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High dilated perivascular space burden: a new MRI-marker for risk of intracerebral hemorrhage

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Abstract

Commonly observed in older community persons, dilated perivascular spaces (dPVS) are thought to represent an emerging MRI-marker of cerebral small vessel disease (cSVD), but their clinical significance is uncertain. We examined the longitudinal relationship of dPVS burden with risk of incident stroke, ischemic stroke, and intracerebral hemorrhage (ICH) in the 3C-Dijon population-based study (N=1,678 participants, mean age 72.7 ± 4.1 years) using Cox regression. dPVS burden was studied as a global score and according to dPVS location (basal ganglia, white matter, hippocampus, brainstem) at baseline. During a mean follow-up of 9.1 ± 2.6 years, 66 participants suffered an incident stroke. Increasing global dPVS burden was associated with a higher risk of any incident stroke (hazard ratio [HR], 1.24, 95%CI [1.06-1.45]) and of incident ICH (HR, 3.12[1.78-5.47]), adjusting for sex and intracranial volume. Association with ICH remained significant after additionally adjusting for vascular risk factors and for other cSVD MRI-markers. High dPVS burden in basal ganglia and hippocampus, but not in white matter or brainstem, were associated with higher risk of any stroke and ICH.

Keywords: Cerebrovascular disease, Stroke, Ischemic Stroke, Intracranial Hemorrhage, Magnetic Resonance Imaging, Epidemiology

1. Introduction

Perivascular spaces are physiological fluid filled structures surrounding vessel walls, as they run from the subarachnoid space through the brain parenchyma, with an MRI signal identical to cerebrospinal fluid (CSF) (Kwee and Kwee, 2007). Quantifiable on brain MRI, dilated perivascular spaces (dPVS), or Virchow-Robin spaces, are an emerging MRI-marker of cerebral small vessel disease (cSVD) (Mestre et al., 2017; Potter et al., 2015; Wardlaw, Joanna M et al., 2013).

dPVS are considered one of the earliest neuroimaging findings in cSVD. Although this is partly debated (Bacynski et al., 2017), dPVS may be part of the “glymphatic” system, involved in waste clearance (for example of beta amyloid peptide) and blood flow regulation (Jessen et al., 2015; Mestre et al., 2017). dPVS burden is associated with advancing age, hypertension (Yao et al., 2014; Zhu et al., 2010), and other MRI-markers of cSVD, including white matter hyperintensities of presumed vascular origin (WMH) and covert MRI-defined lacunes (Potter et al., 2015; Yakushiji et al., 2014; Zhu et al., 2010).

The clinical significance and pathophysiology of dPVS remain unclear. While some studies have suggested an association of high dPVS burden with increased risk of dementia and cognitive decline (MacLulich et al., 2004; Zhu et al., 2010; Passiak et al., 2019; Francis et al., 2019), results need to be confirmed in larger samples. To our knowledge, only one study in the general population examined the association of dPVS burden with incident stroke risk. The authors found an association of dPVS burden with an increased risk of any stroke, only for participants in the highest tertile of blood pressure, after adjusting for vascular risk factors (Gutierrez et al., 2017). The association of dPVS burden with stroke subtypes has not been explored in the general population.

We examined whether high dPVS burden is associated with increased risk of incident stroke, ischemic stroke, and intracerebral hemorrhage (ICH), in the population-based 3C-Dijon study.

2. Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

2.1. Study population

The 3C-Dijon Study is a longitudinal population-based cohort study (The 3C Study Group, 2003). Briefly, 4,931 non-institutionalized persons aged 65 years or older were recruited from the electoral rolls of Dijon, France, between March 1999 and March 2001. Participants are virtually all of European ancestry. Participants enrolled between June 1999 and September 2000 who were younger than 80 years (N=2,763) were proposed to undergo a brain MRI at baseline. Participation rate was high (82.7%), but only 1,924 MRI examinations were performed because of financial limitations. After exclusion of participants with brain tumor (N=8), stroke (N=83), or dementia (N=8) at the time of MRI, participants with technical limitations preventing reliable assessment of dPVS burden (N=45) or intracranial volume (ICV) (N=75), and participants with no follow-up for stroke (N=27), the baseline sample comprised 1,678 participants. The study protocol was approved by the ethical committee of the University Hospital of Kremlin-Bicêtre. All participants provided written informed consent.

2.2. Brain MRI acquisition

MRI acquisition was performed on a 1.5-Tesla Magnetom scanner (Siemens); a three dimensional (3D) high-resolution T1-weighted, as well as T2- and PD- (proton density) weighted brain imaging were acquired (**Supplementary Methods**).

2.3. Rating of dPVS

dPVS were rated in 4 main locations (basal ganglia [BG], white matter [WM], hippocampus and brainstem) by an experienced reader (Y-C.Z). **Intrarater agreement (N=100 MRI) was high (k=0.77 for basal ganglia, and k=0.75 for white matter) (Zhu et al., 2010).** dPVS were defined as lesions with a CSF-like signal (hypointense on T1 and hyperintense on T2) of round, ovoid, or linear shape with a maximum diameter <3 mm, having smooth delineated contours, and located in areas supplied by perforating arteries. Lesions fulfilling the same criteria except for a diameter ≥ 3 mm were carefully examined in the 3 planes (shape, signal intensity) to differentiate them from covert MRI-defined lacunes and WMH. Only lesions with a typical vascular shape (including cystic lesions with an extension of vascular shape) and that followed the orientation of perforating vessels were considered as dPVS (Zhu et al., 2010).

