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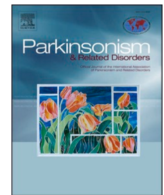

The relationship between plasma biomarkers and amyloid PET in dementia with Lewy bodies

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A R T I C L E I N F O

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A B S T R A C T

Introduction: Amyloid-β (Aβ) deposition is common in dementia with Lewy bodies (DLB) and has been associated with more rapid disease progression. An effective biomarker that identified the presence of significant brain Aβ in people with DLB may be useful to identify and stratify participants for research studies and to inform prognosis in clinical practice. Plasma biomarkers are emerging as candidates to fulfil this role.
Methods: Thirty-two participants with DLB had brain amyloid (18F-florbetapir) PET, of whom 27 also had an MRI to enable the calculation of 18F-florbetapir SUVR. Plasma Aβ42/40, phosphorylated tau (p-tau181), glial fibrillary acidic protein (GFAP) and neurofilament light (NfL) were measured using single molecule array (Simoa). The plasma biomarkers were investigated for correlation with 18F-florbetapir SUVR, discriminant ability to identify Aβ-positive cases based on a predefined SUVR threshold of 1.10 and correlation with subsequent cognitive decline over one year.
Results: All four plasma markers significantly correlated with 18F-florbetapir SUVR ($|\beta| = 0.40$-0.49; $p < .05$). NfL had the greatest area under the receiver operating characteristic curve to identify Aβ-positive cases (AUROC 0.84 (95% CI 0.66, 1); $\beta = 0.46$, $p = .001$), whereas Aβ42/40 had the smallest (AUROC 0.73 (95% CI 0.52, 0.95); $\beta = -0.47$, $p = .01$). Accuracy was highest when combining all four biomarkers (AUROC 0.92 (95% CI 0.80, 1)). Lower plasma Aβ42/40 was significantly associated with more rapid decline in cognition ($\beta = 0.53$, $p < .01$).
Conclusions: Plasma biomarkers have the potential to identify Aβ deposition in DLB. Further work in other cohorts is required to determine and validate optimal cut-offs for these biomarkers.

1. Introduction

The characteristic pathological findings in dementia with Lewy bodies (DLB) are Lewy bodies and Lewy neurites. Many people with DLB also have comorbid Alzheimer's disease pathology, and the presence of AD pathology has been associated with differences in clinical symptoms and rates of disease progression [1–3]. As a result, targeting amyloid-β (Aβ), phosphorylated-tau (p-tau) or the interactions between these proteins and α-synuclein [4,5] are seen as viable targets for disease-modifying treatments in DLB.

The advent of plasma biomarkers for Aβ and p-tau, along with other markers of neurodegeneration such as neurofilament light (NfL) presents an opportunity to investigate the relationships between these biomarkers and clinical and imaging measures of disease progression [6]. It also raises the possibility that these markers could be used to stratify participants for treatment trials targeting specific proteins. In order to do this, it must be demonstrated that plasma markers accurately reflect the presence or absence of the relevant protein in the brain. There

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is growing evidence for this in Alzheimer's disease [7].

Data reporting plasma biomarker levels in DLB are also beginning to emerge. Plasma NfL and glial fibrillary acidic protein (GFAP) were found to be raised in Lewy body dementia (DLB and Parkinson's disease dementia) compared with controls, whereas plasma Aβ42/40 ratio did not differ between Lewy body dementia and controls [8]. Plasma p-tau181 in DLB was greater than controls and lower than AD [9], with a similar pattern observed in MCI-LB [10]. In DLB, plasma p-tau181 was particularly high in cases with abnormal CSF Aβ42 levels, and was also associated with more rapid cognitive decline [9].

The aims of the current study were as follows, to:

1. Investigate the correlation between plasma biomarkers (plasma Aβ42/40, p-tau181, GFAP and NfL) and 18F-florbetapir PET in DLB
2. Examine the discriminant ability of these markers to identify Aβ-positive and -negative DLB cases
3. Determine the relationship between these biomarkers and cognitive decline

2. Methods

2.1. Participants

The methods for recruitment, assessment and imaging have been outlined previously [1,11] and will be summarised here.

