Arterial Stiffness and Cognition Among Adults: A Systematic Review and Meta-Analysis of Observational and Longitudinal Studies

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***Background*—**To estimate the strength of the cross-sectional and longitudinal association between arterial stiffness, measured by pulse-wave velocity, and cognitive function, distinguishing between global cognition, executive functions, and memory and to examine the influence of demographic, clinical, and assessment characteristics on this relationship.

***Methods and Results*—**Systematic review of MEDLINE (via PubMed), Scopus, and WOS databases from their inception to March 2019, to identify cross-sectional and longitudinal studies on the association between pulse-wave velocity and cognitive domains (ie, global cognition, executive functions, and memory) among adult population. A total of 29 cross-sectional and 9 longitudinal studies support the negative relationship between arterial stiffness and cognitive function, including global cognition, executive function, and memory. Demographic, clinical, and assessment characteristics did not substantially modify the strength of this association.

***Conclusions*—**Evidence reveals a negative association between arterial stiffness, measured using pulse-wave velocity, and cognition, specifically executive function, memory, and global cognition. This association seems to be independent of demographic, clinical, and assessment characteristics. These results accumulate evidence supporting that pulse-wave velocity assessment could be a useful tool to identify individuals at high risk of cognitive decline or early stages of cognitive decline, to implement interventions aimed at slowing the progression to dementia. **(*J Am Heart Assoc*. 2020;9:e014621. DOI: 10.1161/JAHA.119.014621.)**

Key Words: cognitive impairment • executive function • global cognition • memory • pulse-wave velocity

Cognitive impairment is becoming an important health concern as the older population continuously grows worldwide.[1] The World Health Organization estimates that by 2050, 2 billion people will be aged >60 years and the number of people living with dementia will be 115.4 million.[2] As such, cognitive impairment is one of the major causes of disability among older people, deteriorating quality of life and producing physical, cognitive, and social disabilities.[3]

Some cardiovascular risk factors, such as hypertension, diabetes mellitus, hypercholesterolemia, smoking status, and adiposity, have been traditionally recognized as playing a primary role in the vascular pathogenesis of cognitive impairment and dementia.[4] In addition, previous research suggests that cerebral small-vessel disease is involved in the pathophysiological characteristics of cognitive decline, vascular dementia, and Alzheimer disease.[5] The cross talk between large and small arterial vessels produces a vicious retrofeeding cycle through which the action of mechanic, inflammatory, metabolic, epigenetic, and hemodynamic factors determines arterial dysfunction and decreases arterial distensibility.[6] Therefore, arterial stiffness could be considered as an indirect measure of small-vessel damage that serves to evaluate not only the quality of brain microcirculation but also the influence that systemic changes in large arteries can produce in microcirculation; thus, arterial stiffness could be the link between vascular health and cognitive decline.[7]

Pulse-wave velocity (PWV) is generally accepted as the most simple, noninvasive, robust, and reproducible method to quantify arterial stiffness.[7,8] PWV is an index closely related to vascular

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Accompanying Data S1 and Tables S1 through S6 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014621

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Clinical Perspective

What Is New?

- This systematic review and meta-analysis synthesizes the cross-sectional and longitudinal association between arterial stiffness, measured by pulse-wave velocity, and global cognition, executive functions, and memory.
- Our data confirm a negative cross-sectional and longitudinal association between pulse-wave velocity and executive function, memory, and global cognition, regardless of demographic, clinical, and assessment characteristics.

What Are the Clinical Implications?

- Our results claim for the usefulness of pulse-wave velocity assessment in the identification of individuals at high risk of cognitive decline or early stages of cognitive decline.

aging that when increased has been negatively associated with global cognition independently of traditional cardiovascular risk factors.[8–10] Although less studied, this association has also been observed for different cognitive function domains, such as executive functions and memory.[11–13]

Previous systematic reviews and meta-analyses[9,14,15] have examined the association between arterial stiffness and cognitive decline. However, the association between arterial stiffness and clinically relevant cognitive domains as well as the potential moderating effect of some variables on this relationship remain unclear. Thus, the aims of this systematic review and meta-analysis were to: (1) provide a pooled estimate of the strength of the cross-sectional association between arterial stiffness, measured by PWV, and cognitive function, distinguishing between global cognition, executive functions, and memory; (2) examine whether this association is confirmed by longitudinal studies; and (3) examine the influence of demographic (ie, age, sex, and body mass index [BMI]), clinical (ie, systolic blood pressure [SBP] and diastolic blood pressure [DBP]), and PWV characteristics (ie, type of measure and devices used to measure PWV) on the relationship between arterial stiffness and cognitive function.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews[16] and Meta-Analysis of Observational Studies in Epidemiology[17] statements and the Cochrane Collaboration Handbook.[18] The protocol for this systematic review and meta-analysis has been previously registered on PROSPERO: CRD42019121426. The authors declare that all supporting data are available within this article and that institutional review board approval and informed consent of patients were not required as the data used for this work have exclusively been extracted from published studies. In addition, all the included trials complied with the current ethical standards and the Declaration of Helsinki.

Data Sources and Searches

A literature search was performed on Medline (via PubMed), Web of Science, and Scopus to identify studies on the association between arterial stiffness, measured using PWV, and cognitive function among adult people, to March 25, 2019. The search strategy included the following terms: "central blood pressure," "arterial stiffness," "pulse-wave velocity," "PWV," "endothelial function," "cognition," "executive," "executive function," "cognitive control," "memory," "attention," "metacognition," "life skills," "goal setting," "problem solving," "self-regulation," "brain development," "brain health," "neural," "neuroelectric," "neurotrophic," "neurotrophin," and "BDNF." In addition, the reference lists of included studies were reviewed for any relevant study.

Study Selection

This systematic review includes studies on the relationship between arterial stiffness, as measured using PWV, and cognitive function among adults. Inclusion criteria were as follows: (1) participants: adults; (2) exposure: arterial stiffness measured through PWV; (3) outcome: cognitive function, including global cognition, executive function, and memory, measured using standardized tests; and (4) study design: cross-sectional and longitudinal studies including at least 100 participants.

Studies were excluded when: (1) they were focused on children or adolescents, (2) arterial stiffness was measured using indicators other than PWV, or (3) they were written in languages other than English, French, Portuguese, or Spanish.

Data Extraction and Quality Assessment

The main characteristics of the included studies were summarized in tables, including information on: (1) subject characteristics (ie, sample size; percentage of women; mean age, BMI, SBP, and DBP; and type of sample), (2) exposure (ie, type of PWV measured [carotid-femoral PWV {cfPWV}, brachial-ankle PWV {baPWV} or aortic PWV]), device used to measure PWV, and mean PWV, and (3) outcome information (ie, test used to measure cognitive function and cognitive domain measured).

The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to evaluate the risk of

bias.[19] This tool evaluates 14 criteria for longitudinal studies; for cross-sectional designs only, 11 were applied. Each criterion could be scored as "yes" when the study achieves the criterion or "no" when the study does not achieve the criterion. Criteria could be also scored as "not reported" when studies did not clearly report the required information.

Literature search, data extraction, and risk of bias assessment were independently performed by 2 researchers (C.A.-B. and I.C.-R.), and disagreements were solved by consensus or involving a third researcher (V.M.-V.).

Data Synthesis and Statistical Analysis

To perform the meta-analysis, measures of association between PWV and cognitive function were included in the analysis. Three cognitive domains were considered for the statistical analysis: (1) global cognition, (2) executive functions, and (3) memory. Separate analyses for unadjusted cross-sectional, adjusted cross-sectional, and longitudinal associations were conducted. Finally, data from studies reporting odds ratio or relative risk were narratively summarized.

Effect sizes (ESs) and 95% CIs were calculated for each observed correlation using Cohen's d index. A pooled ES was estimated for each cognitive domain using a random-effects model based on the Der Simonian and Laird method.[20] Fixed effects models were used when heterogeneity was not excessive.[21] Heterogeneity across studies was assessed using the I^2 statistic,[22] whose values were considered as follows: not important (0%–40%), moderate (30%–60%), substantial (50%–90%), and considerable (75%–100%). Moreover, the corresponding *P* values were also taken into account.[18] Finally, the Cochran's test was also used to evaluate the heterogeneity, being significative when $P<0.1$.[18]

Following similar procedures for longitudinal reports, we estimated the pooled ES for the association between the baseline PWV and the pre-post change in cognitive domains. In addition, when studies reported baseline associations between PWV and cognitive function, these reports were included in the cross-sectional pooled ES estimates.

Some methodological issues should be pointed out. When studies provided ≥2 measurements for the same cognitive domain, these measurements were combined to calculate a single pooled ES for the corresponding domain. For longitudinal and adjusted cross-sectional analyses, those including the largest number of covariates were considered. Finally, when studies reported mean value trends by groups or associations using regression models or correlation coefficients, ES values were calculated.

