

1 Serotonin, beta-amyloid, and cognition in Parkinson disease

2
3 Running title: Serotonin medications in PD

4 Authors

5
6 Vikas Kotagal MD MS^{1,2}, Cathie Spino Sc.D.^{3,4}, Nicolaas I Bohnen MD PhD^{1,2,3,5},
7 Robert A. Koeppe⁵, and Roger L Albin MD^{1,2,3}

- 8
9 1. Department of Neurology, University of Michigan, Ann Arbor, MI
10 2. Veterans Affairs Ann Arbor Health System (VAAAHS), Ann Arbor, Michigan
11 3. University of Michigan Morris K. Udall Center of Excellence for Parkinson's Disease
12 Research, Ann Arbor, MI
13 4. Department of Biostatistics, School of Public Health, University of Michigan, Ann
14 Arbor, MI
15 5. Department of Radiology, Division of Nuclear Medicine, University of Michigan, Ann
16 Arbor, MI

17 Corresponding Author:

18 Vikas Kotagal
19 Building 14, North Campus Research Complex
20 University of Michigan
21 2800 Plymouth Road
22 Ann Arbor MI, 48109
23 vikaskot@med.umich.edu
24 Phone: 734-936-9010
25 Fax: 734-615-4991

26
27
28 Keywords: Parkinson disease, SSRIs, amyloid, cognition, PPMI

29
30 Title character count: 55

31 Running title character count: 27

32 Abstract word count: 250

33 Introduction word count: 437

34 Discussion word count: 1631

35 Manuscript word count: 3917

36 References: 50

37 Figures: 2

38 Tables: 4

39
40
41
42
43
44
45
46 This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of record](#). Please cite this article as [doi:10.1002/ana.25236](https://doi.org/10.1002/ana.25236).

Abstract

Objective: Serotonergic neurotransmission may modulate beta-amyloid peptide (A β) metabolism through up-regulation of alpha-secretase. Early Parkinson disease (PD) shows variable serotonergic denervation, which may impact A β deposition.

Methods: We conducted three analyses to explore associations between serotonergic neurotransmission and cerebral A β burden in PD. The first was a cross-sectional imaging study of PD subjects (n=23) using the serotonergic transporter positron emission tomography (PET) ligand [^{11}C]DASB and amyloid PET Pittsburgh compound B ([^{11}C]PiB). The second was a baseline study of Parkinson's Progression Markers Initiative (PPMI) subjects exploring the influence of serotonergic medications on cerebrospinal fluid (CSF) A β -42 levels (n=389), controlling for age, sex, Geriatric Depression scale (GDS), disease duration, and education. Third, we fit an interval-censored proportional hazard model with longitudinal PPMI data (n=367) to test whether serotonergic medication use associates with reduced risk of PD-cognitive-decline, defined as time to reach a Montreal Cognitive Assessment score ≤ 20 , adjusting for baseline caudate dopamine transporter (DaT)[^{123}I]loflupane single photon emission computed tomography and cerebrospinal fluid A β -42 levels.

Results: Serotonergic DASB distribution volume ratio (DVR) inversely associated with PiB DVR in the cerebral cortex (Pearson's $r=-0.478, p=0.021$) but not the striatum ($r=-0.264, p=0.224$). In the baseline PPMI analysis, serotonergic medication use for ≥ 6 months associated with a lower level of CSF A β -42 ($t=-2.20, p=0.029$). In the longitudinal

1 PPMI model, baseline serotonergic medication use associated with a reduced risk of
2 cognitive decline ($t=-2.03, p=0.043$) after controlling for covariates.

3
4 Interpretation: Cortical A β burden in PD associates inversely with serotonergic
5 innervation. Serotonergic medications may alter A β metabolism and reduce the risk of
6 PD cognitive decline.

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

1 Introduction

2
3 Progressive cerebral beta-amyloid peptide (A β) plaque burden is linked to
4 clinically meaningful outcomes--including cognitive decline^{1, 2} and gait impairments^{3, 4}--
5 in Parkinson disease (PD) and synucleinopathy-associated dementias. A β plaque
6 deposition, assessed by amyloid positron emission tomography (PET), is associated
7 with prevalent cognitive impairment in parkinsonian conditions.⁵ Reduced cerebrospinal
8 fluid (CSF) A β -42 oligomers and factors influencing their metabolism are also
9 consistently reported as risk factors for subsequent cognitive decline in PD without
10 dementia.⁶⁻⁸ Developing strategies to alter the natural history of A β burden in PD may
11 represent an untapped disease-modifying approach and is an emerging research
12 priority.

13 Variable loss of serotonergic nerve terminals in the forebrain, striatum, and
14 brainstem is described in Parkinson disease.^{9, 10} Significant loss of serotonergic
15 terminals is an early feature in a substantial fraction of PD subjects.^{7, 8} Preclinical
16 experiments in Alzheimer disease (AD) mouse models by Cirrito et al. showed that
17 chronic exposure to either serotonin itself or the selective-serotonin reuptake inhibitor
18 (SSRI) citalopram reduced extracellular cerebral A β peptide concentrations and plaque
19 burden in short- and long- term *in vivo* studies.^{11, 12} Serotonin and SSRIs are suggested
20 to stimulate a serotonin G-protein-coupled receptor-linked intracellular cascade that
21 favors the cleavage of Amyloid Precursor Protein (APP) by alpha-secretase, leading to
22 reductions in toxic A β peptide amyloid generation and reduced plaque formation.¹¹
23 Serotonin medications may also promote efflux of toxic A β peptide species from the

1 brain into the blood.¹³ Other preclinical research supports the concept that
2 serotonergic neurotransmission can favorably modulate APP processing.¹⁴⁻¹⁷ If the
3 same protective association between serotonin receptor activation and reduced amyloid
4 burden exists in humans, a disease state such as PD with reductions in serotonergic
5 tone offers a potential model for testing this hypothesis. In a small cohort, we previously
6 reported that regional density of cortical and striatal serotonergic terminals in PD,
7 measured by *in vivo* positron emission tomography (PET), showed inverse correlations
8 with A β plaque burden.¹⁸

9 We present three analyses exploring associations between serotonergic
10 neurotransmission and A β burden in PD, using different experimental designs to
11 address 3 related hypotheses. First, using an identical multimodal imaging approach to
12 our earlier study in a new cohort, we sought to replicate our findings that decreased
13 cortical serotonergic innervation is inversely associated with the severity of cortical A β
14 plaque burden in PD. Second, using baseline data from the multicenter Parkinson
15 Progression Markers Initiative (PPMI), we explored associations between serotonin
16 medication use and CSF A β -42 levels. Third, we used a longitudinal analysis of PPMI
17 data to test whether baseline serotonergic medication use associates with a protective
18 effect on cognitive decline in PD, independent of existing heterogeneity in caudate
19 dopamine transporter binding or baseline cerebral amyloid burden.

