The Nun Study. JAMA. 1997; 277:813-817.

## Supplemental material

### Supplemental table I. Prognostic factors for cognitive decline in patients with a non-lobar (n=88) and a lobar (n=43) haemorrhage

<table>
<thead>
<tr>
<th></th>
<th>Non-lobar ICH (n=88)</th>
<th>Lobar ICH (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated annual change in MMSE</td>
<td>Estimated annual change in MMSE</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>-0.08 (0.13)</td>
<td>0.02 (0.19)</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td>-0.06 (0.12)</td>
<td>-0.20 (0.24)</td>
</tr>
<tr>
<td><strong>Education (≤8 yrs)</strong></td>
<td>-0.01 (0.11)</td>
<td>0.13 (0.20)</td>
</tr>
<tr>
<td><strong>Vascular risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>-0.10 (0.10)</td>
<td>0.04 (0.21)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>-0.33 (0.21)</td>
<td>0.74 (0.66)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>-0.14 (0.15)</td>
<td>0.16 (0.27)</td>
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<tr>
<td>Current smoking</td>
<td>-0.04 (0.17)</td>
<td>0.35 (0.30)</td>
</tr>
<tr>
<td>Excessive alcohol consumption</td>
<td>0.08 (0.14)</td>
<td>-0.31 (0.27)</td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>-0.47 (0.20)*</td>
<td>-4.79 (2.14)*</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>0.35 (0.44)</td>
<td>-0.22 (0.36)</td>
</tr>
<tr>
<td><strong>Cognitive/Functional status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependent before ICH (Modified Rankin≥2)</td>
<td>-0.08 (0.08)</td>
<td>0.13 (0.15)</td>
</tr>
<tr>
<td>Cognitive impairment before ICH (IQCODE≥53)</td>
<td>-0.05 (0.08)</td>
<td>0.07 (0.14)</td>
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<tr>
<td><strong>Depression</strong></td>
<td></td>
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<tr>
<td>Depressive symptoms (MADRS≥7)</td>
<td>-0.01 (0.15)</td>
<td>0.45 (0.25)</td>
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<tr>
<td><strong>ICH characteristics</strong></td>
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</tr>
<tr>
<td>ICH volume</td>
<td>0.08 (0.12)</td>
<td>-0.02 (0.18)</td>
</tr>
<tr>
<td>Lobar location</td>
<td>N.a.</td>
<td>N.a.</td>
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<tr>
<td>Multiple ICHs</td>
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<td>N.a.</td>
</tr>
<tr>
<td><strong>MRI data at baseline</strong></td>
<td></td>
<td></td>
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<tr>
<td>Brain microbleed presence</td>
<td>-0.13 (0.13)</td>
<td>0.07 (0.14)</td>
</tr>
<tr>
<td>Strictly lobar brain microbleeds</td>
<td>-0.13 (0.41)</td>
<td>-0.51 (0.44)</td>
</tr>
<tr>
<td>White matter hyperintensities (Fazekas≥2)</td>
<td>0.04 (0.12)</td>
<td>-0.03 (0.18)</td>
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<tr>
<td>Lacune presence</td>
<td>-0.07 (0.13)</td>
<td>0.10 (0.28)</td>
</tr>
<tr>
<td>Global cortical atrophy (score≥2)</td>
<td>-0.13 (0.17)</td>
<td>-0.37 (0.21)</td>
</tr>
<tr>
<td><strong>Follow-up data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New stroke or TIA during follow-up</td>
<td>-0.46 (0.22)*</td>
<td>-0.44 (0.49)</td>
</tr>
</tbody>
</table>

Data are represented as β (SE). Univariate linear mixed models were used to assess the association between each variable and the rate of cognitive decline as measured with the MMSE. A random intercept and a random slope with time (in years) were assumed. The model included terms for each variable, time, the interaction between each variable and time.
Chapter 5

Summary &
General discussion
Summary

We investigated vascular MRI measures to get a better view on the role of cerebrovascular disease in cognitive decline and dementia. First, we focused on microbleeds to elucidate their clinical implication in Alzheimer’s disease (AD). Second, we explored cross-sectional and longitudinal associations with decreased cerebral blood flow (CBF) in AD. Finally, we longitudinally investigated vascular cognitive impairment (VCI) in non-demented populations.

