



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

## Perivascular space in Parkinson's disease: Association with CSF amyloid/tau and cognitive decline

**Citation for published version:**

Chen, H, Wan, H, Zhang, M, Wardlaw, JM, Feng, T & Wang, Y 2022, 'Perivascular space in Parkinson's disease: Association with CSF amyloid/tau and cognitive decline', *Parkinsonism & Related Disorders*, vol. 95, pp. 70-76. <https://doi.org/10.1016/j.parkreldis.2022.01.002>

**Digital Object Identifier (DOI):**

[10.1016/j.parkreldis.2022.01.002](https://doi.org/10.1016/j.parkreldis.2022.01.002)

**Link:**

[Link to publication record in Edinburgh Research Explorer](#)

**Document Version:**

Peer reviewed version

**Published In:**

Parkinsonism & Related Disorders

**Publisher Rights Statement:**

This is the author's peer-reviewed manuscript as accepted for publication.

**General rights**

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

**Take down policy**

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact [openaccess@ed.ac.uk](mailto:openaccess@ed.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.



[Click here to view linked References](#)

1 **Perivascular Space in Parkinson's disease: Association with CSF Amyloid/Tau and Cognitive**  
2  
3 **decline**

4  
5  
6 Huimin Chen<sup>a,b,c,d</sup>, Huijuan Wan<sup>b,c,d,e</sup>, Meimei Zhang<sup>b,c,d</sup>, Joanna M Wardlaw<sup>f</sup>, Tao Feng<sup>b,c,d</sup>, Yilong  
7  
8  
9 Wang<sup>b,c,d</sup>

10  
11 <sup>a</sup>Department of Neurology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Medicine, Chinese Academy of Medical Sciences, Beijing, China

<sup>b</sup>Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

<sup>c</sup>China National Clinical Research Center for Neurological Diseases (NCRC-ND), Beijing, China

<sup>d</sup>Advanced Innovation Center for Human Brain Projection, Capital Medical University, Beijing, China

<sup>e</sup>Department of Neurology, First Affiliated Hospital, Xiamen University, Xiamen, China

<sup>f</sup>Centre for Clinical Brain Sciences, UK Dementia Research Institute, University of Edinburgh,  
Edinburgh, UK

**Corresponding author:**

Yilong Wang\*, MD, PhD.

**Address:** China National Clinical Research Center for Neurological Diseases, Beijing Tiantan

Hospital, Capital Medical University, No.119 South 4th Ring West Road, Fengtai District, Beijing,

China. 100070.

**E-mail:** yilong528@gmail.com, Tel: +86-139-1166-6571;

**Keywords/Search terms:** Parkinson's disease; Perivascular Space; Cognition; Amyloid; Tau

Title: 97 characteristics; Tables: 2; Figures:2; supplementary table 4; supplementary figure 3;

Reference:28;

Word count: abstract 249; body of the manuscript 3262;

1           **Abstract**

2  
3           **Objective:** Whether perivascular space (PVS) visible on magnetic resonance imaging (MRI) represents  
4  
5  
6           glymphatic dysfunction and whether this imaging marker is pathologic in Parkinson's disease (PD)  
7  
8  
9           have been controversial. The objective was to determine whether PVS visible on MRI is independently  
10  
11           associated with cognitive decline in patients with PD, and to test whether pathologic proteins in the  
12  
13           CSF (such as A $\beta$ <sub>42</sub>) mediate the pathologic role of PVS.  
14  
15

16           **Methods:** A total of 341 patients with Parkinson's disease from Parkinson's Progression Marker  
17  
18           Initiative (PPMI) cohort was included in the present study. PVS in the basal ganglia (BG-PVS) and  
19  
20           centrum semiovale were evaluated with a semiquantitative scale. Changes in the Montreal Cognitive  
21  
22           Assessment (MoCA) score and the absolute MoCA score at the 3-year assessment were considered the  
23  
24           main cognitive outcome. A multivariable linear regression model was used to test the association  
25  
26           between PVS and cognitive decline. A mixed linear model and path analysis were used to test the  
27  
28           interaction among PVS, CSF biomarkers and cognitive decline.  
29  
30  
31  
32  
33  
34  
35

36           **Results:** BG-PVS was associated with cognitive decline in patients with PD at the 3-year follow-up  
37  
38           independent of age, baseline cognition, motor and nonmotor function, presynaptic dopaminergic  
39  
40           deficiency, and CSF biomarkers. The interaction between BG-PVS and A $\beta$ <sub>42</sub>/tTau, A $\beta$ <sub>42</sub>/pTau, and A $\beta$ <sub>42</sub>  
41  
42           levels was significantly predictive of 3-year cognitive decline. Path analysis confirmed that CSF  
43  
44           A $\beta$ <sub>42</sub>/tTau levels partially mediated the pathologic effect of BG-PVS on cognitive outcome in PD.  
45  
46  
47  
48  
49

50           **Conclusions:** BG-PVS is independently associated with cognitive decline in PD, and this association  
51  
52           may be partially mediated by toxic CSF proteins.  
53  
54

55           **Keywords:** Parkinson's disease; Perivascular Space; Cognition; Amyloid; Tau  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3 **1. Introduction**

4 Parkinson's disease (PD) is the second most common neurodegenerative disease, with  $\alpha$ -synuclein ( $\alpha$ -  
5 syn) aggregation and Lewy body deposition being the pathologic hallmarks. Previous studies from  
6  
7 several cohorts consistently reported that Alzheimer's disease (AD)-related CSF biomarkers (i.e., lower  
8  
9 levels of  $A\beta_{42}$  and  $A\beta_{42}$ /Tau ratios and higher levels of total and phosphorylated Tau) were associated  
10  
11 with cognitive impairment in PD cross-sectionally [1-3] and longitudinally [4-6].  
12  
13  
14  
15  
16  
17

18       Emerging evidence has highlighted the role of the perivascular space (PVS) as a glymphatic  
19  
20 pathway for waste clearance in the brain and demonstrated that glymphatic dysfunction reduced  
21  
22 cerebrospinal fluid (CSF) clearance of  $A\beta$  in AD models and in patients with AD [7-9]. Since AD-  
23  
24 related proteins are toxic to neurons and glial cells [10] and are associated with cognitive decline in AD  
25  
26 and PD, it is possible that reduced CSF clearance of toxic proteins as a result of glymphatic  
27  
28 dysfunction may aggregate the neurodegenerative process and facilitate the development of dementia.  
29  
30  
31  
32  
33  
34  
35 A previous cohort from Korea demonstrated that basal-ganglia PVS (BG-PVS) visible on MRI  
36  
37 predicted cognitive decline in PD at the 5-year follow-up [11]. This result needs to be validated in other  
38  
39 cohorts. In addition, if BG-PVS visible on MRI reflects glymphatic dysfunction, there might be an  
40  
41 association between the severity of BG-PVS visible on MRI and higher neurodegenerative burden  
42  
43 measured by CSF biomarkers such as  $A\beta$ .  
44  
45  
46  
47

48       The Parkinson's Progression Marker Initiative (PPMI) is the largest ongoing cohort of PD with  
49  
50 comprehensive clinical, imaging and CSF biomarker data. The PPMI provides an opportunity to  
51  
52 confirm the pathologic role of BG-PVS in PD cognitive outcome. In addition, it provides superb data to  
53  
54 test the relationship between PVS visible on MRI and neurodegenerative burden measured by CSF  
55  
56  
57 biomarkers, which may inform the mechanism and potential therapeutic target of PVS in progressive  
58  
59  
60  
61  
62  
63  
64  
65

1 neurodegenerative processes.  
2  
3  
4  
5

## 6 **2. Method**

### 7 **2.1 Study design and participants**

8  
9  
10 PPMI is an ongoing, multicenter, longitudinal, observational study that started in 2010

11  
12 (<https://www.ppmi-info.org/>). Patients with early, drug-naïve PD and intact cognition were included.

13  
14  
15  
16 The PPMI study was approved by the institutional review board at each site, and participants provided

17  
18 written informed consent to participate. The protocol and more detailed study design of PPMI has been

19  
20 described elsewhere [12]. From the whole PPMI cohort, only PD patients with complete baseline BG-

21  
22 PVS profiles and CSF biomarkers were included in the present analysis. The data used in the current

23  
24  
25  
26 study were downloaded from the PPMI dataset in June 2020.

### 27 28 29 **2.2 Outcome measurements**

30  
31  
32 Cognitive decline was evaluated using the change in the MoCA score from baseline to 3-year follow-

33  
34 up and the absolute MoCA score at the 3-year assessment. The Hopkins Verbal Learning Test (HVLT)

35  
36 (memory), the Benton Judgment of Line Orientation 15-item version (visuospatial function), the

37  
38 Symbol-Digit Modalities Test (processing speed), the Letter Number Sequencing (executive function

39  
40 and working memory), and the semantic (animal) fluency test (language) were also performed. Motor

41  
42 function was measured using the Movement Disorder Society Unified Parkinson's Disease Rating

43  
44 Scale (MDS-UPDRS) part III and Hoehn-Yahr stage. Nonmotor symptoms in the prediction of

45  
46 cognitive decline in PD included rapid eye movement behavior disorder (RBD), which was assessed

47  
48 with the RBD Screening Questionnaire (RBDSQ); sense of smell, which was assessed with the

49  
50 University of Pennsylvania Smell Identification Test (UPSIT); depression, which was assessed with the

1 15-item Geriatric Depression Scale (GDS); and anxiety, which was assessed with the State-Trait  
2  
3 Anxiety Inventory.  
4  
5

### 6 7 **2.3 DAT imaging** 8 9

10 [123I]β-CIT DAT single-photon emission computed tomography (SPECT) imaging was acquired at  
11  
12 PPMI imaging centers in accordance with the PPMI imaging protocol. Mean caudate and putaminal  
13  
14 uptake relative to uptake in the occipital area and asymmetry of caudate and putaminal uptake (side  
15  
16 with highest divided by side with lowest uptake) were computed for the analysis.  
17  
18  
19  
20  
21

### 22 **2.4 History of cardio- and cerebrovascular diseases and risk factors** 23 24

25 Histories of cardio- and cerebrovascular diseases were recorded in the PPMI cohort at patient  
26  
27 screening. Cardiovascular diseases and risk factors include a history of diabetes, hypertension,  
28  
29 hyperlipidemia, hypercholesterolemia, and cardiac diseases. Cerebrovascular diseases included a  
30  
31 history of cerebrovascular accident, transient ischemic attack, ischemic stroke, cervical and carotid  
32  
33 stenosis or occlusion.  
34  
35  
36  
37  
38  
39

### 40 **2.5 Imaging markers of cerebral small vessel disease** 41 42

43 Imaging markers of cerebral small vessel disease (CSVD) were evaluated by a neurologist who was  
44  
45 blind to the patient information (HJ Wan) following the instruction and definition of Standards for  
46  
47 ReportIng Vascular changes on nEuroimaging (STRIVE) [13]. White matter hyperintensity (WMH)  
48  
49 was rated according to the Fazekas rating scale [14]. Perivascular space was defined on MRI as small,  
50  
51 sharply delineated structures of CSF intensity (or close to CSF intensity) following the course of  
52  
53 perforating vessels. PVS in the basal ganglia and centrum semiovale (CS-PVS) were rated separately  
54  
55 on T2 weighted sequence as 0 = none, 1 = 1–10, 2 = 11–20, 3 = 21–40, and 4 = >40 PVS per side, and  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 the worse side was used if there was asymmetry [15, 16]. In the statistical analysis for BG-PVS,  
2  
3 patients were stratified into groups with moderate-to-severe BG-PVS (BG-PVS rating $\geq$ 2) and none-to-  
4  
5 mild BG-PVS (BG-PVS rating $<$ 2). Similarly, in the analysis for WMH and CS-PVS, patients were also  
6  
7 grouped into the high WMH group (Fazekas $>$ 2) versus the low WMH group (Fazekas $\leq$ 2) and the high  
8  
9 CS-PVS group (CS-PVS rating $\geq$ 2) versus the low CS-PVS group (CS-PVS rating $<$ 2). This  
10  
11 stratification was consistent with the distribution of CSVD profiles in our data and was consistent with  
12  
13 studies showing that BG-PVS rating $\geq$ 2 (moderate to severe) was predictive of unfavorable outcomes  
14  
15  
16  
17  
18  
19  
20 [15, 16].  
21

## 22 **2.6 Genotyping**

23  
24  
25 At the screening visit, genomic DNA was extracted from whole blood of the subject. The APOE  
26  
27 genotype was analyzed at the PPMI genetic core as previously described [17]. Subjects were classified  
28  
29 by the presence or absence of *APOE*  $\epsilon$ 4 genotypes.  
30  
31

## 32 **2.7 CSF biomarkers**

33  
34  
35 The concentration of  $\alpha$ -synuclein in CSF samples was analyzed using an ELISA assay available  
36  
37 commercially from BioLegend. CSF A $\beta$ <sub>42</sub>, total tau (tTau) and tau phosphorylated at the threonine 181  
38  
39 position (pTau) were analyzed at Biorepository Core laboratories to the University of Pennsylvania  
40  
41 using Elecsys electrochemiluminescence immunoassays (Roche Diagnostics). More detail and primary  
42  
43 results of the measured CSF biomarkers have been reported previously in the PPMI cohort [17, 18].  
44  
45  
46  
47  
48  
49

## 50 **2.8 Statistics**

51  
52  
53 Continuous variables were compared between groups using the Mann-Whitney test (nonnormal  
54  
55 distribution) or two sample t test (normal distribution), and categorical variables were compared  
56  
57 between groups using the Chi-square test. Univariate and multivariable linear regression models were  
58  
59  
60  
61

1 performed using the MoCA score at the 3-year follow-up and the 3-year change in the MoCA score as  
2  
3 separate dependent variables. The regression models consulted a previous PPMI study using 2-year  
4  
5 cognitive outcomes [19]. Variables showing a tendency to significant association ( $p < 0.1$ ) further  
6  
7 entered the multivariable linear regression analysis simultaneously, while only one significant variable  
8  
9 of the same feature with lower P value was selected to avoid collinearity. As CSF biomarkers were  
10  
11 significantly correlated with each other (supplementary figure 1)[20], each biomarker entered the  
12  
13 multivariable regression model separately.  
14  
15  
16  
17  
18  
19

20 The interaction between BG-PVS and CSF biomarkers in relation to cognition was first explored  
21  
22 by plotting the fitting curve and then by linear mixed models. The change in MoCA score and MoCA  
23  
24 score at the 3-year follow-up was used as dependent variables in linear mixed models, BG-PVS  
25  
26 severity and CSF biomarker with or without interaction term were set as fixed effects, and other  
27  
28 variables showing significant association with cognitive outcomes in multivariable regression were  
29  
30 used as random effects. The Akaike information criterion (AIC) of models with and without the BG-  
31  
32 PVS\*CSF biomarker interaction item was recorded. Path analysis was conducted to investigate how  
33  
34 much CSF biomarkers mediated the effect of BG-PVS on cognition in PD. The standardized coefficient  
35  
36 ( $\beta$ ) of BG-PVS without a mediation effect (direct effect) and with a mediation effect (indirect effect)  
37  
38 and the standardized coefficient ( $\beta$ ) of the CSF biomarker on the change in MoCA were calculated. P  
39  
40 value  $< 0.05$  was defined as significant. Group comparison of CSF biomarkers at each follow-up point  
41  
42 was also performed between PD groups with different BG-PVS severities. P value  $< 0.01$  was defined  
43  
44 as significant in this group comparison for multiple comparison correction (Bonferroni correction for 4  
45  
46 repeated comparisons). Group comparison was conducted in SPSS 25.0 (SPSS, inc., Beijing, China),  
47  
48 and linear regression and linear mixed models were performed in R software version 4.02  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65



1 (<https://www.r-project.org/>).

2  
3 To rule out confounding by other CSVD markers and to investigate the location specificity of  
4  
5  
6 PVS, the relationship among WMH or CS-PVS, CSF biomarkers, and cognitive decline was further  
7  
8  
9 explored using a similar statistical approach.

## 10 11 **2.9 Data Availability Statement.**

12 The data was publicly available on PPMI website (<https://www.ppmi-info.org/access-data-specimens/>).

## 13 14 15 16 17 18 19 20 **3. Results**

### 21 22 **3.1 Baseline features of the included patients**

23  
24  
25 Four hundred and twenty three patients with drug-naïve PD were recruited in PPMI cohort. Among  
26  
27 these subjects, MRI imaging or T2-weighted imaging was missing in 47 patients, and imaging in  
28  
29 another 13 patients was not qualified to rate BG-PVS due to incomplete or nonaxial slices. CSF  
30  
31 biomarkers were missing in another 22 patients with PD. Finally, 341 patients with complete baseline  
32  
33 PVS and CSF biomarkers were included in the present analysis. The included and excluded patients  
34  
35 showed overall similar demographic and behavioral profiles (supplementary table 1).

### 36 37 38 39 40 41 **3.2 Group comparison between patients with lower and higher BG-PVS burdens**

42  
43 Compared with patients with lower BG-PVS burden, patients with more severe BG-PVS were  
44  
45 significantly older; had more impaired motor function at baseline; had a higher prevalence of previous  
46  
47 cardiovascular disease and more severe WMH at baseline; had a higher risk of cognitive impairment  
48  
49 and a greater decline in the MoCA score at the 3-year follow-up despite of similar baseline MoCA  
50  
51 scores; and showed lower levels of CSF  $\alpha$ -synuclein,  $A\beta_{42}/tTau$ ,  $A\beta_{42}/pTau$  and higher levels of CSF  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97  
98  
99  
100  
101  
102  
103  
104  
105  
106  
107  
108  
109  
110  
111  
112  
113  
114  
115  
116  
117  
118  
119  
120  
121  
122  
123  
124  
125  
126  
127  
128  
129  
130  
131  
132  
133  
134  
135  
136  
137  
138  
139  
140  
141  
142  
143  
144  
145  
146  
147  
148  
149  
150  
151  
152  
153  
154  
155  
156  
157  
158  
159  
160  
161  
162  
163  
164  
165  
166  
167  
168  
169  
170  
171  
172  
173  
174  
175  
176  
177  
178  
179  
180  
181  
182  
183  
184  
185  
186  
187  
188  
189  
190  
191  
192  
193  
194  
195  
196  
197  
198  
199  
200  
201  
202  
203  
204  
205  
206  
207  
208  
209  
210  
211  
212  
213  
214  
215  
216  
217  
218  
219  
220  
221  
222  
223  
224  
225  
226  
227  
228  
229  
230  
231  
232  
233  
234  
235  
236  
237  
238  
239  
240  
241  
242  
243  
244  
245  
246  
247  
248  
249  
250  
251  
252  
253  
254  
255  
256  
257  
258  
259  
260  
261  
262  
263  
264  
265  
266  
267  
268  
269  
270  
271  
272  
273  
274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288  
289  
290  
291  
292  
293  
294  
295  
296  
297  
298  
299  
300  
301  
302  
303  
304  
305  
306  
307  
308  
309  
310  
311  
312  
313  
314  
315  
316  
317  
318  
319  
320  
321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335  
336  
337  
338  
339  
340  
341  
342  
343  
344  
345  
346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356  
357  
358  
359  
360  
361  
362  
363  
364  
365  
366  
367  
368  
369  
370  
371  
372  
373  
374  
375  
376  
377  
378  
379  
380  
381  
382  
383  
384  
385  
386  
387  
388  
389  
390  
391  
392  
393  
394  
395  
396  
397  
398  
399  
400  
401  
402  
403  
404  
405  
406  
407  
408  
409  
410  
411  
412  
413  
414  
415  
416  
417  
418  
419  
420  
421  
422  
423  
424  
425  
426  
427  
428  
429  
430  
431  
432  
433  
434  
435  
436  
437  
438  
439  
440  
441  
442  
443  
444  
445  
446  
447  
448  
449  
450  
451  
452  
453  
454  
455  
456  
457  
458  
459  
460  
461  
462  
463  
464  
465  
466  
467  
468  
469  
470  
471  
472  
473  
474  
475  
476  
477  
478  
479  
480  
481  
482  
483  
484  
485  
486  
487  
488  
489  
490  
491  
492  
493  
494  
495  
496  
497  
498  
499  
500  
501  
502  
503  
504  
505  
506  
507  
508  
509  
510  
511  
512  
513  
514  
515  
516  
517  
518  
519  
520  
521  
522  
523  
524  
525  
526  
527  
528  
529  
530  
531  
532  
533  
534  
535  
536  
537  
538  
539  
540  
541  
542  
543  
544  
545  
546  
547  
548  
549  
550  
551  
552  
553  
554  
555  
556  
557  
558  
559  
560  
561  
562  
563  
564  
565  
566  
567  
568  
569  
570  
571  
572  
573  
574  
575  
576  
577  
578  
579  
580  
581  
582  
583  
584  
585  
586  
587  
588  
589  
590  
591  
592  
593  
594  
595  
596  
597  
598  
599  
600  
601  
602  
603  
604  
605  
606  
607  
608  
609  
610  
611  
612  
613  
614  
615  
616  
617  
618  
619  
620  
621  
622  
623  
624  
625  
626  
627  
628  
629  
630  
631  
632  
633  
634  
635  
636  
637  
638  
639  
640  
641  
642  
643  
644  
645  
646  
647  
648  
649  
650  
651  
652  
653  
654  
655  
656  
657  
658  
659  
660  
661  
662  
663  
664  
665  
666  
667  
668  
669  
670  
671  
672  
673  
674  
675  
676  
677  
678  
679  
680  
681  
682  
683  
684  
685  
686  
687  
688  
689  
690  
691  
692  
693  
694  
695  
696  
697  
698  
699  
700  
701  
702  
703  
704  
705  
706  
707  
708  
709  
710  
711  
712  
713  
714  
715  
716  
717  
718  
719  
720  
721  
722  
723  
724  
725  
726  
727  
728  
729  
730  
731  
732  
733  
734  
735  
736  
737  
738  
739  
740  
741  
742  
743  
744  
745  
746  
747  
748  
749  
750  
751  
752  
753  
754  
755  
756  
757  
758  
759  
760  
761  
762  
763  
764  
765  
766  
767  
768  
769  
770  
771  
772  
773  
774  
775  
776  
777  
778  
779  
780  
781  
782  
783  
784  
785  
786  
787  
788  
789  
790  
791  
792  
793  
794  
795  
796  
797  
798  
799  
800  
801  
802  
803  
804  
805  
806  
807  
808  
809  
810  
811  
812  
813  
814  
815  
816  
817  
818  
819  
820  
821  
822  
823  
824  
825  
826  
827  
828  
829  
830  
831  
832  
833  
834  
835  
836  
837  
838  
839  
840  
841  
842  
843  
844  
845  
846  
847  
848  
849  
850  
851  
852  
853  
854  
855  
856  
857  
858  
859  
860  
861  
862  
863  
864  
865  
866  
867  
868  
869  
870  
871  
872  
873  
874  
875  
876  
877  
878  
879  
880  
881  
882  
883  
884  
885  
886  
887  
888  
889  
890  
891  
892  
893  
894  
895  
896  
897  
898  
899  
900  
901  
902  
903  
904  
905  
906  
907  
908  
909  
910  
911  
912  
913  
914  
915  
916  
917  
918  
919  
920  
921  
922  
923  
924  
925  
926  
927  
928  
929  
930  
931  
932  
933  
934  
935  
936  
937  
938  
939  
940  
941  
942  
943  
944  
945  
946  
947  
948  
949  
950  
951  
952  
953  
954  
955  
956  
957  
958  
959  
960  
961  
962  
963  
964  
965  
966  
967  
968  
969  
970  
971  
972  
973  
974  
975  
976  
977  
978  
979  
980  
981  
982  
983  
984  
985  
986  
987  
988  
989  
990  
991  
992  
993  
994  
995  
996  
997  
998  
999  
1000

### 3.3 Univariate linear regression for cognition at the 3-year follow-up

Using the absolute MoCA score at the 3-year follow-up as the dependent variable, age, baseline MoCA score, MDS-UPDRS III score, RBDSQ, UPSIT score, CSF A $\beta$ <sub>42</sub>, tTau, pTau, A $\beta$ <sub>42</sub>/tTau, A $\beta$ <sub>42</sub>/pTau, putamen asymmetry and BG-PVS were significantly associated with cognition at the 3-year follow-up in PD patients (P<0.05).

