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.⁸,⁹ PWV is an index closely related to vascular...
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.

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 and Meta-Analysis of Observational Studies in Epidemiology statements and the Cochrane Collaboration Handbook. 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 \(\text{cfPWV}\), brachial-ankle PWV \(\text{baPWV}\) or aortic PWV \(\text{aPWV}\), 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. 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. Fixed effects models were used when heterogeneity was not excessive. Heterogeneity across studies was assessed using the $I^2$ statistic, 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. Finally, the Cochran’s test was also used to evaluate the heterogeneity, being significant when $P<0.1$.

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 $\geq 2$ 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

| References                          | Subjects Characteristics | Exposure | Type of PWV | PW Average, m/s | Cognitive Measurement | Cognitive Construct                  |
|-------------------------------------|--------------------------|----------|-------------|-----------------|-----------------------|--------------------------------------|
| Abbatecola et al, 2008              | 140 (NR)                 |          |             |                 |                       |                                      |
|                                     | Women, n (%)             | Age, y   | BMI, kg/m²  | SBP, mm Hg      | DBP, mm Hg            | Type of Sample                      |                                      |
|                                     | Normoalbuminuric: 78.0   | 78.0 (5.0) | Normoalbuminuric: 27.4 | 135.0 (19.0) | Impaired glucose tolerance | dPWV |                                      |
|                                     | Normoalbuminuric: 27.4   | 27.8 (2.2) | Microalbuminuric: 155.0 | 88.0 (9.0) |                                      |                                      |
| Al Hazzouri et al, 2015             | 2488 (52.3)              | 74.2 (2.9) | NR          |                 | General population          | dPWV | Model 810-a                         |                                      |
| Angermann et al, 2017               | 201 (29.9)               | 64.5 (15.1) | NR          | 123.8 (16.6)    | Patients undergoing hemodialysis | dPWV | Mobil-O-Graph                       |                                      |
| Benetos et al, 2012                 | 873 (79.0)               | 88.0 (5.0) | 25.8 (4.5)  | 138.0 (17.0)    | General population          | dPWV | PulsePen                            |                                      |
| Cooper et al, 2016                  | 1820 (60.0)              | 80.0 (5.0) | 26.5 (3.9)  | 144.0 (22.0)    | General population          | dPWV | NIHem WF                            |                                      |
| Elias et al, 2009                   | 409 (62.3)               | 61.3 (12.8) | 29.3 (6.0)  | 128.9 (19.7)    | General population          | dPWV | SphygmCor                           |                                      |
| Fukusha et al, 2006                 | 203 (42.9)               | 85.0     | 22.7 (0.2)  | 144.3 (1.7)     | General population          | baPWV | ViSera VS-1000                      |                                      |
|                                     |                          |          |             |                 |                       |                                      |
| DOI: 10.1161/JAHA.119.014621       |                          |          |             |                 |                       |                                      |
| References       | Subjects Characteristics | Age, y | BMI, kg/m² | SBP, mm Hg | DBP, mm Hg | Type of Sample | Type of PWV | PWV Device | PWV Average, m/s | Cognitive Measurement | Cognitive Construct |
|-----------------|--------------------------|--------|------------|------------|------------|----------------|--------------|-------------|-------------------|-----------------------|----------------------|
| Geijtenbeek et al, 2016²⁹ | 396 (54.6) | 60 (8) | 27.2 (4.4) | 128 (14) | 76 (7) | General population | cPWV | SphygmoCor | 8.9 (2.1) | Verbal Learning Test  | Free recall memory               |
|                  |                          |        |            |            |            |                |              |             |                   | Stroop Color Word Test | Processing speed            |
|                  |                          |        |            |            |            |                |              |             |                   | Test (parts I and II), the Concept Shifting Test | Executive function and attention |
|                  |                          |        |            |            |            |                |              |             |                   | Part A and B, and the Letter-Digit Substitution Test |                           |
|                  |                          |        |            |            |            |                |              |             |                   | Stroop Color Word Test (part III) and the Concept Shifting Test |                           |
|                  |                          |        |            |            |            |                |              |             |                   | Test Part C, Letter-Digit Substitution test |                           |
|                  |                          |        |            |            |            |                |              |             |                   |                                     |                           |
| Hajjar et al, 2016²² | 591 (68.0) | 48.8 (9.7) | 28.0 (6.6) | 121.0 (24.3) | 77.0 (12.2) | General population | cPWV | SphygmoCor | 7.2 (1.5) | Mental flexibility | Executive function |
|                  |                          |        |            |            |            |                |              |             |                   | SPOTING the symbol Digit Symbol | Memory                   |
|                  |                          |        |            |            |            |                |              |             |                   | Substitution Test Digit Span Forward | Working memory              |
|                  |                          |        |            |            |            |                |              |             |                   | Executive Function Test |                           |
|                  |                          |        |            |            |            |                |              |             |                   | Focused Attention Sustained Attention Delayed Memory Recall |                           |
|                  |                          |        |            |            |            |                |              |             |                   | Visual Spatial Memory |                           |
|                  |                          |        |            |            |            |                |              |             |                   | Visual Spatial Short-Term Recall |                           |
|                  |                          |        |            |            |            |                |              |             |                   | Digit Span Backwards |                           |
|                  |                          |        |            |            |            |                |              |             |                   |                                     |                           |
| Hanon et al, 2005²⁸ | 308 (64.3) | NCF: 75.0 (8.0) | 132.2 (14.2) | NCF: 119.0 (11.0) | 78.1 (11.3) | Subjects with complaint of memory loss | cPWV | Compilier | 11.5 (2.0) | MMSE | Global cognitive function |
|                  |                          | MCI: 77.0 (8.0) | 139.0 (17.0) | MCI: 80.0 (9.0) | 78.0 (12.0) |                |              |              |                   | Cognitive Efficiency Profile | Cognitive efficiency profile |
|                  |                          | AD: 80.0 (7.0) | 145.0 (20.0) | AD: 81.0 (12.0) | 82.0 (13.0) |                |              |              |                   |                              |                           |
|                  |                          | VaD: 81.0 (7.0) | 159.0 (21.0) | VaD: 82.0 (13.0) | 83.0 (13.0) |                |              |              |                   |                              |                           |
| Kasasaviboud et al, 2018²⁷ | 151 (33.6) | 57.08 (13.7) | 28.2 (5.1) | 137.2 (18.1) | 77.4 (11.3) | Patients with kidney disease | cPWV | SphygmoCor | 6.1 (1.9) | MMSE | Global cognitive function |
|                  |                          |        |            |            |            |                |              |             |                   |                              | Cognitive efficiency profile |
| Kim et al., 2009²² | 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 | Global cognitive function |
|                  |                          |        |            |            |            |                |              |             |                   | (K-MMSE) |                           |
| Kim et al., 2017²³ | 333 (42.0) | 55.0 (13.0) | NR | NR | NR | Patients undergoing hemodialysis | cPWV | SphygmoCor | 10.0 (7.9-12.5) | Trail Making Tests (A and B) | Executive function |
|                  |                          |        |            |            |            |                |              |             |                   | 3MS | Global cognitive function |
| Lamballas et al, 2018²⁴ | 5187 (42.9) | 58.8 (7.3) | 26.8 (3.8) | 130 (18) | 80 (10)-86 (10) | General population | cPWV | Compilier | 9.1 (1.6)-10.3 (2.7) | Color-Word Interference Stroop Task | G-factor |
|                  |                          | 63.6 (5.7) | 27.4 (4.3) | 150 (20) |               |                |              |             |                   | Letter Digit Substitution Test |                           |
|                  |                          |        |            |            |            |                |              |             |                   | Verbal Fluency Test |                           |
|                  |                          |        |            |            |            |                |              |             |                   | Delayed Recall |                           |
|                  |                          |        |            |            |            |                |              |             |                   | Purdue Pegboard Test |                           |