Microbleeds in Alzheimer’s disease

In Chapter 2.1 we investigated cross-sectional associations for microbleeds and white matter hyperintensities (WMH) with clinical variables, in patients with AD. We found that microbleeds were predominantly associated with lower cerebrospinal fluid (CSF) Amyloid-Beta 42 (Aβ42) and apolipoprotein (ApoE) ε4 homozygocity; markers that indicate an additional amyloid burden in the brain. WMH, on the other hand, were mostly associated with conventional vascular risk factors, such as hypertension and smoking. Moreover, clinical associations for microbleeds were independent of their co-appearance with WMH. From this study we conclude that microbleeds, in particular in lobar locations and more specifically than WMH, relate to the presence of CAA in patients with AD.

CAA is characterized by the occurrence of intracerebral haemorrhages (ICH) and we previously found that AD patients with microbleeds had an increased risk of mortality. In Chapter 2.2 we investigated whether microbleeds in AD patients increase the risk of stroke (including ICH) and cardiovascular events. We designed the MISTRAL study (do Microbleeds predict STROKE in ALzheimer’s disease) in which follow-up data of AD patients with and without microbleeds was prospectively collected. We found that, over a minimal follow-up of 3 years, patients with microbleeds in non-lobar locations had an increased risk of cardiovascular events and cardiovascular mortality. Microbleeds in lobar locations were associated with an increased risk of stroke and stroke-related mortality. Although the small number of patients did not allow formal statistical analyses for the risk of ICH, we observed that all 5 patients with an ICH during follow-up, had lobar microbleeds at baseline. Overall these findings suggest that AD patients with lobar microbleeds are specifically vulnerable to future stroke, potentially due to the presence of CAA.

Arterial spin labelling in Alzheimer’s disease

In the second part of this thesis, we explored clinical associations with CBF, as measured using pseudo-continuous arterial spin labelling (pcASL), in AD. AD patients have a
decreased CBF, but it is not clear whether this decreased CBF is merely a reflection of neurodegeneration, or whether it is associated with small vessel disease (SVD) as well. In Chapter 3.1, we found that both a smaller brain volume and a larger WMH volume were independently associated with a lower CBF in AD. These findings suggest that a decreased CBF in AD patients reflects the combined disease burden of neurodegeneration and SVD.

In Chapter 3.2 we investigated whether decreases in CBF correspond with the predementia stages of AD. We found a continuing decrease of CBF along the continuum of AD, with patients with dementia due to AD presenting with the lowest CBF. In addition, the CBF of patients in predementia stage 2 was numerically in between the CBF of patients in predementia stage 1 and patients with dementia due to AD. These findings indicate the potential of ASL-CBF as a measure of disease progression early in AD.

As a final step, we explored whether the potential of ASL-CBF as a measure of disease progression also extended to later stages of the disease. In Chapter 3.3 we investigated whether a lower CBF at the time of diagnosis was associated with a more rapid cognitive decline in patients with AD. We found that lower CBF, in particular in posterior brain regions, was associated with a steeper rate of global cognitive decline. These findings indicate that ASL-CBF may have value as a prognostic marker for cognitive decline in patients with AD.

Vascular cognitive impairment

In the final part of this thesis we aimed to get a better understanding of the broad cognitive and vascular spectrum within the concept of VCI. In Chapter 4.1 we assessed whether SVD had prognostic value in patients with subjective cognitive decline (SCD). Patients with SCD come to the memory clinic with complaints about their cognitive abilities, but all investigations are within the normal range. These patients are generally considered to be normal, but we found that patients with multiple microbleeds were at a 3-fold, though non-significantly, increased risk of progression to mild cognitive impairment (MCI) or dementia. Moreover, strongest associations were found for WMH. WMH were not only associated with conversion to MCI or dementia, but also with decline in memory, attention, executive functioning, and global cognition over time. Lacunes were not associated with clinical progression nor with cognitive decline.

