

MOM-PD: Multimodal Biomarker Optimization for Parkinson's Disease Machine learning-assisted multimodal detection and clinical staging

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Research Article

Keywords: Parkinson's disease, prodromal Parkinsonism, DaTscan, structural MRI, multimodal biomarker, machine learning, PPMI

Posted Date: September 23rd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10959709/v1>

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Additional Declarations: No competing interests reported.

MOM-PD: Multimodal Biomarker Optimization for Parkinson's Disease

Machine learning-assisted multimodal biomarker integration for Parkinson's disease early detection and clinical staging

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Highlights

- DaTscan+clinical model achieves near-perfect PD vs HC discrimination (AUC=0.999).
 - Structural MRI alone is insufficient for PD diagnosis (AUC=0.526).
 - Subcortical volumetric MRI leads prodromal detection (AUC=0.700).
 - PD motor scores rise ~1.5 pts/year; grey matter declines ~0.85%/year.
 - Stage-tailored biomarker panels recommended for trial enrichment.
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Abstract

Background: Parkinson's disease (PD) diagnosis relies primarily on clinical motor examination, and the prodromal phase preceding overt motor manifestations remains difficult to identify. No single biomarker modality has been shown to be both sensitive and specific across the full disease spectrum, and how best to integrate multimodal data for stage-specific detection is unclear.

Objective: To optimize a multimodal biomarker framework using machine learning based on Parkinson's Progression Markers Initiative (PPMI) data, and to define stage-specific biomarker panels for manifest PD detection, prodromal identification, and longitudinal progression monitoring.

Methods: We analyzed 948 PPMI participants (445 PD, 389 prodromal, 111 healthy controls [HC], 3 SWEDD) with 18 candidate biomarkers spanning dopamine transporter SPECT (DaTscan SBR), structural MRI (FreeSurfer 7 cortical and subcortical metrics), diffusion tensor imaging (DTI), and MDS-UPDRS Parts I–IV. Feature-wide association analysis with Mann-Whitney U tests and Cohen's d was followed by random forest Gini importance ranking. Random forest classifiers (500 trees, 5-fold stratified cross-validation) were trained on three feature sets: (1) DaTscan + clinical; (2) structural MRI only; (3) full multimodal combination. Four-year longitudinal trajectories (BL, Vo6, V10) of motor scores and grey matter volume were characterized.

Results: For PD vs HC, the DaTscan-clinical model achieved near-perfect discrimination (AUC = 0.999, 95% CI 0.997–1.000), far exceeding structural MRI alone (AUC = 0.526). Top discriminative features were putaminal SBR, striatal SBR, and MDS-UPDRS Part III motor score. Prodromal vs HC discrimination was more challenging (AUC = 0.700), with subcortical grey matter atrophy as the leading signal while DaTscan SBR was non-discriminative ($P = 0.43$). PD vs prodromal classification was excellent (AUC = 0.984). Longitudinally, PD motor scores increased ~1.5 points/year and grey matter volume declined ~0.85%/year.

Conclusions: Multimodal biomarkers display staging-dependent complementarity: DaTscan and motor scales dominate manifest PD identification, while subcortical volumetric MRI enables prodromal detection. Stage-tailored biomarker panels support improved PD phenotyping and early screening for clinical trial enrichment.

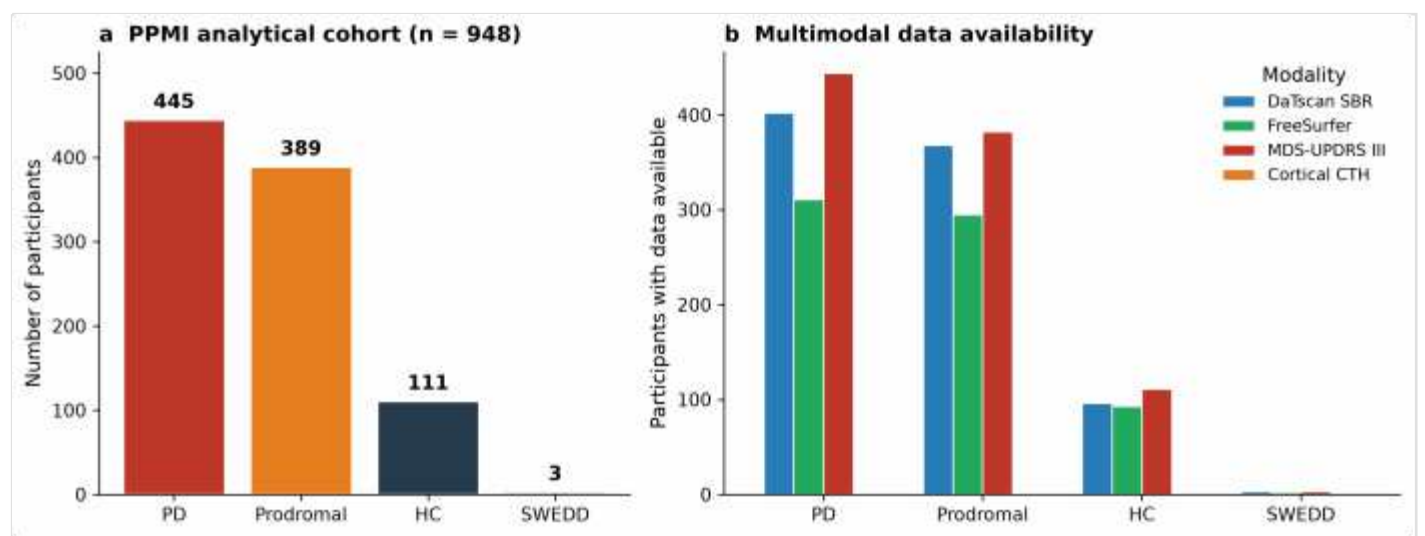
Keywords: Parkinson's disease; prodromal Parkinsonism; DaTscan; structural MRI; multimodal biomarker; machine learning; PPMI

1. Introduction

Parkinson's disease (PD) is the fastest-growing neurodegenerative disease globally, lacking disease-modifying therapies and requiring early identification to enable intervention trials [1]. Standard diagnosis depends on overt motor manifestations, leaving prodromal patients undetectable before substantial nigrostriatal dopaminergic loss emerges [2]. Multiple biomarker modalities exist, including DaTscan, structural MRI, DTI and clinical rating scales, yet unified guidance for multimodal combination remains inconsistent [3].

