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

Marie-Gabrielle Duperron^a, MS, Christophe Tzourio^{a,b}, MD, PhD, Sabrina Schilling^a, PhD, Yi-Cheng Zhu^c, MD, PhD, Aïcha Soumaré^a, PhD, Bernard Mazoyer^d, MD, PhD, Stéphanie Debette^{a,e}, MD, PhD

Affiliations

^aUniv. Bordeaux, Inserm, Bordeaux Population Health Research Center, UMR1219, Bordeaux, France

^bCHU de Bordeaux, Pole de santé publique, Service d'information médicale, Bordeaux, France

^cDepartment of Neurology, Pekin Union Medical College Hospital, Beijing, China

^dUniv. Bordeaux, Institut des Maladies Neurodégénératives, CNRS-CEA UMR5293, France

^eCHU de Bordeaux, Department of Neurology, F-33000 Bordeaux, France

Corresponding author:

Stéphanie Debette, Bordeaux University, 146 rue Léo-Saignat, 33076 Bordeaux, France.

Tel:+33557571659; Fax:+33547304209; e-mail:stephanie.debette@u-bordeaux.fr

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1 **Abstract**

2 Commonly observed in older community persons, dilated perivascular spaces (dPVS) are
3 thought to represent an emerging MRI-marker of cerebral small vessel disease (cSVD), but
4 their clinical significance is uncertain. We examined the longitudinal relationship of dPVS
5 burden with risk of incident stroke, ischemic stroke, and intracerebral hemorrhage (ICH) in
6 the 3C-Dijon population-based study (N=1,678 participants, mean age 72.7±4.1 years) using
7 Cox regression. dPVS burden was studied as a global score and according to dPVS location
8 (basal ganglia, white matter, hippocampus, brainstem) at baseline. During a mean follow-up
9 of 9.1±2.6 years, 66 participants suffered an incident stroke. Increasing global dPVS burden
10 was associated with a higher risk of any incident stroke (hazard ratio [HR], 1.24, 95%CI
11 [1.06-1.45]) and of incident ICH (HR, 3.12[1.78-5.47]), adjusting for sex and intracranial
12 volume. Association with ICH remained significant after additionally adjusting for vascular
13 risk factors and for other cSVD MRI-markers. High dPVS burden in basal ganglia and
14 hippocampus, but not in white matter or brainstem, were associated with higher risk of any
15 stroke and ICH.

16

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

19

1 **1. Introduction**

2

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

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

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

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

4

5 **2. Methods**

6

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

9

10 **2.1. Study population**

11 The 3C-Dijon Study is a longitudinal population-based cohort study (The 3C Study Group,
12 2003). Briefly, 4,931 non-institutionalized persons aged 65 years or older were recruited from
13 the electoral rolls of Dijon, France, between March 1999 and March 2001. **Participants are**
14 **virtually all of European ancestry.** Participants enrolled between June 1999 and September
15 2000 who were younger than 80 years (N=2,763) were proposed to undergo a brain MRI at
16 baseline. Participation rate was high (82.7%), but only 1,924 MRI examinations were
17 performed because of financial limitations. After exclusion of participants with brain tumor
18 (N=8), stroke (N=83), or dementia (N=8) at the time of MRI, participants with technical
19 limitations preventing reliable assessment of dPVS burden (N=45) or intracranial volume
20 (ICV) (N=75), and participants with no follow-up for stroke (N=27), the baseline sample
21 comprised 1,678 participants. The study protocol was approved by the ethical committee of
22 the University Hospital of Kremlin-Bicêtre. All participants provided written informed
23 consent.