21 **Methods**

23 *Study 1: Cross-sectional prospective PET imaging study*

1
2 In a previous PD cohort (n=13), we reported inverse associations between
3 cortical and striatal serotonergic terminal and amyloid PET findings.¹⁸ To determine
4 whether these findings were due to cohort specific effects, we conducted a separate
5 cross-sectional multimodal PET imaging study of 23 PD subjects. Inclusion criteria
6 included age ≥ 45 , a diagnosis of PD as determined by the UK Parkinson's Disease
7 Society Brain Bank Clinical diagnostic criteria,¹⁹ no evidence of atypical parkinsonism or
8 neuroleptic-associated PD, no contraindications to undergo magnetic resonance
9 imaging (MRI) such as indwelling metal hardware in the body, and no exposure to
10 serotonergic medications, anticholinergic medications, or cholinesterase inhibitors in
11 the last 2 months. This study was reviewed by the University of Michigan IRBMED and
12 all subjects signed informed consent prior to study enrollment.

13 Regional serotonin terminal density was assessed with the serotonin transporter
14 PET ligand [¹¹C]3-amino-4-(2-dimethylaminomethyl-phenylsulfaryl)-benzonitrile (DASB)
15 and cerebral amyloid plaque deposition was measured with [¹¹C]Pittsburgh compound B
16 (PiB) PET as described previously.¹⁸ For 22 of the 23 subjects all MRI, DASB, and PiB
17 PET scans took place within 1 week of each other. In one subject, the DASB and PiB
18 scans were separated by 41 days. All PET studies were performed with bolus and
19 infusion dynamic imaging protocols. Cortical and subcortical segmentation was
20 performed with FreeSurfer version 5 in the fully automated mode. Total cortical and
21 striatal regions were used for correlation analysis. All image frames were spatially
22 coregistered within participants with a rigid-body transformation. Motion-corrected PET
23 frames were spatially coregistered to the T1-weighted MRI using standard coregistration

1 procedures in NeuroStat (<https://neurostat.neuro.utah.edu/>). Time activity curves for
2 each VOI were generated from the spatially aligned PET frames. DASB and PiB
3 distribution volume ratios (DVRs) were estimated by the Logan plot graphical analysis
4 method²⁰ with the time-activity curves as the input function and with the inferior posterior
5 cerebellum as reference tissue for both PiB and DASB. Pearson correlation coefficients
6 were used to assess the relationship of PiB and DASB DVRs in the total cortical and
7 striatal regions of interest. Using subject age, disease duration, years of education, and
8 cortical DASB DVR as covariates, we also conducted a multivariable linear regression
9 model with cortical PiB DVR as the outcome variable and a covariate significance level
10 for retention in the final model of 0.1 using a backwards-selection process. Interaction
11 terms were tested in the covariates retained in the final model and were included at a p-
12 value threshold of 0.1.

13

14 *Study 2a: Cross-sectional PPMI Baseline Analysis*

15

16 The Parkinson's Progression Markers Initiative (PPMI) is a multicenter
17 longitudinal observational study of PD (<http://www.ppmi-info.org/>). Curated PPMI
18 datasets containing A β -42 measurements, primary diagnoses, and dopamine
19 transporter (DaT) [¹²³I]loflupane single photon emission computed tomography (SPECT)
20 results were downloaded on 8/22/17. Datasets containing demographics and clinical
21 non-motor testing were downloaded between 10/10/2016 and 1/13/2017. PPMI subjects
22 underwent screening evaluations (month 0), followed by baseline evaluations (typically
23 at month 1), visit 1 evaluations (month 4), and subsequent evaluations on a scheduled

1 basis—initially at 3 month intervals and then at 6 month intervals after visit 4 (month
2 13)—through a possible visit 12 (month 61). All subjects signed informed consent upon
3 enrollment into the PPMI. This project using publically available coded PPMI data was
4 granted not-regulated status by the University of Michigan IRBMED. Analyses were
5 conducted in STATA 15 (College Station, TX) and SAS 9.4 (Cary, NC).

6 Eligible subjects for our baseline analyses were those who were coded as having
7 a primary study diagnosis of “idiopathic PD” at the time of screening visit, a screening
8 visit DaT scan evaluation, who had CSF A β -42 tested at the baseline visit and
9 documentation of serotonin medication use at the time, and who did not accrue an
10 alternative primary study diagnosis at a subsequent study visit. Figure 1 provides an
11 overview of our PPMI study cohorts. We categorized serotonergic medications to
12 include selective serotonin reuptake inhibitors (SSRIs)²¹, serotonin-norepinephrine
13 reuptake inhibitors (SNRIs)²², tricyclic antidepressants (TCAs)¹⁷, bupropion²³, lithium²⁴,
14 and St. John’s Wort²⁵ given that each of these compounds has been shown to influence
15 serotonergic neurotransmission. In this cross-sectional baseline study aimed at
16 understanding the influence of serotonin medications on CSF A β -42, we categorized
17 subjects as those taking serotonin medications for ≥ 6 months (n=45) vs. others (n=344).
18 Serotonin-medication-use was treated as a categorical variable (yes/no) and was not
19 adjusted for dosing or weight. Age was defined as the difference between year of birth
20 and year of study enrollment and disease duration was defined as the number of years
21 between when symptoms were first noticed by the subject and year of study enrollment.
22 According to the study protocol, CSF A β -42 levels²⁶ were measured at the baseline
23 visit.

1 Baseline CSF A β -42 was treated as the outcome variable of interest in a
2 multivariable linear regression using baseline cross-sectional PPMI data. Covariates
3 included serotonin medication use, age, sex, disease duration, self-reported years of
4 education, and baseline Geriatric Depression Scale (GDS) score on the 15-item GDS.
5 We aimed to control for the degree of depressive symptoms using the GDS since the
6 late-life depression is known to associate both with dementia risk and with CSF A β -42
7 burden.^{27, 28} We controlled for years of education to account for the possibility that
8 subjects receiving prescription serotonin medications might have unmeasured
9 differences in socio-economic status relative to those not on serotonin medications.

12 *Study 2b: Longitudinal PPMI Proportional Hazard Analysis*

14 We conducted a survival analysis in the PPMI cohort to explore the effects of
15 serotonergic medications on cognitive decline in PD. PD subjects who had 2 or more
16 Montreal Cognitive Assessment (MoCA) scores recorded over the duration of the study,
17 who underwent DaT SPECT at screening, and who had a screening MoCA score of >20
18 at study entry were eligible for inclusion (Figure 1).