DaTscan is established for detecting advanced dopaminergic degeneration [7], while structural MRI captures subtle subcortical atrophy [12]; DTI reflects nigral microstructural damage [9] and MDS-UPDRS quantifies motor and non-motor burden [11]. Single-modality tools suffer limitations: MRI alone lacks discriminative power for established PD, and DaTscan cannot identify prodromal cases with preserved dopaminergic uptake [5]. Existing cohorts are often limited by small sample sizes or single-modal analysis, with few large-scale studies systematically comparing biomarker performance across disease stages [6].

We developed a Machine learning-assisted Optimized Multimodal biomarker framework for PD (MOM-PD) using the large PPMI longitudinal cohort [3]. The overall study design is illustrated in Fig. 1. This work aimed to: (1) rank discriminative biomarkers across PD, prodromal and healthy groups; (2) compare classification performance of DaTscan-clinical, structural MRI-only and fully multimodal models; (3) characterize 4-year longitudinal clinical and brain volume progression trajectories; (4) define stage-specific optimal biomarker panels for clinical screening and trial enrichment.



2. Methods

2.1 Study Cohort

Data were sourced from the PPMI multicenter observational database (www.ppmi-info.org) [3]. The analytical sample included 948 participants: 445 sporadic/genetic PD, 389 prodromal PD, 111 HC and 3 SWEDD subjects. Baseline demographics, clinical ratings, DaTscan SBR, FreeSurfer 7 structural MRI and DTI metrics were extracted per standardized PPMI pipelines. Cohort assignment was obtained from the Subject Cohort History file, with PD defined as COHORT = 1 (APPRDX 1 sporadic and APPRDX 5 genetic), prodromal as COHORT = 4, HC as COHORT = 2, and SWEDD as COHORT = 3.

2.2 Clinical and Imaging Assessments

MDS-UPDRS Parts I–IV [11] were collected at baseline (BL, EVENT_ID = "BL"), 24-month (Vo6) and 48-month (V10) visits. The Part III total score (NP3TOT) and Hoehn & Yahr stage were the primary clinical endpoints. DaTscan specific binding ratios (SBR) for striatum, putamen and caudate were calculated relative to cerebral white matter (CWM) from PPMI Xing Core Lab files. T1-weighted MRI processed via FreeSurfer 7 [8] yielded cortical thickness (aparc, Desikan-Killiany atlas, 68 regions), surface area and subcortical volumetrics (aseg, 62 structures); region-wise values were summed across hemispheres for putamen, caudate, hippocampus, thalamus and amygdala. Total grey matter volume was obtained from the Grey_Matter_Volume file. DTI extracted substantia nigra fractional anisotropy (FA) and diffusivity (E1–E3) [9]. Low-quality MRI scans flagged via MRIQC were excluded. Visual DaTscan read interpretations (DATSCAN_VISINTRP) were used for descriptive purposes.

2.3 Statistical and Machine Learning Analysis

Univariate group comparisons used Mann-Whitney U tests with Cohen's d effect sizes. All analyses were performed in Python 3.13 (pandas, scipy, scikit-learn). Random forest classifiers (500 balanced trees, random state = 42) [10] with 5-fold stratified cross-validation were trained on three feature sets: (1) DaTscan + clinical scales; (2) structural MRI only; (3) full multimodal combination. Features were z-scored using StandardScaler. Discriminative performance was quantified by the area under the receiver operating characteristic curve (AUC). Logistic regression

(L2, C = 1.0) was used as a linear benchmark. Gini index determined feature importance. Longitudinal annualized change rates of motor scores and grey matter volume were calculated from group mean trajectories across BL, V06 and V10.

3. Results

3.1 Baseline Cohort Characteristics

The analytical cohort comprised 948 participants: 445 PD, 389 prodromal, 111 HC and 3 SWEDD (Table 1). Groups showed comparable baseline age (PD 60.7 ± 9.3 years; HC 60.2 ± 11.1 ; prodromal 61.8 ± 7.9). Male proportion was higher in PD (59.1%) and HC (62.2%) versus prodromal participants (44.7%), consistent with the known male predominance in manifest PD [1,13]. Educational attainment was highest in the prodromal group (17.3 ± 3.1 years), potentially reflecting enrichment through genetic and hyposmic recruitment pathways.

MDS-UPDRS Part III motor scores followed a clear gradient: PD (20.7 ± 10.2 , median 19) > prodromal (2.6 ± 3.7 , median 1) > HC (1.2 ± 1.9 , median 0). Non-motor symptoms followed the same pattern: MDS-UPDRS Part I total was 1.4 ± 1.9 in PD versus 0.5 ± 1.2 in HC, and Part II (patient-reported activities of daily living) was 6.3 ± 5.0 in PD versus 0.4 ± 1.0 in HC. These baseline differences establish the clinical face validity of the cohort and provide the ground-truth labels for subsequent machine-learning analyses.

