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Review

Association between arterial stiffness, cerebral small vessel disease and cognitive impairment: A systematic review and meta-analysis

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ABSTRACT

Arterial stiffness may be a cause of cerebral small vessel disease and cognitive impairment. We therefore performed a systematic review and meta-analysis of studies on the association between stiffness, cerebral small vessel disease and cognitive impairment. For the associations between stiffness (i.e. carotid-femoral pulse wave velocity (cfPWV), brachial-ankle PWV (baPWV), carotid stiffness and pulse pressure) on the one hand and cerebral small vessel disease and cognitive impairment on the other, we identified 23 (n = 15,666/20 cross-sectional; 1 longitudinal; 2 combined cross-sectional/longitudinal) and 41 studies (n = 57,671/26 cross-sectional; 11 longitudinal; 4 combined cross-sectional/longitudinal), respectively. Pooled analyses of cross-sectional studies showed that greater stiffness was associated with markers of cerebral small vessel disease with odds ratios, per +1 SD, of 1.29–1.32 (P < .001). Studies on cognitive impairment could not be pooled due to large heterogeneity. Some (but not all) studies showed an association between greater stiffness and cognitive impairment, and the strength of this association was relatively weak. The present study supports the hypothesis that greater arterial stiffness is a contributor to microvascular brain disease.

Contents

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1. Introduction

Increased arterial stiffness leads to an increased pulsatile pressure and flow load, which can damage the microcirculation (Mitchell, 2008; O'Rourke and Safar, 2005; Tzourio et al., 2014). The brain is more vulnerable for this increased load, because its microcirculation is characterized by low impedance, allowing the pulsatile load to penetrate deeply into its microvascular bed (Mitchell, 2008; O'Rourke and Safar, 2005; Tzourio et al., 2014). In the brain, microvascular damage can manifest itself as white matter hyperintensities (WMH), cerebral microbleeds and lacunar infarcts (Wardlaw et al., 2013b), which may ultimately result in cognitive impairment, including dementia (Mitchell et al., 2011).

Currently, consistent evidence is lacking, however, to support an association between increased arterial stiffness on the one hand and cerebral small vessel disease and cognitive impairment on the other, despite the fact that in recent years a growing number of studies have been done on this issue. Existing studies were done in diverse study populations and evaluated different measures of cerebral small vessel disease, cognitive function and arterial stiffness. Measures of arterial stiffness included carotid-femoral pulse wave velocity (cfPWV), brachial-ankle PWV (baPWV) and local distensibility measurements of the carotid artery (i.e. local carotid stiffness). These indices reflect stiffening of different parts of the arterial tree, and may be differentially associated with cerebral small vessel disease and cognitive impairment (Safar and O'Rourke, 2006). In addition, some studies used pulse pressure (PP) (i.e. the difference between systolic and diastolic blood pressure) as a surrogate measure of arterial stiffness. PP is, however, determined by factors other than arterial stiffness, including stroke volume and wave reflections (Safar and O'Rourke, 2006). This may affect the association between arterial stiffness and cerebral small vessel disease and cognitive impairment.

Three previous reviews (Pase et al., 2012; Rabkin and Jarvie, 2011; Singer et al., 2014) have examined the association between arterial stiffness and microvascular brain disease. However, these studies evaluated only cognitive impairment (Pase et al., 2012; Rabkin and Jarvie, 2011), included a limited number of measures of arterial stiffness and cognitive impairment (Pase et al., 2012; Rabkin and Jarvie, 2011), included only studies done in healthy individuals (Singer et al., 2014), did not perform a study quality assessment (Pase et al., 2012; Rabkin and Jarvie, 2011; Singer et al., 2014) and(or) did not do a meta-analysis (Singer et al., 2014).

In view of the above, we performed a systematic review and meta-analysis of observational studies on the association between, on the one hand, arterial stiffness (i.e. cfPWV, baPWV, local carotid stiffness and PP) and, on the other, markers of cerebral small vessel disease and cognitive impairment.

2. Methods

This systematic review and meta-analysis is reported in accordance with the PRISMA guidelines (Moher et al., 2009) (the PRISMA checklist is provided as Supplementary material).

2.1. Data sources

We identified relevant studies through a search of Medline and Embase from inception to July 18, 2014 (search terms are provided as Supplementary material). In addition, we identified studies by reviewing the reference lists of all relevant articles identified.

2.2. Study selection and evaluation procedure

Two reviewers (TVS and AP) selected independently all relevant studies based on title and abstract, retrieved selected full texts, performed an eligibility assessment, assessed risk of bias and extracted data from each eligible study (described below). Any disagreements between the reviewers were resolved by consensus.