24

1 2.2. Brain MRI acquisition

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

6 2.3. Rating of dPVS

7 dPVS were rated in 4 main locations (basal ganglia [BG], white matter [WM], hippocampus
8 and brainstem) by an experienced reader (Y-C.Z). **Intrarater agreement (N=100 MRI) was**
9 **high (k=0.77 for basal ganglia, and k=0.75 for white matter) (Zhu et al., 2010).** dPVS were
10 defined as lesions with a CSF-like signal (hypointense on T1 and hyperintense on T2) of
11 round, ovoid, or linear shape with a maximum diameter <3 mm, having smooth delineated
12 contours, and located in areas supplied by perforating arteries. Lesions fulfilling the same
13 criteria except for a diameter ≥ 3 mm were carefully examined in the 3 planes (shape, signal
14 intensity) to differentiate them from covert MRI-defined lacunes and WMH. Only lesions
15 with a typical vascular shape (including cystic lesions with an extension of vascular shape)
16 and that followed the orientation of perforating vessels were considered as dPVS (Zhu et al.,
17 2010).

18 In **the** BG, the slice containing the greatest number of dPVS was used for the rating on a 4-
19 grade score: grade 1 for <5 dPVS; grade 2 for 5-10 dPVS; grade 3 for >10 dPVS but still
20 numerable; grade 4 for innumerable dPVS resulting in a cribriform change in **the** BG (**Figure**
21 **1**). In the WM, dPVS were also rated using a 4-grade score: grade 1 for <10 dPVS in the total
22 WM; grade 2 for ≥ 10 dPVS in the total WM and <10 in the slice containing the greatest
23 number of dPVS; grade 3 for 10-20 dPVS in the slice containing the greatest number of
24 dPVS; grade 4 for >20 dPVS in the slice containing the greatest number of dPVS (**Figure 1**)

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

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

12

13 **2.4. Other MRI measurements**

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

23

24 **2.5. Stroke assessment**

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

10

11 **2.6. Statistical Analyses**

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

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

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

1 models: model 1 adjusted for sex and ICV, model 2 additionally adjusted for vascular risk
2 factors (hypertension, diabetes, hypercholesterolemia, current smoking status, and body mass
3 index), model 3 adjusted for the same variables as in model 1 and for APOE ϵ 4-carrier status,
4 model 4 adjusted for the same variables as in model 1 and for covert MRI-defined lacunes
5 and WMHV and model 5 adjusted for the same variables as in model 2 and for
6 antithrombotic drug intake. Analyses were corrected for multiple testing, accounting for the 4
7 dPVS locations (significance threshold after correction for multiple testing: $p < 0.0125$). The
8 trend in risk of incident stroke across dPVS grades in the BG assigned with ordered natural
9 numbers (1, 2, 3 and 4) was tested using the Cox proportional hazards model. We searched
10 for an effect modification by sex, hypertension, median age and APOE ϵ 4-carrier status. We
11 verified the linearity hypothesis with a restricted cubic spline model (Desquilbet and Mariotti,
12 2010) and the proportional hazard assumption using proportionality tests that assess the
13 statistical significance of interaction terms between time and the variables in the model. We
14 also performed cumulative incidence graphs adjusted for age, sex, and total intracranial
15 volume and stratified on global extensive dPVS burden (top quartile versus the rest). The
16 Fine and Gray method has been used to model the cumulative incidence of intracerebral
17 hemorrhage to take into account competitive risks with other stroke subtypes.
18 Analyses were performed using Statistical Analyses System software version 9.3 (SAS
19 Institute, Inc, Cary, NC).

20

21 **3. Results**

22

23 For the 1,678 participants, the average age at baseline was 72.7 years (standard deviation 4.1)
24 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

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

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

11

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

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24 **4. Discussion**

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

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

In two high-risk populations with a history of ischemic stroke or transient ischemic attack (total N=2,002), from the UK (OXVASC) and China (HKU), high dPVS burden in the BG, but not in the WM, was associated with higher risk of recurrent all stroke and ischemic 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.