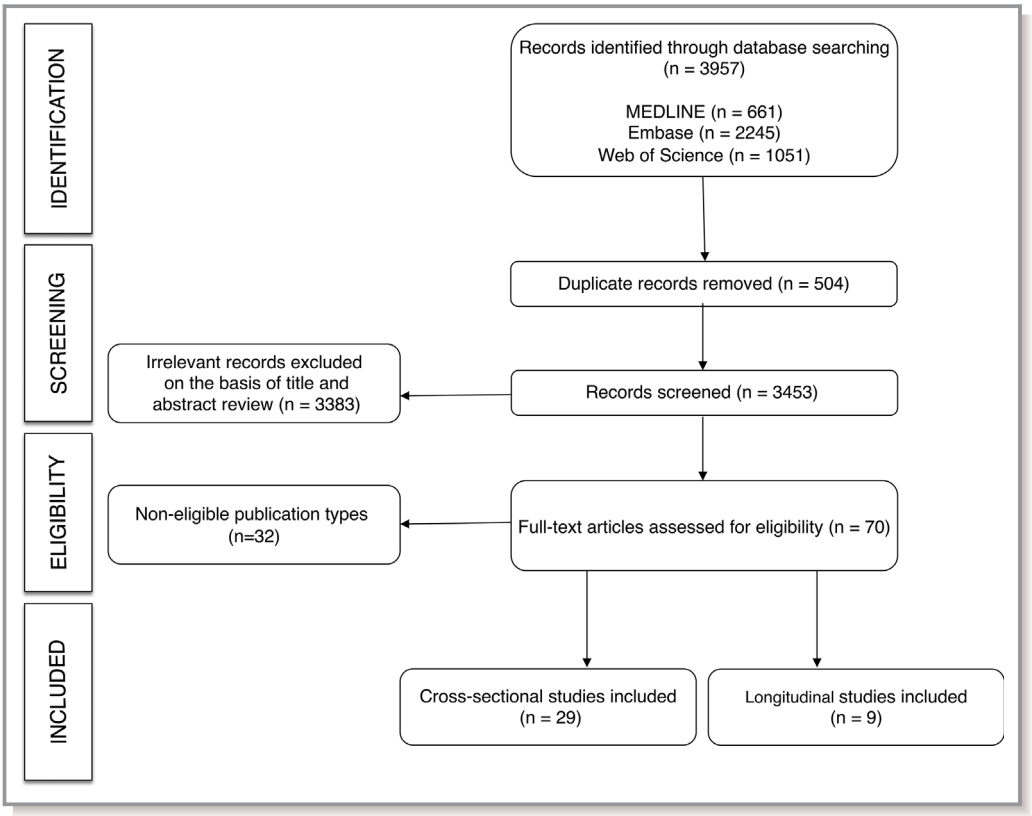

Figure 1. Preferred Reporting Items for Systematic Reviews flowchart.

Table 1. Characteristics of the Studies Included in the Systematic Review and Meta-Analysis on the Association Between Cognition Parameters and PWV

	Subjects Characteristics						Exposure			Outcome	
References	Women, n (%)	Age, y	BMI, kg/m^2	SBP, mm Hg	DBP, mm Hg	Type of Sample	Type of PWV	PWV Device	PWV Average, m/s	Cognitive Measurement	Cognitive Construct
Abbatecola et al, 2008[23]	140 (NR)	Normoalbuminuric: 78.0 (5.0) Microalbuminuric: 78.0 (4.0)	Normoalbuminuric: 27.4 (2.4) Microalbuminuric: 27.8 (2.2)	Normoalbuminuric: 135.0 (19.0) Microalbuminuric: 155.0 (20.0)	Normoalbuminuric: 83.0 (8.0) Microalbuminuric: 88.0 (9.0)	Impaired glucose tolerance	cfPWV	Pulse trace 6000 Micro Medical	Normoalbuminuric: 11.4 (2.1) Microalbuminuric: 13.7 (3.1)	MMSE Trail Making Tests (A and B) Verbal Fluency Test Wechsler Adult Intelligence Scale-Revised Digit Span	Global cognitive function Executive and attention function Memory Mental tracking
Al Hazzouri et al, 2015[24]	2488 (52.3)	74.2 (2.9)	27.4	NR	NR	General population	cfPWV	Model 810-a	NR	3MS	Global cognitive function
Angermann et al, 2017[25]	201 (29.9)	64.5 (15.1)	NR	123.8 (16.6)	74.7 (12.5)	Patients undergoing hemodialysis	cfPWV	Mobil-O-Graph	9.4 (2.2)	Montreal Cognitive Assessment	Global cognitive function
Benetos et al, 2012[26]	873 (79.0)	88.0 (5.0)	25.8 (4.5)	138.0 (17.0)	73.0 (9.0)	General population	cfPWV	PulsePen	14.4 (5.0)	MMSE	Global cognitive function
Cooper et al, 2016[11]	1820 (60.0)	80.0 (5.0)	26.5 (3.9)	144.0 (22.0)	64.0 (10.0)	General population	cfPWV	NIHem WF	13.6 (4.6)	California Verbal Learning Test Digit Symbol Substitution Test, Figure Comparison, and Stroop Test (parts I and II) Digits Backward and the Stroop Test (part III)	Immediate and delayed recall Processing speed Executive function
Elias et al, 2009[27]	409 (62.3)	61.3 (12.8)	29.3 (6.0)	128.9 (19.7)	77.5 (10.1)	General population	cfPWV	SphygmoCor	10.2 (2.8)	Block Design, Object Assembly, Visual Reproductions Immediate and Delayed, Hooper Visual Organization Test, Matrix Reasoning Trail Making Tests (A and B), Digit Symbol Substitution, Symbol Search Logical Memory Immediate and Delayed, Hopkins Verbal Learning Test Digit Span Forward and Backward, Letter-Number Sequence, Controlled Oral Word Associations	Visual-spatial organization and memory Scanning and tracking Verbal episodic memory Working memory
Fukuhara et al, 2006[28]	203 (42.9)	85.0	22.7 (0.2)	144.3 (1.7)	78.8 (1.0)	General population	baPWV	VaSera VS-1000	23.7 (0.4)	MMSE	Global cognitive function

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Table 1. Continued

References	Subjects Characteristics						Exposure			Outcome	
	Women, n (%)	Age, y	BMI, kg/m^2	SBP, mm Hg	DBP, mm Hg	Type of Sample	Type of PWV	PWV Device	PWV Average, m/s	Cognitive Measurement	Cognitive Construct
Geijselaers et al, 2016[29]	396 (54.6)	60 (8)	27.2 (4.4)	128 (14)	76 (7)	General population	cfPWV	SphygmoCor	8.9 (2.1)	Verbal Learning Test Stroop Color Word Test (parts I and II), the Concept Shifting Test Part A and B, and the Letter-Digit Substitution Test Stroop Color Word Test (part III) and the Concept Shifting Test Part C, Letter-Digit Substitution test	Free recall memory Processing speed Executive function and attention
Hajjar et al, 2016[12]	591 (68.0)	48.8 (9.7)	28.0 (6.6)	121.0 (24.3)	77.0 (12.2)	General population	cfPWV	SphygmoCor	7.2 (1.5)	Mental flexibility SPOTING the symbol Digit Symbol Substitution Test Digit Span Forward Executive Function Test Focused Attention Sustained Attention Delayed Memory Recall Visual Spatial Memory Visual Spatial Short-Term Recall Digit Span Backwards	Executive function Memory Working memory
Hanon et al, 2005[30]	308 (64.3)	NCF: 75.0 (8.0) MCI: 77.0 (8.0) AD: 80.0 (7.0) VaD: 81.0 (7.0)	NCF: 24.4 (4.0) MCI: 25.0 (4.0) AD: 24.0 (4.0) VaD: 24.0 (4.0)	NCF: 139.0 (18.0) MCI: 142.0 (17.0) AD: 145.0 (20.0) VaD: 159.0 (21.0)	NCF: 79.0 (11.0) MCI: 80.0 (9.0) AD: 81.0 (12.0) VaD: 82.0 (13.0)	Subjects with complaint of memory loss	cfPWV	Complior	NCF: 11.5 (2.0) MCI: 12.6 (2.6) AD: 13.3 (2.9) VaD: 15.2 (3.9)	MMSE Cognitive Efficiency Profile	Global cognitive function Cognitive efficiency profile
Karasavvidou et al, 2018[31]	151 (33.6)	57.08 (13.7)	28.2 (5.1)	137.2 (18.1)–142.8 (12.8)	77.4 (11.3)–84.7 (9.8)	Patients with kidney disease	cfPWV	SphygmoCor	6.1 (1.9)–6.9 (2.3)	MMSE	Global cognitive function
Kim et al, 2009[32]	370 (51.6)	55.2 (7.3)	24.4 (5.1)	130.8 (16.4)	80.4 (9.3)	General population	baPWV	Plethysmographic device	15.3 (2.9)	Korean version of the mini-mental state examination (K-MMSE)	Global cognitive function
Kim et al, 2017[33]	333 (42.0)	55.0 (13.0)	NR	NR	NR	Patients undergoing hemodialysis	cfPWV	SphygmoCor	10.0 (7.9–12.5)	Trail Making Tests (A and B) 3MS	Executive function Global cognitive function
Lamballais et al, 2018[34]	5187 (42.9)	58.8 (7.3)–63.6 (5.7)	26.8 (3.8)–27.4 (4.3)	130 (18)–150 (20)	80 (10)–86 (10)	General population	cfPWV	Complior	9.1 (1.6)–13.0 (2.8)	Color-Word Interference Stroop Task Letter Digit Substitution Test Verbal Fluency Test Delayed Recall Purdue Pegboard Test	G-factor

