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Originally published:

October 2022

American Journal of Geriatric Psychiatry 30(2022)12, 1298-1309

DOI: <https://doi.org/10.1016/j.jagp.2022.06.007>

Perma-Link to Publication Repository of HZDR:

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**Association of arterial spin labeling parameters with cognitive decline, vascular events
and mortality in a memory-clinic sample**

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Acknowledgments

This work was supported by National Medical Research Council, Singapore [NMRC/CG/NUHS/2010, NMRC/CG/013/2013, NMRC/CIRG/1485/2018, NMRC/CAS-SI/007/2016], NUS start-up grant (R-608-000-257-133) and National University Health System Center grant SEED funding (R-608-000-275-511)

Data statement

The data associated with this manuscript has not been presented elsewhere.

1 **ABSTRACT**

2 **Background:** Cognitive decline in older adults has been attributed to reduced cerebral blood
3 flow (CBF). Recently, the spatial coefficient of variation (sCoV) of ASL has been proposed as
4 a proxy marker of cerebrovascular insufficiency. We investigated the association between
5 baseline ASL parameters with cognitive decline, incident cerebrovascular disease and risk of
6 vascular events and mortality.

7 **Design, Setting and Participants:** 368 memory-clinic patients underwent three-annual
8 neuropsychological assessments and brain MRI scans at baseline and follow-up. MRIs were
9 graded for white matter hyperintensities (WMH), lacunes, cerebral microbleeds (CMBs),
10 cortical infarcts and intracranial stenosis. Baseline gray (GM) and white matter (WM) CBF
11 and GM-sCoV were obtained with ExploreASL from 2D-EPI pseudo-continuous ASL images.
12 Cognitive assessment was done using a validated neuropsychological battery. Data on incident
13 vascular events (heart disease, stroke, transient ischemic attack) and mortality were obtained.

14 **Results:** Higher baseline GM-sCoV was associated with decline in the memory domain over
15 three years of follow-up. Furthermore, higher GM-sCoV was associated with a decline in the
16 memory domain only in participants without dementia. Higher baseline GM-sCoV was
17 associated with progression of WMH and incident CMBs. During a mean follow-up of 3 years,
18 29 (7.8%) participants developed vascular events and 18 (4.8%) died. Participants with higher
19 baseline mean GM-sCoV were at increased risk of vascular events.

20 **Conclusions:** Higher baseline GM-sCoV of ASL was associated with a decline in memory and
21 risk of incident cerebrovascular disease and vascular events, suggesting that cerebrovascular
22 insufficiency may contribute to accelerated cognitive decline and worse clinical outcomes in
23 memory clinic participants.

- 24 **KEYWORDS:** cerebrovascular circulation, aged, brain, spin labels, perfusion, memory-clinic,
25 cerebral blood flow, coefficient of variation

26 **List of Non-standard Abbreviations and Acronyms**

ASL	Arterial spin labeling
AD	Alzheimer's disease
ACA	Anterior cerebral artery
β	Standardized regression coefficient
CBF	Cerebral blood flow
CeVD	Cerebrovascular disease
CIND	Cognitive impairment no dementia
CMBs	Cerebral microbleeds
CI	confidence interval
DSM-IV	Diagnostic and statistical manual of mental disorders
FLAIR	Fluid-attenuated inversion recovery
HR	Hazard ratio
IQR	Inter quartile range
MARS	Microbleed Anatomical Rating Scale
MCA	Medial cerebral artery
MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiography
NCI	No cognitive impairment
OR	Odds ratio
PCA	Posterior cerebral artery
SWI	susceptibility weighted image
SD	Standard deviation;
sCoV	Spatial coefficient of variation
TIA	Transient ischemic attack
VCIND	Vascular cognitive impairment no dementia
VaD	Vascular dementia
WMH	White matter hyperintensities

28 INTRODUCTION

29 Reduced cerebral blood flow (CBF) is considered to be one of the potential underlying
30 mechanisms for cognitive impairment and dementia.¹ There are very few longitudinal studies
31 demonstrating the role of cerebral perfusion on cognition. One study reported an association of
32 lower CBF at baseline with the decline in processing speed and memory in healthy elderly
33 participants in 4-year follow-up,² whereas another study reported a decline in memory domain
34 in participants with mild cognitive impairment (MCI) in 2.7-year follow-up.¹ Furthermore,
35 there is an under-representation of participants with mixed neurodegenerative and
36 cerebrovascular pathology in current literature.³ Despite growing understanding of mixed-
37 pathology,⁴ current literature often categorizes participants into pure neurodegenerative or pure
38 vascular groups.³

39 CBF can be measured quantitatively and non-invasively at the tissue level by arterial spin
40 labeling (ASL) perfusion MRI.⁵ However, in older adults with high burden of cerebrovascular
41 disease (CeVD), the arterial transit time (ATT) of labeled blood to the tissue is often extended.
42 Longer ATT makes it difficult to quantify gray matter (GM) and white matter (WM) CBF in
43 ASL scans due to the presence of vascular artefacts and absence of tissue-perfusion signal.⁶
44 Recently, the spatial coefficient of variation (sCoV) of ASL has been proposed to quantify the
45 presence of vascular artefacts.⁶ It has been shown that sCoV of ASL highly correlates with
46 ATT, age,⁷ sex,⁶ and presence of CeVD,⁸ making it a potential proxy marker of vessel
47 insufficiency. Hence, it has been hypothesized that sCoV of ASL can better quantify perfusion-
48 related changes in the brain than ASL-derived CBF, in populations with a high prevalence of
49 vascular artifacts, and be associated with clinical outcomes.