In **the** BG, the slice containing the greatest number of dPVS was used for the rating on a 4-grade score: grade 1 for <5 dPVS; grade 2 for 5-10 dPVS; grade 3 for >10 dPVS but still numerable; grade 4 for innumerable dPVS resulting in a cribriform change in **the** BG (**Figure 1**). In the WM, dPVS were also rated using a 4-grade score: grade 1 for <10 dPVS in the total WM; grade 2 for ≥ 10 dPVS in the total WM and <10 in the slice containing the greatest number of dPVS; grade 3 for 10-20 dPVS in the slice containing the greatest number of dPVS; grade 4 for >20 dPVS in the slice containing the greatest number of dPVS (**Figure 1**)

(Zhu et al., 2010). In the hippocampus and brainstem, dPVS count was reported ; participants with the largest number of dPVS seen in <2% of the population were grouped with the previous category in order to better fit the statistical model, leading to a variable ranging between 0 and 5 in the hippocampus and between 0 and 6 in the brainstem.

A global dPVS burden variable was constructed by summing up dPVS grades in BG and WM, and adding 1 point for the presence of ≥ 1 dPVS in the hippocampus, and 1 point for the presence of ≥ 1 dPVS in the brainstem. Due to the small number of participants in the highest categories, these were combined (global score ≥ 8), leading to a global dPVS score ranging from 2 to 8. The global variable was normally distributed on visual inspection (Supplementary Methods). Extensive global dPVS burden was defined by the cut-off closest to the top-quartile (score ≥ 7).

2.4. Other MRI measurements

WMH volume (WMHV) was measured using a fully automated and validated procedure (Maillard et al., 2008). Covert MRI-defined brain infarcts were defined as focal lesions ≥ 3 mm with the same signal characteristics as CSF on all sequences, not associated with any history of stroke (exclusion criterion). Covert MRI-defined lacunes were defined as covert MRI-defined brain infarcts with a diameter between 3 and 15 mm, located in the BG, brainstem, or WM (Zhu et al., 2010). The ICV was estimated using voxel-based morphometry by summing up gray matter, WM, and CSF volumes (Lemaitre et al., 2005). The brain parenchymal fraction was estimated by summing up gray and white matter volume and dividing by the ICV.

2.5. Stroke assessment

Incident stroke was defined as a new focal neurological deficit of sudden onset, of presumed vascular origin, that persisted for >24 hours, or leading to death. Diagnosis of stroke, stroke classification (ischemic stroke, ICH, or unspecified) and ischemic stroke subtyping (cardioembolic, large-artery, or small-artery occlusion) was done by an expert panel according to the criteria of the World Health Organization (WHO Monica Project Principal Investigators, 1988). Of note, large-artery ischemic strokes were not studied separately in association with dPVS burden, because there were too few events in this category. Strokes were defined as fatal if followed by death within 28 days. Incident stroke events were ascertained and classified blinded to baseline dPVS rating.

2.6. Statistical Analyses

Global burden of dPVS and dPVS burden in hippocampus and brainstem were studied as a continuous variables, dPVS burden in BG and WM as a dichotomized variable (grade 3-4/1-2). Because WMHV had a skewed distribution, we used natural log-transformed values (natural log of $[\text{Ln}(\text{WMHV}+1)]$). (Verhaaren et al., 2015) Covert MRI-defined lacunes were studied as dichotomous variables (at least one lacune versus none).

To study the association between dPVS burden and incident stroke, we used a Cox regression model with age as a time scale. Follow-up started on the date of the baseline brain MRI and occurrence of a first stroke was used as an endpoint. Participants known to be stroke-free were right censored at the time of non-stroke death or at the time of their last follow-up. For analyses of association with incident stroke subtypes, participants with alternative subtypes were censored at the time of event.

Participants' demographic and cardiovascular risk factors were assessed at baseline (Supplementary Methods). To adjust for potential confounding factors, we constructed 5

models: model 1 adjusted for sex and ICV, model 2 additionally adjusted for vascular risk factors (hypertension, diabetes, hypercholesterolemia, current smoking status, and body mass index), model 3 adjusted for the same variables as in model 1 and for APOEε4-carrier status, model 4 adjusted for the same variables as in model 1 and for covert MRI-defined lacunes and WMHV and model 5 adjusted for the same variables as in model 2 and for antithrombotic drug intake. Analyses were corrected for multiple testing, accounting for the 4 dPVS locations (significance threshold after correction for multiple testing: $p < 0.0125$). The trend in risk of incident stroke across dPVS grades in the BG assigned with ordered natural numbers (1, 2, 3 and 4) was tested using the Cox proportional hazards model. We searched for an effect modification by sex, hypertension, median age and APOEε4-carrier status. We verified the linearity hypothesis with a restricted cubic spline model (Desquilbet and Mariotti, 2010) and the proportional hazard assumption using proportionality tests that assess the statistical significance of interaction terms between time and the variables in the model. We also performed cumulative incidence graphs adjusted for age, sex, and total intracranial volume and stratified on global extensive dPVS burden (top quartile versus the rest). The Fine and Gray method has been used to model the cumulative incidence of intracerebral hemorrhage to take into account competitive risks with other stroke subtypes. Analyses were performed using Statistical Analyses System software version 9.3 (SAS Institute, Inc, Cary, NC).