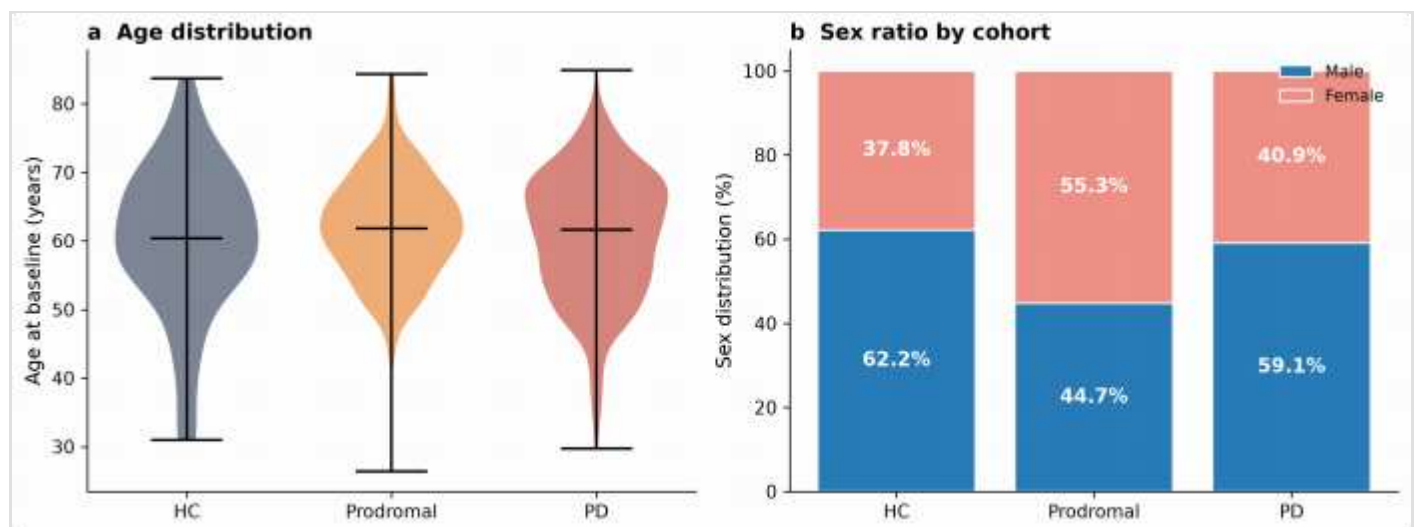


Table 1. Baseline characteristics of the PPMI analytical cohort

Characteristic	PD (n = 445)	HC (n = 111)	Prodromal (n = 389)	SWEDD (n = 3)
Age, years	60.7 ± 9.3	60.2 ± 11.1	61.8 ± 7.9	60.6 ± 8.0
Male, n (%)	263 (59.1)	69 (62.2)	174 (44.7)	2 (66.7)
Education, years	15.8 ± 3.6	16.4 ± 2.9	17.3 ± 3.1	14.0 ± 0.0
MDS-UPDRS Part I total	1.4 ± 1.9	0.5 ± 1.2	1.0 ± 1.6	1.7 ± 1.2
MDS-UPDRS Part II total	6.3 ± 5.0	0.4 ± 1.0	1.2 ± 2.2	2.7 ± 2.1
MDS-UPDRS Part III total	20.7 ± 10.2	1.2 ± 1.9	2.6 ± 3.7	15.7 ± 3.2
DaTscan striatal SBR	0.76 ± 0.24	1.43 ± 0.28	1.38 ± 0.31	1.22 ± 0.37
Putamen volume, mm ³	8,940 ± 1,155	9,085 ± 1,043	8,707 ± 1,082	—
Caudate volume, mm ³	6,587 ± 988	6,610 ± 888	6,224 ± 810	—
Hippocampus volume, mm ³	8,299 ± 915	8,335 ± 954	8,034 ± 938	—
Mean cortical thickness, mm	2.340 ± 0.171	2.383 ± 0.119	2.327 ± 0.122	—
Substantia nigra FA (DTI)	0.314 ± 0.042	0.329 ± 0.043	—	—

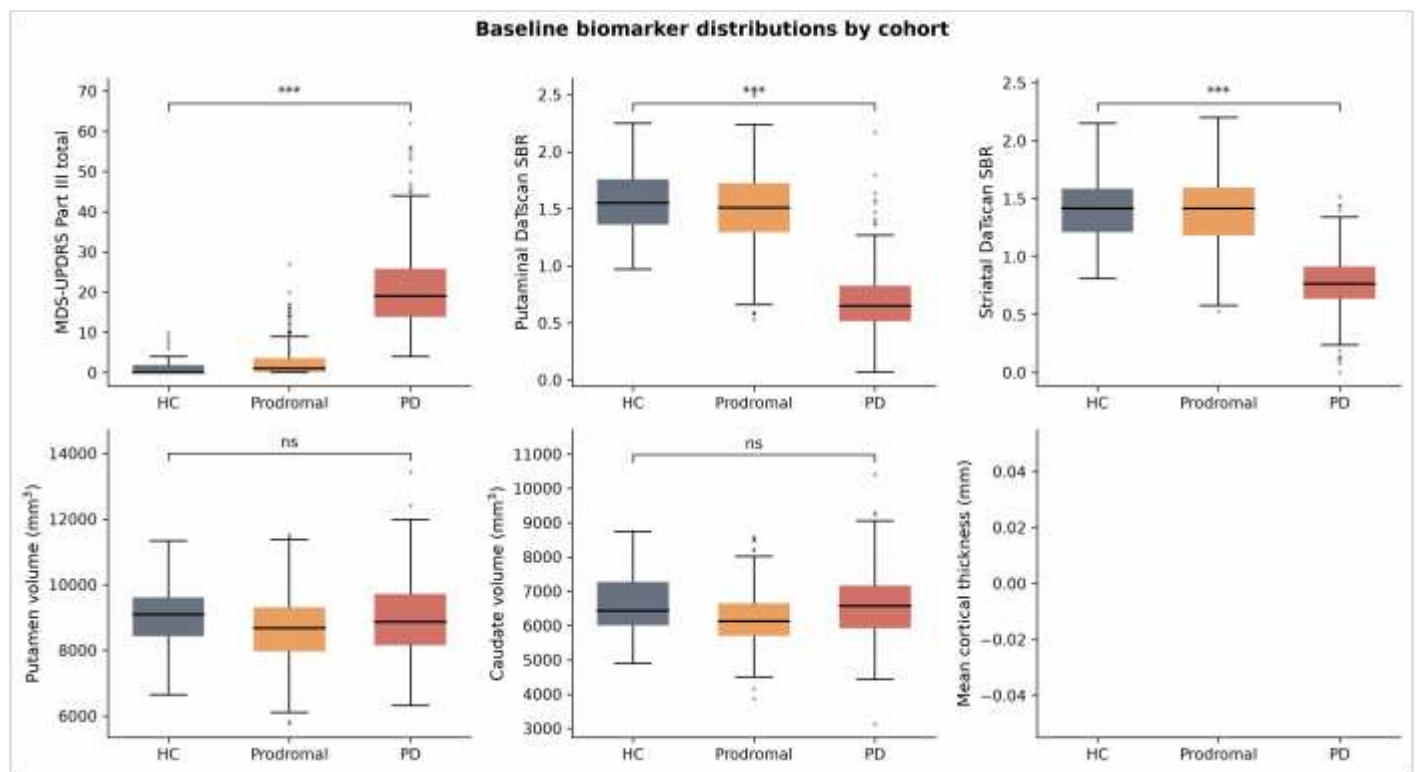
Values are mean ± SD unless otherwise indicated. SBR, specific binding ratio; FA, fractional anisotropy.