Using decline in MoCA score as the dependent variable, age, baseline MoCA score, RBDSQ, UPSIT score, CSF A $\beta$ <sub>42</sub>, tTau, pTau, A $\beta$ <sub>42</sub>/tTau, A $\beta$ <sub>42</sub>/pTau, putamen asymmetry and BG-PVS were significantly associated with cognitive decline during three years in PD patients (P<0.05) (supplementary table 2).

### 3.4 Multivariable linear regression for cognition at the 3-year follow-up

In multivariable regression models, BG-PVS was significantly associated with MoCA score or change in MoCA score, independent of age, baseline cognition, motor function, nonmotor symptoms, presynaptic dopaminergic deficiency, and CSF biomarkers. Baseline CSF A $\beta$ <sub>42</sub>, A $\beta$ <sub>42</sub>/tTau and A $\beta$ <sub>42</sub>/pTau were significantly associated with the MoCA score or change in the MoCA score at 3-year follow-up independent of age, baseline cognition, motor function, nonmotor symptoms, presynaptic dopaminergic deficiency, and BG-PVS. However, baseline CSF tTau and pTau were not significantly associated with either cognitive outcome at year three after adjustment (supplementary table 3).

### 3.5 Interaction between CSF biomarkers and BG-PVS

There was a significant main effect of BG-PVS and CSF A $\beta$ <sub>42</sub>/tTau, A $\beta$ <sub>42</sub>/pTau and A $\beta$ <sub>42</sub> as well as interactions between BG-PVS and these CSF biomarkers (**Table 2**), such that patients with higher BG-PVS and lower A $\beta$ <sub>42</sub>/tTau (**Figure 1A**), A $\beta$ <sub>42</sub>/pTau (**Figure 1B**), or A $\beta$ <sub>42</sub> (**Figure 1C**) showed steeper decline in the MoCA score at the 3-year follow-up. Models containing interaction terms provided a

1 slightly improved fit. As patients with a higher BG-PVS burden had a higher prevalence of  
2  
3 cardiovascular disease and risk factors, we further tested whether the interaction between BG-PVS and  
4  
5 CSF biomarkers was confounded by the presence of cardiovascular disease and risk factors. However,  
6  
7 the correlation between CSF biomarkers and cognitive decline was not stratified by the presence of  
8  
9 cardiovascular disease or related risk factors (supplementary figure 2).  
10  
11  
12

13  
14 We further compared CSF biomarkers at each follow-up timepoint between the BG-PVS groups.  
15  
16 The results revealed that patients with more severe BG-PVS showed significantly higher levels of all  
17  
18 measured CSF biomarkers at baseline, 1-year follow-up, and 2-year follow-up, and the significant  
19  
20 difference in tTau and pTau was still observed at year three (supplementary table 4) with corrected P  
21  
22 values ( $P < 0.01$ ).  
23  
24  
25  
26

### 27 **3.6 Path analysis**

28  
29 In path analysis, CSF  $A\beta_{42}/tTau$  was found to mediate the effect of BG-PVS on cognitive decline (total  
30  
31 effect [original coefficient] = -0.256, direct effect [corrected coefficient] = -0.208, indirect effect = -  
32  
33 0.048) (**Figure 2A**). That is, CSF  $A\beta_{42}/tTau$  mediated 18.8% (indirect effect/total effect) of the BG-  
34  
35 PVS effect on the decrease in MoCA scores during the 3-year follow-up. In path analysis, the  
36  
37 correlation of BG-PVS with  $A\beta_{42}/pTau$  was marginally significant, and that with  $A\beta_{42}$  was not  
38  
39 significant (**Figure 2B and 2C**).  
40  
41  
42  
43  
44  
45  
46

### 47 **3.7 Additional analysis with WMH and CS-PVS**

48  
49 For WMH, no significant difference in baseline CSF biomarkers ( $\alpha$ -syn  $z = -1.337$ ,  $P = 0.181$ ;  $A\beta_{42}$   $z =$   
50  
51 -0.430,  $P = 0.667$ ; pTau  $z = -1.181$ ,  $P = 0.238$ ; tTau  $z = -1.697$ ,  $P = 0.090$ ) was found between groups  
52  
53  
54 with different WMH severity (Fazekas 0-2 vs. Fazekas 3-6). No significant correlation was found  
55  
56  
57 between CSF biomarkers and WMH Fazekas rating according to the Spearman correlation analysis ( $\alpha$ -  
58  
59  
60  
61  
62

1 syn  $r = 0.025$ ,  $P = 0.640$ ;  $A\beta_{42}$   $r = -0.057$ ,  $P = 0.300$ ; pTau  $r = 0.036$ ,  $P = 0.534$ ; tTau  $r = 0.039$ ,  $P =$   
2  
3 0.331). No significant correlation was observed between WMH and cognitive decline or between  
4  
5  
6 WMH and CSF biomarkers ( $A\beta_{42}/tTau$ ,  $A\beta_{42}/pTau$ ,  $A\beta_{42}$ ) in the path analysis (supplementary figure 3).  
7

8  
9 For CS-PVS, no significant difference in baseline CSF biomarkers ( $\alpha$ -syn  $z = -1.391$ ,  $P = 0.164$ ;  
10  
11  $A\beta_{42}$   $z = -0.685$ ,  $P = 0.493$ ; pTau  $z = -1.422$ ,  $P = 0.155$ ; tTau  $z = -1.741$ ,  $P = 0.082$ ) was found between  
12  
13 groups stratified by CS-PVS severity (CS-PVS 0-1 vs. CS-PVS $\geq 2$ ). No significant correlation was  
14  
15 observed between CS-PVS and CSF biomarkers ( $A\beta_{42}/tTau$ ,  $A\beta_{42}/pTau$ ,  $A\beta_{42}$ ) in path analysis  
16  
17 (supplementary figure 3). Although a marginally significant correlation between CS-PVS and cognitive  
18  
19 decline was observed in the path analysis, the significant correlation was not preserved in the  
20  
21 multivariable linear model adjusting for age (coefficient =  $-0.729$ , 95% CI =  $-1.612$ – $0.154$ ,  $P = 0.105$ )  
22  
23 or in the model adjusted for age, baseline MoCA scores, baseline state trait anxiety score, RBDSQ,  
24  
25 UPSIT, and putamen asymmetry (coefficient =  $-0.615$ , 95% CI =  $-1.419$ – $0.188$ ,  $P = 0.132$ ).  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35

#### 36 **4. Discussion**

37  
38  
39 This is the first study that examined the relationship between CSF biomarkers and PVS visible on MRI  
40  
41 in neurodegenerative disease. The main finding demonstrated that BG-PVS was independently  
42  
43 associated with cognitive decline in patients with PD. In addition, BG-PVS modified the pathologic  
44  
45 effect of  $A\beta_{42}/tTau$ ,  $A\beta_{42}/pTau$ , and  $A\beta_{42}$  on cognitive decline in PD. Path analysis confirmed that CSF  
46  
47 biomarkers, especially  $A\beta_{42}/tTau$ , partially mediated the pathologic effect of BG-PVS on cognitive  
48  
49 outcomes in PD. These results suggest that the increased visibility of BG-PVS on MRI may reflect  
50  
51 more advanced glymphatic dysfunction, resulting in higher levels of toxic CSF proteins, which may in  
52  
53 turn accelerate neurodegenerative processes and cognitive decline. It also implies that the glymphatic  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 pathway may serve as a therapeutic target to preserve cognition in neurodegenerative disease.  
2

3 Our results validated a previous study by Park and colleagues and showed that BG-PVS was  
4 associated with 3-year cognitive decline in patients with PD[11]. In addition, the contribution to poor  
5 cognitive outcome and the interaction with CSF proteins were specific for PVS located in the basal  
6 ganglia but not the centrum semiovale. However, the underlying mechanism for the location specificity  
7 remains unclear. Evidence suggests that cerebral arterial pulsation drove CSF-interstitial fluid exchange  
8 mediated by the glymphatic pathway [21], and arterial stiffness was associated with a higher BG-PVS  
9 burden [22]. It is possible that PVS in the basal ganglia may be more prone to arterial damage and  
10 pulsation change during aging. However, we did not test arterial function, such as arterial stiffness and  
11 regulation. Future studies will be needed to test this hypothesis. In addition, BG-PVS differs from CSF-  
12 PVS in structure, as BG-PVS is covered by two leptomeningeal membranes and directly connects CSF  
13 [23]. This means that BG-PVS may be more active in eliminating waste from CSF, and the increased  
14 visibility of BG-PVS may represent an increased effort in waste clearance. Future studies directly  
15 comparing CSF dynamics are needed to investigate the location difference of PVS.  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38

39 Moreover, the results also suggested that PVS visible on MRI may reflect glymphatic dysfunction  
40 and impaired efflux of CSF proteins in patients with PD. In addition, the level of neurodegenerative  
41 CSF proteins ( $A\beta_{42}$ /tTau) partially mediated the effect of BG-PVS on poor cognitive outcome. Taking  
42 that CSF proteins, including  $A\beta$  and Tau, are toxic to neurons and glial cells [10] and AD biomarkers  
43 are predictive of cognitive decline in PD [4-6], the result implies that BG-PVS may contribute to  
44 cognitive decline by elevating toxic CSF proteins in patients with PD. The glymphatic pathway has  
45 drawn much attention in recent years as a novel pathway to exclude neurotoxic proteins and a potential  
46 therapeutic target [24]. In patients with superficial sclerosis, PVS was enlarged beneath the affected  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 area where A $\beta$  was deposited in the cortical arterial wall by biopsy, supporting the notion that enlarged  
2  
3 PVS is a sign of a blocked drainage pathway by proteins such as A $\beta$  [25]. Therefore, PVS visible on  
4  
5  
6 MRI may be a possible way to explore the static glymphatic pathway offline.  
7

8  
9 The interactive effect between BG-PVS and CSF A $\beta_{42}$ , A $\beta_{42}$ /tTau, and A $\beta_{42}$ /pTau on cognitive  
10  
11 decline was a novel finding in our study. This suggests that modification of the glymphatic pathway  
12  
13 may be a potential and crucial therapeutic target to alleviate the pathologic effect of A $\beta_{42}$  and Tau on  
14  
15 cognitive decline in PD. Emerging evidence has demonstrated the interaction between PVS and AD-  
16  
17 related proteins [24], and our result further supported the additive consequence of their interaction in  
18  
19 human cohort. In addition, the benefit of treatment targeting the glymphatic pathway may be beyond  
20  
21 AD-related pathology since PVS has also been highlighted to be involved in the inflammatory process  
22  
23 in multiple sclerosis [26] Sleep intervention may be an effective way to improve glymphatic function,  
24  
25 which may need to be tested in clinical trials or observational studies [27]. Other treatments targeting  
26  
27 pericytes, endothelial cells, perivascular inflammation and other factors pertaining to glymphatic  
28  
29 function also deserve to be investigated.  
30  
31  
32  
33  
34  
35  
36  
37  
38

39 In addition to our initial hypothesis, the factors associated with 3-year cognitive decline were  
40  
41 largely consistent with previous 2-year follow-up analysis [19]. More recently, Irwin and colleagues  
42  
43 reported that AD-related CSF biomarkers were associated with 3-year cognitive decline in a PPMI  
44  
45 cohort [20]. Although finding risk factors associated with cognitive decline was not the main topic of  
46  
47 our study, the consistency with previous data suggests that the present data are representative of the  
48  
49 whole cohort despite missing BG-PVS data in 59 patients (missing rate = 13.9%).  
50  
51  
52  
53  
54  
55

56 We acknowledge several limitations. First, this study did not measure the dynamic function of the  
57  
58 glymphatic pathway in vivo. Currently, dynamic fluid exchange by the glymphatic pathway has been  
59  
60  
61  
62  
63  
64  
65

1 investigated in vivo by intrathecal injection of the contrast agent in neurological diseases such as  
2  
3 idiopathic normal pressure hydrocephalus [9, 28]. These approaches enable tracking uptake and  
4  
5  
6 distribution of tracers dynamically, but they are invasive and may not be applicable in patients with PD.  
7  
8  
9 Second, although CSF A $\beta$ <sub>42</sub> and Tau are consistently found to be associated with cognitive decline in  
10  
11 PD, they are not PD-specific biomarkers. In addition, the findings of the present study only represent  
12  
13 the PD population. Whether proteinaceous waste such as A $\beta$  and Tau drives the increased visibility of  
14  
15 PVS on MRI and potentially mediates its toxicity needs to be tested in the AD population and normal  
16  
17  
18 aging population.  
19  
20

21  
22 In conclusion, we found that BG-PVS may be independently associated with cognitive decline in  
23  
24 PD, which may be partially mediated by toxic CSF proteins. The increased visibility of BG-PVS on  
25  
26 MRI may reflect more advanced glymphatic dysfunction. PVS may serve as a therapeutic target to  
27  
28  
29 preserve cognition in PD.  
30  
31

### 32 33 34 35 36 **Conflict of interest**

37  
38  
39 None  
40  
41

### 42 43 44 **Acknowledgements**

45  
46 PPMI is supported by the Michael J. Fox Foundation for Parkinson's Research and funding partners,  
47  
48 including Abbott, Avid, Biogen idec, Bristol-Myers Squibb, Covance, Elan, GE Healthcare, Genentech,  
49  
50  
51 GSK, Lilly, MERCK, MSD, Pfizer, Roche and UCB (details of the PPMI funding partners found at  
52  
53  
54 [www.ppmiinfo.org/](http://www.ppmiinfo.org/) funding partners). Yilong Wang is supported by grants from the National  
55  
56  
57  
58  
59 Natural Science Foundation of China (81825007), the Ministry of Science and Technology of the  
60  
61

1 People's Republic of China (2017YFC1307900), Beijing Outstanding Young Scientist Program  
2  
3 (BJJWZYJH01201910025030), the third batch of National Ten Thousand Talents Plan, the Beijing  
4  
5  
6 Municipal Science and Technology Commission (Beijing Excellent Talents Training and Supporting  
7  
8  
9 Top Youth Team, D171100003017001 and 2016000021223TD03), and the Youth Beijing Scholar  
10  
11  
12 Program.

13  
14  
15  
16  
17 References:

- 18  
19  
20 [1] G. Alves, K. Bronnick, D. Aarsland, K. Blennow, H. Zetterberg, C. Ballard, M.W. Kurz, U.  
21  
22 Andreasson, O.B. Tysnes, J.P. Larsen, E. Mulugeta, CSF amyloid-beta and tau proteins, and cognitive  
23  
24 performance, in early and untreated Parkinson's disease: the Norwegian ParkWest study, J Neurol  
25  
26 Neurosurg Psychiatry 81(10) (2010) 1080-6.  
27  
28  
29 [2] J.B. Leverenz, G.S. Watson, J. Shofer, C.P. Zabetian, J. Zhang, T.J. Montine, Cerebrospinal fluid  
30  
31 biomarkers and cognitive performance in non-demented patients with Parkinson's disease, Parkinsonism  
32  
33 Relat Disord 17(1) (2011) 61-4.  
34  
35  
36 [3] A.L. Stav, D. Aarsland, K.K. Johansen, E. Hessen, E. Auning, T. Fladby, Amyloid-beta and alpha-  
37  
38 synuclein cerebrospinal fluid biomarkers and cognition in early Parkinson's disease, Parkinsonism Relat  
39  
40 Disord 21(7) (2015) 758-64.  
41  
42  
43 [4] S. Hall, Y. Surova, A. Ohrfelt, F.S. Swedish Bio, K. Blennow, H. Zetterberg, O. Hansson,  
44  
45 Longitudinal Measurements of Cerebrospinal Fluid Biomarkers in Parkinson's Disease, Mov Disord 31(6)  
46  
47 (2016) 898-905.  
48  
49  
50 [5] M. Shahid, J. Kim, K. Leaver, T. Hendershott, D. Zhu, B. Cholerton, V.W. Henderson, L. Tian, K.L.  
51  
52 Poston, An increased rate of longitudinal cognitive decline is observed in Parkinson's disease patients  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65



1 with low CSF Ass42 and an APOE epsilon4 allele, *Neurobiol Dis* 127 (2019) 278-286.

2  
3 [6] M. Delgado-Alvarado, R. Dacosta-Aguayo, I. Navalpotro-Gomez, B. Gago, A. Gorostidi, H.  
4  
5 Jimenez-Urbieto, A. Quiroga-Varela, J. Ruiz-Martinez, A. Bergareche, M.C. Rodriguez-Oroz, Ratios of  
6  
7 proteins in cerebrospinal fluid in Parkinson's disease cognitive decline: prospective study, *Mov Disord*  
8  
9 33(11) (2018) 1809-1813.

10  
11 [7] E.L. Boespflug, M.J. Simon, E. Leonard, M. Grafe, R. Woltjer, L.C. Silbert, J.A. Kaye, J.J. Iliff,  
12  
13 Targeted Assessment of Enlargement of the Perivascular Space in Alzheimer's Disease and Vascular  
14  
15 Dementia Subtypes Implicates Astroglial Involvement Specific to Alzheimer's Disease, *J Alzheimers Dis*  
16  
17 66(4) (2018) 1587-1597.

18  
19 [8] M.K. Rasmussen, H. Mestre, M. Nedergaard, The glymphatic pathway in neurological disorders,  
20  
21 *Lancet Neurol* 17(11) (2018) 1016-1024.

22  
23 [9] M.J. de Leon, Y. Li, N. Okamura, W.H. Tsui, L.A. Saint-Louis, L. Glodzik, R.S. Osorio, J. Fortea, T.  
24  
25 Butler, E. Pirraglia, S. Fossati, H.J. Kim, R.O. Carare, M. Nedergaard, H. Benveniste, H. Rusinek,  
26  
27 Cerebrospinal Fluid Clearance in Alzheimer Disease Measured with Dynamic PET, *J Nucl Med* 58(9)  
28  
29 (2017) 1471-1476.

30  
31 [10] S. Jankeviciute, G. Psemeneckiene, R. Morkuniene, E. Grusauskiene, K. Petrikonis, D. Rastenyte,  
32  
33 V. Borutaite, Cerebrospinal fluids from Alzheimer's disease patients exhibit neurotoxic effects on  
34  
35 neuronal cell cultures, *Eur J Neurosci* 50(2) (2019) 1994-2006.

36  
37 [11] Y.W. Park, N.Y. Shin, S.J. Chung, J. Kim, S.M. Lim, P.H. Lee, S.K. Lee, K.J. Ahn, Magnetic  
38  
39 Resonance Imaging-Visible Perivascular Spaces in Basal Ganglia Predict Cognitive Decline in  
40  
41 Parkinson's Disease, *Mov Disord* 34(11) (2019) 1672-1679.

42  
43 [12] I. Parkinson Progression Marker, The Parkinson Progression Marker Initiative (PPMI), *Prog*  
44  
45

1 Neurobiol 95(4) (2011) 629-35.

2  
3 [13] J.M. Wardlaw, E.E. Smith, G.J. Biessels, C. Cordonnier, F. Fazekas, R. Frayne, R.I. Lindley, J.T.  
4  
5  
6 O'Brien, F. Barkhof, O.R. Benavente, S.E. Black, C. Brayne, M. Breteler, H. Chabriat, C. Decarli, F.E.  
7  
8  
9 de Leeuw, F. Doubal, M. Duering, N.C. Fox, S. Greenberg, V. Hachinski, I. Kilimann, V. Mok, R.  
10  
11  
12 Oostenbrugge, L. Pantoni, O. Speck, B.C. Stephan, S. Teipel, A. Viswanathan, D. Werring, C. Chen, C.  
13  
14  
15 Smith, M. van Buchem, B. Norrving, P.B. Gorelick, M. Dichgans, S.T.f.R.V.c.o. nEuroimaging,  
16  
17  
18 Neuroimaging standards for research into small vessel disease and its contribution to ageing and  
19  
20  
21 neurodegeneration, *Lancet Neurol* 12(8) (2013) 822-38.