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Table 1. Continued

References	Subjects Characteristics						Exposure			Outcome	
	Women, n (%)	Age, y	BMI, kg/m^2	SBP, mm Hg	DBP, mm Hg	Type of Sample	Type of PWV	PWV Device	PWV Average, m/s	Cognitive Measurement	Cognitive Construct
Lee et al, 2014[35]	102 (29.0)	61.0 (9.0)	24.0 (4.0)	124.0 (13.0)	77.0 (9.0)	Stroke patients	cfPWV	SphygmoCor	10.0 (2.0)	K-MMSE	Global cognitive function
Lim et al, 2016[13]	463 (43.2)	MMSE participants: 63.0 (6.1) Neurocognitive domain test participants: 64.2 (6.4)	MMSE participants: 25.0 (4.1) Neurocognitive domain test participants: 24.6 (3.5)	NR	NR	General population	cfPWV	SphygmoCor	MMSE participants: 5.0 (2.6–14.1) Neurocognitive domain test participants: 4.9 (3.0–13.0)	MMSE Digit Span-Forward Color Trails Test 1 Rey Auditory Verbal Learning Test, Story Memory and Recall Boston Naming Test Brief Visuospatial Memory Test-Revised Digit Span- Backward Block Design, Color Trails Test 2 Categorical Verbal Fluency	Global cognitive function Attention Verbal memory Language function Visuospatial ability Executive function
Mitchell et al, 2011[36]	668 (56.6)	Women: 75.0 (4.0) Men: 76.0 (4.0)	Women: 27.0 (4.0) Men: 27.0 (4.0)	Women: 141.0 (20.0) Men: 137.0 (18.0)	Women: 67.0 (9.0) Men: 67.0 (10.0)	General population	cfPWV	NIHem WF	Women: 12.2 (3.7) Men: 13.4 (4.4)	California Verbal Learning Test Digits Forward Digit Symbol Substitution Test Figure Comparison Stroop Test (parts I and II) Digits Backwards Cambridge Neuropsychological Test Automated Battery Spatial Working Memory Stroop Test (part III) MMSE	Memory Processing speed Executive function Global cognitive function
Muela et al, 2018[37]	211 (55.0)	Normotension: 52.2 (13.9) Hypertension stage 1: 52.1 (13.0) Hypertension stage 2: 52.3 (10.1)	Normotension: 26.7 (4.2) Hypertension stage 1: 28.5 (4.6) Hypertension stage 2: 30.1 (4.6)	Normotension: 121.9 (8.3) Hypertension stage 1: 135.0 (13.5) Hypertension stage 2: 147.5 (26.1)	Normotension: 76.5 (6.9) Hypertension stage 1: 83.1 (9.9) Hypertension stage 2: 90.3 (14.5)	Patients with hypertension	cfPWV	Complior	Normotension: 7.5 (1.4) Hypertension stage 1: 7.9 (1.2) Hypertension stage 2: 7.9 (1.2)	MMSE Montreal Cognitive Assessment Boston Naming Test Rey-Osterrieth Complex Delayed Recall Semantic Verbal Fluency animal category Backward Digit Span Test Phonological Verbal Fluency Trail Making Test B Forward Digit Span Test Trail Making Test A Clock Drawing Test Rey Auditory Verbal	Global cognitive function Language function Episodic memory Executive function Attention Visuospatial abilities Processing speed

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Table 1. Continued

References	Subjects Characteristics						Exposure			Outcome	
	Women, n (%)	Age, y	BMI, kg/m^2	SBP, mm Hg	DBP, mm Hg	Type of Sample	Type of PWV	PWV Device	PWV Average, m/s	Cognitive Measurement	Cognitive Construct
										Learning Test Digit Symbols Substitution Test	
Muller et al, 2007[38]	396 (0.0)	No CVD: 54.5 (10.3) Subclinical CVD: 66.8 (8.1) Prevalent CVD: 67.7 (8.8)	No CVD: 25.9 (0.3) Subclinical CVD: 26.5 (0.3) Prevalent CVD: 27.3 (0.5)	No CVD: 134.2 (1.3) Subclinical CVD: 145.5 (1.7) Prevalent CVD: 140.2 (2.5)	NR	General population	cfPWV	SphygmoCor Acuson Aspen	No CVD: 8.5 (0.2) Subclinical CVD: 10.7 (0.2) Prevalent CVD: 10.2 (0.3)	MMSE Rey Auditory Verbal Learning Test Doors Test Digit Span Test List of nouns Digit Symbol Substitution Test Trail Making Test (A and B) Dutch Adult Reading Test	Global cognitive function Verbal episodic memory Memory Visual memory Short-term memory and working memory Verbal fluency Cognitive and perceptual speed Attention and mental flexibility IQ
Nilsson et al, 2014[39]	2637 (60.8)	72.1 (5.6)	NR	135.6 (17.1)	75.6 (8.7)	General population	cfPWV	SphygmoCor	10.5 (2.5)	MMSE Quick test of cognitive speed (AQT)	Global cognitive function Perceptual and cognitive speed
Palta et al, 2019[40]	3703 (59.3)	75.2.(5.0)	27.8 (4.4)	129.9 (17.2)	NR	General population	cfPWV	VP-1000 Plus	NR	Delayed word recall Logical memory Incidental learning Digit Symbol Substitution Test Trail Making Test Digit Span Backwards Semantic and phonemic fluency Boston Naming Test	Memory Executive function/ processing speed Language function
Pase et al, 2016[41]	3207 (53.1)	46.0 (9.0)	NR	116.0 (14.0)	74.0 (9.0)	General population	cfPWV	NIHem WF	6.8 (6.1–7.7)	Trail Making Test (A and B) Victoria Stroop interference task Logical Memory delayed Visual Reproductions delayed Hooper visual organization test (VOT) Digit Span Forward and Backward	Processing speed and executive function Long-term storage and retrieval Visual processing Working memory
Poels et al, 2007[42]	3714 (57.7)	72.0 (6.7)	26.8 (4.0)	NR	NR	General population	cfPWV	Complior	13.5 (3.0)	MMSE Letter-Digit Substitution Task Stroop Test Word Fluency Test	Global cognitive function Executive function

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Table 1. Continued

References	Subjects Characteristics						Exposure			Outcome	
	Women, n (%)	Age, y	BMI, kg/m^2	SBP, mm Hg	DBP, mm Hg	Type of Sample	Type of PWV	PWV Device	PWV Average, m/s	Cognitive Measurement	Cognitive Construct
Ryu et al, 2017[43]	123 (70.7)	PD-NC: 67.0 (9.6) PD-MCI: 70.1 (6.9) PD-D: 73.9 (8.8) DLB: 77.4 (4.9) AD: 76.2 (9.2)	NR	NR	NR	Patients with Parkinson disease and Lewy body disorders	baPWV	VP 1000	PD-NC: 15.3 (3.0) PD-MCI: 18.7 (4.7) PD-D: 21.4 (4.1) DLB: 21.2 (7.0) AD: 20.4 (5.1)	MMSE Seoul Neuropsychological Screening Battery: Korean-Boston Naming Test and Digit Span Test Rey Complex Figure Test Calculation test Seoul Verbal Learning Test Control Oral Word Association Test	Global cognitive function Language function Calculation Visuospatial function and memory Memory
Scuteri et al, 2007[44]	102 (70.2)	79.0 (6.0)	25.7 (4.1)	135.9 (19.2)	78.5 (11.9)	Patients with complaints of memory loss	cfPWV	Complior	13.5 (2.2)	MMSE	Global cognitive function
Singer et al, 2013[45]	319 (51.7)	79.6 (4.2)	26.7 (4.1)	140.9 (19.3)	NR	General population	cfPWV	SphygmoCor	11.2 (2.4)	Digit Symbol Coding and Trail Making Test A Logical Memory Story A (delayed) Rey Auditory Visual Verbal Learning Test Benton Visual Retention Test Animal Naming and the 30-item Boston Naming Test Phonemic Fluency (FAS) Trail Making Test B Stroop Test Block Design	Processing speed Memory Language function Executive function Visuospatial ability
Triantafyllidi et al, 2009[46]	110 (47.0)	56.1 (10.0)	29.7 (4.0)	147.0 (17.0)	88.0 (10.0)	Patients with essential hypertension	cfPWV	Complior SP	10.1 (8.8, 11.2)	MMSE	Global cognitive function
Tsao et al, 2013[47]	1587 (55.0)	61.0 (9.0)	NR	126.0 (19.0)	74.0 (10.0)	General population	cfPWV	SPT-301	9.0 (7.6, 11.0)	Logical memory delayed Trail Making Test (A and B)	Memory Executive function
Tsao et al, 2016[48]	1223 (56.0)	62.0 (9.0)	NR	125.0 (18.0)	NR	General population	cfPWV	SPT-301	9.0 (7.6, 10.9)	Trail Making Test (A and B) Similarities test	Executive function Abstract reasoning

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Table 1. Continued

References	Subjects Characteristics					Exposure			Outcome	
	Women, n (%)	Age, y	BMI, kg/m^2	SBP, mm Hg	DBP, mm Hg	Type of Sample	Type of PWV	PWV Device	PWV Average, m/s	Cognitive Measurement	Cognitive Construct
Watson et al, 2011[49]	552 (52.5)	73.1 (2.7)	27.0 (4.6)	NR	NR	General population	aPWV	Doppler-recorded model 810A	8.9 (3.9)	3MS Buschke Selective Reminding Test Boxes and Digit Copying Pattern and Letter Comparison	Global cognitive function Verbal learning and memory Psychomotor speed Perceptual speed
Zhong et al, 2014[50]	1394 (57.2)	No cfPWV >12 m/s: 73.3 (6.4) cfPWV >12 m/s: 78.4 (7.5)	No cfPWV >12 m/s: 30.7 (5.7) cfPWV >12 m/s: 30.0 (5.5)	NR	NR	General population	cfPWV	Complior SP	11 (3.6)	MMSE Trail Making Test (A and B) Digit Symbol Substitution Test Rey Auditory Verbal Learning Test Verbal Fluency Test	Global cognitive function Executive function, attention, and speed Psychomotor speed and sustained attention Memory Language

3MS indicates modified MMSE; aPWV, aortic PWV; AD, Alzheimer disease; baPWV, brachial-ankle PWV; BMI, body mass index; cfPWV, carotid-femoral PWV; CVD, cardiovascular disease; DBP, diastolic blood pressure; DLB, dementia with Lewy bodies; IQ, intelligence quotient; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NCF, normal cognitive function; NR, not reported; PD-D, Parkinson disease with dementia; PD-MCI, Parkinson disease with MCI; PD-NC, Parkinson disease with normal cognition; PWV, pulse-wave velocity; SBP, systolic blood pressure; VaD, vascular dementia.