50 Therefore, our objective is to investigate the association of baseline ASL parameters (total and
51 regional) with global and domain-specific cognitive decline over 3-year follow-up in a
52 memory-clinic sample with mixed pathology in overall population and stratified by with and

53 without dementia. Furthermore, we aim to analyze the association between baseline ASL
54 parameters with incident CeVD on brain MRI and risk of vascular events [history of stroke,
55 transient ischemic attack (TIA), and heart diseases] and mortality during the follow-up.

56 **METHODS**

57 **Study Sample**

58 Data for this study was drawn from an ongoing memory-clinic study, which recruits
59 participants from National University Hospital, Singapore. Patients diagnosed with no
60 cognitive impairment (NCI), cognitive impairment no dementia (CIND), vascular CIND
61 (VCIND), and Dementia [(Alzheimer's disease (AD), mixed-dementia and vascular dementia
62 (VaD)] at baseline were eligible for inclusion in this study [**Supplemental Digital Content-**
63 **1**].

64 All individuals underwent clinical, physical and neuropsychological assessments along with a
65 3T-MRI examination at the National University of Singapore (NUS). These assessments were
66 performed annually except for MRI, which was offered every 2 years. From August, 2010, to
67 November, 2017, a total of 579 participants were recruited for this study, of whom 464
68 participants with baseline ASL sequence and those with a minimum of 2 cognitive scores
69 including baseline and one of the follow-up scores were included in the further analysis. On
70 quality analysis of 464 ASL images; 96 were labeled as unusable (incomplete scans, ASL
71 labeling failed/severe motion artefacts), 52 as angiography (scans with dominant vascular
72 artefacts, and no or minimal tissue perfusion contrast), 151 acceptable (scans with minor
73 artefacts and reasonable tissue perfusion contrast) and 156 as good (artifact-free scans with
74 tissue perfusion contrast). For analysis with sCoV and clinical outcomes (cognitive decline,
75 incident CeVD, vascular events and mortality), a total of 368 participants were included
76 (participants with ASL sequence labeled as angiography, acceptable, and good scans). For the

77 CBF and clinical outcomes analysis, 316 participants were included (participants with ASL
78 sequence labeled as acceptable and good) [Figure 1].

79 Ethics approval was obtained from the National Healthcare Group Domain-Specific Review
80 Board. Written informed consent was obtained from all participants before they participated in
81 this study. This study was conducted in accordance with Helsinki Declaration.

82 **Neuropsychological Assessment**

83 All participants completed a detailed neuropsychological battery based on the recommendation
84 of the National Institute of Neurological Disorders and Stroke and the Canadian Stroke
85 Network (NINDS-CSN) at baseline (BL), year-1 (Y1), year-2 (Y2), and year-3 (Y3): Executive
86 function, Attention, Language, Visuospatial function, Visuomotor speed, Memory
87 [Supplemental Digital Content-2].

88 All individual test raw scores on the NINDS-CSN battery were transformed to standardized Z-
89 scores using the means and standard deviations (SD) of the comparison group (NCI). The score
90 for each domain was created by averaging the Z-scores of individual tests and standardized
91 using the composite mean and SD of the comparison group. To obtain the global cognition
92 score for each patient, the domain Z-scores were averaged and standardized using the mean
93 and SD of the comparison group. Z-scores at follow-up were obtained similarly using the data
94 of the comparison group at baseline.⁹

95 **Vascular events**

96 At baseline, history of stroke, TIA, and heart diseases were assessed during the study interviews
97 and reviewing medical records. During the follow-up, medical reports were reviewed to verify
98 any new occurrence of stroke, TIA, and heart diseases. The definition of stroke and TIA
99 followed the World Health Organization criteria.¹⁰ Heart disease was defined as the previous

100 history of atrial fibrillation, congestive heart failure, cardiac intervention, or myocardial
101 infarction.

102 Follow-up started after the date of the baseline assessment. Participants were followed-up until
103 the date of stroke, TIA, heart disease, death, date of the last contact in case of loss to follow-
104 up, or end of this study (September 2018), whichever came first. For the analysis, the history
105 of stroke, TIA, and heart disease at follow-up were combined as the incident vascular event.