22  
23 [14] F. Fazekas, R. Kleinert, H. Offenbacher, R. Schmidt, G. Kleinert, F. Payer, H. Radner, H. Lechner,  
24  
25  
26 Pathologic correlates of incidental MRI white matter signal hyperintensities, *Neurology* 43(9) (1993)  
27  
28  
29 1683-9.

30  
31 [15] F.N. Doubal, A.M. MacLulich, K.J. Ferguson, M.S. Dennis, J.M. Wardlaw, Enlarged perivascular  
32  
33  
34 spaces on MRI are a feature of cerebral small vessel disease, *Stroke* 41(3) (2010) 450-4.

35  
36 [16] G.M. Potter, F.N. Doubal, C.A. Jackson, F.M. Chappell, C.L. Sudlow, M.S. Dennis, J.M. Wardlaw,  
37  
38  
39 Enlarged perivascular spaces and cerebral small vessel disease, *Int J Stroke* 10(3) (2015) 376-81.

40  
41  
42 [17] J.H. Kang, B. Mollenhauer, C.S. Coffey, J.B. Toledo, D. Weintraub, D.R. Galasko, D.J. Irwin, V.  
43  
44  
45 Van Deerlin, A.S. Chen-Plotkin, C. Caspell-Garcia, T. Waligorska, P. Taylor, N. Shah, S. Pan, P. Zero,  
46  
47  
48 M. Frasier, K. Marek, K. Kieburz, D. Jennings, C.M. Tanner, T. Simuni, A. Singleton, A.W. Toga, S.  
49  
50  
51 Chowdhury, J.Q. Trojanowski, L.M. Shaw, I. Parkinson's Progression Marker, CSF biomarkers  
52  
53  
54 associated with disease heterogeneity in early Parkinson's disease: the Parkinson's Progression Markers  
55  
56  
57 Initiative study, *Acta Neuropathol* 131(6) (2016) 935-49.

58  
59 [18] B. Mollenhauer, C.J. Caspell-Garcia, C.S. Coffey, P. Taylor, L.M. Shaw, J.Q. Trojanowski, A.  
60  
61  
62

1 Singleton, M. Frasier, K. Marek, D. Galasko, I. Parkinson's Progression Marker, Longitudinal CSF  
2  
3 biomarkers in patients with early Parkinson disease and healthy controls, *Neurology* 89(19) (2017) 1959-  
4  
5  
6 1969.

7  
8  
9 [19] A. Schrag, U.F. Siddiqui, Z. Anastasiou, D. Weintraub, J.M. Schott, Clinical variables and  
10  
11 biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease:  
12  
13 a cohort study, *Lancet Neurol* 16(1) (2017) 66-75.

14  
15  
16 [20] D.J. Irwin, J. Fedler, C.S. Coffey, C. Caspell-Garcia, J.H. Kang, T. Simuni, T. Foroud, A.W. Toga,  
17  
18  
19 C.M. Tanner, K. Kieburtz, L.M. Chahine, A. Reimer, S. Hutten, D. Weintraub, B. Mollenhauer, D.R.  
20  
21 Galasko, A. Siderowf, K. Marek, J.Q. Trojanowski, L.M. Shaw, I. Parkinson's Progression Marker,  
22  
23 Evolution of Alzheimer's Disease Cerebrospinal Fluid Biomarkers in Early Parkinson's Disease, *Ann*  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

[21] J.J. Iliff, M. Wang, D.M. Zeppenfeld, A. Venkataraman, B.A. Plog, Y. Liao, R. Deane, M.  
Nedergaard, Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine  
brain, *J Neurosci* 33(46) (2013) 18190-9.

[22] I. Riba-Llena, J. Jimenez-Balado, X. Castane, A. Girona, A. Lopez-Rueda, X. Mundet, C.I. Jarca, J.  
Alvarez-Sabin, J. Montaner, P. Delgado, Arterial Stiffness Is Associated With Basal Ganglia Enlarged  
Perivascular Spaces and Cerebral Small Vessel Disease Load, *Stroke* 49(5) (2018) 1279-1281.

[23] J.M. Wardlaw, H. Benveniste, M. Nedergaard, B.V. Zlokovic, H. Mestre, H. Lee, F.N. Doubal, R.  
Brown, J. Ramirez, B.J. MacIntosh, A. Tannenbaum, L. Ballerini, R.L. Rungta, D. Boido, M. Sweeney,  
A. Montagne, S. Charpak, A. Joutel, K.J. Smith, S.E. Black, D. colleagues from the Fondation Leducq  
Transatlantic Network of Excellence on the Role of the Perivascular Space in Cerebral Small Vessel,  
Perivascular spaces in the brain: anatomy, physiology and pathology, *Nat Rev Neurol* 16(3) (2020) 137-

1 153.

2  
3 [24] B.L. Sun, L.H. Wang, T. Yang, J.Y. Sun, L.L. Mao, M.F. Yang, H. Yuan, R.A. Colvin, X.Y. Yang,  
4  
5  
6 Lymphatic drainage system of the brain: A novel target for intervention of neurological diseases, *Prog*  
7  
8  
9 *Neurobiol* 163-164 (2018) 118-143.

10  
11 [25] A. Keable, K. Fenna, H.M. Yuen, D.A. Johnston, N.R. Smyth, C. Smith, R. Al-Shahi Salman, N.  
12  
13 Samarasekera, J.A. Nicoll, J. Attems, R.N. Kalaria, R.O. Weller, R.O. Carare, Deposition of amyloid  
14  
15 beta in the walls of human leptomeningeal arteries in relation to perivascular drainage pathways in  
16  
17 cerebral amyloid angiopathy, *Biochim Biophys Acta* 1862(5) (2016) 1037-46.

18  
19 [26] J. Wuerfel, M. Haertle, H. Waiczies, E. Tysiak, I. Bechmann, K.D. Wernecke, F. Zipp, F. Paul,  
20  
21  
22 Perivascular spaces--MRI marker of inflammatory activity in the brain?, *Brain* 131(Pt 9) (2008) 2332-  
23  
24  
25  
26  
27  
28 40.

29  
30 [27] E. Cvejic, S. Huang, U. Vollmer-Conna, Can you snooze your way to an 'A'? Exploring the complex  
31  
32 relationship between sleep, autonomic activity, wellbeing and performance in medical students, *Aust N*  
33  
34  
35  
36  
37  
38 *Z J Psychiatry* 52(1) (2018) 39-46.

39 [28] G. Ringstad, S.A.S. Vatnehol, P.K. Eide, Glymphatic MRI in idiopathic normal pressure  
40  
41  
42 hydrocephalus, *Brain* 140(10) (2017) 2691-2705.  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 **Figure legends**

2  
3 **Figure 1. Correlation between CSF biomarkers and cognitive outcomes stratified by BG-PVS**

4  
5  
6 BG-PVS modified the effect of  $A\beta_{42}/t\text{Tau}$  (A),  $A\beta_{42}/p\text{Tau}$  (B),  $A\beta_{42}$  (C) on cognitive outcome in  
7  
8  
9 Parkinson's disease, as high BG-PVS group showed steeper decline in the MoCA score in relation to  
10  
11  
12 CSF biomarkers at the 3-year follow-up.

13  
14 Abbreviations: BG-PVS, basal-ganglia perivascular space; CSF, cerebrospinal fluid.

15  
16  
17 **Figure 2. Path analysis**

18  
19  
20 A. CSF  $A\beta_{42}/t\text{Tau}$ , but not  $A\beta_{42}/p\text{Tau}$  or CSF  $A\beta_{42}$  significantly mediated the effect of BG-PVS on  
21  
22  
23 cognitive decline in patients with PD. The effect of WMH (B) or CS-PVS (C) on cognitive outcome  
24  
25  
26 was not mediated by CSF biomarkers.

27  
28 Abbreviations: BG-PVS, basal-ganglia perivascular space; CSF, cerebrospinal fluid; WMH, white  
29  
30  
31 matter hyperintensity.

32  
33  
34  
35  
36 Supplementary figures:

37  
38  
39 **FIG. S1. Correlation between CSF biomarkers**

40  
41  
42 Abbreviations: CSF, cerebrospinal fluid.

43  
44  
45 **FIG. S2. Correlation between CSF biomarkers and cognitive decline stratified by the presence of**  
46  
47 **cardiovascular disease**

48  
49  
50 The presence of cardiovascular disease did not modify the effect of CSF biomarkers on cognitive  
51  
52  
53 decline in patients with PD.

54  
55  
56 **FIG. S3. Path analysis for WMH, CS-PVS and CSF biomarkers**

57  
58  
59 CSF biomarkers did not mediate the effect of WMH or CS-PVS on cognitive decline in PD.

Table 1. Demographic information between groups stratified by BG-PVS

	PD with low BG- PVS (N = 286)	PD with high BG- PVS (N = 55)	P value
<i>Demographic</i>			
Age (median, IQR, year)	60.7 (53.5–66.6)	71.1 (67.1–74.8)	<b>&lt;0.001</b>
Gender (F/M)	100/188	15/40	0.269
<i>Disease profile</i>			
Disease duration (median, IQR, month)	4 (2–7)	6 (3–13)	0.066
MoCA Score (median, IQR)	28 (26–29)	27 (25–29)	0.222
Hoehn-Yahr staging (median, IQR)	2 (1–2)	2 (2–2)	<b>0.001</b>
MDS-UPDRS III total (median, IQR)	19 (14–26)	22 (16–27)	<b>0.024</b>
State Trait Anxiety Score (median, IQR)	94 (89–98)	94 (88–97)	0.500
Geriatric Depression Scale (median, IQR)	5 (5–6)	5 (4–6)	0.280
<i>CSF biomarkers</i>			
CSF $\alpha$ -synuclein (median, IQR, pg/ml)	1351.3 (1029.3– 1718.0)	1528.8 (1164.3– 2086.0)	<b>0.016</b>
CSF A $\beta$ <sub>42</sub> (median, IQR, pg/mL)	848.6 (615.1– 1119.0)	822.2 (627.9– 1050.5)	0.860
CSF pTau (median, IQR, pg/mL)	13.0 (10.9–16.7)	15.4 (12.4–21.4)	<b>0.001</b>
CSF tTau (median, IQR, pg/mL)	152.6 (124.0– 192.6)	186.4 (147.2– 237.7)	<b>&lt;0.001</b>
CSF A $\beta$ <sub>42</sub> /tTau	5.81 (4.69–6.69)	4.88 (3.71–6.01)	<b>0.002</b>

CSF A $\beta$ <sub>42</sub> /pTau	69.4 (57.4–80.3)	61.1 (42.7–75.7)	<b>0.002</b>
<i>DAT striatal binding ratios</i>			
Mean caudate uptake (median, IQR)	2.02 (1.67–2.37)	1.88 (1.54–2.21)	0.155
Mean putamen uptake (median, IQR)	1.79 (1.48–2.18)	1.77 (1.34–2.08)	0.270
Caudate asymmetry (median, IQR)	1.19 (1.10–1.31)	1.17 (1.07–1.27)	0.216
Putamen asymmetry (median, IQR)	1.45 (1.19–1.76)	1.39 (1.17–1.73)	0.484
<i>Small vessel disease profile</i>			
WMH Fazekas score (median, IQR)	2 (1–2)	3 (2–4)	<b>&lt;0.001</b>
Cardiovascular diseases (N, %)	224 (52.1%)	57 (77.0%)	<b>&lt;0.001</b>
Cerebrovascular diseases (N, %) <sup>a</sup>	2 (0.5%)	2 (2.7%)	0.195
<i>Genetic profile</i>			
Presence of APOE $\epsilon$ 4 allele (N, %)	68 (23.8%)	13 (23.6)	0.982
<i>Cognition at 3-year follow-up</i>			
Change in MoCA score (median, IQR)	0 (-2–1)	-2 (-5–0.25)	<b>0.004</b>
Cognitive impairment (N, %)	46 (18.9)	22 (48.9%)	<b>&lt;0.001</b>

<sup>a</sup>Correction for continuity was adapted for inadequate event.

Abbreviations: CSF, cerebrospinal fluid; DAT, dopaminergic transporter; IQR, interquartile range;

MDS-UPDRS III, Movement Disorder Society Unified Parkinson's Disease Rating Score part III;

MoCA, Montreal Cognitive Assessment.

16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Table 2. Linear mixed model for interactive effect of CSF markers and BG-PVS on cognitive outcomes

	MoCA score at 3-year follow-up				Change in MoCA from baseline to 3-year follow-up			
	Model without interaction		Model with interaction		Model without interaction		Model with interaction	
	Coefficient	P value	Coefficient	P value	Coefficient	P value	Coefficient	P value
<b>Model 1</b>								
Baseline A $\beta$ <sub>42</sub> /tTau	0.385 (0.153–0.617)	<b>0.001</b>	1.060 (0.619–1.500)	<b>&lt;0.001</b>	0.382 (0.149–0.614)	<b>0.001</b>	1.055 (0.615–1.496)	<b>&lt;0.001</b>
BG-PVS $\geq$ 2	REF		REF				REF	
BG-PVS<2	1.283 (0.287–2.279)	<b>0.012</b>	6.000 (3.174–8.826)	<b>&lt;0.001</b>	1.322 (0.326–2.318)	<b>0.010</b>	6.012 (3.187–8.836)	<b>&lt;0.001</b>
A $\beta$ <sub>42</sub> /tTau*BG-PVS	/		-0.911 (-1.420–-0.400)	<b>0.001</b>	/		-0.907 (-1.416–-0.397)	<b>0.001</b>
<b>Interaction</b>								
AIC	815.5		804.5		817.3		806.3	
<b>Model 2</b>								
Baseline A $\beta$ <sub>42</sub> /pTau	0.031 (0.011–0.050)	<b>0.002</b>	0.092 (0.056–0.129)	<b>&lt;0.001</b>	0.030 (0.011–0.050)	<b>0.003</b>	0.093 (0.056–0.129)	<b>&lt;0.001</b>



16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

BG-PVS $\geq$ 2	REF		REF			REF	
BG-PVS<2	1.309 (0.267–2.350)	<b>0.014</b>	6.580 (3.740–9.419)	<b>&lt;0.001</b>	1.359 (0.317–2.400)	<b>0.011</b>	6.602 (3.763–9.441) <b>&lt;0.001</b>
A $\beta$ <sub>42</sub> /pTau*BG-PVS interaction			-0.08 (-0.13–0.04)	<b>&lt;0.001</b>			-0.084 (-0.126–0.042) <b>&lt;0.001</b>
AIC	774.7		765.8		776.4		767.5
<hr/>							
Model 3							
Baseline A $\beta$ <sub>42</sub>	0.001 (0.000–0.002)	<b>0.035</b>	0.003 (0.001–0.005)	<b>0.004</b>	0.001 (0–0.002)	<b>0.038</b>	0.003 (0.001–0.005) <b>0.004</b>
BG-PVS $\geq$ 2	REF		REF				REF
BG-PVS<2	1.258 (0.252–2.263)	<b>0.015</b>	3.184 (1.084–5.285)	<b>0.003</b>	1.326(0.321–2.330)	<b>0.010</b>	3.301 (1.207–5.396) <b>0.002</b>
A $\beta$ <sub>42</sub> *BG-PVS interaction			-0.002 (-0.004–0.000)	<b>0.039</b>			-0.002 (-0.004–0) <b>0.035</b>
AIC	859.9		867.5		861.5		868.9

CSF biomarkers (A $\beta$ <sub>42</sub>, A $\beta$ <sub>42</sub>/tTau, A $\beta$ <sub>42</sub>/pTau), BG-PVS and their interaction were fixed effect. Age, baseline MoCA score, RBDSQ, and DAT putamen asymmetry were set as random effect for MoCA score at 3-year follow-up, and baseline state trait anxiety inventory was additionally set as random effect for 3-year change in MoCA; Abbreviations:

15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

AIC, Akaike information criterion; BG-PVS, basal ganglia perivascular space; REF, reference.

**Perivascular Space in Parkinson's ~~disease~~Disease: Association with CSF Amyloid/Tau and Cognitive ~~D~~decline**

Huimin Chen<sup>a,b,c,d</sup>, Huijuan Wan<sup>b,c,d,e</sup>, Meimei Zhang<sup>b,c,d</sup>, Joanna M Wardlaw<sup>f</sup>, Tao Feng<sup>b,c,d</sup>, Yilong Wang<sup>b,c,d</sup>

<sup>a</sup>Department of Neurology, Beijing Hospital, National Center of Gerontology-; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China

<sup>b</sup>Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

<sup>c</sup>China National Clinical Research Center for Neurological Diseases (NCRC-ND), Beijing, China

<sup>d</sup>Advanced Innovation Center for Human Brain Projection, Capital Medical University, Beijing, China

<sup>e</sup>Department of Neurology, First Affiliated Hospital, Xiamen University, Xiamen, China

<sup>f</sup>Centre for Clinical Brain Sciences, UK Dementia Research Institute, University of Edinburgh, Edinburgh, UK

**Corresponding author:**

Yilong Wang<sup>\*</sup>, MD, PhD.

**Address:** China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, No.119 South 4th Ring West Road, Fengtai District, Beijing, China. 100070.

**E-mail:** yilong528@gmail.com, Tel: +86-139-1166-6571;

**Keywords/Search terms:** Parkinson's disease; Perivascular Space; Cognition; Amyloid; Tau

Title: 97 characteristics; Tables: 2; Figures:2; supplementary table: 4; supplementary figure 3;

[supplementary result:1](#); Reference:[2829](#);

Word count: abstract 249; body of the manuscript ~~326233~~4208;

## **Abstract**

**Objective:** Whether perivascular space (PVS) visible on magnetic resonance imaging (MRI) represents glymphatic dysfunction and whether this imaging marker is pathologic in Parkinson's disease (PD) have been controversial. The objective was to determine whether PVS visible on MRI is independently associated with cognitive decline in patients with PD, and to test whether pathologic proteins in the CSF (such as  $A\beta_{42}$ ) mediate the pathologic role of PVS.

**Methods:** A total of 341 patients with Parkinson's disease from Parkinson's Progression Marker Initiative (PPMI) cohort was included in the present study. PVS in the basal ganglia (BG-PVS) and centrum semiovale were evaluated with a semiquantitative scale. Changes in the Montreal Cognitive Assessment (MoCA) score and the absolute MoCA score at the 3-year assessment were considered the main cognitive outcome. A multivariable linear regression model was used to test the association between PVS and cognitive decline. A mixed linear model and path analysis were used to test the interaction among PVS, CSF biomarkers and cognitive decline.

**Results:** BG-PVS was associated with cognitive decline in patients with PD at the 3-year follow-up independent of age, baseline cognition, motor and nonmotor function, presynaptic dopaminergic deficiency, and CSF biomarkers. The interaction between BG-PVS and  $A\beta_{42}/t\text{Tau}$ ,  $A\beta_{42}/p\text{Tau}$ , and  $A\beta_{42}$  levels was significantly predictive of 3-year cognitive decline. Path analysis confirmed that CSF  $A\beta_{42}/t\text{Tau}$  levels partially mediated the pathologic effect of BG-PVS on cognitive outcome in PD.

**Conclusions:** BG-PVS is independently associated with cognitive decline in PD, and this association may be partially mediated by toxic CSF proteins.

**Keywords:** Parkinson's disease; Perivascular Space; Cognition; Amyloid; Tau

## 1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, with  $\alpha$ -synuclein ( $\alpha$ -syn) aggregation and Lewy body deposition being the pathologic hallmarks. Previous studies from several cohorts consistently reported that Alzheimer's disease (AD)-related CSF biomarkers (i.e., lower levels of  $A\beta_{42}$  and  $A\beta_{42}$ /Tau ratios and higher levels of total and phosphorylated Tau) were associated with cognitive impairment in PD ~~cross-sectionally [1-3] and longitudinally [1-3]~~ [1-3].

Emerging evidence has highlighted the role of the perivascular space (PVS) as a glymphatic pathway for waste clearance in the brain and demonstrated that glymphatic dysfunction reduced cerebrospinal fluid (CSF) clearance of  $A\beta$  in AD models and in patients with AD [4-6]. Since AD-related proteins are toxic to neurons and glial cells [7] and are associated with cognitive decline in AD and PD [1-3], it is possible that reduced CSF clearance of toxic proteins as a result of glymphatic dysfunction may aggregate the neurodegenerative process and facilitate the development of dementia.

~~Indeed, patients with PD showed impaired meningeal lymphatic drainage assessed by dynamic contrast-enhanced magnetic resonance imaging (MRI), which may facilitate the  $\alpha$ -syn deposition and result in motor dysfunction in PD mice model [8]. A previous cohort from Korea demonstrated that basal ganglia PVS (BG-PVS) visible on MRI predicted cognitive decline in PD at the 5-year follow-up [9][10]. This result needs to be validated in other cohorts. In addition, if BG-PVS visible on MRI reflects glymphatic dysfunction, there might be an association between the severity of BG-PVS visible on MRI and higher neurodegenerative burden measured by CSF biomarkers such as  $A\beta$ .~~

The Parkinson's Progression Marker Initiative (PPMI) is the largest ongoing cohort of PD with comprehensive clinical, imaging and CSF biomarker data. The PPMI provides an opportunity to confirm the pathologic role of BG-PVS in PD cognitive outcome. In addition, it provides superb data to

test the relationship between PVS visible on MRI and neurodegenerative burden measured by CSF biomarkers, which may inform the mechanism and potential therapeutic target of PVS in progressive neurodegenerative processes. [In the current analysis of PPMI data, we hypothesized that BG-PVS may be related with cognitive decline in PD, which may be mediated by CSF neurodegenerative biomarkers.](#)

## **2. Method**

### ***2.1 Study design and participants***

PPMI is an ongoing, multicenter, longitudinal, observational study that started in 2010 (<https://www.ppmi-info.org/>). Patients with early, drug-naïve PD and intact cognition were included. The PPMI study was approved by the institutional review board at each site, and participants provided written informed consent to participate. The protocol and more detailed study design of PPMI has been described elsewhere [9]. From the whole PPMI cohort, only PD patients with complete baseline BG-PVS profiles and CSF biomarkers were included in the present analysis. The data used in the current study were downloaded from the PPMI dataset in June 2020.