Sensitivity analyses were performed excluding studies one by one from the pooled estimates, to evaluate whether any particular study modified the original summary estimate. Meta-regressions were calculated on the basis of sample characteristics: percentage of women and mean age, BMI, SBP, and DBP.

Subgroup analyses were performed by: (1) type of sample identified, considering general population or specific disease group; (2) type of PWV measured (baPWV or cfPWV), and (3) device used to measure PWV, distinguishing between SphygmoCor, Complior, and others (including Pulse Trace 6000 Micro Medical, model 810-a, Mobil-O-Graph, PulsePen, NIHem WF, VaSera VS-1000, plethysmographic device, SPT-301, and Doppler-recorded model 810A). Finally, publication bias was estimated using Egger's test.

Results

Systematic Review

The search retrieved 3957 studies, from which 29 cross-sectional studies* and 9 longitudinal studies† reported data on the association between arterial stiffness and cognition (Figure 1). Studies involved 43 115 participants (Tables 1 and 2). The list of the excluded studies is available in Data S1.

For participants' characteristics: (1) 12 studies reported data from specific disease populations; (2) mean age ranged from 46.0 to 85.0 years; (3) mean BMI ranged from 22.7 to 30.2 kg/m^2; (4) mean SBP ranged from 116.0 to 159.0 mm Hg; and (5) mean DBP ranged from 64.0 to 90.3 mm Hg.

PWV was measured using cfPWV procedures in all studies, but 4 that used baPWV and 1 that used aortic PWV. The reported mean PWV ranged from 4.9 to 6.9 m/s for cfPWV and from 15.3 to 23.7 for baPWV. The devices used to measure PWV varied across studies, although SphygmoCor and Complior were the most widely used devices.

The tests used to measure cognitive function aimed to measure global cognition, executive function, memory, language, attention, processing speed, and visuospatial ability.

Meta-Analysis

The unadjusted pooled ES values for the cross-sectional associations were −0.53 (95% CI, −0.67 to −0.39) for global cognition, −0.35 (95% CI, −0.50 to −0.19) for executive function, and −0.39 (95% CI, −0.70 to −0.09) for memory. The adjusted pooled ES values were −0.21 (95% CI, −0.30 to −0.11) for global cognition, −0.08 (95% CI, −0.14 to −0.03) for executive function, and −0.13 (95% CI, −0.20 to −0.05) for memory (Figures 2 and 3).

*References 11, 13, 23, 25, 27–32, 34–39, 41, 43, 45–47, 50–57.
†References 12, 24, 26, 33, 40, 42, 44, 48, 49.

Table 2. Characteristics of the Studies Included in the Systematic Review and Meta-Analysis on the Association Between Cognition Parameters and PWV for Studies Reporting OR and RR

	Subjects Characteristics						Exposure			Outcome	
References	Women, n (%)	Age, y	BMI, kg/m^2	SBP, mm Hg	DBP, mm Hg	Type of Sample	Type of PWV	PWV Device	PWV Average	Cognitive Measurement	Cognitive Construct
Fujiwara et al, 2005[51]	352 (61.1)	MMSE <24: 75.0 (4.6) MMSE >24: 76.9 (5.6)	MMSE <24: 22.8 (3.3) MMSE >24: 23.2 (3.2)	MMSE <24: 155.2 (20.3) MMSE >24: 147.2 (22.0)	MMSE <24: 84.8 (10.1) MMSE >24: 84.5 (11.0)	General population	baPWV	AT-Form	NR	MMSE	Global cognitive function
Kearney-Schwartz et al, 2009[52]	198 (52.0)	69.3 (6.2)	27.8 (4.3)	129.0 (12.0)	75.0 (9.0)	Hypertensive patients with subjective memory complains	cfPWV	Complior IOTEC	NR	Cognitive Difficulties Scale of McNair MMSE Grober-Buschke Test Benton Visual Retention Test Praxies scale Verbal Fluency Test	Global cognitive function Immediate and delayed memory and language Visuoperceptual and visuospatial Praxies Executive function and long-term verbal memory
Meyer et al, 2017[53]	4461 (58.8)	White normal: 75.2 (4.9) White MCI: 76.8 (5.2) White dementia: 78.7 (5.1) Black normal: 74.0 (4.7) Black MCI: 75.8 (5.1) Black dementia: 79.4 (4.5)	White normal: 27.7 (4.4) White MCI: 27.6 (4.4) White dementia: 26.6 (4.3) Black normal: 29.4 (4.8) Black MCI: 29.1 (4.8) Black dementia: 26.4 (4.8)	White normal: 128.5 (17.0) White MCI: 130.6 (18.3) White dementia: 133.3 (17.4) Black normal: 133.3 (18.0) Black MCI: 135.2 (18.8) Black dementia: 135.6 (19.1)	White normal: 65.7 (10.1) White MCI: 65.1 (10.7) White dementia: 65.1 (9.6) Black normal: 70.0 (10.1) Black MCI: 69.2 (10.9) Black dementia: 68.7 (10.7)	General population	cfPWV	VP-1000 Plus	NR	Digit Symbol Substitution Test Word recall task Word Fluency Test scores	Global cognitive function memory
Nilsson et al, 2017[54]	3056 (60.5)	No dementia: 71.8 (5.5) Prevalent dementia: 76.3 (4.7) Incident dementia: 75.8 (4.7)	NR	No dementia: 135.6 (17.1) Prevalent dementia: 136.5 (18.8) Incident dementia: 137.8 (17.9)	No dementia: 75.7 (8.7) Prevalent dementia: 75.6 (12.3) Incident dementia: 74.6 (8.6)	General population	cfPWV	SphygmoCor	No dementia: 10.5 (2.4) Prevalent dementia: 11.2 (2.6) Incident dementia: 11.3 (2.7)	MMSE AQT Color-Form	Global cognitive function
Sugawara et al, 2010[55]	388 (64.2)	Poor cognition: 70.1 (4.9) Control: 68.3 (5.6)	Poor cognition: 23.5 (3.3) Control: 23.3 (2.9)	Poor cognition: 137.6 (17.8) Control: 136.8 (17.3)	NR	General population	baPWV	Form PWV/ABI	Poor cognition: 18.4 (4.1) Control: 17.4 (3.0)	MMSE	Global cognitive function
Taniguchi et al, 2015[56]	526 (57.8)	71.7 (5.6)	Cognitive decline: 23.3 (2.9) No cognitive decline: 23.3 (3.3)	Cognitive decline: 133.0 (20.0) No cognitive decline: 128.0 (18.0)	Cognitive decline: 77.0 (11.0) No cognitive decline: 75.0 (11.0)	General population	baPWV	BP-203 RPE III	Cognitive decline: 19.3 (3.8) No cognitive decline: 17.5 (3.5)	MMSE	Global cognitive function

Continued

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Table 2. Continued

References	Subjects Characteristics						Exposure			Outcome	
	Women, n (%)	Age, y	BMI, kg/m^2	SBP, mm Hg	DBP, mm Hg	Type of Sample	Type of PWV	PWV Device	PWV Average	Cognitive Measurement	Cognitive Construct
Tuttolomondo et al, 2017[57]	153 (42.5)	Subjects with diabetic foot: 61.6 (10.1) Diabetic subjects without diabetic foot: 60.6 (12.5) Healthy controls: 63.0 (13.9)	Subjects with diabetic foot: 30.2 (6.4) Diabetic subjects without diabetic foot: 29.9 (4.5) Healthy controls: 25.1 (4.3)	Subjects with diabetic foot: 135.0 (21.8) Diabetic subjects without diabetic foot: 124.5 (16.8) Healthy controls: 116.3 (13.4)	Subjects with diabetic foot: 67.9 (10.7) Diabetic subjects without diabetic foot: 70.9 (11.2) Healthy controls: 71.3 (12.7)	Patients with type 2 diabetes mellitus	cfPWV	SphygmoCor	Subjects with diabetic foot: 14.3 (3.8) Diabetic subjects without diabetic foot: 11.9 (2.6) Healthy controls: 9.2 (1.9)	MMSE	Global cognitive function

baPWV indicates brachial-ankle PWV; BMI, body mass index; cfPWV, carotid-femoral PWV; DBP, diastolic blood pressure; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NR, not reported; OR, odds ratio; RR, relative risk; PWV, pulse-wave velocity; SBP, systolic blood pressure.

The pooled ES values for the longitudinal association of PWV and global cognition, executive function, and memory were −0.21 (95% CI, −0.36 to −0.06), −0.12 (95% CI, −0.22 to −0.02), and −0.05 (95% CI, −0.12 to 0.03), respectively (Figure 4).

Sensitivity analysis

Sensitivity analysis showed that: (1) for the unadjusted analysis, pooled ES for memory was modified after excluding Muela et al[37] study; (2) for the adjusted analysis, pooled ES for memory was modified after excluding Palta et al[40] study; and (3) the longitudinal pooled ES for executive functions was modified after removing 2 studies (Hajjar et al[12] and Tsao et al[48]) and for memory after removing the 3 studies included (Hajjar et al,[12] Kim et al,[33] and Poels et al[42]) (Tables S1 through S3).