19 We chose progression to MoCA scores of 20 or less as our endpoint given that
20 this transition value (21->20) has been previously validated against full
21 neuropsychological testing in PD as an optimal diagnostic cutoff point (as opposed to a
22 “screening” cutoff value) for meeting neuropsychological criteria of impairment in at
23 least 2 cognitive domains suggestive of dementia.²⁹ We aimed to define our MoCA

1 endpoint as manifestation of a clear stage-progression milestone, and tried to
2 differentiate this endpoint from a transient drop in scoring that might improve at the next
3 visit. Subsequently, we defined our endpoint as having been met if a subject had 2 or
4 more consecutive visits with MoCA scores ≤ 20 or if their final recorded MoCA score was
5 ≤ 20 . We qualified time-to-event as the month correlating with the planned visit
6 according to the PPMI schedule of activities: screening visit (month 0), visit 4 (month
7 13), visit 6 (month 25), visit 8 (month 37), visit 10 (month 49), through visit 12 (month
8 61). To account for the possibility of missed study visits and the likelihood of that not all
9 study visits took place at the identical time interval, we conducted a survival analysis
10 using interval censoring with a Weibull proportional hazard distribution. Subjects whose
11 MoCA scores progressed from >20 at screening visit (month 0) to ≤ 20 by visit 4 (month
12 13) were identified as having progressed to the MoCA endpoint in an interval between 1
13 and 13 months in order to be categorized as interval-censored rather than left censored. All
14 other subjects were considered right censored at the time of their final recorded MoCA
15 score. Of note, an inclusion criteria for enrollment in the PPMI was that subjects were
16 “not expected to require PD medication within at least 6 months from baseline”
17 (<http://www.ppmi-info.org/study-design/>).³⁰ Subsequently, none of our longitudinal PPMI
18 subjects were on dopaminergic PD medications at study enrollment.

19 We first tested the unadjusted bivariate associations between several different
20 potential explanatory variables including the use of serotonergic medications at the
21 time of baseline evaluation (Supplementary Table 1) in separate Cox-proportional
22 hazard analyses. Next, we tested associations in a multivariable model after adjusting
23 for several baseline confounders. The nigrostriatal dopaminergic system is known to

1 play a role in PD cognitive impairment, specifically dopamine terminal loss in the
2 caudate nucleus.^{31, 32} We estimated this using mean bilateral caudate nucleus DaT
3 SPECT measurements from the PPMI.³³ We sought to control for heterogeneity in
4 baseline amyloid status by using baseline CSF A β -42 levels as a covariate as well.
5 Covariates were tested to explore the assumption of proportional hazards. To test
6 whether a serotonin-medication effect on MoCA decline might vary across drug classes
7 of differing specificity for serotonin-receptor modulation, we conducted two separate
8 sensitivity analyses where the serotonin medication use categorical variable was
9 restricted to either only those subjects taking SSRIs or those subjects taking either
10 SSRIs or TCAs.

11

12 Results

13

14 Demographic characteristics for the *Study 1* cohort are presented in Table 1. In
15 the multi-modal PET imaging study, cortical serotonergic terminal density correlated
16 inversely with cortical amyloid burden (Pearson's $r=-0.478$, $p=0.021$; Figure 2). Striatal
17 serotonergic terminal density did not significantly correlate with striatal amyloid
18 deposition (Pearson's $r=-0.264$, $p=0.224$). In our multivariable linear regression model of
19 cortical PiB DVR, disease duration and cortical DASB DVR were retained at a covariate
20 threshold of $p<0.1$. The final model ($F = 5.11$, $p = 0.0161$) showed an R^2 of 0.338 with a
21 significant association seen for cortical DASB DVR ($t=8.13$, $p = 0.0099$) and a non-
22 significant associative trend for duration of disease ($t=3.32$, $p = 0.0836$). There were no
23 significant interactions between cortical DASB DVR and disease duration.

1 In *Study 2a*, subjects on serotonin medications for at least 6 months at baseline
2 (n=45) did not differ significantly in CSF A β -42 levels from subjects not receiving
3 serotonin medications in unadjusted analyses (mean +/- SE: 348.5 pg/ml +/- 15.0 vs.
4 374.5 pg/ml +/- 5.5; t=1.62, p=0.11). After adjusting for confounders, the multivariable
5 linear regression analyses (n=389; Table 2) showed that male sex and use of serotonin
6 medications for at least 6 months both associated with lower levels of CSF A β -42 at
7 baseline. Age, disease duration, years of education, and GDS score, did not show
8 significant associations.

9 367 subjects met inclusion criteria for the survival analysis (*Study 2b*) predicting
10 time to a decline in MoCA score of ≤ 20 . Of these 367 subjects, 70 (19.1%) were using
11 serotonergic medications at the time of their baseline visit. 28 of the total 367 subjects
12 progressed to develop a MoCA score of 20 as assessed at a subsequent study visit. In
13 a bivariate Cox-proportional hazard analysis, taking a serotonergic medication at
14 baseline did not show a significant association with decline to a MoCA of ≤ 20
15 (Supplementary Table 1). Table 3 shows the results of a multivariable interval-censored
16 model controlling for the confounder effects of screening caudate nucleus DaT SPECT
17 binding ratio and baseline CSF A β -42 levels. In this model, serotonergic medication
18 use at baseline showed a protective association with reduced likelihood of MoCA
19 decline. Sensitivity analyses of this interval-censored multivariable model using
20 different definitions of serotonin-medications revealed comparable but non-significant
21 trends between both SSRI (n=49 out of 367; Hazard ratio = 0.185, SE = 0.189 [95% CI:
22 0.025, 1.372], Z=-1.65, p = 0.099) use and/or the combination of either SSRI or TCA

1 (n=54 out of 367; Hazard ratio = 0.170, SE = 0.173 [95% CI: 0.023, 1.257], Z = -1.74, p
2 = 0.083) use with the risk for MoCA decline.

3

4

5 **Discussion**

6

7 We present findings from converging lines of evidence supporting the
8 hypothesized relationship between serotonergic neurotransmission and cerebral
9 amyloid burden in PD. *Study 1* confirms our previous imaging findings of a relationship
10 between reduced serotonin terminals in the cortex and the increased severity of
11 cerebral amyloid plaque burden in PD. *Study 2a* shows an association between
12 serotonergic medication exposure for ≥ 6 months and lower CSF A β -42 levels. *Study*
13 *2b* suggests that serotonergic medication exposure at baseline is associated with a
14 reduced risk for progression to a MoCA score of ≤ 20 . Collectively, these findings
15 support the concept that serotonergic medications favorably associate and/or alter
16 cerebral A β peptide activity in PD.

17 Post-mortem studies of PD show reductions in serotonin terminal markers in
18 numerous cortical and subcortical regions.^{34, 35} Consistent with *in vivo* PET imaging
19 results, analysis of post-mortem specimens by Buddhala et al. showed that
20 serotonergic terminal loss in PD exhibits considerable variation with many PD subjects
21 exhibiting regional serotonin terminal markers levels comparable to those found in
22 control subjects and other showing marked loss of serotonin terminal markers.³⁴ PET
23 studies suggest that regional serotonin terminal loss is an early event in PD.^{10, 36} This

1 early and heterogeneous loss of serotonergic terminals may suggest a possible
2 causal role for serotonergic modulation of A β peptide generation in PD, the latter of
3 which is a later-stage disease feature that also shows substantial heterogeneity in
4 cortical plaque burden.⁵ In contrast to our initial findings, we did not find a significant
5 correlation between striatal DASB and PiB DVRs in the current cohort. This may reflect
6 stage-specific associations not seen in our cohort given that striatal amyloid burden has
7 been described more commonly in PD with advanced cognitive impairment as opposed
8 to early PD.^{37, 38} Within the range of values seen in our Study 1 cohort however, disease
9 duration did not appear to influence the association between cortical and DSAB and PiB
10 DVRs. Understanding temporal associations between early regional serotonin terminal
11 loss and progressive amyloid plaque deposition leading to local neuronal dysfunction
12 may be a fruitful goal for future PD natural history studies.