2.3. Eligibility criteria

Human studies were eligible if they met the following criteria: (1) cross-sectional or longitudinal in design; (2) sample size $n \geq 150$; (2) investigated an association between, on the one hand, arterial stiffness and, on the other, markers of cerebral small vessel disease and(or) cognitive function; and (3) measured arterial stiffness by cfPWV, baPWV or local carotid arterial stiffness, and(or) measured PP, either at the level of the brachial artery (i.e. peripheral PP) or carotid artery or aorta (i.e. central PP). Case-control studies were excluded, because these studies, in general, have a relatively low internal validity. For cerebral small vessel disease, we selected all studies with data on any of the following magnetic resonance imaging (MRI)-detected markers: WMH, cerebral microbleeds and lacunar infarcts (Wardlaw et al., 2013b). In addition, most silent infarcts (i.e. infarcts detected in individuals without a history of stroke/transient ischaemic attack) and subcortical infarcts (i.e. cerebral infarcts in the deep brain regions not extending into the cortex) are lacunar (Wardlaw et al., 2013b), and were also included. Studies that used computed tomography (CT) to detect markers of cerebral small vessel disease were excluded, because CT is less sensitive than MRI (Wardlaw et al., 2013b). For cognitive function, we selected all studies with data on any measure of global and(or) domain-specific cognitive function. Only papers

written in English were included. For studies that published more than one article based upon overlapping groups of participants, with the same outcome measure and study design, we included the study with the largest number of participants.

2.4. Assessment of risk of bias

Risk of bias was evaluated with a slightly modified version of the Newcastle Ottawa Scale (NOS) (Wells et al.) (NOS is provided as Supplementary material). The NOS includes items on participant selection, validity of measurements, whether or not results were adjusted for age, systolic and(or) mean blood pressure, and (for studies on cognitive function) education, plus (for longitudinal studies) duration and completeness of follow-up.

2.5. Data extraction

Information on the following items was extracted from each study with use of a standardized form: design, sample size, population characteristics, measures of arterial stiffness, cerebral small vessel disease and cognitive impairment, unadjusted and(or) adjusted results and variable(s) that were adjusted for in the original analyses. Classification of cognitive domains and included cognitive function tests are described in Table S1 (Supplementary material). Additional data were requested for two studies (Kearney-Schwartz et al., 2009; Nomura et al., 2010) from corresponding authors; one (Nomura et al., 2010) provided the requested data.

2.6. Statistical analysis

We intended to pool results of studies that were sufficiently homogeneous with regard to study methodology and statistical analysis. However, such a meta-analysis was methodologically possible only for the cross-sectional association between cfPWV, baPWV and local carotid stiffness on the one hand and markers of cerebral small vessel disease on the other. Results of studies on PP or cognitive impairment could not be pooled due to a large heterogeneity between studies (see below).

For the meta-analysis, results were pooled for the association between cfPWV, baPWV and local carotid stiffness on the one hand and a categorical measure of cerebral small vessel disease on the other. When more than two categories were present for WMH, we used the odds ratio (OR) for the highest compared to the lowest category. For studies that measured deep and periventricular WMH separately and did not provide a measure of total WMH, we included the results for periventricular WMH only, because periventricular WMH is more closely related to total WMH (DeCarli et al., 2005). For studies that measured lobar and deep cerebral microbleeds separately and did not provide a measure of total microbleeds, we included the results for deep microbleeds only, because deep microbleeds are more strongly associated with microvascular damage (Poels et al., 2010). Pooled standardized ORs were calculated with the use of the random-effects inverse variance method. If available, we included the fully adjusted value for the OR. Heterogeneity between studies was investigated with Higgins I^2 statistic and Cochran's Q test. An $I^2 > 50\%$ and(or) a Q test P-value < .05 indicated statistical heterogeneity. Funnel plots were used to evaluate potential publication bias. The meta-analysis was performed with Cochrane Review Manager Version 5.2.

3. Results

3.1. Selection process and study characteristics

Fig. 1 shows the selection process of included studies. Of the 23 studies included on cerebral small vessel disease (n = 15,666; 20 cross-sectional; 1 longitudinal; 2 combined cross-sectional/longitudinal), eight evaluated cfPWV (n = 5017), 7 baPWV (n = 3176), 1 local carotid stiffness (n = 912) and 12 PP (n = 10,775; 8 office PP, 2 ambulatory PP, 3 central PP). Of the 41 studies on cognitive impairment (n = 57,671; 26 cross-sectional; 11 longitudinal; 4 combined cross-sectional/longitudinal), 13 evaluated cfPWV (n = 12,578), 4 baPWV (n = 1313), 1 local carotid stiffness (n = 3714) and 28 PP (n = 50,408; 26 office PP, 3 central PP). Markers of cerebral small vessel disease studied were WMH (17 studies), microbleeds (6 studies) and infarcts (10 studies). Measures of cognitive function included dementia (8 studies) and tests of global cognitive