### ***2.2 Outcome measurements***

Cognitive decline was evaluated using the change in the MoCA score from baseline to 3-year follow-up and the absolute MoCA score at the 3-year assessment. ~~The Hopkins Verbal Learning Test (HVLT) (memory), the Benton Judgment of Line Orientation-15-item version (visuospatial function), the Symbol Digit Modalities Test (processing speed), the Letter Number Sequencing (executive function and working memory), and the semantic (animal) fluency test (language) were also performed.~~ Motor function was measured using the Movement Disorder Society Unified Parkinson's Disease Rating

Scale (MDS-UPDRS) part III and Hoehn-Yahr stage. The MDS-UPDRS III score was further divided into four subscores according to the cardinal motor symptoms in PD: tremor (items 15-18), bradykinesia (items 4-8, and item 14), rigidity (item 3), and axial signs (items 1, 2, 9-13). Nonmotor symptoms in the prediction of cognitive decline in PD included rapid eye movement behavior disorder (RBD), which was assessed with the RBD Screening Questionnaire (RBDSQ); sense of smell, which was assessed with the University of Pennsylvania Smell Identification Test (UPSIT); depression, which was assessed with the 15-item Geriatric Depression Scale (GDS); and anxiety, which was assessed with the State-Trait Anxiety Inventory.

### **2.3 DAT imaging**

[123I]β-CIT DAT single-photon emission computed tomography (SPECT) imaging was acquired at PPMI imaging centers in accordance with the PPMI imaging protocol. Mean caudate and putaminal uptake relative to uptake in the occipital area and asymmetry of caudate and putaminal uptake (side with highest divided by side with lowest uptake) were computed for the analysis.

### **2.4 History of cardio- and cerebrovascular diseases and risk factors**

Histories of cardio- and cerebrovascular diseases were recorded in the PPMI cohort at patient screening. Cardiovascular diseases ~~and risk factors~~ include a history of diabetes, hypertension, hyperlipidemia, hypercholesterolemia, and cardiac diseases. Cerebrovascular diseases included a history of cerebrovascular accident, transient ischemic attack, ischemic stroke, cervical and carotid stenosis or occlusion.

### **2.5 Imaging markers of cerebral small vessel disease**

Imaging markers of cerebral small vessel disease (CSVD) were evaluated by a neurologist who was

blind to the patient information (HJ Wan) following the instruction and definition of Standards for Reporting Vascular changes on neuroimaging (STRIVE) [10]. White matter hyperintensity (WMH) was rated according to the Fazekas rating scale [11]. Perivascular space was defined on MRI as small, sharply delineated structures of CSF intensity (or close to CSF intensity) following the course of perforating vessels. PVS in the basal ganglia and centrum semiovale (CS-PVS) were rated separately on T2 weighted sequence as 0 = none, 1 = 1–10, 2 = 11–20, 3 = 21–40, and 4 = >40 PVS per side, and the worse side was used if there was asymmetry [12, 13]. In the statistical analysis for BG-PVS, patients were stratified into groups with moderate-to-severe BG-PVS (BG-PVS rating $\geq$ 2) and none-to-mild BG-PVS (BG-PVS rating $<$ 2). Similarly, in the analysis for WMH and CS-PVS, patients were also grouped into the high WMH group (Fazekas $>$ 2) versus the low WMH group (Fazekas $\leq$ 2) and the high CS-PVS group (CS-PVS rating $\geq$ 2) versus the low CS-PVS group (CS-PVS rating $<$ 2). This stratification was consistent with the distribution of CSVD profiles in our data and was consistent with studies showing that BG-PVS rating $\geq$ 2 (moderate to severe) was predictive of unfavorable outcomes [12, 13].

## **2.6 Genotyping**

At the screening visit, genomic DNA was extracted from whole blood of the subject. The APOE genotype was analyzed at the PPMI genetic core as previously described [14]. Subjects were classified by the presence or absence of *APOE*  $\epsilon$ 4 genotypes.

## **2.7 CSF biomarkers**

The concentration of  $\alpha$ -synuclein in CSF samples was analyzed using an ELISA assay available commercially from BioLegend. CSF A $\beta$ <sub>42</sub>, total tau (tTau) and tau phosphorylated at the threonine 181 position (pTau) were analyzed at Biorepository Core laboratories to the University of Pennsylvania



using Elecsys electrochemiluminescence immunoassays (Roche Diagnostics). More detail and primary results of the measured CSF biomarkers have been reported previously in the PPMI cohort [14, 15].

## 2.8 Statistics

Continuous variables were compared between groups using the Mann-Whitney test (nonnormal distribution) or two sample t test (normal distribution), and categorical variables were compared between groups using the Chi-square test. Univariable and multivariable linear regression models were performed using the MoCA score at the 3-year follow-up and the 3-year change in the MoCA score as separate dependent variables. The regression models consulted a previous PPMI study using 2-year cognitive outcomes [16]. Multivariable regression models were conducted with adjustment of variables showing a tendency to significant association ( $p < 0.05$ ) in the univariable regression analysis further entered the multivariable linear regression analysis simultaneously, while (only one significant variable of the same feature with lower P value was selected to avoid collinearity) and variables that showed significantly unbalanced features between BG-PVS groups. As CSF biomarkers were significantly correlated with each other (supplementary figure 1)[17], each biomarker entered the multivariable regression model separately.

The interaction between BG-PVS and CSF biomarkers in relation to cognition was firstly explored by plotting the fitting curve and then by linear mixed models. The change in MoCA score and MoCA score at the 3-year follow-up was used as dependent variables in linear mixed models. BG-PVS severity and CSF biomarker with or without interaction term were set as fixed effects, and other variables showing significant association with cognitive outcomes in multivariable univariable regression and/or unbalanced features between BG-PVS groups were used as random effects. The Akaike information criterion (AIC) of models with and without the BG-PVS\*CSF biomarker

interaction item was recorded. Path analysis was conducted to investigate how much CSF biomarkers mediated the effect of BG-PVS on cognition in PD. The standardized coefficient ( $\beta$ ) of BG-PVS without a mediation effect (direct effect) and with a mediation effect (indirect effect) and the standardized coefficient ( $\beta$ ) of the CSF biomarker on the change in MoCA were calculated. P value < 0.05 was defined as significant. Group comparison of CSF biomarkers at each follow-up point was also performed between PD groups with different BG-PVS severities. P value < 0.01 was defined as significant in this group comparison for multiple comparison correction ([Bonferroni](#) correction for 4 repeated comparisons [for each CSF biomarker](#)). Group comparison was conducted in SPSS 25.0 (SPSS, inc., Beijing, China), and linear regression and linear mixed models were performed in R software version 4.02 (<https://www.r-project.org/>).

To rule out confounding by ~~other CSVD markers WMH and lacune~~, and to investigate the location specificity of PVS, their relationships ~~among (WMH, the presence of lacune or CS-PVS)~~ with CSF biomarkers, and cognitive decline ~~were~~ further explored using a similar statistical approach.

### ***2.9 Data Availability Statement***

The data was publicly available on PPMI website (<https://www.ppmi-info.org/access-data-specimens/>).

## **3. Results**

### ***3.1 Baseline features of the included patients***

Four hundred and twenty-three patients with drug-naïve PD were recruited in PPMI cohort. Among these subjects, MRI imaging or T2-weighted imaging was missing in 47 patients, and imaging in another 13 patients was not qualified to rate BG-PVS due to incomplete or nonaxial slices. CSF biomarkers were missing in another 22 patients with PD. Finally, 341 patients with complete baseline

Formatted: Font: (Default) Times New Roman

PVS and CSF biomarkers were included in the present analysis. The included and excluded patients showed overall similar demographic and behavioral profiles (supplementary table 1).

### **3.2 Group comparison between patients with lower and higher BG-PVS burdens**

Compared with patients with lower BG-PVS burden, patients with more severe BG-PVS were significantly older; had more impaired motor function at baseline; had a higher prevalence of previous cardiovascular disease; ~~had a higher prevalence of and the presence of lacune presence~~, and more severe WMH at baseline; had a higher risk of cognitive impairment and a greater decline in the MoCA score at the 3-year follow-up despite of similar baseline MoCA scores; and showed lower levels of CSF ~~A $\beta$ <sub>42</sub> $\alpha$ -synuclein~~, A $\beta$ <sub>42</sub>/tTau, A $\beta$ <sub>42</sub>/pTau and higher levels of CSF  ~~$\alpha$ -syn~~, tTau and pTau at baseline (Table 1).

### **3.3 ~~Univariate-Univariable~~ linear regression for cognition at the 3-year follow-up**

Using the absolute MoCA score at the 3-year follow-up as the dependent variable, age, baseline MoCA score, MDS-UPDRS III ~~total score~~, ~~tremor, bradykinesia, and axial subscores~~, RBDSQ, UPSIT score, CSF A $\beta$ <sub>42</sub>, tTau, pTau, A $\beta$ <sub>42</sub>/tTau, A $\beta$ <sub>42</sub>/pTau, putamen asymmetry and BG-PVS were significantly associated with cognition at the 3-year follow-up in PD patients (P<0.05).

Using decline in MoCA score as the dependent variable, age, baseline MoCA score, RBDSQ, UPSIT score, ~~axial subscore of MDS-UPDRS III~~, CSF A $\beta$ <sub>42</sub>, tTau, pTau, A $\beta$ <sub>42</sub>/tTau, A $\beta$ <sub>42</sub>/pTau, putamen asymmetry, and BG-PVS were significantly associated with cognitive decline during three years in PD patients (P<0.05) (supplementary table 2).

### **3.4 Multivariable linear regression for cognition at the 3-year follow-up**

In multivariable regression models, BG-PVS was significantly associated with MoCA score or change in MoCA score, independent of ~~age, past-history cardiovascular diseases, baseline MoCA~~.

~~score, axial subscore of MDS-UPDRS III, RBDSQ, UPSIT, putamen asymmetry, WMH Fazekas score, and the presence of lacunes, and CSF biomarkers. Age, baseline cognition, motor function, nonmotor symptoms, presynaptic dopaminergic deficiency, and CSF biomarkers.~~ Baseline CSF A $\beta$ <sub>42</sub>, A $\beta$ <sub>42</sub>/tTau and A $\beta$ <sub>42</sub>/pTau were significantly associated with the MoCA score or change in the MoCA score at 3-year follow-up independent of ~~age, past-history cardiovascular diseases, baseline MoCA score, axial subscore of MDS-UPDRS III, RBDSQ, UPSIT, putamen asymmetry, WMH Fazekas score, the presence of lacune, and -BG-PVCSF biomarkers, age, baseline cognition, motor function, nonmotor symptoms, presynaptic dopaminergic deficiency, and BG-PVS.~~ However, baseline CSF tTau and pTau were not significantly associated with either cognitive outcome at year three after adjustment (supplementary table 3).

### 3.5 Interaction between CSF biomarkers and BG-PVS

There was a significant main effect of BG-PVS and CSF A $\beta$ <sub>42</sub>/tTau, A $\beta$ <sub>42</sub>/pTau and A $\beta$ <sub>42</sub> as well as interactions between BG-PVS and these CSF biomarkers (**Table 2**), such that patients with higher BG-PVS and lower A $\beta$ <sub>42</sub>/tTau (**Figure 1A**), A $\beta$ <sub>42</sub>/pTau (**Figure 1B**), or A $\beta$ <sub>42</sub> (**Figure 1C**) showed steeper decline in the MoCA score at the 3-year follow-up. Models containing interaction terms provided a slightly improved fit. As patients with a higher BG-PVS burden had a higher prevalence of cardiovascular disease ~~and risk factors~~, we further tested whether the interaction between BG-PVS and CSF biomarkers was confounded by the presence of cardiovascular disease ~~and risk factors~~. However, the correlation between CSF biomarkers and cognitive decline was not stratified by the presence of cardiovascular disease ~~or related risk factors~~ (supplementary figure 2).

We further compared CSF biomarkers at each follow-up timepoint between the BG-PVS groups. The results revealed that patients with more severe BG-PVS showed significantly higher levels of all

measured CSF biomarkers at baseline, 1-year follow-up, and 2-year follow-up, and the significant difference in tTau and pTau was still observed at year three ([supplementary table 4](#)) with corrected P values ( $P < 0.01$ ) ([supplementary table 4](#)).

### 3.6 Path analysis

In path analysis, CSF A $\beta_{42}$ /tTau was found to mediate the effect of BG-PVS on cognitive decline (total effect [original coefficient] = -0.256, direct effect [corrected coefficient] = -0.208, indirect effect = -0.048) (**Figure 2A**). That is, CSF A $\beta_{42}$ /tTau mediated 18.8% (indirect effect/total effect) of the BG-PVS effect on the decrease in MoCA scores during the 3-year follow-up. In path analysis, the correlation of BG-PVS with A $\beta_{42}$ /pTau was marginally significant, and that with A $\beta_{42}$  was not significant (**Figure 2B and 2C**).

### 3.7 Additional analysis with WMH and CS-PVS

To rule out the confounding effect of WMH, lacune and CS-PVS, additional analysis was performed. No significant association was found among WMH, CSF biomarkers, and cognitive outcome; among the presence of lacune, CSF biomarkers, and cognitive outcome; and among CS-PVS, CSF biomarkers, and cognitive outcome (see supplementary figure 3 and supplementary result). For WMH, no significant difference in baseline CSF biomarkers ( $\alpha$ -syn  $z = -1.337$ ,  $P = 0.181$ ; A $\beta_{42}$   $z = -0.430$ ,  $P = 0.667$ ; pTau  $z = -1.181$ ,  $P = 0.238$ ; tTau  $z = -1.697$ ,  $P = 0.090$ ) was found between groups with different WMH severity (Fazekas 0-2 vs. Fazekas 3-6). No significant correlation was found between CSF biomarkers and WMH Fazekas rating according to the Spearman correlation analysis ( $\alpha$ -syn  $r = 0.025$ ,  $P = 0.640$ ; A $\beta_{42}$   $r = -0.057$ ,  $P = 0.300$ ; pTau  $r = 0.036$ ,  $P = 0.534$ ; tTau  $r = 0.039$ ,  $P = 0.331$ ). No significant correlation was observed between WMH and cognitive decline or between WMH and CSF biomarkers (A $\beta_{42}$ /tTau, A $\beta_{42}$ /pTau, A $\beta_{42}$ ) in the path analysis (supplementary figure 3).

~~For CS-PVS, no significant difference in baseline CSF biomarkers ( $\alpha$ -syn  $z = -1.391$ ,  $P = 0.164$ ;  $A\beta_{42}$   $z = -0.685$ ,  $P = 0.493$ ; pTau  $z = -1.422$ ,  $P = 0.155$ ; tTau  $z = -1.741$ ,  $P = 0.082$ ) was found between groups stratified by CS-PVS severity (CS-PVS 0-1 vs. CS-PVS  $\geq 2$ ). No significant correlation was observed between CS-PVS and CSF biomarkers ( $A\beta_{42}/tTau$ ,  $A\beta_{42}/pTau$ ,  $A\beta_{42}$ ) in path analysis (supplementary figure 3). Although a marginally significant correlation between CS-PVS and cognitive decline was observed in the path analysis, the significant correlation was not preserved in the multivariable linear model adjusting for age (coefficient =  $-0.729$ , 95% CI =  $-1.612$   $-0.154$ ,  $P = 0.105$ ) or in the model adjusted for age, baseline MoCA scores, baseline state trait anxiety score, RBDSQ, UPSIT, and putamen asymmetry (coefficient =  $-0.615$ , 95% CI =  $-1.419$   $-0.188$ ,  $P = 0.132$ ).~~

Formatted: Indent: First line: 0 ch

#### 4. Discussion

This is the first study that examined the relationship ~~between among~~ CSF biomarkers, ~~cognitive outcome~~ and PVS visible on MRI in [neurodegenerative disease](#)~~PD~~. The main finding demonstrated that BG-PVS was independently associated with cognitive decline in patients with PD. In addition, BG-PVS modified the pathologic effect of  $A\beta_{42}/tTau$ ,  $A\beta_{42}/pTau$ , and  $A\beta_{42}$  on cognitive decline in PD. Path analysis confirmed that CSF biomarkers, especially  $A\beta_{42}/tTau$ , partially mediated the pathologic effect of BG-PVS on cognitive outcomes in PD. These results suggest that the increased visibility of BG-PVS on MRI may reflect more advanced glymphatic dysfunction, resulting in higher levels of toxic CSF proteins, which may in turn accelerate neurodegenerative processes and cognitive decline. It also implies that the glymphatic pathway may serve as a therapeutic target to preserve cognition in neurodegenerative disease.

Our results validated a previous study by Park and colleagues ~~and showed that BG-PVS was~~

~~associated with 3-year cognitive decline in patients with PD [18], and showed that BG-PVS was associated with 3-year cognitive decline in patients with PD.~~ In addition, the contribution to poor cognitive outcome and the interaction with CSF proteins were specific for PVS located in the basal ganglia but not the centrum semiovale. However, the underlying mechanism for the location specificity remains unclear. Evidence suggests that cerebral arterial pulsation drove CSF-interstitial fluid exchange mediated by the glymphatic pathway [19], and arterial stiffness was associated with a higher BG-PVS burden [20]. It is possible that PVS in the basal ganglia may be more prone to arterial damage and pulsation change during aging. However, we did not test arterial function, such as arterial stiffness and regulation. Future studies will be needed to test this hypothesis. In addition, BG-PVS differs from CS-PVS in structure, as BG-PVS is covered by two leptomeningeal membranes and directly connects CSF [21]. This means that BG-PVS may be more active in eliminating waste from CSF, and the increased visibility of BG-PVS may represent an increased effort in waste clearance. Future studies directly comparing CSF dynamics are needed to investigate the location difference of PVS.

Moreover, the results ~~also~~ suggested that PVS visible on MRI may reflect glymphatic dysfunction, ~~and impaired~~ efflux of CSF proteins ~~and more advanced neurodegeneration~~ in patients with PD. ~~Previous evidence suggested that patients with PD showed higher volume fraction of PVS, especially for those familial patients with genetic mutation [22]. Previous PPMI result data also suggested that PVS in midbrain was associated with neurodegenerative imaging marker— (DAT deficiency) [23]. These findings supported our hypothesis that PVS visible on MRI may be closely linked with neurodegeneration in patients with PD. We found that~~ ~~In addition,~~ the level of neurodegenerative CSF proteins (A $\beta$ <sub>42</sub>/tTau) partially mediated the effect of BG-PVS on poor cognitive outcome. Taking that CSF proteins, including A $\beta$  and Tau, are toxic to neurons and glial cells [7] and AD biomarkers are

predictive of cognitive decline in PD [1-3], the result implies that BG-PVS may contribute to cognitive decline by elevating toxic CSF proteins in patients with PD.

The glymphatic pathway has drawn much attention in recent years as a novel pathway to exclude neurotoxic proteins and a potential therapeutic target [24]. In patients with superficial sclerosis, PVS was enlarged beneath the affected area where A $\beta$  was deposited in the cortical arterial wall by biopsy, supporting the notion that enlarged PVS is a sign of a blocked drainage pathway by proteins such as A $\beta$  [25]. Ding and colleagues specifically tested the meningeal lymphatic flow in patients with PD using dynamic contrast-enhanced MRI, and proved significant reduction of lymphatic flow as well as notable delay in deep cervical lymph node perfusion in these patients. In addition, the delayed meningeal lymphatic drainage was followed by  $\alpha$ -syn pathology in mice model [8, 22]. This study provided direct evidence of impaired glymphatic system in PD and the consequent neurodegeneration (e.g.  $\alpha$ -syn pathology). Therefore, PVS visible on routine MRI may be an alternative a possible-way to explore the static glymphatic pathway offline. [26, 27]

In PD patients with higher BG-PVS burden, CSF  $\alpha$ -syn, tTau and pTau levels were higher, while the CSF A $\beta_{42}$  level was lower compared with patients with mild or none BG-PVS. Hypothetically, reduced efflux as a result glymphatic dysfunction should cause increased CSF protein level. As for A $\beta_{42}$ , it is possible that the decreased CSF A $\beta_{42}$  reflected more extensive peptide aggregation and plaque formation in brain tissue. [30]. Tau and A $\beta$  have independent as well as synergistic effects on cognition [26]. In our analysis, the interaction between CSF biomarker and BG-PVS was more predominant for A $\beta_{42}$ /tTau, and A $\beta_{42}$ /pTau, compared with A $\beta_{42}$  alone. It is possible that glymphatic dysfunction blocked CSF toxic proteins, and the interaction between these increased proteins (e.g. Tau-A $\beta_{42}$  interaction) accelerated the aggregation of amyloid, lowering the amounts of A $\beta_{42}$  being tested in

Formatted: Font: (Default) Times New Roman

Formatted: Font: (Default) Times New Roman

Formatted: Font: 10 pt

Formatted: Font: 10 pt, Subscript

Formatted: Font: 10 pt

Formatted: Font: 10 pt

Formatted: Font: 10 pt

Formatted: Font: 10 pt

Formatted: Font: 10 pt

Formatted: Font: 10 pt

Formatted: Font: (Default) Times New Roman, 10 pt

Formatted: Font: 10 pt



CSF.

CSF A $\beta$ <sub>42</sub>, A $\beta$ <sub>42</sub>/tTau, and A $\beta$ <sub>42</sub>/pTau were not specific PD biomarkers. However, emerging evidence suggests that concurrent proteinopathies and their synergistic interactions, are quite common and may contribute to cognitive decline in patients with PD [27]. There might be concomitant AD pathology playing a role in our findings. Previous studies suggested that PVSs in the centrum semiovale and hippocampus were as associated with the diagnosis of AD [28, 29], and PVSs in the hippocampus was associated with hippocampal atrophy [29]. However, the association between PVS visible on MRI and CSF biomarkers was not statistically significant in cognitively impaired individuals in Neurodegenerative Disorders Early and Reliably (BioFINDER) study [29]. More studies are needed to test the association between PVS visible on MRI and CSF biomarkers in demented and non-demented populations.