106 **Mortality**

107 All-cause mortality was defined as participants who died from any cause during the follow-up
108 period.

109 **Covariates**

110 A detailed questionnaire was administered to all participants to document age, sex, race, and
111 education. Any previous history of hypertension, hyperlipidemia, and diabetes mellitus were
112 noted and verified by medical records. Hypertension was defined as a previous diagnosis of
113 hypertension, or the use of antihypertensive medications. Hyperlipidemia was defined as a
114 previous diagnosis of hyperlipidemia, or the use of lipid-lowering medications. Diabetes
115 mellitus was defined as a previous diagnosis of diabetes mellitus, or the use of glucose-lowering
116 medications.

117 **Neuroimaging**

118 All participants underwent MRI at the Clinical Imaging Research Center of NUS, using a 3T
119 Siemens Magnetom Trio Tim Scanner system, with a 32-channel head coil. Identical MRI
120 protocol at the same 3-T scanner was used for both baseline and follow-up MRIs. MRI markers
121 of CeVD such as cerebral microbleeds, lacunes, white matter hyperintensities, cortical infarcts,
122 intracranial stenosis were graded at baseline and follow-up based on the Standards for
123 Reporting Vascular Changes on Neuroimaging criteria.¹¹ [**Supplemental Digital Content-3**].

124 ***Baseline ASL Parameters***

125 Pseudo-continuous ASL (PCASL) with a 2D gradient-echo echo-planar imaging (EPI) readout
126 was used with the following parameters: voxel size=3x3x5mm³, 24 slices, labeling
127 duration=1656ms, initial post-labeling delay=1500ms, slice readout time=49.94ms, leading to
128 a PLD range of 1500-2649ms across all slices with a mean PLD of 2074ms, TR/TE=4000/9ms,
129 and generalized auto-calibrating partially parallel acquisitions (GRAPPA) factor=3. Two ASL
130 volumes of 23 control-label pairs each were acquired with a 1-hour interval and were
131 concatenated into one ASL time series to decrease physiological fluctuations. Details of ASL
132 image processing have been described elsewhere.^{6, 12} In brief, ASL image processing was
133 performed with ExploreASL and included motion correction, quantification according to the
134 ASL consensus paper,¹³ rigid-body registration of the CBF map to a GM map from a segmented
135 T1-weighted image, and spatial normalization to MNI space via the segmented T1-weighted
136 image.¹⁴ These T1 segmented images were then multiplied by 45 and 15mL/100g/min for GM
137 and WM, respectively (assuming that CBF is homogeneously distributed across these tissue
138 types)¹⁵. These GM and WM images were further smoothed to achieve the same resolution as
139 the ASL acquisition resolution (3x3x7mm). Three ASL parameters were derived from the CBF
140 maps: GM-CBF, WM-CBF and GM-sCoV. CBF reflects perfusion in mL blood/100g
141 tissue/min and was calculated in total GM and WM regions of interest, whereas GM-sCoV was
142 defined as the standard deviation of the CBF divided by mean CBF within GM.⁶ Three
143 parameters were obtained separately for the anterior and posterior flow territories, which were
144 defined using a vascular-territory atlas as territories corresponding to the anterior (ACA) and
145 middle (MCA) cerebral artery, and posterior (PCA) cerebral artery, respectively.¹⁶ Quality
146 assessments of the ASL scans were performed blinded to clinical diagnosis.

147 **Statistical analysis**

148 The baseline ASL parameters (GM-CBF, WM-CBF and GM-sCoV), and ASL parameters
149 obtained from vascular territories (CBF and sCoV in ACA, MCA and PCA) were
150 logarithmically transformed (log10) to ensure a normal distribution. We used a linear
151 regression model with generalized estimating equations to assess associations between ASL
152 parameters and cognitive decline as measured by detailed neuropsychological assessment.
153 GEE was used because it allows us to account for within-subject variation as the correlation of
154 repeated measurements and obtain population mean estimates for the effects of ASL
155 parameters on cognition at each time point including baseline. We specified the correlation
156 structure to be first-order autoregressive and robust variance estimators and identity link
157 functions were used.

158 To investigate whether the effect of the baseline ASL parameter on cognitive scores differs
159 between time points, regression models were constructed between cognition (global and
160 domain-specific cognitive tests) with ASL parameters time and the interaction term ‘ASL
161 parameter x time’ where the following markers were included in separate models: GM-CBF,
162 WM-CBF, and GM-sCoV. These models adjusted for age, sex, and education, while
163 subsequently models additionally adjusted for cardiovascular risk factors (hypertension,
164 hyperlipidemia, and diabetes) and other MRI markers (total intracranial volume, baseline and
165 incident CeVD markers including CMBs, lacunes, WMH, cortical infarcts, and intracranial
166 stenosis). Similar analysis was done for ASL parameters obtained from vascular territories
167 (CBF and sCoV in ACA, MCA and PCA) to analyze the association between region-specific
168 ASL parameters with cognitive decline.

169 In our secondary analysis, between the participants with and without dementia at baseline, we
170 divided our study participants into two groups, i.e., participants with dementia (AD, VaD and
171 mixed-dementia) and with dementia (NCI, CIND and VCIND). The interaction term (ASL

172 parameters*diagnosis) was significant for analysis with global cognition (p=0.027),
173 visuospatial function (p=0.007), visuomotor speed (p=0.023) and memory (p=0.006). Hence,
174 we went on further to perform the stratified analysis for with and without dementia. All the
175 analyses were performed for global and domain-specific cognitive tests as outcomes in all
176 participants and separately for participants with and without dementia.