Participants ≥60 years old were recruited prospectively from June 2013 to February 2016 from secondary care services in the North East of England and Cumbria. All participants had a diagnosis of probable DLB confirmed by two clinicians based on contemporaneous criteria [12] and had an MMSE ≥12. All participants also fulfilled the most recent revised diagnostic criteria for probable DLB [13]. Participants were not included if they had a major concurrent psychiatric illness, severe physical illness, a history of clinical stroke or significant neurological illness or experimental treatment with Aβ targeting or other disease modifying agents.

Participants with mental capacity gave their written informed consent to take part in the study. For those with dementia who lacked capacity, their participation in the study was discussed with a consultee in accordance with the Mental Capacity Act (UK). The study received ethical approval from the National Research Ethics Service Committee North East—Newcastle & North Tyneside 2 (Research Ethics Committee Identification Number 13/NE/0064).

2.2. Clinical assessment, imaging and image analysis

Clinical assessment took place at baseline and one year and included the MMSE.

PET imaging was carried out using a Siemens Biograph-40 PET-CT scanner. A 15-min scan was undertaken, commencing 30–50 min after intravenous injection of 370MBq 18F-florbetapir (Amyvid, Avid/Eli Lilly, Cork). MRI scans were performed on all patients unless contra-indicated (n = 5) using a Philips Achieva 3T scanner (Philips Medical Systems, Eindhoven) with body coil transmission and 8-channel head-coil receiver. Acquisitions included 3D sagittal magnetisation-prepared rapid gradient echo (MPRAGE) as described previously [11].

The amyloid PET image was co-registered with the native space MRI. A mean cortical standardized uptake value ratio (SUVR) was derived from the unweighted mean of frontal, temporal, parietal, and cingulate regions relative to the whole cerebellum [14]. A threshold of 1.10 was used to define Aβ positivity [15].

2.3. Blood sampling, storage and analysis

Venous blood samples were collected in EDTA tubes, centrifuged and plasma samples were aliquoted and stored at −80 °C. Plasma samples were analysed as part of a larger cohort using Single molecule array (Simoa) at the UK Dementia Research Institute Biomarker Laboratory as reported previously [8]. Analysis was undertaken using a Simoa-HD1 analyser and the Quanterix Simoa Human Neurology 4-Plex E (Aβ40, Aβ42, GFAP and NfL) and p-tau181 assays (Quanterix Corp, Billerica, Massachusetts, USA). All samples were analysed at the same time using the same batch of reagents. The mean coefficients of variation were as follows: Aβ42 3.06%, Aβ40 2.55%, p-tau181 6.29%, GFAP 4.12% and NfL 4.08%.

2.4. Statistical Analysis

Statistical analysis was carried out using IBM SPSS Statistics software (version 25; http://www-03.ibm.com/software/products/en/spss-statistics). Plasma biomarker assays were not normally distributed. The following measures achieved normality: Square AB42/40 ratio, log p-tau181, log GFAP, log(log NFL). Unadjusted Pearson's correlations and linear regression including age and sex as covariates were undertaken to compare plasma biomarker levels with 18F-florbetapir SUVR. Years in education was also included as a covariate in the analysis of cognitive decline. The ability of plasma biomarkers to discriminate between Aβ-positive and -negative participants based on the SUVR threshold of 1.10 was analysed using the Area Under the Receiver Operating Characteristic (AUROC). Sensitivity and specificity were determined for each biomarker using discriminant analysis where each participant was classified based on a function derived from all other participants except that individual.

Following this, all four biomarkers were entered into a discriminant analysis. A discriminant function was defined for the whole group. Individual discriminant scores for this function were used to derive an AUROC for the combined biomarker. Sensitivity and specificity were again determined based on a function derived from all other participants excluding the individual to be classified.

3. Results

The demographics of the cohort and plasma biomarker levels are displayed in Supplementary Table 1. Plasma biomarkers were measured in 32 participants with DLB, of whom 27 had 18F-florbetapir SUVR data and 26 had longitudinal MMSE data.

18F-florbetapir SUVR was inversely correlated with plasma Aβ42/40 and positively correlated with plasma phosphorylated tau181, GFAP and NfL (Table 1, Fig. 1). The strength of correlation was very similar across the four biomarkers.