Subgroup analyses and meta-regressions

Subgroup analyses by type of sample, type of PWV (ie, cfPWV, baPWV, and aortic PWV), and type of device (ie, SphygmoCor, Complior, and others) are displayed in Table S4. Pooled ES values were not substantially different in any of the subgroup analyses.

Meta-regressions with longitudinal, unadjusted, and adjusted cross-sectional analyses showed that none any of the considered variables (ie, percentage of women and mean age, BMI, SBP, and DBP) influences the relationship between arterial stiffness and cognitive function (Table S5).

Publication Bias

Publication bias, evaluated by Egger's test and funnel plot asymmetry, was found in the unadjusted cross-sectional analysis for global cognition (P=0.097) and in the adjusted cross-sectional analysis for memory (P=0.035).

Risk of Bias

Cross-sectional studies scored between 4 and 9 points, and longitudinal studies scored between 8 and 12 points. The 4 criteria in which most articles lacked information were: (1) sample size justification, power description, or variance; (2) whether the measurement of the exposure of interest precedes that of the outcome; (3) whether the outcome assessors were blinded to the exposure status of participants; and (4) whether the participation rate of eligible people was at least 50% (Table S6).

Discussion

The relationship between arterial stiffness and cognition has been repeatedly reported, but mostly always has analyzed

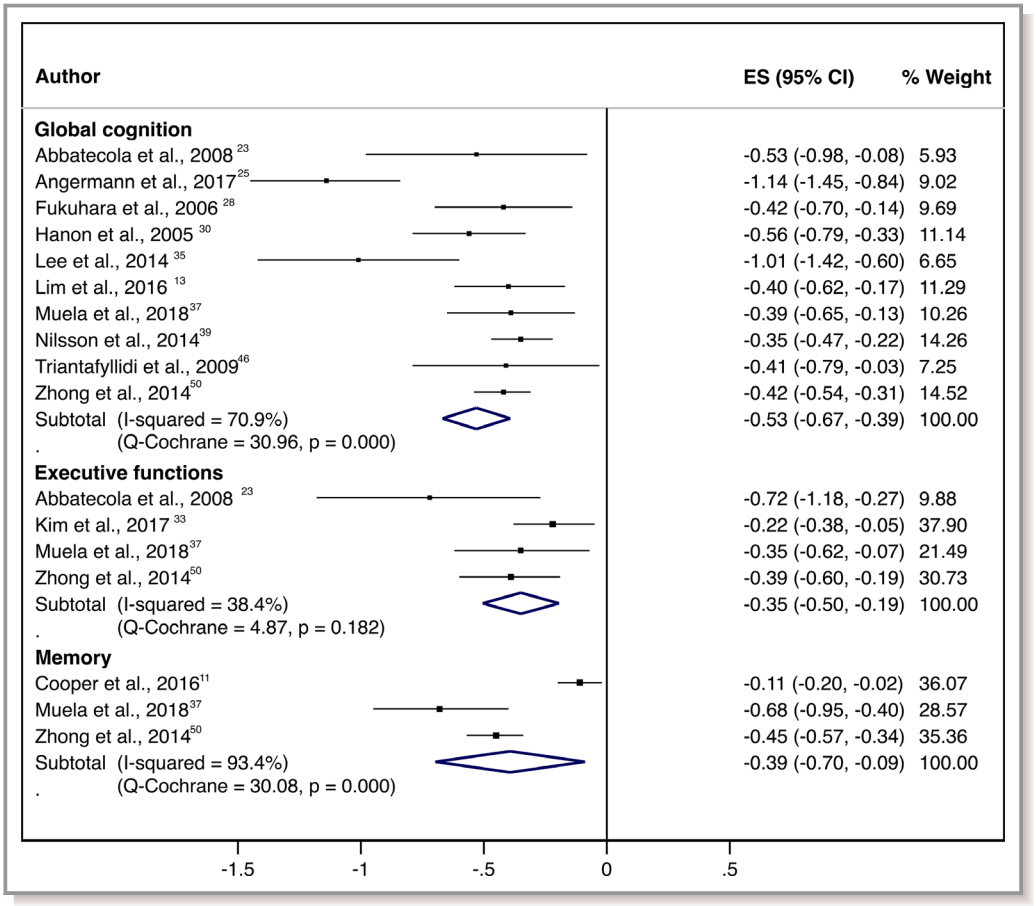

Figure 2. Forest plot for the unadjusted cross-sectional association between arterial stiffness, measured by pulse-wave velocity, and cognitive function domains. ES indicates effect size.

cognition as a dimensionless construct. To our knowledge, this is the first meta-synthesis elucidating this relationship, distinguishing between the several domains that integrate the cognitive function construct. Our results support the negative relationship between arterial stiffness with each cognitive domain, including global cognition, executive function, and memory. Furthermore, analyses of longitudinal studies confirm this negative association. Finally, demographic (age, sex, and type of sample), clinical (BMI, SBP, DBP, or PWV), and assessment characteristics (type of measure and type of device) did not substantially modify the strength of this association.

Executive function has been defined as one of the cognitive domains primarily affected by vascular aging.[39] In addition, global cognition and memory are closely related to both vascular aging and arterial stiffness, and it is clinically relevant to measure cognitive decline and memory loss.[32,58] Although some tests, such as the Mini-Mental State Examination, lack sensitivity to reflect small cognitive changes, the results of our cross-sectional meta-analyses are consistent with previous findings, and confirm global cognition and memory as specific cognitive functions negatively associated with arterial stiffness.[9,14]

Despite the scarcity of longitudinal studies included in each specific cognitive function, the general observed effect suggests that arterial stiffness contributes to deteriorate global cognition and executive function. Thus, these findings indicate that interventions aimed to reduce arterial stiffness could help to delay or prevent cognitive impairment.[59] Loss of memory is one of the most important reasons for consultations among people experiencing cognitive decline.[60] However, more longitudinal research is needed to further elucidate on the potential effects and mechanisms of arterial stiffness on memory.

The negative association between arterial stiffness and cognitive function was maintained after controlling for covariates, such as age, sex, educational level, depression scale score, or cardiovascular risk factors, related to cognitive decline and vascular aging. Moreover, the consistency of these associations was strengthened by the findings from longitudinal studies, regardless of the duration of follow-up.[61] Cardiovascular risk factors, such as diabetes mellitus, hypertension, or smoking, that influence the relationship between cognitive function and arterial stiffness were also considered in some included studies.[14] Finally, some studies accounted for additional factors not usually studied, such as

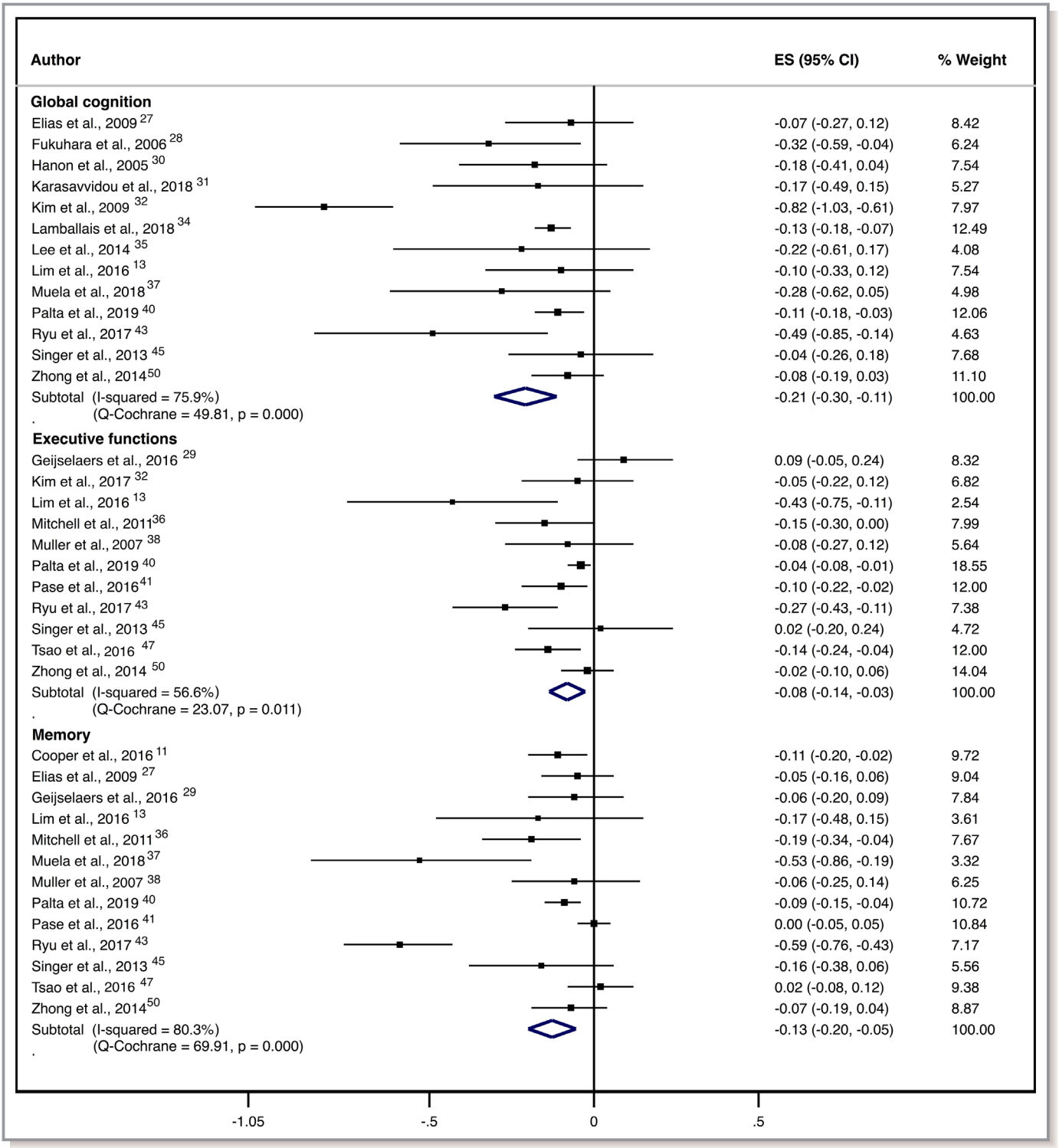

Figure 3. Forest plot for the adjusted cross-sectional association between arterial stiffness, measured by pulse-wave velocity, and cognitive function domains. ES indicates effect size.