177 For each regression model, the standardized regression coefficient (β) and its 95% confidence
178 interval (CI) were obtained. Because of the multiple testing performed within 6 cognitive
179 domains, Bonferroni correction was applied (0.05/6~0.0083). This correction was applied to
180 the overall p-value from the interaction factor and also the p-value from the effect of ASL
181 parameters at each time point (BL, Y1, Y2 and Y3) respectively for each cognitive domain.

182 Logistic regression models with odds ratios (OR) and 95%CI were used to determine the
183 association between ASL parameters with incident and progression of CeVD markers. All the
184 models were adjusted for age, sex, cardiovascular risk factors, and scan interval. We
185 additionally constructed, cox proportional hazard models to obtain estimated hazard ratios
186 (HR) and 95%CI for the association between ASL parameters with incident vascular events
187 and separately for mortality. All models were adjusted for age and sex, cardiovascular risk
188 factors, and additionally for the history of stroke (in vascular event analysis).

189 **RESULTS**

190 Baseline characteristics of 368 participants are shown in **Table 1**. The median age of
191 participants was 73±11 years and 51.9% were female. There was a high prevalence of vascular
192 risk factors and a high proportion of subjects at baseline had MRI markers of CeVD. Of 368
193 participants; 94(25.5%) were diagnosed as NCI, 100(27.2%) CIND, 65(17.7%) VCIND and
194 109(29.6%) dementia [AD: 45(12.2%), mixed-dementia: 44(12%), VaD: 20(5.4%)].

195 Higher GM-sCoV at baseline was associated with the decline in global cognition as well as the
196 decline in memory domain at years 1, 2, and 3 after adjusting for age, sex, and education
197 **[Supplementary Table-1]**. Upon adjustment for cardiovascular risk factors, these associations
198 remained significant **[Supplementary Table-2]**. However, on further adjusting for baseline
199 and incident MRI markers of CeVD in model 3 only the association with GM-sCoV and
200 memory remained significant (BL: β =-1.68, 95%CI=-2.76,-0.60, p =0.002, Y1: β =-2.66,
201 95%CI=-3.88,-1.44, p <0.001, Y2: β =-2.69, 95%CI= -3.95,-1.44, p <0.001, Y3: β = 3.21,
202 95%CI=-4.54,-1.89, p <0.001, p for interaction<0.001) **[Table 2]**. On applying Bonferroni
203 correction, this association survived multiple testing. A negative association was observed
204 between higher GM-sCoV and a decline in global cognition, executive function, and
205 visuomotor speed but the interaction between GM-sCoV and time was not significant.
206 Although there was a significant interaction between reduced GM-CBF and decline in memory
207 domain (p for interaction=0.002), the majority of the decline observed across the different time
208 points were not significant after adjusting for multiple testing. There was no association
209 between WM-CBF and global or domain-specific cognitive decline. Region-specific analysis
210 with ACA, MCA and PCA, we found that lower baseline CBF in PCA is associated with
211 decline in memory **[Supplementary Table-3]**, and higher sCOV in ACA, MCA and PCA is
212 associated with decline in memory **[Supplementary Table-4]**.

213 The association between GM-sCoV and decline in global cognition and memory was observed
214 in all years in participants without dementia. The interaction term between GM-sCoV and time
215 was significant for memory (p =0.004), but for global cognition, it was significant only without
216 Bonferroni correction (p =0.012) **[Supplementary Table-5]**. There was no significant
217 interaction of ASL parameters and time with global and domain-specific cognition in
218 participants with dementia **[Supplementary Table-6]**.

219 During the mean follow-up of 24.5 months, higher GM-sCoV was associated with progression
220 of WMH (OR=6.11, 95%CI=1.01,37.01, p=0.049) and incident CMBs (OR=38.41, 95%CI=
221 5.67,260.16, p<0.001) independent of age, sex, cardiovascular risk factors, and scan interval.
222 However, higher GM-sCoV was not associated with incident lacunes, cortical infarcts, or
223 intracranial stenosis. Lower GM and WM CBF were not associated with incident CeVD
224 markers [**Table 3**].

225 With respect to clinical events, 29 participants (7.8%) developed incident vascular events and
226 18 (4.8%) died over 3-year follow-up. Higher mean GM-sCoV was associated with increased
227 risk of vascular events (HR=7.44, 95%CI=1.03,53.58, p=0.046) independent of age, sex,
228 cardiovascular events and history of stroke, but not with increased risk of mortality. Lower GM
229 and WM CBF were not associated with incident vascular events or mortality [**Table 5**].

230 **DISCUSSION**

231 In this study, we showed that baseline GM-sCoV, was associated with cognitive decline in the
232 memory domain over 3-year follow-up. This cognitive decline was more obvious in
233 participants without dementia. Region-specific analysis showed that lower baseline CBF in
234 PCA and higher sCOV in ACA, MCA and PCA territories were associated with memory
235 decline. Finally, higher GM-sCoV at baseline was associated with progression of WMH,
236 incident CMBs and vascular events at follow-up.