Table 1. Continued
| References | Subjects Characteristics | Exposure | Outcome |
|------------|--------------------------|----------|---------|
| Lee et al., 2014 | Women, n (%) | Age, y | BMI, kg/m² | SBP, mm Hg | DBP, mm Hg | Type of Sample | Type of PWV | PWV Device | PWV Average, m/s | Cognitive Measurement | Cognitive Construct |
|            | 102 (29.0) | 61.0 (9.0) | 24.0 (4.0) | 124.0 (13.0) | 77.0 (9.0) | Stroke patients | cIPWV | SphygmoCor | 10.0 (2.0) | K-MMSE | Global cognitive function |
| Lim et al., 2016 | 463 (43.2) | MMSE participants: 63.0 (6.1) | Neurocognitive domain test participants: 64.2 (6.4) | NR | NR | General population | cIPWV | SphygmoCor | 5.0 (2.6–14.1) | 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 |
| Mitchell et al., 2011 | 668 (56.6) | Women: 75.0 (4.0) | Men: 76.0 (4.0) | Women: 141.0 (20.0) | Men: 137.0 (18.0) | General population | cIPWV | NIHem WF | 12.2 (3.7) | Men: 13.4 (4.4) | Memory Processing speed Executive function |
| Muela et al., 2018 | 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 2: 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 | cIPWV | Compilor | 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-Osterreith 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 |

Continued
### Table 1. Continued

| References | Subjects Characteristics | Exposure | Outcome | Cognitive Measurement | Cognitive Construct |
|------------|--------------------------|----------|---------|-----------------------|---------------------|
| Muller et al, 2007$^38$ | Women: 396 (0.0) No CVD: 54.5 (10.3) Subclinical CVD: 66.8 (8.1) Prevalent CVD: 76.7 (8.8) No CVD: 134.2 (1.3) Subclinical CVD: 145.5 (1.7) Prevalent CVD: 140.2 (2.9) NR | General population cPWV 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$^39$ | Women: 2637 (60.8) No CVD: 72.1 (5.6) NR | General population cPWV SphygmoCor | 10.5 (2.5) | MMSE Quick test of cognitive speed (ADT) | Global cognitive function Perceptual and cognitive speed |
| Palta et al, 2019$^40$ | Women: 3703 (59.3) No CVD: 75.2 (5.0) NR | General population cPWV 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$^41$ | Women: 3207 (53.1) No CVD: 46.0 (0.9) NR | General population cPWV 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$^42$ | Women: 3714 (57.7) No CVD: 72.0 (6.7) NR | General population cPWV Compior | 13.5 (3.0) | MMSE Letter-Digit Substitution Task Stroop Test Word Fluency Test | Global cognitive function Executive function |

Continued
| References            | Subjects Characteristics | Exposure | Outcome |
|-----------------------|--------------------------|----------|---------|
| Ryu et al, 2017^43    | Women, n (%)             | Type of Sample | Type of PWV | Type of PWV | Cognitive Measurement |
|                       | Age, y                   | BMI, kg/m^2 | SBP, mm Hg | DBP, mm Hg | PWV Average, m/s |
|                       |                          | 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 | Global cognitive function | Language function |
|                       |                          | Seoul Neuropsychological | Screening Battery: | Korean-Boston | Calculation test | Seoul Verbal Learning Test | Control Oral Word Association Test | MMSE | Seoul | Global cognitive function | Language function | Calculation | Vascular function and memory | Memory |
| Scuteri et al, 2007^44 | Women, n (%)             | Age, y     | BMI, kg/m^2 | SBP, mm Hg | DBP, mm Hg | PWV Average, m/s |
|                       |                          | PD-NC: 79.0 (6.0) | PD-MCI: 25.7 (4.1) | PD-D: 135.9 (19.2) | DLB: 78.5 (11.9) | AD: 21.2 (7.0) | NR | NR | NR | Patients with complaints of memory loss | dPWV | Complior |
|                       |                          | PD-NC: 79.0 (6.0) | PD-MCI: 25.7 (4.1) | PD-D: 135.9 (19.2) | DLB: 78.5 (11.9) | AD: 21.2 (7.0) | NR | NR | NR | Patients with complaints of memory loss | dPWV | Complior |
|                       |                          | Seoul Neuropsychological | Screening Battery: | Korean-Boston | Calculation test | Seoul Verbal Learning Test | Control Oral Word Association Test | MMSE | Seoul | Global cognitive function | Language function | Calculation | Vascular function and memory | Memory |
| Singer et al, 2013^45  | Women, n (%)             | Age, y     | BMI, kg/m^2 | SBP, mm Hg | DBP, mm Hg | PWV Average, m/s |
|                       |                          | PD-NC: 79.6 (4.2) | PD-MCI: 26.7 (4.1) | PD-D: 140.9 (19.3) | DLB: 78.5 (11.9) | AD: 21.2 (7.0) | NR | NR | NR | General population | dPWV | SphygmoCor |
|                       |                          | PD-NC: 79.6 (4.2) | PD-MCI: 26.7 (4.1) | PD-D: 140.9 (19.3) | DLB: 78.5 (11.9) | AD: 21.2 (7.0) | NR | NR | NR | General population | dPWV | SphygmoCor |
|                       |                          | Seoul Neuropsychological | Screening Battery: | Korean-Boston | Calculation test | Seoul Verbal Learning Test | Control Oral Word Association Test | MMSE | Seoul | Global cognitive function | Language function | Calculation | Vascular function and memory | Memory |
| Triantafyllidi et al, 2009^46 | Women, n (%)             | Age, y     | BMI, kg/m^2 | SBP, mm Hg | DBP, mm Hg | PWV Average, m/s |
|                       |                          | PD-NC: 56.1 (10.0) | PD-MCI: 29.7 (4.0) | PD-D: 147.0 (17.0) | DLB: 88.0 (10.0) | AD: 21.2 (7.0) | NR | NR | NR | Patients with essential hypertension | dPWV | Complior SP |
|                       |                          | PD-NC: 56.1 (10.0) | PD-MCI: 29.7 (4.0) | PD-D: 147.0 (17.0) | DLB: 88.0 (10.0) | AD: 21.2 (7.0) | NR | NR | NR | Patients with essential hypertension | dPWV | Complior SP |
|                       |                          | Seoul Neuropsychological | Screening Battery: | Korean-Boston | Calculation test | Seoul Verbal Learning Test | Control Oral Word Association Test | MMSE | Seoul | Global cognitive function | Language function | Calculation | Vascular function and memory | Memory |
| Tsao et al, 2013^47    | Women, n (%)             | Age, y     | BMI, kg/m^2 | SBP, mm Hg | DBP, mm Hg | PWV Average, m/s |
|                       |                          | PD-NC: 61.0 (9.0) | PD-MCI: 26.7 (4.1) | PD-D: 1260 (19.0) | DLB: 74.0 (10.0) | AD: 21.2 (7.0) | NR | NR | NR | General population | dPWV | SPT-301 |
|                       |                          | PD-NC: 61.0 (9.0) | PD-MCI: 26.7 (4.1) | PD-D: 1260 (19.0) | DLB: 74.0 (10.0) | AD: 21.2 (7.0) | NR | NR | NR | General population | dPWV | SPT-301 |
|                       |                          | Seoul Neuropsychological | Screening Battery: | Korean-Boston | Calculation test | Seoul Verbal Learning Test | Control Oral Word Association Test | MMSE | Seoul | Global cognitive function | Language function | Calculation | Vascular function and memory | Memory |
| Tsao et al, 2016^48    | Women, n (%)             | Age, y     | BMI, kg/m^2 | SBP, mm Hg | DBP, mm Hg | PWV Average, m/s |
|                       |                          | PD-NC: 62.0 (9.0) | PD-MCI: 26.7 (4.1) | PD-D: 1260 (19.0) | DLB: 74.0 (10.0) | AD: 21.2 (7.0) | NR | NR | NR | General population | dPWV | SPT-301 |
|                       |                          | PD-NC: 62.0 (9.0) | PD-MCI: 26.7 (4.1) | PD-D: 1260 (19.0) | DLB: 74.0 (10.0) | AD: 21.2 (7.0) | NR | NR | NR | General population | dPWV | SPT-301 |
|                       |                          | Seoul Neuropsychological | Screening Battery: | Korean-Boston | Calculation test | Seoul Verbal Learning Test | Control Oral Word Association Test | MMSE | Seoul | Global cognitive function | Language function | Calculation | Vascular function and memory | Memory |