apolipoprotein E 4 status, intracranial volume, estimated glomerular filtration rate, or minutes of leisure-time physical activity. Our findings indicate that the association between arterial stiffness and cognitive function is not confounded by these covariates. However, individual subclinical cardiovascular health factors could partially explain the present results.[62]

Arterial stiffness has been associated with brain damage and cognitive decline through several mechanisms. First, it has

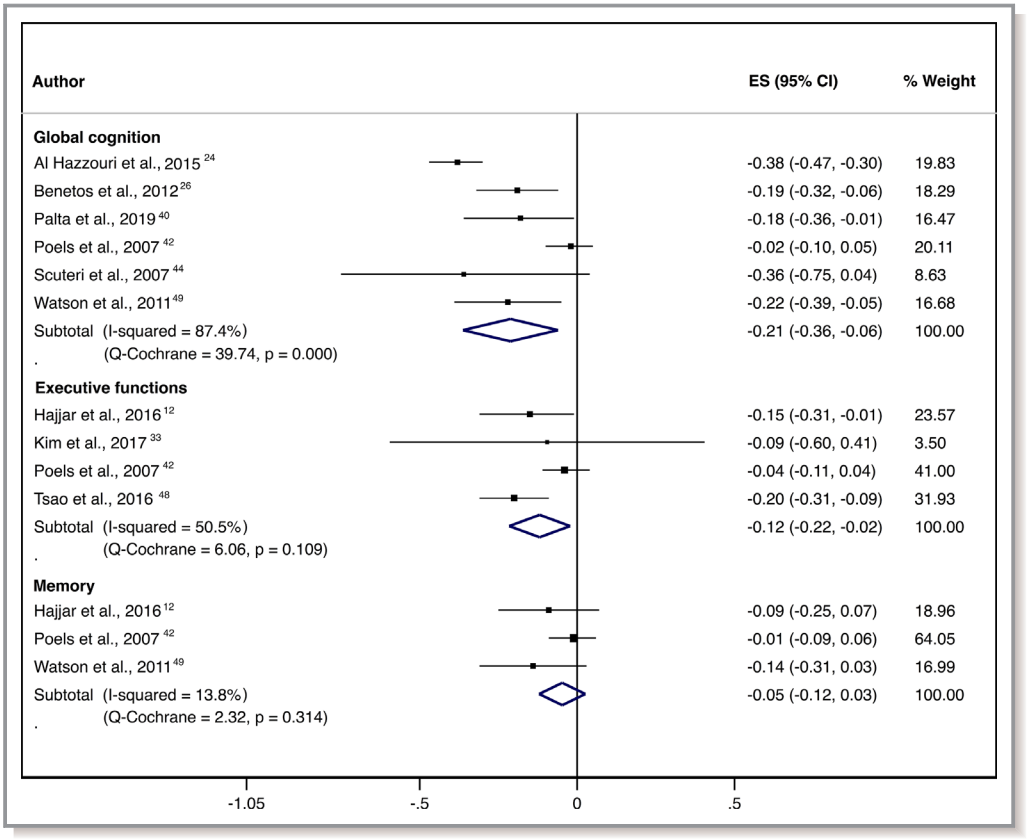

Figure 4. Forest plot for the longitudinal association between arterial stiffness, measured by pulse-wave velocity, and cognitive function domains. ES indicates effect size.

been proposed that cerebral small vessels offer low resistance to the high-pressure fluctuations from large arteries, and this flow transmission could damage small vessels, resulting in cognitive function decline.[63] Second, small vessels tend to progressively reduce their diameter to counteract changes in pulse pressure. This strategy increases microvascular resistance and, therefore, may result in cognitive damage.[64] Finally, some genetic factors, such as increased b-amyloid levels, mediated by the presence of the apolipoprotein E ε4 allele may induce vascular damage and cognitive decline.[65,66]

The results from this study confirm that arterial stiffness, measured by PWV, is a predictor of cognitive decline. Furthermore, this study shows that this association is independent of specific demographic and PWV characteristics. PWV is a low-cost, accurate, and easy method to determine arterial stiffness and, therefore, vascular aging.[14,62,67] Tools for early cognitive decline detection may be relevant from a global and public health perspective, given that the onset of cognitive decline at early ages is associated with higher rates of progression to dementia.[59,68] Thus, PWV assessment could be included as a routine examination in adults at high risk for cognitive decline. Therefore, hemodynamic measurements, such as PWV, should be included in the prevention and control indexes for healthy adults at risk of cardiovascular outcomes and cognitive decline. However, further studies using a neuroimaging approach are needed to overcome the limitations of the research published until now, such as small sample sizes, different covariates adjusted in the analysis, and short follow-up times.

Some limitations of this systematic review and meta-analysis may make us consider these findings with caution. First, there are limitations from meta-analysis design, such as publication bias and selection bias. Additional sources of bias could be: (1) the pooled ES was not estimated using the original data, but those reported in the included articles, (2) the methods and tools used to measure cognitive function widely varied across the included studies, (3) substantial heterogeneity was found among the included studies, (4) publication bias was found for some of the observed outcomes, (5) a cause-effect could not be inferred from the cross-sectional analyses, and (6) language restrictions may have limited the number of included studies. Finally, to include a sample as large as possible, populations included in this meta-analysis come from different settings and vary across studies, but the data of our meta-analysis corroborate findings of the FHS (Framingham Heart Study)[11] and the SLAS (Singapore Longitudinal Ageing Studies),[13] precluding an enlarged (transcontinental) external validity of results.

Conclusions

In conclusion, this systematic review and meta-analysis reveals a negative association between arterial stiffness, measured using PWV, and cognition, specifically executive function, memory, and global cognition. This association seems to be independent of sex, age, blood pressure levels, and PWV measurement characteristics. Separate analyses of longitudinal studies support the negative association between arterial stiffness and cognitive function found in cross-sectional studies. Our results accumulate evidence supporting that PWV assessment could be a useful tool to identify individuals at high risk of cognitive decline or early stages of cognitive decline, to implement interventions aimed at slowing the progression to dementia.

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Disclosures

None.

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Supplemental Material

Data S1.

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Table S1. Sensitivity analyses by removing studies one by one for unadjusted cross-sectional analysis.

Global cogniton						
Author	**es**	**ll**	**ul**	**I^2**	**Q-Cochrane**	**p**
Abbatecola et al., 2008 [23]	-0.53	-0.68	-0.39	74.1	30.86	<0.001
Angermann et al., 2017 [25]	-0.44	-0.53	-0.35	26.4	10.87	0.209
Fukuhara et al., 2006 [28]	-0.54	-0.70	-0.39	74.1	30.88	<0.001
Hanon et al., 2005 [30]	-0.53	-0.68	-0.38	73.5	30.15	<0.001
Lee et al., 2014 [35]	-0.49	-0.62	-0.36	66.4	23.83	0.002
Lim et al., 2016 [13]	-0.55	-0.70	-0.40	73.9	30.68	<0.001
Muela et al., 2018 [37]	-0.55	-0.70	-0.40	73.9	30.68	<0.001
Nilsson et al., 2014 [39]	-0.56	-0.72	-0.40	70.3	26.97	0.001
Triantafyllidi et al., 2009 [46]	-0.54	-0.69	-0.39	74.1	30.90	<0.001
Zhong et al., 2014 [50]	-0.56	-0.73	-0.38	73.6	30.32	<0.001
Executive function						
Author	**es**	**ll**	**ul**	**I^2**		
Abbatecola et al., 2008 [23]	-0.30	-0.41	-0.18	0.0	1.77	0.413
Kim et al., 2017 [33]	-0.42	-0.57	-0.26	0.0	2.00	0.368
Muela et al., 2018 [37]	-0.37	-0.59	-0.15	58.6	4.83	0.089
Zhong et al., 2014 [50]	-0.36	-0.59	-0.12	53.5	4.30	0.117
Memory						
Author	**es**	**ll**	**ul**	**I^2**		
Cooper et al., 2016 [11]	-0.53	-0.74	-0.32	56.3	2.29	0.130
Muela et al., 2018 [37]	-0.28	-0.61	0.06	95.2	20.82	<0.001
Zhong et al., 2014 [50]	-0.38	-0.94	-0.18	93.3	14.91	<0.001

Table S2. Sensitivity analyses by removing studies one by one for adjusted cross-sectional analysis.