237 Our finding that higher GM-sCoV, as well as sCoV in ACA, MCA and PCA flow territories,
238 were associated with the decline in memory domain is partly in line with previous studies.¹ It
239 has been shown that reduced cerebral perfusion has detrimental consequences on brain
240 structure and function¹⁷ such as, disruption of white matter structural integrity and damage in
241 fronto-subcortical network which may affect complex cognitive functions such as memory.^{18,}

242 ¹⁹ Furthermore, reduced cerebral perfusion in PCA and MCA may disrupt thalamo-cortical

243 tract affecting thalamic nuclei, which is important in storage and short-term memory.²⁰ Chronic
244 hypoperfusion is related to cerebrovascular dysfunction, such as increased cerebrovascular
245 stiffening, increased endothelial dysfunction, reduced autoregulation and impaired perivascular
246 drainage, which affects brain function by promoting amyloid-beta and tau accumulation as well
247 as CeVD.²¹ These subsequently affect cognitive function.²¹ Similarly, chronic cerebral
248 hypoperfusion promotes neurodegeneration through several mechanisms; such as increased
249 oxidative stress, increased synaptic dysfunction, as well as neuroinflammation.^{22, 23} Such
250 neurodegeneration and reduced perfusion especially in hippocampus affects memory
251 function.²⁴ Hippocampus is essential in formation of new memories and recall.²⁵ Hippocampus
252 is supplied by branches of PCA.²⁵ Hence, reduced perfusion in PCA territory may affect
253 hippocampus blood supply and function. This is supported by our finding that lower CBF and
254 higher sCoV in PCA flow territory are associated with memory decline.

255 Moreover, we found that higher GM-sCoV of ASL was associated with the decline in memory
256 in participants without dementia. A previous study on the healthy individual over 4-year
257 follow-up showed a strong association between reduced cerebral perfusion with memory
258 impairment.² Memory impairment has been considered as an early sign of AD.²⁶ It has been
259 shown that baseline ASL perfusion can predict conversion of MCI to dementia.¹ Hence, our
260 findings are in accordance with previous studies and suggest that sCoV of ASL can be an early
261 biomarker of cognitive decline in non-demented participants. However, we were not able to
262 find any association between sCoV and cognitive decline in patients with dementia. This may
263 be because the effect of hypoperfusion may be stronger in the early stage of the disease but at
264 the later stage, the effect of vascular insufficiency may be predominated by non-vascular risk
265 factors such as amyloid, tau, neuroinflammation and other comorbidities.²⁷

266 In contrast to previous studies,^{1, 2, 28} we were not able to find any significant association
267 between lower GM and WM-CBF and cognitive decline. It has been shown that low CBF

268 values in WM, as well as higher ATT, especially in deep WM, makes WM-CBF difficult to
269 assess by ASL²⁹ hence, absolute CBF values may not be fully reliable, which may have affected
270 our findings. However, there was significant association between lower CBF and higher sCoV
271 in posterior brain region with decline in memory which is partially in line with previous study
272 which shows that GM-CBF, more specifically CBF in frontal region is associated with
273 memory.² Higher sCoV means that a higher spatial heterogeneity was observed in the ASL
274 signal most likely due to a higher presence of macrovascular artefact, which can be in most
275 cases explained by increased ATT.¹⁴ Moreover, higher sCoV means that there is less certainty
276 about the accuracy of the CBF measurement. Although no direct conclusion can be drawn with
277 respect to CBF and cognitive decline from the present study, further studies with a longer
278 duration of follow-up are required to confirm these findings.

279 We also found that higher baseline GM-sCoV was associated with progression of WMH and
280 incident CMBs, as well as increased risk of future vascular events. Increased sCoV and incident
281 CeVD in this study may be due to amyloid deposition or arteriosclerosis in the blood vessel
282 which contributes to the narrowing of vessels lumen and manifests as brain hemorrhagic and
283 ischemic changes.³⁰ Reduced cerebral perfusion reflects the presence of vascular pathologies
284 in both brain and heart, hence increased sCoV of ASL may be associated with increased risk
285 of vascular events.³¹ Moreover, cardiac events such as atrial fibrillation, congestive heart
286 failure, and myocardial infarction are associated with reduced cardiac output which may result
287 in reduced cerebral perfusion.³² A growing body of evidence showed that patients with
288 cardiovascular diseases are at risk of developing cerebral vascular disease and cognitive decline
289 which is partly due to reduced cerebral perfusion.^{9, 33, 34} Our study, thus, aligns with previous
290 findings suggesting that participants with higher sCoV are at risk of incident vascular event.