13 Our *Study 2a* analysis results indicating lower CSF A β -42 levels in PD subjects
14 taking serotonergic medications are consistent with recent preclinical and clinical data
15 suggesting that increasing serotonergic neurotransmission reduces A β peptide
16 generation. Cirrito et al demonstrated that chronic oral administration of citalopram
17 relative to placebo in an AD model mice diminished extracellular A β peptide levels and
18 led to a 62% reduction in relative cortical amyloid plaque burden after 4 months.¹¹ In a
19 retrospective analysis of 177 healthy controls, the duration of serotonin medication
20 exposure correlated with reduced cortical amyloid PET binding.¹¹ A separate
21 prospective randomized trial of young healthy adults showed that those receiving an
22 acute 60mg dose of citalopram rather than placebo experienced a 38% *reduction* over
23 about 2 days in CSF A β peptide concentrations and the kinetics of this reduction was

1 consistent with reduced A β peptide generation.¹² Although higher A β -42 CSF levels are
2 typically associated with better cognitive outcomes in PD, interpretation of A β -42 CSF
3 level data is not straightforward.

4 CSF A β -42 CSF levels likely reflect complex interactions between A β -42 peptide
5 generation, clearance, and possibly sequestration in amyloid plaques. Some evidence
6 suggests that reduced Abeta-42 levels would be consistent with reduced risk of
7 dementia. In vitro data indicates that the protective APP A673T mutation is associated
8 with reduced A β -42 generation.³⁹ Recent evidence from APP A673T mutation carriers
9 show reduced serum levels of A β -42, which is expected to correlate with CSF A β -42
10 levels.⁴⁰ Similarly, increased A β -42 generation is predicted to increase dementia risk.
11 Statistical modelling of CSF A β -42 data from autosomal dominant Alzheimer disease
12 (ADAD) mutant allele carriers followed in the Dominantly Inherited Alzheimer Network
13 (DIAN) study suggests early elevation of CSF A β -42 levels followed by decline around
14 the estimated onset of manifest disease.⁴¹ In this model, declining CSF A β -42 levels in
15 ADAD subjects is secondary to neurodegeneration causing diminished A β -42 peptide
16 generation and/or A β -42 peptide sequestration in amyloid plaques. The implication is
17 that the association between lower CSF A β -42 levels and dementia risk is a
18 consequence of more advanced pathology.

19 Our finding (*Study 2b*) that baseline serotonergic medication exposure reduced
20 risk of progression to MoCA <20 is also consistent with a beneficial modulatory effect of
21 serotonergic agents on A β -42 peptide generation. Similar results were reported
22 recently in a retrospective analysis of conversion from Mild Cognitive Impairment to
23 dementia in the Alzheimer Disease Neuroimaging (ADNI) cohort.⁴² Antidepressant

1 medications were also suggested to reduce dementia incidence in analyses from
2 Kessing et al. in datasets drawn from large Danish registries of prescription drugs.^{43, 44}
3 Our sensitivity analyses did not show significant associations between SSRIs and
4 SSRIs/TCAs with time to MoCA decline. Given the relatively similar hazard ratios but
5 increased hazard ratio standard errors for the serotonin-medication-use variable in
6 these subgroup analyses, these findings may be a manifestation of an expected
7 reduction in statistical power with fewer subjects subsequently identified as having the
8 exposure of interest.⁴⁵ Alternatively, they may reflect either the possibility that non-
9 serotonin neuronal systems are preferentially involved in altering the risk or PD
10 cognitive decline or the possibility that only a low-degree of serotonin-receptor
11 modulation may be needed to yield a protective cognitive effect.

12 Serotonergic medications are used early and often in PD to treat symptoms of
13 depression, anxiety, sleep disorders, or other non-motor features. In the PPMI cohort,
14 about 20% of subjects were on serotonergic medications at baseline. A community-
15 based PD registry study in Sweden estimated the rate to be 22% in home-dwelling
16 individuals and 50% in those residing in an institution.⁴⁶ To date, PD trials that have
17 focused on the efficacy of SSRIs, SNRIs, or TCAs, typically employed relatively short
18 study assessment periods (weeks to months) focused on symptomatic modification of
19 self-reported affective symptoms and have not measured cerebral amyloid burden.^{47, 48}
20 One post-hoc analysis of a 4-month randomized PD-antidepressant trial showed no
21 clear benefit to paroxetine or nortriptyline on cognitive performance relative to placebo
22 but was limited to a small sample size and short follow-up duration.⁴⁹ The possible
23 beneficial effect of certain TCAs on amyloid-linked cognitive decline may also be

1 confounded by their anticholinergic properties. A systematic review by Moraros et al.
2 investigated the association between antidepressant drugs and dementia risk and found
3 a higher unadjusted dementia risk in subjects initiated on antidepressants before age
4 65.⁵⁰ These findings are likely to be influenced by the severity and variable causes of
5 comorbid depression. They do, however, raise the possibility that there may exist a
6 critical time window for serotonin-neurodegeneration-induced acceleration of cerebral
7 amyloid burden. This may be relevant for the design of future interventional studies. Our
8 *Study 2b* clinical findings would benefit from validation not only in other PD cohorts but
9 also in prospective longitudinal studies of aging that could control for drug class and
10 dosing.

11 Limitations of our study include the possibility of differential censoring. Only a
12 small fraction of eligible subjects progressed to a MoCA score of 20 or less, raising the
13 possibility that some subjects with declining cognition might have been lost to follow-up
14 and would thereby not be captured in this dataset. It is possible that such censoring
15 occurred and may influence these data. Subjects enrolled in the PPMI may represent a
16 skewed population given that their parkinsonian symptoms were not severe enough to
17 require the use of dopaminergic medications at the time of enrollment. This cohort factor
18 may limit the generalizability of our findings. Because of power concerns, we were not
19 able to control for a greater number of covariates given the limited number of subjects
20 who did progress to the MoCA endpoint. Some PPMI subjects showed variability in
21 MoCA scoring from one visit to the next. We chose our endpoint specifically for purpose
22 of accurately identifying newly developed probable dementia rather than as a screening
23 cut-off for subjects at risk for dementia. This effort to more precisely define a cognitive

1 state transition endpoint limited the number of PPMI subjects who met our primary
2 endpoint. This trade-off, however, comes with improved precision as it relates to our
3 assessment of baseline risk factors associated with longitudinal cognitive decline. Our
4 previously published cross-sectional DASB-PiB PD PET imaging cohort¹⁸ had an even
5 higher mean age (68.38) and lower mean MoCA (24.3) than the 23 subject imaging
6 cohort in Study 1. In the present analyses, subjects enrolled in Study 1 were older, had
7 longer disease duration, and lower MoCA scores than subjects in the PPMI. This may
8 limit how translatable findings from Study 1 are to the cohort in Study 2 and vice versa.
9 On the other hand, these findings may also collectively shed light into different aspects
10 of the natural history of serotonergic neurodegeneration across different disease
11 stages in PD.

