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Journal
Journal of Alzheimer's Disease, 42(s4)

ISSN
1387-2877

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Publication Date
2014

DOI
10.3233/jad-141563

Peer reviewed

Published in final edited form as:
J Alzheimers Dis. 2014 ; 42(0 4): S503–S514. doi:10.3233/JAD-141563.

Arterial stiffness and cognitive function in the elderly

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Abstract

Cognitive decline and dementia are a major cause of disability and mortality among older adults. Cross-sectional evidence from observational studies suggests that greater arterial stiffness is associated with worse cognitive performance. These associations have been observed on measures of global cognition and across multiple domains of cognition. Epidemiologic evidence on the association between arterial stiffness and rate of cognitive decline has been less definitive, and very few studies have investigated the risk of developing dementia. This review summarizes the current research on arterial stiffness and cognition, issues around measurement and the effect that potential intervention might have on the course of cognitive aging. The evidence on pharmacological and non-pharmacological (exercise, nutrition, etc) interventions in older adults with arterial stiffness is promising. Yet there are no studies or trials that directly evaluate how interventions of arterial stiffness reduce or prevent cognitive impairment and risk of developing dementia. More research is needed to elucidate the causal link between arterial stiffness and cognitive decline and dementia, and to identify whether potential interventions to prevent or reduce arterial stiffness may benefit cognitive health of the elderly.

Keywords

Aging; Arterial stiffness; Cognitive decline; Dementia; Epidemiology

Cognitive impairment is very common in elderly persons and is associated with increased disability and mortality [1, 2]. In addition, there is a large societal burden associated with cognitive impairment including, caregiver burden and large health care expenditures [3]. As our population continues to age, understanding the epidemiology of cognitive impairment is becoming very important as it may prevent or delay cognitive decline and dementia pathology.

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There is increasing evidence that cardiovascular disease and its risk factors contribute to the development of cognitive impairment and dementia [3-7]. With its rich vascularization and low resistance to flow, the brain is particularly susceptible to cardiovascular dynamics [8-10]. Recently, new vascular markers including, markers of arterial stiffness and arterial pressure [11, 12] have been shown as useful predictors of cardiovascular risk [13-17]. Consequently, there has been increasing interest in evaluating whether these markers are predictors of cognitive impairment and dementia [18-30]. Despite our understanding of the pathophysiologic mechanisms through which arterial stiffness may influence cognitive aging, epidemiologic evidence suggesting its role in cognitive decline and dementia remains unclear and relatively unexplored.

The goal of this review is to summarize the evidence on the relationship between arterial stiffness and cognitive aging. To do so, we will first review evidence from epidemiologic studies on the associations between arterial stiffness and cognitive impairment, cognitive decline, and dementia, then, we will discuss potential underlying mechanisms. Finally, we will summarize current evidence on interventions of arterial stiffness and their influence on the course of cognitive aging.

Cognitive Aging

Cognitive function can be assessed using measures of function for specific cognitive domains or for global cognitive function. We report findings on global cognitive function using measures such as the Mini-Mental State Exam, the Modified Mini Mental State Exam, or some other global composite score. It is suggested that cardiovascular mechanisms, including arterial stiffness, may influence specific cognitive domains [31, 32]. Therefore, we also report findings on specific cognitive domains such as, executive function, memory, and processing speed. There are several ways to characterize cognitive function. While one can examine cognitive performance at a single time point, examining rate of cognitive decline is important for understanding the etiology of cognitive impairment. Therefore, we will provide evidence of associations with both cross-sectional cognitive function and longitudinal/change in cognitive function. Finally, we report studies with findings on dementia. Dementia is defined as a decline in at least two cognitive domains that is severe enough to interfere with functioning [33], and as such dementia provides an important clinical endpoint. Unfortunately, the literature on arterial stiffness and dementia is very scarce and thus does not allow us to examine and report associations with various causes and categories of dementia.

Arterial Aging

As we age, the walls of the aorta undergo increased stiffness that is attributed to changes in the wall structure or function [34-36]. The stiffness is triggered by an increase in collagen and calcium deposition resulting in a thickness of the arterial wall [34-36]. The arterial walls may also undergo hemodynamic-induced elastin fragmentation resulting in loss of function [34-36]. The loss of arterial elastin alters vascular tone and compliance resulting in less extensible walls and thus more stiffened arteries. This has consequences on the ability of the arteries to cushion and accommodate increases in pulse wave propagation.