~~The interactive effect between BG-PVS and CSF A $\beta$ <sub>42</sub>, A $\beta$ <sub>42</sub>/tTau, and A $\beta$ <sub>42</sub>/pTau on cognitive decline was a novel finding in our study. This suggests that modification of the glymphatic pathway may be a potential and crucial therapeutic target to alleviate the pathologic effect of A $\beta$ <sub>42</sub> and Tau on cognitive decline in PD. Emerging evidence has demonstrated the interaction between PVS and AD-related proteins in animal models [28], and our result further supported the additive consequence of their interaction in human cohort. In addition, the benefit of treatment targeting the glymphatic pathway may be beyond AD-related pathology since PVS has also been highlighted to be involved in the inflammatory process in multiple sclerosis [36]. Sleep intervention may be an effective way to improve glymphatic function, which may need to be tested in clinical trials or observational studies [37]. Other treatments targeting pericytes, endothelial cells, perivascular inflammation and other factors pertaining to glymphatic function also deserve to be investigated.~~

In addition to our initial hypothesis, the factors associated with 3-year cognitive decline were largely consistent with previous 2-year follow-up analysis [16]. More recently, Irwin and colleagues reported that AD-related CSF biomarkers were associated with 3-year cognitive decline in a PPMI cohort [17]. Although finding risk factors associated with cognitive decline was not the main topic of our study, the consistency with previous data suggests that the present data are representative of the whole cohort despite missing BG-PVS data in 59 patients (missing rate = 13.9%).

We acknowledge several limitations. First, this study did not measure the dynamic function of the glymphatic pathway in vivo. Currently, dynamic fluid exchange by the glymphatic pathway has been investigated in vivo by intrathecal injection of the contrast agent in neurological diseases such as idiopathic normal pressure hydrocephalus [6]. These approaches enable tracking uptake and distribution of tracers dynamically, but they are invasive and may not be applicable in patients with PD. Second, although CSF A $\beta$ <sub>42</sub> and Tau are consistently found to be associated with cognitive decline in PD, they are not PD-specific biomarkers. In addition, the findings of the present study only represent the PD population. Whether proteinaceous waste such as A $\beta$  and Tau drives the increased visibility of PVS on MRI and potentially mediates its toxicity needs to be tested in the AD population and normal aging population.

In conclusion, we found that BG-PVS may be independently associated with cognitive decline in PD, which may be partially mediated by toxic CSF proteins. The increased visibility of BG-PVS on MRI may reflect more advanced glymphatic dysfunction. PVS may serve as a therapeutic target to preserve cognition in PD.

**Conflict of interest**

None

### Acknowledgements

PPMI is supported by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including Abbott, Avid, Biogen idec, Bristol-Myers Squibb, Covance, Elan, GE Healthcare, Genentech, GSK, Lilly, MERCK, MSD, Pfizer, Roche and UCB (details of the PPMI funding partners found at [www.ppmiinfo.org/ funding partners](http://www.ppmiinfo.org/funding-partners)). Huimin Chen is supported by Beijing Hospital Project (BJ-2021-197). Yilong Wang is supported by grants from the National Natural Science Foundation of China (81825007), the Ministry of Science and Technology of the People's Republic of China (2017YFC1307900), Beijing Outstanding Young Scientist Program (BJJWZYJH01201910025030), the third batch of National Ten Thousand Talents Plan, the Beijing Municipal Science and Technology Commission (Beijing Excellent Talents Training and Supporting Top Youth Team, D171100003017001 and 2016000021223TD03), and the Youth Beijing Scholar Program.

Formatted: Font: (Default) Times New Roman

### References:

- [1] S. Hall, Y. Surova, A. Ohrfelt, F.S. Swedish Bio, K. Blennow, H. Zetterberg, O. Hansson, Longitudinal Measurements of Cerebrospinal Fluid Biomarkers in Parkinson's Disease, *Mov Disord* 31(6) (2016) 898-905.
- [2] M. Shahid, J. Kim, K. Leaver, T. Hendershott, D. Zhu, B. Cholerton, V.W. Henderson, L. Tian, K.L. Poston, An increased rate of longitudinal cognitive decline is observed in Parkinson's disease patients with low CSF ~~A $\beta$ 42~~ and an APOE epsilon4 allele, *Neurobiol Dis* 127 (2019) 278-286.
- [3] M. Delgado-Alvarado, R. Dacosta-Aguayo, I. Navalpotro-Gomez, B. Gago, A. Gorostidi, H.

Formatted: Line spacing: Double

Formatted: Font: (Default) Times New Roman

Formatted: Font: (Default) Times New Roman

Jimenez-Urbieto, A. Quiroga-Varela, J. Ruiz-Martinez, A. Bergareche, M.C. Rodriguez-Oroz, Ratios of proteins in cerebrospinal fluid in Parkinson's disease cognitive decline: prospective study, *Mov Disord* 33(11) (2018) 1809-1813.

[4] E.L. Boespflug, M.J. Simon, E. Leonard, M. Grafe, R. Woltjer, L.C. Silbert, J.A. Kaye, J.J. Iliff, Targeted Assessment of Enlargement of the Perivascular Space in Alzheimer's Disease and Vascular Dementia Subtypes Implicates Astroglial Involvement Specific to Alzheimer's Disease, *J Alzheimers Dis* 66(4) (2018) 1587-1597.

[5] M.K. Rasmussen, H. Mestre, M. Nedergaard, The glymphatic pathway in neurological disorders, *Lancet Neurol* 17(11) (2018) 1016-1024.

[6] M.J. de Leon, Y. Li, N. Okamura, W.H. Tsui, L.A. Saint-Louis, L. Glodzik, R.S. Osorio, J. Fortea, T. Butler, E. Pirraglia, S. Fossati, H.J. Kim, R.O. Carare, M. Nedergaard, H. Benveniste, H. Rusinek, Cerebrospinal Fluid Clearance in Alzheimer Disease Measured with Dynamic PET, *J Nucl Med* 58(9) (2017) 1471-1476.

[7] S. Jankeviciute, G. Psemeneckiene, R. Morkuniene, E. Grusauskiene, K. Petrikonis, D. Rastenyte, V. Borutaite, Cerebrospinal fluids from Alzheimer's disease patients exhibit neurotoxic effects on neuronal cell cultures, *Eur J Neurosci* 50(2) (2019) 1994-2006.

[8] X.B. Ding, X.X. Wang, D.H. Xia, H. Liu, H.Y. Tian, Y. Fu, Y.K. Chen, C. Qin, J.Q. Wang, Z. Xiang, Z.X. Zhang, Q.C. Cao, W. Wang, J.Y. Li, E. Wu, B.S. Tang, M.M. Ma, J.F. Teng, X.J. Wang, Impaired meningeal lymphatic drainage in patients with idiopathic Parkinson's disease, *Nat Med* 27(3) (2021) 411-418.

[9] I. Parkinson Progression Marker, The Parkinson Progression Marker Initiative (PPMI), *Prog Neurobiol* 95(4) (2011) 629-35.

- [10] J.M. Wardlaw, E.E. Smith, G.J. Biessels, C. Cordonnier, F. Fazekas, R. Frayne, R.I. Lindley, J.T. O'Brien, F. Barkhof, O.R. Benavente, S.E. Black, C. Brayne, M. Breteler, H. Chabriat, C. Decarli, F.E. de Leeuw, F. Doubal, M. Duering, N.C. Fox, S. Greenberg, V. Hachinski, I. Kilimann, V. Mok, R. Oostenbrugge, L. Pantoni, O. Speck, B.C. Stephan, S. Teipel, A. Viswanathan, D. Werring, C. Chen, C. Smith, M. van Buchem, B. Norrving, P.B. Gorelick, M. Dichgans, S.T.f.R.V.c.o. nEuroimaging, Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration, *Lancet Neurol* 12(8) (2013) 822-38.
- [11] F. Fazekas, R. Kleinert, H. Offenbacher, R. Schmidt, G. Kleinert, F. Payer, H. Radner, H. Lechner, Pathologic correlates of incidental MRI white matter signal hyperintensities, *Neurology* 43(9) (1993) 1683-9.
- [12] F.N. Doubal, A.M. MacLulich, K.J. Ferguson, M.S. Dennis, J.M. Wardlaw, Enlarged perivascular spaces on MRI are a feature of cerebral small vessel disease, *Stroke* 41(3) (2010) 450-4.
- [13] G.M. Potter, F.N. Doubal, C.A. Jackson, F.M. Chappell, C.L. Sudlow, M.S. Dennis, J.M. Wardlaw, Enlarged perivascular spaces and cerebral small vessel disease, *Int J Stroke* 10(3) (2015) 376-81.
- [14] J.H. Kang, B. Mollenhauer, C.S. Coffey, J.B. Toledo, D. Weintraub, D.R. Galasko, D.J. Irwin, V. Van Deerlin, A.S. Chen-Plotkin, C. Caspell-Garcia, T. Waligorska, P. Taylor, N. Shah, S. Pan, P. Zero, M. Frasier, K. Marek, K. Kiebertz, D. Jennings, C.M. Tanner, T. Simuni, A. Singleton, A.W. Toga, S. Chowdhury, J.Q. Trojanowski, L.M. Shaw, I. Parkinson's Progression Marker, CSF biomarkers associated with disease heterogeneity in early Parkinson's disease: the Parkinson's Progression Markers Initiative study, *Acta Neuropathol* 131(6) (2016) 935-49.
- [15] B. Mollenhauer, C.J. Caspell-Garcia, C.S. Coffey, P. Taylor, L.M. Shaw, J.Q. Trojanowski, A. Singleton, M. Frasier, K. Marek, D. Galasko, I. Parkinson's Progression Marker, Longitudinal CSF

biomarkers in patients with early Parkinson disease and healthy controls, *Neurology* 89(19) (2017) 1959-1969.

[16] A. Schrag, U.F. Siddiqui, Z. Anastasiou, D. Weintraub, J.M. Schott, Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease: a cohort study, *Lancet Neurol* 16(1) (2017) 66-75.

[17] D.J. Irwin, J. Fedler, C.S. Coffey, C. Caspell-Garcia, J.H. Kang, T. Simuni, T. Foroud, A.W. Toga, C.M. Tanner, K. Kiebertz, L.M. Chahine, A. Reimer, S. Hutten, D. Weintraub, B. Mollenhauer, D.R. Galasko, A. Siderowf, K. Marek, J.Q. Trojanowski, L.M. Shaw, I. Parkinson's Progression Marker, Evolution of Alzheimer's Disease Cerebrospinal Fluid Biomarkers in Early Parkinson's Disease, *Ann Neurol* (2020).

[18] Y.W. Park, N.Y. Shin, S.J. Chung, J. Kim, S.M. Lim, P.H. Lee, S.K. Lee, K.J. Ahn, Magnetic Resonance Imaging-Visible Perivascular Spaces in Basal Ganglia Predict Cognitive Decline in Parkinson's Disease, *Mov Disord* 34(11) (2019) 1672-1679.

[19] J.J. Iliff, M. Wang, D.M. Zeppenfeld, A. Venkataraman, B.A. Plog, Y. Liao, R. Deane, M. Nedergaard, Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine brain, *J Neurosci* 33(46) (2013) 18190-9.

[20] I. Riba-Llena, J. Jimenez-Balado, X. Castane, A. Girona, A. Lopez-Rueda, X. Mundet, C.I. Jarca, J. Alvarez-Sabin, J. Montaner, P. Delgado, Arterial Stiffness Is Associated With Basal Ganglia Enlarged Perivascular Spaces and Cerebral Small Vessel Disease Load, *Stroke* 49(5) (2018) 1279-1281.

[21] J.M. Wardlaw, H. Benveniste, M. Nedergaard, B.V. Zlokovic, H. Mestre, H. Lee, F.N. Doubal, R. Brown, J. Ramirez, B.J. MacIntosh, A. Tannenbaum, L. Ballerini, R.L. Rungta, D. Boido, M. Sweeney, A. Montagne, S. Charpak, A. Joutel, K.J. Smith, S.E. Black, D. colleagues from the Fondation Leducq

Transatlantic Network of Excellence on the Role of the Perivascular Space in Cerebral Small Vessel, Perivascular spaces in the brain: anatomy, physiology and pathology, *Nat Rev Neurol* 16(3) (2020) 137-153.

[22] E.K. Donahue, A. Murdos, M.W. Jakowec, N. Sheikh-Bahaei, A.W. Toga, G.M. Petzinger, F. Seppehrband, Global and Regional Changes in Perivascular Space in Idiopathic and Familial Parkinson's Disease, *Mov Disord* 36(5) (2021) 1126-1136.

[23] Y. Li, Z. Zhu, J. Chen, M. Zhang, Y. Yang, P. Huang, Dilated Perivascular Space in the Midbrain May Reflect Dopamine Neuronal Degeneration in Parkinson's Disease, *Front Aging Neurosci* 12 (2020) 161.

[24] B.L. Sun, L.H. Wang, T. Yang, J.Y. Sun, L.L. Mao, M.F. Yang, H. Yuan, R.A. Colvin, X.Y. Yang, Lymphatic drainage system of the brain: A novel target for intervention of neurological diseases, *Prog Neurobiol* 163-164 (2018) 118-143.

[25] A. Keable, K. Fenna, H.M. Yuen, D.A. Johnston, N.R. Smyth, C. Smith, R. Al-Shahi Salman, N. Samarasekera, J.A. Nicoll, J. Attems, R.N. Kalaria, R.O. Weller, R.O. Carare, Deposition of amyloid beta in the walls of human leptomeningeal arteries in relation to perivascular drainage pathways in cerebral amyloid angiopathy, *Biochim Biophys Acta* 1862(5) (2016) 1037-46.

[26] M.A. Busche, B.T. Hyman, Synergy between amyloid-beta and tau in Alzheimer's disease, *Nat Neurosci* 23(10) (2020) 1183-1193.

[27] L. Farotti, F. Paolini Paoletti, S. Simoni, L. Parnetti, Unraveling Pathophysiological Mechanisms of Parkinson's Disease: Contribution of CSF Biomarkers, *Biomark Insights* 15 (2020) 1177271920964077.

[28] G. Banerjee, H.J. Kim, Z. Fox, H.R. Jager, D. Wilson, A. Charidimou, H.K. Na, D.L. Na, S.W. Seo, D.J. Werring, MRI-visible perivascular space location is associated with Alzheimer's disease

independently of amyloid burden, *Brain* 140(4) (2017) 1107-1116.

[29] E.C. Gertje, D. van Westen, C. Panizo, N. Mattsson-Carlgen, O. Hansson, Association of Enlarged Perivascular Spaces and Measures of Small Vessel and Alzheimer Disease, *Neurology* 96(2) (2021) e193-e202.

Formatted: EndNote Bibliography



## Figure legends

### Figure 1. Correlation between CSF biomarkers and cognitive outcomes stratified by BG-PVS

BG-PVS modified the effect of  $A\beta_{42}/t\text{Tau}$  (A),  $A\beta_{42}/p\text{Tau}$  (B),  $A\beta_{42}$  (C) on cognitive outcome in Parkinson's disease, as high BG-PVS group showed steeper decline in the MoCA score in relation to CSF biomarkers at the 3-year follow-up.

Abbreviations: BG-PVS, basal-ganglia perivascular space; CSF, cerebrospinal fluid.

### Figure 2. Path analysis

~~A~~ CSF  $A\beta_{42}/t\text{Tau}$ , but not  $A\beta_{42}/p\text{Tau}$  or CSF  $A\beta_{42}$  significantly mediated the effect of BG-PVS on cognitive decline in patients with PD. ~~The effect of WMH (B) or CS-PVS (C) on cognitive outcome was not mediated by CSF biomarkers.~~

Abbreviations: BG-PVS, basal-ganglia perivascular space; CSF, cerebrospinal fluid; WMH, white matter hyperintensity.

Supplementary figures:

### FIG. S1. Correlation between CSF biomarkers

Abbreviations: CSF, cerebrospinal fluid.

### FIG. S2. Correlation between CSF biomarkers and cognitive decline stratified by the presence of cardiovascular disease

The presence of cardiovascular disease did not modify the effect of CSF biomarkers on cognitive decline in patients with PD.

### FIG. S3. Path analysis for WMH, ~~CS-PVS and CSF biomarker~~lacune, and CS-PVSs

CSF biomarkers did not mediate the effect of WMH, ~~the presence of lacune~~ or CS-PVS on cognitive

decline in PD.

Table 1. Demographic information between groups stratified by BG-PVS

	PD with low BG- PVS (N = 286)	PD with high BG- PVS (N = 55)	P value
<i>Demographic</i>			
Age (median, IQR, year)	60.7 (53.5–66.6)	71.1 (67.1–74.8)	<b>&lt;0.001</b>
Gender (F/M)	100/186	15/40	0.269
<i>Disease profile</i>			
Disease duration (median, IQR, month)	4 (2–7)	6 (3–13)	0.066
MoCA Score (median, IQR)	28 (26–29)	27 (25–29)	0.222
Hoehn-Yahr staging (median, IQR)	2 (1–2)	2 (2–2)	<b>0.001</b>
MDS-UPDRS III total (median, IQR)	19 (14–26)	22 (16–27)	<b>0.024</b>
<u>Tremor subscore (median, IQR)</u>	<u>5 (2–8)</u>	<u>6 (2–9)</u>	<u>0.117</u>
<u>Bradykinesia subscore (median, IQR)</u>	<u>11 (6–15)</u>	<u>14 (9–19)</u>	<b>0.008</b>
<u>Axial subscore (median, IQR)</u>	<u>4 (2–5)</u>	<u>4 (3–7)</u>	<b>0.008</b>
<u>Rigidity subscore (median, IQR)</u>	<u>4 (2–6)</u>	<u>5 (3–9)</u>	<b>0.031</b>
State Trait Anxiety Score (median, IQR)	94 (89–98)	94 (88–97)	0.500
Geriatric Depression Scale (median, IQR)	5 (5–6)	5 (4–6)	0.280
<i>CSF biomarkers</i>			
CSF $\alpha$ -synuclein (median, IQR, pg/ml)	1351.3 (1029.3– 1718.0)	1528.8 (1164.3– 2086.0)	<b>0.016</b>
CSF A $\beta$ <sub>42</sub> (median, IQR, pg/mL)	848.6 (615.1– 1119.0)	822.2 (627.9– 1050.5)	0.860

Formatted: Font: Not Bold

CSF pTau (median, IQR, pg/mL)	13.0 (10.9–16.7)	15.4 (12.4–21.4)	<b>0.001</b>
CSF tTau (median, IQR, pg/mL)	152.6 (124.0–192.6)	186.4 (147.2–237.7)	<b>&lt;0.001</b>
CSF Aβ <sub>42</sub> /tTau	5.81 (4.69–6.69)	4.88 (3.71–6.01)	<b>0.002</b>
CSF Aβ <sub>42</sub> /pTau	69.4 (57.4–80.3)	61.1 (42.7–75.7)	<b>0.002</b>

#### *DAT striatal binding ratios*

Mean caudate uptake (median, IQR)	2.02 (1.67–2.37)	1.88 (1.54–2.21)	0.155
Mean putamen uptake (median, IQR)	1.79 (1.48–2.18)	1.77 (1.34–2.08)	0.270
Caudate asymmetry (median, IQR)	1.19 (1.10–1.31)	1.17 (1.07–1.27)	0.216
Putamen asymmetry (median, IQR)	1.45 (1.19–1.76)	1.39 (1.17–1.73)	0.484

#### *Small vessel disease profile*

WMH Fazekas score (median, IQR)	2 (1–2)	3 (2–4)	<b>&lt;0.001</b>
<u>The presence of lacunes (N, %)</u>	<u>145 (50.7%)</u>	<u>45 (81.8%)</u>	<u><b>&lt;0.001</b></u>
Cardiovascular diseases (N, %)	224 (52.1%)	57 (77.0%)	<b>&lt;0.001</b>
Cerebrovascular diseases (N, %) <sup>a</sup>	2 (0.5%)	2 (2.7%)	0.195

#### *Genetic profile*

Presence of APOE ε4 allele (N, %)	68 (23.8%)	13 (23.6)	0.982
-----------------------------------	------------	-----------	-------

#### *Cognition at 3-year follow-up*

Change in MoCA score (median, IQR)	0 (-2–1)	-2 (-5–0.25)	<b>0.004</b>
Cognitive impairment (N, %)	46 (18.9)	22 (48.9%)	<b>&lt;0.001</b>

<sup>a</sup>Correction for continuity was adapted for inadequate event.

Formatted Table

Abbreviations: CSF, cerebrospinal fluid; DAT, dopaminergic transporter; IQR, interquartile range;

MDS-UPDRS III, Movement Disorder Society Unified Parkinson's Disease Rating Score part III;

MoCA, Montreal Cognitive Assessment.