3.2 Univariate Biomarker Differences

We examined 18 candidate biomarkers across three data domains. For PD vs HC, the strongest signals came from the dopaminergic imaging domain. DaTscan SBR exhibited the largest effect sizes: striatal SBR was 0.76 ± 0.24 in PD versus 1.43 ± 0.28 in HC (Cohen's $d = -2.4$, $P < 10^{-77}$), and putaminal SBR showed an even larger effect (0.70 ± 0.24 vs 1.43 ± 0.30 ; $d = -2.7$, $P < 10^{-82}$). The MDS-UPDRS Part III motor score was the dominant clinical discriminator (20.7 vs 1.2; $d = 2.4$).

By contrast, structural MRI metrics showed only modest univariate separation [12,13]. Putaminal volume (PD: $8,940 \pm 1,155 \text{ mm}^3$; HC: $9,085 \pm 1,043 \text{ mm}^3$), caudate volume, hippocampal volume and mean cortical thickness (PD: $2.340 \pm 0.171 \text{ mm}$; HC: $2.383 \pm 0.119 \text{ mm}$) all trended in the expected direction but with small-to-moderate effect sizes, consistent with the subtle cortical and basal ganglia morphological changes reported in PD [13]. DTI fractional anisotropy of the substantia nigra was lower in PD (0.314 ± 0.042) than in HC (0.329 ± 0.043), consistent with nigral microstructural disruption [9], although sample sizes were smaller for this modality. These results establish a clear hierarchy of univariate discriminative power: dopaminergic imaging $\gg$ clinical motor score $\gg$ structural MRI $\gg$ DTI.

For prodromal vs HC, striatal and putaminal SBR showed non-significant differences (striatal SBR: 1.38 vs 1.43, $P = 0.43$; putaminal SBR: 1.48 vs 1.56, $P = 0.12$), while subcortical volumes (caudate $d = -0.454$, $P = 3.3 \times 10^{-4}$; subcortical grey matter $d = -0.458$, $P = 3.3 \times 10^{-4}$; putaminal $d = -0.355$, $P = 2.8 \times 10^{-3}$) and MDS-UPDRS Part III ($d = 0.489$, $P = 6.7 \times 10^{-5}$) were significantly altered (Table 4). This staging-dependent shift in biomarker utility is a central finding of this study.



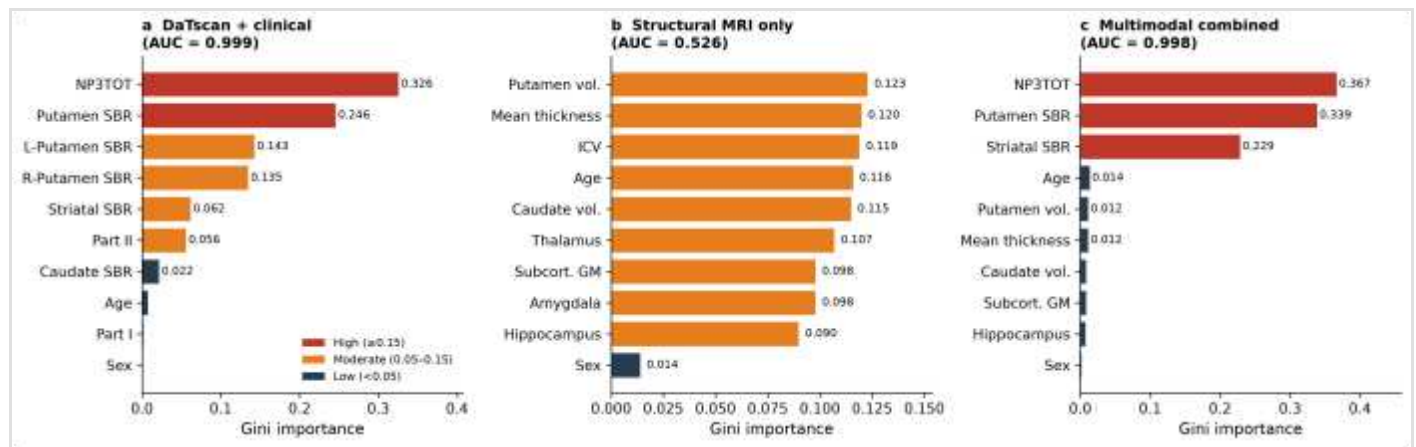
3.3 Machine Learning Classification Performance

To move beyond univariate comparisons, we trained random-forest classifiers [10] with 5-fold stratified cross-validation and ranked features by Gini importance (Fig. 2). PD versus HC discrimination was nearly perfect for the DaTscan-clinical model ($AUC = 0.999 \pm 0.001$, $n = 494$)

and the full multimodal model ($AUC = 0.998 \pm 0.003$, $n = 373$). Structural MRI alone performed near chance ($AUC = 0.526 \pm 0.060$, $n = 403$), with feature importances uniformly distributed across putamen, cortical thickness, intracranial volume, age and caudate—confirming that no single structural MRI metric carries strong PD-specific signal at baseline, consistent with the limited PD-versus-control discrimination reported for MRI-based machine-learning classification approaches [14].