14

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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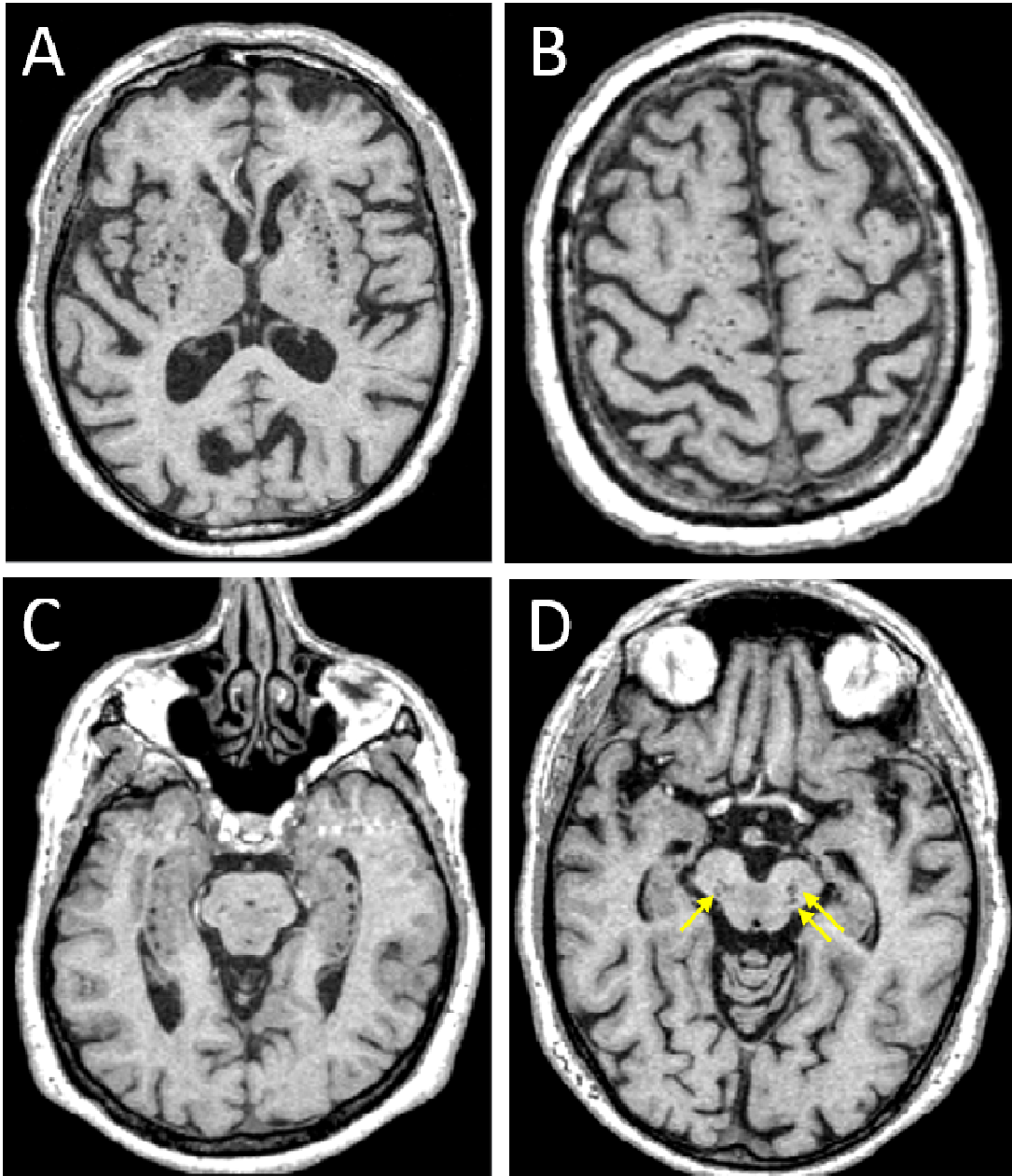


Figure 1. Axial T1-weighted images of high dilated perivascular space burden

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**.

