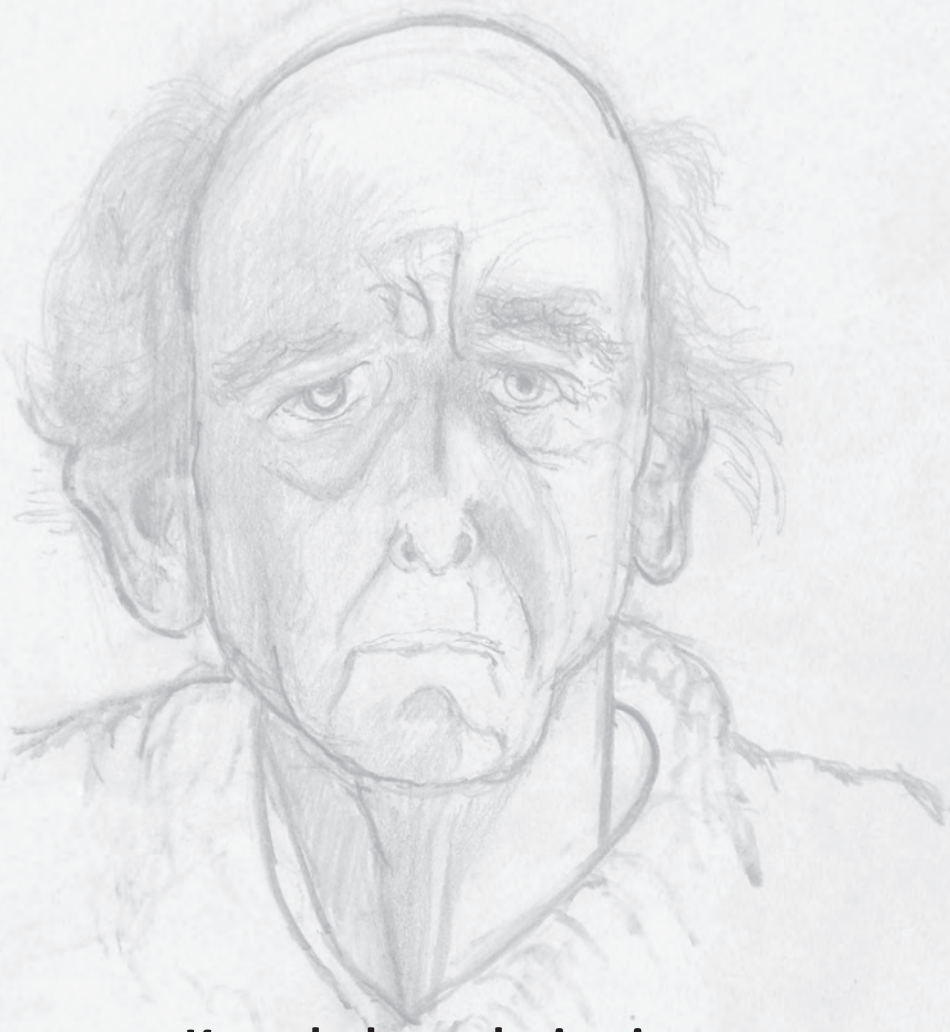
Arterial stiffness



Knowledge valorisation

Knowledge valorisation can be defined as the "process of creating value from knowledge, by making knowledge suitable and/or available for societal purposes, and suitable for translation into competitive products, services, processes, and new commercial activities" (adapted definition based on the National Committee Valorisation 2011:8). In this addendum we describe how society may benefit from the work conducted in this dissertation.