291 Previous studies have reported that reduced cerebral perfusion not only is associated with
292 neuronal injury and cell death but also increases the risk of mortality affecting immune and

293 stress response, energy balance and endocrine regulation.^{31, 35} However, we were not able to
294 prove the hypothesis that the lower CBF and higher sCoV at baseline are associated with
295 increased risk of mortality. This may be because of small sample size (only 4.8% of participants
296 died during this study) as well as the relatively short duration of follow-up. Hence, our
297 hypothesis needs to be further tested in future studies investigating the long-term clinical
298 outcome of cerebral hypoperfusion using ASL images.

299 This study has several limitations. Firstly, we only analyzed ASL parameters at baseline and
300 longitudinal changes in ASL parameters were not studied. Second, even though we accounted
301 for most of the confounders in the regression analysis, non-traditional vascular risk factors,
302 such as hyperhomocysteinemia, inflammation, oxidative stress, amyloid and tau deposition
303 have been linked to cognitive impairment.³⁶ Third, most of the participants in this study are
304 elderly and have CeVD, which compromised the quality of the ASL images. We excluded those
305 scans labeled as angiography and unusable. Those participants who were excluded from the
306 analysis were significantly older (75 vs 73, $p=0.004$), less educated (6 vs 8, $p<0.001$), had a
307 higher burden of cardiovascular risk factors and were more demented (55.9% vs 29.6%) [**Sup-**
308 **plementary Table-7**]. Finally, the effect estimates and confidence intervals of GM-sCoV with
309 WMH progression, incident CMBs and mortality are wide. Hence it is difficult to interpret the
310 clinical relevance of these findings and should be interpreted with caution. The strengths of
311 this study are, first, to our best knowledge this is the only longitudinal study from a memory-
312 clinic sample analyzing the association between baseline ASL parameters with cognitive de-
313 cline over 3-year follow-up in patients with mixed-pathology. Second, an identical neuropsy-
314 chological test battery was used for baseline and follow-up visits which made it possible to
315 capture cognitive decline over time.

316 **CONCLUSIONS**

317 In this study, we found that baseline sCoV of ASL was associated with the decline in memory
318 domain over 3-year follow-up, more specifically in participants without dementia. Higher
319 baseline was associated with WMH progression, incident CMBs and increased risk of vascular
320 events at follow-up. These findings encourage the potential of ASL sCoV as a surrogate
321 endpoint marker for vascular brain injury.

AUTHOR CONTRIBUTION STATEMENT

BG is responsible for study concept and design, participated in data acquisition, performed the statistical analysis, drafting and revising the manuscript. HJMMM processed the ASL images and revised the manuscript. OKR participated in statistical analysis and revising the manuscript. JP was provided intellectual advice and revised the manuscript. CC was responsible for study concept and design, obtaining funding, and revising the manuscript. SH was responsible for study concept and design, data acquisition, obtaining funding, and revising the manuscript.

DISCLOSURE

The authors declare that they have no conflict of interest

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FIGURE LEGENDS

Figure 1

Title: Selection of participants

Legends: ASL, arterial spin labeling; CBF, cerebral blood flow; sCoV, spatial coefficient of variation of ASL

Table 1. Characteristics of study participants

Baseline characteristics	Study participants (n=368)
Age, years, median (IQR)	73 (11)
Female, n (%)	191 (51.9)
Education, years, median (IQR)	8 (8)
Hypertension, Yes, n (%)	253 (68.8)
Hyperlipidemia, Yes, n (%)	270 (73.4)
Diabetes, Yes, n (%)	124 (33.7)
Presence of CMBs, n (%)	159 (43.2)
Presence of lacunes, n (%)	94 (25.5)
Presence of WMH, modified Fazekas \geq 2, n (%)	200 (54.3)
Presence of cortical stroke, n (%)	38 (10.3)
Presence of intracranial stenosis, n (%)	49 (13.3)
Presence of incident CMBs, n (%)	65 (17.7)
Presence of incident lacunes, n (%)	17 (4.6)
Presence of WMH progression, n (%)	194 (52.7)
Presence of incident cortical stroke, n (%)	7 (1.9)
Presence of incident intracranial stenosis, n (%)	8 (2.2)
Gray matter CBF, median (IQR) (n=316)	45.6 (21.5)
White matter CBF, median (IQR) (n=316)	9.4 (7.7)
Gray matter sCoV, median (IQR)	0.6 (0.2)

IQR, interquartile range; CMBs, cerebral microbleeds; CBF, cerebral blood flow, ASL; arterial spin labeling, sCoV; spatial coefficient of variation of ASL, NCI; no cognitive impairment, CIND; cognitive impairment no dementia