Global cognition						
Author	**es**	**ll**	**ul**	**I^2**	**Q-Cochrane**	**p**
Elias et al., 2009 [27]	-0.22	-0.32	-0.12	77.6	49.19	<0.001
Fukuhara et al., 2006 [28]	-0.20	-0.30	-0.10	77.2	48.26	<0.001
Hanon et al., 2005 [30]	-0.21	-0.31	-0.11	77.9	49.72	<0.001
Karasavvidou et al., 2018 [31]	-0.21	-0.31	-0.11	77.9	49.78	<0.001
Kim et al., 2009 [32]	-0.13	-0.16	-0.09	0.0	9.10	0.613
Lamballais et al., 2018 [34]	-0.23	-0.35	-0.10	77.6	49.16	<0.001
Lee et al., 2014 [35]	-0.21	-0.31	-0.11	77.9	49.67	<0.001
Lim et al., 2016 [13]	-0.22	-0.32	-0.12	77.8	49.63	<0.001
Muela et al., 2018 [37]	-0.21	-0.30	-0.11	77.6	49.19	<0.001
Palta et al., 2019 [40]	-0.23	-0.34	-0.11	77.4	48.59	<0.001
Ryu et al., 2017 [43]	-0.19	-0.29	-0.10	76.2	46.18	<0.001
Singer et al., 2013 [45]	-0.22	-0.32	-0.12	77.5	48.87	<0.001
Zhong et al., 2014 [50]	-0.23	-0.33	-0.12	77.2	48.21	<0.001
Executive function						
Author	**es**	**ll**	**ul**	**I^2**		
Geijselaers et al., 2016 [29]	-0.10	-0.15	-0.04	52.5	18.95	0.026
Kim et al., 2017 [32]	-0.09	-0.14	-0.03	61.0	23.06	0.006
Lim et al., 2016 [13]	-0.07	-0.12	-0.02	49.5	17.83	0.037
Mitchell et al., 2011[S36]	-0.08	-0.13	-0.02	58.3	21.56	0.010
Muller et al., 2006 [38]	-0.08	-0.14	-0.02	60.9	23.01	0.006
Palta et al., 2019 [40]	-0.09	-0.16	-0.02	56.6	20.73	0.014
Pase et al., 2016 [41]	-0.08	-0.14	-0.02	59.7	22.32	0.008
Ryu et al., 2017 [43]	-0.06	-0.11	-0.02	44.1	16.10	0.065
Singer et al., 2013 [45]	-0.09	-0.14	-0.03	60.1	22.58	0.007
Tsao et al., 2013 [47]	-0.07	-0.13	-0.02	55.6	20.25	0.016
Zhong et al., 2014 [50]	-0.09	-0.16	-0.03	59.3	22.11	0.009
Memory						
Author	**es**	**ll**	**ul**	**I^2**		
Cooper et al., 2016 [11]	-0.13	-0.21	-0.05	81.7	60.18	<0.001
Elias et al., 2009 [27]	-0.14	-0.22	-0.06	81.9	60.74	<0.001
Geijselaers et al., 2016 [29]	-0.13	-0.21	-0.06	81.9	60.88	<0.001
Lim et al., 2016 [13]	-0.13	-0.20	-0.05	81.8	60.54	<0.001
Mitchell et al., 2011 [36]	-0.12	-0.20	-0.05	81.2	58.48	<0.001
Muela et al., 2018 [37]	-0.11	-0.18	-0.04	79.5	53.70	<0.001
Muller et al., 2006 [38]	-0.13	-0.021	-0.06	81.9	60.89	<0.001
Palta et al., 2019 [40]	-0.14	-0.22	0.05	81.8	60.40	<0.001
Pase et al., 2016 [41]	-0.14	-0.22	-0.06	77.6	49.20	<0.001
Ryu et al., 2017 [43]	-0.07	-0.12	-0.03	50.1	22.06	0.024
Singer et al., 2013 [45]	-0.13	-0.20	-0.05	81.8	60.30	<0.001
Tsao et al., 2013 [47]	-0.14	-0.22	-0.07	80.8	57.33	<0.001
Zhong et al., 2014 [50]	-0.13	-0.21	-0.06	81.9	60.91	<0.001

Table S3. Sensitivity analyses by removing studies one by one for longitudinal analysis.

Global cognition						
Author	**es**	**ll**	**ul**	**I^2**	**Q-Cochrane**	**p**
Al Hazzouri et al., 2013 [24]	-0.15	-0.26	-0.04	62.2	10.59	0.032
Benetos et al., 2012 [26]	-0.22	-0.41	-0.03	89.9	39.73	<0.001
Palta et al., 2019 [40]	-0.22	-0.40	-0.04	89.9	39.73	<0.001
Poels et al., 2007 [42]	-0.26	-0.37	-0.16	54.8	8.86	0.065
Scuteri et al., 2007 [44]	-0.20	-0.36	-0.04	89.7	38.97	<0.001
Watson et al., 2011 [49]	-0.21	-0.39	-0.03	89.9	39.56	<0.001
Executive function						
Author	**es**	**ll**	**ul**	**I^2**		
Hajjar et al., 2016 [12]	-0.11	-0.25	0.02	64.0	5.55	0.062
Kim et al., 2017 [33]	-0.12	-0.23	-0.01	67.0	6.06	0.048
Poels et al., 2007 [42]	-0.18	-0.27	-0.09	0.0	0.39	0.822
Tsao et al., 2013 [48]	-0.06	-0.13	0.00	0.0	1.67	0.434
Memory						
Author	**es**	**ll**	**ul**	**I^2**		
Hajjar et al., 2016 [12]	-0.05	-0.17	0.07	46.8	1.88	0.170
Kim et al., 2017 [42]	-0.11	-0.23	0.03	0.0	0.18	0.675
Poels et al., 2007 [49]	-0.02	-0.09	0.04	0.0	0.79	0.375

Table S4. Subgroup analyses for the association between PWv and cognition domains by type of sample, PWv measured and device used.

	Longitudinal data					Cross-sectional data									
						Unadjusted					Adjusted				
	n	ES (95%CI)	I^2	Q-Cochrane	p	n	ES (95%CI)	I^2	Q-Cochrane	p	n	ES (95%CI)	I^2	Q-Cochrane	p
Global cognition															
Type of sample															
General population	5	-0.20 (-0.36, -0.04)	89.7	38.97	<0.001	4	-0.39 (-0.47, -0.32)	0.0	0.70	0.872	8	-0.19 (-0.31; -0.08)	84.5	45.22	<0.001
Specific disease population	1	-0.36 (-0.76, 0.04)	NA	NA	NA	6	-0.67 (-0.92, -0.41)	73.8	19.10	0.002	5	-0.25 (-0.38, -0.11)	0.0	2.42	0.659
Type pf PWv															
cfPWv	5	-0.21 (-0.39, -0.03)	89.9	39.56	<0.001	9	-0.55 (-0.70, -0.39)	74.1	30.88	<0.001	10	-0.12 (-0.16, -0.08)	0.0	2.98	0.965
baPWv	0	NA	NA	NA	NA	1	-0.42 (-0.70, -0.14)	NA	NA	NA	3	-0.56 (-0.88, -0.23)	76.6	8.55	0.014
aPWv	1	-0.22 (-0.39, -0.05)	NA	NA	NA	0	NA	NA	NA	NA	0	NA	NA	NA	NA
Type of device															
Sphygmocor	0	NA	NA	NA	NA	3	-0.52 (-0.81, -0.24)	78.0	9.11	0.011	5	-0.09 (-0.20, 0.02)	0.0	0.91	0.923
Complior	2	-0.13 (-0.45, 0.18)	63.6	2.75	0.097	4	-0.44 (-0.53, -0.35)	0.0	1.33	0.723	4	-0.13 (-0.17, -0.08)	0.0	1.73	0.210
Other	4	-0.26 (-0.37, -0.14)	65.7	8.74	0.033	3	-0.70 (-1.19, -0.22)	83.8	12.37	0.002	4	-0.43 (-0.81, -0.05)	92.9	42.25	<0.001
Executive function															
Type of sample															
General population	3	-0.12 (-0.23, -0.01)	67.0	6.06	0.048	3	-0.36 (-0.59, -0.12)	53.5	4.30	<0.001	9	-0.07 (-0.12, -0.01)	50.3	16.10	0.041
Specific disease population	1	-0.09 (-0.80,0.41)	NA	NA	NA	1	-0.39 (-0.60, -0.19)	NA	NA	NA	2	-0.16 (-0.38, 0.05)	70.7	3.41	0.065
Type of PWv															
cfPWv	4	-0.12 (-0.22, -0.02)	83.1	6.06	0.001	4	-0.35 (-0.51, -0.20)	38.4	4.87	0.182	10	-0.06 (-0.11, -0.02)	44.1	16.10	0.065
baPWv	0	NA	NA	NA	NA	0	NA	NA	NA	NA	1	-0.27 (-0.43, -0.11)	NA	NA	NA
aPWv	0	NA	NA	NA	NA	0	NA	NA	NA	NA	0	NA	NA	NA	NA
Type of device															
Sphygmocor	2	-0.15 (-0.29, 0.00)	0.0	0.04	0.836	1	-0.22 (-0.39, -0.05)	NA	NA	NA	5	-0.05 (-0.19, 0.08)	56.1	9.12	0.058
Complior	1	-0.04 (-0.11, 0.04)	NA	NA	NA	2	-0.38 (-0.54, -0.21)	0.0	0.05	0.819	1	-0.02 (-0.10, 0.06)	NA	NA	NA
Other	1	-0.20 (-0.31, -0.09)	NA	NA	NA	1	-0.72 (-1.18, -0.27)	NA	NA	NA	5	-0.12 (-0.19, -0.04)	67.0	12.11	0.017
Memory															
Type of sample															
General population	3	-0.05 (-0.12, 0.03)	13.8	2.32	0.314	2	-0.28 (-0.61, 0.06)	95.2	20.82	<0.001	11	-0.06 (-0.10, -0.02)	30.4	14.38	0.156
Specific disease population	0	NA	NA	NA	NA	1	-0.68 (-0.96, -0.41)	NA	NA	NA	2	-0.58 (-0.73, -0.43)	0.0	0.10	0.753
Type of PWv															
cfPWv	2	-0.02 (-0.09, 0.04)	0.0	0.79	0.375	3	-0.39 (-0.70, -0.10)	93.4	30.08	<0.001	12	-0.08 (-0.12, -0.03)	50.1	22.06	0.024
baPWv	0	NA	NA	NA	NA	0	NA	NA	NA	NA	1	-0.59 (-0.76, -0.43)	NA	NA	NA
aPWv	1	-0.14 (-0.31, 0.03)	NA	NA	NA	0	NA	NA	NA	NA	0	NA	NA	NA	NA
Type of device															
Sphygmocor	1	-0.09 (-0.25, 0.07)	NA	NA	NA	0	NA	NA	NA	NA	5	-0.07 (-0.15, 0.00)	0.0	1.18	0.881
Complior	1	-0.01 (-0.09, 0.07)	NA	NA	NA	2	-0.53 (-0.74, -0.32)	56.3	2.29	0.130	2	-0.27 (-0.72, 0.04)	84.6	6.48	0.011
Other	1	-0.14 (-0.31, 0.03)	NA	NA	NA	1	-0.11 (-0.20, -0.02)	NA	NA	NA	6	-0.14 (-0.25, -0.03)	90.5	52.52	<0.001