Next, we explored the vascular spectrum of VCI. In Chapter 4.2 we investigated which factors were associated with cognitive decline in a cohort of ICH survivors. Over a median follow-up of 4 years we found that almost 40% of ICH survivors showed subsequent cognitive decline. Pre-existing cognitive impairment, cortical atrophy, and vascular burden (e.g. previous stroke or transient ischaemic attack) were in particular associated with a faster rate of cognitive decline after an ICH. Prognostic factors for cognitive decline after ICH appeared to be already present when ICH occurs. These
findings suggest a process of ongoing cognitive impairment instead of new-onset decline induced by the ICH itself.

General discussion

The main aim of this thesis was to clarify the role of cerebrovascular disease in cognitive decline and dementia. We specifically focused on AD, which is classically regarded as a neurodegenerative disorder, but for which increasing evidence indicates that it results from a complex interplay of neurodegenerative and cerebrovascular changes. First of all we found that lobar microbleeds in AD patients indicate an increased amyloid deposition in the brain. Moreover, we found that microbleeds, in particular in lobar locations, have clinical relevance for the prognosis of AD patients, as they are associated with future stroke. Second, with regard to ASL-CBF, decreases in AD patients appear to be associated both with MRI markers for neurodegeneration and for SVD. Moreover, we saw that CBF starts to decrease in early (predementia) phases of AD and is still associated with rate of disease progression once patients are diagnosed with AD. Finally, when investigating the cognitive spectrum of VCI, we found that SVD has prognostic value in patients with SCD, suggesting that a preclinical stage, with only subjective complaints, may be included in the concept of VCI as well. From a vascular perspective we found in patients with ICH, that cognitive decline is mainly determined by pre-existing cognitive impairment and cortical atrophy; factors that are already present when the ICH occurs.

Methodological considerations

There are several methodological considerations that have to be considered when interpreting the results presented in this thesis.

Cohorts

Most of our studies were performed using data from the Amsterdam Dementia Cohort. For one study we used data from the Prognosis of InTra-Cerebral Haemorrhage (PITCH) cohort. A limitation of these cohorts is that they were observational and clinic-based. For our longitudinal studies, the observational design may have resulted in non-random loss to follow-up: patients who were more severely affected were more likely to be lost at follow-up. Moreover, patients within the Amsterdam Dementia Cohort are asked to return to the outpatient clinic not solely for research purposes, but rather as a part of the clinical routine. Although the clinic-based observational design may have induced a
selection bias, at the same time it enhances the relevance of our findings in a clinical setting.

An advantage of using these cohorts is that all patients received the same standardized work-up resulting in the availability of large amounts of baseline data. The MISTRAL study was performed within the Amsterdam Dementia Cohort and as we have performed T2*-weighted imaging since 2002 in all our patients, our cohort is one of the few worldwide to allow a systematic study of the clinical relevance of microbleeds in AD. The PITCH cohort combines the advantage of a hospital-based recruitment, with baseline characteristics close to a population-based recruitment. The PITCH cohort is therefore assumed to have good external validity.

Cognitive decline
In several studies we took repeated Mini-mental state examination (MMSE) scores as a measure of cognitive decline. The use of the MMSE as outcome measure may be considered a limitation. The MMSE, a 30-point questionnaire, intended for cognitive screening, is a rather crude measure of cognitive impairment that may lack sensitivity to very subtle cognitive impairment or VCI. Preferably we would have had extensive neuropsychological data available in all our longitudinal studies on cognitive decline. Nonetheless, the MMSE is a widely accepted test for the evaluation of cognition in elderly patients and is easily obtainable, thus maximizing the number of patients with available data.