Table 2: The effect of baseline ASL parameters on cognitive scores across time

		Global Z-score β (95%CI)	Executive function β (95%CI)	Attention β (95%CI)	Language β (95%CI)	Visuospatial function β (95%CI)	Visuomotor speed β (95%CI)	Memory β (95%CI)
CBF gray matter †	Baseline	-2.24 (-4.28, -0.20) p=0.031	-2.43 (-4.42, -0.44) p=0.017	-1.10 (-2.34, 0.14) p=0.082	-2.62 (-5.64, 0.39) p=0.088	-1.36 (-3.28, 0.55) p=0.163	-0.96 (-2.05, 0.13) p=0.084	-0.90 (-2.47, 0.67) p=0.264
	Year 1	-2.41 (-4.69, -0.13) p=0.038	-2.28 (-4.31, -0.26) p=0.027	-0.55 (-1.74, 0.65) p=0.369	-3.11 (-6.85, 0.64) p=0.104	-1.39 (-3.31, 0.53) p=0.156	-1.20 (-2.30, -0.09) p=0.033	-1.59 (-3.26, 0.08) p=0.063
	Year 2	-3.34 (-5.80, -0.87) p=0.008 [#]	-3.16 (-5.31, -1.02) p=0.004	-1.27 (-2.56, 0.02) p=0.055	-4.45 (-8.80, -0.09) p=0.045	-1.67 (-3.52, 0.18) p=0.076	-1.29 (-2.38, -0.20) p=0.021	-2.26 (-3.96, -0.56) p=0.009
	Year 3	-3.43 (-6.10, -0.75) p=0.012	-2.28 (-4.51, -0.05) p=0.045	-1.53 (-2.96, -0.09) p=0.037	-6.51 (-11.29, -1.73) p=0.008	-0.74 (-2.76, 1.27) p=0.469	-1.21 (-2.40, -0.02) p=0.047	-2.17 (-4.00, -0.34) p=0.020
	p*	0.090	0.109	0.179	0.142	0.591	0.469	0.002 [#]
CBF white matter †	Baseline	-0.63 (1.63, -0.38) p=0.221	-0.72 (11.70, 0.26) p=0.148	-0.65 (-1.27, -0.02) p=0.042	0.03 (-1.56, 1.62) p=0.970	-0.46 (-1.36, 0.45) p=0.321	-0.46 (-0.94, 0.02) p=0.063	-0.36 (-1.12, 0.41) p=0.360
	Year 1	-0.64 (1.71, -0.44) p=0.245	-0.65 (-1.66, 0.35) p=0.201	-0.49 (-1.04, 0.06) p=0.082	0.17 (-1.68, 2.02) p=0.857	-0.57 (-1.45, 0.32) p=0.208	-0.47 (-0.96, 0.03) p=0.064	-0.64 (-1.42, 0.14) p=0.108
	Year 2	-0.79 (1.94, -0.37) p=0.183	-0.84 (-1.92, 0.24) p=0.127	-0.71 (-1.36, -0.07) p=0.030	-0.11 (-2.12, 1.91) p=0.918	-0.54 (-1.39, 0.32) p=0.218	-0.45 (-0.95, 0.05) p=0.080	-0.67 (-1.51, 0.16) p=0.115
	Year 3	-1.03 (2.34, -0.28) p=0.122	-0.30 (-1.45, 0.85) p=0.610	-1.07 (-1.92, -0.22) p=0.013	-1.43 (-3.69, 0.84) p=0.217	-0.45 (-1.37, 0.46) p=0.330	-0.49 (-1.02, 0.04) p=0.072	-0.66 (-1.56, 0.25) p=0.154
	p*	0.593	0.319	0.384	0.132	0.957	0.990	0.440

sCoV gray matter ‡	Baseline	-2.40 (-3.92, -0.88) p=0.002 [#]	-2.56 (-3.96, -1.16) p<0.001 [#]	-0.79 (-1.76, 0.17) p=0.108	-2.23 (-5.07, 0.62) p=0.125	-1.54 (-2.77, -0.31) p=0.014	-1.21 (-1.92, -0.50) p=0.001 [#]	-1.68 (-2.76, -0.60) p=0.002 [#]
	Year 1	-2.75 (-4.29, -1.21) p<0.0001 [#]	-2.64 (-4.03, -1.25) p<0.001 [#]	-0.47 (-1.45, 0.51) p=0.348	-2.87 (-5.75, 0.01) p=0.051	-1.52 (-2.75, -0.29) p=0.015	-1.31 (-2.05, -0.58) p<0.001 [#]	-2.66 (-3.88, -1.44) p<0.001 [#]
	Year 2	-3.14 (-4.80, -1.49) p<0.001 [#]	-3.32 (-4.80, -1.84) p<0.001 [#]	-0.82 (-1.92, 0.28) p=0.145	-3.19 (-6.31, -0.07) p=0.045	-1.77 (-2.93, -0.60) p=0.003	-1.40 (-2.13, -0.66) p<0.001 [#]	-2.69 (-3.95, -1.44) p<0.001 [#]
	Year 3	-3.53 (-5.55, -1.52) p=0.001 [#]	-2.73 (-4.30, -1.16) p=0.001 [#]	-1.25 (-2.43, -0.06) p=0.039	-5.35 (-9.92, -0.78) p=0.022	-0.82 (-2.19, 0.56) p=0.245	-1.44 (-2.20, -0.68) p<0.001 [#]	-3.21 (-4.54, -1.89) p<0.001 [#]
	p*	0.142	0.251	0.354	0.344	0.302	0.691	<0.001 [#]