3. Results

For the 1,678 participants, the average age at baseline was 72.7 years (standard deviation 4.1) and 61.1% were women (Table 1). Over a mean follow-up period of 9.1 ± 2.6 years, 66

1 participants (3.9%) developed an incident stroke (52 ischemic strokes, 10 ICH, and 4 strokes
2 of unspecified type). Of the 52 incident ischemic strokes, the subtype was cardioembolic
3 (N=14), small-artery occlusion (N=11), large artery (N=1), other etiologies (N=2), and
4 undetermined (N=24). Among the 10 participants who developed an ICH, 4 participants were
5 treated by antithrombotic drugs during the follow-up before the event ; and the ICH
6 localization was deep in 4 participants, lobar in 1 participant and undetermined in 5
7 participants. Of the 66 strokes, 10 were fatal, of which 4 were ischemic strokes (8% fatality
8 rate) and 4 were ICHs (40% fatality rate).

9
10 All participants had some dPVS. Of these, 218 (13%) had an extensive global dPVS burden.
11 The presence of an extensive global dPVS burden was significantly associated with older age,
12 hypertension, systolic and diastolic blood pressure and antihypertensive drug intake, but not
13 other vascular risk factors. We also observed a significant association of extensive global
14 dPVS burden with covert MRI-defined lacunes and WMHV (Table 1).

15
16 In a model adjusted for sex and ICV, higher global dPVS burden was associated with an
17 increased risk of developing new strokes. Considering stroke subtypes, higher global dPVS
18 burden was associated with an increased risk of ICH, but not ischemic stroke risk (overall and
19 by individual subtypes). Higher dPVS burden in the BG and in the hippocampus were
20 significantly associated with an increased risk of developing new strokes, and especially ICH,
21 but not ischemic stroke (Table 2; Supplementary Table 1).

22 These associations remained substantially unchanged after further adjustment for vascular
23 risk factors, antithrombotic drug intake, or APOEε4-carrier status. Higher burden of dPVS in
24 all locations and in the hippocampus, but not in the BG, was still associated with ICH risk

after adjustment for other MRI-markers of cSVD (**Table 2**). The association between dPVS in BG and ICH risk was no longer significant after adjustment for WMHV only (**Supplementary Table 2**). There was no deviation from linearity for the association with hippocampal dPVS. We did not observe any significant association between dPVS burden in the WM or brainstem and incident stroke risk, although there was a non-significant trend ($p=0.06-0.07$) towards an association of extensive dPVS in the WM with increased risk of ICH (**Table 2; Supplementary Table 1**).

When testing the association of increasing dPVS grades in the BG with incident stroke, we found a significant trend test after correction for multiple testing, with increasing effect sizes for increasing BG dPVS grades (**Table 3**).

In secondary analyses, adjusting for brain parenchymal fraction instead of ICV did not change the results (**Supplementary Table 3**). We did not find any modifying effect of sex, hypertension, median age, or APOE ϵ 4-carrier status on the relationship of global dPVS or dPVS subtypes with incident stroke (data not shown). Considering that most ICH cases in the general population are caused by cSVD, as is the small-artery occlusion ischemic stroke subtype, we ran secondary analyses combining these subtypes. Associations of dPVS burden in all locations, the hippocampus and the BG with this composite cSVD stroke phenotype were slightly more significant with narrower confidence intervals than for ICH alone (**Supplementary Table 4**). When testing the association of dPVS burden separately with incident fatal and non-fatal stroke, although results were not significant, slightly larger effect sizes were found for associations with fatal stroke (**Supplementary Table 5**).

4. Discussion

1
2 In a large population-based cohort study of 1,678 persons aged 65+ we found a significant
3 association between global dPVS burden and risk of incident ICH, but no association with
4 incident ischemic stroke risk. A high dPVS burden in the BG and in the hippocampus was
5 significantly associated with an increased risk of ICH, independently of vascular risk factors,
6 antithrombotic drug intake, and APOEε4-carrier status, and also independently of other MRI-
7 markers of cSVD for dPVS in the hippocampus.

8
9 In a recent population-based study of predominantly Hispanic origin (NOMAS, N=1,228) an
10 association of a global dPVS burden score with any stroke risk was observed, only for
11 participants in the highest tertile of blood pressure, in a model accounting for cofounders
12 (Gutierrez et al., 2017). There was no association of dPVS burden in the WM, BG, brainstem,
13 and posterior fossa with any stroke risk. Despite a similar age of both study populations, the
14 burden of dPVS seemed to be less in NOMAS than in 3C-Dijon (9% of the NOMAS
15 population had a dPVS score of 0 vs. none in the 3C-Dijon study), possibly related to ethnic
16 differences, lower blood pressure in NOMAS, and variations in dPVS detection and scoring
17 (Lau et al., 2017). The somewhat smaller sample size in NOMAS may also have contributed
18 to the absence of significant association of dPVS burden with incident stroke (Gutierrez et al.,
19 2017). Moreover, importantly, neither dPVS in the hippocampus, nor stroke subtypes were
20 considered in the NOMAS study.

21 In two high-risk populations with a history of ischemic stroke or transient ischemic attack
22 (total N=2,002), from the UK (OXVASC) and China (HKU), high dPVS burden in the BG,
23 but not in the WM, was associated with higher risk of recurrent all stroke and ischemic
24 stroke, but not ICH (Lau et al., 2017). However all participants in this population had a

1 history of cerebral ischemia and were therefore at particularly high risk of ischemic stroke
2 versus ICH. Finally, in a study carried out in 229 cerebral amyloid angiopathy (CAA)-related
3 ICH patients, high dPVS burden in the WM (≥ 20 dPVS) was associated with an increased
4 risk of ICH recurrence (other dPVS locations were not examined) (Boulouis et al., 2017).