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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/m²; (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.
| References                  | Subjects Characteristics | Exposure | Outcome |
|-----------------------------|--------------------------|----------|---------|
| **Subjects Characteristics**|                          |          |         |
| Women, n (%)                | Age, y                   | BMI, kg/m² | SBP, mm Hg |
| Fujiwara et al, 2005⁵¹      | 352 (61.1)               | 75.0 (4.6) | 22.8 (3.2) |
| Women, n (%)                | Age, y                   | BMI, kg/m² | SBP, mm Hg |
| Kearney-Schwartz et al, 2009²² | 198 (52.0)              | 69.3 (6.2) | 27.8 (4.3) |
| Meyer et al, 2017³⁷         | 4461 (58.8)              | 75.2 (4.9) | 27.7 (4.4) |
| Nilsson et al, 2017²⁴       | 3056 (60.5)              | 71.8 (5.5) | 23.7 (4.2) |
| Sugawara et al, 2010⁵⁵      | 388 (64.2)               | 71.7 (5.6) | 23.3 (2.9) |
| Taniguchi et al, 2015²⁶     | 526 (57.8)               | 71.7 (5.6) | 23.3 (2.9) |
| **Cognitive Characteristics**|                          |          |         |
| Cognitive measurement       |                          |          |         |
| Cognitive construct         |                          |          |         |
| Alzheimers Disease          |                          |          |         |
| Dementia                    |                          |          |         |
| Normal                      |                          |          |         |
| MCI                         |                          |          |         |
| Dementia                    |                          |          |         |
| No dementia                 |                          |          |         |
| Prevalent dementia          |                          |          |         |
| Incidental dementia         |                          |          |         |
| **Type of PWV**             |                          |          |         |
| **Cognitive Measurement**   |                          |          |         |
| MMSE                        |                          |          |         |
| Global cognitive function   |                          |          |         |
| Immediate and delayed memory and language | | | |
| Executive function and long-term verbal memory | | | |

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Arterial Stiffness and Cognition Among Adults

**SYSTEMATIC REVIEW AND META-ANALYSIS**

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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\(^3\) 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 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...
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. 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. 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.

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. Loss of memory is one of the most important reasons for consultations among people experiencing cognitive decline. 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. 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. Finally, some studies accounted for additional factors not usually studied, such as...
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

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**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.
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. 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. Finally, some genetic factors, such as increased b-amyloid levels, mediated by the presence of the apolipoprotein E e4 allele may induce vascular damage and cognitive decline.