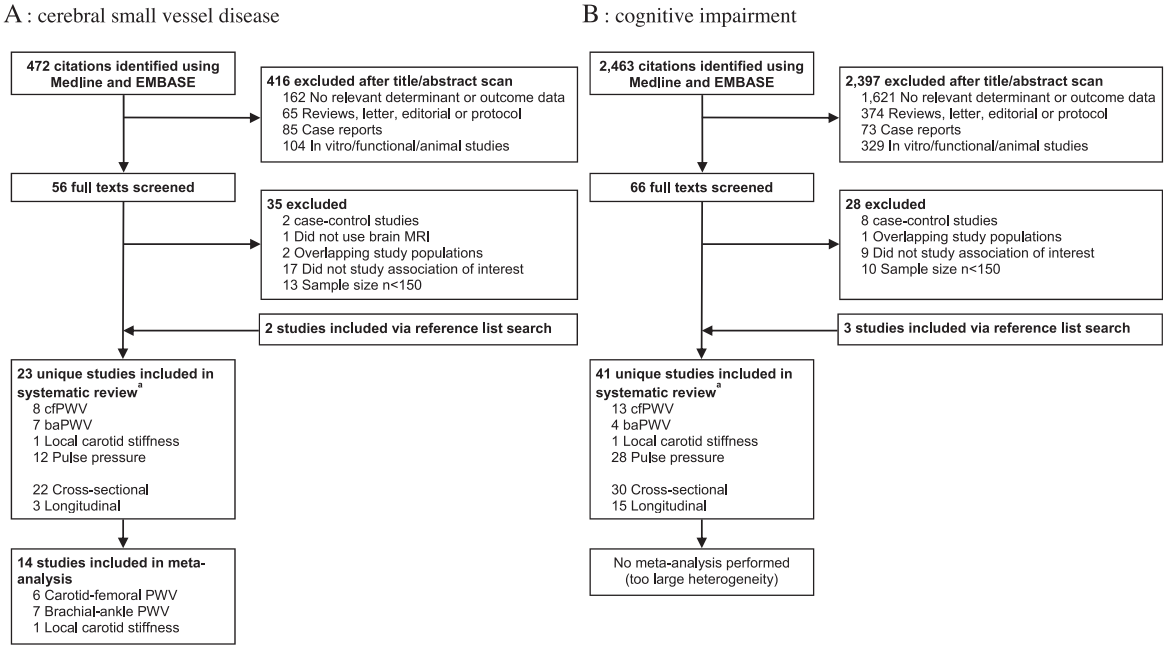

Fig. 1. Flow diagram of selection process of eligible studies on the association between arterial stiffness and cerebral small vessel disease (panel A) and cognitive impairment (panel B). [a]Some studies evaluated multiple stiffness indices and included both a cross-sectional and a longitudinal data analysis.