Table 2. Linear mixed model for interactive effect of CSF markers and BG-PVS on cognitive outcomes

	MoCA score at 3-year follow-up				Change in MoCA from baseline to 3-year follow-up			
	Model without interaction		Model with interaction		Model without interaction		Model with interaction	
	Coefficient	P value	Coefficient	P value	Coefficient	P value	Coefficient	P value
Model 1								
Baseline A $\beta$ <sub>42</sub> /tTau	<del>0.385 (0.154-0.617)</del>	<del>0.001</del>	1.087 (0.650-1.524)	<del>&lt;0.001</del>	0.388 (0.156-0.619)	<del>0.001</del>	1.086 (0.649-1.523)	<del>&lt;0.001</del>
BG-PVS $\geq$ 2	REF		<del>REF</del>		REF		<del>REF</del>	
BG-PVS<2	<del>1.302 (0.271-2.334)</del>	<del>0.014</del>	6.364 (3.515-9.214)	<del>&lt;0.001</del>	1.317 (0.285-2.349)	<del>0.013</del>	6.357 (3.507-9.207)	<del>&lt;0.001</del>
A $\beta$ <sub>42</sub> /tTau*BG-PVS	/		-0.953 (-1.460-)	<del>&lt;0.001</del>	/		-0.949 (-1.456--0.441)	<del>&lt;0.001</del>

Formatted Table

interaction			<u>0.445</u> (-0.911 - 1.420)					<u>0.907</u> (-1.416 - 0.397)	
			<u>0.400</u>						
AIC	<u>823.48</u> 15.5		<u>811.48</u> 04.5			<u>823.28</u> 17.3		<u>811.38</u> 06.3	
Model 2									
Baseline Aβ <sub>42</sub> /pTau	<u>0.031</u> (0.011-0.050)	<u>0.031</u> ( <del>0.031</del> )	<u>0.002</u> <del>0.002</del>	<u>0.095</u> (0.059-	<u>&lt;0.001</u> <del>&lt;0.001</del>	<u>0.031</u> (0.011-	<u>0.002</u> <del>0.003</del>	<u>0.095</u> (0.059-	<u>&lt;0.001</u> <del>&lt;0.001</del>
	<del>(-0.011 - 0.050)</del>		<u>0.131</u> <del>0.092</del> (-0.056-		<u>0.050</u> <del>0.030</del> (-0.011-		<u>0.131</u> <del>0.093</del> (-0.056-		
			<del>0.129)</del>		<del>0.050)</del>		<del>0.129)</del>		
BG-PVS≥2	<u>REF</u> <del>REF</del>		<u>REF</u> <del>REF</del>		<u>REF</u>		<u>REF</u> <del>REF</del>		
BG-PVS<2	<u>1.364</u> (0.282-2.445)	<u>1.309</u> <del>1.309</del>	<u>0.014</u> <del>0.014</del>	<u>7.040</u> (4.170-	<u>&lt;0.001</u> <del>&lt;0.001</del>	<u>1.387</u> (0.305-	<u>0.013</u> <del>0.014</del>	<u>7.057</u> (4.186-	<u>&lt;0.001</u> <del>&lt;0.001</del>
	<del>(-0.267 - 2.350)</del>		<u>9.909</u> <del>6.580</del> (-3.740-		<u>2.468</u> <del>1.359</del> (-0.317-		<u>9.927</u> <del>6.602</del> (-3.763-		
			<del>9.419)</del>		<del>2.400)</del>		<del>9.441)</del>		
Aβ <sub>42</sub> /pTau*BG-PVS	<u>/</u>		<u>-0.088</u> (-0.130-	<u>&lt;0.001</u> <del>&lt;0.001</del>	<u>/</u>	<u>-0.088</u> (-0.130-	<u>-0.088</u> (-0.130-	<u>-0.088</u> (-0.130-	<u>&lt;0.001</u> <del>&lt;0.001</del>
interaction			<u>0.046</u> (-0.08 - 0.13)					<u>0.084</u> (-0.126 - 0.042)	

Formatted: Font: (Default) Times New Roman

AIC	<u>782.6774.7</u>	<u>765.8772.5</u>	<u>782.4776.4</u>	<u>772.3767.5</u>
Model 3				
Baseline Aβ <sub>42</sub>	<u>0.001 (0-0.002)0.001-</u> <u>(-0.000-0.002)</u>	<b><u>0.0330.035</u></b>	<u>0.003 (0.001--</u> <u>0.005)0.003 (-0.001-</u> <u>0.005)</u>	<b><u>0.0030.004</u></b>
BG-PVS≥2	<u>REFREF</u>	<u>REFREF</u>	<u>REF</u>	<u>REFREF</u>
BG-PVS<2	<u>1.286 (0.253-2.318)1.258-</u> <u>(-0.252-2.263)</u>	<b><u>0.0150.015</u></b>	<u>3.328 (1.224-</u> <u>5.432)3.184 (-1.084-</u> <u>5.285)</u>	<b><u>0.0020.003</u></b>
Aβ <sub>42</sub> *BG-PVS interaction	<u>/</u>	<u>-0.002 (-0.004-0)-</u> <u>0.002 (-0.004-0.000)</u>	<b><u>0.0290.039</u></b>	<u>/</u>
AIC	<u>867.6859.9</u>	<u>867.874.8.5</u>	<u>867.9861.5</u>	<u>875.2868.9</u>



CSF biomarkers ( $A\beta_{42}$ ,  $A\beta_{42}/t\text{Tau}$ ,  $A\beta_{42}/p\text{Tau}$ ), BG-PVS and their interaction were fixed effect; age, baseline MoCA score, axial subscore of MDS-UPDRS III, RBDSQ, UPSIT, and putamen asymmetry, WMH Fazekas score, the presence of lacunes, past history cardiovascular diseases were set as random effect. ~~CSF biomarkers ( $A\beta_{42}$ ,  $A\beta_{42}/t\text{Tau}$ ,  $A\beta_{42}/p\text{Tau}$ ), BG-PVS and their interaction were fixed effect. Age, baseline MoCA score, RBDSQ, and DAT-putamen asymmetry were set as random effect for MoCA score at 3 year follow up, and baseline state trait anxiety inventory was additionally set as random effect for 3 year change in MoCA;~~ Abbreviations: AIC, Akaike information criterion; BG-PVS, basal ganglia perivascular space; REF, reference.

1 **Perivascular Space in Parkinson's Disease: Association with CSF Amyloid/Tau and Cognitive**

2  
3 **Decline**

4  
5  
6 Huimin Chen<sup>a,b,c,d</sup>, Huijuan Wan<sup>b,c,d,e</sup>, Meimei Zhang<sup>b,c,d</sup>, Joanna M Wardlaw<sup>f</sup>, Tao Feng<sup>b,c,d</sup>, Yilong  
7  
8  
9 Wang<sup>b,c,d</sup>

10  
11 <sup>a</sup>Department of Neurology, Beijing Hospital, National Center of Gerontology; Institute of Geriatric  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Medicine, Chinese Academy of Medical Sciences, Beijing, China

<sup>b</sup>Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

<sup>c</sup>China National Clinical Research Center for Neurological Diseases (NCRC-ND), Beijing, China

<sup>d</sup>Advanced Innovation Center for Human Brain Projection, Capital Medical University, Beijing, China

<sup>e</sup>Department of Neurology, First Affiliated Hospital, Xiamen University, Xiamen, China

<sup>f</sup>Centre for Clinical Brain Sciences, UK Dementia Research Institute, University of Edinburgh,  
Edinburgh, UK

**Corresponding author:**

Yilong Wang\*, MD, PhD.

**Address:** China National Clinical Research Center for Neurological Diseases, Beijing Tiantan

Hospital, Capital Medical University, No.119 South 4th Ring West Road, Fengtai District, Beijing,

China. 100070.

**E-mail:** yilong528@gmail.com, Tel: +86-139-1166-6571;

**Keywords/Search terms:** Parkinson's disease; Perivascular Space; Cognition; Amyloid; Tau

Title: 97 characteristics; Tables: 2; Figures:2; supplementary table: 4; supplementary figure 3;

supplementary result:1; Reference:29;

Word count: abstract 249; body of the manuscript 3308;

1           **Abstract**

2  
3           **Objective:** Whether perivascular space (PVS) visible on magnetic resonance imaging (MRI) represents  
4  
5  
6           glymphatic dysfunction and whether this imaging marker is pathologic in Parkinson's disease (PD)  
7  
8  
9           have been controversial. The objective was to determine whether PVS visible on MRI is independently  
10  
11           associated with cognitive decline in patients with PD, and to test whether pathologic proteins in the  
12  
13           CSF (such as A $\beta$ <sub>42</sub>) mediate the pathologic role of PVS.  
14  
15

16           **Methods:** A total of 341 patients with Parkinson's disease from Parkinson's Progression Marker  
17  
18           Initiative (PPMI) cohort was included in the present study. PVS in the basal ganglia (BG-PVS) and  
19  
20           centrum semiovale were evaluated with a semiquantitative scale. Changes in the Montreal Cognitive  
21  
22           Assessment (MoCA) score and the absolute MoCA score at the 3-year assessment were considered the  
23  
24           main cognitive outcome. A multivariable linear regression model was used to test the association  
25  
26           between PVS and cognitive decline. A mixed linear model and path analysis were used to test the  
27  
28           interaction among PVS, CSF biomarkers and cognitive decline.  
29  
30  
31  
32  
33  
34  
35

36           **Results:** BG-PVS was associated with cognitive decline in patients with PD at the 3-year follow-up  
37  
38           independent of age, baseline cognition, motor and nonmotor function, presynaptic dopaminergic  
39  
40           deficiency, and CSF biomarkers. The interaction between BG-PVS and A $\beta$ <sub>42</sub>/tTau, A $\beta$ <sub>42</sub>/pTau, and A $\beta$ <sub>42</sub>  
41  
42           levels was significantly predictive of 3-year cognitive decline. Path analysis confirmed that CSF  
43  
44           A $\beta$ <sub>42</sub>/tTau levels partially mediated the pathologic effect of BG-PVS on cognitive outcome in PD.  
45  
46  
47  
48  
49

50           **Conclusions:** BG-PVS is independently associated with cognitive decline in PD, and this association  
51  
52           may be partially mediated by toxic CSF proteins.  
53  
54

55           **Keywords:** Parkinson's disease; Perivascular Space; Cognition; Amyloid; Tau  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

## 1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, with  $\alpha$ -synuclein ( $\alpha$ -syn) aggregation and Lewy body deposition being the pathologic hallmarks. Previous studies from several cohorts consistently reported that Alzheimer's disease (AD)-related CSF biomarkers (i.e., lower levels of  $A\beta_{42}$  and  $A\beta_{42}/\text{Tau}$  ratios and higher levels of total and phosphorylated Tau) were associated with cognitive impairment in PD [1-3].

Emerging evidence has highlighted the role of the perivascular space (PVS) as a glymphatic pathway for waste clearance in the brain and demonstrated that glymphatic dysfunction reduced cerebrospinal fluid (CSF) clearance of  $A\beta$  in AD models and in patients with AD [4-6]. Since AD-related proteins are toxic to neurons and glial cells [7] and are associated with cognitive decline in AD and PD [1-3], it is possible that reduced CSF clearance of toxic proteins as a result of glymphatic dysfunction may aggregate the neurodegenerative process and facilitate the development of dementia. Indeed, patients with PD showed impaired meningeal lymphatic drainage assessed by dynamic contrast-enhanced magnetic resonance imaging (MRI), which may facilitate the  $\alpha$ -syn deposition and result in motor dysfunction in PD mice model [8]. If BG-PVS visible on MRI reflects glymphatic dysfunction, there might be an association between the severity of BG-PVS visible on MRI and higher neurodegenerative burden measured by CSF biomarkers such as  $A\beta$ .

The Parkinson's Progression Marker Initiative (PPMI) is the largest ongoing cohort of PD with comprehensive clinical, imaging and CSF biomarker data. The PPMI provides an opportunity to confirm the pathologic role of BG-PVS in PD cognitive outcome. In addition, it provides superb data to test the relationship between PVS visible on MRI and neurodegenerative burden measured by CSF biomarkers, which may inform the mechanism and potential therapeutic target of PVS in progressive neurodegenerative processes. In the current analysis of PPMI data, we hypothesized that BG-PVS may

1 be related with cognitive decline in PD, which may be mediated by CSF neurodegenerative  
2  
3 biomarkers.  
4  
5  
6  
7

## 8 **2. Method**

### 9 ***2.1 Study design and participants***

10 PPMI is an ongoing, multicenter, longitudinal, observational study that started in 2010  
11  
12 (<https://www.ppmi-info.org/>). Patients with early, drug-naïve PD and intact cognition were included.  
13  
14  
15  
16  
17  
18

19 The PPMI study was approved by the institutional review board at each site, and participants provided  
20  
21 written informed consent to participate. The protocol and more detailed study design of PPMI has been  
22  
23 described elsewhere [9]. From the whole PPMI cohort, only PD patients with complete baseline BG-  
24  
25 PVS profiles and CSF biomarkers were included in the present analysis. The data used in the current  
26  
27 study were downloaded from the PPMI dataset in June 2020.  
28  
29  
30  
31  
32

### 33 ***2.2 Outcome measurements***

34  
35  
36 Cognitive decline was evaluated using the change in the MoCA score from baseline to 3-year follow-  
37  
38 up and the absolute MoCA score at the 3-year assessment. Motor function was measured using the  
39  
40 Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III and  
41  
42 Hoehn-Yahr stage. The MDS-UPDRS III score was further divided into four subscores according to the  
43  
44 cardinal motor symptoms in PD: tremor (items 15-18), bradykinesia (items 4-8, and item14), rigidity  
45  
46 (item 3), and axial signs (items 1, 2, 9-13). Nonmotor symptoms in the prediction of cognitive decline  
47  
48 in PD included rapid eye movement behavior disorder (RBD), which was assessed with the RBD  
49  
50 Screening Questionnaire (RBDSQ); sense of smell, which was assessed with the University of  
51  
52 Pennsylvania Smell Identification Test (UPSIT); depression, which was assessed with the 15-item  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 Geriatric Depression Scale (GDS); and anxiety, which was assessed with the State-Trait Anxiety  
2  
3 Inventory.  
4  
5

### 6 7 **2.3 DAT imaging**

8  
9  
10 [123I]β-CIT DAT single-photon emission computed tomography (SPECT) imaging was acquired at  
11  
12 PPMI imaging centers in accordance with the PPMI imaging protocol. Mean caudate and putaminal  
13  
14 uptake relative to uptake in the occipital area and asymmetry of caudate and putaminal uptake (side  
15  
16 with highest divided by side with lowest uptake) were computed for the analysis.  
17  
18  
19  
20  
21

### 22 **2.4 History of cardio- and cerebrovascular diseases and risk factors**

23  
24  
25 Histories of cardio- and cerebrovascular diseases were recorded in the PPMI cohort at patient  
26  
27 screening. Cardiovascular diseases include a history of diabetes, hypertension, hyperlipidemia,  
28  
29 hypercholesterolemia, and cardiac diseases. Cerebrovascular diseases included a history of  
30  
31 cerebrovascular accident, transient ischemic attack, ischemic stroke, cervical and carotid stenosis or  
32  
33 occlusion.  
34  
35  
36  
37  
38  
39

### 40 **2.5 Imaging markers of cerebral small vessel disease**

41  
42 Imaging markers of cerebral small vessel disease (CSVD) were evaluated by a neurologist who was  
43  
44 blind to the patient information (HJ Wan) following the instruction and definition of Standards for  
45  
46 ReportIng Vascular changes on nEuroimaging (STRIVE) [10]. White matter hyperintensity (WMH)  
47  
48 was rated according to the Fazekas rating scale [11]. Perivascular space was defined on MRI as small,  
49  
50 sharply delineated structures of CSF intensity (or close to CSF intensity) following the course of  
51  
52 perforating vessels. PVS in the basal ganglia and centrum semiovale (CS-PVS) were rated separately  
53  
54 on T2 weighted sequence as 0 = none, 1 = 1–10, 2 = 11–20, 3 = 21–40, and 4 = >40 PVS per side, and  
55  
56  
57  
58  
59  
60  
61  
62

1 the worse side was used if there was asymmetry [12, 13]. In the statistical analysis for BG-PVS,  
2  
3 patients were stratified into groups with moderate-to-severe BG-PVS (BG-PVS rating $\geq$ 2) and none-to-  
4  
5 mild BG-PVS (BG-PVS rating $<$ 2). Similarly, in the analysis for WMH and CS-PVS, patients were also  
6  
7 grouped into the high WMH group (Fazekas $>$ 2) versus the low WMH group (Fazekas $\leq$ 2) and the high  
8  
9 CS-PVS group (CS-PVS rating $\geq$ 2) versus the low CS-PVS group (CS-PVS rating $<$ 2). This  
10  
11 stratification was consistent with the distribution of CSVD profiles in our data and was consistent with  
12  
13 studies showing that BG-PVS rating $\geq$ 2 (moderate to severe) was predictive of unfavorable outcomes  
14  
15  
16  
17  
18  
19  
20 [12, 13].  
21

## 22 **2.6 Genotyping**

23  
24  
25 At the screening visit, genomic DNA was extracted from whole blood of the subject. The APOE  
26  
27 genotype was analyzed at the PPMI genetic core as previously described [14]. Subjects were classified  
28  
29  
30  
31 by the presence or absence of *APOE*  $\epsilon$ 4 genotypes.  
32

## 33 **2.7 CSF biomarkers**

34  
35  
36 The concentration of  $\alpha$ -synuclein in CSF samples was analyzed using an ELISA assay available  
37  
38 commercially from BioLegend. CSF A $\beta$ <sub>42</sub>, total tau (tTau) and tau phosphorylated at the threonine 181  
39  
40 position (pTau) were analyzed at Biorepository Core laboratories to the University of Pennsylvania  
41  
42 using Elecsys electrochemiluminescence immunoassays (Roche Diagnostics). More detail and primary  
43  
44  
45  
46  
47 results of the measured CSF biomarkers have been reported previously in the PPMI cohort [14, 15].  
48  
49

## 50 **2.8 Statistics**

51  
52  
53 Continuous variables were compared between groups using the Mann-Whitney test (nonnormal  
54  
55 distribution) or two sample t test (normal distribution), and categorical variables were compared  
56  
57  
58  
59 between groups using the Chi-square test. Univariable and multivariable linear regression models were  
60  
61

1 performed using the MoCA score at the 3-year follow-up and the 3-year change in the MoCA score as  
2  
3 separate dependent variables. The regression models consulted a previous PPMI study using 2-year  
4  
5 cognitive outcomes [16]. Multivariable regression models were conducted with adjustment of variables  
6  
7 showing a significant association ( $p < 0.05$ ) in the univariable regression analysis (only one significant  
8  
9 variable of the same feature with lower P value was selected to avoid collinearity), and variables that  
10  
11 showed significantly unbalanced features between BG-PVS groups. As CSF biomarkers were  
12  
13 significantly correlated with each other (supplementary figure 1)[17], each biomarker entered the  
14  
15 multivariable regression model separately.  
16  
17  
18  
19  
20  
21

22 The interaction between BG-PVS and CSF biomarkers in relation to cognition was firstly explored  
23  
24 by plotting the fitting curve and then by linear mixed models. The change in MoCA score and MoCA  
25  
26 score at the 3-year follow-up was used as dependent variables in linear mixed models. BG-PVS  
27  
28 severity and CSF biomarker with or without interaction term were set as fixed effects, and other  
29  
30 variables showing significant association with cognitive outcomes in univariable regression or  
31  
32 unbalanced features between BG-PVS groups were used as random effects. The Akaike information  
33  
34 criterion (AIC) of models with and without the BG-PVS\*CSF biomarker interaction item was  
35  
36 recorded. Path analysis was conducted to investigate how much CSF biomarkers mediated the effect of  
37  
38 BG-PVS on cognition in PD. The standardized coefficient ( $\beta$ ) of BG-PVS without a mediation effect  
39  
40 (direct effect) and with a mediation effect (indirect effect) and the standardized coefficient ( $\beta$ ) of the  
41  
42 CSF biomarker on the change in MoCA were calculated. P value  $< 0.05$  was defined as significant.  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52 Group comparison of CSF biomarkers at each follow-up point was also performed between PD groups  
53  
54 with different BG-PVS severities. P value  $< 0.01$  was defined as significant in this group comparison  
55  
56 for multiple comparison correction (correction for 4 repeated comparisons for each CSF biomarker).  
57  
58  
59  
60  
61  
62  
63  
64  
65



1 Group comparison was conducted in SPSS 25.0 (SPSS, inc., Beijing, China), and linear regression and  
2  
3 linear mixed models were performed in R software version 4.02 (<https://www.r-project.org/>).  
4  
5

6 To rule out confounding by WMH and lacune, and to investigate the location specificity of PVS,  
7  
8 their relationships (WMH, the presence of lacune or CS-PVS) with CSF biomarkers and cognitive  
9  
10 decline were further explored using a similar statistical approach.  
11  
12

### 13 ***2.9 Data Availability Statement***

14 The data was publicly available on PPMI website (<https://www.ppmi-info.org/access-data-specimens/>).  
15  
16  
17  
18  
19  
20  
21

## 22 **3. Results**

### 23 ***3.1 Baseline features of the included patients***

24  
25 Four hundred and twenty-three patients with drug-naïve PD were recruited in PPMI cohort. Among  
26  
27 these subjects, MRI imaging or T2-weighted imaging was missing in 47 patients, and imaging in  
28  
29 another 13 patients was not qualified to rate BG-PVS due to incomplete or nonaxial slices. CSF  
30  
31 biomarkers were missing in another 22 patients with PD. Finally, 341 patients with complete baseline  
32  
33 PVS and CSF biomarkers were included in the present analysis. The included and excluded patients  
34  
35 showed overall similar demographic and behavioral profiles (supplementary table 1).  
36  
37  
38  
39  
40  
41  
42  
43

### 44 ***3.2 Group comparison between patients with lower and higher BG-PVS burdens***

45  
46 Compared with patients with lower BG-PVS burden, patients with more severe BG-PVS were  
47  
48 significantly older; had more impaired motor function at baseline; had a higher prevalence of previous  
49  
50 cardiovascular disease; had a higher prevalence of lacune presence and more severe WMH at baseline;  
51  
52 had a higher risk of cognitive impairment and a greater decline in the MoCA score at the 3-year follow-  
53  
54 up despite of similar baseline MoCA scores; and showed lower levels of CSF  $A\beta_{42}$ ,  $A\beta_{42}/t\text{Tau}$ ,  
55  
56  
57  
58  
59  
60  
61  
62

1 A $\beta_{42}$ /pTau and higher levels of CSF  $\alpha$ -syn, tTau and pTau at baseline (**Table 1**).

### 2 3 4 **3.3 Univariable linear regression for cognition at the 3-year follow-up**

5  
6 Using the absolute MoCA score at the 3-year follow-up as the dependent variable, age, baseline MoCA  
7  
8 score, MDS-UPDRS III total score, tremor, bradykinesia, and axial subscores, RBDSQ, UPSIT score,  
9  
10 CSF A $\beta_{42}$ , tTau, pTau, A $\beta_{42}$ /tTau, A $\beta_{42}$ /pTau, putamen asymmetry and BG-PVS were significantly  
11  
12 associated with cognition at the 3-year follow-up in PD patients (P<0.05).  
13  
14  
15

16  
17 Using decline in MoCA score as the dependent variable, age, baseline MoCA score, RBDSQ,  
18  
19 UPSIT score, axial subscore of MDS-UPDRS III, CSF A $\beta_{42}$ , tTau, pTau, A $\beta_{42}$ /tTau, A $\beta_{42}$ /pTau,  
20  
21 putamen asymmetry, and BG-PVS were significantly associated with cognitive decline during three  
22  
23 years in PD patients (P<0.05) (supplementary table 2).  
24  
25  
26  
27