The aortic pressure waveform is comprised of two pressure waves: a forward pressure wave and a backward reflected pressure wave. In a low-stiffness or non-stiffened aorta, the reflected waves return to the central aorta in early diastole. However in a stiffened aorta, the speed of the arterial wave propagation (i.e. arterial pulse wave velocity (PWV)) increases, and thus the reflected waves that normally return to the central aorta in early diastole return prematurely during systole. The latter will cause an increase in the maximal systolic blood pressure (BP) and aortic central pulse pressure (PP) [8, 9, 37].

Detection of arterial stiffness: markers of arterial aging

The most common measures used to assess arterial stiffness include carotid-femoral pulse wave velocity (cf-PWV), aortic PP, and augmentation index [9, 38-40]. Cf-PWV is regarded as the gold standard measure of arterial stiffness; measurement consists of using applanation tonometry, which measures the velocity of the forward and backward propagation waves between the carotid and femoral arteries. The distance between the carotid and femoral arteries is also measured above the body surface, typically using a measuring tape. Cf-PWV is then calculated as the distance between the carotid and femoral arteries divided by the time differential for the pressure wave to reach both arteries (i.e. PWV=time/distance). As a result of increasing arterial stiffness, the wave propagates faster and the time between the carotid systolic peak and femoral systolic peak decreases, resulting in an increase in PWV. Using ultrasound, PWV may also be measured at the brachial-ankle (ba-PWV) [41] or at the aorta itself (aPWV) [42]. Other measures of arterial stiffness include PP and augmentation index. PP is an indirect measure of arterial stiffness and is calculated as systolic blood pressure minus diastolic blood pressure. Augmentation index is the percentage of aortic pressure augmentation relative to pulse pressure [9]. Measures of PWV, especially the cf-PWV, provide more direct measures of arterial stiffness than other measures such as PP and augmentation index. The increase in central pulse pressure is the consequence of the change in the speed of the arterial wave propagation (described earlier). As such, compared to PP, cfPWV is a more direct measure of arterial stiffness as it measures the speed and distance traveled by the waveform. Furthermore, PP is more dependent on hemodynamic factors, such as arterial diameter and ejection fraction, which makes an increase in PP not necessarily related to arterial stiffness, and thus further making PP not as accurate as cfPWV.

Epidemiologic literature on the cross-sectional association between arterial stiffness and cognitive function

Table 1 summarizes results from cross-sectional studies examining the association between arterial stiffness and cognitive function [18-21, 23, 25, 27-30]. Overall, the evidence suggests that greater arterial stiffness is associated with worse cognitive function. The majority of studies that examined the association between arterial stiffness and global cognitive function, as measured by the MMSE or 3MS, showed consistent results suggesting that greater stiffness is associated with worse global function [18-20, 23, 25, 27, 30]. Similarly, studies reported an association between arterial stiffness and cognitive function in one or more domains, including executive function, processing speed, or verbal memory, but across studies, there is not a consistent association in individual domains. Only one study,

the Sidney Memory and Aging Study, failed to find a cross-sectional association between arterial stiffness and at least one domain from various measures of cognitive function [28].

Epidemiologic literature on the longitudinal association between arterial stiffness and cognitive function

Examining rate of cognitive decline is important for understanding the etiology of cognitive impairment. Furthermore, longitudinal studies offer a better study design than cross-sectional studies by allowing to establishing temporality. Table 2 summarizes results from longitudinal epidemiologic studies examining the association between arterial stiffness and cognitive decline. As evident in Table 2, only a handful studies have addressed this research question and have reported inconsistent findings [7, 22-26, 43]. Many studies report an association between arterial stiffness and decline in one or more domains, but across studies, there is not a consistent association between arterial stiffness and decline in individual domains.

Findings from the Rotterdam study failed to find an association between arterial stiffness (c-f PWV) and cognitive decline on global cognitive function and domain-specific function. These participants were free of dementia when neuropsychological testing was first performed, and then were followed over an average of five years after which neuropsychological testing was performed again (i.e. two time points), which may not be enough time to observe significant cognitive decline [23]. Furthermore, the Rotterdam study included middle-aged and older-aged participants, which may have diluted any association. In contrast, findings from the Baltimore Longitudinal Study suggest an association between greater arterial stiffness (c-f PWV and PP) and decline in verbal learning memory and non-verbal memory functioning (free recall and visual memory) over 11 years of follow-up of a community-dwelling cohort free of dementia and cerebrovascular diseases [22]. Furthermore, an association was observed between arterial stiffness (c-f PWV) and decline in psychomotor speed in the Cognitive Vitality Substudy of the Health, Aging and Body Composition study [25]. Further findings from the full cohort of the Health, Aging, and Body Composition study, a cohort of well-functioning older adults, showed an association between arterial stiffness (c-f PWV) and decline in global cognitive function measured using the modified Mini Mental Status Exam (3MS) [7]. Similarly, results from the PARTAGE study of patients aged 80+ and without dementia showed an association between greater arterial stiffness and decline in performance on the MMSE over 1 year of follow-up [26]. Similar results were observed among elderly patients followed over a year on average, showing greater c-f PWV associated with decline in MMSE score [24, 43].