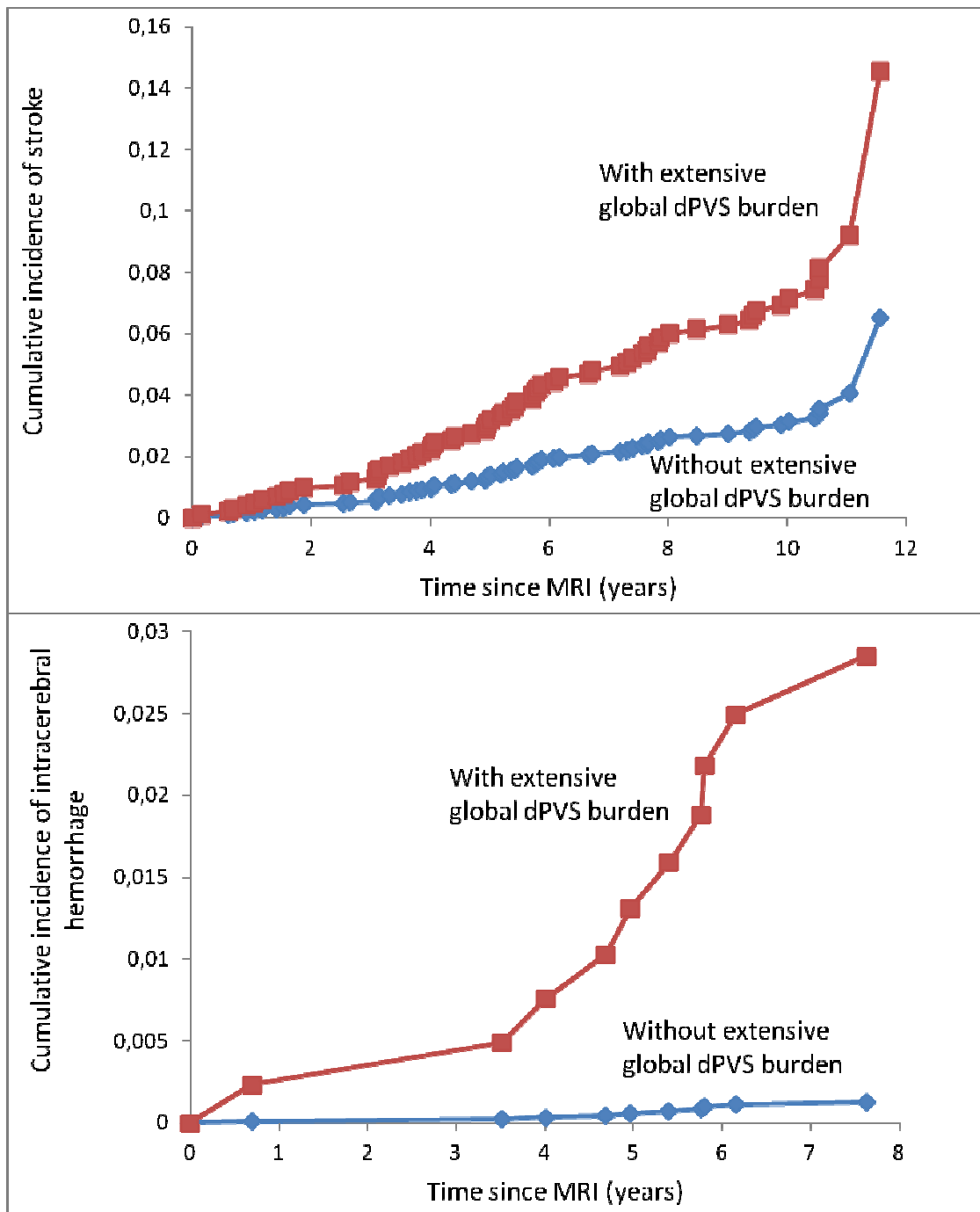


Figure 2. Cumulative incidence of stroke and intracerebral hemorrhage based on age, sex and total intracranial volume adjusted Cox models and stratified on global dPVS burden (extensive global dPVS burden [dPVS global score ≥ 7] versus the rest).

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.