Based on an SUVR cut-off of 1.10, 16 participants were Aβ-positive and 11 were Aβ-negative. The potential for plasma biomarkers to differentiate between Aβ-positive and -negative participants was investigated. NfL had the greatest AUROC (0.84; 95% CI 0.66, 1; sensitivity 75%, specificity 82%; Table 1). Combining the four biomarkers resulted in a numerically greater AUROC compared with NfL alone (AUROC 0.92; 95%CI 0.80, 1; sensitivity 81%, specificity 82%).

3.1. Correlation between plasma biomarkers

P-tau181, GFAP and NFL were all positively correlated with each other. The strongest correlation was between GFAP and NFL ($r = .67$, $p < .001$). Aβ42/40 correlated inversely with GFAP, but did not correlate significantly with p-tau181 or NfL (Table 2).

3.2. Correlation of plasma biomarkers with clinical progression

Plasma Aβ42/40 and the combined biomarker correlated with cognitive decline over one year measured by the MMSE with age, sex and years in education included as covariates (Table 3). Lower plasma Aβ42/40 (which is associated with increased brain Aβ deposition) was associated with more rapid decline ($\beta = 0.53$, 95% CI 0.19, 0.86, $p = .004$). The other individual biomarkers did not correlate with cognitive decline.

Table 1
Comparison of plasma biomarkers with 18F-florbetapir PET SUVR.

	Correlation				Discrimination			
	Unadjusted		Adjusted					
	R	p	Beta (95% CI)	P	AUROC (95% CI)	P	Sens (%)	Spec (%)
Square Aβ42/40	−.58	.002	−.47 (−.79, −.15)	.01	.73 (.52, .95)	.04	75	64
log p-tau181	.58	.001	.40 (.04, .77)	.03	.82 (.66, .98)	.01	69	64
log GFAP	.60	.001	.49 (.17, .81)	.004	.81 (.62, 1)	.01	81	73
log(log NfL)	.60	.001	.46 (.10, .83)	.02	.84 (.66, 1)	.004	75	82
Combined	.81	<.001	.76 (.46, 1.05)	<.001	.92 (.80, 1)	<.001	81	82

Adjusted: general linear model with age and sex as covariates. N = 27. Aβ – amyloid-β; p-tau – phosphorylated tau; GFAP – glial fibrillary acidic protein; NfL – neurofilament light; AUROC – area under the receiver operating characteristic; Sens – sensitivity; Spec – specificity.