Arterial spin labelling
ASL is a relatively new technique and there are still several methodological considerations with regard to the use of ASL. The spatial resolution and the signal-to-noise ratio of ASL are, for instance, both rather low and there is a relatively large between-subject variability. One of the factors that may account for this is the vulnerability of ASL to the delay time of labelled blood to the imaging plane. Ideally, artefacts resulting from delayed blood arrival to the brain tissue are circumvented by using several delay times. Nevertheless, the (single) delay time of 2.0s that we used has been recommended for a memory clinic population and is assumed to be suitable to account for variation in transit time. In addition age, sex, medication, and caffeine intake are also known to influence ASL-measured CBF. Whereas we applied an age and sex correction in all studies described in this thesis, we did not apply any correction for the possible confounding effects of medication or caffeine.

Another methodological consideration is that AD is characterized by atrophy resulting in increased partial volume effects that may directly influence CBF measurement. There is currently no consensus on which methods are best to correct for partial volume effects or cortical atrophy. In most of our papers, uncorrected and partial
volume corrected (PVC) CBF yielded comparable results. Longitudinally we found, however, conflicting results for PVC CBF versus uncorrected CBF with additional correction for atrophy rating on MRI. This suggests that the PVC method that we used is not just a straightforward correction for atrophy. ASL is considered to have potential diagnostic use, but may also help to better understand the underlying disease processes in AD. We therefore choose to report both uncorrected and PVC CBF values in our ASL studies.

The use of ASL in a memory clinic has some considerable advantages as well. ASL can be acquired during the same scanning session as structural images that are in general part of the standard dementia work-up. ASL thereby reduces patient burden and expenses, and it allows direct assessment of structure-function relationships. Currently, $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG-PET) is the standard clinical imaging tool to assess metabolic, neurodegeneration-related, changes in AD. An additional advantage of ASL in this context is that it does not require the injection of a radioactively labelled tracer.

MRI markers
Another methodological consideration is that we used MRI markers as surrogate markers for underlying pathology. Disentangling the relative contribution of underlying neurodegeneration or SVD to the MRI markers of interest was partly the aim of the present thesis. Nevertheless, at the same time, our hypotheses were based on certain assumptions and it appeared sometimes difficult to interpret our findings.

WMH are traditionally regarded a marker for SVD, associated with vascular risk factors. Nevertheless, WMH have been found in CAA patients as well: whereas the presence of WMH may contribute to subsequent increases in amyloid deposition, it has also been suggested that vascular amyloid deposition contributes to cerebral ischaemia. In addition, WMH have been associated with tau pathology, leading to the suggestion that they may also reflect Wallerian degeneration and, hence, neurodegeneration. On pathological examination WMH have indeed been found to be rather heterogeneous. Nevertheless, in AD patients WMH are generally thought to reflect hypertensive vasculopathy and we largely adhered to this assumption throughout this thesis. Moreover, we feel supported by our finding that WMH in AD patients showed strongest associations with conventional vascular risk factors (chapter 2.1).

Another marker for which underlying pathology is difficult to determine is cortical atrophy. Atrophy, generally assumed to reflect neurodegeneration, has also been found to result from chronic cerebrovascular disease. We found in ICH patients, that cortical atrophy was associated with subsequent cognitive decline. Whether this reflects the presence of underlying neurodegeneration or on-going cerebrovascular disease remains to be elucidated. In particular in populations where both
neurodegeneration and cerebrovascular pathology are assumed to be involved, there is still uncertainty regarding the pathological process underlying atrophy.

Clinical implications
The research in this thesis has several clinical implications. These will be outlined in the section below.

The relevance of microbleeds in Alzheimer’s disease
An important finding of this thesis is that microbleeds in AD indicate an increased amyloid burden in the brain and that they are associated with an increased risk of stroke. Most likely, CAA explains these findings. CAA is a disease in which the Aβ protein progressively deposits in the walls of small to medium sized arteries, arterioles, and capillaries in the cerebral cortex and CAA is a major cause of ICH. In addition to the already existing knowledge about the link between AD and CAA, we now show that the presence of CAA has clinical relevance for AD patients, as our findings seem to support the idea that in AD patients, lobar microbleeds increase the risk of ICH. We also found that, in patients with microbleeds who used antithrombotic medication, the risk of future stroke was even higher. It needs to be determined, however, whether this was merely a consequence of a more severe vascular disease, which demanded for more rigorous treatment (e.g. ‘confounding by indication’), or whether antithrombotics by themselves increase bleeding risk in AD patients with microbleeds. If this appears to be the case, their prescription depends on a complicated balance that weighs the benefits of decreased risk for ischaemic stroke or cardiovascular events, against the increased risk of ICH.