PWv: Pulse Wave Velocity; cf: carotid-femoral; ba: brachial-ankle; a: aortic; NA: Not Available

Table S5. Meta-regression of PWV and cognition domains by percentage of females and mean age, BMI, SBP and DBP of included studies.

		% female			Age			BMI			SBP			DBP	
	n	**ß (95%CI)**	**p**	**n**	**ß (95%CI)**	**p**	**n**	**ß (95%CI)**	**p**	**n**	**ß (95%CI)**	**p**	**n**	**ß (95%CI)**	**p**
Global cognition															
Longitudinal data	4	-0.00 (-0.03, 0.02)	0.690	6	-0.01 (-0.04, 0.03)	0.643	6	-0.04 (-0.31, 0.24)	0.727	4	-0.02 (-0.07, 0.03)	0.227	3	-0.02 (-0.04, 0.01)	0.142
Cross-sectional data															
Unadjusted	9	0.00 (-0.01, 0.02)	0.497	10	0.00 (-0.02, 0.02)	0.649	8	0.02 (-0.02, 0.05)	0.338	8	0.02 (-0.00, 0.05)	0.062	8	0.03 (-0.03, 0.09)	0.256
Adjusted	13	-0.00 (-0.01, 0.01)	0.991	13	0.01 (-0.01, 0.02)	0.348	12	0.04 (-0.02, 0.11)	0.173	10	0.01 (-0.02, 0.04)	0.554	8	-0.01 (-0.13, 0.11)	0.878
Executive function															
Longitudinal data	4	-0.00 (-0.05, 0.05)	0.910	4	0.01 (-0.02, 0.03)	0.449	3	-0.05 (-0.79, 0.68)	0.512	3	-0.01 (-0.27, 0.25)	0.824	2	NA	NA
Cross-sectional data															
Unadjusted	3	-0.00 (-0.05, 0.05)	0.993	4	-0.01 (-0.03, 0.02)	0.286	3	0.06 (-1.19, 1.31)	0.640	2	NA	NA	2	NA	NA
Adjusted	11	-0.00 (-0.01, 0.00)	0.548	11	0.00 (-0.01, 0.01)	0.839	7	0.03 (-0.01, 0.08)	0.127	7	0.00 (-0.01, 0.01)	0.837	4	0.00 (-0.05, 0.06)	0.757
Memory															
Longitudinal data	3	0.00 (-0.12, 0.12)	0.949	3	0.00 (-0.06, 0.07)	0.833	3	-0.05 (-1.28, 1.18)	0.684	1	NA	NA	1	NA	NA
Cross-sectional data															
Unadjusted	3	0.01 (-0.06, 0.07)	0.404	3	0.02 (-0.11, 0.15)	0.492	3	-0.09 (-1.53, 1.35)	0.587	2	NA	NA	2	NA	NA
Adjusted	13	0.00 (-0.01, 0.01)	0.853	13	-0.00 (-0.01, 0.01)	0.584	10	0.01 (-0.02, 0.05)	0.343	10	-0.00 (-0.01, -0.00)	0.027	7	-0.01 (-0.03, 0.02)	0.653

NA: Not Available

Table S6. Risk of bias of cross-sectional and longitudinal included studies.

References	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Abbatecola et al., 2008 [23]	Y	Y	NR	Y	NR	NR	Y	N	Y	Y	Y	NR	Y	Y	9
Al Hazzouri et al., 2013 [24]	Y	Y	Y	Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y	12
Angermann et al., 2017 [25]	Y	Y	NR	Y	NR	Y	-	Y	Y	-	Y	NR	-	N	7
Benetos et al., 2012 [26]	Y	Y	NR	Y	NR	Y	Y	Y	Y	N	Y	NR	N	Y	9
Cooper et al., 2016 [11]	Y	Y	Y	Y	NR	NR	-	N	Y	-	Y	NR	-	Y	7
Elias et al., 2009 [27]	Y	Y	Y	Y	NR	Y	-	Y	Y	-	Y	NR	-	Y	9
Fujiwara et al., 2005 [51]	Y	Y	N	Y	NR	NR	-	Y	Y	-	Y	NR	-	Y	7
Fukuhara et al., 2006 [28]	Y	Y	Y	Y	NR	NR	-	N	Y	-	Y	NR	-	Y	7
Geijselaers et al., 2016 [29]	Y	Y	Y	Y	NR	NR	-	Y	Y	-	Y	NR	-	Y	8
Hajjar et al., 2016 [12]	Y	Y	NR	Y	NR	NR	Y	Y	Y	Y	Y	NR	Y	Y	10
Hanon et al., 2005 [30]	Y	Y	NR	Y	NR	NR	-	Y	Y	-	Y	Y	-	Y	8
Karasavvidou et al., 2018 [31]	Y	Y	Y	Y	NR	NR	-	Y	Y	-	Y	NR	-	Y	8
Kearney-Schwartz et al., 2009 [52]	Y	Y	Y	Y	Y	NR	-	Y	Y	-	Y	Y	-	Y	10
Kim et al., 2009 [32]	Y	Y	N	Y	NR	NR	-	N	Y		N	NR	-	N	4
Kim et al., 2017 [33]	Y	Y	Y	Y	NR	NR	Y	Y	Y	Y	Y	NR	Y	Y	11
Lamballais et al, 2018 [34]	Y	Y	Y	Y	NR	NR	-	N	Y	-	Y	NR	-	Y	7
Lee et al., 2014 [35]	Y	Y	Y	Y	NR	NR	-	N	Y	-	Y	NR	-	Y	7
Lim et al., 2016 [13]	Y	Y	NR	Y	NR	NR	-	N	Y	-	Y	NR	-	Y	6
Meyer et al, 2017 [53]	Y	Y	N	Y	N	NR	-	Y	Y	-	Y	NR	-	Y	7
Mitchell et al., 2011 [36]	Y	Y	N	Y	NR	NR	-	Y	Y	-	Y	NR	-	Y	7
Muela et al., 2018 [37]	Y	Y	NR	Y	NR	NR	-	Y	Y	-	Y	Y	-	Y	8
Muller et al., 2006 [38]	Y	Y	N	Y	NR	NR	-	Y	Y	-	Y	NR	-	Y	7
Nilson et al., 2014 [39]	Y	Y	N	Y	NR	NR	-	Y	Y	-	Y	NR	-	Y	7
Nilson et al., 2017 [54]	Y	Y	N	Y	NR	NR	-	Y	Y	-	Y	NR	-	Y	7
Palta et al., 2019 [40]	Y	Y	Y	Y	NR	Y	Y	Y	Y	N	Y	NR	N	Y	10
Pase et al., 2016 [41]	Y	Y	Y	Y	NR	NR	-	Y	Y	-	Y	Y	-	Y	9
Poels et al., 2007 [42]	Y	Y	N	Y	NR	NR	Y	N	Y	Y	Y	Y	N	Y	9
Ryu et al., 2017 [43]	Y	Y	NR	Y	NR	NR	-	N	Y	-	Y	N	-	N	5
Scuteri et al., 2007 [44]	Y	Y	Y	Y	NR	NR	-	N	Y	-	Y	Y	-	Y	8
Singer et al., 2013 [45]	Y	Y	N	Y	NR	NR	-	Y	Y	-	Y	NR	-	Y	7
Sugawara et al., 2010 [55]	Y	Y	Y	Y	NR	NR	-	Y	Y	-	Y	NR	-	Y	8
Taniguchi et al., 2014 [56]	Y	Y	Y	Y	NR	NR	-	Y	Y	-	Y	Y	-	Y	9
Triantafyllidi et al., 2009 [46]	Y	Y	Y	Y	NR	NR	-	Y	Y	-	Y	Y	-	Y	9
Tsao et al., 2013 [47]	Y	Y	Y	Y	NR	NR	-	N	Y	-	Y	Y	-	Y	8
Tsao et al., 2016 [48]	Y	Y	Y	Y	NR	Y	Y	Y	Y	N	Y	Y	Y	Y	12
Tuttolomondo et al., 2017 [57]	Y	Y	NR	Y	NR	NR	-	Y	Y	-	Y	NR	-	Y	7
Watson et al., 2011 [49]	Y	Y	NR	Y	NR	Y	Y	Y	Y	N	Y	NR	Y	Y	10
Zhong et al., 2014 [50]	Y	Y	NR	NR	NR	NR	-	Y	Y	-	Y	NR	-	Y	6

Y: Yes; N: No; NR: Not Reported