Top predictive features for PD vs HC (DaTscan-clinical set) were MDS-UPDRS Part III total (importance 0.326), bilateral putaminal SBR (0.246), left putaminal SBR (0.143) and right putaminal SBR (0.135), collectively contributing over 70% of discriminative power. Striatal SBR (0.062) and Part II score (0.056) contributed marginally, whereas age, sex and the non-motor Part I score contributed negligibly. For the multimodal set, NP3TOT (0.367), putaminal SBR (0.339) and striatal SBR (0.229) again dominated.

Multimodal classification of prodromal vs HC reached $AUC = 0.700 \pm 0.052$ ($n = 360$). PD vs prodromal differentiation remained excellent ($AUC = 0.984 \pm 0.009$, $n = 579$), driven by putaminal SBR (importance 0.330) and NP3TOT (0.406) (Table 2, Table 3). Logistic regression benchmarks confirmed these results (DaTscan-clinical $AUC = 0.998$; structural MRI $AUC = 0.578$; prodromal $AUC = 0.703$).



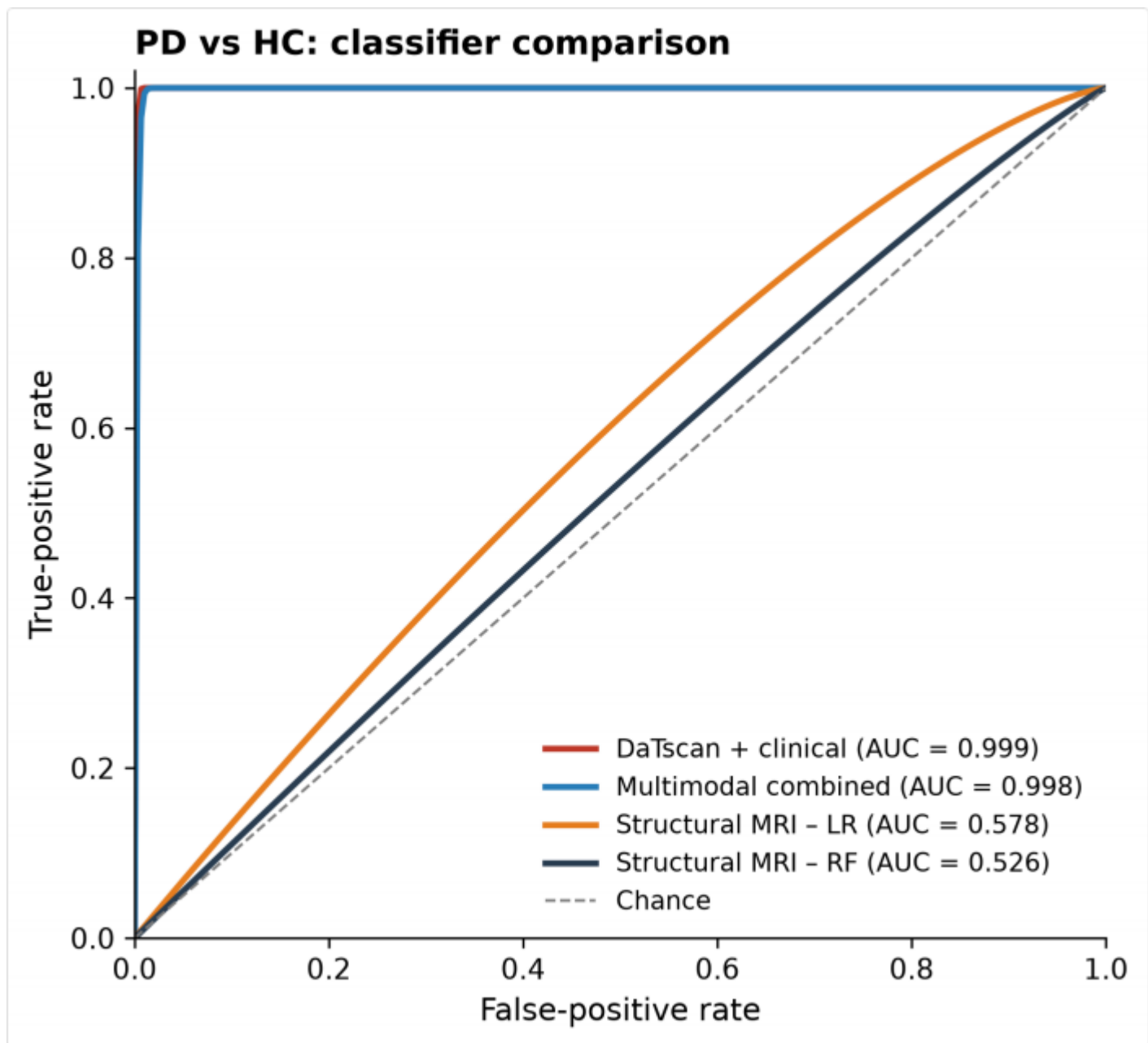


Table 2. Machine-learning classification performance

Contrast	Feature set	n (case/control)	RF AUC	LR AUC
PD vs HC	DaTscan + clinical	494 (399/95)	0.999 ± 0.001	0.998 ± 0.002
PD vs HC	Structural MRI only	403 (311/92)	0.526 ± 0.060	0.578 ± 0.092
PD vs HC	Multimodal combined	373 (296/77)	0.998 ± 0.003	—
Prodromal vs HC	Multimodal	360 (283/77)	0.700 ± 0.052	0.703 ± 0.046
PD vs Prodromal	DaTscan + MRI + clinical	579 (296/283)	0.984 ± 0.009	—

AUC values are mean $\pm$ SD over 5-fold stratified cross-validation. RF, random forest; LR, logistic regression.