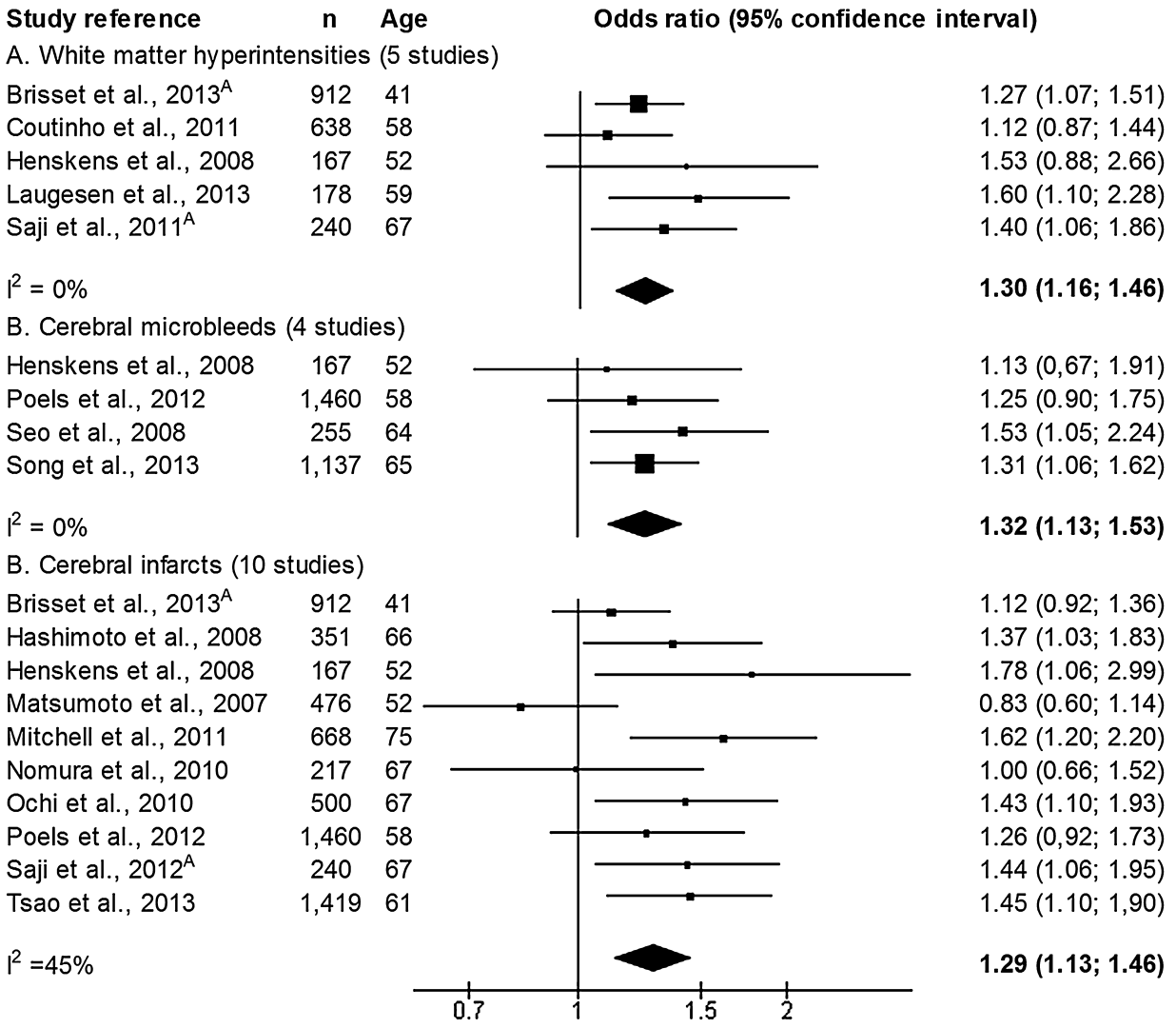

Fig. 2. Results of the pooled analysis of the association between arterial stiffness and white matter hyperintensities (panel A), cerebral microbleeds (panel B) and cerebral infarcts (panel C). Odds ratios are expressed per +1SD of each stiffness index. [A]All included studies had adjusted the results for age and mean or systolic blood pressure, with the exception of Brisset et al. (2013), Ochi et al. (2010), and Saji et al. (2011, 2012), which had not adjusted for mean or systolic blood pressure. SD, standard deviation; carotid, local carotid stiffness; cfPWV, carotid-femoral pulse wave velocity; baPWV, brachial-ankle pulse wave velocity (Brisset et al., 2013; Coutinho et al., 2011; Henskens et al. 2008; Laugesen et al., 2013; Hashimoto et al. 2008; Matsumoto et al., 2007; Ochi et al. 2010; Tsao et al. 2013; Saji et al. 2011, 2012; Poels et al., 2012; Seo et al., 2008; Song et al., 2013; Mitchell et al. 2011; Nomura et al., 2010).

function (26 studies), memory (14 studies), processing speed (13 studies) and executive function/attention (16 studies). The studies were conducted in the general population, or in selected clinical populations (e.g. individuals with diabetes, hypertension, stroke or Alzheimer's disease) (references and full study characteristics are provided as Supplementary material, Tables S2–S5).

3.2. Association between arterial stiffness and cerebral small vessel disease

3.2.1. CfPWV, baPWV and local carotid stiffness (Fig. 2)

Of the 15 cross-sectional studies included on the association between cfPWV, baPWV and local carotid stiffness on the one hand and markers of cerebral small vessel disease on the other, eleven (73%) showed a statistically significant association between greater arterial stiffness and cerebral small vessel disease.

The one longitudinal study (Rosano et al., 2013) (Health Ageing and Body Composition study; $n = 303$, mean follow-up duration 7 years) showed a significant association between baseline cfPWV and WMH volume in the left superior longitudinal fasciculus at follow-up (for $\geq$ versus < median WMH volume in this region, standardized OR: 1.47 (95%CI 1.10; 1.95)).

For the pooled analysis, 14 cross-sectional studies ($n = 8618$) were included (no longitudinal studies), of which six had measured cfPWV, seven baPWV and one local carotid stiffness. One cross-sectional study ($n = 184$) (Kearney-Schwartz et al., 2009) was excluded from this analysis because this study did not provide sufficient data. The pooled analyses showed that arterial stiffness was statistically significantly associated with WMH (Fig. 2, panel A), cerebral microbleeds (panel B) and cerebral infarcts (panel C). There was no significant statistical heterogeneity (Fig. 2). In addition, there was no funnel plot asymmetry (see Supplementary material, Fig. S1). When we performed the pooled analyses separately for baPWV and cfPWV, both indices were associated with markers of cerebral small vessel disease (ORs for +1SD cfPWV 1.39 (95%CI 1.21; 1.60) and for +1SD baPWV 1.26 (95%CI 1.08; 1.46)) (see Supplementary material, Fig. S2). In addition, when we repeated the analysis after excluding studies with a relatively high risk of bias (NOS score ≤ 3; two studies), results did not materially change (data not shown).

Table 1
Summary of study results on the association between pulse pressure and cerebral small vessel disease.

Reference	Index	*n*	Age (y)	Standardized effect estimate or direction of association[a]			Adjustments	
				WMH	Microbleeds	Infarcts	Age	Blood pressure
Cross-sectional studies (12 studies)								
Poels et al. (2010)/Verhaaren et al. (2013)[b]	off	3979	60	β 0.08*	OR 1.09		x	
Tsao et al. (2013)	cent	1419	61	β 0.002		OR 0.97	x	x
Liao et al. (1997) (1)[c]	off	843	63	OR 1.32			x	
Liao et al. (1997) (2)[c]	off	728	61	OR 2.17*			x	
Aribisala et al. (2014)	off	694	73	β 0.04			x	
Kim et al. (2011)	off	692	63	+*			x	x
Mitchell et al. (2011)	cent	668	75	β −0.02		OR 1.71*	x	x
Ochi et al. (2010)[d]	off	500	67			OR 1.10	x	
Kim et al. (2012)	off	236	66	+*			x	
Naganuma et al. (2011)	off	179	58		OR 1.73*			x
Kwon et al. (2014)	amb	169	66	+			x	x
Henskens et al. (2008)	amb	167	52	OR 0.90	OR 0.93	OR 0.93	x	x
De Leeuw et al. (2004)	off	152	68	+			x	
Longitudinal studies (2 studies)								
Verhaaren et al. (2013)	off	655	62	+*			x	
Van Dooren et al. (2014)	amb	169	53		OR 1.95		x	