According to a recent meta-analysis by Pase et al. 2012 [44], there was an overall association between arterial stiffness and cognitive decline measured on the MMSE. However, the association was of small magnitude which, as the authors note, could be due to ceiling effects and the inability of the neuropsychological test, in this case the MMSE, to detect cognitive changes in well-functioning and healthy adults. As for the association between arterial stiffness and decline in specific cognitive domains, the findings are inconsistent across studies but with many studies reporting an association between arterial stiffness and decline in one or more domains [22, 25].

The inconsistency of results across studies may reflect a weak relationship between arterial stiffness and cognitive decline, or may be due to differences in the cognitive domains assessed, differences in aspects of the study design, including the specific neuropsychological tests used, how rate of cognitive decline was modeled, length of follow-up, inclusion and exclusion criteria, or differences in participants' characteristics. The sensitivity of some of the neuropsychological tests such as the MMSE may be compromised in well-functioning and healthier cohorts, which may explain some of the inconsistencies between studies. Furthermore, shared determinants of arterial stiffness and cognitive decline may confound the association and result in between-studies inconsistency. Possible confounders include age, socioeconomic factors, behavioral factors, such as diet, smoking, and physical activity, and co-morbidities, such as obesity, hypertension, diabetes, and depressive symptoms. While many studies adjust for some or all of these factors, residual confounding may still mask the true association. Future studies, especially those with a wide age range, should examine whether the association between arterial stiffness and cognitive function is age-dependent. Finally, potential publication bias may have also contributed to an underrepresentation of null findings from longitudinal studies.

Epidemiologic literature on the association between arterial stiffness and dementia

The association between arterial stiffness and dementia remains relatively unexplored. Cross-sectional evidence from one study of elderly with memory complaints attending a geriatric clinic suggests that subjects with mild cognitive impairment, vascular dementia, and Alzheimer's disease show greater arterial stiffness (c-f PWV) compared to those with normal cognitive function [45]. Other cross-sectional results have reported that subjects with vascular dementia show greater arterial stiffness than subjects with AD or without dementia [46]. There is only one prospective study of dementia that has been conducted, the Rotterdam study, and which failed to find an association between arterial stiffness and risk of dementia [23].

Taken together, current epidemiologic evidence suggests that arterial stiffness is associated with cognitive impairment and less definitely with cognitive decline. There is less evidence to make any conclusions about the association of arterial stiffness and risk of dementia. More research is needed to better understand the pathological effects of arterial stiffness on the brain and to evaluate any causal link.

Pathophysiologic mechanisms between arterial stiffness and cognitive function

As described earlier, age-related changes in arterial stiffness cause an increase in arterial pulse pressure which ultimately results in hemodynamic stress in the heart and in high-flow end-organs such as the brain. The brain has low resistance to flow. When subjected to high pulsatile stress, the brain arteries become compromised, especially with age and in the presence of certain cardiovascular diseases such as hypertension [8-10, 40].

A low stiffened aorta has the ability to cushion pulsatile flow so that it is delivered to the brain in a non-pulsatile form. However in the presence of stiffness, the aorta loses its cushioning capacity and thus pulsatile pressure is transmitted to the brain. Pulsatile pressure predisposes the brain to damages of its small cerebral vessels and results in small arterial diseases [9, 40]. Indeed, high levels of central PP in the brain result in structural changes and dysfunction of its microcirculation [8, 47], resulting in microvascular damage and impaired microvascular function. This in turn may lead to brain atrophy and impaired or loss of cognitive function [8]. In particular, small-vessel disease of the brain has been shown to be associated with changes in the frontal-subcortical regions of the brain that control executive and motor functions; thus suggesting that arterial stiffness may be associated with these specific cognitive domains[31, 32].