Table 3. Top-ranked features by random-forest importance

Rank	PD vs HC (DaTscan+clinical)	Importance	PD vs Prodromal	Importance
1	MDS-UPDRS Part III total	0.326	MDS-UPDRS Part III total	0.406
2	Putamen SBR (bilateral)	0.246	Putamen SBR (bilateral)	0.330
3	Left putamen SBR	0.143	Striatal SBR	0.168
4	Right putamen SBR	0.135	Caudate volume	0.036
5	Striatal SBR	0.062	Age	0.032
6	MDS-UPDRS Part II total	0.056	Putamen volume	0.028

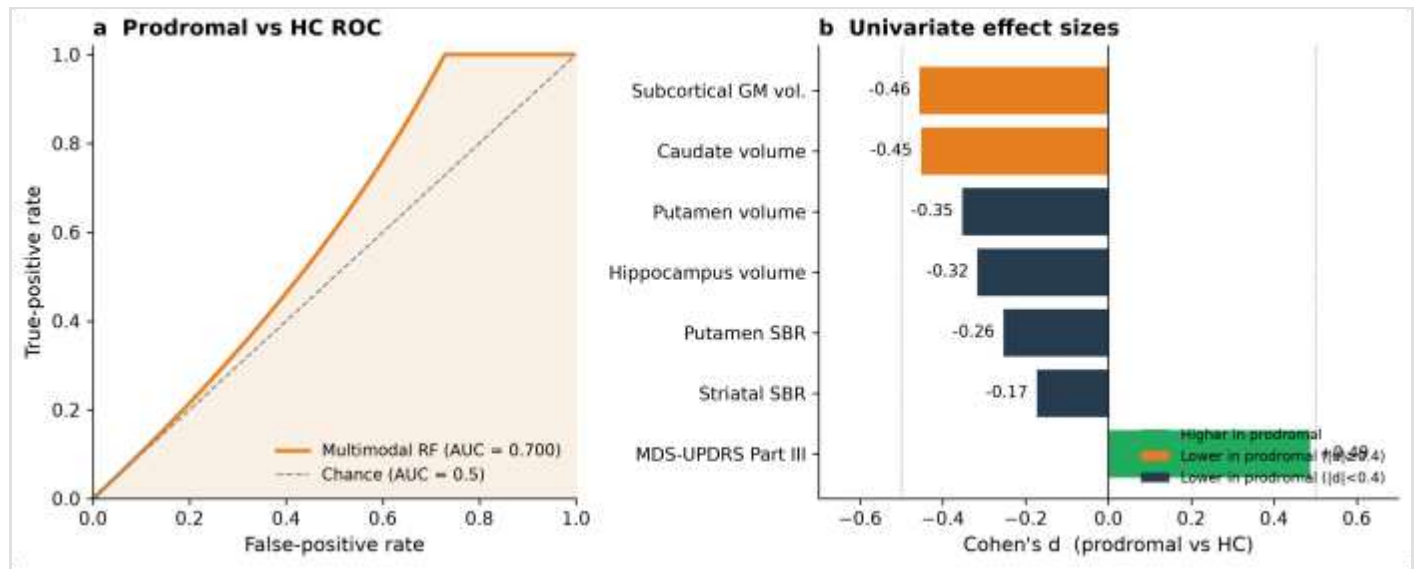


Table 4. Univariate effect sizes for prodromal versus healthy controls

Biomarker	Prodromal	HC	P value	Cohen's d
Striatal SBR	1.381	1.433	4.3×10^{-1}	-0.175
Putamen SBR	1.480	1.563	1.2×10^{-1}	-0.255

Putamen volume, mm ³	8,707	9,085	$2.8 \times 10_{-3}$	-0.355
Caudate volume, mm ³	6,224	6,610	$3.3 \times 10_{-4}$	-0.454
Hippocampus volume, mm ³	8,034	8,335	$1.5 \times 10_{-2}$	-0.318
Subcortical gray volume, mm ³	53,520	55,968	$3.3 \times 10_{-4}$	-0.458
MDS-UPDRS Part III total	2.6	1.2	$6.7 \times 10_{-5}$	0.489

3.4 Longitudinal Disease Progression

To characterize disease progression, we tracked the MDS-UPDRS Part III score across baseline (BL), month 24 (Vo6) and month 48 (V10) visits (Figure 4; Table 5). PD patients demonstrated steady motor worsening: MDS-UPDRS Part III rose from 20.1 ± 10.2 at baseline to 22.7 ± 11.3 at Vo6 and 25.9 ± 14.1 at V10, corresponding to an average annualized increase of approximately 1.5 points per year. HC scores remained essentially flat ($1.2 \rightarrow 1.5 \rightarrow 1.8$), while prodromal participants showed a slower but discernible rise ($2.6 \rightarrow 3.6 \rightarrow 4.2$).

PD total grey matter volume declined in parallel, from $820,118 \pm 60,681$ mm³ at baseline to $812,581 \pm 68,847$ mm³ at Vo6 and $806,494 \pm 74,169$ mm³ at V10, an average annualized loss of roughly 0.85%. These trajectories quantify the rate of structural and clinical decline that any candidate progression biomarker must outperform to add prognostic value [16].