Studies are ordered from largest to smallest sample size.
[a] If available, (fully adjusted) standardized effect estimates are presented. If not, direction of association is presented.
+: higher PP associated with higher prevalence/incidence of markers of cerebral small vessel disease.
−: higher PP associated with lower prevalence/incidence of markers of cerebral small vessel disease.
=: no association between PP and cerebral small vessel disease; direction of association not indicated in original manuscript.
[b] Studies based on an overlapping population (Rotterdam study). Poels et al. (2010) describes the association between PP and microbleeds in the total population (*n* = 3979). Verhaaren et al. (2013) describes in a subsample (*n* = 655) the association between PP and WMH.
[c] Analyses stratified for European-Americans (1) and African-Americans (2). Results not available for the total study population.
[d] Ochi et al. (2010) also evaluated the association between office PP and WMH; results for office PP were qualitatively similar to results for central PP.
y, years; WMH, white matter hyperintensities; OR, odds ratio; off, office pulse pressure; amb, ambulatory pulse pressure; cent, central pulse pressure.
* *P* < .05.

3.2.2. Pulse pressure (Table 1)

Studies on the association between PP and cerebral small vessel disease differed markedly with regard to the statistical analysis performed. For instance, studies modelled PP as a continuous and categorical variable and calculated standardized and unstandardized effect estimates. Hence, a pooled analysis was not possible. Nevertheless, 6 of the 12 (50%) cross-sectional studies included showed a statistically significant association between higher PP and markers of cerebral small vessel disease. The reported standardized regression coefficients ranged from −0.02 to 0.08, and the standardized ORs from 0.90 to 2.17.

Of the two longitudinal studies, one (Verhaaren et al., 2013) (Rotterdam Study; *n* = 655, mean follow-up duration 3.5 years) showed a statistically significant association between higher baseline PP and increase in WMH over time (regression coefficient per +1 SD PP for decline in ml WMH volume/year: −0.04 (95%CI 0.00; 0.08)). The other study (Van Dooren et al., 2014) included individuals with hypertension (*n* = 169; mean follow-up duration 2 years) and showed a not statistically significant association between higher baseline ambulatory PP and progression of CMB over time (standardized OR 1.95 (95%CI 0.95; 3.90)).

3.2.3. Risk of bias and heterogeneity between studies

Risk of bias among the included studies is presented in detail in Table S6 (Supplementary material). There was a moderate risk of bias of across the studies on cerebral small vessel disease (79% of the studies scored ≥80% of the total points on the NOS). A lower NOS score was primarily due to the failure to adjust in the analysis for systolic or mean blood pressure (46% of the studies). In general, the directionality of the effects did not relate to risk of bias. Studies that found a significant association between greater arterial stiffness and cerebral small vessel disease as compared to those studies which did not find such an association did not differ with regard to the variables that they adjusted for in the analysis (i.e. 50% of significant studies had adjusted for age and blood pressure versus 54% of the nonsignificant studies, *P*-value = .83). In addition, there were no differences between significant and nonsignificant studies with regard to sample size (mean *n* = 778 versus *n* = 521), age of the study population (mean age: 65.5 versus 60.8 years), type of population studied (56% and 44% of significant studies were conducted in general healthy populations and selected clinical populations, respectively, versus 31% and 69% of the nonsignificant studies), and total NOS score (for cross-sectional studies, mean score: 4.1 versus 3.8 points; for longitudinal studies, mean score: 6.0 versus 4.0 points) (*P*-values > .07).

3.3. Association between arterial stiffness and cognitive impairment

3.3.1. CfPWV, baPWV and local carotid stiffness (Table 2)

Studies on the association between cfPWV, baPWV and local carotid stiffness on the one hand and cognitive impairment on the other differed markedly with regard to the methodology used. For instance, studies used many different tests of cognitive function and performed different statistical analyses. Hence, a pooled analysis was not possible. Of the 11 cross-sectional studies included on global cognitive impairment (i.e. assessment of dementia or global cognition test), six (55%) showed a statistically significant association with greater arterial stiffness. In addition, memory was studied in eight cross-sectional studies: two found a statistically significant negative association with greater arterial stiffness. For processing speed, two out of seven, and for executive function/attention, one out of seven cross-sectional studies reported a statistically significant negative association. The reported standardized regression coefficients ranged from −0.05 to 0.20.

Of the four longitudinal studies included (mean follow-up duration ranged from 1 to 11 years), three showed a significant association between greater arterial stiffness and global cognitive decline. Three longitudinal studies also reported data on cognitive decline in specific domains. Only one study found a

Table 2
Summary of study results on the association between cfPWV, baPWV and local carotid stiffness on the one hand and cognitive impairment on the other.