12 We acknowledge that our findings do not directly test the protective causal
13 mechanism that we hypothesize exists between serotonergic medications, alpha-
14 secretase activity, and the degree of cerebral amyloid burden in PD. It is possible that
15 subjects in this cohort receiving serotonergic medications from their personal
16 clinicians may have other unmeasured factors that influence amyloid burden and/or
17 cognition, including severity and subtypes of affective symptoms or factors that
18 associate with greater access to care and prescription medications. Given the wide
19 variety, dosing, and duration of use of serotonergic medications by subjects, we were
20 not able to explore a dose-response relationship.

21 Developing treatments for different causes of cerebral amyloid burden is a goal
22 relevant not only to PD but to a majority of patients affected by neurodegenerative
23 diseases. Our PD findings are strengthened by the multi-center nature of the PPMI but

1 would benefit from replication in other representative PD datasets. Serotonergic
2 medications are well tolerated in PD patients and trials of SSRIs targeted against
3 cerebral amyloid burden merit consideration for future PD clinical trials. Such trials
4 might be usefully enhanced by use of serotonin terminal imaging to select or stratify the
5 subject population.

6

7

8

9 **Acknowledgements**

10 We thank all study participants who generously donated their time and effort.

11

12 **Author contributions**

13 VK, RLA, and NIB designed the study, VK, CS, RLA, and RAK acquired and analyzed
14 the data. VK, NIB, and RLA drafted the manuscript which was reviewed and revised by
15 all coauthors.

16

17

18 **Potential Conflicts of Interest**

19 None to report

20

21

22

23

24

25

26

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23

References

1. Aarsland D, Creese B, Politis M, et al. Cognitive decline in Parkinson disease. *Nature reviews Neurology*. 2017 Apr;13(4):217-31.
2. Petrou M, Bohnen NI, Muller ML, Koeppe RA, Albin RL, Frey KA. Abeta-amyloid deposition in patients with Parkinson disease at risk for development of dementia. *Neurology*. 2012 Sep 11;79(11):1161-7.
3. Rochester L, Galna B, Lord S, et al. Decrease in Abeta42 predicts dopa-resistant gait progression in early Parkinson disease. *Neurology*. 2017 Apr 18;88(16):1501-11.
4. Muller ML, Frey KA, Petrou M, et al. beta-Amyloid and postural instability and gait difficulty in Parkinson's disease at risk for dementia. *Movement disorders : official journal of the Movement Disorder Society*. 2013 Mar;28(3):296-301.
5. Petrou M, Dwamena BA, Foerster BR, et al. Amyloid deposition in Parkinson's disease and cognitive impairment: a systematic review. *Movement disorders : official journal of the Movement Disorder Society*. 2015 Jun;30(7):928-35.

- 1 6. Terrelonge M, Jr., Marder KS, Weintraub D, Alcalay RN. CSF beta-Amyloid 1-42
2 Predicts Progression to Cognitive Impairment in Newly Diagnosed Parkinson Disease.
3 Journal of molecular neuroscience : MN. 2016 Jan;58(1):88-92.
- 4 7. Brockmann K, Lerche S, Dilger SS, et al. SNPs in Abeta clearance proteins:
5 Lower CSF Abeta1-42 levels and earlier onset of dementia in PD. Neurology. 2017 Nov
6 08.
- 7 8. Johar I, Mollenhauer B, Aarsland D. Cerebrospinal Fluid Biomarkers of Cognitive
8 Decline in Parkinson's Disease. International review of neurobiology. 2017;132:275-94.
- 9 9. Albin RL, Koeppe RA, Bohnen NI, Wernette K, Kilbourn MA, Frey KA. Spared
10 caudal brainstem SERT binding in early Parkinson's disease. Journal of cerebral blood
11 flow and metabolism : official journal of the International Society of Cerebral Blood Flow
12 and Metabolism. 2008 Mar;28(3):441-4.
- 13 10. Pagano G, Niccolini F, Fusar-Poli P, Politis M. Serotonin transporter in
14 Parkinson's disease: A meta-analysis of positron emission tomography studies. Annals
15 of neurology. 2017 Feb;81(2):171-80.
- 16 11. Cirrito JR, Disabato BM, Restivo JL, et al. Serotonin signaling is associated with
17 lower amyloid-beta levels and plaques in transgenic mice and humans. Proceedings of
18 the National Academy of Sciences of the United States of America. 2011 Sep
19 06;108(36):14968-73.
- 20 12. Sheline YI, West T, Yarasheski K, et al. An antidepressant decreases CSF Abeta
21 production in healthy individuals and in transgenic AD mice. Science translational
22 medicine. 2014 May 14;6(236):236re4.

- 1 13. Brenn A, Grube M, Jedlitschky G, et al. St. John's Wort reduces beta-amyloid
2 accumulation in a double transgenic Alzheimer's disease mouse model-role of P-
3 glycoprotein. *Brain Pathol.* 2014 Jan;24(1):18-24.
- 4 14. Nitsch RM, Deng M, Growdon JH, Wurtman RJ. Serotonin 5-HT_{2a} and 5-HT_{2c}
5 receptors stimulate amyloid precursor protein ectodomain secretion. *The Journal of*
6 *biological chemistry.* 1996 Feb 23;271(8):4188-94.
- 7 15. Postina R. Activation of alpha-secretase cleavage. *Journal of neurochemistry.*
8 2012 Jan;120 Suppl 1:46-54.
- 9 16. Lezoualc'h F. 5-HT₄ receptor and Alzheimer's disease: the amyloid connection.
10 *Experimental neurology.* 2007 Jun;205(2):325-9.
- 11 17. Li X, Wang Q, Hu T, et al. A tricyclic antidepressant, amoxapine, reduces
12 amyloid-beta generation through multiple serotonin receptor 6-mediated targets.
13 *Scientific reports.* 2017 Jul 10;7(1):4983.
- 14 18. Kotagal V, Bohnen NI, Muller ML, Koeppe RA, Frey KA, Albin RL. Cerebral
15 amyloid deposition and serotonergic innervation in Parkinson disease. *Archives of*
16 *neurology.* 2012 Dec;69(12):1628-31.
- 17 19. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of
18 idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *Journal of*
19 *neurology, neurosurgery, and psychiatry.* 1992 Mar;55(3):181-4.
- 20 20. Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL. Distribution
21 volume ratios without blood sampling from graphical analysis of PET data. *Journal of*
22 *cerebral blood flow and metabolism : official journal of the International Society of*
23 *Cerebral Blood Flow and Metabolism.* 1996 Sep;16(5):834-40.