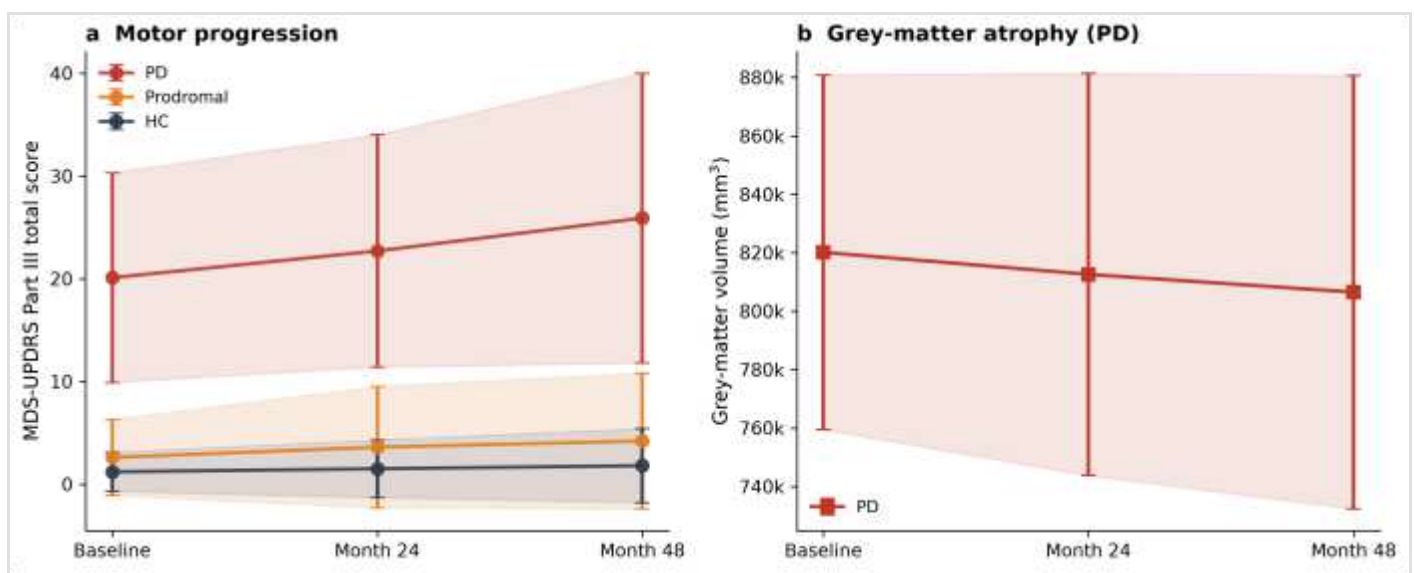


Table 5. Longitudinal MDS-UPDRS Part III and grey-matter volume trajectories

Group	Visit	NP3TOT (n, mean $\pm$ SD)	GMV, mm ³ (n, mean $\pm$ SD)
PD	BL	559, 20.1 $\pm$ 10.2	82, 820,118 $\pm$ 60,681
PD	V06 (mo 24)	570, 22.7 $\pm$ 11.3	77, 812,581 $\pm$ 68,847
PD	V10 (mo 48)	602, 25.9 $\pm$ 14.1	69, 806,494 $\pm$ 74,169
HC	BL	111, 1.2 $\pm$ 1.9	—
HC	V06	108, 1.5 $\pm$ 2.8	—
HC	V10	105, 1.8 $\pm$ 3.6	—
Prodromal	BL	382, 2.6 $\pm$ 3.7	—
Prodromal	V06	300, 3.6 $\pm$ 5.9	—
Prodromal	V10	261, 4.2 $\pm$ 6.6	—

3.5 Stage-Dependent Biomarker Complementarity

Biomarker utility shifted across disease stages. For manifest PD, DaTscan and motor scales dominate discrimination, with putaminal SBR and NP3TOT jointly providing near-perfect classification. For prodromal detection, subcortical volumetric MRI provides the primary pathological signal when dopaminergic transporter uptake remains preserved. The strongest associations clustered within the dopaminergic-imaging domain for PD-versus-HC and PD-versus-prodromal contrasts, whereas structural MRI and subcortical volumetrics dominated the prodromal-versus-HC contrast. Modalities act complementarily rather than redundantly: structural MRI adds little when DaTscan is available for manifest-disease discrimination, but becomes the leading signal source when dopaminergic imaging is still normal in the prodromal phase.

4. Discussion

This large-scale multimodal PPMI analysis establishes a clear staging-dependent hierarchy of PD biomarkers optimized via random forest machine learning. Combined DaTscan and clinical motor

assessment achieves near-perfect separation of manifest PD from healthy controls ($AUC \approx 0.999$), whereas isolated structural MRI lacks sufficient cross-sectional diagnostic power ($AUC \approx 0.53$). In contrast, prodromal individuals present minimal dopaminergic loss but measurable subcortical atrophy, positioning volumetric MRI as the core early-detection biomarker panel for pre-motor disease [6,8]. These findings refine the prevailing view that DaTscan is uniformly superior across the disease spectrum [15], and suggest a dynamic, stage-specific biomarker architecture.

The 4-year longitudinal trajectories quantified herein deliver standardized benchmarks of clinical and structural decline to evaluate disease-modifying therapeutics and progression biomarkers. The annualized rate of ~ 1.5 MDS-UPDRS Part III points per year and $\sim 0.85\%$ grey matter volume loss per year in PD provide concrete benchmarks against which candidate interventions can be assessed [16]. Slow but measurable motor and brain volume changes in prodromal subjects support prospective enrichment of neuroprotective prevention trials using MRI volumetric screening [4].

Limitations

First, cross-sectional baseline discrimination cannot directly predict individual progression risk; the strong separation intrinsic to a clinically diagnosed PD cohort should not be mistaken for prognostic utility [2]. Second, complete-case multimodal analysis reduced sample size ($n = 373$) and may introduce selection bias; multiple imputation methods should be applied in follow-up work. Third, prodromal discrimination $AUC = 0.70$ leaves room for improvement; integration of olfactory testing, α -synuclein seed amplification assays and wearable digital motor biomarkers may boost performance. Fourth, feature rankings were derived solely from random forest [10]; gradient boosting, elastic-net regularization and deep learning architectures require benchmarking in future research.