Reference	Index	*n*	Age (y)	Standardized effect estimate or direction of association[a]					Adjustments	
				Dementia	Global score	Memory	Processing speed	EF/A	Age	Blood pressure
Cross-sectional studies (15 studies)										
Poels et al. (2007)[b]	cfPWV	3714	72		+		+	+*	x	x
Tsao et al. (2013)	cfPWV	1578	61			β −0.01		β 0.07	x	x
Zhong et al. (2013)	cfPWV	1433	75		+*	+*	+	+	x	
Mitchell et al. (2011)	cfPWV	668	75			β 0.10*	β −0.03	β 0.08	x	x
Watson et al. (2011)	cfPWV	552	73		β 0.11*	β 0.07	β 0.12*		x	x
Elias et al. (2009)	cfPWV	409	61		=	=	β 0.13*		x	x
Muller et al. (2007)	cfPWV	396	60			β 0.01	β 0.02	β 0.01	x	
Sugawara et al. (2010)	baPWV	388	69		+				x	x
Kim et al. (2009)	baPWV	370	55		=					
Fujiwara et al. (2005)	baPWV	352	77		+*				x	x
Singer et al. (2013)	cfPWV	319	80		β −0.05	β 0.20	β 0.05	β −0.03	x	x
Hanon et al. (2005)	cfPWV	308	78	OR 2.63*	+*				x	x
Scuteri et al. (2013)	cfPWV	280	78		+*				x	
Fukuhara et al. (2006)	baPWV	203	85		+*				x	x
Kearney-Schwartz et al. (2009)	cfPWV	198	69			=		=		
Longitudinal studies (4 studies)										
Poels et al. (2007)[b]	cfPWV	2767	71	HR 0.91	OR 0.93[c]		OR 1.09[c]	OR 1.10[c]	x	x
Zeki Al Hazzouri et al. (2013)/Watson et al. (2011)[d]	cfPWV	2488	74		+*	+	–		x	x
Benetos et al. (2012)	cfPWV	873	88		+*				x	x
Waldstein et al. (2008)	cfPWV	582	54		+*	+*	+	+	x	x

Studies are ordered from largest to smallest sample size.

[a] If available, (fully adjusted) standardized effect estimates are presented. If not, direction of association is presented. Mean effect estimates are presented if multiple results were available for the same cognitive domain.

+: greater arterial stiffness associated with worse cognitive function.

–: greater arterial stiffness associated with better cognitive function.

=: no association between arterial stiffness and cognitive function; direction of association not indicated in original manuscript.

[b] Poels et al. (2007) also evaluated the association between carotid stiffness and cognitive impairment; results for carotid stiffness were qualitatively similar to results for carotid-femoral pulse wave velocity.

[c] Cognitive decline specified as >−1SD change of the mean difference between examinations.

[d] Studies based on an overlapping study population (health, ageing, and body composition study). Zeki Al Hazzouri et al. (2013) describes the association between carotid-femoral pulse wave velocity and global cognitive decline in the total population ($n = 2488$). Watson et al. (2011) describes in a subsample ($n = 522$) the association between carotid-femoral pulse wave velocity and global cognitive decline, memory and processing speed.

y, years; EF/A, executive function/attention; OR, odds ratio; HR, hazard ratio; cfPWV, carotid-femoral pulse wave velocity; carotid, local carotid stiffness; baPWV, brachial-ankle pulse wave velocity.

* $P < .05$.

statistically significant association between greater arterial stiffness and decline in memory. Associations with cognitive decline in other specific domains (i.e. processing speed and executive function/attention) were not statistically significant. The reported standardized ORs/HRs ranged from 0.91 to 1.10.

3.3.2. *Pulse pressure (Table 3)*

In general, studies on the association between PP and cognitive impairment had more heterogeneous results than those on cfPWV, baPWV and local carotid stiffness and cognitive impairment. Of the 13 cross-sectional studies included on global cognitive impairment, four (31%) showed a statistically significant association with greater PP. In addition, memory was studied in seven cross-sectional studies: four found a statistically significant negative association with greater PP. For processing speed, two out of six, and for executive function/attention, two out of nine cross-sectional studies reported a statistically significant negative association. The reported standardized regression coefficients ranged from −0.02 to 0.16. In contrast, three studies (Davis et al., 2003; Molander et al., 2010; van Bruchem-Visser et al., 2009) found a statistically significant association, but in the opposite direction, i.e. between higher PP and better (global and(or) domain-specific) cognitive function (Table 3). These studies were done in individuals with Alzheimer's disease (Davis et al., 2003; van Bruchem-Visser et al., 2009) or in the oldest old (i.e. individuals ≥85 years) (Molander et al., 2010).

Of the 13 longitudinal studies on global cognitive decline (mean duration of follow-up ranged from 1 to 14 years), three (23%) showed a statistically significant association with greater PP. In addition, three longitudinal studies also reported data on cognitive decline in specific domains. All studies found a significant association with decline in executive function/attention and one with decline in memory, but none found a statistically significant association with processing speed. In addition, one study (Qiu et al., 2003) found a U-shaped association between PP and cognitive decline, whereas one study (Sabayan et al., 2012) found a statistically significant association between higher PP and lower cognitive decline. The latter two studies were both done in older individuals (mean age 82 and 85 years, respectively) (Table 3). The reported standardized ORs ranged from 0.85 to 1.21.

3.3.3. *Risk of bias and heterogeneity between studies*

There was a moderate risk of bias of across the studies on cognitive impairment (62% of the studies scored ≥80% of the total points on the NOS) (individual NOS scores are provided as Supplementary material, Table S6). A lower NOS score was primarily due to the failure to adjust in the analysis for systolic or mean blood pressure (52% of the studies). Studies that found a significant association between arterial stiffness and cognitive impairment as compared to those studies which did not find such an association had a smaller sample size (mean $n = 1190$ versus $n = 1737$), but this difference was not statistically significant (P-value = .49). There were no differences between significant and nonsignificant studies with regard to the variables that they adjusted for in the analysis (i.e. 58% of significant studies had adjusted for age, education and blood pressure versus 39% of the nonsignificant studies), age of the study population (mean age: 70.0 versus 71.4 years), type of population studied

Table 3
Summary of study results on the association between pulse pressure and cognitive impairment.