### 28 **3.4 Multivariable linear regression for cognition at the 3-year follow-up**

29  
30 In multivariable regression models, BG-PVS was significantly associated with MoCA score or  
31  
32 change in MoCA score, independent of age, past-history cardiovascular diseases, baseline MoCA score,  
33  
34 axial subscore of MDS-UPDRS III, RBDSQ, UPSIT, putamen asymmetry, WMH Fazekas score, the  
35  
36 presence of lacune, and CSF biomarkers. Baseline CSF A $\beta_{42}$ , A $\beta_{42}$ /tTau and A $\beta_{42}$ /pTau were  
37  
38 significantly associated with the MoCA score or change in the MoCA score at 3-year follow-up  
39  
40 independent of age, past-history cardiovascular diseases, baseline MoCA score, axial subscore of  
41  
42 MDS-UPDRS III, RBDSQ, UPSIT, putamen asymmetry, WMH Fazekas score, the presence of lacune,  
43  
44 and BG-PVS. However, baseline CSF tTau and pTau were not significantly associated with either  
45  
46 cognitive outcome at year three after adjustment (supplementary table 3).  
47  
48  
49  
50  
51  
52  
53  
54

### 55 **3.5 Interaction between CSF biomarkers and BG-PVS**

56  
57  
58 There was a significant main effect of BG-PVS and CSF A $\beta_{42}$ /tTau, A $\beta_{42}$ /pTau and A $\beta_{42}$  as well as  
59  
60  
61  
62  
63  
64  
65

1 interactions between BG-PVS and these CSF biomarkers (**Table 2**), such that patients with higher BG-  
2  
3 PVS and lower A $\beta_{42}$ /tTau (**Figure 1A**), A $\beta_{42}$ /pTau (**Figure 1B**), or A $\beta_{42}$  (**Figure 1C**) showed steeper  
4  
5 decline in the MoCA score at the 3-year follow-up. Models containing interaction terms provided a  
6  
7 slightly improved fit. As patients with a higher BG-PVS burden had a higher prevalence of  
8  
9 cardiovascular disease, we further tested whether the interaction between BG-PVS and CSF biomarkers  
10  
11 was confounded by the presence of cardiovascular disease. However, the correlation between CSF  
12  
13 biomarkers and cognitive decline was not stratified by the presence of cardiovascular disease  
14  
15 (supplementary figure 2).  
16  
17  
18  
19  
20  
21

22 We further compared CSF biomarkers at each follow-up timepoint between the BG-PVS groups.  
23  
24 The results revealed that patients with more severe BG-PVS showed significantly higher levels of all  
25  
26 measured CSF biomarkers at baseline, 1-year follow-up, and 2-year follow-up, and the significant  
27  
28 difference in tTau and pTau was still observed at year three with corrected P values (P<0.01)  
29  
30 (supplementary table 4).  
31  
32  
33  
34  
35

### 36 *3.6 Path analysis*

37  
38 In path analysis, CSF A $\beta_{42}$ /tTau was found to mediate the effect of BG-PVS on cognitive decline (total  
39  
40 effect [original coefficient] = -0.256, direct effect [corrected coefficient] = -0.208, indirect effect = -  
41  
42 0.048) (**Figure 2A**). That is, CSF A $\beta_{42}$ /tTau mediated 18.8% (indirect effect/total effect) of the BG-  
43  
44 PVS effect on the decrease in MoCA scores during the 3-year follow-up. In path analysis, the  
45  
46 correlation of BG-PVS with A $\beta_{42}$ /pTau was marginally significant, and that with A $\beta_{42}$  was not  
47  
48 significant (**Figure 2B and 2C**).  
49  
50  
51  
52  
53  
54

### 55 *3.7 Additional analysis with WMH and CS-PVS*

56  
57 To rule out the confounding effect of WMH, lacune and CS-PVS, additional analysis was performed.  
58  
59  
60  
61  
62  
63  
64  
65

1 No significant association was found among WMH, CSF biomarkers, and cognitive outcome; among  
2  
3 the presence of lacune, CSF biomarkers, and cognitive outcome; and among CS-PVS, CSF biomarkers,  
4  
5 and cognitive outcome (see supplementary figure 3 and supplementary result).  
6  
7  
8  
9

#### 10 11 **4. Discussion**

12  
13  
14 This is the first study that examined the relationship among CSF biomarkers, cognitive outcome and  
15  
16 PVS visible on MRI in PD. The main finding demonstrated that BG-PVS was independently associated  
17  
18 with cognitive decline in patients with PD. In addition, BG-PVS modified the pathologic effect of  
19  
20  $A\beta_{42}/t\text{Tau}$ ,  $A\beta_{42}/p\text{Tau}$ , and  $A\beta_{42}$  on cognitive decline in PD. Path analysis confirmed that CSF  
21  
22 biomarkers, especially  $A\beta_{42}/t\text{Tau}$ , partially mediated the pathologic effect of BG-PVS on cognitive  
23  
24 outcomes in PD. These results suggest that the increased visibility of BG-PVS on MRI may reflect  
25  
26 more advanced glymphatic dysfunction, resulting in higher levels of toxic CSF proteins, which may in  
27  
28 turn accelerate neurodegenerative processes and cognitive decline. It also implies that the glymphatic  
29  
30 pathway may serve as a therapeutic target to preserve cognition in neurodegenerative disease.  
31  
32  
33  
34  
35  
36  
37  
38

39 Our results validated a previous study by Park and colleagues [18], and showed that BG-PVS was  
40  
41 associated with 3-year cognitive decline in patients with PD. In addition, the contribution to poor  
42  
43 cognitive outcome and the interaction with CSF proteins were specific for PVS located in the basal  
44  
45 ganglia but not the centrum semiovale. However, the underlying mechanism for the location specificity  
46  
47 remains unclear. Evidence suggests that cerebral arterial pulsation drove CSF-interstitial fluid exchange  
48  
49 mediated by the glymphatic pathway [19], and arterial stiffness was associated with a higher BG-PVS  
50  
51 burden [20]. It is possible that PVS in the basal ganglia may be more prone to arterial damage and  
52  
53 pulsation change during aging. However, we did not test arterial function, such as arterial stiffness and  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 regulation. Future studies will be needed to test this hypothesis. In addition, BG-PVS differs from CS-  
2  
3 PVS in structure, as BG-PVS is covered by two leptomeningeal membranes and directly connects CSF  
4  
5  
6 [21]. This means that BG-PVS may be more active in eliminating waste from CSF, and the increased  
7  
8  
9 visibility of BG-PVS may represent an increased effort in waste clearance. Future studies directly  
10  
11  
12 comparing CSF dynamics are needed to investigate the location difference of PVS.

13  
14 Moreover, the results suggested that PVS visible on MRI may reflect glymphatic dysfunction,  
15  
16  
17 impaired efflux of CSF proteins and more advanced neurodegeneration in patients with PD. Previous  
18  
19  
20 evidence suggested that patients with PD showed higher volume fraction of PVS, especially for those  
21  
22  
23 familial patients with genetic mutation [22]. Previous PPMI data also suggested that PVS in midbrain  
24  
25  
26 was associated neurodegenerative imaging marker (DAT deficiency) [23]. These findings support our  
27  
28  
29 hypothesis that PVS visible on MRI may be closely linked with neurodegeneration in patients with PD.  
30  
31  
32 We found that the level of neurodegenerative CSF proteins ( $A\beta_{42}/tTau$ ) partially mediated the effect of  
33  
34  
35 BG-PVS on poor cognitive outcome. Taking that CSF proteins, including  $A\beta$  and Tau, are toxic to  
36  
37  
38 neurons and glial cells [7] and AD biomarkers are predictive of cognitive decline in PD [1-3], the result  
39  
40  
41 implies that BG-PVS may contribute to cognitive decline by elevating toxic CSF proteins in patients  
42  
43  
44 with PD.

45  
46  
47 The glymphatic pathway has drawn much attention in recent years as a novel pathway to exclude  
48  
49  
50 neurotoxic proteins and a potential therapeutic target [24]. In patients with superficial sclerosis, PVS  
51  
52  
53 was enlarged beneath the affected area where  $A\beta$  was deposited in the cortical arterial wall by biopsy,  
54  
55  
56 supporting the notion that enlarged PVS is a sign of a blocked drainage pathway by proteins such as  $A\beta$   
57  
58  
59 [25]. Ding and colleagues specifically tested the meningeal lymphatic flow in patients with PD using  
60  
61  
62 dynamic contrast-enhanced MRI, and proved significant reduction of lymphatic flow as well as notable  
63  
64  
65

1 delay in deep cervical lymph node perfusion in these patients. In addition, the delayed meningeal  
2  
3 lymphatic drainage was followed by  $\alpha$ -syn pathology in mice model [8, 22]. This study provided  
4  
5 direct evidence of impaired glymphatic system in PD and the consequent neurodegeneration (e.g.  $\alpha$ -syn  
6  
7 pathology). PVS visible on routine MRI may be an alternative way to explore the static glymphatic  
8  
9 pathway offline.  
10  
11  
12

13  
14 In PD patients with higher BG-PVS burden, the CSF  $A\beta_{42}$  level was lower compared with patients  
15  
16 with mild or none BG-PVS. Hypothetically, reduced efflux as a result glymphatic dysfunction should  
17  
18 cause increased CSF protein level. As for  $A\beta_{42}$ , it is possible that the decreased CSF  $A\beta_{42}$  reflected  
19  
20 more extensive peptide aggregation and plaque formation in brain tissue. Tau and  $A\beta$  have independent  
21  
22 as well as synergistic effects on cognition [26]. In our analysis, the interaction between CSF biomarker  
23  
24 and BG-PVS was more predominant for  $A\beta_{42}/tTau$ , and  $A\beta_{42}/pTau$ , compared with  $A\beta_{42}$  alone. It is  
25  
26 possible that glymphatic dysfunction blocked CSF toxic proteins, and the interaction between these  
27  
28 increased proteins (e.g. Tau-  $A\beta_{42}$  interaction) accelerated the aggregation of amyloid, lowering the  
29  
30 amounts of  $A\beta_{42}$  being tested in CSF.  
31  
32  
33  
34  
35  
36  
37  
38

39 CSF  $A\beta_{42}$ ,  $A\beta_{42}/tTau$ , and  $A\beta_{42}/pTau$  were not specific PD biomarkers. However, concurrent  
40  
41 proteinopathies and their synergistic interactions are quite common and may contribute to cognitive  
42  
43 decline in patients with PD [27]. There might be concomitant AD pathology playing a role in our  
44  
45 findings. Previous studies suggested that PVS in the centrum semiovale and hippocampus was  
46  
47 associated with the diagnosis of AD [28, 29], and PVS in the hippocampus was associated with  
48  
49 hippocampal atrophy[29]. However, the association between PVS visible on MRI and CSF biomarkers  
50  
51 was not statistically significant in cognitively impaired individuals in Neurodegenerative Disorders  
52  
53 Early and Reliably (BioFINDER) study [29]. More studies are needed to test the association between  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 PVS visible on MRI and CSF biomarkers in demented and non-demented populations.  
2

3 In addition to our initial hypothesis, the factors associated with 3-year cognitive decline were  
4 largely consistent with previous 2-year follow-up analysis [16]. More recently, Irwin and colleagues  
5 reported that AD-related CSF biomarkers were associated with 3-year cognitive decline in a PPMI  
6 cohort [17]. Although finding risk factors associated with cognitive decline was not the main topic of  
7 our study, the consistency with previous data suggests that the present data are representative of the  
8 whole cohort despite missing BG-PVS data in 59 patients (missing rate = 13.9%).  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19

20 We acknowledge several limitations. First, this study did not measure the dynamic function of the  
21 glymphatic pathway in vivo. Currently, dynamic fluid exchange by the glymphatic pathway has been  
22 investigated in vivo by intrathecal injection of the contrast agent in neurological diseases such as  
23 idiopathic normal pressure hydrocephalus [6]. These approaches enable tracking uptake and  
24 distribution of tracers dynamically, but they are invasive and may not be applicable in patients with PD.  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

66 In conclusion, we found that BG-PVS may be independently associated with cognitive decline in  
67 PD, which may be partially mediated by toxic CSF proteins. The increased visibility of BG-PVS on  
68 MRI may reflect more advanced glymphatic dysfunction. PVS may serve as a therapeutic target to  
69 preserve cognition in PD.

1 **Conflict of interest**

2  
3 None

4  
5  
6  
7  
8 **Acknowledgements**

9  
10 PPMI is supported by the Michael J. Fox Foundation for Parkinson's Research and funding partners,  
11 including Abbott, Avid, Biogen idec, Bristol-Myers Squibb, Covance, Elan, GE Healthcare, Genentech,  
12 GSK, Lilly, MERCK, MSD, Pfizer, Roche and UCB (details of the PPMI funding partners found at  
13 [www.ppmiinfo.org/](http://www.ppmiinfo.org/funding-partners) funding partners). Huimin Chen is supported by Beijing Hospital Project (BJ-2021-  
14 197). Yilong Wang is supported by grants from the National Natural Science Foundation of China  
15 (81825007), the Ministry of Science and Technology of the People's Republic of China  
16 (2017YFC1307900), Beijing Outstanding Young Scientist Program (BJJWZYJH01201910025030), the  
17 third batch of National Ten Thousand Talents Plan, the Beijing Municipal Science and Technology  
18 Commission (Beijing Excellent Talents Training and Supporting Top Youth Team, D171100003017001  
19 and 2016000021223TD03), and the Youth Beijing Scholar Program.

20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42 **References:**

- 43  
44 [1] S. Hall, Y. Surova, A. Ohrfelt, F.S. Swedish Bio, K. Blennow, H. Zetterberg, O. Hansson,  
45 Longitudinal Measurements of Cerebrospinal Fluid Biomarkers in Parkinson's Disease, *Mov Disord* 31(6)  
46 (2016) 898-905.  
47  
48 [2] M. Shahid, J. Kim, K. Leaver, T. Hendershott, D. Zhu, B. Cholerton, V.W. Henderson, L. Tian, K.L.  
49 Poston, An increased rate of longitudinal cognitive decline is observed in Parkinson's disease patients  
50 with low CSF A $\beta$ 42 and an APOE epsilon4 allele, *Neurobiol Dis* 127 (2019) 278-286.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65



- 1 [3] M. Delgado-Alvarado, R. Dacosta-Aguayo, I. Navalpotro-Gomez, B. Gago, A. Gorostidi, H.  
2  
3 Jimenez-Urbieta, A. Quiroga-Varela, J. Ruiz-Martinez, A. Bergareche, M.C. Rodriguez-Oroz, Ratios of  
4  
5 proteins in cerebrospinal fluid in Parkinson's disease cognitive decline: prospective study, *Mov Disord*  
6  
7 33(11) (2018) 1809-1813.  
8  
9
- 10 [4] E.L. Boespflug, M.J. Simon, E. Leonard, M. Grafe, R. Woltjer, L.C. Silbert, J.A. Kaye, J.J. Iliff,  
11  
12 Targeted Assessment of Enlargement of the Perivascular Space in Alzheimer's Disease and Vascular  
13  
14 Dementia Subtypes Implicates Astroglial Involvement Specific to Alzheimer's Disease, *J Alzheimers Dis*  
15  
16 66(4) (2018) 1587-1597.  
17  
18
- 19 [5] M.K. Rasmussen, H. Mestre, M. Nedergaard, The glymphatic pathway in neurological disorders,  
20  
21 *Lancet Neurol* 17(11) (2018) 1016-1024.  
22  
23
- 24 [6] M.J. de Leon, Y. Li, N. Okamura, W.H. Tsui, L.A. Saint-Louis, L. Glodzik, R.S. Osorio, J. Fortea, T.  
25  
26 Butler, E. Pirraglia, S. Fossati, H.J. Kim, R.O. Carare, M. Nedergaard, H. Benveniste, H. Rusinek,  
27  
28 Cerebrospinal Fluid Clearance in Alzheimer Disease Measured with Dynamic PET, *J Nucl Med* 58(9)  
29  
30 (2017) 1471-1476.  
31  
32
- 33 [7] S. Jankeviciute, G. Psemeneckiene, R. Morkuniene, E. Grusauskiene, K. Petrikonis, D. Rastenyte, V.  
34  
35 Borutaite, Cerebrospinal fluids from Alzheimer's disease patients exhibit neurotoxic effects on neuronal  
36  
37 cell cultures, *Eur J Neurosci* 50(2) (2019) 1994-2006.  
38  
39
- 40 [8] X.B. Ding, X.X. Wang, D.H. Xia, H. Liu, H.Y. Tian, Y. Fu, Y.K. Chen, C. Qin, J.Q. Wang, Z. Xiang,  
41  
42 Z.X. Zhang, Q.C. Cao, W. Wang, J.Y. Li, E. Wu, B.S. Tang, M.M. Ma, J.F. Teng, X.J. Wang, Impaired  
43  
44 meningeal lymphatic drainage in patients with idiopathic Parkinson's disease, *Nat Med* 27(3) (2021) 411-  
45  
46 418.  
47  
48
- 49 [9] I. Parkinson Progression Marker, The Parkinson Progression Marker Initiative (PPMI), *Prog*  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 Neurobiol 95(4) (2011) 629-35.

2  
3 [10] J.M. Wardlaw, E.E. Smith, G.J. Biessels, C. Cordonnier, F. Fazekas, R. Frayne, R.I. Lindley, J.T.  
4  
5  
6 O'Brien, F. Barkhof, O.R. Benavente, S.E. Black, C. Brayne, M. Breteler, H. Chabriat, C. Decarli, F.E.  
7  
8  
9 de Leeuw, F. Doubal, M. Duering, N.C. Fox, S. Greenberg, V. Hachinski, I. Kilimann, V. Mok, R.  
10  
11  
12 Oostenbrugge, L. Pantoni, O. Speck, B.C. Stephan, S. Teipel, A. Viswanathan, D. Werring, C. Chen, C.  
13  
14  
15 Smith, M. van Buchem, B. Norrving, P.B. Gorelick, M. Dichgans, S.T.f.R.V.c.o. nEuroimaging,  
16  
17  
18 Neuroimaging standards for research into small vessel disease and its contribution to ageing and  
19  
20  
21 neurodegeneration, *Lancet Neurol* 12(8) (2013) 822-38.

22  
23 [11] F. Fazekas, R. Kleinert, H. Offenbacher, R. Schmidt, G. Kleinert, F. Payer, H. Radner, H. Lechner,  
24  
25  
26 Pathologic correlates of incidental MRI white matter signal hyperintensities, *Neurology* 43(9) (1993)  
27  
28  
29 1683-9.

30  
31 [12] F.N. Doubal, A.M. MacLulich, K.J. Ferguson, M.S. Dennis, J.M. Wardlaw, Enlarged perivascular  
32  
33  
34 spaces on MRI are a feature of cerebral small vessel disease, *Stroke* 41(3) (2010) 450-4.

35  
36 [13] G.M. Potter, F.N. Doubal, C.A. Jackson, F.M. Chappell, C.L. Sudlow, M.S. Dennis, J.M. Wardlaw,  
37  
38  
39 Enlarged perivascular spaces and cerebral small vessel disease, *Int J Stroke* 10(3) (2015) 376-81.

40  
41  
42 [14] J.H. Kang, B. Mollenhauer, C.S. Coffey, J.B. Toledo, D. Weintraub, D.R. Galasko, D.J. Irwin, V.  
43  
44  
45 Van Deerlin, A.S. Chen-Plotkin, C. Caspell-Garcia, T. Waligorska, P. Taylor, N. Shah, S. Pan, P. Zero,  
46  
47  
48 M. Frasier, K. Marek, K. Kieburz, D. Jennings, C.M. Tanner, T. Simuni, A. Singleton, A.W. Toga, S.  
49  
50  
51 Chowdhury, J.Q. Trojanowski, L.M. Shaw, I. Parkinson's Progression Marker, CSF biomarkers  
52  
53  
54 associated with disease heterogeneity in early Parkinson's disease: the Parkinson's Progression Markers  
55  
56  
57 Initiative study, *Acta Neuropathol* 131(6) (2016) 935-49.

58  
59 [15] B. Mollenhauer, C.J. Caspell-Garcia, C.S. Coffey, P. Taylor, L.M. Shaw, J.Q. Trojanowski, A.  
60  
61  
62  
63  
64  
65

1 Singleton, M. Frasier, K. Marek, D. Galasko, I. Parkinson's Progression Marker, Longitudinal CSF  
2  
3 biomarkers in patients with early Parkinson disease and healthy controls, *Neurology* 89(19) (2017) 1959-  
4  
5  
6 1969.

7  
8  
9 [16] A. Schrag, U.F. Siddiqui, Z. Anastasiou, D. Weintraub, J.M. Schott, Clinical variables and  
10  
11 biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease:  
12  
13 a cohort study, *Lancet Neurol* 16(1) (2017) 66-75.

14  
15  
16  
17 [17] D.J. Irwin, J. Fedler, C.S. Coffey, C. Caspell-Garcia, J.H. Kang, T. Simuni, T. Foroud, A.W. Toga,  
18  
19  
20 C.M. Tanner, K. Kieburtz, L.M. Chahine, A. Reimer, S. Hutten, D. Weintraub, B. Mollenhauer, D.R.  
21  
22 Galasko, A. Siderowf, K. Marek, J.Q. Trojanowski, L.M. Shaw, I. Parkinson's Progression Marker,  
23  
24  
25 Evolution of Alzheimer's Disease Cerebrospinal Fluid Biomarkers in Early Parkinson's Disease, *Ann*  
26  
27  
28 *Neurol* (2020).

29  
30  
31 [18] Y.W. Park, N.Y. Shin, S.J. Chung, J. Kim, S.M. Lim, P.H. Lee, S.K. Lee, K.J. Ahn, Magnetic  
32  
33  
34 Resonance Imaging-Visible Perivascular Spaces in Basal Ganglia Predict Cognitive Decline in  
35  
36  
37 Parkinson's Disease, *Mov Disord* 34(11) (2019) 1672-1679.

38  
39 [19] J.J. Iliff, M. Wang, D.M. Zeppenfeld, A. Venkataraman, B.A. Plog, Y. Liao, R. Deane, M.  
40  
41  
42 Nedergaard, Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine  
43  
44  
45 brain, *J Neurosci* 33(46) (2013) 18190-9.