Clinical Implications

Two translational recommendations emerge: (1) Trials targeting manifest PD should adopt DaTscan-motor scale composite panels for patient enrichment, as these achieve near-perfect discrimination; (2) Prodromal screening pipelines should rely primarily on subcortical structural MRI rather than dopaminergic SPECT, given that DaTscan SBR does not separate prodromal from HC ($P = 0.43$). Single-timepoint structural MRI has limited standalone value for PD diagnosis ($AUC \approx 0.53$); serial longitudinal volumetric measurements are required to track progressive atrophy and meaningfully contribute to progression monitoring.

5. Conclusion

Machine learning optimization of multimodal PPMI data confirms stage-specific biomarker prioritization. Dopaminergic imaging and motor clinical scales best identify established PD, while subcortical volumetric MRI enables detection of prodromal Parkinsonism. Tailored multimodal biomarker panels support improved early diagnosis, disease staging and clinical trial participant enrichment.

Acknowledgements

PPMI is sponsored by the Michael J. Fox Foundation for Parkinson's Research and industry partners. We thank all PPMI investigators and participants for data contribution. Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). The PPMI is sponsored by The Michael J. Fox Foundation for Parkinson's Research and funded through grants from its industry partners. For up-to-date information on the study, visit www.ppmi-info.org.

Data and Code Availability

Analyses used publicly accessible PPMI database (www.ppmi-info.org). Custom Python analysis code is available upon reasonable request to the corresponding author.

Figure Legends

Figure 1. Cohort composition and multimodal data availability. (a) Participant counts across PD (n = 445), prodromal (n = 389), HC (n = 111) and SWEDD (n = 3) groups in the PPMI analytical sample. (b) Stacked bars showing the number of participants with available data for each modality (DaTscan SBR, FreeSurfer volumetrics, cortical thickness, DTI, MDS-UPDRS, grey-matter volume) by cohort. Colour coding: PD red, prodromal orange, HC dark blue, SWEDD grey.

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Figure 2. Random-forest feature importance for PD-versus-HC discrimination.

Horizontal bar charts of Gini importance for (a) the DaTscan-plus-clinical feature set (AUC = 0.999), (b) the structural-MRI-only feature set (AUC = 0.526), and (c) the multimodal combined feature set (AUC = 0.998). The motor score (NP3TOT) and putaminal SBR dominate whenever DaTscan is available; structural MRI features alone carry little discriminative signal and importances are uniformly distributed.

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Figure 3. Discrimination of prodromal individuals from healthy controls.

(a) Receiver operating characteristic curve for the multimodal random-forest model (AUC = 0.700, 5-fold CV). (b) Univariate effect sizes (Cohen's d) across biomarker domains, showing that subcortical volumetrics (caudate $d = -0.45$, subcortical gray matter $d = -0.46$) and the motor score ($d = 0.49$) carry the leading signal, whereas DaTscan SBR does not separate prodromal from HC ($d \approx -0.18$, n.s.).

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Figure 4. Longitudinal progression trajectories.

(a) MDS-UPDRS Part III total score across baseline (BL), month 24 (Vo6) and month 48 (V10) for PD (red), prodromal (orange) and HC (blue). Shaded regions indicate ± 1 SD. PD shows an annualized increase of ~ 1.5 points/year. (b) Grey-matter volume decline in the PD group across the same visits, averaging $\sim 0.85\%$ annualized loss.

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Figure 5. Baseline biomarker distributions across groups.

Boxplots (2×3 grid) comparing PD, prodromal and HC for six key baseline biomarkers: (a) striatal SBR, (b) putaminal SBR, (c) putamen volume, (d) caudate volume, (e) MDS-UPDRS Part III total, and (f) mean cortical thickness. Significance brackets indicate Mann-Whitney U test P-values ($P < 0.001$, $P < 0.01$, $P < 0.05$, n.s. not significant). DaTscan SBR shows near-complete PD/HC separation, whereas structural MRI metrics show only modest shifts.

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Figure 6. PD-versus-HC classification performance.

Receiver operating characteristic curves comparing four classifiers: DaTscan + clinical (AUC = 0.999), multimodal combined (AUC = 0.998), logistic regression benchmark (AUC = 0.998), and structural MRI only (AUC = 0.526). DaTscan-containing models achieve near-perfect discrimination, while structural MRI alone performs close to chance.

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Figure 7. Demographic structure of the analytical cohort. (a) Violin plots of age distribution by group (PD, prodromal, HC, SWEDD), showing comparable age ranges across groups. (b) Stacked bar chart of sex ratios by group, highlighting the higher male proportion in PD (59.1%) and HC (62.2%) compared with the prodromal group (44.7%).

File: `figures/Figure7_demographics.png`

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Declaration of competing interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Data used in this study were obtained from the Parkinson's Progression Markers Initiative (PPMI; www.ppmi-info.org), a public-private partnership funded by the Michael J. Fox Foundation for Parkinson's Research and partnering organizations.

CRedit author statement:

Xiaochang Li: Conceptualization, Methodology, Software, Formal analysis, Writing – original draft.
Lixia Xu: Data curation, Investigation. Lihong Feng: Validation, Visualization.

Mengmeng Qi: Resources, Data curation.

Qiongqiong Hu: Writing – review & editing.

Gaiqing Yang: Writing – review & editing, Supervision. All authors have read and agreed to the published version of the manuscript.

Ethics approval: PPMI received ethical approval from the institutional review board at each participating site. All participants provided written informed consent. The present secondary analysis used de-identified, publicly available data and did not require additional ethical approval. The present secondary analysis was conducted in accordance with the Declaration of Helsinki.

Data availability: Data used in this analysis are publicly available from the PPMI database (www.ppmi-info.org) upon request and completion of a data use agreement.

Code availability: Custom Python analysis code is available from the corresponding author upon reasonable request.