Reference	Index	*n*	Age (y)	Standardized effect estimate or direction of association[a]					Adjustments	
				Dementia	Global score	Memory	Processing speed	EF/A	Age	Blood pressure
Cross-sectional studies (17 studies)										
Tsivgoulis et al. (2009)	off	19,836	65		OR 0.98				x	
Obisesan et al. (2008)	off	5408	71		+*				x	
Tsao et al. (2013)	cent	1578	61			β 0.07*		β 0.02	x	x
Robbins et al. (2005)	off	1563	49		+*	+*	+*	=	x	x
Mitchell et al. (2011)	cent	668	75			β 0.11*	β −0.02	β 0.09	x	x
Davis et al. (2003)	off	609	74		−*	−*	=	−*	x	
Sabayan et al. (2012)	off	572	85		−				x	
Chrysohoou et al. (2012)	off	535	75		OR 1.41*				x	
Pase et al. (2013)[b]	cent	493	53			β 0.12*	β 0.14*	β 0.16*	x	x
Molander et al. (2010)	off	476	90		−*				x	
Fujiwara et al. (2005)	off	352	77		+*				x	
Yasar et al. (2011)	off	337	74		−	=	+	+	x	
van Bruchem-Visser et al. (2009)	off	327	77		−*				x	
Giang et al. (2013)	off	314	63		+	+	+	−	x	
Kalaitzidis et al. (2013)	off	256	53		+			+*	x	
Fukuhara et al. (2006)	off	203	85		+				x	x
Raz et al. (2011)	off	158	52					=	x	
Longitudinal studies (13 studies)										
Peters et al. (2013)	off	3337	84	+*						
Freitag et al. (2006) (1)[c]	off	2505	58	+					x	
Freitag et al. (2006) (2)[c]	off	2505	77	−					x	
Lee et al. (2013)	off	1925	73		+				x	x
Ogunniyi et al. (2011)	off	1753	76	OR 1.21*					x	
Waldstein et al. (2008)	off	1749	57		+*	+*	+	+*	x	x
Taylor et al. (2013)	off	1484	50		−				x	
Qiu et al. (2003)	off	1270	82	U*,[d]					x	x
Benetos et al. (2012)	off	873	88		=				x	x
Morris et al. (2001)	off	634	72	OR 0.85					x	
McFall et al. (2014)	off	599	71					+*		
Yang et al. (2011)	off	594	76	OR 1.00					x	
Sabayan et al. (2012)	off	572	85		−*				x	
Yasar et al. (2011)	off	337	74		+	+	+	+*	x	

Studies are from largest to smallest sample size.

[a] If available, (fully adjusted) standardized effect estimates are presented. If not, direction of association is presented. Mean effect estimates are presented if multiple results were available for the same cognitive domain.

+: higher PP associated with worse cognitive function.

−: higher PP associated with better cognitive function.

=: no association between PP and cognitive function; direction of association not indicated in original manuscript.

[b] Pase et al. (2013) also evaluated the association between office PP and cognitive impairment; results for office PP were qualitatively similar to results for central PP.

[c] Study evaluated PP measured at a mean age of 58 (1) and 72 years (2), respectively.

[d] U-shaped association between PP and cognitive decline.

Y, years; EF/A, executive function/attention; OR, odds ratio; off, office pulse pressure; cent, central pulse pressure.

* $P < .05$.

(62% and 38% of significant studies were conducted in general healthy populations and selected clinical populations, respectively, versus 79% and 21% of the nonsignificant studies), total NOS score (for cross-sectional studies, mean score: 3.9 versus 3.6 points; for longitudinal studies, mean score: 6.0 versus 6.8 points) and, for longitudinal studies, duration of follow-up (7.5 versus 7.9 years) (*P*-values > .13).

4. Discussion

4.1. Main findings

The present systematic review and meta-analysis had two main findings. First, with regard to the systematic review, most studies showed an independent association between greater arterial stiffness, as measured by cfPWV, baPWV, local carotid stiffness and PP, and markers of cerebral small vessel disease. In addition, studies found an association between higher cfPWV, baPWV and local carotid stiffness on the one hand and cognitive impairment on the other, but the strength of this association was relatively weak. In addition, results on the association between PP and cognitive impairment were inconsistent. Second, with regard to the meta-analysis, pooled analysis showed a statistically significant and strong association between greater arterial stiffness and markers of cerebral small vessel disease.

4.2. Association between arterial stiffness and cerebral small vessel disease

The results of the pooled analysis of cross-sectional studies showed that higher cfPWV, baPWV and local carotid stiffness were statistically significantly associated with markers of cerebral small vessel disease with standardized ORs of 1.29–1.32. These results strongly suggest that arterial stiffness is an important risk indicator of microvascular disease, with a strength of the association comparable to that of the association between arterial stiffness and measures of atherosclerosis (e.g. ankle-brachial index and coronary calcium score; Safar and O'Rourke, 2006).

4.3. Association between arterial stiffness and cognitive impairment

Some studies also showed an association between higher cfPWV, baPWV and local carotid stiffness on the one hand and cognitive impairment on the other. Estimated effect sizes were, however, relatively small and this association was statistically

significant in a relatively low number of studies. This weak association may be due to the fact that mechanisms other than microvascular disease play a role in the pathobiology of cognitive impairment, including neurodegenerative pathology and the process of atherothrombosis.