This two-part thesis focused on arterial stiffness, which has recently emerged as a risk factor for cardiovascular disease (CVD) [1,2], including coronary artery disease [3,4], stroke [4,5] and cerebral small vessel disease (CSVD) [6], and its role in the development of two of the most debilitating neuropsychiatric disorders of old age, namely late-life depression and cognitive dysfunction, as well as on its pathophysiology. The proportion of elderly individuals is expected to almost double from 12% to 22% between 2015 and 2050 [7] and more than 20% of these individuals will suffer from at least one neuropsychiatric disorder, such as late life depression, cognitive dysfunction or dementia [7]. In past years, the vascular etiology of these disorders, has received growing scientific attention. According to these vascular hypotheses [8,9], accumulation of sub-cortical and peri-ventricular CSVD disrupts neuronal circuits, which, in turn, impairs cerebral affective and executive functions, thus resulting in depression and cognitive decline. In support of these theories, the development and the accumulation of CSVD has been cross-sectionally and longitudinally associated with depression [10], cognitive impairment [9], vascular-type dementia [9] and, in some cases, even Alzheimer dementia [11]. In the **part 1** of this thesis we, therefore, expanded on these hypotheses by analysing the role of arterial stiffness in the development of depression and cognitive dysfunction in the hope to uncover additional targets for their treatment or prevention. In **part 2** we then focused on the pathophysiology of arterial stiffening, in particular on the role of advanced glycation end products (AGEs), which may offer a target for lowering arterial stiffness in addition to blood pressure lowering medication.

Our findings were largely inconclusive as most of the associations were modest and predominantly non-significant. This may suggest that only very large reductions in arterial stiffness could effectively reduce the risk of developing neuropsychiatric disorders in the general population; though currently available arterial de-stiffening strategies may improve the treatment outcomes of depressive patients. This thesis nevertheless emphasises the need to develop more effective arterial de-stiffening strategies and, in the second part we showed that AGEs may preferentially influence the most elastic descending thoracic and abdominal aortas, but not the less elastic carotid or the muscular femoral and brachial arteries. Thus, the implementation of our results in additional scientific research might improve patient care in the future.

1. Arterial stiffness and depression

The first key finding of our dissertation is that aortic stiffness, as measured by the carotid-femoral pulse wave velocity (cfPWV), may contribute to the development of depression and depressive symptoms in middle-aged (40 – 60 years) men and to a lesser extent in middle-aged women. Unfortunately, due to the cross-sectional design of the Maastricht Study we cannot prove causality, nor can we exclude reverse causality, thus, our results need to be confirmed by other (longitudinal) population-based studies before they are implemented in clinical practice. Nevertheless, this thesis does highlight the need to incorporate arterial de-stiffening therapies in the treatment of depression in middle-aged patients. Anti-hypertensive drugs, such as ACE-inhibitors, angiotensin receptor blockers and calcium-channel blockers lower arterial stiffness most effectively beyond blood pressure [12,13]. To date, two trials [14,15] have shown that in patients with MRI-confirmed vascular depression, the use of the calcium-channel blocker nimodipine in order to achieve optimal blood pressure in addition to anti-depressive medication reduces the time to remission of a major depression episode; however, these studies were small and should be confirmed in larger settings. Life-style interventions, such as aerobic exercise [16-19], dairy enriched [20] and low-sodium diets [21,22] can also decrease aortic stiffness; however, it is yet unknown whether these effects are clinically relevant. Therefore, depressive middle-aged patients with hypertension and a high aortic stiffness (ie. cfPWV > 10 m/s [23]) should be treated with de-stiffening antihypertensives in addition to adopting a healthy lifestyle in order to achieve maximal treatment effects. A possible issue in middle age is that aortic stiffness may occur in the absence of hypertension [24], in which case blood pressure lowering therapies should be carefully titrated in order to avoid hypotension and cerebral hypoperfusion. Furthermore, additional research is required to identify new drugs that lower arterial stiffness without affecting mean arterial pressure, such as compound 21 [25] and AGE-reducing therapies [26]. The second key finding of this thesis was that in elderly individuals (> 60 years) aortic stiffness is not cross-sectionally associated with depression; nor is carotid artery stiffening either cross-sectionally or longitudinally associated with more self-reported depressive symptoms after eight years follow-up. However, we cannot exclude that arterial de-stiffening therapies may have a positive impact on the outcome and prognosis of depression in the elderly as the studies included in this thesis may have been hampered by the small number of depression cases. Possibly restricting any arterial de-stiffening interventions to patients with MRI-confirmed vascular depression may be beneficial. Indeed, in his two studies with nimodipine, Taragano et al. [14,15] included only middle-aged and elderly patients with MRI-confirmed vascular depression.