Linear regression model with generalized estimating equations for the associations between ASL parameters and cognitive decline at each time

point [values represent as standardized regression coefficient (β) and 95% confidence interval (CI), degree of freedom=16]

† β represents mean difference in cognitive scores per decrease in log10 of CBF

‡ β represents mean difference in cognitive scores per increase in log10 of sCoV

All values adjusted for age, sex, education, cardiovascular risk factors, total brain volume, presence of baseline, and incident CeVD

p*=p value two-way interaction factor between ASL parameters and time (p*<0.05, significant decline in specific cognitive domain over time)

p<0.05 considered as statistically significant association [[#] significant after Bonferroni correction (0.05/6~0.0083)]

CBF, cerebral blood flow; ASL, arterial spin labeling; sCoV, spatial coefficient of variation of ASL; CeVD, cerebrovascular disease

Table 3: Association between ASL parameters with progression and incidence of CeVD

	WMH progression OR (95%CI) (n=166[†], 194[‡])	Incident lacunes OR (95%CI) (n=14[†], 17[‡])	Incident CMBs OR (95%CI) (n=47[†], 65[‡])	Incident cortical infarcts OR (95%CI) (n=5[†], 7[‡])	Incident intracranial stenosis OR (95%CI) (n=6[†], 8[‡])
CBF gray matter	6.12 (0.64, 57.84) p=0.114	8.38 (0.08, 927.28) p=0.376	5.29 (0.30, 93.06) p=0.254	0.30 (0.01, 147.56) p=0.782	0.01 (0.01, 0.01) p=0.145
CBF white matter	1.15 (0.36, 3.67) p=0.805	1.20 (0.08, 17.35) p=0.895	1.30 (0.31, 5.48) p=0.724	2.74 (0.03, 237.24) p=0.658	0.01 (0.01, 1.38) p=0.065
sCoV gray matter	6.11 (1.01, 37.01) p=0.049	6.89 (0.33, 143.06) p=0.212	38.41 (5.67, 260.16) p<0.001	0.19 (0.01, 52.36) p=0.559	0.01 (0.01, 8.69) p=0.188

Linear regression model for the association between ASL parameters with WMH progression, incident lacunes, incident CMBs, incident cortical infarcts and incident intracranial stenosis [values represent as odds ratio (OR) and 95% confidence interval (CI)]

All values adjusted for age, sex, cardiovascular risk factors and scan interval

[†] numbers of incident CeVD in CBF analysis

[‡] numbers of incident CeVD in sCoV analysis

p<0.05 considered as statistically significant association

CBF, cerebral blood flow; ASL, arterial spin labeling; sCoV, spatial coefficient of variation of ASL; CeVD; cerebrovascular disease, WMH, white matter hyperintensities; CMBs, cerebral microbleeds

Table 4: Association between ASL parameters with incident vascular events and mortality

Cardiac biomarkers	Vascular events[#]	Mortality[*]
	HR (95%CI)	HR (95%CI)
	(n=19[†], 29[‡])	(n=12[†], 18[‡])
CBF gray matter	4.97 (0.10, 241.22) p=0.418	0.01 (0.01, 1.23) p=0.059
CBF white matter	2.71 (0.39, 18.67) p=0.310	0.43 (0.02, 7.38) p=0.559
sCoV gray matter	7.44 (1.03, 53.58) p=0.046	5.77 (0.39, 85.94) p=0.203

Cox proportional hazard regression model for the association between ASL parameters with incident vascular events and mortality [values represent hazard ratio (HR) and 95% confidence interval (CI)]

[#]adjusted for age, sex, cardiovascular risk factors, and history of stroke

^{*}adjusted for age, sex, cardiovascular risk factors

[†] numbers of vascular events and mortality in CBF analysis

[‡] numbers of vascular events and mortality in sCoV analysis

p<0.05 considered as statistically significant association

HR: hazard ratio; OR: odds ratio; CI, confidence interval; CBF, cerebral blood flow; ASL, arterial spin labeling; sCoV, spatial coefficient of variation of ASL

LIST OF SUPPLEMENTAL DIGITAL CONTENT

Supplemental Digital Content 1: Diagnostic criteria and inclusion/exclusion criteria

Supplemental Digital Content 2: Neuropsychological assessment

Supplemental Digital Content 3: MRI markers of CeVD

Supplemental References

Supplemental Table 1: The effect of baseline ASL parameters on cognitive scores across time
(adjusted for age, sex and education)

Supplemental Table 2: The effect of baseline ASL parameters on cognitive scores across time
(adjusted for age, sex, education and cardiovascular risk factors)

Supplemental Table 3: The effect of baseline ASL parameters (CBF flow territories) on
cognitive scores across time

Supplemental Table 4: The effect of baseline ASL parameters (sCoV flow territories) on
cognitive scores across time

Supplemental Table 5: The effect of baseline ASL parameters on cognitive scores across time
(patients without dementia)

Supplemental Table 6: The effect of baseline ASL parameters on cognitive scores across time
(patients with dementia)

Supplemental Table 7: Characteristics of participants (included and excluded in the study)