5 In the present study the association of dPVS burden with risk of stroke and stroke subtypes
6 differed according to the dPVS location, the most significant associations being observed
7 with dPVS in the BG and hippocampus. Patterns of association of dPVS burden with risk
8 factors differ depending on dPVS location. dPVS in the BG are more strongly associated with
9 hypertension (Yang et al., 2017; Zhu et al., 2010) and blood pressure variability (Yang et al.,
10 2017) than dPVS in the WM, while the latter show stronger correlations with Alzheimer
11 disease (Banerjee et al., 2017; Ramirez, 2015; Roher et al., 2003) and CAA (Charidimou et
12 al., 2017). This, together with the strong association of high blood pressure levels and
13 antihypertensive treatment with dPVS burden in our sample, and considering the well-
14 established major effect of hypertension on stroke risk, which is even stronger for ICH than
15 for ischemic stroke (O'Donnell et al., 2010), could suggest that the observed association
16 between dPVS burden and incident stroke could partly reflect the effect of hypertension on
17 both. However, associations were maintained after adjusting for hypertension and other
18 vascular risk factors, suggesting that other mechanisms are at play, although some degree of
19 residual confounding cannot be excluded.

20 The particularly strong association of dPVS burden with incident ICH is intriguing. It is
21 consistent with previous reports showing that MRI-markers of cSVD, even if not
22 hemorrhagic in nature, such as WMH or covert MRI-defined lacunes, are associated with an
23 increased risk of ICH (Folsom et al., 2012; Kaffashian et al., 2016; Windham et al., 2015).

1 This highlights the importance of assessing the benefit-risk ratio of antiplatelet agents in
2 persons with covert cSVD (frequently prescribed empirically in clinical practice) in a
3 randomized clinical trial setting. The similar effect estimates for associations of dPVS burden
4 with incident small-artery occlusion ischemic stroke, with enhanced significance when
5 combining with incident ICH, are also in favor of effects mediated by cSVD. A direct
6 topographical association has been described between juxtacortical dPVS and CAA severity
7 in the cortex, in the specific context of Alzheimer disease patients with CAA (Veluw et al.,
8 2016). The population-based setting of our study and the relatively small number of incident
9 ICH cases did not enable us to explore the associations of dPVS burden with lobar vs. non-
10 lobar ICH. Interestingly, cross-sectional studies have described a higher prevalence of dPVS
11 in the BG in patients with ICH in deep structures and of WM dPVS in patients with lobar
12 ICH (Charidimou et al., 2017). This observation is in line with the stronger correlation of BG
13 dPVS with hypertension (Yang et al., 2017; Zhu et al., 2010), and of WM dPVS with CAA
14 (Charidimou et al., 2017; Veluw et al., 2016), as deep ICH is more often caused by
15 hypertension and lobar ICH by CAA (Graff-Radford et al., 2017; Greenberg et al., 2009).
16 We can hypothesize that some of the mechanisms underlying the association between dPVS
17 burden and stroke, especially for dPVS in the BG, are common with the other MRI-markers
18 of cSVD, particularly with WMHV (Kaffashian et al., 2016). Indeed, associations with BG
19 dPVS were attenuated and only nominally significant after adjusting for WMHV.
20 Corroborating this we recently described a strong phenotypic and genetic correlation between
21 dPVS in BG and WMHV (Duperron et al., 2018). However, interestingly, the association of
22 hippocampal dPVS burden with incident stroke and ICH was independent of other MRI-
23 markers of cSVD, suggesting that other mechanisms may be involved here. dPVS and WMH
24 colocalize spatially, with WMH appearing around dPVS (Wardlaw, J. M. et al., 2013),

1 however this is not the case of the hippocampus that consists almost exclusively of grey
2 matter; this distinctive feature could perhaps partly explain that the associations with
3 hippocampal dPVS remain independent of other cSVD features, measured primarily in the
4 WM. Although they have common risk factors with dPVS in BG and WM (Yao et al., 2014),
5 dPVS in hippocampus may differ from the other locations as it has been suggested that they
6 may at least in part result from incomplete fusion of the hippocampus fissure during
7 development (Yao et al., 2014; Zhu et al., 2010).

8 dPVS may reflect “glymphatic” fluid stasis and play a role in the pathogenesis of cSVD
9 (Jessen et al., 2015; Mestre et al., 2017). dPVS dilatation could be the consequence of blood
10 brain barrier dysfunction, arterial wall stiffening, or endothelial cell disconnection, and
11 involve microglial cells and perivascular macrophages (Faraco et al., 2016; Ramirez et al.,
12 2016). Perivascular macrophages, a specific population of resident brain macrophages located
13 in dPVS, have a pathogenic role in neurovascular and cognitive function associated with
14 hypertension, in particular by generating large amounts of reactive oxygen species, which
15 may lead to blood brain barrier disruption (Faraco et al., 2016). Interestingly ICH patients
16 have high levels of oxidative stress (Gonullu et al., 2014).