- 1 21. Dempsey CM, Mackenzie SM, Gargus A, Blanco G, Sze JY. Serotonin (5HT),
2 fluoxetine, imipramine and dopamine target distinct 5HT receptor signaling to modulate
3 *Caenorhabditis elegans* egg-laying behavior. *Genetics*. 2005 Mar;169(3):1425-36.
- 4 22. Wong DT. Duloxetine (LY 248686): an inhibitor of serotonin and noradrenaline
5 uptake and an antidepressant drug candidate. *Expert opinion on investigational drugs*.
6 1998 Oct;7(10):1691-9.
- 7 23. Pandhare A, Pappu AS, Wilms H, Blanton MP, Jansen M. The antidepressant
8 bupropion is a negative allosteric modulator of serotonin type 3A receptors.
9 *Neuropharmacology*. 2017 Feb;113(Pt A):89-99.
- 10 24. Januel D, Massot O, Poirier MF, Olie JP, Fillion G. Interaction of lithium with 5-
11 HT(1B) receptors in depressed unipolar patients treated with clomipramine and lithium
12 versus clomipramine and placebo: preliminary results. *Psychiatry research*. 2002 Aug
13 30;111(2-3):117-24.
- 14 25. Butterweck V, Nahrstedt A, Evans J, et al. In vitro receptor screening of pure
15 constituents of St. John's wort reveals novel interactions with a number of GPCRs.
16 *Psychopharmacology*. 2002 Jul;162(2):193-202.
- 17 26. Kang JH, Irwin DJ, Chen-Plotkin AS, et al. Association of cerebrospinal fluid
18 beta-amyloid 1-42, T-tau, P-tau181, and alpha-synuclein levels with clinical features of
19 drug-naïve patients with early Parkinson disease. *JAMA neurology*. 2013
20 Oct;70(10):1277-87.
- 21 27. Defrancesco M, Marksteiner J, Kemmler G, Fleischhacker WW, Blasko I,
22 Deisenhammer EA. Severity of Depression Impacts Imminent Conversion from Mild

- 1 Cognitive Impairment to Alzheimer's Disease. *Journal of Alzheimer's disease* : JAD.
2 2017;59(4):1439-48.
- 3 28. Nascimento KK, Silva KP, Malloy-Diniz LF, Butters MA, Diniz BS. Plasma and
4 cerebrospinal fluid amyloid-beta levels in late-life depression: A systematic review and
5 meta-analysis. *Journal of psychiatric research*. 2015 Oct;69:35-41.
- 6 29. Hoops S, Nazem S, Siderowf AD, et al. Validity of the MoCA and MMSE in the
7 detection of MCI and dementia in Parkinson disease. *Neurology*. 2009 Nov
8 24;73(21):1738-45.
- 9 30. The Parkinson Progression Marker Initiative (PPMI). *Progress in neurobiology*.
10 2011 Dec;95(4):629-35.
- 11 31. Pellecchia MT, Picillo M, Santangelo G, et al. Cognitive performances and DAT
12 imaging in early Parkinson's disease with mild cognitive impairment: a preliminary study.
13 *Acta neurologica Scandinavica*. 2015 May;131(5):275-81.
- 14 32. Marquie M, Locascio JJ, Rentz DM, et al. Striatal and extrastriatal dopamine
15 transporter levels relate to cognition in Lewy body diseases: an (11)C altropane positron
16 emission tomography study. *Alzheimer's research & therapy*. 2014;6(5-8):52.
- 17 33. Schrag A, Siddiqui UF, Anastasiou Z, Weintraub D, Schott JM. Clinical variables
18 and biomarkers in prediction of cognitive impairment in patients with newly diagnosed
19 Parkinson's disease: a cohort study. *The Lancet Neurology*. 2017 Jan;16(1):66-75.
- 20 34. Buddhala C, Loftin SK, Kuley BM, et al. Dopaminergic, serotonergic, and
21 noradrenergic deficits in Parkinson disease. *Annals of clinical and translational
22 neurology*. 2015 Oct;2(10):949-59.

- 1 35. Ogawa T, Matson WR, Beal MF, et al. Kynurenine pathway abnormalities in
2 Parkinson's disease. *Neurology*. 1992 Sep;42(9):1702-6.
- 3 36. Politis M, Wu K, Loane C, et al. Staging of serotonergic dysfunction in
4 Parkinson's disease: an in vivo 11C-DASB PET study. *Neurobiology of disease*. 2010
5 Oct;40(1):216-21.
- 6 37. Kalaitzakis ME, Walls AJ, Pearce RK, Gentleman SM. Striatal Abeta peptide
7 deposition mirrors dementia and differentiates DLB and PDD from other parkinsonian
8 syndromes. *Neurobiology of disease*. 2011 Feb;41(2):377-84.
- 9 38. Shah N, Frey KA, Muller ML, et al. Striatal and Cortical beta-Amyloidopathy and
10 Cognition in Parkinson's Disease. *Movement disorders : official journal of the Movement
11 Disorder Society*. 2016 Jan;31(1):111-7.
- 12 39. Maloney JA, Bainbridge T, Gustafson A, et al. Molecular mechanisms of
13 Alzheimer disease protection by the A673T allele of amyloid precursor protein. *The
14 Journal of biological chemistry*. 2014 Nov 7;289(45):30990-1000.
- 15 40. Martiskainen H, Herukka SK, Stancakova A, et al. Decreased plasma beta-
16 amyloid in the Alzheimer's disease APP A673T variant carriers. *Annals of neurology*.
17 2017 Jul;82(1):128-32.
- 18 41. Fagan AM, Xiong C, Jasielec MS, et al. Longitudinal change in CSF biomarkers
19 in autosomal-dominant Alzheimer's disease. *Science translational medicine*. 2014 Mar
20 5;6(226):226ra30.
- 21 42. Bartels C, Wagner M, Wolfsgruber S, Ehrenreich H, Schneider A. Impact of SSRI
22 Therapy on Risk of Conversion From Mild Cognitive Impairment to Alzheimer's