Recent brain imaging studies have found arterial stiffness to be associated with cerebral microvascular disease and structural brain changes, including stroke [48], white matter hyperintensities, lacunar infarctions, and cortical brain atrophy [47, 49, 50]. Furthermore, high central PP may result in structural changes to cerebral blood vessels which may in turn interfere with the transport of important nutrients to the brain as well as interfere with the clearance of toxic byproducts out of the brain [51]. Arterial stiffness has also been demonstrated as an independent predictor of cardiovascular events and cardiovascular risk factors [21, 52-54] which are in turn important predictors of cognitive decline. Figure 1 illustrates the potential causal pathways linking arterial stiffness and cognitive decline and dementia.

Markers of arterial stiffness: potential for intervention

In prior sections, we discussed how arterial stiffness can be detected using various measures that assess pulse wave propagation. To be used as prognostic factors, markers of arterial stiffness have to be easy to implement and of clinical utility. Most measures of arterial stiffness are relatively simple and performed non-invasively. The carotid-femoral PWV, which is the gold standard measure of arterial stiffness, is robust and reproducible and has well-documented clinical reference values [9, 55]. One limitation of measures of PWV is that they are more time consuming compared to other simpler measures of arterial stiffness (e.g. brachial BP), and may require a trained technician [9].

The public health significance of markers of arterial stiffness depends on whether arterial stiffness is modifiable meaning whether it can be reduced, and consequently reduce risk of cognitive aging. The literature on potential pharmacologic treatments of arterial stiffness has largely focused on anti-hypertensive drugs that reduce blood pressure [9, 10, 37, 40, 56, 57] due to the role and potential causal link between hypertension, vascular stiffness, and cognitive impairment. Anti-hypertensive therapy and drugs such as ACEIs (angiotensin-converting-enzyme inhibitors), ARBs (angiotensin receptor blockers), CCBs (calcium channel blockers), and nitrates have been shown to reduce arterial stiffness by reducing the backward-traveling wave reflections which consequently reduces central augmentation and PP [58-60]. While reduction in arterial stiffness may benefit the microvascular function [61], it remains unknown whether modification of arterial stiffness will be causally related to cognitive decline and dementia incidence. This is an important area of future examination.

Non-pharmacological interventions that reduce arterial stiffness have been promising. There is a growing literature suggesting that lifestyle and dietary changes may reduce blood pressure and arterial stiffness [62, 63]. Indeed, aerobic exercise through improved endothelial function [64, 65], smoking cessation [62], and dietary factors such as omega-3 and flavonoids have been shown to reduce blood pressure and arterial stiffness. While it remains unknown whether reduction in arterial stiffness will be causally related to a reduced risk of cognitive decline and dementia, many of these behavioral and lifestyle factors have been shown to benefit cognitive health.

CONCLUSION

There is evidence that arterial stiffness in the elderly is cross-sectionally associated with cognitive impairment. The evidence of an association with cognitive decline is less definitive, and conclusions about its association with dementia incidence cannot yet be made. Future research should carefully implement cognitive testing that is sensitive to subtle cognitive changes, especially in younger and healthier populations. Future studies should also seek to understand whether arterial stiffness has a causal effect on cognitive decline and dementia and if so, through what mechanisms. Finally, the evidence that exists on interventions in older adults with arterial stiffness, especially non-pharmacological, is promising. Thus, the beneficial effects of these interventions on reducing or preventing cognitive decline are yet to be determined.

Acknowledgments

Sources of funding Dr. Zeki Al Hazzouri was supported by a grant from the NIH, National Institute on Aging (K01AG047273) and the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number KL2TR000143.

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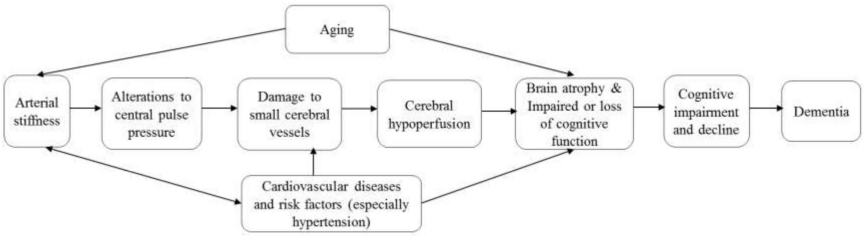

Figure 1.