17
18 Strengths of our study include the population-based setting and longitudinal design with a
19 large sample size, stroke classification and validation by an expert panel, and rating of dPVS
20 by the same experienced reader on 3D-T1 images with differentiation from WMH and covert
21 MRI-defined lacunes using careful examination in the 3 planes and exploration of T2- and
22 PD-sequences. While the resolution in later generation 7T MRI scanners is higher, smaller
23 PVS that are not detectable on 1.5T scanners may perhaps reflect physiological rather than

1 pathological processes. Our study has limitations. dPVS were rated on a visual scale, and
2 although intra-rater agreement was good (Zhu et al., 2010), automated dPVS quantification
3 scales would provide more reproducible measures, however such software are not yet
4 available. Caution is warranted when interpreting effect sizes given the relatively small
5 number of ICH cases, confirmation in independent samples is required. Participants included
6 in the analysis were on average younger and had fewer vascular risk factors than 3C-Dijon
7 participants not included (**Supplementary Table 6**), which may have led to underestimated
8 results. Presence of cerebral microbleeds was shown to be associated with increased risk of
9 ischemic stroke and ICH (Debette et al., 2019; Wilson et al., 2016), and cortical superficial
10 siderosis was found to be associated with incident ICH (Wollenweber et al., 2019).
11 Unfortunately, the 3C-Dijon study brain imaging protocol from 1999 did not include any T2*
12 images, hence were were unable to assess the impact of cerebral microbleeds and cortical
13 superficial siderosis on the association between dPVS burden and incident stroke.

15 **Conclusions**

16 Our findings, if confirmed in independent samples, imply that dPVS burden in the BG and in
17 the hippocampus may be a strong MRI-marker of incident ICH risk, providing novel insight
18 into the clinical significance of dPVS and regional variations thereof.

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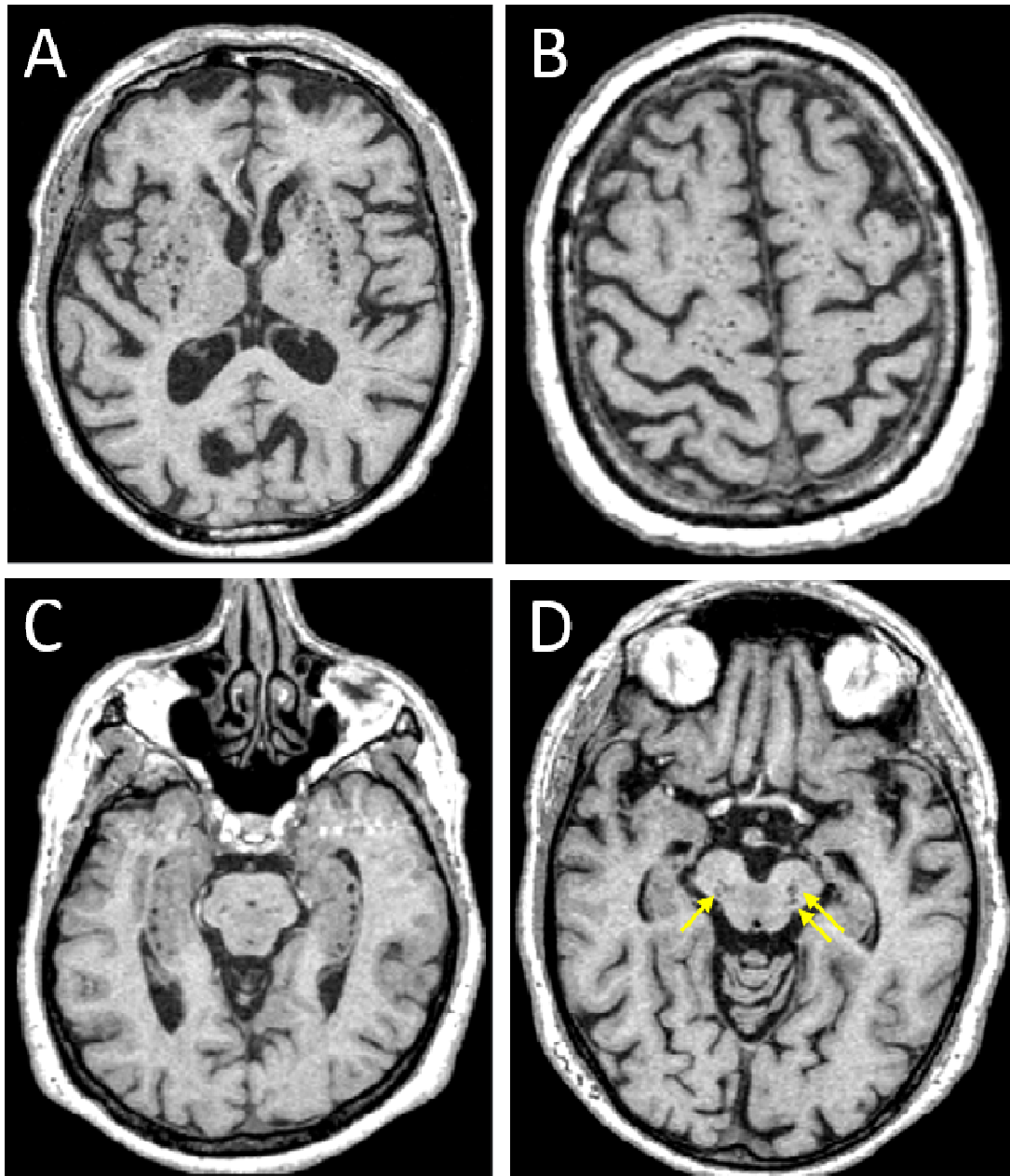


Figure 1. Axial T1-weighted images of high dilated perivascular space burden

High dilated perivascular spaces burden in basal ganglia (A, grade 4) white matter (B, grade 4), hippocampus (C) and mesencephalon (D), 3C-Dijon study (Zhu et al., 2010)