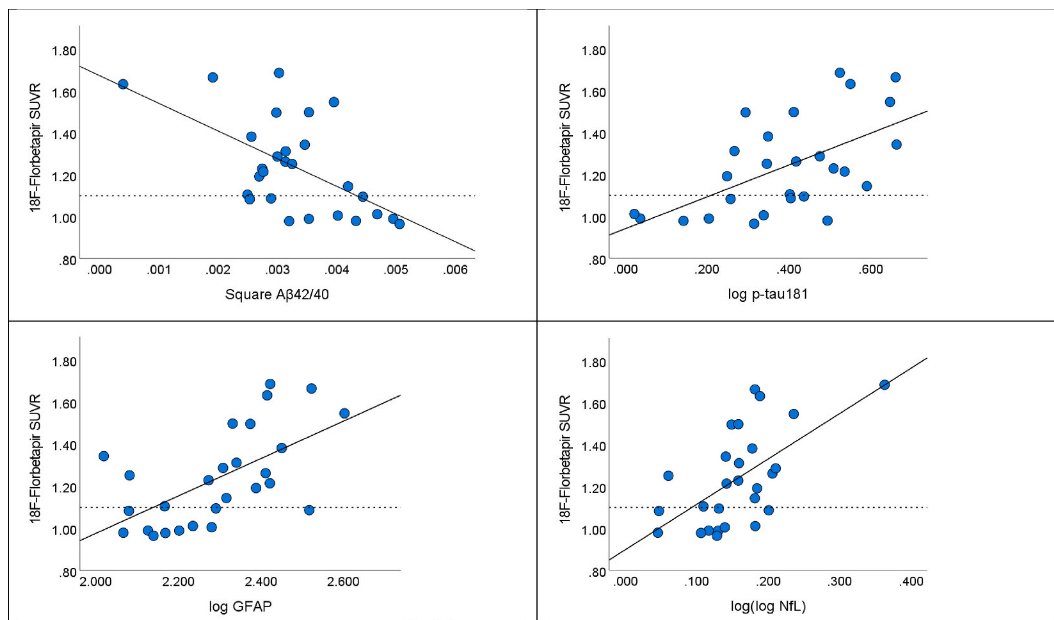

Fig. 1. Correlation between plasma biomarkers and 18F-florbetapir PET. SUVR – standardised uptake value ratio; Aβ – amyloid-β; p-tau – phosphorylated tau; GFAP – glial fibrillary acidic protein; NfL – neurofilament light. Solid line – line of best fit. Dashed line – SUVR threshold of 1.10.

Table 2
Pearson's correlation between plasma biomarkers.

	log p-tau181	log GFAP	log log NFL
Square AB42/40 ratio	−.26	−.39*	−.17
log p-tau181	–	.40*	.36*
log GFAP	–	–	.67***

*p < .05; **p < .01; ***p < .001. Aβ – amyloid-β; p-tau – phosphorylated tau; GFAP – glial fibrillary acidic protein; NfL – neurofilament light. N = 32.

Table 3
Correlation of plasma markers with change in MMSE score over 1 year.

	Unadjusted		Adjusted	
	Pearson's r	p	Beta (95% CI)	P
Square Aβ 42/40 ratio	.62	.001	.53 (.19, .86)	.004
log tau 181	−.51	.01	−.35 (−.77, .08)	.11
log GFAP	−.27	.18	−.25 (−.70, .20)	.26
log log NFL	−.24	.23	−.17 (−.57, .24)	.39
Combined	−.65	<.001	−.55 (−.93, −.17)	.01

Adjusted: general linear model with age, sex and years in education as covariates. N = 26. Aβ – amyloid-β; p-tau – phosphorylated tau; GFAP – glial fibrillary acidic protein; NfL – neurofilament light.

4. Discussion

4.1. Summary

We found that plasma Aβ42/40, p-tau181, GFAP and NfL all correlated with brain Aβ deposition measured by 18F-florbetapir PET. The magnitude of the correlation was similar for the four biomarkers ($|\beta|$ = 0.40-0.49). NfL showed the strongest discriminant ability, and Aβ42/40 the weakest, though the 95% confidence intervals overlapped for all the markers. P-tau181, GFAP and NfL all correlated with each other, and GFAP also correlated with Aβ42/40. Lower plasma Aβ42/40 was associated with more rapid cognitive decline over one year.

4.2. Correlation between plasma biomarkers and 18F-florbetapir SUVR

4.2.1. Aβ42/40

Aβ42/40 correlated with 18F-florbetapir SUVR with similar strength to the other plasma markers. Although the sample size here is insufficient to allow an adequately powered direct statistical comparison between different plasma biomarkers, the AUROC for the three other biomarkers was numerically greater than for the Aβ42/40 ratio. Plasma Aβ42/40 ratio has been shown to be reduced in Aβ-positive controls and AD, but the difference between the groups was lower than that observed for CSF Aβ42/40 and significant overlap was observed between Aβ-positive and -negative cases [7,16]. The accuracy of plasma Aβ42/40 to

differentiate between Aβ-positive and -negative PET participants in the current DLB cohort was similar previous reports using immunoassays across the AD continuum (accuracy 62–79%) [7]. Mass-spectroscopy based assays may provide better differentiation (accuracy 82–97%) [7].

4.2.2. Tau

p-Tau181 has been found to be raised in neurodegenerative diseases including Alzheimer's disease [17] and, to a lesser extent DLB [9], but not in 'pure' tauopathies, such as progressive supranuclear palsy and nonfluent primary progressive aphasia [17]. As a result, plasma p-tau181 is considered a marker of tau phosphorylation in the presence of Aβ. It has been shown to correlate with both amyloid and tau PET measures in Alzheimer's disease and Aβ-positive MCI [18] and with medial temporal tau deposition on tau PET and CSF Aβ in DLB [19]. It is unsurprising then, that p-tau181 showed correlation with ^{18}F-florbetapir SUVR in the current DLB cohort. Plasma p-tau181 has also been previously demonstrated to differentiate between Aβ-positive and -negative cases in a mixed dementia/MCI/control cohort [20] and a Lewy body dementia cohort (based on CSF measures of Aβ) [19] with similar accuracy to that reported here.