In addition, PP was less consistently associated with cognitive impairment than cfPWV, baPWV and local carotid stiffness. Some studies showed an association between higher PP and worse cognitive function, whereas other studies found an inverted association, i.e. higher PP was associated with better cognitive function. These studies (Davis et al., 2003; Molander et al., 2010; Sabayan et al., 2012; van Bruchem-Visser et al., 2009) were all done in (biologically) older individuals. The presence of an inverted association in these individuals may have several explanations. Possibly, cognitive impairment or the process of neurodegeneration may cause dysregulation of blood pressure and, thereby, a decline in PP (Muller et al., 2014). Alternatively, in frail older individuals low blood pressure (including low PP) may, as a result of a dysfunctional vascular system, comprise perfusion of the brain, which may manifest as cognitive impairment (Muller et al., 2014).

4.4. Methodological considerations

Some methodological issues warrant consideration. First, the associations found might have been overestimated due to publication bias. The funnel plot of studies on the association between arterial stiffness and cerebral small vessel disease did not show (substantial) asymmetry (such asymmetry may indicate the presence of publication bias). However, studies on the association between arterial stiffness and cognitive impairment that found a significant association as compared to those studies which did not find such an association had a relatively smaller sample size. This may indicate the presence of publication bias, and suggests that the association between arterial stiffness and cognitive impairment may have been overestimated in earlier research. Second, most of the included studies were cross-sectional by design, which precludes a conclusion about the temporality of the studied associations. Nevertheless, the few studies with a longitudinal design did show that greater arterial stiffness was present before the presence of cerebral small vessel disease or cognitive impairment. Third, the present review included observational studies and we, therefore, cannot draw definite conclusions on causality. Fourth, a relatively high number of the studies did not adjust for systolic or mean blood pressure. Blood pressure is an important confounder in the association between arterial stiffness and microvascular disease. In those studies that did adjust for blood pressure, however, the association between arterial stiffness and cerebral small vessel disease/cognitive impairment remained. Fifth, results of studies on PP or cognitive impairment could not be pooled due to a large heterogeneity. Sixth, due to the design of the present systematic review and (aggregate-data) meta-analysis, it was not possible to make a direct comparison between different stiffness indices with regard to the strength of their association with cerebral small vessel disease/cognitive impairment. This issue requires further study. Seventh, only a limited number of studies measured local carotid stiffness, and ambulatory PP or central PP (almost all studies evaluated brachial office PP). Evidence for an association between these indices and microvascular brain disease is, therefore, weak and this issue requires further study. Finally, it is not fully clear why some studies found a significant association between arterial stiffness and cerebral small vessel disease/cognitive impairment and others did not. There were no differences between significant and nonsignificant studies with regard to the populations studied (i.e. general healthy populations versus selected clinical populations and age of the study population) and risk of bias (NOS scores).

4.5. Assumptions underlying the studied associations

Important assumptions underlying the associations evaluated in the present review are that markers of cerebral small vessel disease are valid indicators of cerebral microvascular damage, and that microvascular damage is involved in the pathobiology of cognitive impairment. Previous studies (Fisher, 1979; Wardlaw et al., 2013a, 2013b; Young et al., 2008) have indeed demonstrated that markers of cerebral small vessel disease represent both abnormal cerebral microvascular structure and function. For instance, studies have demonstrated that WMH, cerebral microbleeds and lacunar infarcts are associated with disruption and a greater permeability of the blood-brain layer as well as arteriosclerotic changes in small arteries/arterioles. In addition, previous studies (Gorelick et al., 2011; Mitchell, 2008; Mitchell et al., 2011; Wardlaw et al., 2013b) have shown a consistent association between cerebral small vessel disease and cognitive impairment.

4.6. Underlying mechanisms

The mechanism that may underlie the observed associations is that greater arterial stiffness leads to microcirculatory damage via an increased pulsatile pressure and flow load. This increased load may directly cause cerebral microvascular damage, despite blood-pressure-related protective autoregulatory mechanisms (Mitchell, 2008; O'Rourke and Safar, 2005; Tzourio et al., 2014). Alternatively, the increased pulsatile load may induce a microvascular remodelling response, which initially serves to limit the penetration of the pressure load on the microcirculatory system by raising vascular resistance. Yet, this protective response may ultimately become unfavourable, leading to impaired vasoreactivity and microvascular ischaemia. It is, moreover, likely that these mechanisms operate simultaneously.

5. Conclusion

The present systematic review and meta-analysis shows a consistent association across different cross-sectional studies between greater arterial stiffness and markers of cerebral small vessel disease. This supports the hypothesis that greater arterial stiffness is a contributor to microvascular brain disease. The strength of the association between greater arterial stiffness and cognitive impairment was, however, relatively weak, and might have been overestimated due to publication bias. Arterial stiffness may be a therapeutic target for the prevention of microvascular brain disease and, possibly, cognitive impairment. However, further well-powered longitudinal studies are warranted that investigate the temporality of the association between arterial stiffness, cerebral small vessel disease and cognitive impairment.

Conflicts of interest

None of the authors report any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2015.03.011.

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