Table 1. Baseline characteristics of the study population

| | Total population (N=1678) | dPVS (global) ≥ 7 (N=218) | dPVS (global) < 7 (N=1460) |
|---|------------------------------|-----------------------------------|---------------------------------|
| Age at MRI, years, mean \pm standard deviation | 72.7 \pm 4.1 | 74.1 \pm 4.1** | 72.5 \pm 4.1** |
| Women, N (%) | 1026 (61.1) | 115 (52.8)* | 911 (62.4)* |
| Educational level >baccalaureate [†] | 613 (36.6) | 90 (41.3) | 523 (35.9) |
| Hypertension status [‡] | 1286 (76.7) | 188 (86.2)* | 1098 (75.2)* |
| Antihypertensive treatment intake | 714 (42.6) | 125 (57.3)** | 589 (40.3)** |
| Systolic blood pressure, mmHg | 148.8 \pm 22.6 | 153.7 \pm 21.0* | 148.0 \pm 22.8* |
| Diastolic blood pressure, mmHg | 85.0 \pm 11.5 | 87.2 \pm 11.4* | 84.6 \pm 11.5* |
| Pulse pressure, mmHg | 63.8 \pm 17.1 | 66.6 \pm 16.6 | 63.4 \pm 17.2 |
| Antithrombotic drug intake | 623 (37.1) | 95 (43.6) | 528 (36.2) |
| Body mass index, kg/m ² | 25.4 \pm 3.8 | 25.4 \pm 3.6 | 25.4 \pm 3.8 |
| Current smoker | 96 (5.7) | 14 (6.4) | 82 (5.6) |
| Diabetes mellitus [§] | 136 (8.2) | 19 (8.7) | 117 (8.1) |
| Hypercholesterolemia | 945 (56.7) | 119 (54.6) | 826 (57.0) |
| Lipid lowering treatment intake | 552 (32.9) | 71 (32.6) | 481 (33.0) |
| Total cholesterol, mmol/L | 5.8 \pm 0.9 | 5.7 \pm 0.9 | 5.8 \pm 0.9 |
| Low-density lipoprotein, mmol/L | 3.6 \pm 0.8 | 3.5 \pm 0.8 | 3.6 \pm 0.8 |
| Triglycerides, mmol/L | 1.2 \pm 0.5 | 1.2 \pm 0.6 | 1.2 \pm 0.5 |
| HDL cholesterol, mmol/L | 1.7 \pm 0.4 | 1.6 \pm 0.4 | 1.7 \pm 0.4 |
| History of cardiovascular disease [#] | 67 (4.0) | 11 (5.1) | 56 (3.8) |
| Apolipoprotein E $\epsilon 4$ carrier status | 366 (22.0) | 43 (19.7) | 323 (22.3) |
| Intracranial volume, cm ³ | 1363.7 \pm 135.3 | 1388.0 \pm 136.1 | 1360.1 \pm 134.8 |
| Covert MRI-defined lacunes | 121 (7.3) | 45 (21.3)** | 76 (5.3)** |
| Covert MRI-defined brain infarct | 146 (8.7) | 52 (23.9)** | 94 (6.4)** |
| White matter hyperintensity volume, cm ³ | 5.5 \pm 5.0 | 7.8 \pm 5.6** | 5.2 \pm 4.8** |

Logistic regression between participants with a global dPVS burden score ≥ 7 versus < 7 adjusted for age and sex:

* $p < 0.05$

** $p < 0.0001$

[†]Final high-school degree in France [‡]Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or antihypertensive drugs; [§]Blood glucose ≥ 7 mmol/L \pm antidiabetic drugs; ^{||}Total cholesterol level ≥ 6.2 mmol/L; [#]Including myocardial infarction, peripheral artery disease, cardiac and vascular surgery (patients with stroke excluded).

Table 2. Association between dilated perivascular spaces burden and incident stroke

