain is an expression of a systemic failure in arteriolar function: a unifying hypothesis. *Stroke, 40*(5), e322-330.

Tracy, R. P. (2003). Emerging relationships of inflammation, cardiovascular disease and chronic diseases of aging. *Int J Obes Relat Metab Disord, 27 Suppl 3*, S29-34.

Triantafyllidi, H., Arvaniti, C., Lekakis, J., Ikonomidis, I., Siafakas, N., Tzortzis, S., et al. (2009). Cognitive impairment is related to increased arterial stiffness and microvascular damage in patients with never-treated essential hypertension. *Am J Hypertens, 22*(5), 525-530.

van Gelder, B. M., Tijhuis, M. A., Kalmijn, S., Giampaoli, S., & Kromhout, D. (2007). Decline in cognitive functioning is associated with a higher mortality risk. *Neuroepidemiology, 28*(2), 93-100.

van Iersel, M. B., Kessels, R. P., Bloem, B. R., Verbeek, A. L., & Olde Rikkert, M. G. (2008). Executive functions are associated with gait and balance in community-living elderly people. *J Gerontol A Biol Sci Med Sci, 63*(12), 1344-1349.

van Popele, N. M., Grobbee, D. E., Bots, M. L., Asmar, R., Topouchian, J., Reneman, R. S., et al. (2001). Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke, 32*(2), 454-460.

Vermeer, S. E., Longstreth, W. T., Jr., & Koudstaal, P. J. (2007). Silent brain infarcts: a systematic review. *Lancet Neurol, 6*(7), 611-619.

Waldstein, S. R., Rice, S. C., Thayer, J. F., Najjar, S. S., Scuteri, A., & Zonderman, A. B. (2008). Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore Longitudinal Study of Aging. *Hypertension, 51*(1), 99-104.

Wardlaw, J. M., Sandercock, P. A., Dennis, M. S., & Starr, J. (2003). Is breakdown of the blood-brain barrier responsible for lacunar stroke, leukoaraiosis, and dementia? *Stroke, 34*(3), 806-812.

Wechsler Adult Intelligence Scale F Revised. (1981). San Antonio, TX: Psychological Corporation.

Yao, S. T., Hobbs, J. T., & Irvine, W. T. (1969). Ankle systolic pressure measurements in arterial disease affecting the lower extremities. *Br J Surg, 56*(9), 676-679.

Zeger, S. L., Liang, K. Y., & Albert, P. S. (1988). Models for longitudinal data: a generalized estimating equation approach. *Biometrics, 44*(4), 1049-1060.

Zieman, S. J., Melenovsky, V., & Kass, D. A. (2005). Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol, 25*(5), 932-943.