Besides its therapeutic implications, additional population-based studies are needed to analyse whether aortic de-stiffening medication can prevent depression in middle-aged and elderly individuals. Current data suggests that the mental health status of the

Dutch population aged 65 or younger over the previous decade has not changed, despite improvements in the treatment and prevention of CVD [27]. Similarly, despite intensified CVD risk factor management in the past 20 years, the prevalence of depression was similar in our study as to that reported by Beekman et al. in a systematic review in 1999 [28] and to that reported by Tiemeier et al. in the Rotterdam population between the years 1997-1999 [29]. In line with these findings, the associations in this thesis were modest and predominantly non-significant, which might suggest that only very large reductions in arterial stiffness could effectively reduce the risk of developing depressive disorders in the general population. Therefore, this thesis emphasises the need to develop more effective arterial de-stiffening therapies, such as A-II type 2 receptor agonists and AGE inhibitors [25,26].

2. Arterial stiffness and cognitive dysfunction

The third key finding of this thesis is that in elderly (> 60 years) individuals, carotid artery stiffness is not associated with any of three main cognitive performance domains of cognitive dysfunction after six years of follow-up. Aortic stiffening, however, was associated with a lower information processing speed, but not with a lower attention and executive function, or memory in a small sub-population. These differential associations should be confirmed in much larger study samples, as our study was too small to compensate for the selective attrition during follow-up and, also did not allow for the testing of interactions with age, sex and type 2 diabetes. Also, the lack of associations of carotid artery stiffness with cognitive dysfunction in our study is in accordance with the only other available community-based study [30]; however, both studies may have been hampered by the measurement of these two variables at only two time points. Possibly, larger observational studies that measure carotid artery stiffness and cognitive function at multiple time points would offer a better chance of identifying any associations. Also, some have suggested that cognitive dysfunction and dementia may not necessarily form a continuum [31], therefore the association of arterial stiffness with dementia should also be researched longitudinally in a similar fashion.

Nevertheless, our current results may stimulate clinicians to lower blood pressure in elderly individuals with a high aortic stiffness. As opposed to depression, several large population-based randomised controlled trials (RCTs) [32,33] have already shown that blood pressure reduction could modestly preserve cognitive function in the elderly. These small effects could be attributed to the adverse effects of intensive blood pressure lowering, which may excessively lower diastolic and mean arterial pressure [34-36], which, in turn, may adversely affect cognitive function [37]. This may be of especial importance in patients with arterial stiffness who may also suffer from impaired reactivity of the cerebral vasculature [38] and may thus be unable to maintain constant cerebral flow at lower blood pressure

levels [39]. Specific AGE reducing therapies and AT-II type 2 receptor agonists [25,26] could reduce arterial stiffness without affecting mean arterial pressure de however, additional research is required to confirm their safety and effectiveness.