4.2.3. GFAP

Aβ and tau deposition have been found to be associated with increased GFAP expression and astrocytosis in post mortem brain tissue [21]. Increase plasma GFAP has been demonstrated in AD and Lewy body dementia [8,22]. GFAP correlated with amyloid PET in AD [22]. Here we demonstrated that GFAP was correlated with PET amyloid in DLB. The discriminant ability for plasma GFAP to identify Aβ-positive and -negative cases in DLB was similar to that reported in AD [22].

4.2.4. NfL

Neurofilament light is a non-specific marker of neurodegeneration and is raised to varying degrees in a range of diseases including HIV-related dementia, multiple sclerosis, progressive supranuclear palsy, DLB, AD and PD [23]. We have previously demonstrated that NfL is raised in Lewy body dementia [8]. Here, we demonstrate that NfL correlated with 18F-Flobetapir PET SUVR and discriminated between Aβ-positive and -negative cases in DLB. The discriminant ability is numerically greater than was reported in a mixed AD/unimpaired cohort [22].

4.3. Combined biomarkers and correlation between biomarkers

Despite the remarkable similarity in results when comparing the four biomarkers to amyloid PET (Table 1), correlation between the biomarkers was generally only moderate (Table 2). There was significant correlation between p-tau181, GFAP and NfL, but only GFAP correlated with Aβ42/40 ratio. Based on this observation we investigated whether combining the biomarkers would show increased accuracy to identify Aβ-positive and -negative cases. When all four biomarkers were combined, the AUROC increased from 0.84 (for NfL alone) to 0.92. The sample size was not sufficient to statistically compare the accuracy of the combined biomarker with the individual biomarkers.

4.4. Correlation between plasma biomarkers and cognitive decline

Aβ42/40 correlated with cognitive decline over one year measured by the MMSE. This is in keeping with other reports of a relationship between Aβ (measured using PET or CSF) and clinical progression in DLB [1,24]. We previously reported no association between Aβ42/40 and cognitive decline measured by the Addenbrooke's Cognitive Examination in a mixed group of DLB and PDD participants that included the DLB cases reported here. The difference in findings may relate to the different cognitive examinations used and heterogeneity in the larger study related to the inclusion of two diagnostic groups and participants from several different clinical studies.

There was no significant relationship between cognitive decline and p-tau181, GFAP or NfL. A small, but statistically significant association between p-tau181 and clinical progression was recently reported in a large DLB sample, though stronger correlation was found with p-tau231 [9]. The absence of significant correlation here is most likely due to the modest sample size.

4.5. Implications for research and clinical practice

An effective biomarker that differentiates Aβ-positive and -negative DLB cases could have potential uses for research and the clinic for the following purposes.

1. Identifying participants for trials of Aβ targeting therapeutics
2. Identifying participants for trials of treatment that target Aβ/α-synuclein interactions
3. Stratifying DLB participants for any trial based on prognosis
4. Advising patients on disease prognosis

A blood-based biomarker has the potential for rapid introduction to research and clinical practice. However, more research is needed to identify and validate the biomarker or biomarker panel to fulfil this need. We have shown that the relationship between Aβ and plasma biomarkers appears similar in DLB to AD. Therefore, it may be possible to use biomarkers developed in AD cohorts in DLB, after appropriate validation.

4.6. Strengths/weaknesses

This data is from a well-characterised cohort of DLB cases with state of the art measurement of plasma biomarkers using Simoa and amyloid imaging with 18F-florbetapir PET. We demonstrated a relationship between amyloid PET and plasma Aβ42/40, p-tau181, GFAP and NfL that is in keeping with the literature in Alzheimer's disease. This adds to the small, but growing literature in DLB.