- 1 Dementia in Individuals With Previous Depression. *The American journal of psychiatry*.
2 2017 Nov 28;appiajp201717040404.
- 3 43. Kessing LV, Forman JL, Andersen PK. Do continued antidepressants protect
4 against dementia in patients with severe depressive disorder? *International clinical*
5 *psychopharmacology*. 2011 Nov;26(6):316-22.
- 6 44. Kessing LV, Sondergard L, Forman JL, Andersen PK. Antidepressants and
7 dementia. *Journal of affective disorders*. 2009 Sep;117(1-2):24-9.
- 8 45. Hajian-Tilaki K. Sample size estimation in epidemiologic studies. *Caspian journal*
9 *of internal medicine*. 2011 Fall;2(4):289-98.
- 10 46. Haasum Y, Fastbom J, Johnell K. Use of antidepressants in Parkinson's disease:
11 A Swedish register-based study of over 1.5 million older people. *Parkinsonism & related*
12 *disorders*. 2016 Jun;27:85-8.
- 13 47. Menza M, Dobkin RD, Marin H, et al. A controlled trial of antidepressants in
14 patients with Parkinson disease and depression. *Neurology*. 2009 Mar 10;72(10):886-
15 92.
- 16 48. Richard IH, McDermott MP, Kurlan R, et al. A randomized, double-blind, placebo-
17 controlled trial of antidepressants in Parkinson disease. *Neurology*. 2012 Apr
18 17;78(16):1229-36.
- 19 49. Dobkin RD, Menza M, Bienfait KL, et al. The impact of antidepressant treatment
20 on cognitive functioning in depressed patients with Parkinson's disease. *The Journal of*
21 *neuropsychiatry and clinical neurosciences*. 2010 Spring;22(2):188-95.
- 22 50. Moraros J, Nwankwo C, Patten SB, Mousseau DD. The association of
23 antidepressant drug usage with cognitive impairment or dementia, including Alzheimer

1 disease: A systematic review and meta-analysis. Depression and anxiety. 2017
2 Mar;34(3):217-26.

3

4

5

Author Manuscript

Table 1: Subjects Characteristics

	Study 1: PD PET imaging cohort	Study 2a: PPMI Cross-sectional Baseline cohort	Study 2b: PPMI Longitudinal cohort
	Mean (SD) [min-max] or Count (%)		
N	23	389	367
Baseline Age in years	66.2 (6.7) [48-79]	61.8 (9.6) [34-85]	61.7 (9.7) [34-85]
Male Sex	17 (74%)	253 (65%)	238 (65%)
Disease Duration in years	4.9 (4.1) [1-12]	1.9 (2.0) [0-21]	1.9 (2.0) [0-21]
Hoehn and Yahr score	HY1=6 HY2 =15 HY3 =2	HY1=191 HY2=198	HY1=180 HY2=187
Years of education	16.9 (3.1) [12-25]	15.6 (3.0) [5-26]	15.5 (2.9) [5-26]
Montreal Cognitive Assessment (MoCA) Score at Screening	25.6 (2.4) [20-29]	27.2 (2.3) [17-30]	27.2 (2.1) [21-30]
Final MoCA Score at the time of event/censoring	NA	NA	26.4 (3.3) [15-31]
Mean absolute decline in MoCA score between screening and final score at the time of event/censoring	NA	NA	0.8 (3.0) [-6 - +13]
Geriatric Depression score at baseline	7.2 (4.5)* [1-15]	5.1 (1.6) [0-10]	5.1 (1.6) [0-10]
Cerebrospinal Fluid A β -42 (pg/ml) levels at baseline	---	371.5 (101.5) [129.2-796.5]	373.2 (102.2) [129.2-796.5]
Mean Cortical Amyloid PiB PET Distribution Volume Ratio	1.06 (0.021) [1.04-1.11]	---	---

*This score represents the 30-item Geriatric Depression Scale score, whereas the PPMI cohorts used the 15-item Geriatric Depression Scale.

NA = Not Applicable

Table 2: Baseline PPMI cross-sectional multivariable linear regression analysis (n=389)

Dependent Variable: Baseline CSF A β -42 (pg/ml); Overall Model F=2.35, p=0.0305					
Covariates	Beta	Standard Error	t-score	p-value	95% Confidence Interval for Beta values
Age in years	-0.810	0.533	-1.52	0.129	-1.859, 0.238
Male Sex	-28.971	11.002	-2.63	0.009	-50.603, -7.338
Disease duration in years	1.241	2.533	0.49	0.625	-3.740, 6.221
Years of Education	0.067	1.718	0.04	0.969	-3.311, 3.446
Geriatric Depression scale (GDS-15) score	-4.262	3.142	-1.36	0.176	-10.440, 1.915
(+) Serotonin medication status for \geq 6 months	-35.874	16.341	-2.20	0.029	-68.004, -3.745

Table 3: Study 2b Multivariable Proportional Hazard model of time to reach Montreal Cognitive Assessment Score of ≤ 20 .

Overall Model Likelihood Ratio Chi square = 22.70, $p < 0.0001$, 3 degrees of freedom					
<i>Covariates</i>	<i>Hazard Ratio</i>	<i>Standard Error</i>	<i>Z-score</i>	<i>p-value</i>	<i>95% Confidence Interval for Hazard Ratio</i>
Mean bilateral caudate DaT SPECT binding ratio at screening	0.456	0.183	-1.96	0.050	0.208, 1.000
Serotonergic medication status at baseline	0.223	0.165	-2.03	0.043	0.052, 0.952
Mean baseline A β -42 (pg/ml)	0.993	0.002	-3.25	0.001	0.989, 0.997

Figure 1: Diagram of subject selection from Parkinson's Progression Markers Initiative (PPMI)

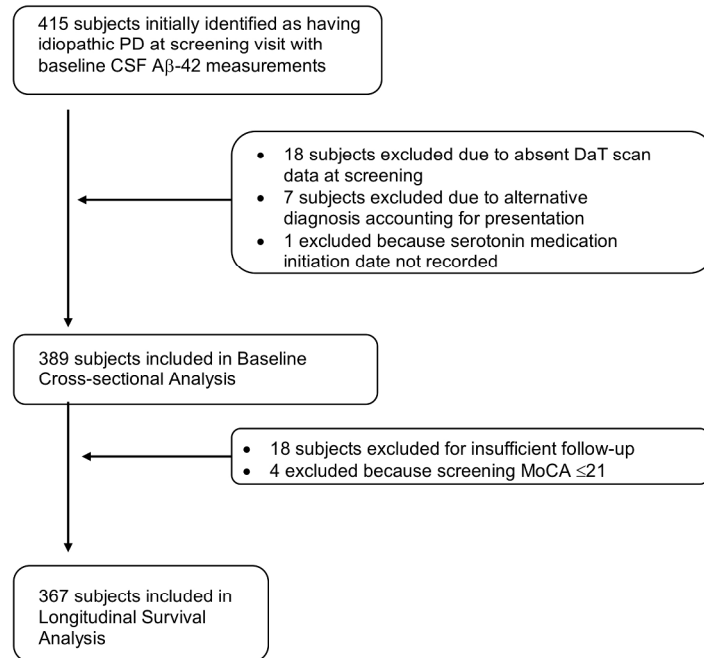


Figure 1: Diagram of subject selection from Parkinson's Progression Markers Initiative (PPMI)

215x279mm (300 x 300 DPI)