3. AGEs and the stiffening of the carotid, femoral and brachial arteries

The fourth key finding of this thesis is that neither tissue nor plasma Advanced Glycation End Products (AGEs) were associated with the stiffening of either the elastic carotid artery or the muscular femoral or brachial arteries. Although non-significant, our results offer additional insight in the pathophysiology of arterial stiffness and could have several clinical implications. The Maastricht Study already showed that both tissue and plasma AGEs are associated with higher aortic stiffness as measured by the cfPWV and central (ascending aortic) pulse pressure [40]. The cfPWV, however, represents the properties of the highly elastic descending thoracic and abdominal aortas, as well as of the muscular iliac and femoral arteries. Our lack of significant associations of AGEs within the same Maastricht Study population could imply that the most elastic thoracic and abdominal aortas are more prone to AGE accumulation than the less elastic carotid artery or the muscular femoral or brachial arteries. Thus, if confirmed in larger populations, our results may suggest that AGE-reducing therapies may be more effective in lowering aortic rather than carotid artery stiffness; and that they should therefore be included in CVD risk management strategies. Amongst others, ACE-inhibitors, statins and vitamins B 1 and 6 have been shown to have some AGE reducing properties [26]; however, no specific AGE-reducing drugs are yet available on the market. Clinicians could however inform individuals with a moderate and high CVD risk, as well as type 2 diabetes patients about the need to reduce dietary AGEs by cooking foods with water-based moisture (ie. steaming, stewing, poaching, and braising) and by avoiding processed, barbecued, grilled or fried meat. If these dietary changes are also shown to be beneficial in population-based settings [41], informational campaigns could be co-ordinated in order to raise awareness concerning this topic. Also, we cannot exclude that AGE reduction could also positively influence carotid artery stiffness, as our study was quite small and included relatively healthy T2D patients that were systematically treated with more antihypertensive and lipid-modifying therapies. Speculatively more prolonged exposure to higher concentrations of AGEs, such as occur in kidney failure patients or patients with poorly controlled T2D with micro-and macrovascular complications [42] could accelerate carotid artery stiffening. Indeed, plasma pentosidine was associated with carotid artery stiffness in a small sample of dialysis patients [43]. These hypotheses need to be confirmed first before they can be implemented in clinical practice.

Lastly, we also found that tissue AGE accumulation as measured by Skin Autofluorescence (SAF) was robustly associated with a dilation of the carotid wall but not with its thickening, which implies a relative thinning of its wall. These changes are accompanied by a higher

wall stress; which will ultimately lead to arterial stiffening by accelerating elastic fibre degradation. Furthermore, carotid artery dilation could also decrease the wall shear stress [44], which, in turn could stimulate atherosclerotic plaque formation [45]. We cannot exclude that our findings are due to the play of chance, however if our results are confirmed in larger population-based studies it could be speculated that AGE-reducing therapies may reverse carotid artery stiffening and atherosclerotic plaque formation in its incipient stages prior to elastic fibre degradation.

4. Future research avenues

In conclusion, in this valorisation addendum we expanded on the possible societal and clinical relevance of our findings. In this thesis we attempted to improve current understanding of the role played by arterial stiffening in the development of late-life depression and cognitive dysfunction. Most of the associations observed were modest and predominantly non-significant, which may suggest that only very large reductions in arterial stiffness could effectively reduce the risk of developing neuropsychiatric disorders in the general population. Physicians should nevertheless be aware of the possible adverse effects of aortic stiffening on the development of depression in middle-aged individuals and should encourage middle-aged depressive patients to adopt a healthy life-style and could consider adding de-stiffening antihypertensives in order to improve treatment outcomes. Furthermore, physicians should consider optimising systolic hypertension with de-stiffening antihypertensives in order to delay the development of cognitive dysfunction in the elderly. In the second part of this thesis we explored additional de-stiffening therapies and showed that AGEs could accelerate the stiffening of the most elastic descending thoracic and abdominal aortas. Physicians therefore also consider informing individuals with a moderate and high CVD risk, as well as type 2 diabetes patients about the need to reduce dietary AGEs.

Although the conclusions of this dissertation have several clinical and social applications, it should be noted that our significant results were based on cross-sectional data and that our longitudinal associations were largely inconclusive; thus, our knowledge is momentarily best implemented in additional scientific research that might improve patient care in the future. The Maastricht Study could offer some opportunities to analyse these research questions as it is one of the world's largest observational, prospective population-based cohort studies that focuses on the aetiology, pathophysiology, complications and comorbidities of type 2 diabetes mellitus [46].

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