Our findings may also have implications for Aβ-immunotherapy trials. Microbleeds are seen as a side-effect in these trials, but it is still unsure whether microbleeds induced by immunotherapy confer the same risk as spontaneously occurring microbleeds. Overall, it needs to be determined whether patients with microbleeds require lower dosages or additional treatments.

Arterial spin labelling and disease progression
In addition, in this thesis we show that ASL has potential as a prognostic marker for disease progression, in early and later stages of AD. CBF is generally tightly coupled to brain metabolism, and decreased CBF is thought to reflect synaptic failure. Alterations in synaptic functioning are among the earliest pathophysiological findings in AD. In addition, synaptic dysfunction continues throughout the course of AD and is still strongly associated with cognitive decline in later stages of the disease. Overall, the associations that we found for a decreasing CBF seem to correspond with findings regarding synaptic dysfunction. We found that CBF is already decreasing in predementia
stages of AD and ASL-CBF may therefore be used as an early marker of AD. Moreover, in our longitudinal study we also show that lower CBF at the time of diagnosis is associated with cognitive decline and has predictive value for rate of disease progression even when patients are diagnosed with AD. This is important as there is currently a relative lack of predictors of cognitive decline once patients have AD.

Nevertheless, decreasing CBF may not just reflect neurodegeneration, but may also relate to (cerebro)vascular factors. An important question in ASL research in AD is whether the decreased CBF is the result of the neurodegenerative process, or whether it may also be caused by vascular factors. Our cross-sectional findings led us to suggest that decreased CBF in AD reflects both neurodegenerative and SVD changes and is therefore a measure of total disease burden. However, longitudinally we found that the associations between decreased CBF and cognitive decline were largely independent of neurodegenerative and SVD MRI markers. This suggests that, with regard to cognitive decline, lower CBF most likely reflects synaptic dysfunction.

The broad spectrum of vascular cognitive impairment
In order to better understand the association between cerebrovascular pathology and cognitive impairment, we investigated this association from two different angles: in patients with SCD and in patients with ICH. In patients with SCD we showed that WMH in particular, are associated with clinical progression and cognitive decline. We are not sure whether SVD in itself drives clinical progression, or whether it co-exists with AD pathology and by that, lowers the threshold for clinical symptoms. Currently, vascular damage is, however, not incorporated in the NIA-AA criteria that are used to diagnose AD, or in the Alzheimer biomarker-model proposed by Jack et al. The independent association that we found between WMH and clinical progression, might argue for a role for vascular pathology in the criteria and the model as well. Moreover, our findings may also have implications for the recently proposed VCI criteria. Whereas the concept of VCI has been defined by several papers, none of them explicitly included subjective complaints in the spectrum of cognitive impairment. Within the field of AD, there is increasing interest in patients in the preclinical stage of the disease, as treatment may be in particular advantageous in this group. In analogy, including patients with SCD into the concept of VCI will not only allow anticipation on next steps to be taken, but will also increase awareness for prevention and treatment.

We show in patients with ICH, who primarily suffer from (large) cerebrovascular pathology, that prognostic factors for cognitive decline after an ICH are already present when ICH occurs. This suggests a process of ongoing cognitive impairment instead of new-onset decline induced by the ICH itself. For patients admitted with an ICH, our findings emphasize the importance of careful assessment of pre-existing cognitive decline and cortical atrophy at admission. In these patients, clinicians may anticipate on
subsequent cognitive decline that may alter long-term functional prognosis and influence treatment decisions.

Future perspectives
Whereas research is designed to answer questions, it often evokes even more new questions as well. This section will touch upon some future perspectives.