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Table 1

Studies of the cross-sectional association between arterial stiffness and cognitive function

Publication	Cohort	Age (years)	Arterial stiffness measure	Cognitive tests assessed	Result
Elias et al., 2009 [21]	Maine-Syracuse Longitudinal study, (N=409), USA	24-92	Carotid-femoral PWV	• Visual-spatial organization and memory: Hooper visual organization test, matrix reasoning, block design, and object assembly • Scanning and tracking: Trail making Tests A and B, Digit substitution, and symbol search • Verbal episodic memory: immediate and delayed, and Hopkins Verbal Learning Test • Working Memory: Digit span forward and backward, letter-number sequence, and controlled oral word associations • Global composite score	• Greater PWV was associated with worse performance on tests measuring visualspatial organization ($p<0.05$), verbal memory ($p<0.05$), and global cognitive function ($p<0.05$) • The decrement in cognitive performance associated with greater PWV increases with age
Fukuhara et al., 2006 [18]	From community, Japan (N=203)	85	Brachial-Ankle PWV	• Global cognition: MMSE	• Greater PWV was associated with lower score on the MMSE ($\beta=-0.157$; $P=0.003$)
Mitchell et al., 2011 [27]	AGES-Reykjavik Study, (N=668), Iceland	69-93	Carotid-femoral PWV, Pulse Pressure (PP)	• Memory: California verbal learning test (immediate and delayed) • Processing speed: Digit Substitution Test, Figure comparison, Stroop tests I (word naming) and II (Color naming) • Executive function: Digit Backward, Stroop test III, and Shortened Cambridge Test Automated battery	• Greater PWV was associated with worse performance on tests assessing memory ($\beta=-0.095$; $p=0.028$) and executive function ($\beta=-0.076$; $p=0.09$) • Greater PP was associated with worse performance on tests assessing memory ($\beta=-0.114$; $p=0.013$) and executive function ($\beta=-0.094$; $p=0.05$)
Poels et al., 2007 [23]	Rotterdam Study, (N=3714), Netherlands	55+	Carotid-femoral PWV	• Global cognition: MMSE • Executive function: Letter digit substitution task, Stroop test, and word fluency test	• Greater PWV was associated with worse performance on the Stroop ($\beta=-1.13$; 95%CI=0.26; 1.99)
Scuteri et al., 2005 [19]	From hospital, (N=84), Italy	78±5	Carotid-femoral PWV	• Global cognition: MMSE	• Greater PWV was correlated with worse score on the MMSE ($\beta=-0.28$; $p<0.01$)
Singer et al., 2013 [28]	The community-based Sidney Memory and Aging Study (N=319), Australia	70-90	Carotid-femoral PWV	• Processing speed: digit symbol coding, and trail making test A	• No significant associations between PWV and cognitive function

Publication	Cohort	Age (years)	Arterial stiffness measure	Cognitive tests assessed	Result
				• Memory: Rey Auditory Visual Verbal Learning test, Benton Visual Retention Test (BVRT), and Logical Story A (delayed) • Language: Animal naming, and Boston Naming Test • Executive function: Phonemic fluency, Trail making Test B, and Stroop Test • Visualspatial ability: block design • Global composite score	
Triantafyllidi et al., 2009 [20]	From Hospital, (N=110), Greece	40-80	Carotid-femoral PWV	• Global cognition: MMSE	• Greater PWV was associated with worse score on the MMSE (β=−0.36; p=0.026)
Tsao et al., 2013 [29]	Framingham Offspring cohort study, (N=1559), USA	61±9	Carotid-femoral PWV, Pulse pressure	• Logical Memory delayed recall • Executive: Trail making Test part B minus Part A score	• Greater PWV was not associated with measures of cognitive function • Greater PP was associated with worse performance on the Logical Memory delayed recall test (β=−0.07; p<0.05)
Watson et al., 2011 [25]	The Cognitive Vitality Substusy (N=552), in the Health, Aging, and Body Composition Study, USA	73.1±2.7	Carotid-femoral PWV	• Global cognition: the Modified Mini Mental Status Exam (3MS) • Verbal learning and memory: The Buschke selective reminding test • Psychomotor speed: The boxes and Digit copying test • Perceptual speed: the Pattern and letter comparison test	• Greater PWV was associated with worse scores on tests assessing global function (β=−0.55; 95%CI=−0.91; −0.19), psychomotor speed (β=−1.59; 95%CI=−3.03; −0.15), and perceptual speed (β=−0.60; 95%CI= −0.98; −0.22).
Zhong et al., 2014 [30]	The Epidemiology of Hearing Loss Study, (N=1436), USA	43-84	Carotid-femoral PWV	• Global cognition: MMSE • Executive function, attention, and speed: Trail making tests A and B, Digit symbol substitution test • Memory: Rey Auditory Verbal learning test • Semantic memory: verbal fluency test	• High PWV, defined as >12 m/s, was associated with worse performance on the MMSE (β=−0.31; p=0.005), RAVLT (β=−1.10; p=0.01), and the composite score (β=−0.10; p=0.04)