| | All strokes | | | Ischemic stroke | | | Intracerebral hemorrhage | | |
|----------------------|-------------|------------------|--------------|-----------------|------------------|---------|--------------------------|--------------------|-----------------------------|
| | n/N | HR[95%CI] | P-Value | n/N | HR[95%CI] | P-Value | n/N | HR[95%CI] | P-Value |
| Model 1* | | | | | | | | | |
| dPVS (global) | 66/1678 | 1.24 [1.06-1.45] | 0.006 | 52/1678 | 1.05 [0.88-1.26] | 0.577 | 10/1678 | 3.12 [1.78-5.47] | 6.91x10⁻⁵ |
| dPVS (basal ganglia) | | 2.28 [1.28-4.04] | 0.005 | | 1.30 [0.61-2.80] | 0.496 | | 11.47 [3.15-41.70] | 0.0002 |
| dPVS (white matter) | | 1.21 [0.70-2.09] | 0.484 | | 0.77 [0.39-1.54] | 0.463 | | 3.13 [0.90-10.86] | 0.072 |
| dPVS (hippocampus) | | 1.23 [1.07-1.42] | 0.004 | | 1.04 [0.87-1.26] | 0.651 | | 2.55 [1.69-3.86] | 7.95x10⁻⁶ |
| dPVS (brain stem) | | 1.06 [0.94-1.21] | 0.332 | | 1.09 [0.95-1.26] | 0.209 | | 1.14 [0.83-1.55] | 0.417 |
| Model 2† | | | | | | | | | |
| dPVS (global) | 66/1659 | 1.23 [1.05-1.44] | 0.009 | 52/1659 | 1.03 [0.86-1.24] | 0.719 | 10/1659 | 3.63 [1.93-6.83] | 6.44x10⁻⁵ |
| dPVS (basal ganglia) | | 2.23 [1.26-3.97] | 0.006 | | 1.25 [0.58-2.69] | 0.564 | | 11.98 [3.25-44.11] | 0.0002 |
| dPVS (white matter) | | 1.19 [0.69-2.05] | 0.531 | | 0.75 [0.37-1.49] | 0.408 | | 3.38 [0.96-11.88] | 0.057 |
| dPVS (hippocampus) | | 1.23 [1.07-1.42] | 0.005 | | 1.03 [0.86-1.24] | 0.753 | | 2.84 [1.82-4.45] | 4.84x10⁻⁶ |
| dPVS (brain stem) | | 1.06 [0.94-1.20] | 0.337 | | 1.09 [0.95-1.25] | 0.231 | | 1.14 [0.84-1.56] | 0.407 |
| Model 3‡ | | | | | | | | | |
| dPVS (global) | 66/1666 | 1.24 [1.06-1.45] | 0.008 | 52/1666 | 1.04 [0.87-1.25] | 0.655 | 10/1666 | 3.11 [1.77-5.46] | 7.30x10⁻⁵ |
| dPVS (basal ganglia) | | 2.27 [1.28-4.02] | 0.005 | | 1.30 [0.60-2.78] | 0.507 | | 11.46 [3.16-41.64] | 0.0002 |
| dPVS (white matter) | | 1.20 [0.69-2.06] | 0.516 | | 0.76 [0.38-1.52] | 0.437 | | 3.10 [0.89-10.76] | 0.074 |
| dPVS (hippocampus) | | 1.23 [1.07-1.42] | 0.005 | | 1.04 [0.86-1.25] | 0.684 | | 2.56 [1.70-3.87] | 7.96x10⁻⁶ |
| dPVS (brain stem) | | 1.06 [0.93-1.20] | 0.378 | | 1.09 [0.94-1.25] | 0.249 | | 1.14 [0.83-1.55] | 0.422 |
| Model 4§ | | | | | | | | | |
| dPVS (global) | 66/1649 | 1.13 [0.96-1.34] | 0.134 | 52/1649 | 0.97 [0.81-1.17] | 0.770 | 10/1649 | 2.52 [1.41-4.50] | 0.002 |
| dPVS (basal ganglia) | | 1.42 [0.73-2.73] | 0.301 | | 0.83 [0.35-1.93] | 0.658 | | 4.83 [1.07-21.92] | 0.041 |
| dPVS (white matter) | | 1.03 [0.60-1.80] | 0.905 | | 0.67 [0.33-1.36] | 0.269 | | 2.32 [0.63-8.47] | 0.204 |
| dPVS (hippocampus) | | 1.18 [1.02-1.36] | 0.025 | | 1.01 [0.84-1.22] | 0.907 | | 2.32 [1.53-3.50] | 7.09x10⁻⁵ |
| dPVS (brain stem) | | 1.04 [0.92-1.18] | 0.502 | | 1.08 [0.94-1.24] | 0.285 | | 1.08 [0.79-1.47] | 0.644 |
| Model 5** | | | | | | | | | |
| dPVS (global) | 66/1659 | 1.23 [1.05-1.43] | 0.010 | 52/1659 | 1.03 [0.86-1.23] | 0.728 | 10/1659 | 3.68 [1.95-6.96] | 5.81x10⁻⁵ |
| dPVS (basal ganglia) | | 2.21 [1.24-3.93] | 0.007 | | 1.24 [0.58-2.66] | 0.585 | | 12.06 [3.26-44.56] | 0.0002 |
| dPVS (white matter) | | 1.19 [0.69-2.05] | 0.531 | | 0.75 [0.37-1.49] | 0.410 | | 3.38 [0.96-11.85] | 0.058 |

| | | | | | | |
|--------------------|------------------|--------------|------------------|-------|------------------|-----------------------------|
| dPVS (hippocampus) | 1.23 [1.06-1.42] | 0.006 | 1.03 [0.85-1.24] | 0.769 | 2.88 [1.83-4.53] | 4.99x10⁻⁶ |
| dPVS (brain stem) | 1.06 [0.94-1.20] | 0.365 | 1.08 [0.94-1.25] | 0.253 | 1.14 [0.84-1.56] | 0.400 |

dPVS (global) includes dPVS in basal ganglia (grade 3-4/1-2), white matter (grade 3-4/1-2), hippocampus (dPVS count, 0-5+) and brainstem (dPVS count, 0-6+); n/N, number of participants with stroke/total number of participants at risk, **significance threshold after correction for multiple testing : p<0.0125**. *Model 1: adjusted for sex and intracranial volume; †Model 2: as model 1, additionally adjusted for hypertension, diabetes mellitus, hypercholesterolemia, current smoking status, body mass index; ‡Model 3: as model 1, additionally adjusted for APOE ε4 carrier status; §Model 4: as model 1, additionally adjusted for white matter hyperintensities volume and covert MRI-defined lacunes; **Model5: **as model 2, additionally adjusted for antithrombotic drug intake**.