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. 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. 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) and the SLAS (Singapore Longitudinal Ageing Studies), 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
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References
1. The World Health Report: Primary Health Care Now More Than Ever. Geneva, Switzerland: World Health Organization; 2008.
2. Mavrodaris A, Powell J, Thorogood M. Prevalences of dementia and cognitive impairment among older people in sub-Saharan Africa: a systematic review. Bull World Health Organ. 2013;91:773–783.
3. Barberge- Gateau P, Fabrigoule C. Disability and cognitive impairment in the elderly. Disabil Rehabil. 1997;19:175–193.
4. Dae H, Hsiung GYR, Liu-Ambrose T. The role of exercise in mitigating subcortical ischemic vascular cognitive impairment. J Neurochem. 2018;144:582–594.
5. Rosenberg GA, Wallin A, Wardlaw JM, Markus HS, Montaner J, Wolfgang L, ladeocla C, Zlokovic BV, Jouet A, Dichgans M, Duering M, Schmidt R, Korczyn AD, Gribning LT, Chui HC, Hachinski V. Consensus statement for diagnosis of subcortical small vessel disease. J Cereb Blood Flow Metab. 2016;36:6–25.
6. Lacolley P, Regnaut V, Avolio AP. Smooth muscle cell and arterial aging: basic and clinical aspects. Cardiovasc Res. 2018;114:513–528.
7. Laurent S, Cockroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; on behalf of the PARTAGE Study Investigators. Prediction of future vascular events in the elderly. Circ J. 2006;70:283–290.
8. Elias MF, Robbins MA, Budge MM, Abhayaratna WP, Dore GA, Elias PK. Arterial stiffness and aging: historical methods. Cardiovasc Res. 2006;70:765–768.
9. Geijseelaers SL, Sip SJ, Schram MT, van Boxtel MP, van Sloten TT, Kooij PF. Arterial stiffness as a marker of cognitive function in elderly subjects with complaints of memory loss. Stroke. 2005;36:2193–2197.
10. Barroso N, Dores V, Freire C, Cordeiro J, Tavares A, Jesus A, Lopes F, Macedo A, Viegas M. Association of arterial stiffness and central pressure with cognitive impairment in hemodialysis patients. J Clin Hypertens. 2008;10:215–219.
11. Singer J, Trollor JN, Baune BT, Sachdev PS, Smith E. Arterial stiffness, the brain and cognition: a systematic review. Ageing Res Rev. 2014;15:16–27.
12. van Sloten TT, Proogerou A, Henry RM, Schram MT, Launer LJ, Stehouwer CD. Association between arterial stiffness, cerebral small vessel disease and cognitive impairment: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2015;53:121–130.
13. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.
14. Stroup DF, Berlin JA, Morton SC, Olinik I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB; for the Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA. 2008;283:2008–2012.
15. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at: www.handbook.cochrane.org.
16. National Heart, Lung, and Blood Institute. Quality assessment tool for observational cohort and cross-sectional studies. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed January 31, 2018.
17. DerSimonian R, Kacker R. Random-effects models for meta-analysis of clinical trials: an update. Contemp Clin Trials. 2007;28:105–114.
18. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22:719–748.
19. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–1558.
20. Abbatangelo AM, Barbieri M, Rizzo MR, Grella R, Laierta MT, Quaranta E, Molinari AM, Cioffi M, Fioretto P, Paolasso G. Arterial stiffness and cognition in elderly persons with impaired glucose tolerance and microalbuminuria. J Gerontol A Biol Sci Med Sci. 2008;63:991–996.
21. AlHazzouri AZ, Vittinghoff E, Sidney S, Reis JP, Jacobs DR Jr, Yaffe K. Intima-media thickness and cognitive function in stroke-free middle-aged adults: findings from the Coronary Artery Risk Development in Young Adults Study. Stroke. 2015;46:2190–2196.
22. Angermann S, Baumann M, Wassertepper S, Mayer CC, Steufl D, Hauser C, Sattmann Y, Reichelt AL, Satanevskij R, Lorenz G, Lukas M, Haller B, Heemann U, Gimmer T, Schmaderer C. Pulse-wave velocity is associated with cognitive impairment in hemodialysis patients. Clin Sci. 2017;131:1483–1493.
23. Benetos A, Watfa G, Hanon O, Salvi P, Fantin F, Toulza O, Manckounda P, Agnoletti D, Labat C, Gautier S; PARTAGE Study Investigators. Pulse wave velocity is associated with cognition and aging in chronic kidney disease patients. J Am Med Dir Assoc. 2012;13:239–243.
24. Elias MF, Robbins MA, Budge MM, Abhayaratna WP, Dore GA, Elias PK. Arterial pulse wave velocity and cognition with advancing age. Hypertension. 2009;55:663–678.
25. Fukuhara M, Matsumura K, Ansa T, Takata Y, Sonoki K, Akifusa S, Wakisaka M, Hamaaki T, Fushisawa K, Yoshida A, Fuji K, Iida M, Takehara T. Prediction of cognitive function by arterial stiffness in the very elderly. Cir J. 2007;70:756–761.
26. Hanso N, Haulon S, Lenoir H, Saelens EM, Rigaudo AS, Safar E, Girerd X, Forette F. Arterial stiffness and cognitive function in elderly subjects with complaints of memory loss. Stroke. 2005;36:2193–2197.
27. Karasavvidou D, Boutouyrie P, Kalatzidis R, Kettab H, Pappas K, Stagiakas D, Antonakis N, Tsalikakis D, Elsaid M, Laurent S. Arterial damage and cognitive decline in chronic kidney disease patients. J Clin Hypertens. 2018;20:1276–1284.
28. Kim YS, Kim DH, Choi BH, Sohn EH, Lee AY. Relationship between brachial-ankle pulse wave velocity and cognitive function in an elderly community-dwelling population with metabolic syndrome. Arch Gerontol Geriatr. 2009;49:176–182.
29. Kim ED, Meoni LA, Jaar BG, Shafi T, Kao WHL, Estrella MM, Parekh R, Sozio SM. Association of arterial stiffness and central pressure with cognitive function in incident hemodialysis patients: the FACE Study. Kidney Int Rep. 2017;2:1149–1159.
30. Lamballais S, Sajjad A, Leening MJ, Gaillard R, Franco OH, Mattace-Raso FU, Jaddoe VWV, Roza SJ, Tiemeier H, Irskam MA. Association of blood pressure and arterial stiffness with cognition in 2 population-based child and adult
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cohorts. J Am Heart Assoc. 2018;7:e009847. DOI: 10.1161/JAHA.118.009847.

35. Lee YH, Yoon ES, Park SH, Heffernan KS, Lee C, Jae SY. Associations of arterial stiffness and cognitive function with physical fitness in patients with chronic stroke. J Rehabil Med. 2014;46:413–417.

36. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, Garcia M, Apselund T, Harris TB, Gudnason V, Launer LJ. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Sex, Stroke: Environment Susceptibility-Royjak study. Brain. 2011;134:3398–3407.

37. Muela HC, Costa-Hong VA, Yassuda MS, Moraes NC, Memória CM, Machado MF, Bor-Seng-Shu E, Nogueira RC, Mansur AJ, Massaro NR, Nitiri R, Macedo TA, Bortolotto LA. Higher arterial stiffness is associated with lower cognitive performance in patients with hypertension. J Clin Hypertens. 2018;20:22–30.

38. Muller M, Grobbe DE, Alemán A, Bots M, Van der Schouw YT. Cardiovascular disease and cognitive performance in middle-aged and elderly men. Atherosclerosis. 2007;190:143–149.

39. Nilsson ED, Elmståhl S, Minthon L, Nilsson PM, Piispanen M, Tuokkola E, Nagga K. Non-linear association between pulse wave velocity and cognitive function: a population-based study. J Hypertens. 2014;32:2152–2157.

40. Palta P, Sharrett AR, Wei J, Meyer ML, Kucharska-Newton A, Power MC, Deal Pase MP, Himali JJ, Mitchell GF, Beiser A, Maillard P, Tsao C, Larson MG, Muller M, Grobbe DE, Alemán A, Bots M, Van der Schouw YT. Cardiovascular disease and cognitive function with physical fitness in patients with hypertension. J Clin Hypertens. 2018;20:22–30.

41. Poels MM, van Oijen M, Mattace-Raso FU, Hofman A, Koudstaal PJ, Wijtermans JC, Breiter MMB. Arterial stiffness, cognitive decline, and risk of dementia: the Rotterdam study. Stroke. 2007;38:886–892.