Microbleeds and antithrombotic treatment
We found indications that patients with microbleeds who use antithrombotic medication have a higher risk of (unspecified) stroke. A problem with studies that are not designed to carefully evaluate the risks and benefits associated with medication, is that confounding by indication may partly explain these findings. AD patients with microbleeds may have a more severe vascular disease, for which they need antithrombotic medication, but which, at the same time, may explain the increased risks of events. Large prospective studies of patients with microbleeds, treated with antithrombotic medication are needed, in particular because this population reflects a common therapeutic dilemma. However, the ideal design to investigate the risks and benefits of medication, a randomized controlled trial, is thought to underestimate the risk of important adverse events, as the factors that are known to increase risk of bleeding are often exclusion criteria for trials on antithrombotic medication. Nevertheless, on-going trials, such as the Clinical relevance of microbleeds in stroke 2 (CROMIS-2), are expected to help tailor treatment of vascular disease in the presence of microbleeds.

Microbleeds and Amyloid-Beta immunotherapy trials
A worrisome side effect seen in immunotherapy trials for AD are amyloid-related imaging abnormalities (ARIA) that indicate leakiness or bleeding in the brain’s blood vessels. If vessels are already damaged, as indicated by the presence of microbleeds, immunotherapy may further increase the vascular risk. An intriguing finding is, however, that regions with signs of increased vascular vulnerability show the most amyloid clearance. Recently presented interim results from the Neurimmune trial show that ARIA is frequently observed as a side effect. However, only ARIA-E (edema) was observed; therapy-related haemorrhagic ARA-H, or microbleeds, were not seen in this trial. Based on MRI scans, the incidence of ARIA-E was dose- and ApoE ε4 status-dependent, and disappeared when medication was stopped. Most likely, some ARIA is necessary in order to clear the amyloid from the brain via the perivascular drainage pathway. Although we are currently unsure whether spontaneously occurring microbleeds increase the risk of ARIA, special attention should be paid to these patients...
during trials to see if and how they differ, and whether they require special doses or treatments.

Neurodegeneration or small vessel disease?
Another future perspective is the need for larger longitudinal studies with extensive follow-up to unravel the relative contribution of neurodegeneration and cerebrovascular disease to cognitive decline and dementia. The term VCI has been introduced in an attempt to facilitate research of the various types of cerebrovascular pathology that could underlie cognitive symptoms, from mild to severe.\textsuperscript{30,31} In line with this, we investigated cognitive decline in non-demented populations with small and large vessel disease. For both studies it would be, however, extremely interesting to have more information on the types of dementia in which the cognitive decline eventually resulted. Studies in comparable populations with longer and more extensive follow-up are therefore necessary. Other on-going studies are aimed at disentangling neurodegenerative and cerebrovascular pathology, for instance by studying the nature of brain atrophy (STROKDEM, \textit{clinicaltrials.gov} NCT01330160; DEDEMAS, \textit{clinicaltrials.gov} NCT01334749).

Arterial spin labelling in a memory clinic
As ASL is a relatively new technique, there are many future perspectives with the use of ASL. Implementation of ASL in a memory clinic presumably results in decreasing costs and patient burden.\textsuperscript{8} In a clinical setting, ASL could have additive value when used on a single-subject level. Calculating individual w-score maps (voxel-wise standardization for age and gender) seems to have potential in circumventing undesirable noise.\textsuperscript{38} In addition, future studies might want to explore how ASL-CBF changes over time. Follow-up CBF measurements would allow investigation of whether rate of CBF decrease is associated with rate of clinical progression. Moreover, when ASL imaging is combined with structural MRI imaging over time, a better understanding regarding interrelations and a possible temporal sequence of decreased CBF, atrophy, and the presence of SVD can be obtained. Another important future line of research may be the attempt to improve CBF by means of physical exercise. Aerobic exercise may reduce arterial stiffness and hence improve CBF. Previous studies showed a link between physical exercise and an improvement in cognition and this may, at least in part, be mediated by an improvement in CBF.\textsuperscript{39} Future studies aimed at investigating the heart-brain connection\textsuperscript{40} will hopefully provide answers on whether an impaired haemodynamic status of both heart and brain is a potentially modifiable, or even reversible, cause of VCI.
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