46  
47  
48 [20] I. Riba-Llena, J. Jimenez-Balado, X. Castane, A. Girona, A. Lopez-Rueda, X. Mundet, C.I. Jarca, J.  
49  
50  
51 Alvarez-Sabin, J. Montaner, P. Delgado, Arterial Stiffness Is Associated With Basal Ganglia Enlarged  
52  
53  
54 Perivascular Spaces and Cerebral Small Vessel Disease Load, *Stroke* 49(5) (2018) 1279-1281.

55  
56 [21] J.M. Wardlaw, H. Benveniste, M. Nedergaard, B.V. Zlokovic, H. Mestre, H. Lee, F.N. Doubal, R.  
57  
58  
59 Brown, J. Ramirez, B.J. MacIntosh, A. Tannenbaum, L. Ballerini, R.L. Rungta, D. Boido, M. Sweeney,

- 1 A. Montagne, S. Charpak, A. Joutel, K.J. Smith, S.E. Black, D. colleagues from the Fondation Leducq  
2  
3 Transatlantic Network of Excellence on the Role of the Perivascular Space in Cerebral Small Vessel,  
4  
5 Perivascular spaces in the brain: anatomy, physiology and pathology, *Nat Rev Neurol* 16(3) (2020) 137-  
6  
7 153.  
8  
9  
10  
11 [22] E.K. Donahue, A. Murdos, M.W. Jakowec, N. Sheikh-Bahaei, A.W. Toga, G.M. Petzinger, F.  
12  
13 Sepehrband, Global and Regional Changes in Perivascular Space in Idiopathic and Familial Parkinson's  
14  
15 Disease, *Mov Disord* 36(5) (2021) 1126-1136.  
16  
17  
18 [23] Y. Li, Z. Zhu, J. Chen, M. Zhang, Y. Yang, P. Huang, Dilated Perivascular Space in the Midbrain  
19  
20 May Reflect Dopamine Neuronal Degeneration in Parkinson's Disease, *Front Aging Neurosci* 12 (2020)  
21  
22 161.  
23  
24  
25 [24] B.L. Sun, L.H. Wang, T. Yang, J.Y. Sun, L.L. Mao, M.F. Yang, H. Yuan, R.A. Colvin, X.Y. Yang,  
26  
27 Lymphatic drainage system of the brain: A novel target for intervention of neurological diseases, *Prog*  
28  
29 *Neurobiol* 163-164 (2018) 118-143.  
30  
31  
32 [25] A. Keable, K. Fenna, H.M. Yuen, D.A. Johnston, N.R. Smyth, C. Smith, R. Al-Shahi Salman, N.  
33  
34 Samarasekera, J.A. Nicoll, J. Attems, R.N. Kalaria, R.O. Weller, R.O. Carare, Deposition of amyloid  
35  
36 beta in the walls of human leptomeningeal arteries in relation to perivascular drainage pathways in  
37  
38 cerebral amyloid angiopathy, *Biochim Biophys Acta* 1862(5) (2016) 1037-46.  
39  
40  
41 [26] M.A. Busche, B.T. Hyman, Synergy between amyloid-beta and tau in Alzheimer's disease, *Nat*  
42  
43 *Neurosci* 23(10) (2020) 1183-1193.  
44  
45  
46 [27] L. Farotti, F. Paolini Paoletti, S. Simoni, L. Parnetti, Unraveling Pathophysiological Mechanisms of  
47  
48 Parkinson's Disease: Contribution of CSF Biomarkers, *Biomark Insights* 15 (2020) 1177271920964077.  
49  
50  
51 [28] G. Banerjee, H.J. Kim, Z. Fox, H.R. Jager, D. Wilson, A. Charidimou, H.K. Na, D.L. Na, S.W. Seo,  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 D.J. Werring, MRI-visible perivascular space location is associated with Alzheimer's disease  
2  
3 independently of amyloid burden, *Brain* 140(4) (2017) 1107-1116.  
4

5  
6 [29] E.C. Gertje, D. van Westen, C. Panizo, N. Mattsson-Carlgen, O. Hansson, Association of Enlarged  
7  
8 Perivascular Spaces and Measures of Small Vessel and Alzheimer Disease, *Neurology* 96(2) (2021)  
9  
10 e193-e202.  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 **Figure legends**

2  
3 **Figure 1. Correlation between CSF biomarkers and cognitive outcomes stratified by BG-PVS**

4  
5  
6 BG-PVS modified the effect of  $A\beta_{42}/t\text{Tau}$  (A),  $A\beta_{42}/p\text{Tau}$  (B),  $A\beta_{42}$  (C) on cognitive outcome in  
7  
8  
9 Parkinson's disease, as high BG-PVS group showed steeper decline in the MoCA score in relation to  
10  
11  
12 CSF biomarkers at the 3-year follow-up.

13  
14 Abbreviations: BG-PVS, basal-ganglia perivascular space; CSF, cerebrospinal fluid.

15  
16  
17 **Figure 2. Path analysis**

18  
19  
20 CSF  $A\beta_{42}/t\text{Tau}$ , but not  $A\beta_{42}/p\text{Tau}$  or CSF  $A\beta_{42}$  significantly mediated the effect of BG-PVS on  
21  
22  
23 cognitive decline in patients with PD.

24  
25 Abbreviations: BG-PVS, basal-ganglia perivascular space; CSF, cerebrospinal fluid; WMH, white  
26  
27  
28 matter hyperintensity.

29  
30  
31  
32  
33  
34 Supplementary figures:

35  
36 **FIG. S1. Correlation between CSF biomarkers**

37  
38  
39 Abbreviations: CSF, cerebrospinal fluid.

40  
41  
42 **FIG. S2. Correlation between CSF biomarkers and cognitive decline stratified by the presence of**  
43  
44 **cardiovascular disease**

45  
46  
47 The presence of cardiovascular disease did not modify the effect of CSF biomarkers on cognitive  
48  
49  
50 decline in patients with PD.

51  
52  
53 **FIG. S3. Path analysis for WMH, lacune, and CS-PVS**

54  
55  
56 CSF biomarkers did not mediate the effect of WMH, the presence of lacune or CS-PVS on cognitive  
57  
58  
59 decline in PD.

Table 1. Demographic information between groups stratified by BG-PVS

	PD with low BG- PVS (N = 286)	PD with high BG- PVS (N = 55)	P value
<i>Demographic</i>			
Age (median, IQR, year)	60.7 (53.5–66.6)	71.1 (67.1–74.8)	<b>&lt;0.001</b>
Gender (F/M)	100/186	15/40	0.269
<i>Disease profile</i>			
Disease duration (median, IQR, month)	4 (2–7)	6 (3–13)	0.066
MoCA Score (median, IQR)	28 (26–29)	27 (25–29)	0.222
Hoehn-Yahr staging (median, IQR)	2 (1–2)	2 (2–2)	<b>0.001</b>
MDS-UPDRS III total (median, IQR)	19 (14–26)	22 (16–27)	<b>0.024</b>
Tremor subscore (median, IQR)	5 (2–8)	6 (2–9)	0.117
Bradykinesia subscore (median, IQR)	11 (6–15)	14 (9–19)	<b>0.008</b>
Axial subscore (median, IQR)	4 (2–5)	4 (3–7)	<b>0.008</b>
Rigidity subscore (median, IQR)	4 (2–6)	5 (3–9)	<b>0.031</b>
State Trait Anxiety Score (median, IQR)	94 (89–98)	94 (88–97)	0.500
Geriatric Depression Scale (median, IQR)	5 (5–6)	5 (4–6)	0.280
<i>CSF biomarkers</i>			
CSF $\alpha$ -synuclein (median, IQR, pg/ml)	1351.3 (1029.3– 1718.0)	1528.8 (1164.3– 2086.0)	<b>0.016</b>
CSF A $\beta$ <sub>42</sub> (median, IQR, pg/mL)	848.6 (615.1– 1119.0)	822.2 (627.9– 1050.5)	0.860

CSF pTau (median, IQR, pg/mL)	13.0 (10.9–16.7)	15.4 (12.4–21.4)	<b>0.001</b>
CSF tTau (median, IQR, pg/mL)	152.6 (124.0–	186.4 (147.2–	<b>&lt;0.001</b>
	192.6)	237.7)	
CSF A $\beta$ <sub>42</sub> /tTau	5.81 (4.69–6.69)	4.88 (3.71–6.01)	<b>0.002</b>
CSF A $\beta$ <sub>42</sub> /pTau	69.4 (57.4–80.3)	61.1 (42.7–75.7)	<b>0.002</b>
<i>DAT striatal binding ratios</i>			
Mean caudate uptake (median, IQR)	2.02 (1.67–2.37)	1.88 (1.54–2.21)	0.155
Mean putamen uptake (median, IQR)	1.79 (1.48–2.18)	1.77 (1.34–2.08)	0.270
Caudate asymmetry (median, IQR)	1.19 (1.10–1.31)	1.17 (1.07–1.27)	0.216
Putamen asymmetry (median, IQR)	1.45 (1.19–1.76)	1.39 (1.17–1.73)	0.484
<i>Small vessel disease profile</i>			
WMH Fazekas score (median, IQR)	2 (1–2)	3 (2–4)	<b>&lt;0.001</b>
The presence of lacune (N, %)	145 (50.7%)	45 (81.8%)	<b>&lt;0.001</b>
Cardiovascular diseases (N, %)	224 (52.1%)	57 (77.0%)	<b>&lt;0.001</b>
Cerebrovascular diseases (N, %) <sup>a</sup>	2 (0.5%)	2 (2.7%)	0.195
<i>Genetic profile</i>			
Presence of APOE $\epsilon$ 4 allele (N, %)	68 (23.8%)	13 (23.6)	0.982
<i>Cognition at 3-year follow-up</i>			
Change in MoCA score (median, IQR)	0 (-2–1)	-2 (-5–0.25)	<b>0.004</b>
Cognitive impairment (N, %)	46 (18.9)	22 (48.9%)	<b>&lt;0.001</b>

<sup>a</sup>Correction for continuity was adapted for inadequate event.



1 Abbreviations: CSF, cerebrospinal fluid; DAT, dopaminergic transporter; IQR, interquartile range;

2  
3 MDS-UPDRS III, Movement Disorder Society Unified Parkinson's Disease Rating Score part III;

4  
5  
6 MoCA, Montreal Cognitive Assessment.  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Table 2. Linear mixed model for interactive effect of CSF markers and BG-PVS on cognitive outcomes

	MoCA score at 3-year follow-up				Change in MoCA from baseline to 3-year follow-up			
	Model without interaction		Model with interaction		Model without interaction		Model with interaction	
	Coefficient	P value	Coefficient	P value	Coefficient	P value	Coefficient	P value
<b>Model 1</b>								
Baseline A $\beta$ <sub>42</sub> /tTau	0.385 (0.154–0.617)	<b>0.001</b>	1.087 (0.650–1.524)	<b>&lt;0.001</b>	0.388 (0.156–0.619)	<b>0.001</b>	1.086 (0.649–1.523)	<b>&lt;0.001</b>
BG-PVS $\geq$ 2	REF		REF		REF		REF	
BG-PVS<2	1.302 (0.271–2.334)	<b>0.014</b>	6.364 (3.515–9.214)	<b>&lt;0.001</b>	1.317 (0.285–2.349)	<b>0.013</b>	6.357 (3.507–9.207)	<b>&lt;0.001</b>
A $\beta$ <sub>42</sub> /tTau*BG-PVS	/		-0.953 (-1.460–-0.445)	<b>&lt;0.001</b>	/		-0.949 (-1.456–-0.441)	<b>&lt;0.001</b>
<b>Interaction</b>								
AIC	823.4		811.4		823.2		811.3	
<b>Model 2</b>								
Baseline A $\beta$ <sub>42</sub> /pTau	0.031 (0.011–0.050)	<b>0.002</b>	0.095 (0.059–0.131)	<b>&lt;0.001</b>	0.031 (0.011–0.050)	<b>0.002</b>	0.095 (0.059–0.131)	<b>&lt;0.001</b>

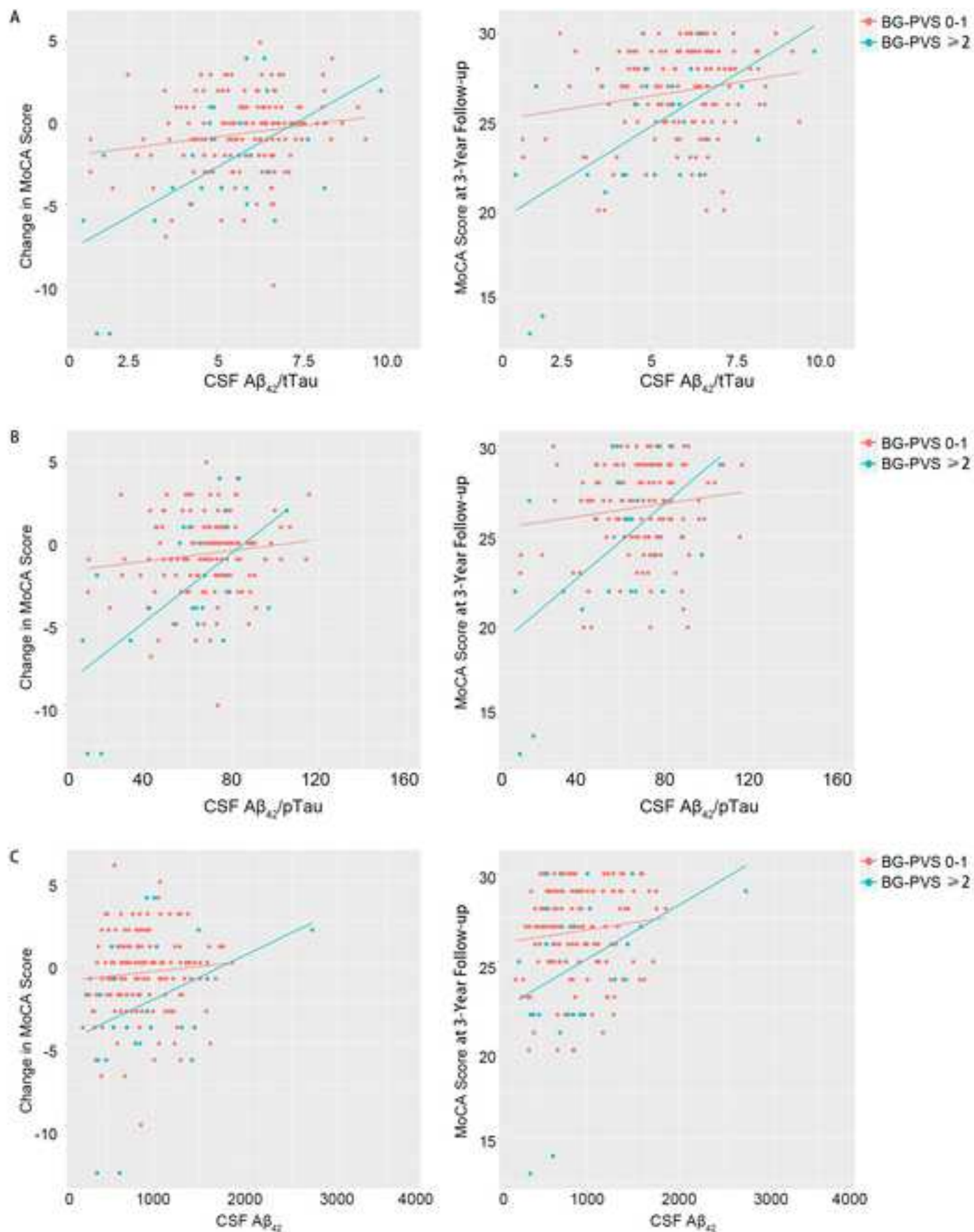
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

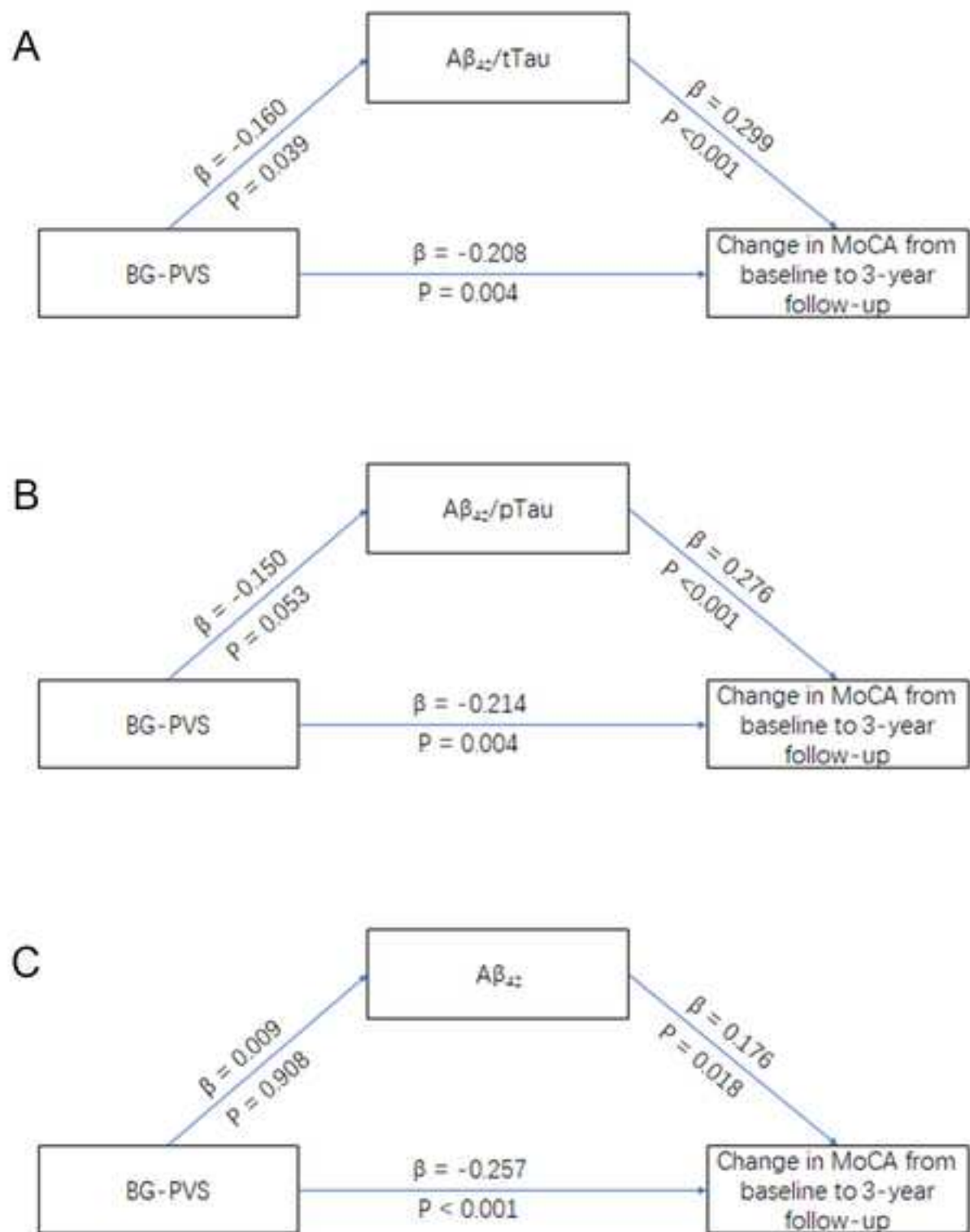
BG-PVS $\geq$ 2	REF		REF		REF		REF	
BG-PVS<2	1.364 (0.282–2.445)	<b>0.014</b>	7.040 (4.170–9.909)	<b>&lt;0.001</b>	1.387 (0.305–2.468)	<b>0.013</b>	7.057 (4.186–9.927)	<b>&lt;0.001</b>
A $\beta$ <sub>42</sub> /pTau*BG-PVS interaction	/		-0.088 (-0.130–0.046)	<b>&lt;0.001</b>	/		-0.088 (-0.130–0.046)	<b>&lt;0.001</b>
AIC	782.6		772.5		782.4		772.3	
<hr/>								
Model 3								
Baseline A $\beta$ <sub>42</sub>	0.001 (0–0.002)	<b>0.033</b>	0.003 (0.001–0.005)	<b>0.003</b>	0.001 (0–0.002)	<b>0.034</b>	0.003 (0.001–0.005)	<b>0.003</b>
BG-PVS $\geq$ 2	REF		REF		REF		REF	
BG-PVS<2	1.286 (0.253–2.318)	<b>0.015</b>	3.328 (1.224–5.432)	<b>0.002</b>	1.299 (0.266–2.331)	<b>0.014</b>	3.326 (1.221–5.430)	<b>0.002</b>
A $\beta$ <sub>42</sub> *BG-PVS interaction	/		-0.002 (-0.004–0)	<b>0.029</b>	/		-0.002 (-0.004–0)	<b>0.030</b>
AIC	867.6		874.8		867.9		875.2	

CSF biomarkers (A $\beta$ <sub>42</sub>, A $\beta$ <sub>42</sub>/tTau, A $\beta$ <sub>42</sub>/pTau), BG-PVS and their interaction were fixed effect; age, baseline MoCA score, axial subscore of MDS-UPDRS III, RBDSQ, UPSIT, and putamen asymmetry, WMH Fazekas score, the presence of lacune, past history cardiovascular diseases were set as random effect.; Abbreviations: AIC, Akaike

15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

information criterion; BG-PVS, basal ganglia perivascular space; REF, reference.







[Click here to access/download](#)

**Optional E-Only Supplementary Files**

Fig. S1.tif





[Click here to access/download](#)

**Optional E-Only Supplementary Files**

Fig. S2.tif







[Click here to access/download](#)

**Optional E-Only Supplementary Files**

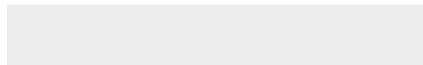
Fig. S3.tif





[Click here to access/download](#)

**Optional E-Only Supplementary Files**  
supplementary result.docx





[Click here to access/download](#)

**Optional E-Only Supplementary Files**  
Supplementary tables\_R2\_clean.docx