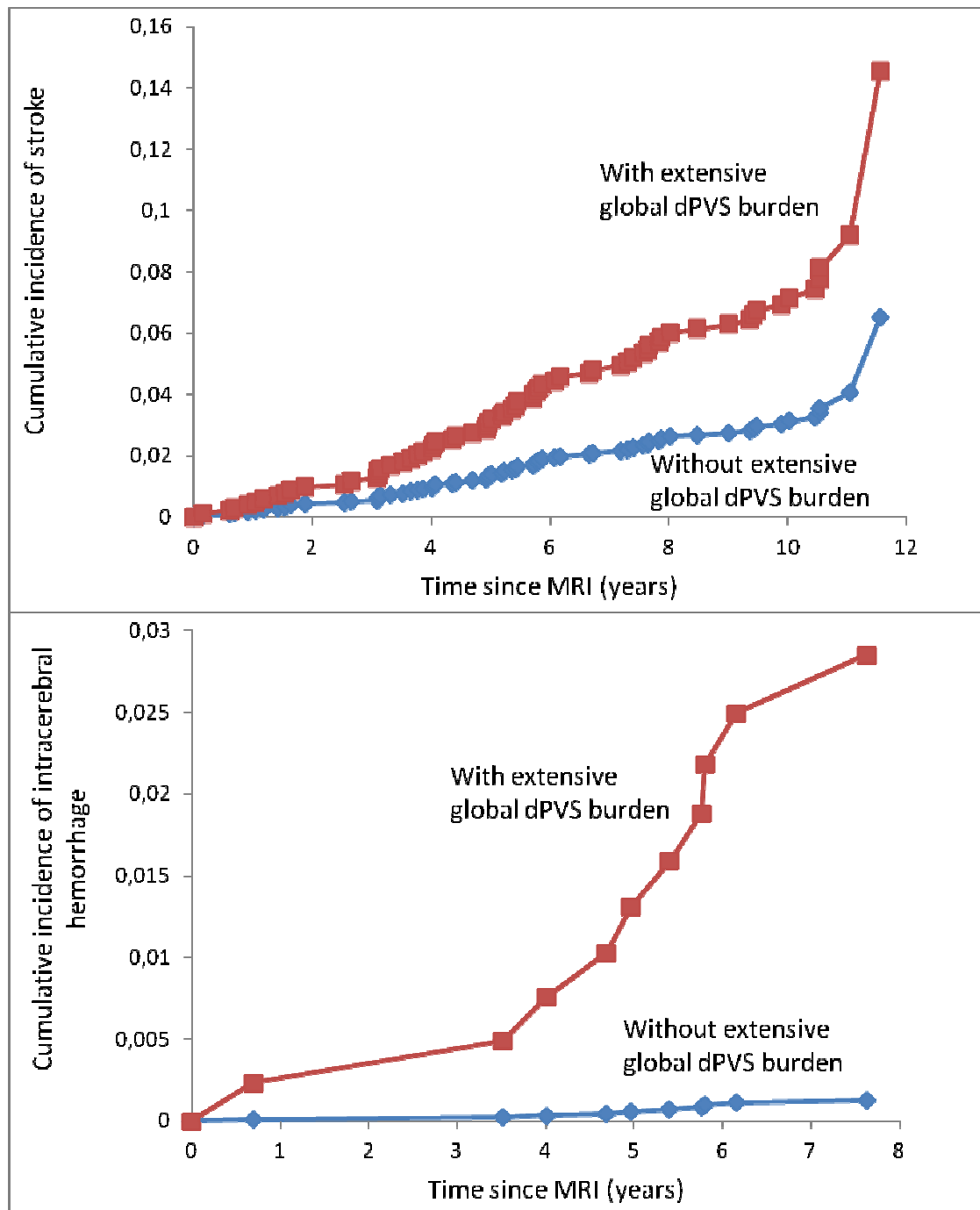


Figure 2. Cumulative incidence of stroke and intracerebral hemorrhage based on age, sex and total intracranial volume adjusted Cox models and stratified on global dPVS burden (extensive global dPVS burden [dPVS global score ≥ 7] versus the rest).

Table 3. Association between grades of dilated perivascular spaces in basal ganglia and incident stroke

| All stroke | | | | | | | | | | | | |
|-----------------------------|----------------------|-------------------|--------------|----------------------|-------------------|--------------|----------------------|-------------------|--------------|----------------------|------------------|-------------|
| | Model 1 [*] | | | Model 2 [†] | | | Model 3 [‡] | | | Model 4 [§] | | |
| | n/N | HR[95%CI] | P for trend | n/N | HR[95%CI] | P for trend | n/N | HR[95%CI] | P for trend | n/N | HR[95%CI] | P for trend |
| dPVS (basal ganglia) | | | 0.002 | | | 0.003 | | | 0.002 | | | 0.205 |
| Grade 1 | 25/916 | Referent | | 25/906 | Referent | | 25/911 | Referent | | 25/905 | Referent | |
| Grade 2 | 25/581 | 1.49 [0.86-2.61] | | 25/574 | 1.47 [0.84-2.57] | | 25/575 | 1.50 [0.86-2.61] | | 25/570 | 1.30 [0.74-2.29] | |
| Grade 3 | 14/161 | 2.70 [1.39-5.24] | | 14/159 | 2.61 [1.33-5.09] | | 14/160 | 2.68 [1.38-5.21] | | 14/156 | 1.68 [0.79-3.55] | |
| Grade 4 | 2/20 | 3.04 [0.71-13.01] | | 2/20 | 3.23 [0.75-13.91] | | 2/20 | 3.08 [0.72-13.18] | | 2/18 | 1.39 [0.29-6.60] | |

n/N, number of participants with stroke/total number of participants at risk. ^{*}Model 1: adjusted for sex and intracranial volume; [†]Model 2: as model 1, additionally adjusted for hypertension, diabetes mellitus, hypercholesterolemia, current smoking status, body mass index; [‡]Model 3: as model 1, additionally adjusted for APOE ε4 carrier status; [§]Model 4: as model 1, additionally adjusted for white matter hyperintensities volume and covert MRI-defined lacunes.