Work is ongoing to determine the best plasma biomarkers in neurodegenerative disease. Other biomarkers, such as p-tau231 may have closer correlation with clinical progression in DLB [9]. Mass-spectroscopy assays may be more effective in differentiating between Aβ-positive and -negative cases than Simoa [7].

We did not undertake corrections for multiple comparisons due to the risk of missing important positive findings. As such, the findings should be regarded as exploratory. However, the fact that the positive findings identified here are in keeping with the performance of these biomarkers in AD supports the accuracy of the findings.

The good performance of a combination of biomarkers in discriminating between Aβ-positive and negative DLB requires replication in other cohorts. In general, further work is needed to identify reproducible biomarker cut-offs to identify positive and negative cases that could be applied across different cohorts and different sites.

We previously reported a larger cohort of DLB and PDD participants with 18F-florbetapir PET and 11C-Pittsburgh compound B that included the participants in the present manuscript [8]. The previous study did not analyse correlation between the plasma markers and amyloid PET SUVR or discriminant ability to identify Aβ-positive and -negative cases. The previous study found no difference between Aβ-positive and -negative cases in any of the four biomarkers tested. The ability to detect a significant difference may have been adversely impacted by heterogeneity due to the inclusion of different disease populations (PDD and DLB) in the same analysis, the fact that data from two sites were combined, potential differences in sample processing, and the inclusion of two different imaging ligands (florbetapir and PiB) and two different PET scanners.

5. Conclusions

Aβ42/40, p-tau181, GFAP and NfL all correlate with brain Aβ measured by 18F-florbetapir PET and can discriminate between Aβ-positive and -negative DLB cases. A combination of biomarkers may improve accuracy. Plasma biomarkers have potential uses in research and the clinic. Further work is required to determine optimal and reproducible cut-offs to determine the presence or absence of significant Aβ deposition in DLB.

Declarations

Dr. Donaghy reports grants from Alzheimer's Research UK, Alzheimer's Society, Lewy Body Society, Weston Brain Institute and the Medical Research Council. Dr. Firbank has nothing to disclose. Dr. Petrides reports honoraria from GE Healthcare for educational presentations and personal fees for scan reporting from GE Healthcare and Alliance Medical Limited. Dr. Lloyd has nothing to disclose. Ms Barnett has nothing to disclose. Ms Olsen has nothing to disclose. Prof. Zetterberg HZ is a Wallenberg Scholar supported by grants from the Swedish Research Council (#2018–02532), the European Research Council (#681712), Swedish State Support for Clinical Research (#ALFGBG-720931), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), the UK Dementia Research Institute at UCL (UKDRI-1003), the Wellcome Trust and an anonymous donor. He has served at scientific advisory boards and/or as a consultant for Abbvie, Alector, Annexon, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Pinteon Therapeutics, Red Abbey Labs, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). Dr Heslegrave has nothing to disclose. Prof. Thomas reports grants from Alzheimer's Research UK, Alzheimer's Society, Economic and Social Research Council, Medical Research Council, National Institute of Health Research, Lewy Body Society and GE Healthcare. Prof. O'Brien reports grants from Alzheimer's Research UK, Alzheimer's Society, Lewy Body Society, Medical Research Council, National Institute of Health Research, Avid/Lilly, Alliance Medical and Merck; personal fees from TauRx, Eisai, Axon, Biogen, Novo Nordisk, GE Healthcare and Roche; honoraria from the British Association of Psychopharmacology; Royalties from Taylor and Francis.

Author contributions

PCD – 1 A,B,C; 2 A,B,C; 3 A, MF – 1 A,B,C; 2 A,C; 3B, GP - 1 A; 2 C; 3 B, JL – 1 A; 2 C; 3 B, NB – 1 B,C; 3 B, KO – 1 B,C; 3 B, AH – 1 B,C; 2 C; 3 B, HZ – 1 B,C; 2 C; 3 B, AJT – 1 A,B; 2 C; 3 B, JTO'B – 1 A,B,C; 2 A,C; 3 B, Key: 1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique, All authors have approved the final manuscript.

Data statement

Data are available upon reasonable request via Dementias Platform UK (www.dementiasplatform.uk).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2022.07.008.

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