42. Ryu DW, Kim JS, Lee JE, Park JW, Oh YS, An JY, Lee KS. Association of arterial stiffness with cognition in patients with Lewy body disorder. Neurosci Lett. 2017;38:1307–1313.

43. Scuteri A, Tesouro M, Appolloni S, Preziosi F, Brancati AM, Volpe M. Arterial stiffness as an independent predictor of longitudinal changes in cognitive function in the older individual. J Hypertens. 2007;25:1035–1040.

44. Singer J, Trolor JN, Crawford J, O’Rourke MF, Baune BT, Brodaty H, Samaras K, Kochan NA, Campbell L, Sachdev PS, Smith E. The association between pulse wave velocity and cognitive function: the Sydney Memory and Ageing Study. PLoS One. 2013;8:e61855.

45. Triantafyllidou H, Arvaniti L, Lekakis J, Ikonomidou I, Siafakas N, Tzortzis S, Trivilou P, Zerva L, Tsambousis DT, Kremastinos DT. Cognitive impairment is correlated to cognitive performance and white matter hyperintensities in older hypertensive patients with subjective memory complaints. Stroke. 2009;40:1229–1236.

46. Meyer ML, Palta P, Tanaka H, Deal JA, Wright J, Knopman DS, Griswold ME, Mosley TH, Heiss G. Association of central arterial stiffness and pressure pulsatility with mild cognitive impairment and dementia: the Atherosclerosis Risk in Communities-Neurocognitive Study (ARIC-NCS). J Alzheimer’s Dis. 2017;57:195–204.

47. Nilsson ED, Elmståhl S, Minthon L, Piispanen M, Nilsson PM, Hasson O, Nagga K. Is independent association between pulse wave velocity and dementia: a population-based, prospective study. J Hypertens. 2017;35:2462–2467.

48. Sugawara N, Yasaki-Furukori N, Umeda T, Kaneda A, Sato Y, Takahashi I, Matsuzaka M, Danjo K, Nakaji S, Kaneko S. Comparison of ankle-brachial pressure index and pulse wave velocity as markers of cognitive function in a community-dwelling population. BMC Psychiatry. 2010;10:46.

49. Taniguchi Y, Fujiwara Y, Nofuyu Y, Nishi M, Murayama H, Seino S, Tajima R, Matsuyama Y, Shinaki S. Prospective study of arterial stiffness and subsequent cognitive decline among community-dwelling older Japanese. J Epidemiol. 2015;25:592–599.

50. Tuttolomondo A, Casuccio A, Guerco G, Maida C, Del Cuore A, Di Raimondo D, Simonetta I, Di Bona D, Pecoraro R, Della Corte V, Giulotta E, Giulotta P, Pinto A. Arterial stiffness, endothelial and cognitive function in subjects with type 2 diabetes in accordance with absence or presence of diabetic foot syndrome. Cardiovasc Diabetol. 2017;16:2.

51. Scuteri A, Tesouro M, Guglini L, Lauro D, Fini M, Di Manie N. Aortic stiffness and hypertension episodes are associated with impaired cognitive function in older subjects with subjective complaints of memory loss. Int J Cardiol. 2013;169:371–377.

52. Blondell SJ, Hammersley-Mather R, Veerman JL. Does physical activity prevent cognitive decline and dementia? A systematic review and meta-analysis of longitudinal studies. BMC Public Health. 2014;14:510.

53. Adams ML, Deokar AJ, Anderson LA, Edwards VJ. Self-reported increased confusion or memory loss and associated functional difficulties among adults aged 60 years—21 states, 2011. MMWR Mortal Mortal Wty Rep. 2013;62:345–350.

54. Sun X, Rundek T. Does increased arterial stiffness herald cognitive impairment? Stroke. 2016;47:2171–2172.

55. Pase MP. Modifiable vascular markers for cognitive decline and dementia: the importance of arterial aging and hemodynamic factors. J Alzheimers Dis. 2012;32:653–663.

56. O’Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension. 2005;46:200–204.

57. Scuteri A, Nilsson PM, Tzourio C, Redon J, Laurent S. Microvascular brain damage with aging and hypertension: pathophysiological consideration and clinical implications. J Hypertens. 2011;29:1469–1477.

58. Panza F, D’Introno A, Colaciocco AM, Capurso C, Del Parigi A, Capurso SA, Caselli RJ, Pilotta A, Scafato E, Capurso A, Solfrizzi V. Cognitive frailty: predementia syndrome and vascular risk factors. Neurobiol Aging. 2006;27:933–940.

59. Cambronero FE, Liu D, Neal JE, Moore EE, Gifford KA, Terry JG, Nair S, Pechman KR, Osborn KE, Hohman TJ, Bell SP, Sweat JD, Wang TJ, Beckman JA, Carr JJ, Jefferson AL. APOE genotype modifies the association between central arterial stiffening and cognition in older adults. Neurobiol Aging. 2018;67:120–127.

60. Takeda JRT, Matos TM, Souza-Talarico JND. Cardiovascular risk factors and cognitive performance in aging. Dement Neuropsychol. 2017;11:442–448.

61. Scuteri A, Volpe M, Asmar R. Arterial stiffness and cognitive impairment in the elderly. High Blood Press Cardiovasc Prev. 2007;14:33–37.
Supplemental Material
References excluded from the meta-analysis

1. Arntzen KA, Schirmer H, Johnsen SH, Wilsgaard T, Mathiesen EB. Carotid atherosclerosis predicts lower cognitive test results: a 7-year follow-up study of 4,371 stroke-free subjects - the Tromsø study. Cerebrovasc Dis. 2012; 33:159-165.: report on IMT
2. Borror A. Brain-derived neurotrophic factor mediates cognitive improvements following acute exercise. Med Hypotheses. 2017; 106: 1-5.: report on BDNF
3. Brant L, Bos D, Araujo LF, Ikram MA, Ribeiro AL, Barreto SM. Microvascular endothelial function and cognitive performance: The ELSA-Brasil cohort study. Vasc Med. 2018;23:212-218.: report on peripheral arterial tonometry and microvascular endothelial function.
4. Casado-Naranjo I, Romero Sevilla R, Portilla Cuenca JC, Duque de San Juan B, Calle Escobar ML, Fernández Pereira L, Fuentes JM, Ramírez-Moreno JM. Association between subclinical carotid atherosclerosis, hyperhomocysteinaemia and mild cognitive impairment. Acta Neurol. Scand. 2016;134;154-159.: report on subclinical markers of atherosclerosis.
5. Cohen RA, Poppas A, Forman DE, Hoth KF, Haley AP, Gunstad J, Jefferson AL, Tate DF, Paul RH, Sweet LH, Ono M, Jerskey BA, Gerhard-Herman M. Vascular and cognitive functions associated with cardiovascular disease in the elderly. J. Clin. Exp. Neuropsychol. 2009;31:96-110.: report on flow mediated brachial artery reactivity, and carotid intima media thickness.
6. Cooper LL, Himali J, Torjesen A, Tsao CW, Beiser A, Hamburg NM, DeCarli C, Vasan RS, Seshadri S, Pase MP, Mitchell G. Inter-Relations of Orthostatic Blood Pressure Change, Aortic Stiffness, and Brain Structure and Function in Young Adults. J Am Heart Assoc. 2017;17:e006206.: report on brain structure.