AU

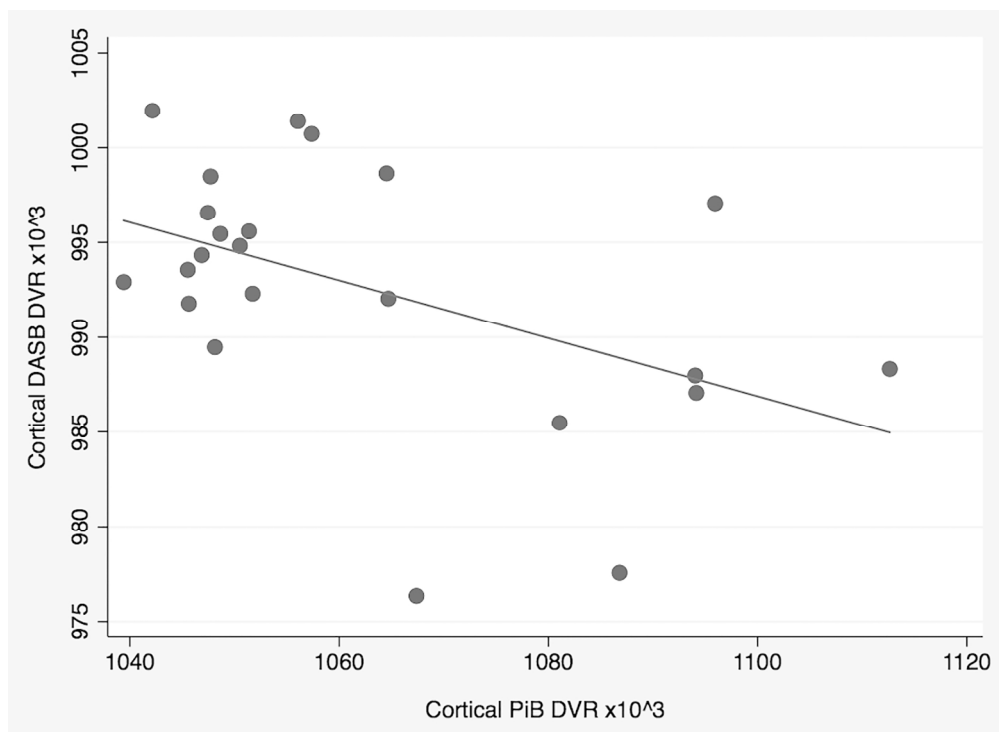


Figure 2: Cortical PiB (amyloid) vs DASB (serotonin) PET DVR (n=23)

190x138mm (300 x 300 DPI)

Author |

Supplementary Materials

Supplementary Table 1: Exploratory Independent Cox-proportional hazard models testing bivariate associations with time to reach Montreal Cognitive Assessment score of ≤ 20 .

<i>Independent Variables each tested in separate models</i>	<i>Hazard Ratio</i>	<i>Standard Error</i>	<i>Z-score</i>	<i>p-value</i>	<i>95% Confidence Interval for Hazard Ratio</i>
Age in years	1.114	0.0273	4.41	<0.001	1.062, 1.169
Male Sex	2.316	1.144	1.70	0.089	0.880, 6.096
Disease duration in years	1.015	0.095	0.16	0.873	0.845, 1.220
Years of Education	0.996	0.0674	-0.06	0.950	0.872, 1.137
Baseline Geriatric Depression scale (GDS-15) score	0.990	0.116	-0.09	0.930	0.786, 1.246
(+) Serotonin medication at baseline	0.329	0.241	-1.51	0.130	0.078, 1.386
Mean bilateral caudate DaT SPECT binding ratio at screening	0.415	0.157	-2.32	0.020	0.197, 0.871
Mean baseline A β -42 (pg/ml)	0.992	0.002	-3.60	<0.001	0.988, 0.996

Table 1: Subjects Characteristics

	Study 1: PD PET imaging cohort	Study 2a: PPMI Cross-sectional Baseline cohort	Study 2b: PPMI Longitudinal cohort
	Mean (SD) [min-max] or Count (%)		
N	23	389	367
Baseline Age in years	66.2 (6.7) [48-79]	61.8 (9.6) [34-85]	61.7 (9.7) [34-85]
Male Sex	17 (74%)	253 (65%)	238 (65%)
Disease Duration in years	4.9 (4.1) [1-12]	1.9 (2.0) [0-21]	1.9 (2.0) [0-21]
Hoehn and Yahr score	HY1=6 HY2 =15 HY3 =2	HY1=191 HY2=198	HY1=180 HY2=187
Years of education	16.9 (3.1) [12-25]	15.6 (3.0) [5-26]	15.5 (2.9) [5-26]
Montreal Cognitive Assessment (MoCA) Score at Screening	25.6 (2.4) [20-29]	27.2 (2.3) [17-30]	27.2 (2.1) [21-30]
Final MoCA Score at the time of event/censoring	NA	NA	26.4 (3.3) [15-31]
Mean absolute decline in MoCA score between screening and final score at the time of event/censoring	NA	NA	0.8 (3.0) [-6 - +13]
Geriatric Depression score at baseline	7.2 (4.5)* [1-15]	5.1 (1.6) [0-10]	5.1 (1.6) [0-10]
Cerebrospinal Fluid A β -42 (pg/ml) levels at baseline	---	371.5 (101.5) [129.2-796.5]	373.2 (102.2) [129.2-796.5]
Mean Cortical Amyloid PiB PET Distribution Volume Ratio	1.06 (0.021) [1.04-1.11]	---	---

*This score represents the 30-item Geriatric Depression Scale score, whereas the PPMI cohorts used the 15-item Geriatric Depression Scale.

NA = Not Applicable

Table 2: Baseline PPMI cross-sectional multivariable linear regression analysis (n=389)

Dependent Variable: Baseline CSF A β -42 (pg/ml); Overall Model F=2.35, p=0.0305					
Covariates	Beta	Standard Error	t-score	p-value	95% Confidence Interval for Beta values
Age in years	-0.810	0.533	-1.52	0.129	-1.859, 0.238
Male Sex	-28.971	11.002	-2.63	0.009	-50.603, -7.338
Disease duration in years	1.241	2.533	0.49	0.625	-3.740, 6.221
Years of Education	0.067	1.718	0.04	0.969	-3.311, 3.446
Geriatric Depression scale (GDS-15) score	-4.262	3.142	-1.36	0.176	-10.440, 1.915
(+) Serotonin medication status for \geq 6 months	-35.874	16.341	-2.20	0.029	-68.004, -3.745

Table 3: Study 2b Multivariable Proportional Hazard model of time to reach Montreal Cognitive Assessment Score of ≤ 20 .

Overall Model Likelihood Ratio Chi square = 22.70, $p < 0.0001$, 3 degrees of freedom					
<i>Covariates</i>	<i>Hazard Ratio</i>	<i>Standard Error</i>	<i>Z-score</i>	<i>p-value</i>	<i>95% Confidence Interval for Hazard Ratio</i>
Mean bilateral caudate DaT SPECT binding ratio at screening	0.456	0.183	-1.96	0.050	0.208, 1.000
Serotonergic medication status at baseline	0.223	0.165	-2.03	0.043	0.052, 0.952
Mean baseline A β -42 (pg/ml)	0.993	0.002	-3.25	0.001	0.989, 0.997