Table 2

Studies of the longitudinal association between arterial stiffness and cognitive function

Publication	Cohort	Age (years)	Follow-up	Arterial stiffness measure	Cognitive tests assessed	Result
Benetos et al., 2012 [26]	PARTAGE study, (N=873), institutionalized patients from France and Italy	80+	1 year	Carotid-femoral PWV	• Global cognition: MMSE	• Greater tertile of PWV was associated with greater change in MMSE (PWV Tertile 1: Δ MMSE= −1.42±3.60; PWV Tertile 2: Δ MMSE= −1.78±4.08; PWV Tertile 3: Δ MMSE= −2.20±3.98); P<0.03
Poels et al., 2007 [23]	Rotterdam Study, (N=3714), Netherlands	55+	Average 5 years	Carotid-femoral PWV	• Global cognition: MMSE • Executive function: Letter digit substitution task, Stroop test, and word fluency test	• Greater PWV was not associated with greater odds of cognitive decline
Scuteri et al., 2007 [24]	From hospital, N=102, Italy	79±6	Median of 12 months (range: 10 to 32)	Carotid-femoral PWV	• Global cognition: MMSE	• Greater PWV was associated with greater annual decline in MMSE score (β=−0.736; p<0.001)
Scuteri et al., 2013 [43]	From hospital, N=105, Italy	77±5	Median of 15 months	Carotid-femoral PWV	• Global cognition: MMSE	• Having high PWV in the upper quartile was associated with worse MMSE score
Waldstein et al., 2008 [22]	Baltimore Longitudinal Study of Aging, N=1749 (PP analysis) and N=582 (PWV analysis), USA	57.1±17.2 (PP) 54.3±17.1 (PWV)	14 years	Carotid-femoral PWV, Pulse Pressure	• Global cognition: MMSE, and Blessed Information memory test • Attention and Concentration: Digit forward and backwards • Verbal learning and memory: California verbal learning test, and Boston naming test • Non-verbal memory: Benton visual retention test • Phonetic and semantic: letter and category fluency • Executive function, speed and mental flexibility: Trail making Tests A and B	• Greater PWV was associated with faster cognitive decline on the Blessed Information memory test, California verbal learning test, and the Benton visual retention test (all p-values <0.05) • Greater PP was associated with faster cognitive decline on the Blessed Information memory test, California verbal learning test, and the Benton visual retention test (all pvalues <0.05)
Watson et al., 2011 [25]	The Cognitive Vitality Substusy (N=552), in the Health, Aging, and Body Composition	73.1±2.7	6 years	Carotid-femoral PWV	• Global cognition: the Modified Mini Mental Status Exam (3MS)	• Greater PWV was associated with greater odds of cognitive decline in

Publication	Cohort	Age (years)	Follow-up	Arterial stiffness measure	Cognitive tests assessed	Result
	Study, USA				• Verbal learning and memory: The Buschke selective reminding test • Psychomotor speed: The boxes and Digit copying test • Perceptual speed: the pattern and letter comparison test	psychomotor speed (OR= 1.42; 95%CI=1.06; 1.90)
Zeki Al Hazzouri et al., 2013 [7]	Health, Aging, and Body Composition Study, (N=2,488), USA	74.2±2.9	9 years	Carotid-femoral PWV	• Global cognition: the Modified Mini Mental Status Exam (3MS)	• Greater PWV was associated with faster rate of cognitive decline. Annual cognitive decline by tertile of PWV: Low PWV tertile (β= −0.30; 95%CI=−0.37; −0.22); Middle PWV tertile (β=−0.46; 95%CI=−0.54; −0.39); High PWV tertile (β=−0.45; 95%CI=−0.53; −0.38) • Having middle or high PWV was associated with greater odds of cognitive impairment (decline of 5 or more points), compared to having low PWV (Middle PWV: OR=1.40; 95%CI=1.03; 1.92. High PWV: OR=1.59; 95%CI=1.16; 2.18)