7. Dias Eda M1, Giollo LT Jr, Martinelli DD, Mazeti C, Júnior HM, Vilela-Martin JF, Yugar-Toledo JC. Carotid intima-media thickness is associated with cognitive deficiency in hypertensive patients with elevated central systolic blood pressure. Cardiovasc Ultrasound. 2012;10:41.: report on intima-media thickness.

8. Espeland MA, Beavers KM, Gibbs BB, Johnson KC, Hughes TM, Baker LD, Jakicic J, Korytkowski M, Miller M, Bray GA. Ankle-brachial index and inter-artery blood pressure differences as predictors of cognitive function in overweight and obese older adults with diabetes: results from the Action for Health in Diabetes movement and memory study. Int J Geriatri Psychiatry. 2015;30:999-1007.: report on ankle-brachial index

9. Espeland MA, Newman AB, Sink K, Gill TM, King AC, Miller ME, Guralnik J, Katula J, Church T, Manini T, Reid KF, McDermott MM; LIFE Study Group. Associations Between Ankle-Brachial Index and Cognitive Function: Results From the Lifestyle Interventions and Independence for Elders Trial. J AM Med Dir Assoc. 2015;16:682-689.: report on ankle-brachial index

10. van Exel E1, Gussekloo J, Houx P, de Craen AJ, Macfarlane PW, Bootsma-van der Wiel A, Blauw GJ, Westendorp RG. Atherosclerosis and cognitive impairment are linked in the elderly. The Leiden 85-plus Study. Atherosclerosis. 2002;165:353-359.: report assessing the atherosclerotic burden.

11. Feinkohl I, Keller M, Robertson CM, Morling JR, Williamson RM, Nee LD, McLachlan S, Sattar N, Welsh P, Reynolds RM, Russ TC, Deary IJ, Strachan MW, Price
JF; Edinburgh Type 2 Diabetes Study (ET2DS) Investigators. Clinical and subclinical macrovascular disease as predictors of cognitive decline in older patients with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetes care. 2013;36:2779-2786.: report on ankle-brachial index, and intima media thickness.

12. Fergenbaum JH1, Bruce S, Spence JD, Lou W, Hanley AJ, Greenwood C, Young TK. Carotid atherosclerosis and a reduced likelihood for lowered cognitive performance in a Canadian First Nations population. Neuroepidemiology. 2009;33:321-328.: report on carotid values.

13. Frazier DT, Seider T, Bettcher BM, Mack WJ, Jastrzab L, Chao L, Weiner MW, DeCarli C, Reed BR, Mungas D, Chui HC, Kramer JH. The role of carotid intima-media thickness in predicting longitudinal cognitive function in an older adult cohort. Cerebrovasc Dis. 2014;38:441-447.: report on intima media thickness

14. Forman DE, Cohen RA, Hoth KF, Haley AP, Poppas A, Moser DJ, Gunstad J, Paul RH, Jefferson AL, Tate DF, Ono M, Wake N, Gerhard-Herman M. Vascular Health and Cognitive Function in Older Adults with Cardiovascular Disease. Artery Res. 2008;2:35-43.: report on flow-mediated.

15. Gale CR1, Deary IJ, Fowkes FG, Batty GD. Intelligence in early adulthood and subclinical atherosclerosis in middle-aged men: the Vietnam Experience Study. J Epidemiol Community Health. 2012;66:e13.: report on ankle brachial index.

16. Gardener H, Caunca MR, Dong C, Cheung YK, Elkind MSV, Sacco RL, Rundek T, Wright CB. Ultrasound Markers of Carotid Atherosclerosis and Cognition: The Northern Manhattan Study. Stroke. 2017;48:1855-1861.: report on intima media thickness

17. Gatto NM, Henderson VW, St John JA, McCleary C, Detrano R, Hodis HN, Mack WJ Subclinical atherosclerosis is weakly associated with lower cognitive function in
healthy hyperhomocysteinemic adults without clinical cardiovascular disease. Int J Geriatr Psychiatry. 2009;24:390-399.: report on intima media thickness

18. Gutierrez J, Marshall RS, Lazar RM. Indirect measures of arterial stiffness and cognitive performance in individuals without traditional vascular risk factors or disease. JAMA Neurol. 2015;72:309-315.: report on increasing age, sedentary lifestyle, and the use of dihydropyridine calcium channel blockers

19. Huck DM, Hanna DB, Rubin LH, Maki P, Valcour V, Springer G, Xue X, Lazar J, Hodis HN, Anastos K, Kaplan RC, Kizer JR. Carotid Artery Stiffness and Cognitive Decline Among Women With or at Risk for HIV Infection. J Acquir Immune Defic Syndr. 2018;78:338-347.: report on carotid artery stiffness

20. Johnson NF, Gold BT, Brown CA, Anggelis EF, Bailey AL, Clasey JL, Powell DK. Endothelial Function Is Associated with White Matter Microstructure and Executive Function in Older Adults. Front Aging Neurosci. 2017;9:255.: report on brain structure.

21. Kidher E, Harling L, Sugden C, Ashrafian H, Casula R, Evans P, Nihoyannopoulos P, Athanasioua T. Aortic stiffness is an indicator of cognitive dysfunction before and after aortic valve replacement for aortic stenosis. Interact Cardiovasc Thorac Surg. 2014;19:595-604.: less than 100 participants.

22. Kuller LH, Lopez OL, Gottdiener JS, Kitzman DW, Becker JT, Chang Y, Newman AB. Subclinical Atherosclerosis, Cardiac and Kidney Function, Heart Failure, and Dementia in the Very Elderly. J Am Heart Assoc. 2017;6.: report on predictors of arterial stiffness.

23. Masley SC, Masley LV, Gualtieri CT. Cardiovascular biomarkers and carotid IMT scores as predictors of cognitive function. J Am Coll Nutr. 2014;33:63-69.: report on intima media thickness.
24. Mehrabian S, Raycheva M, Gateva A, Todorova G, Angelova P, Traykova M, Angelova P, Traykova M, Stankova T, Kamenov Z, Traykova L. Cognitive dysfunction profile and arterial stiffness in type 2 diabetes. J Neurol Sci. 2012;322:152-156.: less than 100 participants.

25. Nieboer D, Douw L, van Dijk BW, Heymans MW, Stam CJ, Twisk JW. Relation between carotid stiffness, cognitive performance and brain connectivity in a healthy middle-aged population: an observational neurophysiological cohort study with magnetoencephalography. BMJ Open. 2016;6:e013441.: report on carotid stiffness.

