Neuroscience and Biobehavioral Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

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

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ARTICLE INFO

Article history:
Received 24 July 2014
Received in revised form
14 December 2014
Accepted 22 March 2015
Available online xxx

Keywords:
Arterial stiffness
Cerebral small vessel disease
White matter hyperintensities
Cerebral microbleeds
Cerebral infarcts
Cognitive impairment
Dementia
Meta-analysis
Systematic review

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 = 15,666/22 cross-sectional/3 longitudinal) and 41 studies (n = 57,671/30 cross-sectional/15 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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http://dx.doi.org/10.1016/j.neubiorev.2015.03.011
0149-7634/

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

Please cite this article in press as: van Sloten, T.T., et al., Association between arterial stiffness, cerebral small vessel disease and cognitive impairment: A systematic review and meta-analysis. Neurosci. Biobehav. Rev. (2015), http://dx.doi.org/10.1016/j.neubiorev.2015.03.011