26. Rogne SO1, Solbu MD, Arntzen KA, Herder M, Mathiesen EB, Schirmer H. Albuminuria and carotid atherosclerosis as predictors of cognitive function in a general population. Eur Neurol. 2013;70:340-348.: report on carotid intima-media thickness and carotid total plaque area.

27. Scuteri A, Brancati AM, Gianni W, Assisi A, Volpe M. Arterial stiffness is an independent risk factor for cognitive impairment in the elderly: a pilot study. J Hypertens. 2005;23:1211-1216.: less than 100 participants.

28. Suleman R, Padwal R, Hamilton P, Senthilselvan A, Alagiakrishnan K. Association between central blood pressure, arterial stiffness, and mild cognitive impairment. Clin Hypertens. 2017;23:2.: less than 100 participants.

29. Tarumi T, Gonzales MM, Fallow B, Nualnim N, Pyron M, Tanaka H, Andreana P. Central artery stiffness, neuropsychological function, and cerebral perfusion in sedentary and endurance-trained middle-aged adults. J Hypertens. 2013;31:2400-2409: less than 100 participants.

30. Viticchi G, Falsetti L, Vernieri F, Altamura C, Bartolini M, Luzzi S, Provinciali L, Silvestrini M. Vascular predictors of cognitive decline in patients with mild cognitive
impairment. Neurobiol Aging. 2012;33:1127.e1-9.: report on intima-media thickness and
carotid plaque index

31. Wendell CR, Waldstein SR, Evans MK, Zonderman AB. Subclinical carotid
atherosclerosis and neurocognitive function in an urban population. Atherosclerosis.
2016;249:125-131.: report on carotid measurements.

32. Xiang J, Zhang T, Yang QW, Liu J, Chen Y, Cui M, Yin ZG, Li L, Wang YJ, Li J,
Zhou HD. Carotid artery atherosclerosis is correlated with cognitive impairment in an
elderly urban Chinese non-stroke population. J Clin Neurosci. 2013;20:1571-1575:
research on intima-media thickness.
Table S1. Sensitivity analyses by removing studies one by one for unadjusted cross-sectional analysis.

| Author                     | Global cognition | Executive function | Memory |
|----------------------------|------------------|--------------------|--------|
|                            | \( es \) | \( ll \) | \( ul \) | \( I^2 \) | \( Q \)-Cochrane | \( p \) | \( es \) | \( ll \) | \( ul \) | \( I^2 \) | \( Q \)-Cochrane | \( p \) | \( es \) | \( ll \) | \( ul \) | \( I^2 \) | \( Q \)-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 |                    |                  |                              |                              |                          |                      |          |
Table S2. Sensitivity analyses by removing studies one by one for adjusted cross-sectional analysis.

| Author                        | es  | ll  | ul  | I²  | Q-Cochrane | p     |
|-------------------------------|-----|-----|-----|-----|------------|-------|
| **Global cognition**          |     |     |     |     |            |       |
| 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 37           | -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         | -0.22 | -0.32 | -0.12 | 77.5 | 48.87 | <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**        |     |     |     |     |            |       |
| Geijslaers 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 36      | -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**                    |     |     |     |     |            |       |
| 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 |
| Geijslaers 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 | -0.21 | -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.

| Author                      | Global cognition |                      |            |            |       |       |       |       |
|-----------------------------|------------------|----------------------|------------|------------|-------|-------|-------|-------|
|                             | es               | I²                   | Q-Cochrane | p          |       |       |       |       |
| Al Hazzouri et al., 2013    | -0.15            | -0.26                | 0.04       | 62.2       | 10.59 | 0.032 |       |       |
| Benetos et al., 2012        | -0.22            | -0.41                | 0.03       | 89.9       | 39.73 | <0.001|       |       |
| Palta et al., 2019          | -0.22            | -0.40                | 0.04       | 89.9       | 39.73 | <0.001|       |       |
| Poels et al., 2007          | -0.26            | -0.37                | 0.16       | 54.8       | 8.86  | 0.065 |       |       |
| Scuteri et al., 2007        | -0.20            | -0.36                | 0.04       | 89.7       | 38.97 | <0.001|       |       |
| Watson et al., 2011         | -0.21            | -0.39                | 0.03       | 89.9       | 39.56 | <0.001|       |       |

| Author                      | Executive function | es       | I² |       |       |       |       |       |
|-----------------------------|---------------------|----------|----|-------|-------|-------|-------|
| Hajjar et al., 2016         | -0.11               | -0.25    | 0.02| 64.0  | 5.55  | 0.062 |       |       |
| Kim et al., 2017            | -0.12               | -0.23    | -0.01| 67.0  | 6.06  | 0.048 |       |       |
| Poels et al., 2007          | -0.18               | -0.27    | -0.09| 0.0   | 0.39  | 0.822 |       |       |
| Tsao et al., 2013           | -0.06               | -0.13    | 0.00| 0.0   | 1.67  | 0.434 |       |       |

| Author                      | Memory              | es       | I² |       |       |       |       |       |
|-----------------------------|---------------------|----------|----|-------|-------|-------|-------|
| Hajjar et al., 2016         | -0.05               | -0.17    | 0.07| 46.8  | 1.88  | 0.170 |       |       |
| Kim et al., 2017            | -0.11               | -0.23    | 0.03| 0.0   | 0.18  | 0.675 |       |       |
| Poels et al., 2007          | -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 |
|-------------------------|------------------|----------------------|
|                         | n   | ES (95% CI) | \( \chi^2 \) | Q-Cochrane | p  | n   | ES (95% CI) | \( \chi^2 \) | Q-Cochrane | p   |
| **Global cognition**    |     |             |               |            |    |     |             |               |            |     |
| Type of sample          |     |             |               |            |    |     |             |               |            |     |
| General population      | 5   | -0.20 (-0.36, -0.04) | 67.0 | 0.06 | 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     | -0.36 (-0.76, 0.04) | 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                   | 5   | -0.21 (-0.39, -0.03) | 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 | 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 | 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 (-0.30, 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 | 1   | -0.42 (-0.70, -0.14) | NA | NA | NA | 3   | -0.56 (-0.88, -0.23) | 76.6 | 8.55 | 0.014 |
| aPWv                    | 0   | NA | NA | NA | NA | 0   | NA | NA | NA | NA | 0 | NA | 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) | 0.0 | 0.91 | 0.923 |
| 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 | 0 | NA | NA | NA | NA | NA |
| aPWv                    | 1   | -0.14 (-0.31, 0.03) | NA | NA | NA | 0   | NA | NA | NA | NA | 0 | NA | 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.

|                      | Global cognition | Executive function | Memory |
|----------------------|------------------|--------------------|--------|
|                      | Longitudinal data | Cross-sectional data | Longitudinal data | Cross-sectional data | Longitudinal data | Cross-sectional data |
|                      | Unadjusted       | Adjusted           | Unadjusted       | Adjusted           | Unadjusted       | Adjusted           |
|                      |                  |                    |                  |                    |                  |                    |
| % female             |                   |                    |                  |                    |                  |                    |
| n                    | 4                | 9                  | 4                | 3                  | 11               | 13                |
| ß (95% CI)           | (-0.03, 0.02)    | (-0.01, 0.02)      | (-0.05, 0.05)    | (-0.05, 0.0)      | (-0.01, 0.01)    | (-0.01, 0.01)     |
| Age                  | 0.690            | 0.497              | 0.512            | 0.910             | 0.949            | 0.548             |
| p                    | 0.01             | 0.00               | 0.00             | 0.01              | 0.00             | 0.01              |
| BMI                  | 0.643            | 0.649              | 0.286            | 0.449             | 0.833            | 0.00              |
| p                    | 0.04             | 0.02               | 0.06             | 0.05              | 0.05             | 0.00              |
| SBP                  | 0.727            | 0.338              | 0.640            | 0.512             | 0.684            | 0.587             |
| p                    | 0.02             | 0.02               | 2                | 0.824             | 1                | 2                 |
| DBP                  | 0.227            | 0.062              | NA               | NA                | NA               | 0.837             |
| p                    | 0.02             | 0.03               | NA               | 0.757             | 0.00             | 0.00              |

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                        | Y  | Y  | NR | Y  | NR | NR | Y  | N  | Y  | Y  | Y  | NR | Y  | Y  | 9    |
| Al Hassour et al., 2013                        | Y  | Y  | Y  | NR | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | 12   |
| Angermann et al., 2017                        | Y  | Y  | NR | Y  | NR | Y  | -  | Y  | Y  | -  | Y  | NR | Y  | Y  | 7    |
| Benetos et al., 2012                          | Y  | Y  | NR | Y  | NR | Y  | Y  | Y  | Y  | N  | Y  | NR | N  | Y  | 9    |
| Cooper et al., 2016                           | Y  | Y  | Y  | NR | NR | Y  | -  | Y  | Y  | -  | Y  | NR | Y  | Y  | 7    |
| Elias et al., 2009                            | Y  | Y  | Y  | NR | Y  | -  | Y  | Y  | -  | Y  | NR | Y  | Y  | Y  | 9    |
| Fujisawa et al., 2005                         | Y  | Y  | N  | Y  | NR | Y  | -  | Y  | Y  | -  | Y  | NR | Y  | Y  | 7    |
| Fukuhara et al., 2006                         | Y  | Y  | Y  | Y  | NR | -  | Y  | N  | Y  | -  | Y  | NR | Y  | Y  | 7    |
| Geijsselers et al., 2016                       | Y  | Y  | Y  | NR | NR | Y  | -  | Y  | Y  | -  | Y  | NR | Y  | Y  | 8    |
| Hafaj et al., 2016                            | Y  | Y  | NR | Y  | NR | Y  | Y  | Y  | Y  | Y  | NR | Y  | Y  | Y  | 10   |
| Hanon et al., 2005                            | Y  | Y  | NR | Y  | NR | -  | Y  | Y  | -  | Y  | Y  | -  | Y  | 8    |
| Karamavdou et al., 2018                        | Y  | Y  | Y  | NR | NR | -  | Y  | Y  | -  | Y  | NR | -  | Y  | 8    |
| Kearney-Schwartz et al., 2009                  | Y  | Y  | Y  | Y  | NR | -  | Y  | Y  | -  | Y  | Y  | -  | Y  | 10   |
| Kim et al., 2009                               | Y  | Y  | N  | Y  | NR | -  | N  | Y  | Y  | -  | Y  | NR | Y  | Y  | 4    |
| Kim et al., 2017                               | Y  | Y  | Y  | NR | NR | Y  | Y  | Y  | Y  | NR | Y  | Y  | Y  | Y  | 11   |
| Lamballais et al., 2018                        | Y  | Y  | Y  | NR | NR | -  | N  | Y  | -  | Y  | NR | -  | Y  | 7    |
| Lee et al., 2014                               | Y  | Y  | Y  | NR | NR | -  | N  | Y  | -  | Y  | NR | -  | Y  | 7    |
| Lim et al., 2016                               | Y  | Y  | NR | Y  | NR | -  | N  | Y  | -  | Y  | NR | -  | Y  | 6    |
| Meyer et al., 2017                             | Y  | Y  | N  | Y  | NR | -  | Y  | Y  | -  | Y  | NR | -  | Y  | 7    |
| Mitchell et al., 2016                          | Y  | Y  | N  | Y  | NR | -  | Y  | Y  | -  | Y  | NR | -  | Y  | 7    |
| Muela et al., 2018                             | Y  | Y  | NR | Y  | NR | -  | Y  | Y  | -  | Y  | Y  | -  | Y  | 8    |
| Poels et al., 2018                             | Y  | Y  | N  | Y  | NR | -  | Y  | Y  | -  | Y  | NR | -  | Y  | 7    |
| Ryu et al., 2017                               | Y  | Y  | NR | Y  | NR | -  | N  | Y  | -  | Y  | N  | -  | N  | 5    |
| Scuteri et al., 2007                           | Y  | Y  | Y  | NR | NR | -  | N  | Y  | -  | Y  | Y  | -  | Y  | 8    |
| Singer et al., 2013                            | Y  | Y  | N  | Y  | NR | -  | N  | Y  | -  | Y  | NR | -  | Y  | 7    |
| Sugawara et al., 2010                          | Y  | Y  | Y  | NR | NR | -  | Y  | Y  | -  | Y  | NR | -  | Y  | 8    |
| Taniguchi et al., 2014                         | Y  | Y  | Y  | NR | NR | -  | Y  | Y  | -  | Y  | NR | -  | Y  | 9    |
| Triantafyllid et al., 2009                      | Y  | Y  | Y  | NR | NR | -  | Y  | Y  | -  | Y  | Y  | -  | Y  | 8    |
| Tsao et al., 2013                              | Y  | Y  | Y  | NR | NR | -  | Y  | Y  | -  | Y  | Y  | -  | Y  | 12   |
| Tsao et al., 2016                              | Y  | Y  | Y  | NR | NR | -  | Y  | Y  | -  | Y  | NR | -  | Y  | 7    |
| Tuttolomondo et al., 2017                       | Y  | Y  | NR | Y  | NR | -  | Y  | Y  | -  | Y  | NR | -  | Y  | 7    |
| Watson et al., 2011                            | Y  | Y  | NR | Y  | NR | Y  | Y  | Y  | N  | Y  | NR | Y  | Y  | 10   |
| Zhong et al., 2014                             | Y  | Y  | NR | NR | NR | -  | Y  | Y  | -  | Y  | NR | -  | Y  | 6    |

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